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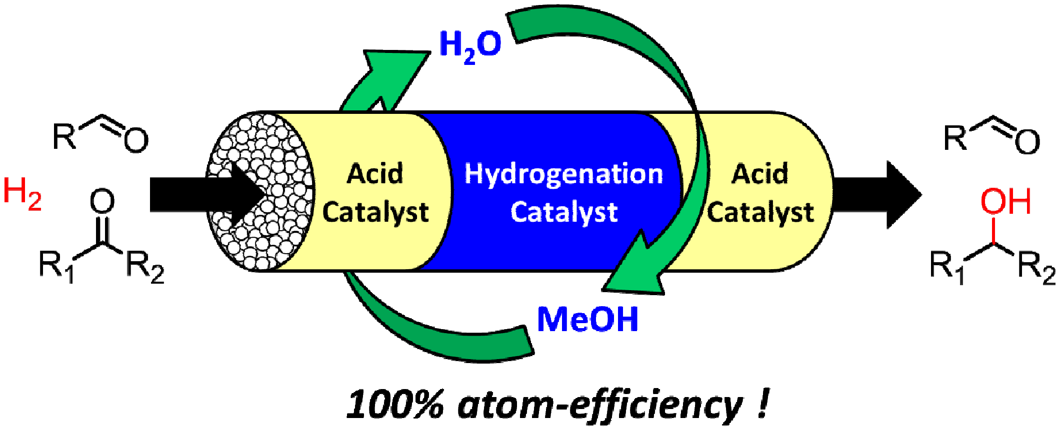

The first demonstration of 100%-atom efficient ketone selective hydrogenation was achieved using heterogeneous catalyst.

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ARTICLE TYPE

Highly Atom-Efficient and Chemoselective Reduction of Ketones in the Presence of Aldehydes Using Heterogeneous Catalysts

Yusuke Takahashi,[a] Takato Mitsudome,[a] Tomoo Mizugaki,[a] Koichiro Jitsukawa[a] and Kiyotomi Kaneda*[a,b]

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The first demonstration of a 100% atom-efficient selective reduction of less reactive ketones over aldehydes using heterogeneous catalysts is reported. Extremely high selectivities for intra- and intermolecular reductions of ketones over aldehydes were achieved. This system was also applicable to a column reactor, leading to a gram-scale synthesis.

Selective reduction of a targeted functional group in the presence of other reducible functionalities is of great interest in organic synthesis.[1] In this context, chemoselective reduction of a ketone group in the presence of an aldehyde is an important methodology to synthesize valuable intermediates for drugs and natural products.[2] However, the selective reduction of ketones over aldehydes is highly challenging because ketones are generally less reactive than aldehydes. Luche developed the pioneering and strong method for the selective reduction of ketones over aldehydes using the $CeCl_3$-EtOH-$NaBH_4$ system (Luche reduction), which included acetalization of aldehydes followed by reduction of ketones and then deprotection of the acetals.[3] To date, several similar approaches have been proposed.[4-9] However, these methods have the fatal problem of low atom efficiency due to the necessity of stoichiometric protecting reagents, metal hydrides, and toxic acids for the deprotection, producing large amounts of waste (Figure 1a). More recently, Tsuji and co-workers reported a well-designed copper catalyst with a bowl-shaped phosphine ligand, which showed excellent selectivity toward ketones over aldehydes in the reduction.[10] Although this system avoids the protection and deprotection steps for the aldehyde groups, a hydrosilane is inevitably required as a reducing reagent, resulting in low atom-efficiency. This protocol also suffers from the lack of generality due to the requirement of a complicated preparation method for the special ligand and the strictly controlled conditions (-40 °C). These above reported methods, furthermore, involve homogeneous catalysts that are difficult to recover and reuse. Therefore, the highly atom-efficient reduction of ketones in the presence of aldehydes using heterogeneous catalysts is still the subject of considerable interest.

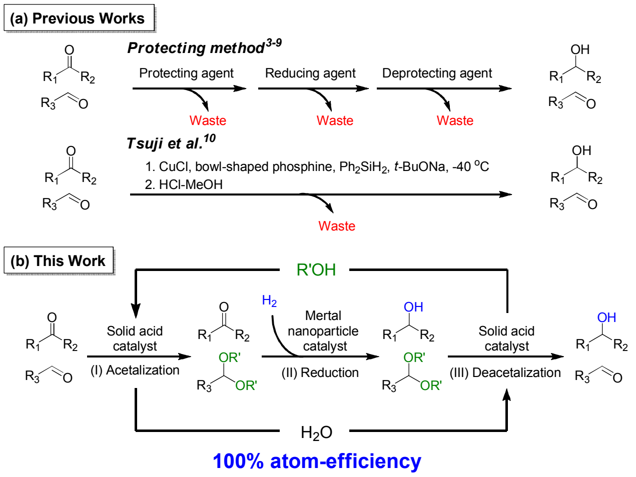

Fig. 1 Strategy for the waste-free ketone-selective hydrogenation using heterogeneous catalysts

Herein, we report the first demonstration of a 100% atom-efficient selective reduction of ketones in the presence of aldehydes using reusable heterogeneous catalysts (Figure 1b). This catalytic method is simple, and achieves extremely high ketone selectivities over aldehydes in one-pot reaction sequences through (I) acetalization, (II) hydrogenation using H_2 and (III) deacetalization. The alcohols and water used are regenerated and H_2 is available as a waste-free reducing agent, providing 100% atom-efficiency for the ketone-selective hydrogenation. Furthermore, the present waste-free heterogeneous catalyst system was applicable to a flow column reactor, leading to the success of a gram-scale synthesis.

To demonstrate the highly atom-efficient selective reduction of 2-octanone (**2**) over *n*-octanal (**1**) as a model reaction, the acetalization step of **1** was initially investigated in the presence of **2** using Ti^{4+} cation-exchanged montmorillonite (Ti-mont) (Scheme 1). This is because that Ti-mont was found to act as an efficient solid acid catalyst for acetalization.[11] As expected, the acetalization of **1** proceeded efficiently in the presence of **2** in MeOH solvent at 30 °C under Ar atmosphere to afford the

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† Electronic Supplementary Information (ESI) available: Experimental details, EXAFS analysis and TEM images. See DOI: 10.1039/b000000x/

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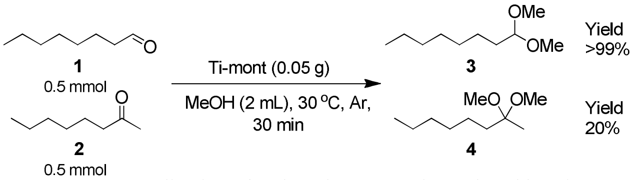
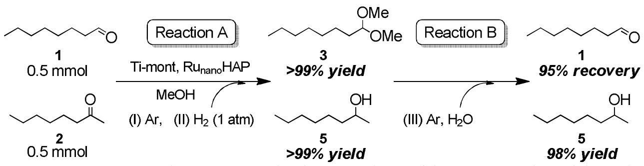


Scheme 1 Acetalization of carbonyl compounds catalyzed by Ti-mont

corresponding octanal dimethyl acetal (**3**) in >99% yield accompanied by 20% yield of 2-octanone dimethyl ketal (**4**).[12]

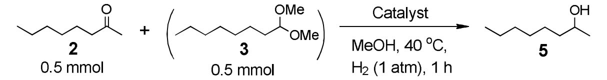
Next, the hydrogenation of **2** in the presence of **3** was studied using various supported metal nanoparticle catalysts under 1 atm of H_2 at 40 °C (Table 1). Interestingly, hydroxyapatite (HAP)-supported Ru nanoparticle catalyst (Ru_{nano}HAP) showed excellent activity for the selective hydrogenation of **2**.[13] The corresponding 2-octanol (**5**) was quantitatively obtained while **3** was intact and fully recovered after the reaction (entry 1). Among the organic and inorganic supports for Ru nanoparticles tested, HAP was the best (entries 1-5). HAP-supported on other transition metal nanoparticles showed less catalytic activity than Ru_{nano}HAP (entries 6-9 vs. 1). The use of Rh and Cu nanoparticles resulted in lower yields of **5**. Pt and Pd nanoparticles gave **5** in moderate yields, but hydrogenolysis of **3** to methyl octyl ether occurred simultaneously.[14] These results revealed that the combination of Ru nanoparticles with HAP support is effective for the selective hydrogenation of **2** to **5** in the presence of **3** under mild reaction conditions.

Based on these results, we attempted the combination of these two heterogeneous catalyst systems in a one-pot hydrogenation of **2** in the presence of **1**. Namely, the one-pot chemoselective transformation of **2** to **5** through the acetalization of **1** followed by the hydrogenation of **2** was investigated, employing both Ti-mont and Ru_{nano}HAP (Scheme 2). Notably, Ti-mont and Ru_{nano}HAP worked independently without any mutual deactivation to afford the desired product **5** in excellent yield together with the quantitative recovery of **3** (Scheme 2 Reaction A). As shown in Scheme 1, ketal **4** was also formed in the acetalization step by the use of Ti-mont alone. In contrast, **4** was not detected at all in the one-pot sequence. This is because the hydrogenation of **2** to **5** shifts the equilibrium between **2** and **4** to the production of **2**. Consequently, **2** was converted quantitatively to afford **5**. After the selective hydrogenation of **2**, the addition of water to the reaction mixture including Ti-mont and Ru_{nano}HAP followed by heating at 80 °C promoted the smooth deacetalization of **3** to recover **1** without any loss (Scheme 2 Reaction B). The deprotection is due to the presence of the solid acid catalyst of Ti-mont.[15] Namely, Ti-mont was found to act as an efficient dual catalyst for both the acetalization and deacetalization steps in the one-pot reaction. The combination catalyst of Ti-mont with Ru_{nano}HAP enabled the successful promotion of the successive acetalization-hydrogenation-deacetalization sequence, leading to the 100% atom-efficient selective reduction of **2** to **5** with quantitative recovery of **1**.



Scheme 2 Successive one-pot hydrogenation of ketone catalyzed by Ti-mont and Ru_{nano}HAP. Reaction conditions: (I) Ti-mont (0.05 g), Ru_{nano}HAP (0.05 g), MeOH (2 mL), 30 °C, 0.5 h. (II) 40 °C, 1 h. (III) H_2O (4 mL), 80 °C, 0.5 h.

Table 1 Hydrogenation of **2** in the presence of **3** using various supported metal nanoparticle catalysts[a]



Entry	Catalyst	Conv.[b] (%) **2**	Conv.[b] (%) **3**	Yied of **5**[b] (%)	Recovery of **3**[b] (%)
1	Ru_{nano}HAP	>99	0	>99	>99
2	Ru_{nano}/SiO_2	59	0	59	>99
3	Ru_{nano}/Al_2O_3	38	0	38	>99
4	Ru_{nano}/TiO_2	36	0	36	>99
5	Ru_{nano}/C	27	0	27	>99
6	Pt_{nano}HAP	82	48	82	52[c]
7	Pd_{nano}HAP	36	56	36	44[c]
8	Rh_{nano}HAP	26	0	26	>99
9	Cu_{nano}HAP	16	0	16	>99

[a] Reaction conditions: catalyst (metal: 10 mol%), MeOH (2 mL). [b] Determined by GC using an internal standard technique. [c] **3** was hydrogenolyzed to methyl octyl ether.

The present Ti-mont-Ru_{nano}HAP catalyst system could be extended to various pairs of ketones and aldehydes in the one-pot selective hydrogenation of ketones (Table 2). Aliphatic and alicyclic ketones such as 2-octanone, 4-octanone and cyclopentanone were selectively hydrogenated to the corresponding alcohols in excellent yields together with quantitative recoveries of the original aldehydes (entries 1-4). Selective hydrogenation of cyclohexanone over *n*-octanal was also achieved when using 1,3-propanediol in place of MeOH (entry 5).[16] An aromatic ketone was also selectively hydrogenated to the corresponding alcohol by the addition of DMSO without hydrogenation of the aromatic ring or hydrogenolysis of the benzyl hydroxyl group (entry 6).[17] Furthermore, the present catalyst system could be employed for the intramolecular selective hydrogenation of ketones over aldehydes. Various ketoaldehydes were efficiently hydrogenated to give the corresponding hydroxyl aldehydes (entries 7-9). Interestingly, the hydrogenation of a diketone to the corresponding hydroxycyclohexanone was also performed, and the less-reactive ketone moiety could be preferentially hydrogenated (entry 10).

A further advantage of the present heterogeneous catalyst system is the applicability to a continuous flow reactor. A flow reactor in which the first and third columns were filled with Ti-mont and the second column with Ru_{nano}HAP was designed as shown in Scheme 3. When 8-oxononanal (100 mmol, 15.6 g) in MeOH (0.20 M) was introduced to the reactor, it flowed continuously through the three columns and was transformed into the desired 8-hydroxynonanal in 94% isolated yield (14.7 g) via the acetalization-hydrogenation-deacetalization sequence.

Furthermore, after the flow reaction, no Ru and Ti ions were detected in the reaction mixture by ICP analysis, and the resulting mixture of water and MeOH is easily recovered and separated.[18] This demonstrates the success in simplifying the purification process of the desired products with high efficiency. The combination use of heterogeneous catalysts provides a powerful method to replace the low atom-efficient chemical synthesis with

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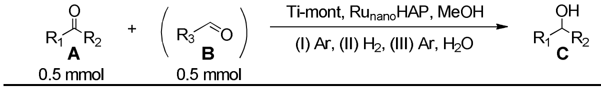
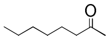
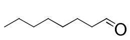
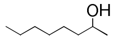
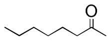
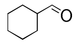
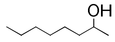
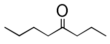
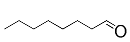
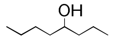
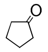
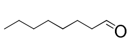
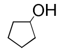
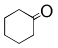
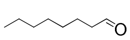
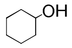
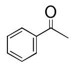
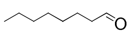
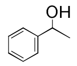
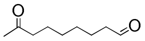
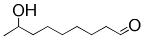
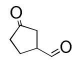
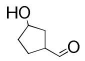
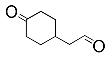
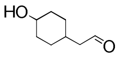
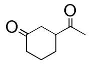
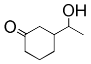
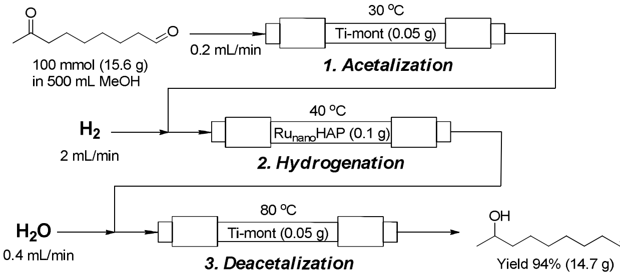
Table 2 Selective hydrogenation of ketones over aldehydes[a]



Entry	Substrate A	Substrate B	Product C	Time (h)	Yield of C^b (%)	Recoverry of B^b (%)
1				3	98	95
2				2	98	95
3				3	99	95
4				3	99	95
5[c]				6	97	95
6[d]				12	94	95
7				6	95	
8				6	94	
9[c]				12	93	
10[e]				12	90	

[a] Reaction conditions: Ti-mont (0.05 g), Ru$_{nano}$HAP (0.05 g, Ru: 10 mol%), MeOH (2 mL), (I) 30 °C, Ar, 0.5 h; (II) 40 °C, H_2 (1 atm); (III) H_2O (4 mL), 80 °C, Ar, 1 h. [b] Determined by GC using an internal standard technique. [c] 1,4-Dioxane (2 mL) and 1,3-propanediol (2 mmol) were used in place of MeOH. [d] Ru$_{nano}$HAP (0.1 g, Ru: 20 mol%), MeOH (2 mL), DMSO (100 mol%), 60 °C. [e] 1,4-Dioxane (2 mL) and ethyleneglycol (2 mmol) were used in place of MeOH.



Scheme 3 Continuous flow reactor system consisting of Ti-mont and Ru$_{nano}$HAP for ketone-selective hydrogenation

a high atom-efficient one, leading to greener industrial production of fine chemicals.

In conclusion, we developed a 100% atom-efficient heterogeneous catalyst system for the one-pot selective hydrogenation of less reactive ketones over aldehydes. This catalyst system has great advantages such as (i) high selectivity for various ketones over aldehydes in inter-and intramolecular hydrogenations, (ii) reusable catalysts and reagents, (iii) simple and easy reaction method, and (iv) the applicability to flow reactors.

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13 The preparation and characterization of Ru$_{nano}$HAP are described in the Supporting Information.

14 It is well known that acetals are decomposed to ethers in H_2 atmosphere with Pt or Pd catalysts: (*a*) M. Verzele, M. Acke and M. Anteun, *J. Chem. Soc.*, 1963, 5598; (*b*) V. Bethmont, F. Fache and M. Lemaire, *Tetrahedron Lett.*, 1995, **36**, 4235; (*c*) Y. Fujii, H. Furugaki, E. Tamura, S. Yano and K. Kita, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 456.

15 T. Kawabata, M. Kato, T. Mizugaki, K. Ebitani and K. Kaneda, *Chem. Lett.*, 2003, **32**, 648; see also ref. 11(*a*) and 11(*b*).

16 When using MeOH solvent in entries 5 and 9, not only aldehydes but also ketone moieties of cyclohexanones were protected, causing no occurrence of the hydrogenation of cyclohexanones to cyclohexanols. On the other hand, when choosing 1,3-propanediol in place of MeOH, 1,3-propanediol could act as an efficient aldehyde-selective protecting agent to promote the selective hydrogenation of cyclohexanones to cyclohexanols in the presence of aldehyde groups.

17 We found that the addition of DMSO to the reaction mixture could suppress the hydrogenation of the aromatic ring or hydrogenolysis of the benzyl hydroxyl group. Similar effects of DMSO for the semihydrogenation of alkynes have also been reported, see: (*a*) Y. Takahashi, N. Hashimoto, T. Hara, S. Shimazu, T. Mitsudome, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Chem. Lett.*, 2011, **40**, 405; (*b*) T. Mitsudome, Y. Takahashi, S. Ichikawa, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Angew. Chem. Int. Ed.*, 2013, **52**, 1481.

18 MeOH and water can be efficiently separated by rectification or membrane separation: D. W. Green and R. H. Perry, *Perry's*

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