

Unprecedented selectivity behaviour in the hydrogenation of an α,β -unsaturated ketone: hydrogenation of ketoisophorone over alumina-supported Pt and Pd

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Abstract

The partial hydrogenation of 2,6,6-trimethyl-2-cyclohexen-1,4-dione (ketoisophorone) was studied over alumina-supported Pt and Pd catalysts. The influence of solvent, pressure, catalyst pretreatment, and Lewis acid and base additives was investigated. Chemoselectivities over 90% were achieved in the saturation of the C=C or the sterically hindered C=O double bonds over Pt and Pd, respectively. This seems to be the first example for the selective reduction of an α,β -unsaturated ketone to an unsaturated alcohol using dihydrogen. Enantioselective hydrogenation of the carbonyl group over cinchonidine-modified Pt afforded only 14% ee. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Hydrogenation; Chemoselectivity; Enantioselectivity; Pt/alumina; Pd/alumina; Ketoisophorone

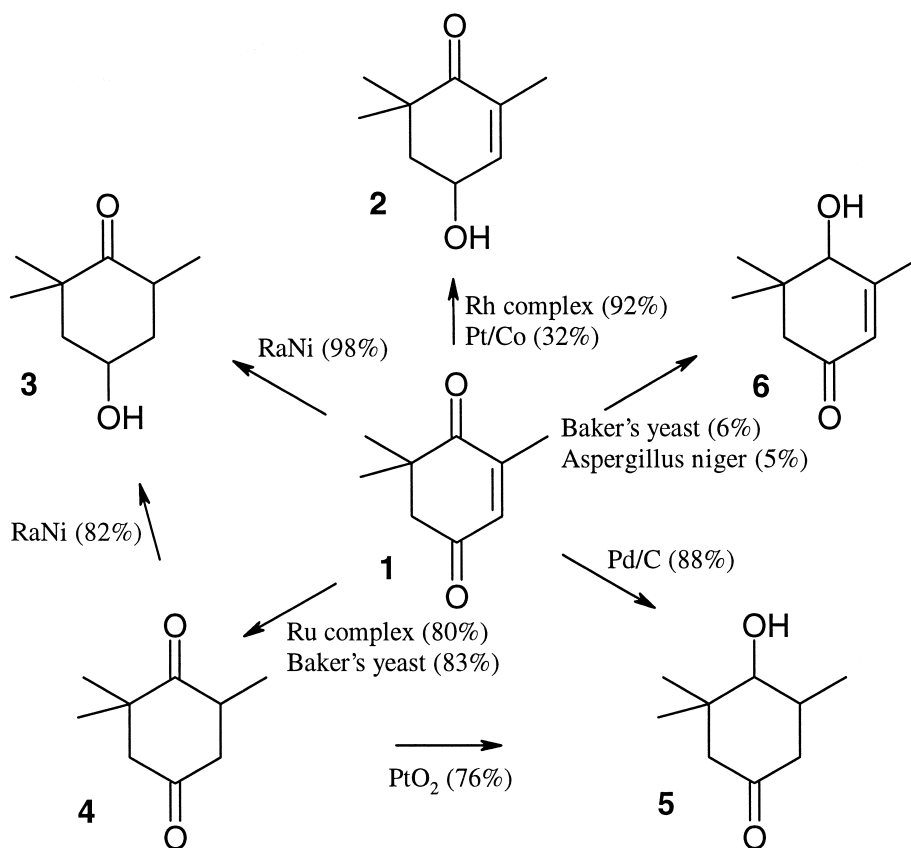
1. Introduction

Ketoisophorone **1** is a highly functionalized cyclic compound whose catalytic hydrogenation and enzymatic reduction afford a number of different products (**2** to **6**), as illustrated in Scheme 1 [1–8]. The hydrogenation of ketoisophorone has already been the topic of different studies. The *R*-enantiomer of **4** (and in a newer method **2**) represents a key building block in the synthesis of different 3-hydroxy-car-

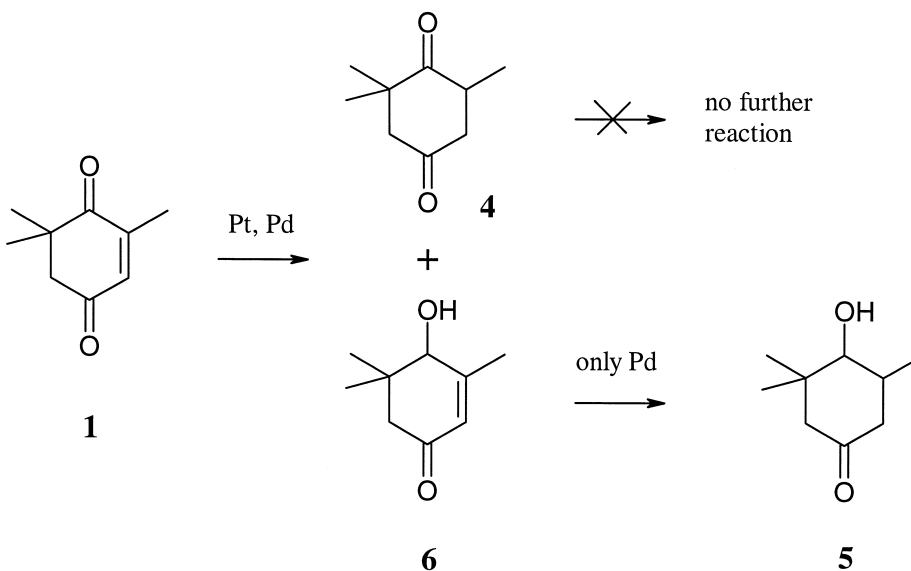
tinoids, such as Zeaxanthin and Cryptoxanthin [1,3,4].

Interestingly, none of the heterogeneous catalysts, including Raney-Ni (RaNi) and supported noble metals, afford the selective hydrogenation of any of the carbonyl groups without the simultaneous hydrogenation of the C=C double bond. The only exception is the formation of **2** with a poor yield of 32% over a Pt/Co catalyst [2]. In recent reviews Ponc [9] and Augustine [10] point out that up-to-date there exists no report on successful selective, heterogeneous catalytic hydrogenation of an α,β -unsaturated ketone to the corresponding unsaturated alcohol by molecular hydrogen.

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Scheme 1. Overview on the possible products in the catalytic hydrogenation and enzymatic reduction of ketoisophorone **1** (yields are given in brackets).



Scheme 2. Course of the reaction over Pt/alumina and Pd/alumina catalysts.

It is well known that some metal salt additives (Fe^{2+} , Zn^{2+} , Ni^{2+} , K^+ , etc.) enhance the chemoselectivity in the hydrogenation of α,β -unsaturated aldehydes to allylic alcohols [10–14]. Most of these studies have been performed on two model reactions: the hydrogenation of crotonaldehyde or cinnamaldehyde. The observed effects are attributed to the Lewis acidity of the metal cations, interacting with the α,β -unsaturated aldehyde. However, all the authors mention that their results are not transferable to the hydrogenation of α,β -unsaturated ketones.

Here we report the hydrogenation of ketoisophorone **1** over alumina supported platinum and palladium catalysts, which afforded the products **4–6**. The selectivity of the noble metal catalysts could be tuned by the appropriate choice of modifiers and reaction conditions.

2. Experimental

Commercially available 5-wt.% Pt/alumina (Engelhard 7004, metal dispersion: 0.30, determined by TEM) and 5-wt.% Pd/alumina (Engelhard 5004, metal dispersion: 0.16, determined by H_2 chemisorption) catalysts were used as received. For some experiments, they were prerduced or preoxidised in a flow of hydrogen or air at 400°C for 1.5 h.

Ketoisophorone **1** (Aldrich 98%) and all the amines and ionic additives were used as received (Fluka).

Hydrogenations were carried out in a 100-ml stainless steel autoclave. A 50-ml glass liner with a Teflon cap and stirrer were used to keep the system inert. If not otherwise stated, *procedure A* was used: 25 mg catalyst, 0.5 g (3.3 mmol) **1** and 20 ml solvent. The prerduced catalyst was transferred to the reactor under exclusion of oxygen. The reaction mixture was stirred magnetically (1000 rpm) at room temperature under a hydrogen pressure between 1 and 50 bar. When metal salts were applied, the reactions were performed according to *procedure B*: To the mixture of catalyst and solvent,

the desired amount (1 molar equivalent related to the amount of noble metal) of additive was added as a 0.1-M aqueous solution. This mixture was stirred at 10 bar of hydrogen for 30 min. Afterwards 0.5 g **1** was added and hydrogenated.

During reaction, the pressure was held at a constant value by a computerized constant volume-constant pressure equipment (Büchi BPC 9901). The reaction was followed by monitoring the hydrogen uptake.

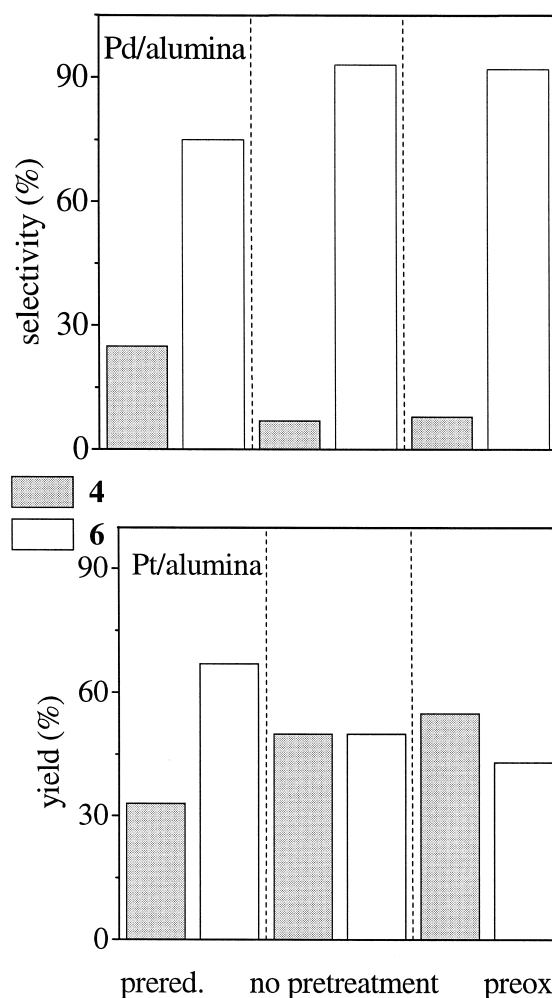


Fig. 1. Influence of reductive (H_2) and oxidative (air) pretreatments at 400°C (Procedure A in a mixture of 20 ml methanol and 0.19 ml acetic acid, at 10 bar (Pt/alumina) and 1 bar (Pd/alumina)).

The products **4**, **5** (*cis* and *trans*) and **6** were isolated by flash column chromatography (silica gel 60, 40–63 μm , Fluka) and identified by NMR-spectroscopy [8] and GC–MS analysis. Conversion, yield and selectivity were determined by an HP 6890 gas chromatograph using a fused silica capillary column HP-5. For the separation of enantiomers a J&W cyclosilB (112–6632) column was used. Enantiomeric excess is expressed as $ee (\%) = 100 \times |(R - S)| / (R + S)$.

3. Results

3.1. Product composition over Pt and Pd

Preliminary experiments revealed that, independent of the reaction conditions, the reaction stopped over Pt/alumina after a hydrogen uptake of exactly one molar equivalent related to ketoisophorone (**1**). However, when using Pd/alumina, the reaction stopped only after a hydrogen uptake of up to two equivalents. Analysis of the products revealed the parallel and consecutive reactions over Pt and Pd as illustrated in Scheme 2. Pt produced a mixture of the dicarbonyl compound **4** and the allylic alcohol **6**, whereas Pd provided the saturated diketone **4** and the hydroxy-ketone **5**. If the reaction was stopped after a hydrogen uptake of one equivalent, the products over Pd were **4** and **6**. A series of experiments with increasing hydro-

gen uptake showed that the amount of **4** remained constant, while **6** was converted to **5**.

The selective transformation of **1** to **5** over a supported Pd catalyst has already been described by Weyerstahl and Licha [7]; hence, this reaction has not been further examined. All further investigations of the Pd catalyzed reactions aimed at exploring the first reaction step. Accordingly, the reaction was always stopped between 90 and 100% conversion of **1** and the selectivities at close to complete conversion are shown in the figures and tables.

3.2. Influence of catalyst pretreatment

Catalyst prereluction at elevated temperature had reverse effects on the chemoselectivities of the Pt- and Pd-catalyzed reactions (Fig. 1). In protic polar solvents, the untreated Pd/alumina was highly selective to **6** and its prereluction decreased the selectivity from 93 to 75%. On the other hand, untreated Pt/alumina provided almost equal amounts of **4** and **6** (Fig. 1). Reductive pretreatment changed this ratio significantly in favour of **6**. It will be shown below that the reaction parameters and some additives had the opposite effect on product distribution and good selectivity to **4** could be achieved with Pt. Preoxidation of Pt or Pd had only minor or negligible influence on selectivities. Accordingly, the further experiments were carried out without any pretreatment of the catalysts.

Table 1

Influence of solvents on the reaction rate and product distribution over Pd/alumina (procedure A, 10 bar, see Section 2)

Solvent	Time (min)	Conversion (%)	Selectivity to 6 (%)
Methanol	54	90	76
Acetic acid	15	91	68
Methanol + 1 equiv. acetic acid ^a	17	85	92
Methanol + 1 equiv. acetic acid ^a	18	92	90
Methanol + 1 equiv. acetic acid ^a	18	96	84
Methanol + 1 equiv. CF ₃ COOH ^a	3	94	76
Methanol + 1 equiv. water ^a	80	98	64
Tetrahydrofurane	400	95	57
Hexane	480	96	64

^aOne equivalent related to **1**.

Table 2

Influence of pressure on the reaction rate and selectivity over Pd/alumina (procedure A, solvent: 20 ml methanol and 0.19 ml (1 equiv. related to **1**) of acetic acid)

Pressure (bar)	Time (min)	Conversion (%)	Selectivity to 6 (%)
1	40	94	93
10	18	96	84
50	12	95	76

3.3. Selective hydrogenation of the sterically hindered carbonyl group over Pd/alumina

3.3.1. Solvent effect

Solvent polarity had a dramatic influence on the rate of the Pd catalyzed reaction (Table 1). The reaction time necessary to achieve ca. 95% conversion was reduced by a factor of 160 in a methanol/trifluoroacetic acid mixture, compared to the time required in hexane. The highest selectivity of 90% to **6** was obtained in a methanol/acetic acid mixture.

It is known, that acids promote the hydrogenation of carbonyl groups [15] due to the partial protonation of the carbonyl oxygen. For this reason, the reaction was faster when adding acetic acid and the enhanced rate of carbonyl

reduction also favoured the selectivity to the allylic alcohol **6**. In pure acetic acid or when adding the stronger trifluoroacetic acid (TFA), however, the selectivities were significantly lower. Kinetic measurements revealed that in strongly acidic medium the further reduction of **6** to **5** begins before the complete conversion of **1**, diminishing the selectivity to **6** at close to one equivalent hydrogen uptake. The influence of conversion on the selectivity to the intermediate **6** is illustrated by three sets of data obtained in the best solvent methanol/acetic acid (Table 1).

3.3.2. Influence of pressure

Between 1 and 50 bar, the selectivity to **6** increased with decreasing pressure (Table 2). The loss of selectivity at high pressure was due to the poor separation of the consecutive steps **1** → **6** → **5**. Seemingly, high surface hydrogen concentration enhanced the rate of hydrogenation of **6** to **5** to a larger extent than the conversion of **1** to **6**.

On the basis of this limited parameter study we can conclude that the highest selectivity to **6** (93% at 90–94% conversion) can be achieved at

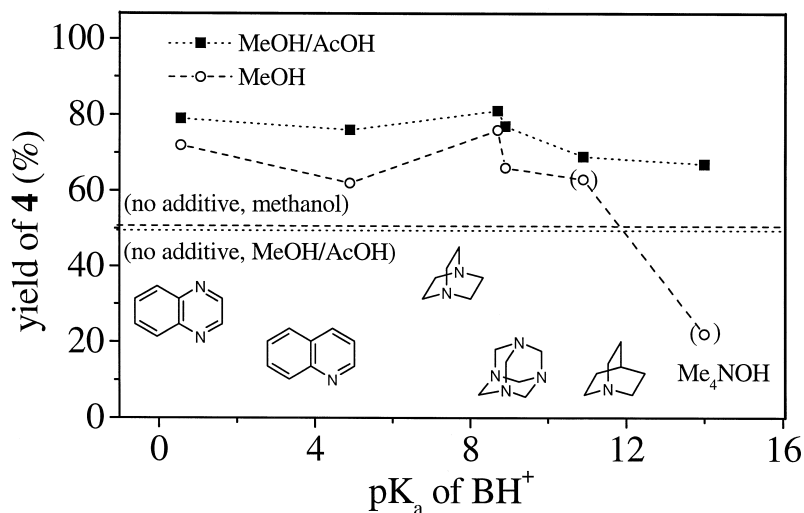


Fig. 2. Influence of the basic strength of amine additives on the chemoselectivity of Pt/alumina. The pK_a values correspond to the protonated forms of the bases. The two circles in brackets indicate incomplete reactions due to catalyst poisoning. Note that without amine additive the yield of **4** was 50% under the specified conditions (Procedure A in pure methanol or methanol/acetic acid (20 ml/1.9 ml) at 10 bar. Amount of amines: 3.6 mol% related to **1**).

1 bar in methanol/acetic acid, as shown in Fig. 1.

3.4. Selective hydrogenation of the C=C double bond over Pt/alumina

Hydrogen pressure and solvent polarity barely influenced the chemoselectivity of Pt, leading to **4** and **6** in a 1:1 ratio. Modification of the product distribution by applying various Lewis acid and base additives was more successful. The influence of six different tertiary and quaternary amines on the hydrogenation of ketoisophorone is shown in Fig. 2. The presence of catalytic amounts (3.6 mol%) of amines improved the yield to the saturated diketone **4** in both solvents. In pure methanol, the effect was smaller by 5–14%.

The basicity of the amines played a significant role only at $pK_a > 9$. The highest yield to **4** was achieved with 1,4-diazabicyclo[2.2.2]octane, possessing a pK_a value of 8.7. When applying quinuclidine or tetramethylammonium-hydroxide, a complete catalyst deactivation was observed in methanol at 77% and 22% conversion, respectively. It is assumed that the lower selectivity and the catalyst deactivation in

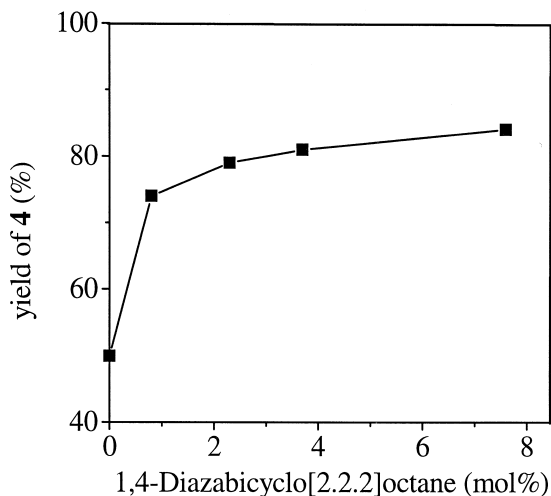


Fig. 3. Influence of the amount of base modifier 1,4-diazabicyclo[2.2.2]octane on Pt/alumina (Procedure A in methanol/acetic acid (20 ml/1.9 ml) at 10 bar. The amount of base is indicated in mol% related to **1**).

Table 3

Influence of 1,4-diazabicyclo[2.2.2]octane and $NiCl_2$ additives on the hydrogenation of ketoisophorone over Pt/alumina (procedure B in methanol/acetic acid (20 ml/1.9 ml) at 10 bar; full conversion of **1**)

Entry	Amine (mmol)	$NiCl_2 \cdot 6H_2O$ (mmol)	Time (min)	Yield of 4 (%)
1	–	–	45	50
2	–	0.006 ^a	150	66
3	0.12 ^b	–	25	81
4	0.12	0.006	45	87
5	0.25	0.006	50	90

^a0.18 wt.% related to **1**; $Ni^{2+}/Pt_s = 3.3$.

^b3.6 mol% related to **1**.

methanol are due to the too strong adsorption of these basic amines. Similarly, the generally observed higher yields in the presence of acetic acid is attributed to the weaker adsorption of the protonated amines. The molar ratio of acetic acid to amine was always 28. NMR analysis indicated that in ethanol about two equivalents acetic acid were sufficient to protonate the quinuclidine nitrogen atom of cinchonidine [16].

The yield of **4** could be further improved by increasing the amount of base. The saturation type curve in Fig. 3 indicates that the positive effect of amine was small above 4 mol% related to **1**. Note that in the whole range investigated, acetic acid was present in a large excess (100 mol% related to **1**).

Interestingly, metal salts which have been frequently applied in the partial hydrogenation of unsaturated aldehydes [10,13,14,17], were

Table 4

Enantioselectivity in the formation of **6** over chiral modified Pt/alumina catalyst (procedure A in methanol/acetic acid (20 ml/1.9 ml) at 10 bar, with 2 mg of modifier)

Modifier ^a	ee (%)
CD	3
CD	14 ^b
N-Ala	3
N-Pa	4
Boc-Try	4
N-Bea	3
Dan-P	5

^aStructures are shown in Scheme 3.

^bAt 30% conversion.

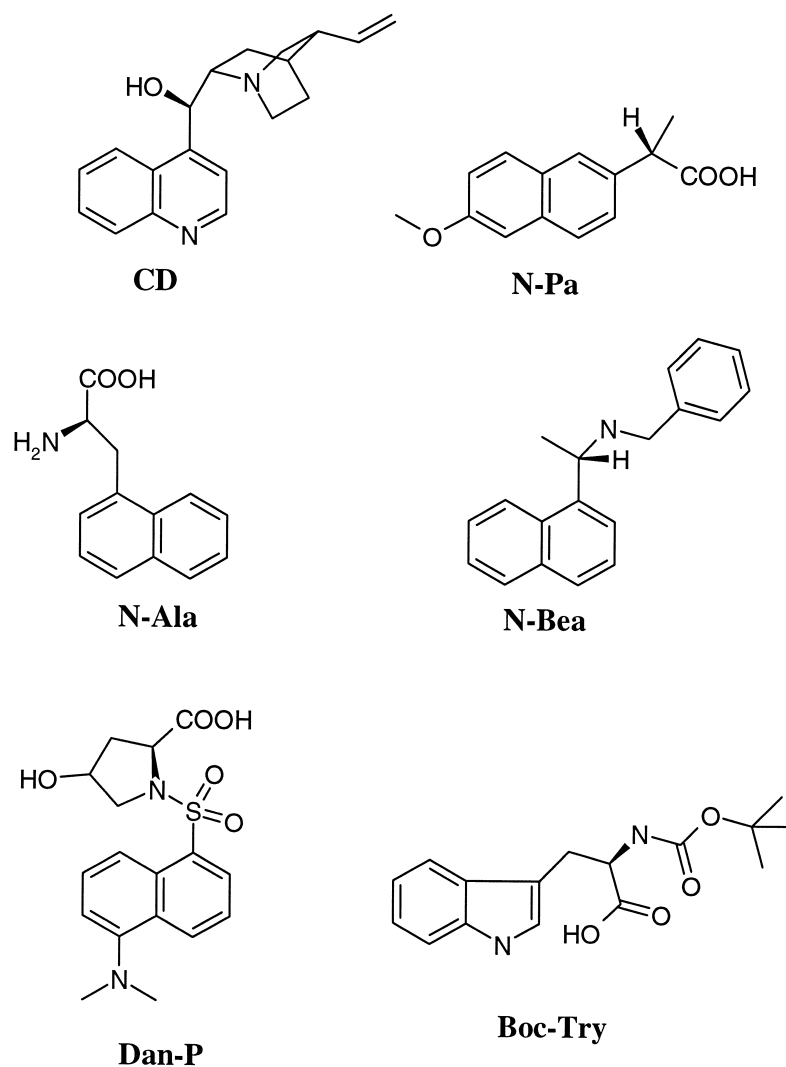
barely efficient in controlling the selective hydrogenation of ketoisophorone. For example, FeCl_2 had no detectable influence on the selectivity but resulted in a partial or complete deactivation of the catalyst. The only exception was NiCl_2 , which in small amounts promoted the selective hydrogenation of the $\text{C}=\text{C}$ double bond leading to preferential formation of the dicarbonyl compound **4** (Table 3). A similar effect of NiCl_2 was observed by Augustine and Meng [14] in the hydrogenation of crotonaldehyde.

Fortunately, the positive effects of amines and NiCl_2 on the selective hydrogenation of the

$\text{C}=\text{C}$ double bond were cumulative. Ninety percent yield could be attained in presence of both additives, even though the reaction conditions were not optimized. Some representative examples are collected in Table 3.

3.5. Enantioselective hydrogenation

Beside cinchonidine (CD) a series of chiral amines, alcohols and acids were tested as chiral modifiers on both catalysts. All compounds possessed an extended, flat aromatic ring system, which can facilitate the fixed adsorption of the



Scheme 3. Chiral modifiers for the enantioselective hydrogenation of **1** to **6**.

modifier on the metal surface [18–20]. None of these modifiers afforded a measurable enantioselectivity in the saturation of the C=C double bond leading to the formation of **4**. However, the Pt–CD system provided some small enantio-differentiation in the hydrogenation of the sterically hindered carbonyl group (**1** → **6**). At medium conversions the ee was somewhat higher. The results are given in Table 4 and the structures of the modifiers are shown in Scheme 3. Over Pd, a maximum value of 5% ee was obtained with CD (not shown in the table).

4. Discussion

Our study on the partial hydrogenation of ketoisophorone (**1**) revealed that Pd is more selective for the reduction of the sterically hindered carbonyl group leading to the unsaturated alcohol (**6**), whereas Pt favours the saturation of the C=C double bond resulting in the cyclic diketone (**4**, Scheme 2). This observation contrasts the usual behaviour of Pt and Pd in the partial hydrogenation of unsaturated carbonyl compounds. A wealth of data confirms that (i) only (modified) Pt affords good selectivities in the hydrogenation of α,β -unsaturated aldehydes to allylic alcohols, and (ii) poor selectivities are characteristic to all Pt metals in the partial reduction of unsaturated ketones to allylic alcohols [9,10,14,21]. An important reason for the unusual chemoselectivity may be the electron deficiency of the C=C double bond in unsaturated aldehydes due to the presence of the α -carbonyl group, which effect is compensated by the second carbonyl group in **1**. Interestingly, none of the noble metals tested were able to hydrogenate the sterically unhindered carbonyl group of **1**.

In general, good selectivity to an intermediate in a consecutive reaction series can be expected only when either the reactivity or the free energy of adsorption of the intermediate is considerably lower than that of the reactant [22]. In

our case, an explanation based on kinetic effects can be excluded. The reaction rate in the hydrogenation of **6** to **5** was at least as high as in the first reaction step (**1** → **6**). This relation is illustrated by an example in Fig. 4. Under other conditions the separation of the two processes by the rate of hydrogen consumption was hardly discernible, but still good selectivities to **6** could be achieved. Apparently, the consecutive reduction over Pd/alumina and the excellent selectivity to **6** is due to the weaker adsorption of **6**, as compared to **1**. Applying a methanol–acetic acid solvent mixture at low hydrogen pressure favours this situation. The selectivity decreased below 90% only above 90% conversion of **1** (Table 1). Protonation of the carbonyl group in more acidic solvents facilitated the carbonyl reduction [15] and diminished the selectivity to **6**, as expected.

Enantioselective hydrogenation of ketoisophorone, using Pt or Pd in presence of a strongly adsorbing chiral compound, was less successful. The Pt–cinchonidine system afforded 14% ee in the **1** → **6** transformation at moderate conversion; other modifiers were even less selective. Due to the limitations in chemoselectivity, an improvement of the enantio-differentiation without the loss of chemoselectivity remains an intriguing target for future investigations.

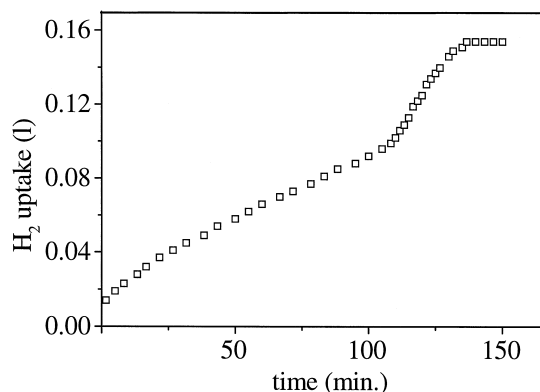


Fig. 4. Stepwise hydrogen consumption curve over Pd/alumina (**1** → **6** → **5**). (Procedure B in methanol at 10 bar and with 1 equiv (related to Pd) of KOAc).

5. Conclusions

The appropriate choice of catalyst and reaction conditions afforded 90% or higher selectivities in the partial hydrogenation of ketoisophorone **1** to the corresponding unsaturated hydroxy-carbonyl compound **6** or the cyclic diketone **4**. This is the first example for the selective hydrogenation by molecular hydrogen of an unsaturated ketone to the corresponding allylic alcohol.

As concerns the chemoselectivity, the hydrogenation of ketoisophorone catalyzed by Pt/alumina and Pd/alumina is comparable to the efficient reductions by homogeneous catalysts and enzymes. Unfortunately, only the optically pure form of **4** is useful for the synthesis of carotinoids. The versatile allylic alcohol **6** may be an important building block in the synthesis of other biologically active products.

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