Chemoselective Hydrogenation

Chemoselective Reduction of Complex α,β-Unsaturated Ketones to Allylic Alcohols over Ir-Metal Particles on β Zeolites**

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Through chemoselective catalysis one aims to address only one of several similar functional groups in a molecule. The hydrogenation of an unsaturated carbonyl compound to an allylic alcohol in a chemoselective manner is a major challenge. Allylic alcohols have a wide range of applications, for example, as fragrances, or in the pharmaceutical industry.[1,2] The reduction of unsaturated aldehydes to primary allylic alcohols proceeds well on supported Pt^0 or Ru^0.[3,4] These metals may be modified by Lewis acids (Sn^{n+}, Fe^{3+},…) or by specific supports, such as zeolites.[5] The chemoselective reduction of α,β-unsaturated ketones is much more difficult. Until recently, the most successful procedure was $CeCl_3$-assisted reduction with $NaBH_4$.[6] A homogeneous catalytic procedure has been proposed by Noyori and co-workers, which involves the use of a Ru–phosphane complex, a chiral diamine, and a base.[7] However, although the observed chemoselectivity is excellent, recuperation of the homogeneous catalyst is still a problem. Moreover, the selective activation of the C=O group of an unsaturated ketone on a simple, supported metal catalyst remains a formidable scientific challenge. Only two such reactions have been described: Ketoisophorone can be reduced by Pd/Al_2O_3 in $MeOH/CH_3COOH$ to the corresponding allylic alcohol,[8] and 4-phenyl-3-buten-2-one undergoes reduction to the unsaturated alcohol in the presence of Au/Fe_2O_3.[9] In both cases, the reaction has only been demonstrated for a single substrate. Thus, a catalyst with wider scope is required. One strategy toward the discovery of new, highly selective catalysts is to investigate the formation of metal particles on well-defined, porous supports.[10]

Herein we report that a new heterogeneous Ir catalyst facilitates the chemoselective reduction of a variety of unsaturated ketones and aldehydes to allylic alcohols. A strong-acid zeolite with a large external surface area, for example H-β, makes an optimal support. Iridium was selected because it is more oxophilic than other metals of the Pt group.[3] With a focus on specialty chemicals, seven unsaturated ketones and three unsaturated aldehydes were selectively transformed into allylic alcohols.

The standard catalyst was prepared by impregnation of a commercial H-β zeolite from PQ (surface area $= 740\,m^2\,g^{-1}$, average crystallite size $= 0.2\,\mu m$, $Si/Al = 12$) with $Ir(acac)_3$ (acac = acetylacetone) as a solution in toluene. After calcination and reduction, the catalyst was tested on a series of α,β-unsaturated aldehydes. The desired allylic alcohols were obtained with high selectivity at high aldehyde conversion (Table 1). In the hydrogenation of citral, the isolated double bond was left intact, and a mixture of the allylic alcohols geraniol and nerol was obtained. When a Ru-containing catalyst was used under identical conditions, substantially lower chemoselectivity was observed in the hydrogenation of cinnamaldehyde (Table 1, entry 2). This demonstrates that Ir is essential for high selectivity in the reaction.

Table 1: Hydrogenation of α,β-unsaturated aldehydes.[a]

Entry	Catalyst	Substrate	*P* [MPa]	*t* [h]	Conv. [%]	Sel. [%]
1	Ir/H-β (2%)	cinnamaldehyde	3	18	71	82
2	Ru/H-β (2%)	cinnamaldehyde	3	35	81	52
3	Ir/H-β (2%)	α-CH_3-cinnamaldehyde	3	3	72	89
4	Ir/H-β (2%)	citral	2.4	2.25	>98	90

[a] Conditions: substrate (50 mg), isopropyl alcohol (6.5 g), catalyst (25 mg; calcined at 300°C and reduced at 450°C). Conv. = conversion, Sel. = selectivity.

To extend the scope of the catalyst to α,β-unsaturated ketones, the reaction of the complex enone testosterone (**1**) was attempted (Scheme 1). We anticipated that the structural rigidity of this cyclic enone would lead to a decrease in the reactivity of the sterically hindered C=C double bond and an increase in the susceptibility of the carbonyl group to reduction, relative to enones in more flexible systems. The reaction was carried out with a 1% loading of Ir on H-β in

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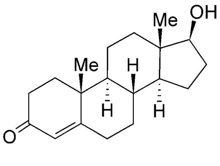

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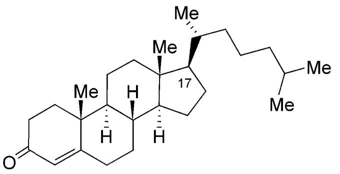

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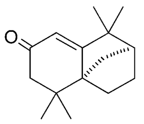

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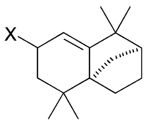
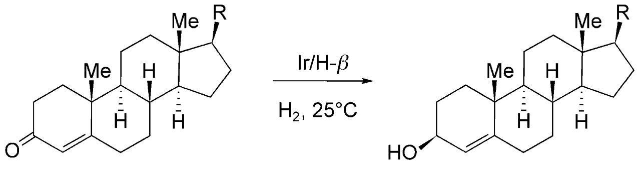


3a: X = OH
3b: X = O*i*Pr



Scheme 1. Ir/H-β-catalyzed hydrogenation of **1** and **2**.

*i*PrOH, and the selectivities observed for the allylic alcohol were found to depend on the H_2 pressure used. Thus, the selectivity increased with increasing pressure to reach a maximum of 64% at ~2 MPa and ~60% conversion (Table 2, entries 1–5). With other zeolites, the selectivities observed were lower, for example, with H-USY (Si/Al = 5.75; Table 2, entry 7). When a H-Mordenite (Mor) with a Si/Al ratio of 11 was used, the selectivity remained relatively high (Table 2, entry 6). An increase in the Ir loading of H-β led to a dramatic decrease in reaction times and was also beneficial in terms of the selectivities observed, with 76% selectivity at 87% conversion (Table 2, entries 9–10). When isoamyl alcohol was used as the solvent, the selectivities could be further improved, for example, to 100% chemoselectivity at 30% enone conversion (Table 2, entries 8 and 10). The use of other solvents, such as methanol, invariably led to the formation of the saturated alcohol. In each of the above-mentioned cases, the allylic alcohol androst-4-ene-3β,17β-diol was formed with high diastereoselectivity (d.r. > 97:3).[11,12]

Table 2: Hydrogenation of testosterone (**1**) over Ir/zeolite catalysts.[a]

Entry	Catalyst	*P* [MPa]	Solvent	*t* [h]	Conv. [%]	Sel. [%]
1	Ir/H-β (1%)	0.8	*i*PrOH	5	60	17
2	Ir/H-β (1%)	1.2	*i*PrOH	5	61	22
3	Ir/H-β (1%)	1.6	*i*PrOH	5	59	36
4	Ir/H-β (1%)	2.0	*i*PrOH	9	54	64
5	Ir/H-β (1%)	2.4	*i*PrOH	10	65	57
6	Ir/H-Mor (1%)	2.0	*i*PrOH	2	60	48
7	Ir/H-USY (1%)	2.0	*i*PrOH	25	67	32
8	Ir/H-β (1%)	2.0	*i*AmOH	9	30	100
9	Ir/H-β (2%)	2.0	*i*PrOH	0.75	87	76
10	Ir/H-β (2%)	2.0	*i*AmOH	1	75	86

[a] Conditions: testosterone (50 mg), solvent (6.5 g), catalyst (25 mg), 25 °C. Catalysts were calcined at 300 °C and reduced at 450 °C. USY = ultra-stable Y zeolite, *i*Am = isoamyl.

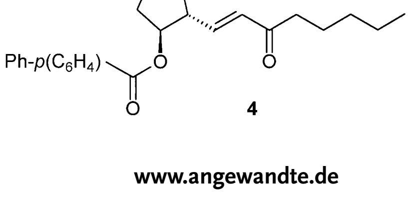
Table 3: Hydrogenation of cholestenone (**2**) and isolongifolenone (**3**) with Ir on zeolite H-β.[a]

Entry	Substrate	Catalyst	*P* [MPa]	*t* [h]	Conv. [%]	Selectivity [%]
1	**1**	Ir/H-β (2%)	2.4	0.75	87	76
2	**2**	Ir/H-β (2%)	2.4	1	85	41
3	**2**	Ir/H-β (3%)	2.8	0.67	100	> 98
4	**3**	Ir/H-β (1%)	6.0	47	59	21[b] (52)[c]
5	**3**	Ir/Na-β (1%)	6.0	184.5	35	100[b]

[a] Conditions: as in Table 2, but with cholestenone (66 mg) or isolongifolenone (40 mg) in *i*PrOH. [b] Racemic allylic alcohol. [c] Racemic isolongifolenyl ether.

Next, the reaction of cholestenone (**2**, structurally related to **1**) was tested. As the large alkyl group at position 17 was found to affect the selectivity for allylic alcohol formation (Table 3, entries 1 and 2), slightly different conditions were required. With a Ir loading on H-β of 3%, the allylic alcohol was obtained within 1 h in 98% yield (Table 3, entry 3). As observed for testosterone, the formation of the 3-β-hydroxy-4-ene allylic alcohol was highly diastereoselective (d.r. > 97:3). In the reduction of the tricyclic compound (−)-isolongifolen-9-one (**3**) with Ir/H-β (1%) in *i*PrOH, the main product isolated was isolongifolen-9-yl isopropyl ether (**3b**; Table 3, entry 4). Such isolongifolenyl ethers are important fragrance compounds.[13] This two-step process mediated by a bifunctional metal/acid zeolite is more straightforward and more environmentally sound than alternative reduction–etherification procedures, in which, for example, NaH and 2-bromopropane are used. However, if desired, the etherification activity of the catalyst can be suppressed by supporting the Ir^0 on a Na-β zeolite (Table 3, entry 5). With this modified catalyst, complete chemoselectivity for the allylic alcohol is observed, even if the reaction is slow.

Prostaglandins are important drugs and drug precursors. The Ir/H-β catalyst was used to reduce the two enone intermediates **4** and **5** in the prostaglandin synthesis,[2,14] which each contain a linear rather than a cyclic enone. In contrast with the reactions of the steroidal enones, the reduction of these prostaglandin intermediates was found to be more chemoselective when performed in MeOH, rather



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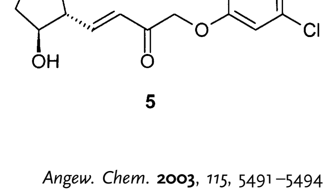

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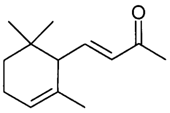
than in *i*PrOH (Table 4, entries 1 and 2). When **5** was used as the starting enone, the high selectivity of the reaction (80%) can be maintained up to very high conversion (95%), which implies that the corresponding unsaturated alcohol is a poor substrate for the Ir-catalyzed hydrogenation (Table 4, entry 3). Precalcination of the support at 700°C to convert part of the Brønsted acidity into Lewis acidity led to decreased chemoselectivity in the formation of the allylic alcohol, thus showing that the zeolite protons are important for the chemoselectivity of the catalyst (Table 4, entry 4). In contrast with the reactions of the steroids **1** and **2**, the reduction of the prostaglandin enones resulted in significant but low diastereoselectivities, typically about d.r 60:40.

Table 4: Hydrogenation of prostaglandin intermediates **4** and **5** over Ir/H-β (1%).[a]

Entry	Substrate	Solvent	*P* [MPa]	*t* [min]	Conv. [%]	Sel. [%]
1	**4**	*i*PrOH	1.0	60	43	46
2	**4**	MeOH	1.0	120	59	71
3	**5**	MeOH	0.2	60	95	80
4[b]	**5**	MeOH	0.2	15	50	55

[a] Conditions: **4** (18.6 mg) or **5** (14 mg), solvent (7 g), Ir/H-β (1%; 25 mg), 25°C. Catalyst was calcined at 300°C and reduced at 450°C. [b] H-β precalcined at 700°C prior to loading with Ir.

Finally, as representatives of smaller unsaturated ketones, α-ionone (**6**) and β-ionone (**7**) were subjected to the Ir/H-β-catalyzed reduction (Table 5). As anticipated based on the experiments with citral, hydrogenation of the isolated double bond in **6** is only a minor reaction, and 71% selectivity for the allylic alcohol is obtained at high conversion (Table 5, entries 1 and 3). Along with α-ionol (**6a**), some β-ionol (**7a**) is also formed, probably by isomerization to β-ionone, followed by reduction. With the Na zeolite, observed selectivities for the allylic alcohol were lower, thus providing further evidence that proton acidity is important for the chemoselectivity of the hydrogenation (Table 5, entry 2). Control experiments with α-ionol showed that further hydrogenation of α-ionol is very slow, which is consistent with the high chemoselectivity observed for the allylic alcohol. β-Ionone (**7**), in which the carbonyl group is conjugated to two double bonds, reacts much faster than α-ionone (**6**), and a selectivity of 65% for the allylic alcohol β-ionol was observed with Ir/H-β (2%) (Table 5, entry 8). Selectivities were lower or even much lower in the reactions of both **6** and **7** when commercial catalysts such as Ir/C, transition-metal-doped Ir/C (5%, Degussa), and Ir/$CaCO_3$ were used, as well as with Ir/Al_2O_3 and Ir/TiO_2 (Table 5, entries 4–7 and 9–13). These data unequivocally demonstrate the essential role of H-β as a selectivity-promoting support.



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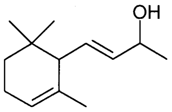

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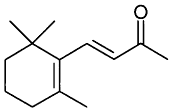

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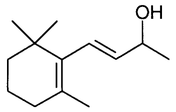

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Table 5: Hydrogenation of **6** and **7** over Ir/H-β catalysts.[a]

Entry	Substrate	Catalyst	*P* [MPa]	*t* [h]	Conv. [%]	Sel. [%][b]
1	**6**	Ir/H-β (2%)	3.6	11	75	71
2	**6**	Ir/Na-β (2%)	3.6	5.8	69	45
3	**6**	Ir/H-β (3%)	2.8	22.2	92	70
4	**6**	Ir/C (1%)	4.4	19	97	50
5	**6**	Ir/$CaCO_3$ (5%)	2	2.3	75	15
6	**6**	Ir/Al_2O_3 (1%)	2.4	4	98	12
7[c]	**6**	Ir/TiO_2 (1%)	4.4	48	90	47
8	**7**	Ir/H-β (2%)	3.6	1.5	84	65
9	**7**	Ir/C (1%)	4.4	2	73	7
10	**7**	Ir/C (5%), doped	3.6	18	94	10
11	**7**	Ir/$CaCO_3$ (5%)	2	0.8	70	2
12	**7**	Ir/Al_2O_3 (1%)	2.4	4	86	4
13	**7**	Ir/TiO_2 (1%)	4.4	23	77	14

[a] Conditions: substrate (70 mg), isopropanol (6.5 g), 25°C, catalyst (25 mg). Catalysts calcined at 300°C and reduced at 450°C (except in entries 4, 9, and 10). [b] Selectivity for ionols. [c] Catalyst: 50 mg, contains water (50%).

Although the exact optimum conditions, for example, of pressure, solvent, and Ir content, vary from one substrate to another, it is very clear that the Ir/H-β (1–3 wt%) catalyst has unprecedented generality for the chemoselective reduction of unsaturated ketones and aldehydes. Combined CO-chemisorption/TEM/TPR studies have shown that at low Ir content (0.5–1 wt%), the Ir is finely distributed over the support, with hardly any TEM (transmittance electron microscopy)-detectable metal particles, and with Ir dispersions of up to 30%. The catalysts with a higher Ir content, which were more effective for many substrates, contain Ir^0 particles in the range of 2–10 nm, thus showing that extracrystalline Ir^0 particles play an important role. It should be stressed that the enones **1**–**7** are unable to enter the intracrystalline voids of zeolites with *BEA topology.[15] Based on TPR (temperature-programmed reduction, it appears that most of the Ir is in the metallic state. Reduction at high temperature is in any case required to obtain chemoselective catalysts.

In conclusion, by combining the carbonyl affinity of metallic iridium with the promotion effect of the H-β zeolite, which is a strong Brønsted acid, one can reduce a variety of α,β-unsaturated aldehydes and ketones to allylic alcohols effectively. Excellent conversions were paired with high selectivities. Thus, this Ir/H-β catalyst constitutes a breakthrough in selective reduction on heterogeneous catalysts, especially as many of the substrates used are highly relevant for fine-chemicals production.[14]

Experimental Section

The catalyst was prepared by impregnation of zeolite H-β with Ir(acac)$_3$ as a solution in toluene (1.3 mM; 2 mL g^{-1} zeolite). The catalyst was dried at 60°C for 2 h, after which it was calcined at 300°C for 4 h. The reduction of the unsaturated ketone or aldehyde in the presence of the catalyst (25 mg) was performed in the solvent indicated (6.5 g) under a stream of H_2 at 450°C for 6 h. Commercial catalysts were purchased from Alfa Aesar (Ir/C (1%), Ir/$CaCO_3$ (5%)) or were obtained as a generous gift from Degussa (transition-metal-doped Ir/C (5 %)). The reactions were performed at room temperature. Analysis of the reaction and products was performed by GC(MS), LC, and ^{1}H and ^{13}C NMR.

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