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The Heterogeneous Enantioselective Hydrodehalogenation of α,α-Dichlorobenzazepinone-2: A Unique Case of Substrate Specificity.

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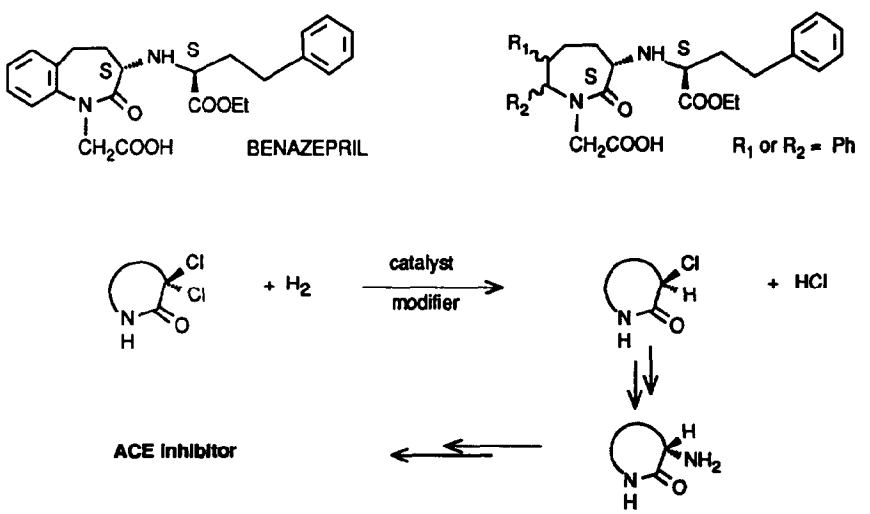
Abstract: The enantioselective hydrodehalogenation of α,α-dichlorobenzazepinone-2 with cinchona modified Pd- and Pt-catalysts was investigated using a random screening approach. The effect of important reaction parameters was determined and optimized. The best optical yields (50% ee) were obtained with a 5% $Pd/BaSO_4$ catalyst modified with cinchonine in THF with NBu_3 as HCl acceptor. Very high modifier and catalyst concentrations were necessary to get good optical yields and reasonable rates because the modifier decreases the catalyst activity. The absolute configuration of α-chlorobenzazepinone-2 was determined. Attempts to extend this enantioselective dehalogenation reaction to other α,α-dihalogen substituted acid derivatives were unsuccessful.

Introduction

The synthesis of several active ACE (angiotensin converting enzyme) inhibitors involves the SN_2-reaction of an N-nucleophile with a racemic α-halo-lactam[2-4]. Since only one of the enantiomers formed is usually desired, it would be preferable to start not with the racemic but with the enantiomerically pure halide

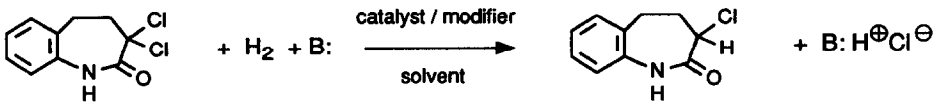


Scheme 1

as an alternative to resolving the resulting amine at a later stage[5] (Scheme 1). This communication describes studies which are concerned with the enantioselective mono-hydrodehalogenation of α,α-dichlorobenzazepinone-2 using cinchona modified Pd- and Pt-catalysts. Also described are (unsuccessful) attempts to generalize the reaction for the enantioselective preparation of other chiral α-halo-acid derivatives starting from the corresponding α,α-dihalo compounds.

Results

Enantioselective mono-hydrodehalogenation of α,α-dichlorobenzazepinone-2



Preliminary experiments. Based on our experience with enantioselective hydrogenations[6] and on literature reports on selective dehalogenation reactions[7-9], we carried out some preliminary experiments with a heterogeneous Pd/C catalyst modified with cinchonidine and with a homogeneous Rh-(DIOP) complex. Both catalysts gave the desired α-chlorobenzazepinone-2 with good chemoselectivity and, to our amazement, with exactly the same optical rotation $[\alpha]_D^{25} \approx -10$ (we later found that this corresponded to an optical yield of about 3%). Because the Rh/DIOP catalyst exhibited very low activity, we decided to continue our investigations with heterogeneous catalysts.

Screening of catalysts, bases and solvents. At the start we did not know which of the many parameters would affect the activity and selectivity of this catalytic system. Therefore, we decided to carry out a broad screening program, changing both quantitative and qualitative parameters. In a first series we used cinchonidine as modifier and investigated the influence of the metal, the support, the solvent and the nature of the base. We chose five types of catalysts, four solvents and three bases (see Table 1) and performed 15 experiments using **random** catalyst/solvent/base combinations (of the 60 possible). Some of the experiments were repeated in order to check reproducibility and a few additional catalysts and solvents were tested as well. The reaction conditions used in this screening phase and the measured optical rotations are summarized in Table 1. For experimental reasons we worked with very dilute solutions at 3 bars of hydrogen pressure. Preliminary experiments indicated that quite high catalyst and modifier concentrations were needed under these conditions. Generally, the chemoselectivity was good and the reproducibility was also satisfactory although in a few cases we later obtained somewhat higher enantioselectivities without apparent changes in the reaction conditions.

Screening of modifiers. In a second series, the influence of the modifier was investigated under the best conditions ($Pd/BaSO_4$, THF, NBu_3) found in the first series of experiments. In addition to a number of cinchona derivatives, several alkaloids which have been described to be effective for the enantioselective electroreduction of dihalides[10, 11] were also screened (Table 2).

Effect of reaction conditions and catalyst type. Once the best combination of catalyst ($Pd/BaSO_4$), modifier (cinchonine or 10,11-dihydrocinchonine), solvent (THF) and base (NBu_3) was determined, the influence of temperature, pressure and of the concentrations of substrate, catalyst and modifier were investigated. These

Table 1. Dehalogenation of α,α-dichlorobenzazepinone-2. Influence of metal, support, base and solvent on optical rotation, $[\alpha]_D^{20}$ (c=0.5, MeOH). Modifier cinchonidine, 3 bar H_2, room temperature. Reaction times varied between 1 and 24 h.

Catalyst	Pd/C			$Pd/BaSO_4$			$Pd/CaCO_3$			Pt/C		$Pt/BaSO_4$		Pd/Al_2O_3	Pt/Al_2O_3	Rh/C	Ru/C	Ra-Ni
Base	1)	2)	3)	1)	2)	3)	1)	2)	3)	1)	2)	1)	2)	2)	1)	2)	2)	2)
Solvent																		
THF	-58 -57	-90	-37	-39 -56	-123 -129					-25 -35			-66	-62	-5	-63	0	.[6]
AcOEt	-31	-60 -52		-70 -72	-97 -101		-26	-31	-27	-44	-40		-80					
EtOH	-28[5]		-4[4]			0[4]				-6		-5						
t-BuOMe	-47				-71	-66							-60					
CH_2Cl_2		-61																
Toluene		-13																

1) Na-acetate 2) NBu_3 3) MgO 4) Na_2CO_3 5) low chemoselectivity 6) RaneyNi; no reaction

Table 2. Dehalogenation of α,α-dichlorobenzazepinone-2; modifier screening. 500 mg substrate, 100 mg catalyst, 100 mg modifier, 1.3 equiv. NBu_3, 150 ml THF, 3 bar H_2, room temperature. Reaction times varied between 1 and 24 h.

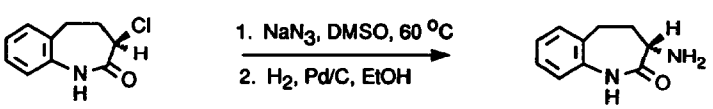
Modifier	X[1)]	Y[1)]	R[1)]	$[\alpha]_D^{25}$ (c=0.5-1, MeOH)
cinchonidine derivatives	OH	H	$CH{=}CH_2$	-123, -129
	OH	H	CH_2CH_3	-121, -122, -140, -146
	OMe	H	CH_2CH_3	0, -2
	H	H	CH_2CH_3	0
	H	Cl	CH_2CH_3	+2
N_1-benzyl-cinchonidinium chloride	OH	H	$CH{=}CH_2$	-78, -83[2)], -5[3)]
cinchonine derivatives (Z = H)[1)]			$CH{=}CH_2$	+177, +179
			CH_2CH_3	+150, +179
chinidine derivatives (Z = OMe)[1)]			$CH{=}CH_2$	+112
			CH_2CH_3	+85
N-methylephedrine				-5
brucine				-2
yohimbine				+4
strychnine				-2

1) For formulas see Scheme 5 2) AcOEt 3) Toluene

parameters were expected to influence the catalytic activity and selectivity in analogy to the enantioselective hydrogenation of α-keto esters by the Pt/Al_2O_3-cinchonidine system[6]. In addition, $Pd/BaSO_4$ catalysts of different suppliers were tested and compared to other Pd catalysts. The results are summarized in Tables 3, 4 and 5. The reproducibility of the optical yields was generally satisfactory, the activity data (reaction time / conversion) scattered somewhat more.

Determination of the absolute configuration of α-chlorobenzazepinone-2.

In order to establish the absolute configuration of α-chlorobenzazepinone-2 three product mixtures with different optical rotations were converted to α-aminobenzazepinone-2 via the corresponding azide[2] (Scheme 2). Even though the optical purity of the resulting amine was lower than that of the starting chloro derivative there is no doubt that (+)-α-chlorobenzazepinone-2 gave (-)-α-aminobenzazepinone-2, which is known to have S-configuration, $[\alpha]_D^{25}$= -442 (c=1, MeOH), whereas the (-)-enantiomer gave (+)-α-aminobenzazepinone-2. Assuming inversion of configuration for the substitution of Cl by N_3 and retention for the reduction of the azide group[5], we conclude that **(+)-α-chlorobenzazepinone has R-configuration.**



$[\alpha]_D^{25}$ (c= 0.5, MeOH)	ee (%)	$[\alpha]_D^{25}$ (c= 1, MeOH)	ee (%)
+107	30	- 43	10
+105	29	- 61	14
- 95	27	+20	5

Scheme 2

Table 3. Dehalogenation of α,α-dichlorobenzazepinone-2; effect of reaction parameters on conversion, chemoselectivity and optical yield. Modifier cinchonine, catalyst 5% $Pd/BaSO_4$. 500 mg substrate, 1.3 equiv. NBu_3, 30 ml THF.

Cinchonine (mg)	$Pd/BaSO_4$ (mg)	temp. (°C)	pressure (bar)	reaction time (h)	conv. (%)	chemosel. (%)	ee (%)
500	500	25	3	0.5	100	94	48
"	100	25	3	2.0	94	94	47
300	300	25	3	1.0/1.2	100/100	96/98	50/45
"	"	25	20	22.0	100	76	44
"	"	25	20	6.0	99	94	27[1]
"	"	25	80	2.0	100	82	45
"	"	50	20	0.9/4.0	100/100	68/69	48/44
"	100	25	3	2.3	95	95	44
200	200	25	3	3.2	100	97	31[2]
150	150	25	20	6.0	100	95	29[2]
100	100	25	3	4.5	100	94	38
"	"	25	3	7.5	94	90	50[3]
"	300	25	3	1.0	93	93	41
"	500	25	3	0.5	97	97	39
30	30	25	20	2.3/5.7	81/100	95/95	16/16
"	"	50	20	5.7	100	90	15
25	25	25	20	0.5	32	93	14
20	20	25	3	2.1	49	97	33[4]
5	5	25	20	6.0/0.5	54/8	98/100	5/4

1) 2 g substrate 2) 1 g substrate 3) 150 ml THF (preliminary exp.) 4) 0.1 g substrate

Table 4. Dehalogenation of α,α-dichlorobenzazepinone-2; effect of modifier concentration on conversion, chemoselectivity and optical yield. 25 mg 5% $Pd/BaSO_4$, 500 mg substrate, 1.3 equiv. NBu_3, 30 ml THF, 20 bar H_2, 25 °C.

modifier type	(mg)	reaction time (h)	conv. (%)	chemosel. (%)	ee (%)
a) cinchonine	0	0.5	36	85	0
	5	0.5	15	91	4
	25	0.5	32	93	14
	125	0.5	13	93	38
	300	0.5	6	-	36
b) dihydrocinchonine	0	2.0	55	89	0
	25	2.0	39	97	14
	50	4.0	50	97	23
	100	4.0	21	97	27
	125	2.0	53	98	28
	150	4.0	44	98	33
	300	2.0	18	95	21

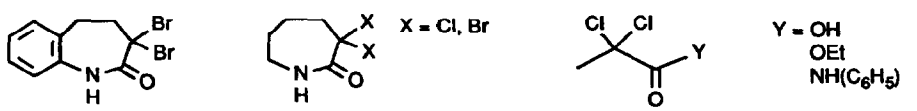
Table 5. Dehalogenation of α,α-dichlorobenzazepinone-2; comparison of conversion, chemoselectivity and optical yield for different types of Pd catalysts. a) 150 mg catalyst, 150 mg cinchonine, 1.0 g substrate, 1.3 equiv. NBu_3, 30 ml THF, 20 bar H_2, 25 °C. b) 500 mg substrate, 100 mg catalyst, 100 mg modifier, 1.3 equiv. NBu_3, 150 ml THF, 3 bar H_2, room temperature.

catalyst	type	Pd cont. (%)	Pd surf. (m^2/g)	BET surf. (m^2/g)	reaction time[1] (h)	conv. (%)	chemosel. (%)	ee (%)
a) Modifier: cinchonine								
$Pd/BaSO_4$	4607	5	0.85	5.6	6.0 (6.0)	100	95	29
	Fluka	5	-	-	6.0 (5.0)	100	87	28
	E50R/D	5	1.3	8.8	6.0 (2.0)	100	90	29
	E50N	5	0.05	13	6.0 (1.0)	100	60	23
b) Modifier: cinchonidine, preliminary experiments								
$Pd/BaSO_4$	E50N	5	0.05	13	5.5	100	~86	38
	Fluka	10	-	-	6.7	100	~94	31
	4607	5	0.85	5.6	6.0	100	~90	39
$Pd/CaCO_3$	Fluka	5	-	-	22.0	57	100	9[2]
Pd/Al_2O_3	4530	5	3.0	170	6.2	100	98	17
Pd/C	4522	5	4.1	900	1.7	100	97	25

1) in parenthesis time until 100% H_2 uptake 2) in AcOEt

Dehalogenation of various α,α-dihaloacid derivatives.

In an attempt to generalize this novel enantioselective hydrogenolysis reaction we synthesized various analogues of α,α-dichlorobenzazepinone and some other α,α-dihalogen substituted acid derivatives (Scheme 3) and applied the best catalyst system under optimal reaction conditions. To our amazement and disappointment the reactions to the corresponding mono halides occurred with satisfactory chemoselectivities but without the slightest optical induction!



Scheme 3

Discussion

The catalytic mono-hydrodehalogenation of several geminal dihalogen compounds has been described to proceed with good chemoselectivities using heterogeneous Ni- or Pd-catalysts, usually in the presence of a base[7, 8]. The application of Rh-phosphine complexes as homogeneous dehalogenation catalysts has also been reported[9] but to our knowledge no chiral catalyst has ever been employed in order to obtain one of the two enantiomeric mono-halogen compounds selectively. The only successful approach reported up to now is the enantioselective electrochemical dehalogenation of the two dihalogen compounds A and B (Scheme 4) on Hg electrodes modified with alkaloids. The best optical yields were obtained with emetine (44% ee for the dibromide A)[10] and strychnine (26% ee for the dichloride B)[11] as modifier.

Much more is known on the enantioselective hydrogenation of functionalized ketones by modified hete-

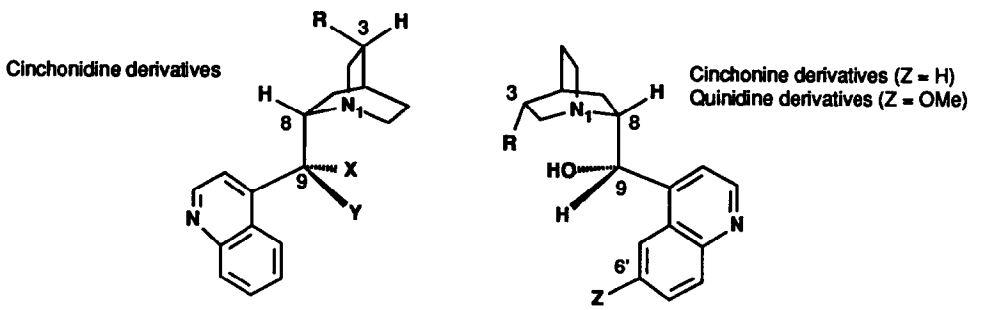
rogeneous catalysts and of special interest to us were the cinchona modified Pt catalysts used successfully for the hydrogenation of α-keto esters[6]. In the following discussion we will refer to the results obtained for these systems for comparison.

Scheme 4

Influence of modifier, catalyst and solvent.

The results summarized in Table 1 and 2 show that these are the most important parameters which affect the optical yield in the dehalogenation of α,α-dichlorobenzazepinone-2. The modifier determines which enantiomer is formed in excess i.e. the sense of the optical induction, while catalyst and solvent influence only the magnitude of the optical yield. The effect of the base often is not very strong but all four components must be matched optimally in order to get the highest enantiomeric excess. The combination of cinchonine, $Pd/BaSO_4$ in THF in the presence of tributylamine is clearly favored.

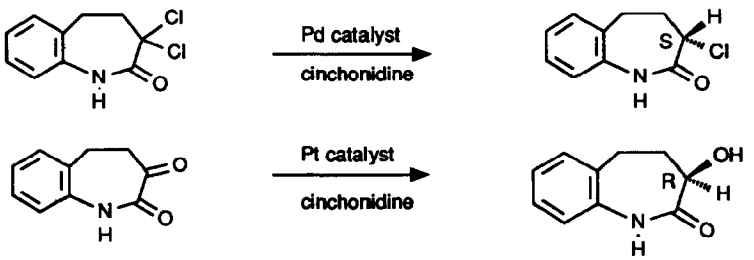
Of the several types of modifiers tested only the cinchona alkaloids lead to a significant optical induction. Strychnine or brucine which have been reported to be quite selective in the asymmetric electroreduction[10, 11] are not effective at all. The absolute configuration at C_8 and C_9 of the alkaloid (Scheme 5) determines which enantiomer of α-chlorobenzazepinone-2 is formed in excess: irrespective of catalyst, solvent or base, cinchonidine (8S, 9R) derivatives give predominantly S-product while the "pseudo-enantiomeric" cinchonine and quinidine (8R, 9S) preferentially lead to the R-form. This behavior is typical when cinchona alkaloids are used as enantioselective catalysts[12] or modifiers[6].



Scheme 5

The substituent X at C_9 of the cinchona alkaloids must be OH; if X is H or OMe the enantioselectivity is lost completely. If N_1 is alkylated the optical yields are lower but still significant. This is in contrast to the asymmetric hydrogenation of α-keto esters where alkylation of N_1 leads to racemic products whereas the

enantioselectivity is either unchanged (X = OMe) or only reduced (X = H) when the substituent at C_9 is changed[6]. For both reaction types there is little difference in enantioselectivity whether R at C_3 is $CH{=}CH_2$ or CH_2CH_3 (probably because the vinyl group is hydrogenated during the reaction) and in both cases the introduction of a OMe substituent at C_6, lowers the ee values somewhat. We therefore conclude that the interaction between the α,α-dichlorobenzazepinone-2 and C_9-OH, but not with the lone pair of N_1, is responsible for the control of the stereochemistry while for the α-keto esters the interaction with N_1 is more important. This different modifier - substrate interactions might be the reason why with a given modifier the hydrogen in the α-chlorobenzazepinone-2 is introduced from the opposite enantioface than the one in α-hydroxybenzazepinone-2 (Scheme 6).



Scheme 6

Pd catalysts are known to be very efficient for C-X hydrogenolysis[7, 8] and it seems that they are also best suited for the enantioselective hydrogenation of the dichlorobenzazepinone. Pt and Rh too give moderate ee's, Ru and Ni are not suitable under our reaction conditions. The type of support has a strong influence on the activity, the chemo- and enantioselectivity of the modified catalyst. Different $Pd/BaSO_4$ catalysts differ mainly in their activity (time until 100% H_2 uptake) but little in their selectivity. We could not find a good correlation between the measured catalyst parameters and the catalytic performance except that small metal and total surface areas are advantageous. Similar observations have been described for modified Ni and Pt hydrogenation catalysts[6].

The solvent effect is significant and our screening results suggest that the enantioselectivity of Pd and Pt catalysts correlate with the polarity of the solvent (see Fig. 1a). Best results are obtained with aprotic solvents with medium to low dielectric constants but we have not investigated whether different solvents require different modifier concentrations for optimal results. The base seems to play a relatively minor role and it probably acts mainly as HCl acceptor.

Influence of reaction parameters.

The results summarized in Tables 3 and 4 can be commented as follows:

- Catalyst concentration, pressure and temperature have little effect on the enantiomeric excess, but affect activity (reaction time / conversion) and also somewhat the chemoselectivity. There are no indications that the enantioselectivity is affected by the degree of conversion.
- Surprisingly the substrate concentration strongly influences the enantioselectivity if the other parameters are kept constant. This is clearly visible in Fig. 1b: the best optical yields are obtained at very low concentrations of dichlorobenzazepinone.

The dependence of ee and conversion / reaction time on the modifier concentration is the most interesting correlation. Earlier, we have shown that this parameter has a decisive effect on the rate and enantioselectivity of a cinchonidine modified Pt/Al_2O_3 catalyst in the hydrogenation of ethyl pyruvate and the observed dependences could be modelled with a simple reaction scheme assuming an equilibrium between modified (enantioselective) and unmodified (unselective) catalytic sites. In addition, it was shown that a "ligand acceleration" effect was operative[13]. If we use the same model but assume a lower activity for the modified catalyst we get a surprisingly good fit between the calculated and experimental values (Fig. 2) i.e. in this case we observe a "ligand deceleration" effect. The correlation does not hold for very high modifier concentrations because the ee values decrease again if too much cinchonine is added (this is not the case for higher catalyst loadings, see Fig. 1b).

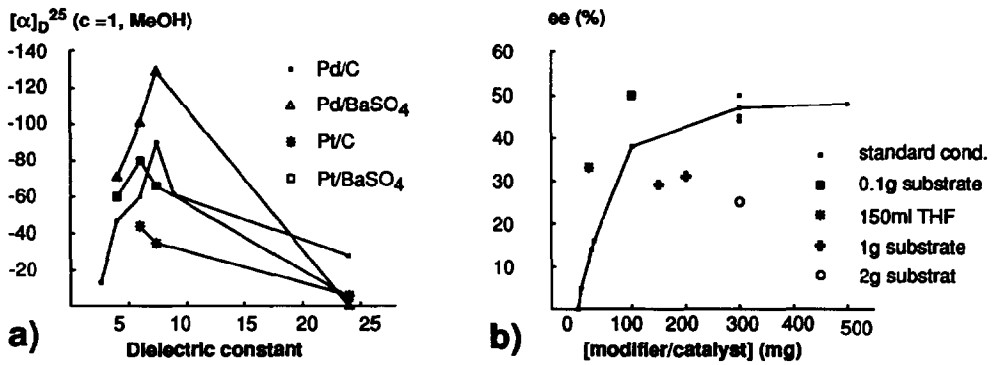


Fig. 1: a) Effect of solvent polarity on optical rotation (screening phase, modifier cinchonidine, data from Table 1). b) Effect of modifier / catalyst and substrate concentration on optical yield (modifier cinchonine, $Pd/BaSO_4$, data from Table 3)

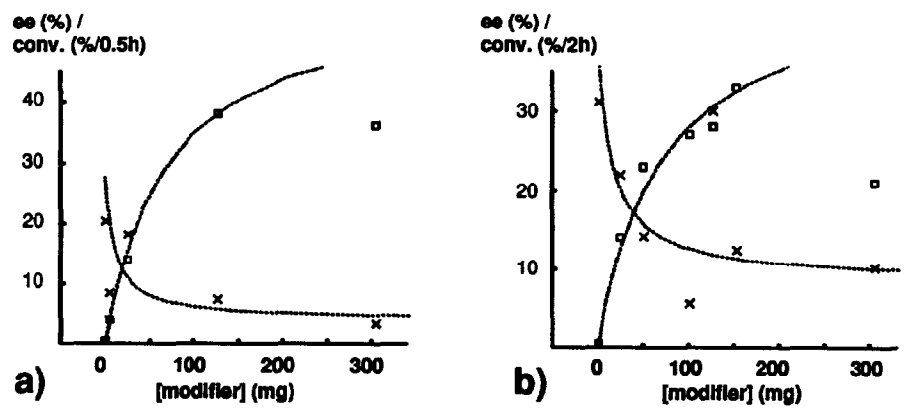


Fig. 2: Effect of modifier concentration on optical yields (□) and conversion (x). a) modifier cinchonine (Table 4a); b) modifier 10,11-dihydrocinchonine (Table 4b).

Mechanistic considerations

The mechanism of C-X hydrogenolysis is not well understood but it is known that activated halogens are removed readily[14]. Most reaction schemes that have been proposed assume that the R-X molecule is adsorbed on the metal surface either via the halogen or the R group or both[15]. On the other hand, the electrochemical reduction of an organic halide is assumed to involve electron transfer steps leading to a carbanion which is then protonated. This mechanism has also been discussed for the enantioselective electroreduction of the dibromo-diphenylcyclopropane A mentioned above where it is proposed that the electrode is rendered chiral by adsorption of the modifier (e.g. strychnine) and that the protonation of the carbanion occures enantioselectively via the protonated form of the basic modifier[10]. Interestingly, the dependence of the optical yield of the electroreduction of A on the modifier concentration is similar to our case. It can also be modelled assuming an adsorption equilibrium except at high modifier concentrations where the ee's decrease as well.

The results for the catalytic hydrogenolysis (especially the effect of the modifier structure) are not easily explained by an electron transfer - protonation mechanism. Another possibility we can rule out is the formation of an α,β-unsaturated lactam by base catalyzed HCl elimination followed by the enantioselective hydrogenation of the resulting C=C bond. We find that in the absence of catalyst the substrate is stable under reaction conditions and it has been reported that HCl elimination of α,α-dichlorolactams is catalyzed by Lewis acids rather than by bases[16].

Most but not all of our observations discussed above for the enantioselective hydrodehalogenation of α,α-dichlorobenzazepinone-2 can be explained if we make the following assumptions: i) modifier and substrate competitively and reversibly adsorb on the Pd surface, ii) the adsorbed substrate is hydrogenated either on unmodified sites (fast, racemic) or on modified sites (slower, enantioselective), iii) the interaction between adsorbed substrate and modifier is very specific and involves hydrogen bridging between C_9-OH and the C=O group of the lactam, iv) the second dehalogenation occurs as a consecutive reaction. In many respects, this mechanistic picture is very close to that proposed by us for the enantioselective hydrogenation of α-keto esters[6, 13] except that there we have no indication of a competition between substrate and modifier and, more importantly, that the modified catalyst is at least ten times more active than the unmodified one resulting in much higher optical yields for the α-hydroxy ester.

Conclusions

The hydrodehalogenation reaction catalyzed by cinchona modified Pd and Pt catalysts discussed above is a new entry in the growing list of enantioselective catalytic syntheses. At this stage the preparative value of the method is negligible because it works only for α,α-dichlorobenzazepinone-2 and even there the optical yields are too low and the required modifier concentrations too high in order to be of practical importance. It is possible that this is due to a weak adsorption of the modifier on the catalyst and to the fact that the modification leads to a loss in catalyst activity. The results obtained during our screening make it probable that we have not yet found the optimal catalyst and the best conditions and that further improvement is possible.

We think that the significance of our findings lies more on a fundamental level. First, we have shown that new enantioselective reaction types can be found by applying an approach that one could call "screening with a concept" and than can be improved by optimization of the system parameters. Second, our results confirm that very many parameters have to match in order to achieve good enantioselection (but the extreme substrate

selectivity was still quite surprising). Third, we have added a few more pieces to the puzzle of the mode of action of chirally modified heterogeneous catalysts.

Experimental

Materials

If not mentioned otherwise all organic chemicals were purchased from Fluka and used as received. THF was distilled before use.

α,α-Dichlorobenzazepinone-2, α-chlorobenzazepinone-2, α-azidobenzazepinone-2 and α-aminobenzazepinone-2 were prepared according to described procedures[2]. Different batches of α,α-dichlorobenzazepinone-2 had a mono-chloro content between 0.5 and 2% and gave slightly different activities and enantioselectivities under standard conditions.

For the determination of the absolute configuration of α-chlorobenzazepinone-2 three samples with different enantiomeric composition were used without further purification. The optical rotations of the azido- and aminoderivatives were recorded of the crude reaction mixtures. The absolute configuration of (-)-α-aminobenzazepinone-2 and its optical rotation $[\alpha]_D^{20}$ = -442 (c=1, MeOH) was determined by transformation to the corresponding (S)-N-(t-butylcarboxymethyl)-derivative with the known $[\alpha]_D^{20}$ = -267 (c=1, MeOH)[3].

The cinchona derivatives used were prepared by modification of commercially available cinchonidine, quinidine and cinchonine, respectively. The structures given are in good agreement with their elemental analysis, UV, IR, MS and NMR spectra.

The catalysts screened (used as dry powders) were standard types from Engelhard, two $Pd/BaSO_4$ were from Fluka and two from Degussa (E50R/D and E50N). The metal surface areas were determined by pulse CO adsorption, the total surface areas (BET) from N_2 adsorption measurements. Pretreatment (H_2 at 400 °C)[6] did not lead to increased enantioselectivities of the $Pd/BaSO_4$ catalysts.

Hydrogenation reaction

The screening experiments (3 bar H_2) were carried out in a 300 ml Parr shaker with 150 ml THF, the reactions at higher pressures were run in a 50 ml three-phase slurry reactor with a magnetic stirring bar (ca. 750 rpm). In both cases the reactor was connected via a reducing valve to a reservoir. Because of the low substrate concentrations used it was not possible to get rate data but the reaction time (100% H_2 consumption) was recorded. In a typical experiment, 100 mg of 5% Pd catalyst, 30 ml of solvent, 500 mg of α,α-dichlorobenzazepinone-2, 100 mg of cinchonine and 1.3 equiv. (NaOAc, NBu_3) or 10 equiv. (MgO) of base were introduced into the 50 ml autoclave. The autoclave was purged 5 times with argon (20 bar) under stirring, and then both the reservoir and autoclave were pressurized 5 times with hydrogen (20 bar). Experiments were started by turning the stirrer on. At the end of the reaction the catalyst was filtered off and the filtrate evaporated to dryness. The residue was dissolved in 50 ml dichloromethane and extracted 3 times with 30 ml 2N H_2SO_4. The GLC analysis was carried out after drying the organic phase with Na_2SO_4, the optical rotation was measured after removal of the solvent.

Analytical procedures

The composition of the product mixture was determined by GLC (2m OV 101, FID). The weight % were

calculated from the area % using the following correction factors: α,α-dichlorobenzazepinone-2: 1.8, α-chlorobenzazepinone-2: 1.0, benzazepinone-2: 1.0.

The enantiomeric excess of the α-chlorobenzazepinone-2 was generally determined by the optical rotation of the reaction mixture (corrected for mono-chloro content) or in some cases measured directly with HPLC either on tribenzoylcellulose, dinitrobenzoylleucine or a combination of a Chiralcel OC and a Chiralcel OB column. The separation of the signals of the two enantiomers and/or of the starting material was not always complete. Using these data the specific optical rotation of the pure enantiomers of α-chlorobenzazepinone-2 was calculated to be $[\alpha]_D^{20}$ = 370 ± 20 (c=0.5, MeOH) for the R-form and -370 ± 20 (c=0.5, MeOH) for the S-form.

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