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Hydrogenation of Aldehydes Catalyzed by an Available Ruthenium Complex

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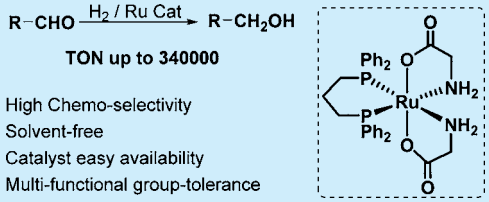
Supporting Information

ABSTRACT: A readily available ruthenium(II) catalyst was developed for the catalytic hydrogenation of aldehydes with a TON (turnover number) up to 340000. It can be performed without base and solvent, showing highly industrial potential. High chemoselectivity can be achieved in the presence of alkenyl and ketone groups. Further application of this protocol in glucose reduction showed good efficiency. Theoretical studies revealed that the rate-determining step is the hydrogenation step, not the carboxylate-assisted H_2 activation step.



Aldehyde is an abundant natural product, and its reduction to the corresponding alcohol plays a significant role in modern synthetic chemistry. Compared to stoichiometric used reducing reagents[1] (e.g., $NaBH_4$), catalytic hydrogenation with transition metal complexes afforded a sustainable and alternative way for this essential transformation. Notably, the [(diphosphine)(diamine)-$RuCl_2$] catalysts developed by Noyori and co-workers gave prominent performance for carbonyl compounds reduction.[2] Although this methodology has been widely used for asymmetric hydrogenation of ketones due to its high efficiency under the basic conditions,[2,3] few examples were reported in the case of aldehydes.[3a,4] A facile self-aldol side reaction under the basic conditions limits application of the catalytic hydrogenation of aldehydes. Hence, hydrogenation of aldehydes under neutral or acidic conditions is highly desirable.

Noyori and co-workers developed a base-free system using the catalyst RuH(BH_4) (BINAP) (diamine) for ketone reduction.[5] Morris and co-workers reported the RuH(CCPh) (diamine) $(PPh_3)_2$ complexes for the acetophenone reduction in the absence of the adding base.[6] However, these systems were sensitive to various reaction parameters, such as specific functional groups and moisture. Dupau and co-workers explored the anionic ligand effect, replacing the halide ion in [(diphosphine) (diamine)$RuCl_2$] with a carboxylate ion, which led to a great improvement of catalytic efficiency and a high selective hydrogenation of aldehydes in the presence of alkenes.[7] However, this [(diphosphine) (diamine)Ru$(RCO_2)_2$] catalyst needs 1 mol % of special acid (e.g., benzoic acid) as additive to obtain a higher TON (turnover number). Recently, investigation of inexpensive metals, such as iron[8] and cobalt,[9] led to a new path of this reduction. Other researches focused on the modification of ligand, such as substitution of phosphine ligand to sulfur[10] and NHCs.[11]

To satisfy the practical industrial use, a catalyst with high efficiency, high chemoselectivity, easy availability, multifunctional group tolerance, and even solvent-free conditions is highly desirable. Herein, we developed a well-defined catalyst for highly efficient catalytic hydrogenation of aldehydes. The catalyst features a 1,3-bis(diphenylphosphino)propane (DPPP) ligand and two glycine anion ligands to form the ruthenium(II) complexes **Ru1** (Figure 1). **Ru1** can be easily obtained by a one-step synthesis using the inexpensive phosphine ligand and amino acid. **Ru1** has been crystallographically characterized, and its molecular geometry is presented in Figure 1.[12] When we applied this kind of the catalysts to catalytic hydrogenation of aldehydes under neutral and solvent-free conditions, unexpected efficiency (TON up to 340000) was obtained. The hydrogenation is chemoselective not only to C=C bond but also to the more challenging ketone moiety. A very challenging substrate in homogeneous catalytic reaction, glucose, has been chemoselectively hydrogenated to sorbitol with good efficiency.

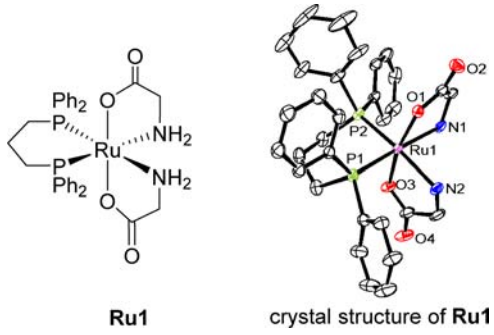


Figure 1. Chemical and crystal structure of **Ru1**.

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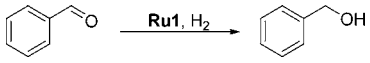
Table 1. Solvent Effect for Hydrogenation of Benzaldehyde Using Ru1[a]



entry	solvent	S/C	yield[b] (%)
1	MeOH	200000	96
2	MeOH	500000	60
3	*i*-PrOH	200000	>99
4	*i*-PrOH	500000	62
5	THF	200000	>99
6	THF	500000	29
7	1,4-dioxane	200000	97
8	1,4-dioxane	500000	8
9	hexane	200000	>99
10	hexane	500000	37
11	toluene	200000	>99
12	toluene	500000	19
13	DCM	100000	<1
14		200000	>99
15		500000	64

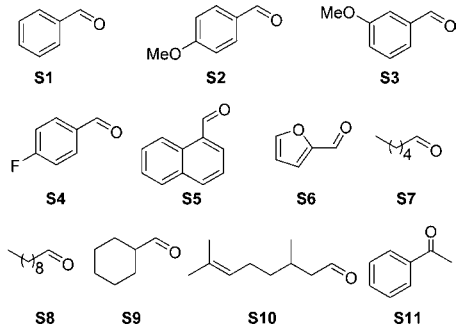
[a]Reaction conditions: benzaldehyde (10 mmol), H_2 (50 bar), solvent (2 mL), 100 °C, 24 h. [b]Yield was determined by GC analysis; *n*-tridecane was used as internal standard.

Initially, we investigated the hydrogen pressure effect by altering the pressure from 10 to 70 atm in the hydrogenation of benzaldehyde at 100 °C. Results showed that the higher pressure was beneficial to this reaction. We then explored the solvent effect using benzaldehyde as standard substrate at 100 °C and 50 atm of H_2 (Table 1). Many solvents were compatible for this reaction, except dichloromethane. Even under solvent-free conditions, there is no obvious activity difference compared to the best performing solvent *i*-PrOH.

Then, we explored the substrate scope in the presence of **Ru1** without any additives (Table 2). A variety of substrates can be hydrogenated to the corresponding alcohols with extremely high efficiency. In the case of benzaldehyde reduction, a TON of 340000 was obtained on gram scale (50 mmol, 5.3 g), which demonstrated great potential for industrial production (Table 2, entries 1 and 2). For the other aryl aldehydes, the π-electron-donating methoxy group, whether para- or meta-substituted, gave better results than the electron-withdrawing fluorine group (Table 2, entries 3−8). The hindered 1-naphthaldehyde can also be reduced smoothly with a TON of 750000 under the standard conditions. The heterocyclic aryl compound, furfural, can also be efficiently hydrogenated to form a furfuryl alcohol. For aliphatic aldehydes, primary and secondary substitution at α-position both performed well with almost the same reaction activities (Table 2, entries 13−18). In addition, this catalyst has a high chemoselective ability to C═C double bonds, e.g., citronellol (Table 2, entries 19 and 20). No C═C bond reduction product was detected. Moreover, when a mixture of benzaldehyde and acetophenone was used as substrate (Table 2, entry 21), we observed 100% conversion of benzaldehyde to the alcohol, and no acetophenone reduction product appeared.

It is well-known that the most abundant biomass, cellulose, is composed of glucose unit, essentially a hemiacetal, and there exists an equilibrium between its hemiacetal and aldehyde forms in water. We envision using the catalytic hydrogenation reaction to reduce the aldehyde to alcohol, leading the equilibrium toward the aldehyde, and then the aldehyde is reduced to alcohol (sorbitol, Table 3). Because of the high density of the hydroxyl

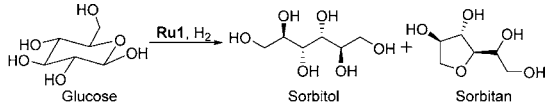
Table 2. Substrate Scope of the Hydrogenation Catalyzed by Ru1[a]



entry	substrate	S/C	yield[b] (%)
1[c]	**S1**	300000	91 (94)
2[c]	**S1**	400000	81 (85)
3	**S2**	150000	94 (>99)
4	**S2**	200000	86 (91)
5	**S3**	200000	96 (>99)
6	**S3**	250000	82 (82)
7	**S4**	20000	94 (96)
8	**S4**	50000	67 (72)
9	**S5**	50000	92 (97)
10	**S5**	100000	71 (75)
11	**S6**	100000	98 (>99)
12	**S6**	150000	79 (81)
13	**S7**	100000	92 (93)
14	**S7**	150000	77 (81)
15	**S8**	100000	94 (97)
16	**S8**	150000	86 (88)
17	**S9**	100000	92 (96)
18	**S9**	150000	77 (80)
19	**S10**	100000	96 (97)
20	**S10**	150000	90 (94)
21[d]	**S1** + **S11**	100000	95:0

[a]Reaction conditions: aldehyde (10 mmol), H_2 (50 atm), 100 °C, 24 h. [b]isolated yield; yield in parenthese was determined by GC. [c]Substrate (50 mmol). [d]**S1** + **S11** (5 mmol:5 mmol), Ru1 (1×10^{-4} mmol).

Table 3. Hydrogenation of Glucose Catalyzed by Ru1[a]



				product (%)[b]		
entry	S/C	*T*(°C)	additive (M)	sorbitol	glucose	sorbitan
1	1000	100		95	3	0.6
2	2000	100		59	27	1.4
3	1000	120		95	2	0.6
4	2000	120		58	35	1
5	1000	140		92	<1	0.4
6	2000	100	$MeSO_3H$ (0.1)	83	7	4
7	5000	100	$MeSO_3H$ (0.1)	73	6	9
8	2000	100	H_3PO_4 (0.5)	83	7	3
9	5000	100	H_3PO_4 (0.5)	64	17	3

[a]Reaction conditions: glucose monohydrate (2 mmol), *i*-PrOH/H_2O (1 mL:1 mL), H_2 (50 atm), 24 h. [b]Yield was determined by HPLC analysis; manitol was used as internal standard.

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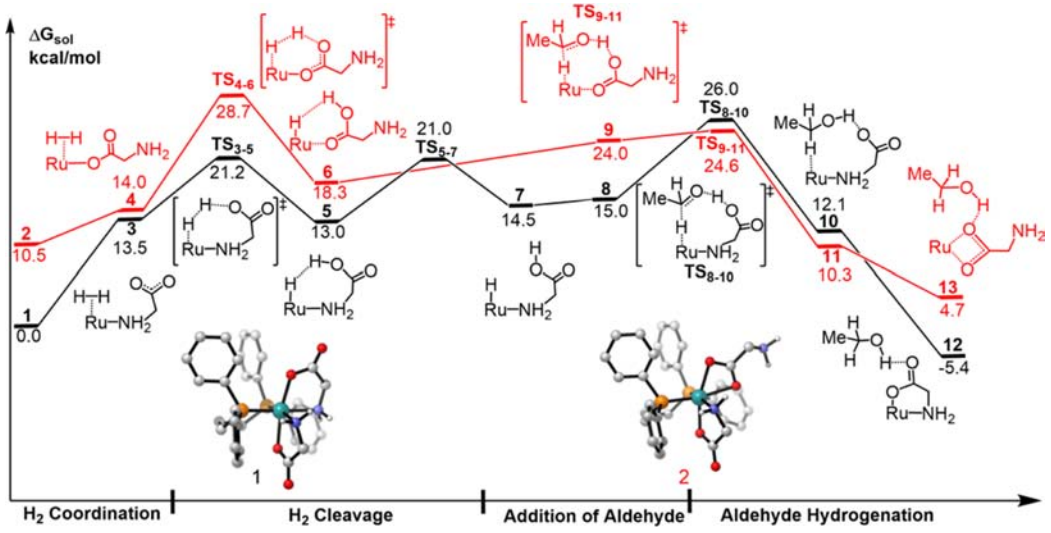

Figure 2. Free-energy reaction profile of the Ru-catalyzed hydrogenation of aldehyde in solution for two reaction models.

group in glucose, a multifunctional group tolerant catalyst is highly desirable in its reduction. First, we carried out this hydrogenation under neutral conditions by changing the temperature from 100 to 140 °C (Table 3, entries 1−5). However, the temperature has no obvious influence on the yield of sorbitol, and the TON can only reach up to 1180 (Table 3, entry 2) with a low conversion of glucose and trace dehydration product sorbitan. We envisioned that the lower percentage of the aldehyde form in solution prevented the reaction. Therefore, we tried some acid additives to promote the formation of aldehyde form rapidly. Several acids were tested as additives under different concentrations. Methanesulfonic acid under 0.1 M gave the best result (TON 3650, Table 3, entry 7), and phosphoric acid also showed positive effect on this reaction (Table 3, entry 9).

To elucidate the reaction mechanism of this Ru-catalyzed hydrogenation of aldehydes, we carried out density functional theory (DFT, using B3LYP-D3 method) calculations with the real **Ru1** catalyst (Figures 2 and SY in Supporting Information).[13] Two different mechanistic pathways involving H_2 activation followed by hydrogen transfer of aldehyde were examined, depending on the coordination mode of the amine moiety of the ligand (models **1** and **2**). As shown in Figure 2, the pathway with the coordination of the amine part (model **1**) is energetically more favorable than that with dissociation of the amine part (model **2**) by 3.7 and 2.7 kcal/mol in gas phase and solution, respectively. Both pathways start with the addition of one H2 molecule to the Ru catalyst, followed by heterolytic cleavage of the H−H bond catalyzed by a carboxylate oxygen of the ligand and by the metal to give Ru(II) hydride intermediates **5** and **6**. The computed free-energy barrier for the H2 activation via **TS3−5** is about 21.2 kcal/mol in solution, which is much lower in free energy than that via **TS4−6** for the model **2** by 7.5 kcal/mol in solution. After rotation and the addition of the aldehyde, a stable intermediate **8** is formed with the formation of one new hydrogen bonding between the aldehyde and the carboxylic group (along with a loss of hydrogen bond between the carboxylic group and hydride ligand). Then, concerted proton transfer with hydride transfer through 9-m-r **TS8−10** takes place in an outer-sphere manner and directly gives a Ru(II)−alcohol intermediate **10** with the barrier of 26.0 kcal/mol above **1** in solution. Finally, dissociation of the alcohol and rechelation of the carboxylate group to the metal regenerate the catalyst **Ru1**.

The overall reaction is computed to be exergonic by 5.4 kcal/mol. The initial H2 activation step was found to be the rate-determining step with the free-energy barrier of 20.1 kcal/mol for the model **1** in the gas phase, which is 3.7 kcal/mol lower than that for the model **2**. The barrier via **TS3−5** is slightly increased to 21.2 kcal/mol in solution, whereas the activation barrier for the subsequent hydrogenation step is significantly increased to 26.0 kcal/mol in solution. Therefore, the hydrogenation step becomes the rate-determining step in solution for the favorable path with the model **1**. The rate-determining outer-sphere H^+/H^- transfer step in model **1** account for the high chemoselectivity of the hydrogenation of aldehyde and ketone.

In conclusion, a highly efficient catalyst for the catalytic hydrogenation of aldehydes to alcohols was developed successfully. The brief reaction conditions, high efficiency (TON up to 340000), high chemoselectivity, and functional group tolerance indicated its potential of industrial practical production. It is noteworthy that the challenging substrate, glucose, can be hydrogenated with good efficiency. Theoretical studies revealed that the rate-determining step is the hydrogenation step, not the carboxylate-assisted H_2 activation step, which perfectly explained the highly chemoselective hydrogenation of aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00060.

Synthesis and characterization of catalyst, detailed experimental procedures, and computational details (PDF)

X-ray crystallgraphic data for **Ru1** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) The X-ray crystal data of **Ru1** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1063360. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: + 44 (1223)336033 or E-mail: deposit@ccdc.cam.ac.uk].
(13) See computational details and results in the Supporting Information.

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