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Enantioselective reduction of isatin derivatives over cinchonidine modified Pt/alumina

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Abstract

The enantioselective hydrogenation of several isatine derivatives over cinchonidine modified Pt/Al_2O_3 was investigated. A maximum enantiomeric excess (e.e.) of 45% was found for (*R*)-5,7-dimethylisatin. The enantiomeric excess was limited by racemization catalyzed by the basic cinchonidine in solution, leading to low enantiomeric excess at high cinchonidine concentration. The modifier in solution also catalyzed the formation of the corresponding isatide. High cinchonidine concentration favored isatide formation, whereas low cinchonidine concentration and high hydrogen pressure favored alcohol formation. The isatide, formed from the isatin reactant and the alcohol, underwent disproportionation. Though both hydrogenation and isatide formation are fast reactions, isatide formation was considerably faster at least at the beginning of the reaction. Substitution of the isatin reactant had relatively little effect on enantiomeric excess but affected considerably the rate of racemization.

Keywords: Enantioselective; Asymmetric; Reduction; Hydrogenation; Cinchonidine; Platinum; Alumina; Isatine derivatives, Isatide

1. Introduction

The enantioselective reduction of prochiral carbonyl compounds is of great synthetic importance. Many different ketols exist in nature and play a crucial role in various physiological processes [1]. Although most of the catalytic methods known today for the enantioselective reduction of carbonyl compounds are based on homogeneous catalysis [2], considerable progress has also been made in heterogeneous enantioselective catalysis in the past decade [3–9]. Among the heterogeneous catalytic methods, the heterogenous enantioselective hydrogenation over platinum modified by cinchona alkaloids is one of the promising strategies. Substantial effort has been spent in recent years to gain a better understanding of the mechanism of enantiodifferentiation and to extend the scope of reactants. Today, various carbonyl compounds that can be hydrogenated with good enantioselectivity using the Pt–cinchona alkaloid system are known, including α-ketoesters [10], α-ketolactone [11,12], α-ketoacetals [13,14], α,α,α-trifluoroketones [15–19], α-diketones [20–24] and linear and cyclic α-ketoamide [25–27]. Nevertheless, the extension of the scope of reactions remains one of the major challenges.

With this in mind we have studied the enantioselective hydrogenation of isatin and its derivatives (Table 1) using the Pt–cinchonidine system. We found that the corresponding isatide, which is a pinacol, is also formed depending on reaction conditions. 3-Hydroxyindolin-2-one (**8**) and its derivatives are of interest for the pharmaceutical industry as antiallergic, antiinflammatory and analgesic agents [28,29]. In a previous study pyruvamide and its N-alkylated derivatives, which bear some chemical similarity to isatin, have been hydrogenated to the corresponding alcohols with enantiomeric excess (e.e.) up to 60% using the Pt–cinchonidine system [25,30].

2. Experimental

The 5 wt.% Pt/Al_2O_3 catalyst (Engelhard 4759) was prereduced in flowing hydrogen for 90 min at 400 °C. The platinum dispersion after heat treatment was 0.27 as determined by TEM measurements. The solvents were degassed with

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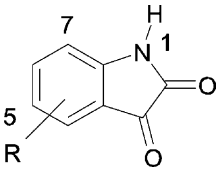
Table 1
Isatin and its derivatives used in catalytic studies



Compound	R1	R5	R7
5-Methylisatin (**1**)	H	CH_3	H
1-Methylisatin (**4**)	CH_3	H	H
Isatin (**7**)	H	H	H
Acetylisatin (**10**)	CO–CH_3	H	H
5,7-Dimethylisatin (**13**)	H	CH_3	CH_3
5-Methoxyisatin (**14**)	H	OCH_3	H
Phenylisatin (**15**)	phenyl	H	H

helium prior to use. Dioxane (Fluka, >99.5% over molecular sieve), dioxane (Baker, >99% stabilized), tetrahydrofuran (Riedel-de Haën Spectranal), tetrahydrofuran (Fluka, >99.5% stabilized) and ethylacetate (Fluka, >99.5%) were used. The reactants were used as received (see Table 1): 5-methylisatin (**1**) (Sigma, 98%), 1-methylisatin (**4**) (Lancaster, 97%), isatin (**7**) (Fluka, 99%), acetylisatin (**10**) (Lancaster, 97%), 5,7-dimethylisatin (**13**) (Lancaster, 96%), 5-methoxyisatin (**14**) (Avocado, 98%), and 1-phenylisatin (**15**) (Lancaster, 98%). Cinchonidine (Fluka, >98) and trifluoroacetic acid (TFA) (Fluka, >98%) were used as received. The hydrogenation reactions were carried out in a multiple reactor (Argonaut Technologies) equipped with eight 10 ml glass liners, which are mechanically stirred ($n = 500\,\mathrm{min}^{-1}$). Under standard conditions, 21 ± 1 mg prereduced catalyst, 0.55 mmol substrate, 0.34 μmol modifier and 5 ml solvent were used and the reaction carried out at 20 bar and room temperature.

For the investigation of the time behavior a 100 ml stainless-steel autoclave was used, equipped with a 50 ml glass liner, PTFE cover and a valve with septum, which allowed taking samples during reaction. Volumes of the sample of 1 ml were withdrawn using a steel needle and a syringe. The reactor was magnetically stirred ($n = 500\,\mathrm{min}^{-1}$). The pressure was held at a constant value by computerized constant-volume–constant-pressure equipment (Büchi BPC 9901). In this case, 84 ± 1 mg prereduced catalyst was used, 2.2 mmol substrate, 1.36, 27.2 or 217.6 μmol modifier and 20 ml dioxane. The reactions were carried out at 5 bar and room temperature.

The e.e. was determined using a MERCK LaChrom HPLC-System and a chiral column (CHIRALCEL OB/4.6 mm internal diameter/250 mm length/10 μm particle size). The measurements were carried out at 15 °C and 0.5 ml/min solvent flow and the UV-detector was set at 210 nm. For 5-methylisatin (**1**), a mixture of *n*-hexane/ethanol 75%/25% was used as eluent. To improve the separation five drops of acetic acid were added to the samples. Enantiomeric excess is expressed as e.e. $(\%) = 100 \times (|R - S|)/(R + S)$.

For the hydrogenation product (**2**) of 5-methylisatin, the absolute configuration of the major enantiomer was determined using CD spectroscopy. A sample with an enantiomeric excess of 34% was used for this purpose. CD spectra were measured on a Jasco 500 instrument in ethanol. In order to assign the absolute configuration quantum chemical calculations were performed using time-dependent density functional theory (TD-DFT) [31]. Calculations were performed using the GAUSSIAN suite of programs with a hybrid density functional method (b3pw91) and a 6-31G(d, p) basis set [32]. The molecule was first completely optimized in the ground state by relaxing all degrees of freedom. Rotational strengths were then calculated using TD-DFT. In order to compare with the experimental spectrum a synthetic spectrum was generated using Gaussians centered at the excitation energies and scaled with the calculated rotational strengths. The reliability of the method was checked by comparison with reported experimental and calculated CD spectra of pentahelicene [31]. Fig. 1 shows a comparison of experimental and calculated CD spectra. The latter was performed on the (*R*)-alcohol and the comparison shows that the major enantiomer corresponds to the (*R*)-alcohol. Note that for a cyclic imidoketone, which bears some resemblance with the five-ring unit of isatine, the (*R*)-alcohol was found in excess using cinchonidine modified Pt [33].

Besides the reactant (isatin or derivative) and hydrogenation product (corresponding alcohol) a dimer (corresponding isatide) was formed, depending on the reaction conditions. Due to the same retention time of the reactant and the dimer on the column the determination of the relative concentration of the compounds was not possible by chromatography. The relative amount of reactant, alcohol and dimer was therefore determined by ^{1}H NMR. For this, the solvent was evaporated and the residue was dried in vacuum generated by a membrane pump. The sample was dissolved in d_6-DMSO. The ^{1}H and ^{13}C spectra were recorded on a Bruker Avance spectrometer operating at 500 and 125.75 MHz, respectively, with chemical shifts related to TMS ($\delta = 0$).

5,5′-Dimethylisatide (**3**) (Scheme 1) was identified through mass spectrometry and NMR: Maldi: 363 $[M\mathrm{K}]^+$, 347 $[M\mathrm{Na}]^+$, 307 $[M - \mathrm{OH}]^+$ ($M = 324.3$ g/mol; $C_{18}H_{16}N_2O_4$). ESI (rel. intensity): 347 (28) $[M\mathrm{Na}]^+$, 342 (100) $[M\mathrm{NH_4}]^+$, 338 (42), 325 (17), 307 (13), 179 (67). ^{1}H NMR (d_6-DMSO): 10.18 (s, 2H), 7.03 (d, 7.7 Hz, 2H), 6.61 (d, 7.8 Hz, 2H), 6.65–6.55 (br, 2H), 6.11 (s, 2H), 2.11 (s, 6H).

3-Hydroxy-5-methyl-indolin-2-one (**2**) (Scheme 1) ^{1}H NMR (d_6-DMSO): 10.09 (s, 1H), 7.08 (s, 1H), 6.99 (d, 7.8 Hz, 1H), 6.66 (d, 7.8 Hz, 1H), 6.09 (d, 7.5 Hz, 1H), 4.78 (d, 7.5 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (d_6-DMSO): 178.5 (C=O), 140.3 (C-7′), 130.9 (C-3′), 130.0 (C-5), 129.6 (C-6), 126.1 (C-4), 109.8 (C-7), 69.9 (C-OH), 39.7 (CH_3). The carbon signals were assigned with a C–H correlation measurement.

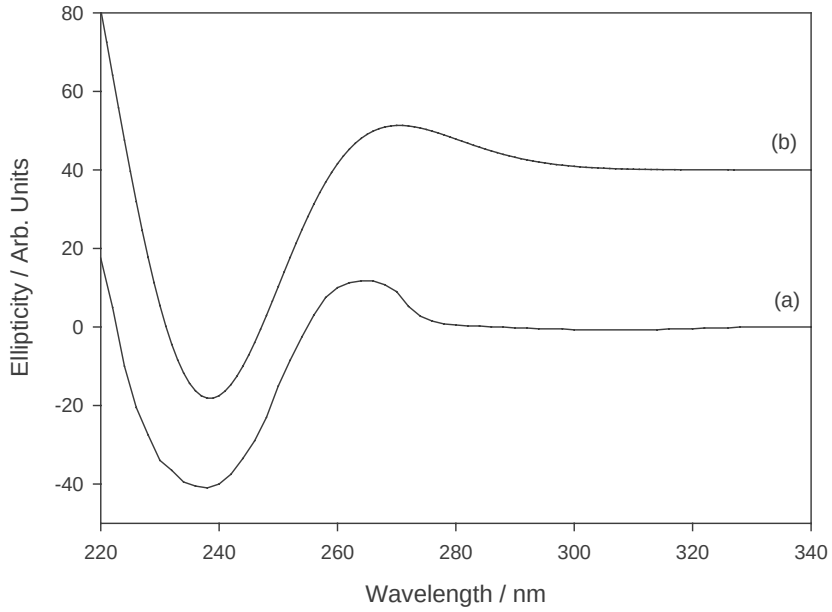


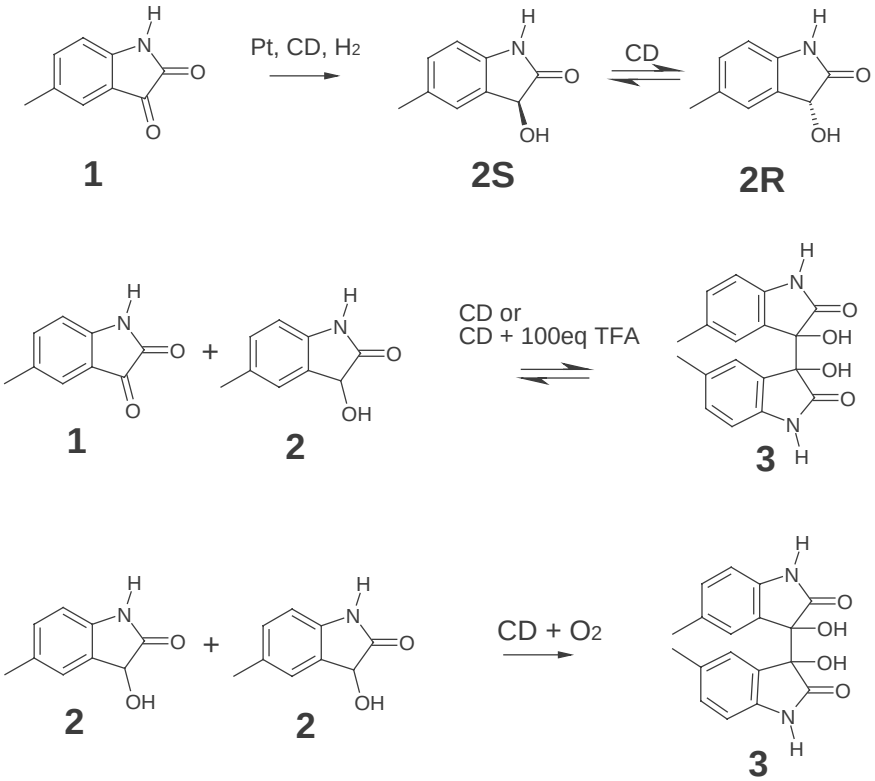
Fig. 1. Comparison between experimental (a) and calculated (b) CD spectra of the (*R*)-enantiomer of alcohol **2**. See Section 2 for details.

The ^{1}H NMR of isatide (**9**) and *N*,*N*′-dimethylisatide (**6**) were in agreement with the ones reported by Koch and coworkers [34]. For 1,1′-diacetylisatide (**12**) an additional signal at 2.34 ppm (s) associated with the N–CO–CH_3 group was observed. For quantification the ^{1}H NMR signals given in Table 2 were used for the different isatin derivatives.

3. Results

3.1. General behavior and effect of modifier concentration

The enantioselective hydrogenation of 5-methylisatin (**1**) resulted in e.e. of 38.5% to the (*R*)-alcohol **2** (dioxane,



Scheme 1. Summary of the reactions observed during hydrogenation of 5-methylisatin (**1**) over CD modified Pt/Al_2O_3.

Table 2
Chemical shifts of ^{1}H NMR signals used for quantification of the reaction mixtures

Compound	Observed signal	Chemical shift (ppm)	Signal type	Number of H
5-Methylisatin (**1**)	CH arom.	7.39	s	1H
Alcohol **2**	CH–OH	4.78	d	1H
Dimer **3**	CH_3	2.10	s	6H
1-Methylisatin (**4**)	N–CH_3	3.12	s	3H
Alcohol **5**	N–CH_3	3.06	s	3H
Dimer **6**	N–CH_3	2.87	s	3H
Isatin (**7**)	CH arom.	7.47	m	1H
Alcohol **8**	CH–OH	4.80	d	1H
Dimer **9**	CH arom.	6.72	d	1H
Acetylisatin (**10**)	N–CO–CH_3	2.58	s	3H
Alcohol **11**	N–CO–CH_3	2.56	s	3H
Dimer **12**	N–CO–CH_3	2.34	s	6H

standard conditions, 0.25 mg (0.85 μmol) CD). The e.e. depended strongly on the cinchonidine concentration showing highest values between 0.05 and 0.25 mg CD (Fig. 2). Higher CD concentrations were detrimental for enantioselectivity. The strong decrease of e.e. at higher CD concentration is rather unusual for the Pt–cinchonidine system [4,24]. Fig. 2 indicates also that the product distribution is strongly influenced by the amount of CD in the system. Above 0.25 mg CD the amount of alcohol **2** in the reaction mixture decreased strongly at the expense of the corresponding isatide (5,5′-dimethylisatide, dimer **3**), as identified by NMR and mass spectrometry (see Section 2).

CD acts not only as modifier but also as Lewis-base and thus catalyses keto-enol tautomerism and racemization of the alcohol. This effect could be observed when the e.e. was followed in time. Fig. 3 shows the e.e. for reactions carried out with 8 and 2 mg, respectively, of cinchonidine per 5 ml dioxane (parameters as described for the investigation of the time behavior, see Section 2). After about 30 min reaction

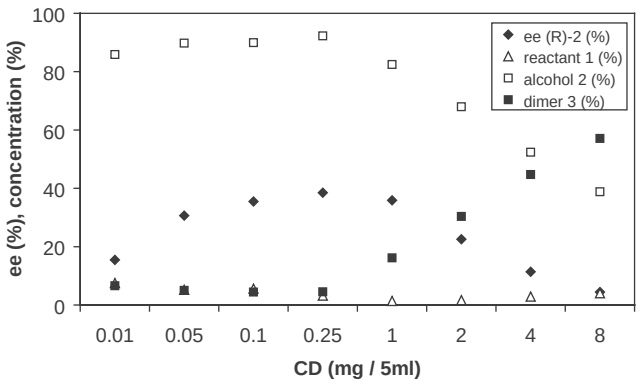


Fig. 2. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** and relative amount of reactant (5-methylisatin (**1**)), alcohol **2** and dimer **3** (isatide) as a function of cinchonidine (CD) in the reaction mixture. Conditions: 21 ± 1 mg prereduced catalyst, 0.55 mmol substrate **1**, 5 ml dioxane, 20 bar, room temperature, 30 min reaction time.

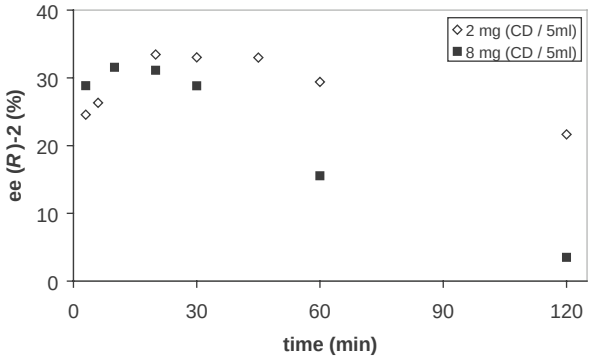


Fig. 3. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** as a function of time for the enantioselective hydrogenation of 5-methylisatin (**1**). Results are given for two different CD concentrations. Conditions: 84 ± 1 mg prereduced catalyst, 2.2 mmol substrate, 20 ml dioxane, 5 bar, room temperature.

time, almost all reactant was consumed. Interestingly, the e.e. decreased still after total consumption of the reactant. This is due to racemization which is faster at higher CD concentration. Higher CD concentration promotes both the formation of isatide **3** and racemization of the alcohol (*R*)-**2**. In a control experiment, racemization of the alcohol (*R*)-**2** was followed in dioxane in the presence of only CD (8 mg/5 ml) that is in the absence of catalyst and isatide. Within 2 h, the e.e. dropped from 34 to 3%.

Fig. 2 shows that in the case of 5-methylisatin (**1**) the content of alcohol **2** and the enantioselectivity start decreasing at the same CD concentration of 0.25 mg/5 ml. The decrease of e.e. at higher CD concentration, observed for the hydrogenation of 5-methylisatin (**1**) in dioxane, could also be observed in ethylacetate and tetrahydrofuran, as emerges from Fig. 4. Also in these solvents the amount of dimer increased with higher CD concentration.

Note that the solvents were degassed with helium before the reaction was started, as described in the Section 2. However, experiments without degassing the solvents were also carried out. Under these conditions a little bit of oxygen is dissolved in the solvent, which is reduced to water during reaction. Although no influence on the e.e. was observed, the amount of dimer **3** was a bit lower and the amount of alcohol

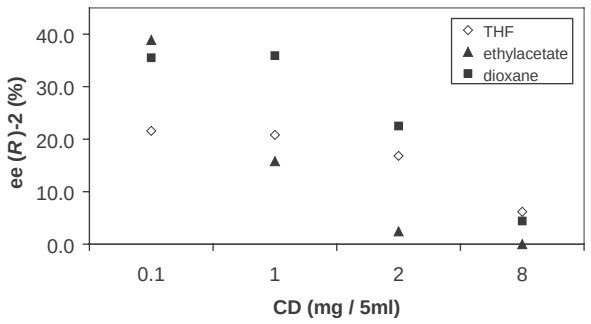


Fig. 4. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** for the enantioselective hydrogenation of 5-methylisatin (**1**) in different solvents and different CD concentrations. For other conditions, see Fig. 2.

(*R*)-**2** a bit higher (by 5–10%) in non-degassed solvent. This may be explained by the fact that the dimer **3** is not stable in water, as was confirmed by ^{1}H NMR spectroscopy.

3.2. Effect of trifluoroacetic acid

As mentioned above, CD as a base can catalyze racemization of the alcohol (*R*)-**2**. Addition of an acid should therefore have a significant influence on the reaction. Furthermore it has been reported previously [35,36] that TFA has a strong effect on the hydrogenation over CD modified Pt. TFA was therefore added in different concentrations to a reaction mixture with 2 mg CD (Fig. 5). At 1 eq. TFA with respect to the CD the quinuclidine nitrogen is protonated [35]. For 1 eq., the e.e. is at the maximum and the dimer **3** concentration at the minimum. The fact that the e.e. for 10, 50 and 100 eq. TFA decreases can be explained by two different effects. On the one hand by acid catalyzed keto-enol tautomerism, and on the other hand by the interaction of TFA with CD. It has been reported [35] for the hydrogenation of ethyl-4,4,4-trifluoroacetoacetate that the e.e. gradually decreases with higher amounts of TFA in toluene (but not in THF), likely due to the interaction of the acid with the CD. The interaction between CD and TFA has previously been studied by infrared and vibrational circular dichroism (VCD) spectroscopy. The investigation provided evidence for specific acid–base interaction complexes between the two molecules stabilized by two hydrogen bonds [37].

Fig. 6 shows that addition of 1 equivalent TFA leads to a less pronounced dependence of the e.e. on CD concentration. At 2 and 8 mg CD, the e.e. is higher with 1 eq. TFA than without addition of TFA. At 0.1 and 1 mg CD, the addition of TFA leads to a decrease of e.e.

It has been shown above that the amount of dimer **3** increases with increasing CD concentration (Fig. 2). A similar effect is observed by addition of 100 eq. TFA. Table 3 summarizes the findings for experiments carried out with addition of 100 eq. TFA with respect to CD. The increasing

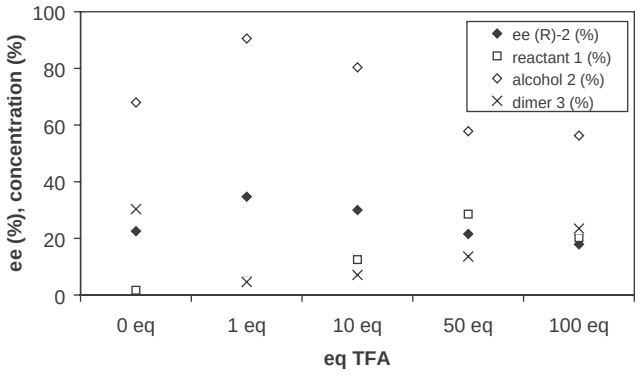


Fig. 5. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** and relative amount of reactant (5-methylisatin (**1**)), alcohol **2** and dimer **3** (isatide) as a function of trifluoroacetic acid (TFA) added to the reaction mixture. Equivalents of TFA are given with respect to CD. For other conditions, see Fig. 2.

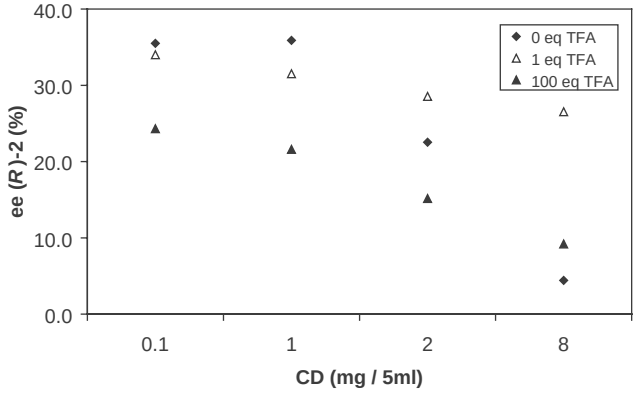


Fig. 6. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** as a function of CD concentration for different equivalents of trifluoroacetic acid (TFA) added to the reaction mixture. Equivalents of TFA are given with respect to CD. For other conditions, see Fig. 2.

fraction of dimer in the solution with higher TFA (and CD) concentration indicates that the dimerization can also be acid catalyzed by activation of the carbonyl group. Compared to the reaction in the absence of TFA the amount of unreacted **1** is somewhat larger in the presence of TFA. Interestingly, the fraction of unreacted **1** has a maximum at 2 mg CD and 100 eq. TFA.

3.3. Time dependence of the reaction

To gain further insight into the reaction network the time dependence of the reaction of 5-methylisatin (**1**) was studied (2 mg CD in 5 ml dioxane). Fig. 7 shows the change of relative amounts of reactant **1**, alcohol **2** and dimer **3** in the reaction mixture. During the first 60 min the e.e. was quite stable at about 30% (see Fig. 3). After 120 min the e.e. had dropped to 21.7% due to racemization. Fig. 7 reveals a maximum for the amount of dimer **3** after 15 min. At the same time, reactant **1** had almost completely disappeared (about 10% remaining). With increasing reaction time the amount of dimer **3** decreased again, whereas the amount of alcohol **2** increased. This indicates that the alcohol **2** was formed from the dimer. However, after 45 min the amount of dimer remained stable at 35%.

The time behavior of the relative amounts of reactant **1**, alcohol **2** and dimer **3** depended on CD concentration. The time dependence was also investigated for the reactions

Table 3
Enantiomeric excess of alcohol (*R*)-**2** and relative amount of reactant **1**, alcohol **2** and dimer **3** for different concentrations of CD and TFA

CD (mg) + 100 eq. TFA	e.e. (%)	Reactant **1** (%)	Alcohol **2** (%)	Dimer **3** (%)
0.1	24.3	14.3	81.2	4.4
1	21.6	27.1	59	13.8
2	15.2	31.7	42.1	26.1
8	9.2	17.2	32.7	50.1

100 eq. TFA with respect to CD. Other conditions: see Section 2.

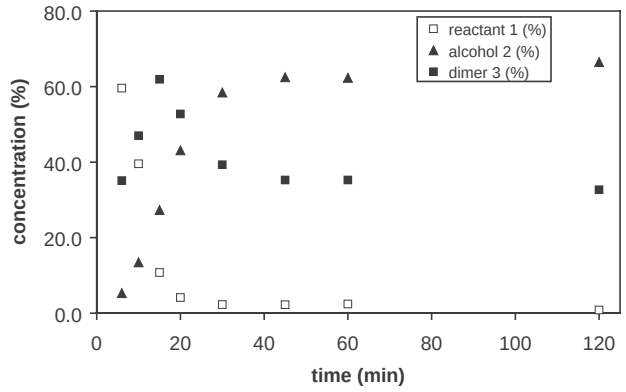


Fig. 7. Relative amount of reactant (5-methylisatin (**1**)), alcohol **2** and dimer **3** (isatide) as a function of time for the enantioselective hydrogenation of 5-methylisatin **1**. For other conditions, see Fig. 3.

performed with 8 and 0.1 mg CD, respectively. Fig. 8 shows that the maximum in the fraction of dimer **3**, which was found for the reaction with 2 mg CD, was much less pronounced at higher and lower CD concentration. Interestingly the concentration of CD is decisive for the value, at which the amount of dimer **3** stabilizes after some time. In the reaction with 8 mg CD, the amount of dimer **3** was stable at 70% after about 20 min. In the reaction with 0.1 mg CD, the amount of dimer **3** was stable at the level of 10%.

Fig. 9 compares the time dependence of the amount of dimer **3** for three different experiments. The only parameter that was changed was the addition of TFA to the reaction mixture (2 mg CD, other conditions see Section 2). In one experiment no acid was added, in a second experiment 1 eq. TFA with respect to CD was added at the beginning of the reaction and in a third experiment 1 eq. TFA was added after 10 min reaction time. The acid addition had a significant influence on the amount of dimer **3**. When the acid was added at the beginning the amount of dimer **3** never reached a high level. When the acid was added after 10 min. the amount of dimer **3** decreased abruptly compared to the experiment without acid addition.

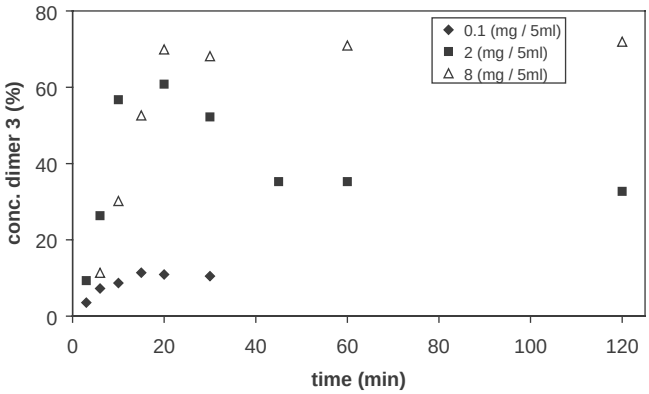


Fig. 8. Concentration of the dimer **3** as a function of time for the enantioselective hydrogenation of 5-methylisatin (**1**) for different amounts of CD. For other conditions, see Fig. 3.

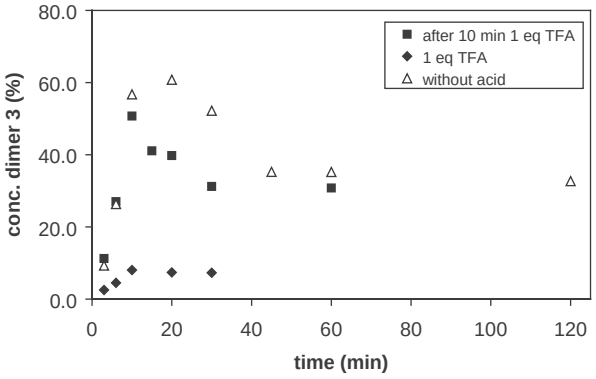


Fig. 9. Concentration of the dimer **3** as a function of time for the enantioselective hydrogenation of 5-methylisatin (**1**) for three different runs. Open triangles: no trifluoroacetic acid (TFA) added. Rotated squares: 1 eq. TFA with respect to CD added at the beginning. Squares: 1 eq. TFA with respect to CD added after 10 min. For other conditions, see Fig. 2.

3.4. Pressure dependence

The pressure dependence of the e.e. was investigated for 5-methylisatin **1** reduction (2 h reaction time, other parameters as under standard conditions, see Section 2). Fig. 10 reveals a maximum at around 20 bar with 38% e.e. and a slightly lower, but stable e.e. at higher pressure. Note that the e.e. did not change anymore with increasing hydrogen pressure up to 99 bar.

3.5. Behavior of other isatine derivatives

The e.e. values obtained for different isatin derivatives at different conditions are listed in Table 4. For the isatin derivatives, which are not derivatized at the amid nitrogen an e.e. between 37 and 45% was obtained. For the derivatives which are derivatized at the amid nitrogen the e.e. was between 7 and 27%. Note that the e.e. of the second group was remarkably lower than the e.e. for the first group. However, under standard conditions (20 bar H_2, 30 min, 0.1 mg CD, 5 ml dioxane, 21 mg catalyst, 0.55 mmol reactant, column 2 in Table 4) the difference between the two groups of

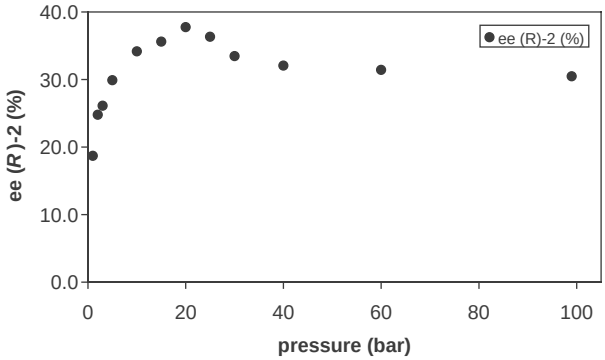


Fig. 10. Enantiomeric excess (e.e.) of the alcohol (*R*)-**2** as a function of pressure for the enantioselective hydrogenation of 5-methylisatin (**1**). For other conditions, see Fig. 2.

Table 4
Enantiomeric excess obtained in reduction of isatin and derivatives

Compound	e.e. (%)[a]	e.e. (%)[b]
5-Methylisatin (**1**)	36.7	35.5
Isatin (**7**)	42.1	39.1
5,7-Dimethylisatin (**13**)	45.3	
5-Methoxyisatin (**14**)	38.8	
1-Methylisatin (**4**)	27.4	40
Acetylisatin (**10**)	11.7	25.3
Phenylisatin (**15**)	6.9	

[a] Conditions: 25 bar H_2, 2 h, 0.1 mg CD, 5 ml dioxane, 21 mg catalyst, 0.131 mmol reactant.
[b] Conditions: 20 bar H_2, 30 min, 0.1 mg CD, 5 ml dioxane, 21 mg catalyst, 0.55 mmol reactant.

reactants was less pronounced. This indicates that the enantioselectivity was not strongly depending on the substitution but that the latter had significant influence on the racemization rate.

Formation of the corresponding isatide (dimer) was also observed for isatin (**7**), 1-methylisatin (**4**) and acetylisatin (**10**). In general, higher CD concentrations lead to a larger amount of the isatide. Isatin (**7**) dimerized easily, 49.9% isatide (**9**) were formed at 0.1 mg CD and 52.7% at 2 mg CD. At 0.1 mg CD, 24.5% 1-methylisatin (**4**) and at 2 mg CD 62.8% were dimerized. For acetylisatin (**10**) 11.8% dimer was found at 0.1 mg CD and 77.5% at 2 mg CD.

4. Discussion

The results presented above indicate a rather complex reaction network. The relative rates of the individual reactions are strongly influenced by the CD concentration. As a consequence the amount of CD in the reaction mixture allows one to push the reaction towards either the alcohol (hydrogenation) or the corresponding isatide, which is a pinacol (C–C bond formation).

Formation of the alcohol and the corresponding isatide (dimer) can be viewed as competing reactions. This competition, which limits the chemoselectivity of the isatine reduction is most evident in the initial period of the reaction. Fig. 7 shows (for the case of 2 mg CD in the reaction mixture) that the disappearance of the reactant is very fast. After 20 min, almost all the reactant has disappeared. However, it is also obvious that at the very beginning formation of the isatide (dimer) is faster than formation of the alcohol. Fig. 7 shows that after 5 min reaction time about 35% isatide **3** has been formed, whereas the amount of alcohol **2** is only about 5%.

The question arises how the isatide is formed. It has been reported that the dimer **9** is formed from the corresponding alcohol by oxidation with oxygen in basic solution [38]. The analogous reaction (Scheme 1, bottom) could also be observed in our case when the reaction mixture after full conversion and separation (filtration) of the catalyst was left standing in air. However, this reaction cannot occur under the reductive reaction conditions. Hence, isatide formation from the alcohol in basic solution (CD base) in the presence of oxygen is a possible reaction, however it cannot account for isatide formation under hydrogenation conditions, as observed in our study. Control experiments revealed no isatide formation for reactant **1** in CD solution even in air. Furthermore, no conversion of **1** was observed under standard condition without catalyst. However, an independent experiment showed that isatide **3** is formed from a mixture of reactant **1** and alcohol **2** in CD solution (8 mg CD) without catalyst (Scheme 1, middle) (Table 5). Control experiments showed that this reaction does not occur without CD, not even in the presence of Al_2O_3. Hence, the acidic support did not catalyze the reaction. The finding that the corresponding isatide can be formed by the CD catalyzed reaction of reactant **1** and alcohol **2** is in accordance with literature: isatide (**9**) can be prepared by piperidine-catalyzed condensation of isatin (**7**) and 3-hydroxy-indolin-2-one (**8**) [39,40].

Table 5
Isatide formed in CD solution without catalyst

Time (min)	Reactant **1** (%)	Alcohol **2** (%)	Dimer **3** (%)
0	55.5	38.5	6.0
60	28.5	11.7	59.8
255	27.0	8.8	64.2

Conditions: 8 mg CD, 5 ml dioxane, 10 bar N_2.

The mechanism for the isatide formation discussed above explains the time behavior of the products at the beginning of the reaction: formation of the alcohol is retarded, since the alcohol undergoes a fast consecutive reaction with the reactant to the isatide. This shows that the formation of the alcohol (the reduction) is limiting the isatide formation at the beginning of the reaction. This also implies that the hydrogenation to the alcohol is very fast, since isatide formation depends on it (see Fig. 7). However, an alternative reaction pathway to the isatide cannot be excluded: the formation of the isatide on the platinum surface. Such a reaction can be envisaged by the nucleophilic attack of the α-deprotonated amide of the alcohol **2** on an electrophilic half hydrogenated reactant molecule. Note that such a half hydrogenated state (one H is transferred from the Pt catalyst to the O atom of the ketone carbonyl group) has been postulate for the enantioselective hydrogenation of ketones over CD modified Pt in apolar solvents [41].

The control experiments discussed in the previous paragraph clearly confirm that isatide can be formed in solution, catalyzed by CD. Whether isatide can also be formed on the Pt catalyst under reaction conditions is more difficult to prove, due to the CD in solution, which could promote isatide formation.

The alcohol is formed exclusively in a reduction on the Pt surface, whereas isatide formation occurs predominantly in solution. One can therefore anticipate an influence of hydrogen pressure on product distribution, since hydrogen pressure should influence the hydrogenation rate but not the

dimerization reaction in solution. The comparative experiment at 5 and 99 bar hydrogen pressure (8 mg CD, dioxane, 1h reaction time, otherwise standard conditions) revealed 70% isatide in the former but only 40% isatide in the latter case, which supports the reaction network discussed above. At higher pressure the hydrogenation to the alcohol is accelerated with respect to the isatide formation and thus the amount of isatide is lower.

Fig. 2 shows that the amount of dimer in the reaction solution is low up to a CD amount of 0.25 mg/5 ml. At higher CD concentration, it starts increasing. Possibly at lower CD concentration basically all modifier is adsorbed on the catalyst (Pt and support) [42], and consequently dimerization (and racemization) catalyzed by dissolved CD is prevented.

It should be noted that a radical mechanism for the isatide formation is unlikely under our conditions, since the dimer was formed even in stabilized dioxane and tetrahydrofuran.

Fig. 7 reveals that the amount of isatide exhibits a maximum in the course of the reaction. This implies that the dimer can further react. ^{1}H NMR revealed that there are no other compounds in significant amounts present in the reaction mixture besides the isatide **3**, the reactant **1** and the alcohol **2**. Hence, we conclude that the isatide does not decompose but reacts back to reactant and alcohol. Such a disproportionation was reported by Romanin and coworkers [43] for dimer **9** in DMF. Since the forward reaction (isatide formation from alcohol and reactant) is catalyzed by CD, the disproportionation has to be CD catalyzed as well.

Due to the disproportionation the reaction does not run to completion but rather leads to an equilibrium or steady state after some time. The steady state concentrations depend strongly on the CD concentration (and on H_2 pressure). High CD concentration pushes the equilibrium towards the isatide (see Fig. 8), high hydrogen pressure towards the alcohol. This equilibrium also explains why a small but significant amount of reactant can be observed even after quite long reaction time (see, for example, Fig. 7 after 1 h). Note that after some time (after about 15–20 min in Fig. 7) the small reactant concentration limits the isatide formation.

Addition of acid likely affects both the hydrogenation and the isatide formation, since in both the basic CD is involved as modifier (on the Pt surface) or catalyst (in solution). The transient experiment in Fig. 9 shows that the addition of 1 eq. TFA with respect to CD after 10 min to a reaction with 2 mg CD lead to an abrupt decrease of the amount of the dimer **3**. Obviously, the addition of acid pushes the system towards the alcohol. This can be explained in several ways for example by an increased rate of alcohol formation (hydrogenation of the isatine) with respect to isatide formation in the presence of acid.

For the investigated isatine derivatives a moderate e.e. of up to 45% was obtained for the corresponding (*R*)-alcohol, though there is some potential for optimization. Due to the relatively complex reaction network the e.e. strongly depends on time and CD concentration. One reason for the moderate e.e. is the racemization catalyzed by CD, which becomes a dominant reaction at high CD concentration and long reaction time, as demonstrated in Fig. 3 for 5-methylisatin (**1**).

The e.e. of the (*R*)-alcohol depends on several competing reactions: obviously, it depends on the direct enantioselective hydrogenation of the isatine reactant (Scheme 1, top). It also depends on the rate of racemization. Furthermore, the equilibrium reaction isatine + alcohol → isatide likely also influences the e.e., not least because the chiral CD catalyses the forward and backward reaction.

It has been reported by Yamada and coworkers [44] that an NADH-linked carbonyl reductase purified from Candida parapsilosis IFO 0708 reduces 1-methylisatin with an e.e. >99% at 28% conversion.

To the best of our knowledge pinacol (dimer) formation was not reported up to now for the Pt/CD catalytic system. For the enantioselective hydrogenation of α,α,α-trifluoroacetophenone and ethylbenzoylformate we investigated whether the pinacol is formed in significant amounts. Standard reaction condition with 2, 4 and 8 mg CD were chosen for these experiments. However, we could not identify the corresponding dimers by ^{1}H NMR spectroscopy neither in $CDCl_3$ nor in d_6-DMSO. This indicates that the dimer formation is a peculiarity of the isatines, may be due to the stability of the corresponding pinacol (isatide).

5. Conclusions

Scheme 1 summarizes the relatively complex reaction network observed during hydrogenation of isatine derivatives over cinchonidine modified Pt/Al_2O_3 catalysts. Besides the hydrogenation of the ketone to the corresponding alcohol on the modified Pt catalyst (Scheme 1, top), the resulting alcohol reacts with one equivalent of the reactant to the corresponding isatide (Scheme 1, middle). This reaction is reversible, that is the isatide can disproportionate, and both forward and backward reactions are catalyzed by CD and occur without the presence of platinum in solution. Some pinacol may also be formed directly on the catalyst surface from the nucleophilic attack of the α-deprotonated amide of the alcohol **2** on the electrophilic half hydrogenated reactant molecule. Pinacol can also be formed from the alcohol in the presence of base (CD) and oxygen (Scheme 1 bottom), however, this pathway is not relevant under hydrogenation conditions. The relative amount of alcohol and isatide depends strongly on CD concentration and to a lesser extent on hydrogen pressure. By properly adjusting the CD concentration the reaction can be pushed either towards the desired alcohol or the isatide. Racemization of the alcohol, which is also CD catalyzed, is one limiting factor for the enantiomeric excess. For 5,7-dimethylisatin, an e.e. of 45% was observed for the corresponding (*R*)-alcohol. The pinacol formation with the Pt–cinchonidine catalytic system seems to be a peculiarity of the isatines, may be due to the stability of the corresponding pinacol.

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