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Highly Efficient Tetradentate Ruthenium Catalyst for Ester Reduction: Especially for Hydrogenation of Fatty Acid Esters

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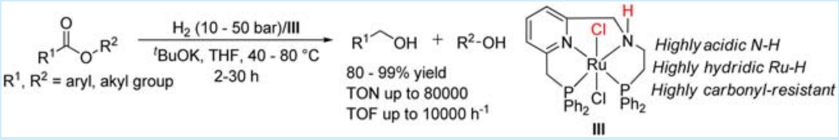
S *Supporting Information*



ABSTRACT: A new tetradentate ruthenium complex has been developed for hydrogenation of esters. The catalyst's structure features a pyridinemethanamino group and three tight chelating five-membered rings. The structure character is believed to be responsible for its high stability and high carbonylation-resistant properties. Thus, this catalyst shows outstanding performance in the catalytic hydrogenation of a variety of esters, especially for fatty acid esters, which may be used in practical applications. New insight on designing hydrogenation catalyst for reducing esters to alcohols has been provided through theoretical calculations.

The reduction of esters to their corresponding alcohols is one of the most important fundamental chemical transformations. Compared with traditional methods using stoichiometric metal hydride reagents, such as $LiAlH_4$ and $NaBH_4$,[1] this catalytic method using H_2 as hydrogen source is green, easy to operate, safe, and economic. Therefore, catalytic hydrogenation of esters is an attractive method. However, because of the lower reactivity of carbonyl group in esters relative to ketones,[2] the practical industrial process of the reduction of esters with H_2 is usually carried out with heterogeneous catalysts under harsh conditions (200–300 °C, 200–300 atm).[3] Thus, development of a super-homogeneous catalyst for highly efficient reduction of esters with H_2 under mild conditions is highly desirable.

Although great efforts have been made in the past decades, homogeneous catalytic hydrogenation of esters had been confined to special substrates and under harsh conditions,[4] until a significant breakthrough was made by Milstein in 2006. Since then, catalytic hydrogenation of esters developed rapidly, and several efficient homogeneous catalysts were reported by Milstein,[5] Saudan (in Firmenich SA),[6] Kuriyama (in Takasago),[7] Gusev,[8] et al.[9] A few reviews were also published.[10] We noticed that both Milstein's (complex **I**) and Takasago's (complex **II**) tridentate ruthenium catalysts feature a tridentate ligand and a CO ligand (Figure 1). Compared with mono- and bidentate ligands, tridentate ligand exhibited high carbonylation-resistant ability.[7d] While CO is a strong π-acceptor ligand, introduction of CO weakened the hydridity of the metal hydrides, which may have a negative influence on its ability to reduce esters.

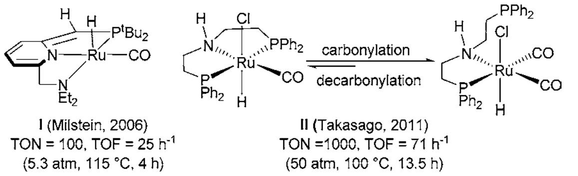


Figure 1. Two representative catalysts for hydrogenation of esters.

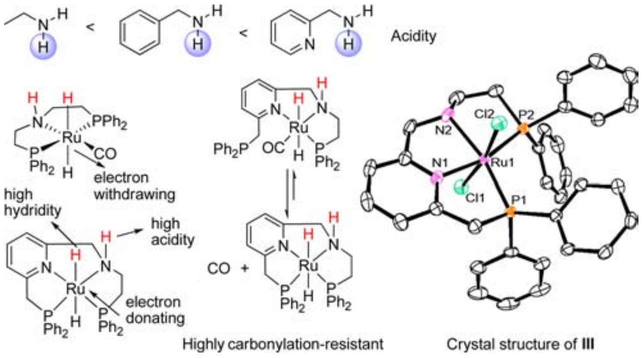


Figure 2. Design and crystal structure of **III**.

In seeking more efficient hydrogenation that operates under lower temperature and pressure to save energy and costs, homogeneous hydrogenation catalysts with super high activities (e.g., TON > 50000) show great potential.

On the basis of the bifunctional concept and the mechanism study,[11] we proposed that the catalysts' activity for reducing esters may be correlated to the hydridity of the metal hydride and the acidity of the N–H group. High hydridity of the metal hydride can improve its nucleophilicity and help to attack the less polar C=O bond of esters. On the other hand, the high acidity of the N–H group can play the role of Lewis acid to activate the

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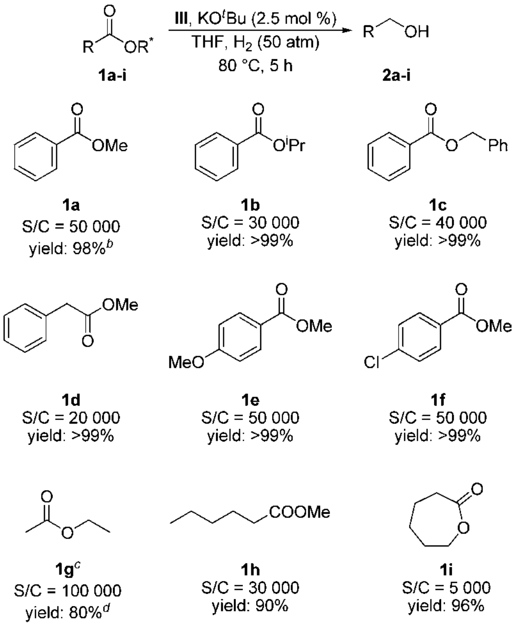
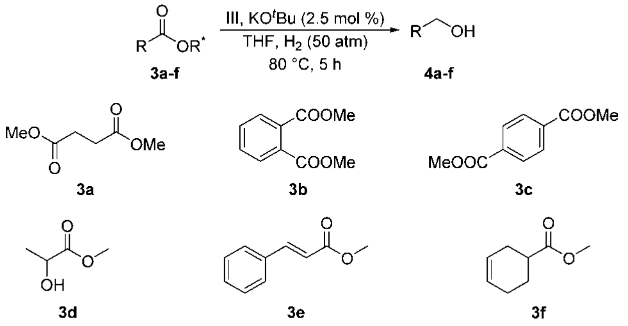
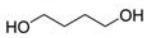
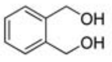
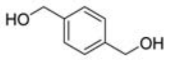
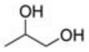
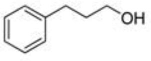
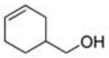
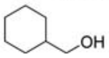
Scheme 1. Hydrogenation of Esters Catalyzed by III^{a}



^{a}Reaction conditions: substrate (10 mmol), KO^{t}Bu (0.25 mmol), THF (4 mL), H_2 (50 atm), 80 °C for 5 h. ^{b}All yields except for **1g** were determined by GC analysis (*n*-tridecane as internal standard). ^{c}Substrate (50 mmol), KO^{t}Bu (1.25 mmol), solvent free, 80 °C for 30 h. ^{d}Yield was determined by the ratio of EA/EtOH.

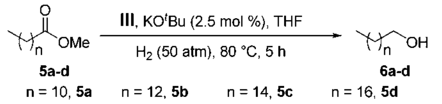
Table 1. Hydrogenation of Functionalized Esters Catalyzed by III^{a}

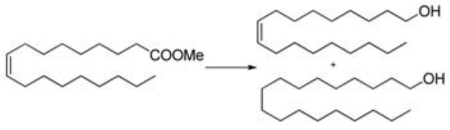


entry	substrate	product	S/C	solvent	yield [%]^b
1	**3a**		5 000	toluene	82
2^c	**3b**		1 000	THF	84
3	**3c**		5 000	THF	96
4	**3d**		2 000	THF	92
5	**3e**		5 000	toluene	>95^d
6	**3f**	 	10 000	THF	94 3

^{a}Reaction conditions: substrate (5.0 mmol), KO^{t}Bu (0.125 mmol), H_2 (50 atm), 80 °C for 5 h. ^{b}Yield was determined by GC. ^{c}100 °C for 5 h. ^{d}Yield was determined by ^{1}H NMR.

Table 2. Hydrogenation of Fatty Acid Esters in the Presence of III^{a}



Esters	RCH_2OH	S/C	yield^b
5a		30 000	92%
5b		50 000	97%
5c		50 000	99%
5d		60 000	88%
5e		20 000	90%^{c} 5%^{c}

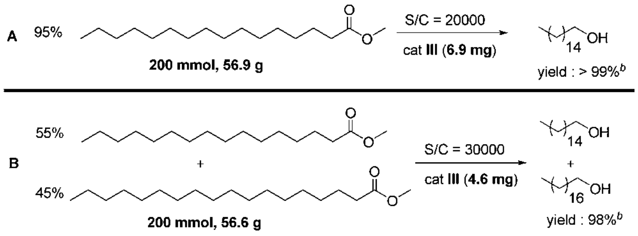
^{a}Reaction conditions: substrate (5.0 mmol), KO^{t}Bu (0.125 mmol), THF (2.5 mL), H_2 (50 atm), 80 °C for 5 h. ^{b}Isolated yield. ^{c}Yield was determined by GC analysis.

C═O groups of esters. A comparison of the acidity of aliphatic amine, benzylamine, and pyridinemethanamine is outlined in Figure 2; we chose the most acidic pyridinemethanamine as a key fragment of our new catalyst.[9b,12] We also introduced two electron-rich diphenylphosphino groups into our catalyst rather than CO ligand. The new designed catalyst **III** has been crystallographically characterized, and its molecular geometries are presented in Figure 2.[13] Compared with catalysts **I** and **II** that contain an electron-withdrawing ligand CO, catalyst **III** exhibits a tetradentate coordination model with two electron-donating phosphino groups. The structure characteristics of catalyst **III** provide high carbonylation-resistant ability, high hydridity of metal hydride, and highly acidic N−H. Thus, catalyst **III** showed outstanding performance in the catalytic hydrogenation of a variety of esters, especially since it provided an efficient and convenient conversion of fatty acid esters to long-chain fatty alcohols.

A series of solvents were investigated for the hydrogenation of methyl benzoate catalyzed by complex **III** under 50 atm of H_2, 80 °C (see the Supporting Information). The reaction is compatible for multiple solvents and solvent-free conditions. KO^{t}Bu gave the best result with a 1 mol % loading when used as base, whereas NEt_3 and inorganic base Cs_2CO_3 gave unsatisfactory results. The reaction temperature and H_2 pressure were also examined, and we found that the yield of alcohol was high (91%) after 2 h even at a low pressure of 10 atm. A lower reaction temperature (40 °C) gave the product in a lower yield of 73%.

We have examined the substrate scope and the catalyst efficiency under the optimized conditions (50 atm H_2, 80 °C, 2.5 mol % KO^{t}Bu, THF) (Scheme 1). To our delight, most of the unfunctionalized esters can be reduced with much higher turnover numbers relative to the best reported results. Halogenated esters **1f**, a challenging substrate for hydrogenation, were smoothly converted by catalyst **III** with high activities. It is noteworthy that solvent-free hydrogenation of ethyl acetate (**1g**) gave a very high TON of 80000 (S/C = 100000, 80% yield) over 30 h, which was the highest TON to our best knowledge for homogeneous catalytic hydrogenation of esters. A lower TON was observed for the hydrogenation of *ε*-caprolactone **1i**, which might be due to a

Scheme 2. Scale up Hydrogenation of Samples A and B[a]



[a]Reaction conditions: substrate (200 mmol), KO^{t}Bu (2.5 mol %), H_2 (30−50 atm), THF (80 mL), 80 °C for 5 h. [b]Isolated yield.

ring-opening polymerization (ROP) process in the presence of KO^{t}Bu and other bases.[14]

We then switched our attention to the functionalized esters as substrates for hydrogenation reaction in the presence of **III** (Table 1). Compared with unfunctionalized esters, the TON decreased one order of magnitude (except for C═C as a functional group), which may be due to the coordination effect of the function groups, such as carbonyl, double bond, and heteroatoms, together with the carbonyl group of esters, which can inhibit the catalytic activity through chelation. Dimethyl succinate (**3a**) and dimethyl terephthalate (**3c**) could be hydrogenated with a TON of 4100 and 4800, respectively, while dimethyl phthalate (**3b**) could only reach a TON of 840, which we considered to be the product inhibition with ortho-position substitution in favor of chelation with the metal center. Hydroxyl groups containing substrates such as methyl lactate (**3d**) could be reduced with a TON of 1840. For *α*,*β*-unsaturated esters, methyl cinnamate (**3e**), the double bond was also hydrogenated, while for the unconjugated unsaturated esters such as methyl 3-cyclohexenecarboxylate (**3f**) and methyloleate (Table 2, **5e**), good chemoselectivity was observed and the reduction mainly occurred in the ester part.

In the biomass conversion, fatty alcohols play a very important role in fine chemical industry, and their derivatives are often used as surfactants. Gusev has reported a ruthenium dimer catalyst for fatty acid esters reduction with moderate efficiency.[8b] In this text, we investigated the activity of complex **III** for hydrogenation of fatty acid esters (Table 2) and found that complex **III** showed unprecedented high activity for hydrogenation of fatty esters. We tested the C12−C18 saturated natural fatty acid esters, all of which gave outstanding results. The unsaturated fatty acid ester such as methyl oleate led to a slight drop of TON compared with saturated fatty esters. To the best of our knowledge, this is the highest turnover number reported so far for homogeneous hydrogenation of methyloleate.

A large-scale hydrogenation of two industrialized samples (**A**: methyl palmitate 95%, **B**: a mixture of methyl palmitate 55% and methyl stearate 45%. purchased from a local industry) was carried out at 30−50 atm H_2/80 °C (Scheme 2) with catalyst **III**. Excellent catalytic transformation has been observed, suggesting great potential for industrial applications.

Based on the bifunctional concept and the early mechanistic studies,[11] we consider that the complete catalytic cycle can be separated into two parts (Figure 3, model **0_Na**), reduction of ester to aldehyde and further reduction to alcohol. In order to gain more mechanistic insight for the high efficiency for catalytic hydrogenation of using catalyst **III**, we carried out DFT calculations based on the proposed mechanism for three model catalysts, **0_Na_CO**, **0_Na_Py**, and **0_Na** (Figure 3). Figure 3 shows and compares the free energy profiles calculated for the three model catalysts. In Figure 3, a simplified version illustrating key transition states and intermediates is given. The complete energy profiles are given in the Supporting Information. The DFT results show that for each case the first part corresponds to the hydrogenation of ester to aldehyde is endergonic, while the second part corresponds to further reduction to alcohol is exergonic. Interestingly, instead of the

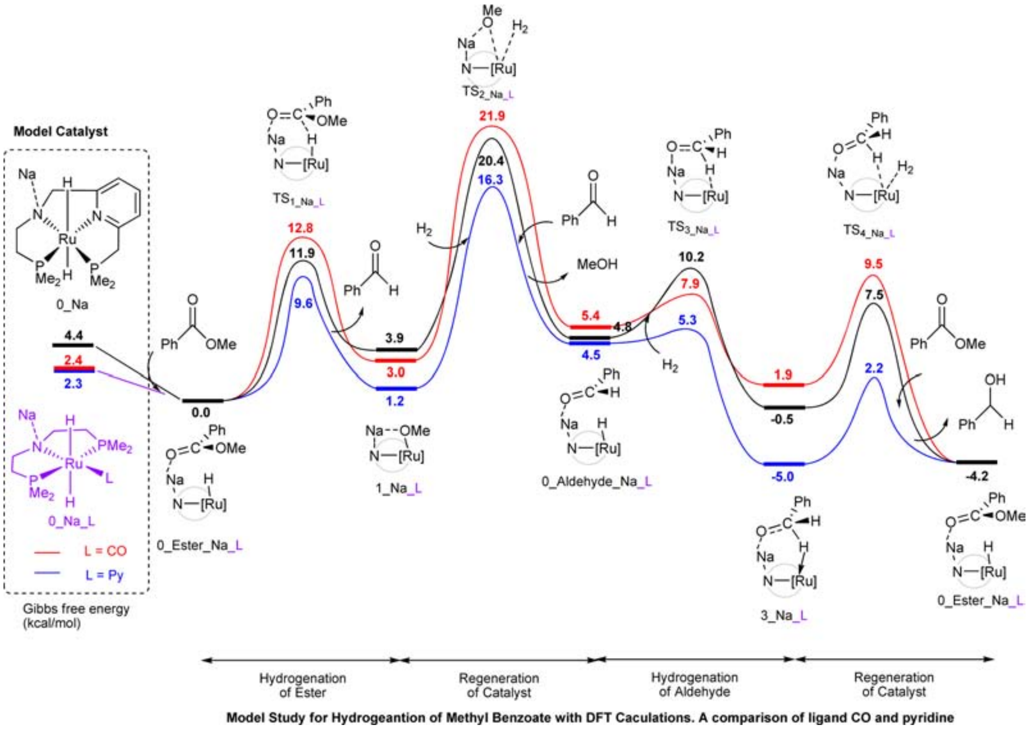


Figure 3. Free energy profiles (kcal/mol) calculated using three model catalysts.

hydride transfer, the H_2 complexation in the first part of the catalytic cycle is the rate-determining step (ca. formation of **$TS_{2\_Na\_L}$**), with an overall free energy barrier of 21.9 kcal/mol calculated for the model catalyst **0_Na_CO**, 16.3 kcal/mol for the model catalyst **0_Na_Py**, and 20.4 kcal/mol for the model catalyst **0_Na**. Replacement of the carbonyl ligand in **0_Na_L** with a pyridine ligand results in a significant decrease in the overall barrier by 5.6 kcal/mol, suggesting that a pyridine ligand has great promoting effect relative to CO. A carbonyl ligand weakens the complexation ability of the metal center for H_2 and therefore gives rise to a higher overall barrier. The model catalyst **0_Na** gives an overall barrier of 20.4 kcal/mol, 1.5 kcal/mol lower than the model catalyst **0_Na_CO** does. A difference of 1.5 kcal/mol in the overall barrier represents about 10 times difference in the reaction rate when we apply the Arrhenius rate equation. Besides, in our calculations, when the sodium cation in **0_Na** is replaced by a potassium cation (giving the model catalyst **0_K**), an overall barrier was calculated to be 18.5 kcal/mol, which is 1.9 kcal/mol lower when compared with that using the model catalyst **0_Na**, consistent with the experimental observation of rate enhancement.[15]

In conclusion, we have developed a highly efficient (TON up to 80000, TOF up to 10000 h^{-1}) tetradentate ruthenium complex for ester reduction. In particular, the hydrogenations of fatty acid esters to fatty alcohols showed excellent results, which hold potential to replace the heterogeneous hydrogenation process. Deep insight into the bifunctional mechanism helped to develop the highly efficient catalyst, and DFT studies explained a possible reason for the high efficiency of catalyst **III**. This insight will help us develop more efficient catalysts for hydrogenation of esters to alcohols, a fundamental process in chemical transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The X-ray crystal data of **III** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 989213. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44 (1223)336033 or E-mail: deposit@ccdc.cam.ac.uk].

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