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Diastereoselective hydrogenation of a cyclic β-ketoformyl derivative on supported metal catalysts

Raluca Malacea[a,c,1], Mircea Banciu[a], Mircea Pop[b], Michèle Besson[c], Catherine Pinel[c,*]

[a] *University Politehnica of Bucharest, Department of Organic Chemistry, 313 Splaiul Independentei, Bucharest, Romania*
[b] *CDNenitescu Institute of Organic Chemistry, Romanian Academy, Splaiul Independentei 202B, Bucharest, Romania*
[c] *IRC–CNRS, 2 Avenue Albert Einstein, 69626 Villeurbanne Cedex, France*

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Abstract

The hydrogenation of 9,10-dihydro-12-hydroxymethylene-9,10-ethanoanthracene-11-one was studied over ruthenium- and platinum-supported catalysts. The influence of several parameters on the activity and the diastereoselectivity of the reaction was studied and it was shown that the nature of the metal played a significant role. In the presence of platinum, both carbonyl groups were reduced with low diastereoselectivity towards the *cis* diol, while in the presence of ruthenium the diastereoselectivity could reach 60% in favour of the *trans* diol.

Keywords: Diastereoselectivity; Hydrogenation; Platinum; Ruthenium; Supported catalysts

1. Introduction

Catalytic hydrogenation is widely applied for the reduction of a variety of functional groups. In the synthesis of fine chemicals, a large number of molecules are polyfunctional substrates and the preferential hydrogenation of one functional group in presence of other reducible functional groups has received growing attention in recent years [1]. Chemoselective hydrogenation of keto groups is still challenging. Noble metals are efficient for selective hydrogenation of keto groups such as, for example, Pt-based catalysts that were used to reduce selectively a polyketo-steroid to the corresponding ketoalcohol up to 60% selectivity [2]. Furthermore, diastereoselective hydrogenation of substituted cyclic products can be performed over heterogeneous catalysts. Hydrogenation of (6:7,8:9)-dibenzobicyclo[3,2,2]nona-6,8-dien-2-one over ruthenium-supported catalyst was reported previously [3]. At low pressure and 80 °C, not only the keto group was reduced but also the aromatic ring. Recently, zeolite-supported ruthenium catalysts were tested in the hydrogenation of a β-ketoformyl, namely, 5-hydroxymethylene-5H-6,7-dihydrodibenzo[a,c] cyclohepten-6-one [4]. The main products were the corresponding ketone and alcohol resulting from the direct hydrogenolysis of the CHO group of the ketoformyl followed by a subsequent hydrogenation of the ketone. It was suggested that the hydrogenolysis step was due to the acidity of the support. In the present work, the heterogeneous catalytic hydrogenation of 9,10-dihydro-12-hydroxymethylene-9,10-ethanoanthracene-11-one **2** was investigated in order to determine the influence of the reaction conditions on the chemo- and diastereoselectivity of the reaction.

We will focus on platinum-based catalysts that are well known to reduce carbonyl groups while they exhibit very low activity towards aromatic hydrogenation [5]. Ruthenium-based catalysts will also be tested.

* Corresponding author. Tel.: +33 472 44 5483; fax: +33 472 44 53 99.
E-mail address: pinel@catalyse.cnrs.fr (C. Pinel).
[1] Present address: University of Toulouse, France.

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2. Experimental

2.1. 9,10-Dihydro-12-hydroxymethylene-9,10-ethanoanthracene-11-one (2)

To a cold benzenic (15 ml) suspension of dry sodium methoxide, freshly prepared from sodium (400 mg, 17.4 mmol) and methanol (15 ml), a solution of ketone **1** (1.5 g, 6.8 mmol) and freshly distilled anhydrous ethyl formate (2.5 g, 33.8 mmol), in benzene (15 ml), was added. The stirring was continued for 5 h at room temperature and the suspension was filtered under vacuum. The crude solid was poured in a mixture of 50 ml water and 10 ml HCl 33%. A 1.47 g of a beige solid was obtained (87%) [6]. mp = 143–144 °C, IR (KBr, cm^{-1}): 950w, 1058m, 1139s, 1387w, 1461m, 1603m ($\nu_{C=C\ conj}$), 1671vs ($\nu_{C=O\ conj}$), 3000–3300w. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.2 (d, 3 Hz, H^{12}), 4.8 (s, H^{10}), 4.9 (d, 10 Hz, H^9), 7.1–7.5 (m, H arom.), 9.4 (s, H^{13}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.5 (C^9), 47.6 (C^{10}), 62.1 (C^{12}), 122–127 (C arom.), 167.8 (C^{13}), 195.9 (C^{11}).

2.2. Reduction with $NaBH_4$

To a cold solution of formyl ketone **2** (0.4 g, 1.6 mmol) in CH_3OH (30 ml), a solution of $NaBH_4$ (1.5 g, 13 mmol) and NaOH (0.08 g, 2 mmol) in CH_3OH (20 ml) and H_2O (2 ml) was slowly added. After 18 h stirring at room temperature, three-forth of solvent was removed and 20 ml of H_2O was added. After extraction with Et_2O, the organic layer was washed and dried ($CaCl_2$), and concentrated to give 0.38 g of a white solid. The GC analysis showed the presence of the diols **4a** and **4b**, 44 and 56%, respectively, which were identified after column chromatography as *cis* and *trans* isomers (vide infra). NMR analysis of the product with the lowest retention time was performed. The different signals were attributed thanks to DEPT, COSY and ^{13}C–^{1}H correlation. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.1 (s_{broad}, 2H, OH), 2.27(m, H^{12}), 3.21 (dd, 9.7, 11 Hz, H^{13}), 3.54 (dd, 5.4, 11 Hz, $H^{13'}$), 4.01 (d, 2 Hz, H^9), 4.27 (d, 3.4 Hz, H^{10}) 4.31 (dd, 3.4, 6.5 Hz, H^{11}). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 44.9 (C^{12}), 46.7 (C^9), 52.3 (C^{10}), 63.9 (C^{13}), 71.1 (C^{11}), 123.1, 124.8, 124.9, 125.9, 126.3, 126.4, 126.6 (CH arom.), 138.7, 139.8, 141.0, 143.7 (C arom.).

2.3. Catalysts

The catalysts used in the hydrogenation were 5% Ru/C (Aldrich 28,147-6), 5% Ru/Al_2O_3 (Aldrich 22,853-2) and 6.2% Pt/C (prepared in the laboratory by cationic exchange with $Pt(NH_3)_4Cl_2$ [7]). Transmission electron microscopy showed that most of the ruthenium particles were in the size range 1–4 nm and the platinum particles in the size range 2–2.5 nm. In both cases the particles were homogeneously distributed inside the grain.

2.4. Hydrogenation experiments

The hydrogenation of substrate **1** or **2** was carried out in a 30 ml stainless steel autoclave magnetically stirred under 50 bar and at room temperature or 50 °C. Standard experiments were performed using 0.2 mmol of substrate dissolved in 15 ml solvent. The amount of the catalyst was calculated so that the metal/substrate ratio was 1/20. Samples were taken out during the reaction and were analyzed by GC [HP 5 column, T_{inj} = 270 °C, T_{det} = 290 °C, T_{oven} = 170 °C (1 min), then 5 °C/min up to 260 °C (2 min)]. The conversion and the selectivity were calculated from GC area.

The retention time of the different products were the following: t_R(**1**) = 6.5 min; t_R(**2**) = 8.5 min; t_R(**3**) = 6.2 min; t_R(**4a**) = 10.5 min; t_R(**4b**) = 10.7 min; t_R(**5**) = 9.8 min; t_R(anthracene) = 4.5 min.

3. Results and discussion

3.1. Hydrogenation of 1

First, the activity and chemoselectivity of catalysts were tested in the hydrogenation of ketone **1**. Independently of the catalyst, this reaction yielded nearly quantitatively the corresponding alcohol **3**. In some cases, anthracene was detected but in very small amount (<2%).

The influence of the nature of the catalytic metal (Pt or Ru), reaction solvent, temperature and pressure on the initial reaction rates (R_i) are reported in Table 1.

In the presence of Ru/C at room temperature, the reaction was very slow even at 50 bar H_2 (entry 1). Heating at 50 °C allowed reasonable transformation to the alcohol without hydrogenolysis (entry 2). The choice of the solvent is also very important: almost no reaction occurred in CH_2Cl_2 (entry 4), while the initial reaction rate was significant in alcoholic solvent (4.1 and 6.3 mol h^{-1} mol_{Ru}^{-1} in EtOH and MeOH, respectively). Complete conversion was achieved within a reaction time of 6 h and less than 5% of unknown by-products were detected together with anthracene. Cleavage of C–C bonds in similar polycyclic compounds was already reported over Ru-colloids [8]. The nature of the support played also an important role; while the carbon-supported ruthenium

Table 1
Influence of reaction conditions on initial reaction rate for hydrogenation of **1** (hydrogenation conditions: 0.2 mmol **1**, 15 ml solvent, 5% mol metal)

Entry	Catalyst	Solvent	P (bar)/T (°C)	R_i (mol h^{-1} mol_{met}^{-1})
1	Ru/C	MeOH	50/RT	0.3
2	Ru/C	MeOH	50/50	6.3
3	Ru/C	EtOH	50/50	4.1
4	Ru/C	CH_2Cl_2	50/50	0.1
5	Ru/Al_2O_3	MeOH	50/50	0.8
6	Pt/C	MeOH	5/RT	0.3
7	Pt/C	MeOH	50/RT	2.8
8	Pt/C	EtOH	50/RT	2.5
9	Pt/C	CH_2Cl_2	50/RT	1

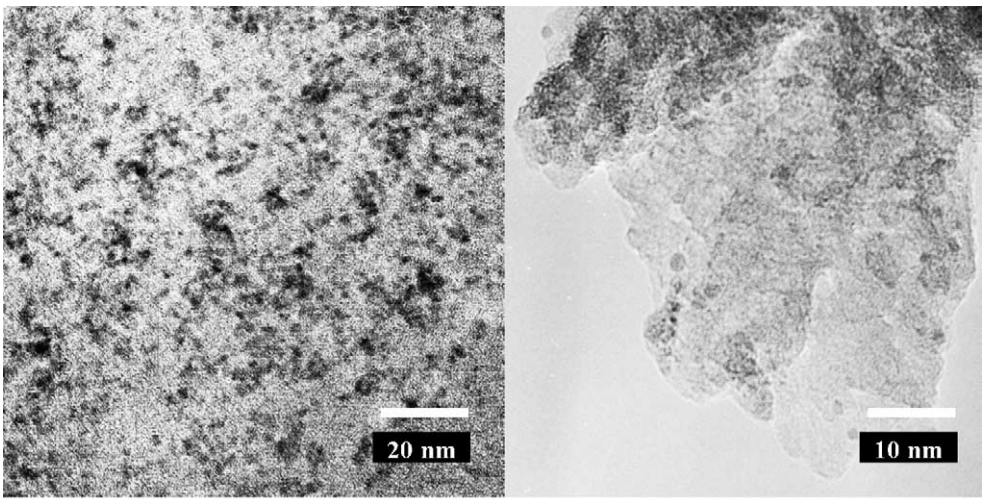


Fig. 1. TEM of (a) Ru/C and (b) Ru/Al_2O_3.

catalyst was very active in methanol ($6.3\,mol\,h^{-1}\,mol_{Ru}^{-1}$), the alumina-supported catalyst exhibited very low activity ($0.8\,mol\,h^{-1}\,mol_{Ru}^{-1}$) under the same reaction conditions (entries 2 and 5, respectively). By transmission electron microscopy, ruthenium particles in both catalysts were found in the same size range 2–4 nm. Therefore, the difference in activities cannot be related to different dispersions, but it can be explained by the change in the morphology of the ruthenium particles which may modify the approach of the reactant to the metallic surface. In Ru/C, spherical particles were observed (Fig. 1a) while in Ru/Al_2O_3 (Fig. 1b), the contrast between the particles and the support was much lower than that of carbon-supported particles suggesting that lens-shaped particles interacting with the support were present, as was observed previously on rhodium-supported catalysts [9].

When supported on carbon, the platinum catalyst was active for ketone hydrogenation even under mild pressure. The increase of pressure from 5 to 50 bar H_2 in alcoholic solvent caused a significant increase of activity at room temperature ($2.5–2.8\,mol\,h^{-1}\,mol_{Pt}^{-1}$ instead of 0.3). In both cases, the hydrogenation was very chemoselective and no by-product was detected. When CH_2Cl_2 was used as the solvent, not only the initial reaction rate was lower but significant amounts of unknown by-products were detected by GC analysis (10% after 24 h reaction).

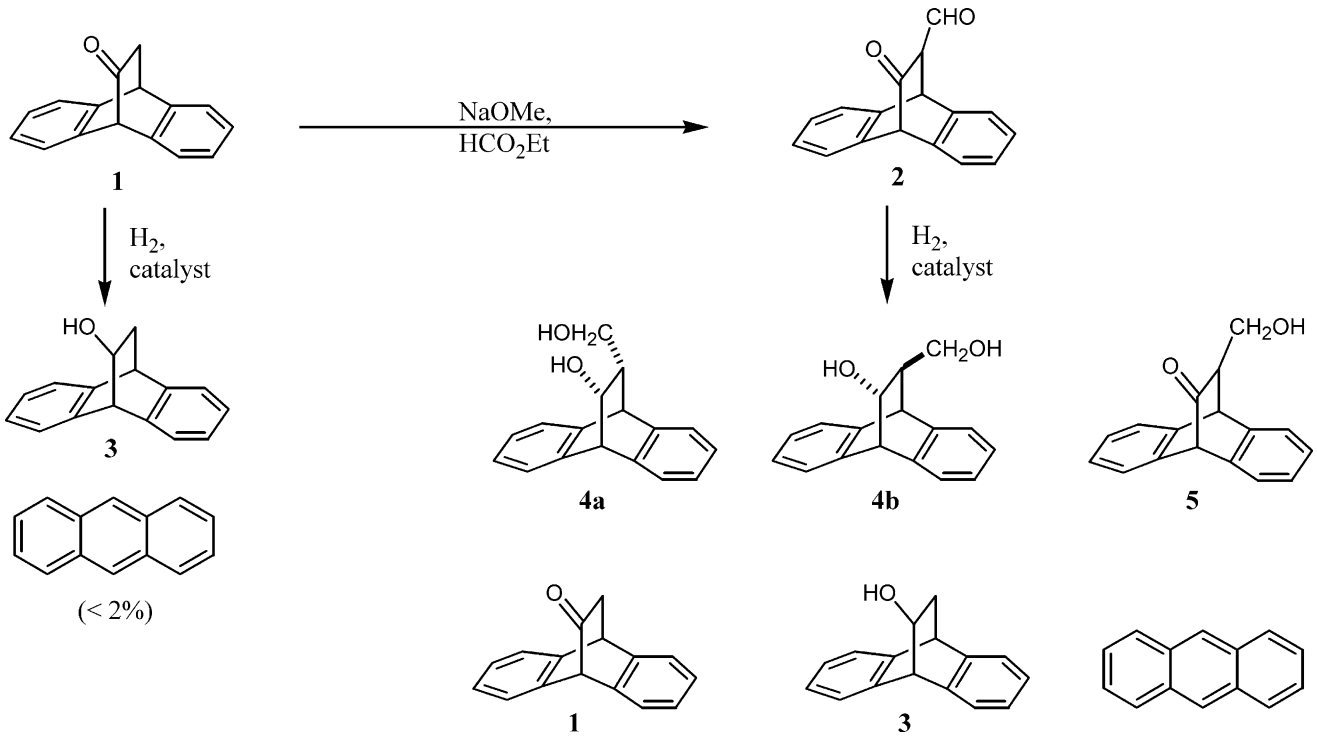
3.2. Hydrogenation of **2**

3.2.1. Identification of the reaction products

The hydrogenation of the β-ketoformyl **2** in methanol under 50 bar hydrogen pressure, yielded several compounds which were detected by GC (Scheme 1). Comparison with authentic samples allowed to identify anthracene, 9,10-ethanoanthracene-9,10-dihydro-11-one **1** and 9,10-ethanoanthracene-9,10-dihydro-11-ol **3** described in the first part of this study, as well as the two expected isomers 9,10-ethanoanthracene-9,10-dihydro-12-hydroxymethyl-11-ol **4a** and **4b**. An additional peak was detected during the course of the reaction which could not be identified. Indeed, attempts to purify this compound on silica or alumina columns were unsuccessful as it was decomposed during the operation. GC–MS analysis was not possible as well, since all these compounds were too sensitive and only the mass corresponding to anthracene could be observed. However, this compound was formed as an intermediate and under some reaction conditions, it was subsequently transformed to the diols **4a** and **4b**. We assumed that the formation of this intermediate corresponded to the hydrogenation of only one of the two carbonyl groups. Furthermore, ^1H NMR analysis of the crude reaction mixture, after complete disappearance of the starting material, showed no signal corresponding to the aldehyde function. So we could conclude that the partially hydrogenated product was 9,10-ethanoanthracene-9,10-dihydro-12-hydroxymethyl-11-one **5** with the keto group remaining intact.

3.3. Identification of cis and trans diastereoisomers

The reduction of **2** was performed with $NaBH_4$ yielding the two diastereoisomers in a 44/56 ratio. After purification on chromatography column, ^1H and ^{13}C NMR analysis of the diastereoisomer with the lowest retention time was performed. The coupling constant $J_{11,12}$ was determined to be 6.5 Hz. In the literature, several *cis* and *trans* 7,8-disubstituted dibenzobicyclo[2,2,2]octadiene were synthesized by condensation of anthracene with *cis* or *trans* 1,3-disubstituted alkene. Selective couplings of the *trans* and *cis* derivatives are reported in Table 2. The constant couplings of the *cis* 7,8-disubstituted dibenzobicyclo[2,2,2]octadiene derivatives were in the range of 6–9 Hz while the constant couplings of the corresponding *trans* compounds were much lower in the range 2.5–3.3 Hz



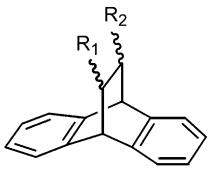
Scheme 1. Hydrogenation of 9,10-dihydro-12-hydroxymethylene-9,10-ethanoanthracene-11-one.

[10,11]. By analogy, we attributed this diastereoisomer to the *cis* isomer **4a**. The diastereoselectivity of the reaction is defined from the *cis*/*trans* ratio.

3.4. Hydrogenation over a platinum catalyst

Fig. 2a shows the product distribution as a function of time during the hydrogenation of 9,10-dihydro-12-hydroxymethylene-9,10-ethanoanthracene-11-one **2** over 6.2 wt.% Pt/C catalyst in methanol at room temperature under 50 bar H_2. The ketoformyl disappeared very rapidly to form mainly compound **5** with a maximum yield of 40%, as well as the two diols **4a** and **4b** in nearly same amount with a small preference towards the *trans* **4b**. The initial reaction rate was 26.3 mol h^{-1} mol_{Pt}^{-1} indicating that the formyl group is much more reactive compared to the keto function of **1** (R_i = 2.8 mol h^{-1} mol_{Pt}^{-1} under the same conditions). Then **5** was consecutively hydrogenated at a lower reaction rate preferentially to the *cis* diol **4a** (Fig. 2b). From the beginning of the reaction, by-products up to 20% were detected. Among them we could identify anthracene as well as ketone **1** and alcohol **3**.

Table 2
Selective coupling data of 7,8-disubstituted dibenzobicyclo[2,2,2]octadiene compounds (according to [8,9])



R_1	R_2	$J_{7,8}$ *trans* (Hz)	$J_{7,8}$ *cis* (Hz)
Cl	SPh	3.0	9.0
Cl	OAc	2.5	8.0
NH_2	H	3.0	9.5
Cl	CH_2Cl	2.5	6.0
OAc	CH_3	3.0	7.0

The influence of the pressure on the reaction rate and the selectivity of the reaction was studied (Fig. 3). A pressure increase favoured the direct hydrogenation of the formyl ketone to the diols, certainly by accelerating the reaction rate of intermediate **5**. Whatever the pressure, after 3 h, the two diols were formed in the same proportion showing that the reduction of the cyclic β-ketoformyl **2** was non-selective over Pt/C catalyst. When the β-hydroxyketone intermediate **5** was further hydrogenated, the diol **4a** (*cis*) was obtained in a higher amount and some diastereoselectivity could be observed: after 24 h of reaction at 80 bar and room temperature, 57 and 43% of **4a** and **4b** were obtained, respectively. When the reaction was performed at 50 °C, the diol **4a** was obtained preferentially to **4b** (54 and 46%, respectively).

The nature of the solvent (solubility, polarity, etc.) may also play a key role on the activity and the selectivity of catalysts in diastereoselective hydrogenation [12]. Indeed, we found the selectivity changed with the solvents (alcohols, THF or toluene) (Fig. 4).

Whatever the solvent, after 24 h of reaction, at room temperature and under 50 bar H_2, the conversion of **2** was complete. In aprotic solvent (THF, toluene), ketoalcohol **5** was the main product. Less than 20% of diols **4a** and **4b** were de-

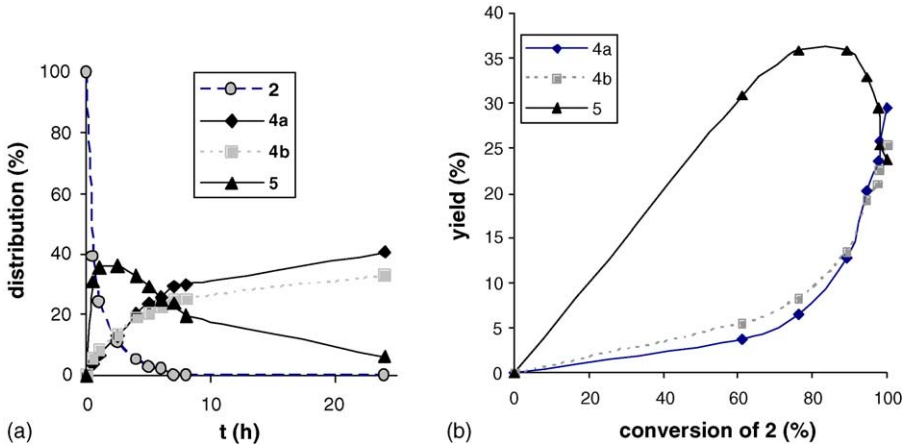


Fig. 2. (a) Distribution of the products as a function of time during hydrogenation of **2**; (b) yield of products vs. conversion (6.2% Pt/C, P_{H_2} = 50 bar, RT, MeOH).

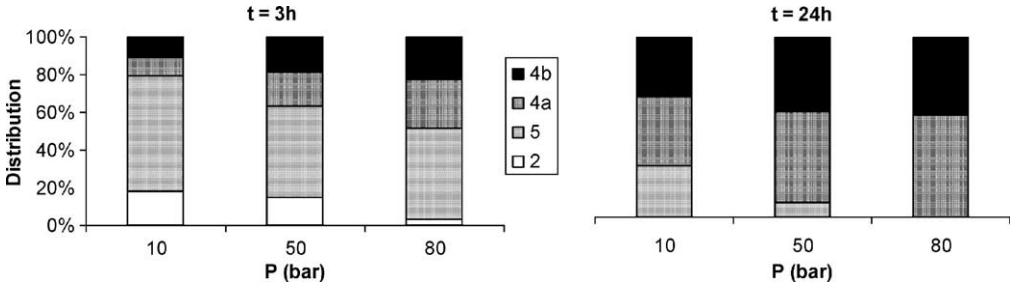


Fig. 3. Distribution of the ketoformyl (**2**) and the main products of the reaction as a function of pressure after 3 and 24 h reaction time. Reaction conditions: 6.2% Pt/C, MeOH, RT.

tected. In toluene, up to 86% of ketoalcohol was selectively formed and the hydrogenation of the keto group was minor. In alcoholic solvents, the yields in diols were 40 and 70% in iPrOH and MeOH, respectively. A similar influence was observed during hydrogenation of **1**: the reaction rate was higher in alcoholic solvent compared to aprotic solvent (Table 1). Addition of HCl, inhibited the catalyst, while higher yield of diols were obtained in the presence of NEt_3. Unfortunately, with all kind of solvents, very low *cis*/*trans* diastereoselectivities (<10%) were achieved.

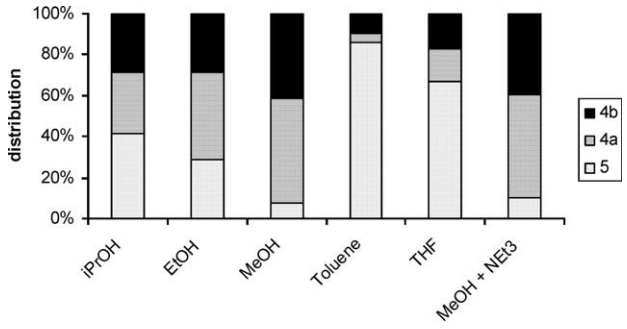


Fig. 4. Modification of the product distribution as a function of the solvent over 6.2% Pt/C (P_{H_2} = 50 bar, RT, 24 h).

3.5. Hydrogenation over a ruthenium catalyst

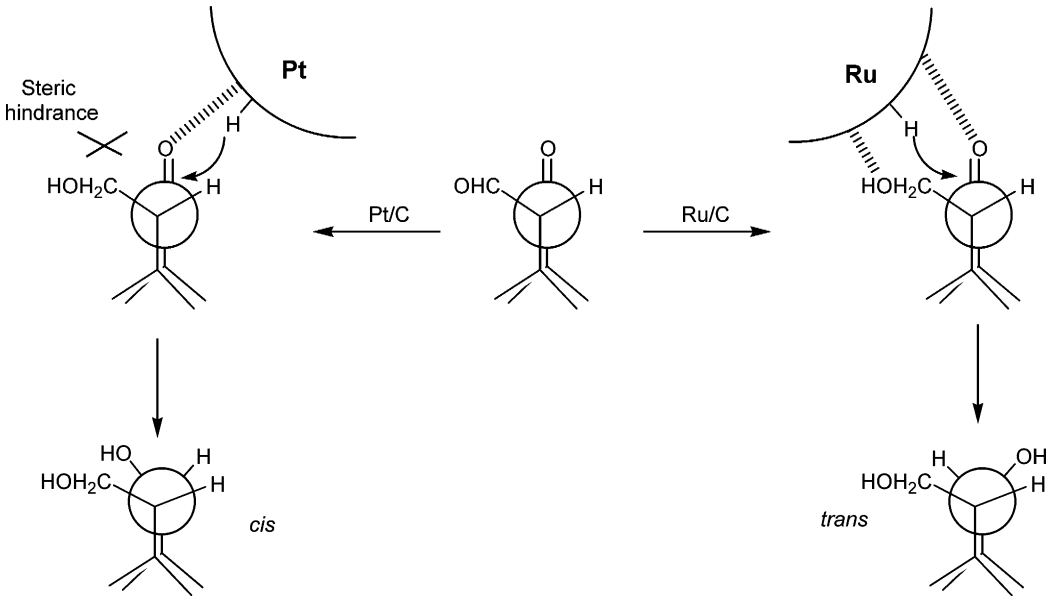
The catalytic results in the presence of ruthenium catalysts are given in Table 3.

Ru/C was much less active for the hydrogenation of **2** than Pt/C (initial reaction rate 0.3 and 26.3 mol h^{-1} mol_{met}^{-1}, respectively) as it was already observed during the hydrogenation of ketone **1**. Over Pt/C, after 24 h of reaction, the two diols were the major compounds formed with a slight excess in favour of the *cis* diastereoisomer **4a**. In the presence of Ru/C, the main product was the ketoalcohol **5**. Less than 30% of diols were formed after 24 h, but the diastereoselectivity of the reaction was dramatically enhanced and reached 60%. Moreover, the main isomer produced in the presence of ruthenium was the *trans* isomer **4b**, in contrast to that obtained predominantly in the presence of the platinum catalyst. Hydrogenation of a similar cyclic β-ketoester has been performed over Ru-supported catalyst yielding the *cis* hydroxyester as main product [13]. A higher yield of diols could be obtained by performing the reaction at higher pressure (entry 3) without significantly affecting the diastereoselectivity of the reaction.

The *trans* selectivity can be explained by the high oxophilicity of the ruthenium. Indeed, ruthenium is a more

Table 3
Hydrogenation of **2** (MeOH, RT, 24 h)

Entry	Catalyst	P (bar)	R_i (mol h^{-1} mol_{met}^{-1})	**5** (%)	**4a** + **4b** (%)	de (%)
1	Pt/C	50	26.3	6	74	11 (*cis*)
2	Ru/C	50	0.4	66	28	60 (*trans*)
3	Ru/C	70	0.8	53	44	57 (*trans*)



Scheme 2. Schematic representation of the hydrogenation of **1** and **2** as a function of the metallic catalyst.

electropositive metal than platinum, which further enhances its affinity for oxygen atoms as previously reported [14,15]. We suggest that the diols are mainly produced via a two-step reaction. In the first step, the aldehyde group is hydrogenated to yield the alcohol compound **5**. This alcohol is subsequently selectively hydrogenated mainly to the *trans* product thanks to a specific interaction between the ruthenium particles and the hydroxyl function according to Scheme 2.

On the other hand, over platinum-supported catalyst, both diols were formed at similar level with a slight preference towards the *cis* one. The steric hindrance directed the diastereoselectivity of the hydrogenation of the keto group through the less hindered face. However, the constraints are not prominent and the diastereoselectivity achieved with Pt catalyst was modest.

4. Conclusion

In conclusion, a dramatic influence of the nature of the catalyst on the chemo- and diastereoselectivity of hydrogenation of β-ketoformyl derivatives was observed. In the presence of a platinum-based catalyst, the hydrogenation of the two carbonyl groups was achieved with very high activity, but with very low diastereoselectivity in favour of the *cis* diol. In contrast, in the presence of a ruthenium-based catalyst, the aldehyde group was reduced rapidly, but more severe conditions must be applied to get complete hydrogenation of the ketone. In that case, the diastereoselectivity was significantly improved and the *trans* diastereoisomer was obtained with up to 60% de.

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