Catalytic Hydrogenation

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Dihydrogen Reduction of Carboxylic Esters to Alcohols under the Catalysis of Homogeneous Ruthenium Complexes: High Efficiency and Unprecedented Chemoselectivity

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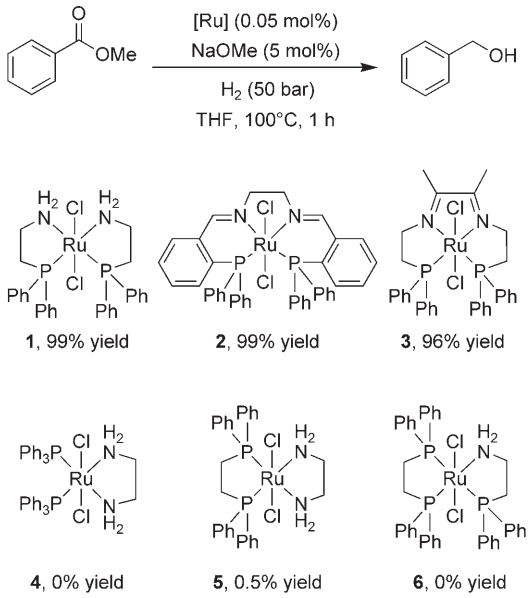
Dedicated to Prof. Valentin (Max) Rautenstrauch on the occasion of his 70th birthday

The reduction of carboxylic acid esters to alcohols is commonly effected with a stoichiometric amount of a highly reactive metal-hydride reagent (e.g. $LiAlH_4$). The amount of waste generated by this procedure would decrease strongly through the use of H_2 as the reducing agent. The homogeneous catalytic reduction of carboxylic esters to alcohols with H_2 is still a challenging process.[1] The use of mild conditions ($p(H_2) < 10$ bar, $T < 100\,°C$) in combination with an efficient catalyst (TON > 2000, TOF > 1000 h^{-1}; TON = turnover number, TOF = turnover frequency) has never been reported, although promising results were described recently by Milstein and co-workers with a ruthenium complex.[2] Herein we report our contribution[3] to the search for a highly efficient catalyst for the reduction of carboxylic esters with H_2 under mild conditions.

As ruthenium complexes with N,P ligands[4] are among the most efficient catalysts for the mild hydrogenation of ketones to alcohols,[5] we questioned their unreported use in the H_2 reduction of esters to alcohols. In early experiments aimed at the reduction of methyl benzoate to benzyl alcohol, we were very pleased to find that complex **1**[6] showed unexpectedly high catalytic activity (Scheme 1), and we optimized the conditions for this transformation (Table 1; see also the Supporting Information).

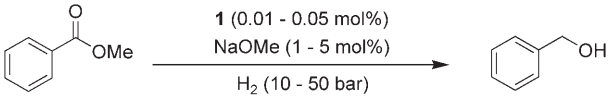
The best yields were observed in ethereal solvents, and THF was chosen as the most convenient. In contrast, almost no reaction was observed in MeOH. A base was required to transform the ruthenium complex **1** into an active catalyst in situ. NaOMe (1–10 mol%) gave the best results, whereas Et_3N and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) were inefficient. A hydrogen pressure of 50 bar and a temperature of 100 °C were sufficient for fast reactions with a low catalyst loading.

We also examined the ruthenium complexes **2**–**6**[7–10] in the reduction of methyl benzoate to benzyl alcohol under the previously optimized conditions (see Scheme 1). To our surprise, complexes **2** and **3** were as active as **1**, whereas Noyori-type complexes **4** and **5** were inefficient. A characterizing feature of complexes **1**–**3**, and a feature which distinguishes them from complexes **4** and **5**, is the presence of two



Scheme 1. Reduction of methyl benzoate by H_2 in the presence of complexes **1**–**6**.[11]

Table 1: Reduction of methyl benzoate by H_2 in the presence of complex **1**.[a]



Entry	**1** [mol%]	NaOMe [mol%]	*T* [°C]	H_2 [bar]	*t* [h]	Yield[b] [%]
1	0.05	5	100	50	0.25	78
2	**0.05**	**5**	**100**	**50**	**1**	**99** (**97**[c])
3	0.05	1	100	50	1	96
4	0.025	5	100	50	1	95
5	0.01	5	100	50	4	88
6	0.05	5	100	30	1	96
7	0.05	5	100	10	4	47
8	0.05	5	60	50	2	90

[a] Methyl benzoate: 20 mmol, THF: 10 mL. [b] The yield was determined by GC with *n*-tridecane as an internal standard. [c] Yield of the isolated product.

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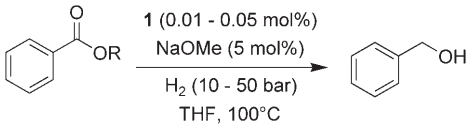
amino–phosphino-bridged ligands. Moreover, complex **6**, which incorporates only one amino–phosphino-bridged ligand, was inactive.

The most efficient complexes, **1** and **2**, were then used to examine the scope of this process.[12] Linear and branched alkyl benzoates were also reduced efficiently (Table 2). The use of isopropyl benzoate instead of methyl benzoate allowed a decrease in either the catalyst loading (0.01 mol%; Table 2, entry 3) or the H_2 pressure (10 bar; Table 2, entry 4). This improvement is probably due to the quasi-absence of MeOH in the reaction mixture. The MeOH that forms during the reduction of methyl benzoate by H_2 may deactivate the catalyst through carbonylation of the metal. Furthermore, the reduction of benzyl benzoate (Table 2, entry 7) was particularly efficient (TON = 2000, TOF = 2000 h^{-1}) relative to the equivalent reaction with the ruthenium catalysts described by Teunissen and Elsevier (TON = 2071, TOF = 129 h^{-1} at $p(H_2) = 85$ bar, $T = 120\,°C$),[1b] and by Milstein and co-workers (TON = 99, TOF = 14 h^{-1} at $p(H_2) = 5$ bar, $T = 115\,°C$).[2] Aliphatic methyl esters (Table 3, entries 1–8) and lactones (Table 3, entries 9–12) were also reduced efficiently to provide the corresponding alcohols and diols in high yields (82–96%).

Next, the chemoselectivity of the process was examined with esters that contained a C=C bond (Table 4). The reduction of methyl 3-cyclohexenecarboxylate (Table 4, entry 1) was investigated with complexes **1**–**3**. Although only moderate conversion was observed with **1** (50%), good conversions were observed with **2** (95%) and **3** (81%), and in all cases the C=C bond was affected only minimally (unsaturated/saturated product >95:5). Complex **2**, which showed the highest reactivity and chemoselectivity, was then used to investigate the scope and limitations of the reaction with respect to the structure of the unsaturated ester substrate.[12] As illustrated in Table 4, the number of substituents on the alkene group had a crucial effect on the chemoselectivity. An ester and a lactone that incorporated an acyclic

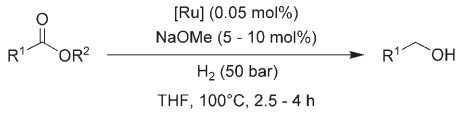
Table 2: Reduction of alkyl benzoates by H_2 in the presence of complex **1**.[a]

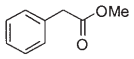
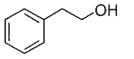
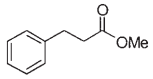
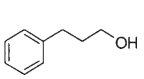
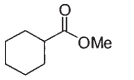
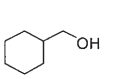
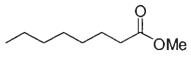
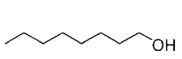
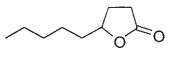
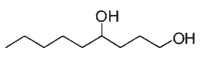
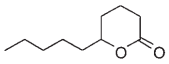
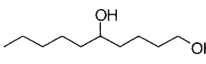


Entry	R	**1** [mol%]	H_2 [bar]	*t* [h]	Yield[b] [%]
1	Et	0.05	50	1	99
2	*i*Pr	0.05	50	1	99
3	*i*Pr	**0.01**	50	4	**99**
4	*i*Pr	0.05	**10**	4	**99**
5	*n*Bu	0.05	50	1	99
6	*t*Bu	0.05	50	1	99
7	CH_2Ph	0.05	50	1	99

[a] Alkyl benzoate: 20 mmol, THF: 10 mL. [b] The yield was determined by GC with *n*-tridecane as an internal standard.

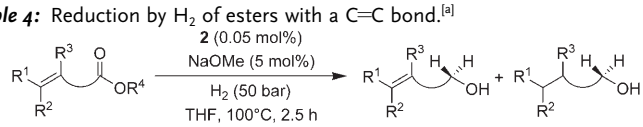
Table 3: Reduction of aliphatic esters by H_2 in the presence of complex **1** or **2**.[a]

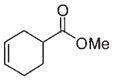
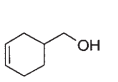
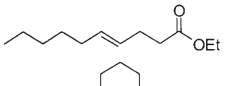
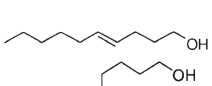
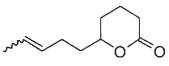
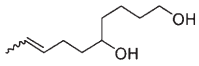
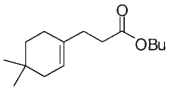
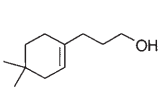
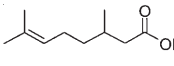
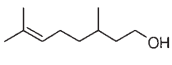
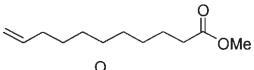
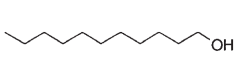
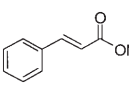
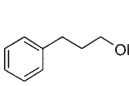


Entry	Ester	Alcohol	[Ru]	*t* [h]	Yield [%][b]
1			**1**	2.5	82
2			**2**	2.5	83
3			**1**	2.5	96
4			**2**	2.5	90
5			**1**	2.5	88
6			**2**	2.5	89
7			**1**	2.5	94
8			**2**	2.5	87
9[c]			**1**	4	87
10[c]			**2**	4	91
11[c]			**1**	4	93
12[c]			**2**	4	86

[a] Ester: 20 mmol, THF: 14 mL. [b] Yield of the isolated product after column chromatography. [c] THF was replaced by toluene, and NaOMe by KOMe.

Table 4: Reduction by H_2 of esters with a C=C bond.[a]

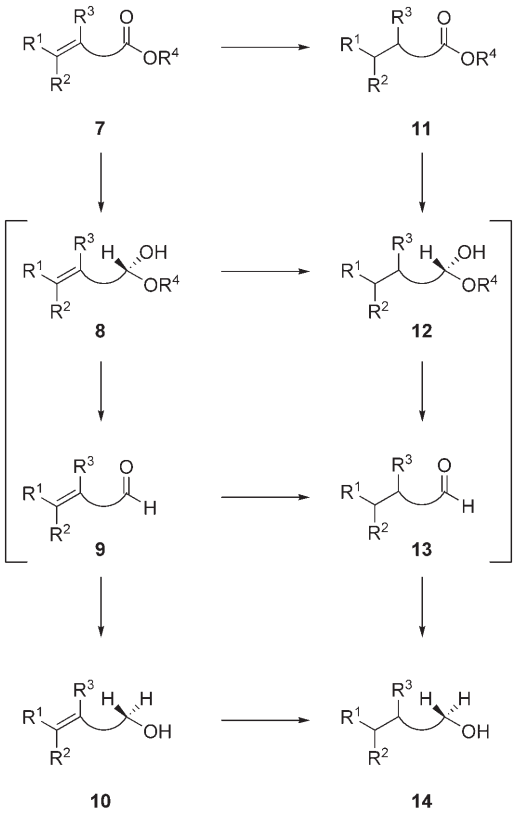


Entry	Ester	Major alcohol	Product ratio[b]	Yield [%][c]
1			98:2	90
2			99:1	93
3[d]			98.5:1.5	85
4			>98:2	95
5			99:1	94
6			35:65	94
7			12:88	87

[a] Ester: 20 mmol, THF: 10 mL. [b] The product ratio (unsaturated alcohol/saturated alcohol) was determined by GC analysis of the crude reaction mixture. [c] Yield of the isolated product as a mixture of unsaturated and saturated alcohols after column chromatography or distillation. [d] THF was replaced by toluene, and NaOMe by KOMe; reaction time: 3 h.

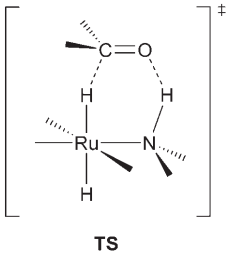
disubstituted alkene (Table 4, entries 2 and 3) were reduced with high chemoselectivity (> 98:2), and the desired unsaturated alcohol and diol were obtained in high yields. Esters with a cyclic or an acyclic trisubstituted alkene were also reduced successfully under the same conditions (Table 4, entries 4 and 5). In contrast, methyl 10-undecenoate, an ester with a monosubstituted alkene functionality, was reduced with competitive hydrogenation of the C=C bond to give the saturated alcohol as the major product (65:35; Table 4, entry 6). When this reaction was stopped after 23 min, GC analysis of the reaction mixture showed the following composition: unsaturated ester (25%), saturated ester (3%), unsaturated alcohol (47%), saturated alcohol (5%), transesterified products (20%). This result indicates that the hydrogenation of the C=C bond is slower than the reduction of the ester functionality. Therefore, the amount of unsaturated alcohol obtained could be maximized by further optimization of the reaction conditions. The extent of C=C bond hydrogenation was even higher in the reduction of an α,β-unsaturated ester (Table 4, entry 7). When this reaction was stopped after 15 min, GC analysis of the reaction mixture showed the following composition: unsaturated ester (10%), saturated ester (35%), unsaturated alcohol (35%), saturated alcohol (10%), transesterified products (10%). In this case, the hydrogenation of the activated C=C bond appears to be as fast as the reduction of the ester.

At present, little is known about the mechanism of this process and the nature of the active catalyst. Scheme 2 describes the different possible reactions that could occur under the conditions of Table 4 with an ester that contains an isolated C=C bond. The H_2 reduction of such an ester **7** to the corresponding alcohol **10** could start with the hydrogenation of the C=O bond of **7** to give the hemiacetal **8**. The fragmentation of **8** into aldehyde **9** followed by hydrogenation of the C=O bond of **9** to give alcohol **10** could then terminate the reaction. The unsaturated compounds **7**–**10** could also undergo hydrogenation of the C=C bond to give the corresponding saturated products **11**–**14**. In analogy to the reduction of **7** to **10**, the saturated ester **11** could be reduced to alcohol **14**. A comprehensive reaction scheme should also include the possible transesterification of esters **7** and **11** with alcohols **10** and **14**.



Scheme 2. The possible reaction pathways of an ester **7** with an isolated C=C bond under the hydrogenation conditions.

In the hydrogenation of ketones with diamine–diphosphine ruthenium complexes, the active catalyst is presumed to be a *trans*-dihydride complex formed from the corresponding dichloride complex upon reaction with an alkoxide base in the presence of H_2.[13] The transition state of this ketone reduction is postulated to involve the assistance of a NH ligand and does not involve the coordination of the C=O bond to the metal center.[5a,13] Similarly, the C=O hydrogenation steps in Scheme 2 could imply a *trans*-dihydride catalyst formed from complex **1**[4b] or **2**,[5c] and the same type of outer-sphere proton–hydride transfer could occur via the transition state **TS**.



The substitution of the NH_2 groups in complex **1** with NMe_2 groups[14] led to a complete shutdown of the catalytic activity. This effect was also reported for the hydrogenation of ketones[5a] and strengthens the hypothesis of an NH-assisted mechanism. Moreover, the results in Scheme 1 show clearly that two amino–phosphino-bridged ligands are needed. However, the relationship between this structural arrangement and the high catalytic activity has not yet been established.

In the H_2 reduction of esters that contain an isolated C=C bond, the reduction of the ester group was rapid relative to the hydrogenation of a di- or trisubstituted C=C bond (Table 4, entries 1–5). Even in the presence of a less sterically hindered monosubstituted C=C bond (Table 4, entry 6), good chemoselectivity (90:10) was observed in the early stages of the reaction. The observed hydrogenation of C=C bonds in these compounds probably occurs through coordination to the metal center and is therefore sterically more demanding than the proposed outer-sphere hydrogenation of the C=O bond. This difference may explain the faster hydrogenation of the C=O bond relative to that of the C=C bond for almost all compounds studied.

In summary, we have developed a reduction of aliphatic and aromatic carboxylic esters to alcohols with H_2 under the highly efficient catalysis (TON ≈ 2000, TOF = 800–2000 h^{-1}) of homogeneous ruthenium complexes with N,P ligands. Under the relatively mild conditions required ($p(H_2)$ = 50 bar, T = 100 °C), esters with a di- or trisubstituted C=C bond were reduced to the corresponding unsaturated alcohols

with high chemoselectivity (unsaturated/saturated product > 98:2) in greater than 85% yield. The operative mechanism has not yet been elucidated and is currently under investigation. Finally, this process constitutes a significant step towards the discovery of a perfect alternative to waste-generating ester reduction with stoichiometric metal-hydride reagents.

Experimental Section

Representative procedure: Complex **1** (6.7 mg, 0.01 mmol), solid NaOMe (54.8 mg, 1.0 mmol), and THF (5 mL) were placed in a stainless-steel 75-mL autoclave equipped with a magnetic stirring bar under argon. A solution of methyl benzoate (2.73 g, 20 mmol) in THF (5 mL) was added, and the autoclave was purged by three successive cycles of pressurization/venting with H_2 (20 bar), then pressurized with H_2 (50 bar), closed, and placed in a oil bath with a thermostat at 100 °C for 1 h. The autoclave was then cooled in an ice/water bath and vented. The reaction mixture was diluted with methyl *tert*-butyl ether (MTBE; 50 mL) and washed successively with saturated aqueous $NaHCO_3$ (25 mL) and saturated aqueous NaCl (2 × 25 mL). The combined aqueous phases were extracted with MTBE (2 × 25 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under vacuum. Kugelrohr distillation of the residue gave the benzyl alcohol (2.1 g, 19.4 mmol, 97%) as a colorless liquid.

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