ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 6656

Received 11th April 2014,
Accepted 1st May 2014

DOI: 10.1039/c4cc02675f

www.rsc.org/chemcomm

Catalytic hydrogenation of amino acids to amino alcohols with complete retention of configuration†

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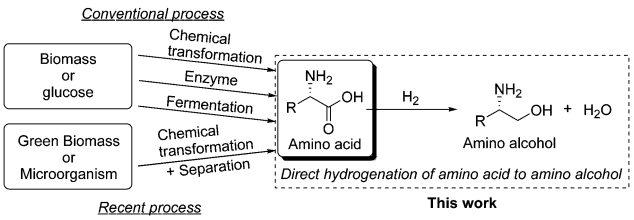
Rh-MoO_x/SiO_2 is an effective heterogeneous catalyst for selective hydrogenation of amino acids to amino alcohols in a water solvent. MoO_x modification of Rh drastically enhanced the activity and improved the selectivity and ee. Various amino alcohols were obtained in high yields (90–94%) with complete retention of configuration.

Amino acids are important organic compounds because they are intermediates in metabolism as well as essential building blocks of proteins, and furthermore, they are also used as versatile chemicals such as animal feed additives, catalysts, flavour enhancers and intermediates for medicines. Amino acids can be readily prepared by fermentation, enzymatic transformation, chemical transformation and extraction.[1] Particularly, in fermentation, amino acids are produced in high volume from glucose that is one of the important platform chemicals for biorefinery. In addition, recently, amino acid synthesis from green biomass (grass or leaf)[2] or microorganisms (microalgae or cyanobacteria)[3] has attracted much attention because these materials are potential renewable biomass resources (Scheme 1). Therefore, amino acids can be regarded as important key chemicals for biorefinery, and the development of transformation methods of amino acids will become more and more significant.[4]

Aminoalcohols are important components included in many synthetic and natural products, and are especially used as intermediates for synthesis of pharmaceuticals, insecticidal reagents and chiral auxiliaries.[5] In addition, amino alcohols can be easily converted with CO_2 to cyclic carbamates including oxazolidinones,[6] which have many applications like chiral auxiliaries, solvents and pharmaceutical agents.[6] Therefore, development of efficient synthetic methods for chiral aminoalcohols is an intriguing target for chemists. Conventionally, amino alcohols have been synthesized by hydrogenation of amino acids with metal hydrides[7] or reaction of epoxides with amines.[8] However, these methodologies suffer from production of a large amount of salts, use of expensive reagents and/or use of large excessive reagents. To overcome these problems, improved methods[9] and new methodologies such as aminohydroxylation of terminal C=C bonds,[10] hydrogenation of amino acids or esters by H_2,[11] hydroxymethylation of imines[12] and addition of acyloxymethyl to imine and hydrolysis[13] have been intensively developed. Among these methodologies, direct hydrogenation of amino acids[11a–e] by hydrogen is the most ideal from the viewpoint of green chemistry because the by-product is only water (Scheme 1) and amino acid is a potential feedstock as mentioned above. Ru/C[11a–d] and Ru–Re[11e] were reported to be effective catalysts, however catalysis of Ru/C has serious drawbacks such as high temperature, low activity and loss of optical purity, and that of Ru–Re has drawbacks such as high pressure, low yield and low activity (Table S1, ESI†). In particular, maintaining the optical purity of the substrate is important because aminoalcohol forms a main structure of medicines and chiral auxiliaries. Therefore, the effective catalysts that can realize both high activity and complete chirality retainment under mild reaction conditions ($T < 363$ K, $H_2 < 10$ MPa) in hydrogenation of amino acids are desired to be developed.

Up to now, our group[14] and other groups[15] have reported that the reducible metal oxide ($M'O_x$: ReO_x, WO_x, MoO_x) modified noble metal (M) catalyst (M-$M'O_x$ catalyst) is effective for the selective hydrogenolysis of polyols or cyclic ethers and selective hydrogenation of carboxylic acids, amides or α,β-unsaturated aldehydes. Expanding the potential of the M-$M'O_x$ catalyst will provide a new synthetic method and a new direction in the design of heterogeneous catalysts.



Scheme 1 Process for preparation of amino alcohols *via* amino acids from biomass resources.

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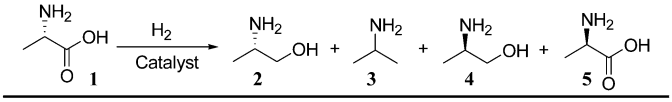
† Electronic supplementary information (ESI) available: Experimental details including catalyst preparation and test and HPLC data. See DOI: 10.1039/c4cc02675f

In this communication, we report that Rh-MoO_x/SiO_2 acts as a highly efficient heterogeneous catalyst for direct hydrogenation of amino acids to amino alcohols with complete retention of substrate configuration in a water solvent at low temperatures (313–323 K).

Initially, catalyst screening in the hydrogenation of L-alanine (**1**) to L-alaninol (**2**) at 353 K and 8 MPa H_2 with H_3PO_4aq as a model reaction was carried out using various carbon supported M-M′O_x catalysts (M-M′O_x/C: M = Rh, Ru, Pd and Pt, M′O_x = MoO_x, WO_x and ReO_x) and SiO_2 supported Rh-M′O_x catalysts (Rh-M′O_x/SiO_2) (Table 1). The loading amount of noble metals was 5 wt% for M/C and M-M′O_x/C, and 4 wt% for Rh-M′O_x/SiO_2. The molar ratio of M′ to M was 1/8. Among the M/C catalysts, Ru/C showed higher activity than the other M/C catalysts, followed by Rh/C (entries 1, 9, 13 and 17). As for carbon supported M-M′O_x catalysts, addition of M′O_x to Rh/C and Pt/C drastically changed the catalytic performance, leading to high yield and/or high selectivity (entries 1–4 and 17–20), although the changes of yield and selectivity were hardly observed in the other carbon supported M-M′O_x catalysts (entries 9–16). Particularly, MoO_x and WO_x modified Rh/C catalysts showed excellent catalytic performance. Then, Rh-M′O_x/SiO_2 catalysts were examined in the same reaction (entries 5–8). Compared with Rh-M′O_x/C catalysts, Rh-M′O_x/SiO_2 catalysts showed higher activities, and Rh-MoO_x/SiO_2 provided the highest yield and selectivity among Rh-M′O_x/SiO_2 catalysts. It should be noted that the activity and selectivity of Rh-MoO_x/SiO_2 (entry 6) are much higher than those of Rh/SiO_2 (entry 5) and MoO_x/SiO_2 (entry 21). These results indicate that the high activity and high selectivity are generated by the synergy between Rh and MoO_x. In terms of activity and selectivity, Rh-MoO_x/SiO_2 is regarded as the best catalyst for the reaction.

Table 1 Hydrogenation of **1** over various catalysts



Entry	Catalyst	Conv./%	Yield (**2**)/%	Select./% **2**	**3**	**4**	**5**
1	Rh/C	2.0	1.8	87.6	12.4	0.0	0.0
2	Rh-MoO_x/C	23.8	21.8	91.5	8.5	0.0	0.0
3	Rh-WO_x/C	29.6	26.1	88.2	11.8	0.0	0.0
4	Rh-ReO_x/C	16.1	13.4	83.2	16.8	0.0	0.0
5	Rh/SiO_2	3.7	3.1	84.4	15.6	0.0	0.0
6	Rh-MoO_x/SiO_2	46.8	42.2	90.2	11.0	0.0	0.0
7	Rh-WO_x/SiO_2	41.7	36.2	86.9	13.1	0.0	0.0
8	Rh-ReO_x/SiO_2	25.3	21.4	84.5	15.5	0.0	0.0
9	Ru/C	7.5	7.0	94.2	5.8	0.0	0.0
10	Ru-MoO_x/C	6.9	6.2	90.1	9.9	0.0	0.0
11	Ru-WO_x/C	7.4	6.7	90.8	9.2	0.0	0.0
12	Ru-ReO_x/C	9.1	8.0	87.5	12.5	0.0	0.0
13	Pd/C	0.0	0.0	—	—	—	—
14	Pd-MoO_x/C	0.0	0.0	—	—	—	—
15	Pd-WO_x/C	0.0	0.0	—	—	—	—
16	Pd-ReO_x/C	1.3	1.2	95.2	4.8	0.0	0.0
17	Pt/C	0.3	0.3	0.3	0.0	0.0	0.0
18	Pt-MoO_x/C	11.4	9.4	82.5	17.5	0.0	0.0
19	Pt-WO_x/C	15.4	13.8	89.4	10.6	0.0	0.0
20	Pt-ReO_x/C	3.8	3.2	83.9	16.1	0.0	0.0
21	MoO_x/SiO_2	0.0	0.0	—	—	—	—

Reaction conditions: catalyst (M′/M = 1/8) 50 mg, L-alanine 0.4 g, H_3PO_4aq (0.29 M) 20 g, H_2 8 MPa, 353 K, 4 h.

In order to determine the optimized amount of MoO_x in Rh-MoO_x/SiO_2 catalysts, the effect of MoO_x amount was studied by changing the molar ratio of MoO_x to Rh from 0 to 1 (Table S2, ESI†). The activity showed volcano-type tendency and the highest activity was obtained with a Mo/Rh molar ratio of 1/8. On the other hand, the selectivity is gradually increased with increasing Mo/Rh molar ratio. From the viewpoints of selectivity and activity, Rh-MoO_x/SiO_2 with a Mo/Rh molar ratio of 1/8 is an optimal catalyst for the reaction.

The effect of added acids was examined using mineral acids like H_2SO_4 and H_3PO_4, and solid acids like ZSM-5 and SiO_2-Al_2O_3 (Table S3, ESI†). Without any acids, the yield was very low (4.1%), while the selectivity was high. The same result was obtained using solid acids, which indicates that solid acids did not act as an acid. On the other hand, mineral acids such as H_2SO_4 and H_3PO_4 promoted the reaction to afford **2** in more than five times higher yields than solid acids and no additive. H_2SO_4 provided a twice higher yield than H_3PO_4, indicating that H_2SO_4 is the most suitable in this reaction system.

The reusability of Rh-MoO_x/SiO_2 was examined (Fig. S1, ESI†). The catalyst can be easily retrieved from the reaction mixture by centrifugation. The recovered catalyst was washed by water and used for the reusability test. The catalyst can be reused at least two times without loss of activity and selectivity.

The time-course in the hydrogenation of **1** over Rh-MoO_x/SiO_2 is shown in Fig. 1. The reaction proceeds smoothly to reach full conversion of **1**. The selectivity of **2** hardly changed during the course of the reaction and even after the full conversion of **1**, which suggests that no over-reaction of **2** takes place. In addition, no racemization of **1** and **2** was observed, resulting in high enantio excess (ee) of **2** (>99.9%). On the other hand, isopropylamine (**3**) was produced at the initial stage, and the selectivity was unchanged during the reaction, suggesting that **3** was produced simultaneously with **2**. Therefore, the Rh-MoO_x/SiO_2 catalyst is quite suitable for selective synthesis of amino alcohol without loss of optical purity of the starting material.

The performance of Rh-MoO_x/SiO_2 was compared with that of Rh/SiO_2 (Scheme 2). The selectivity and ee of Rh-MoO_x/SiO_2 were

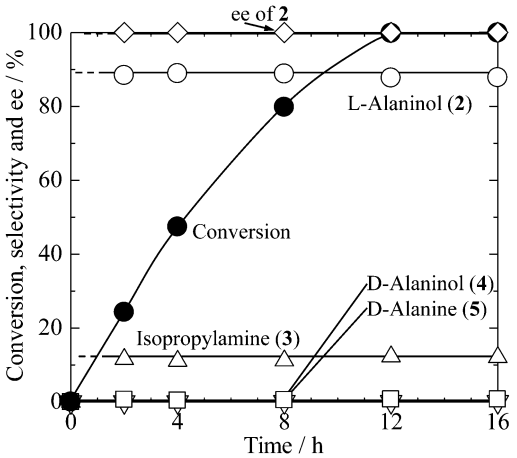
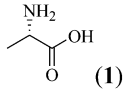
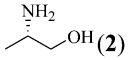
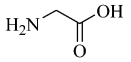
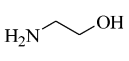
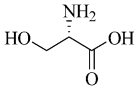
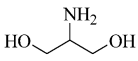
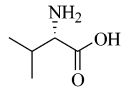
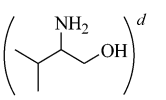
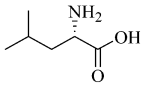
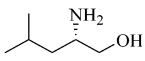
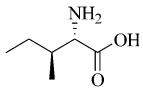
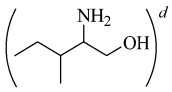
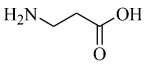
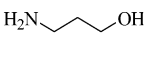
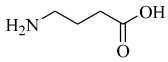
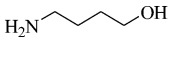


Fig. 1 Time-course of hydrogenation of L-alanine over Rh-MoO_x/SiO_2. Reaction conditions: Rh-MoO_x/SiO_2 (Mo/Rh = 1/8) 100 mg, L-alanine 2 g, H_2SO_4 22 mmol, H_2O 19.3 g, H_2 8 MPa, 353 K.

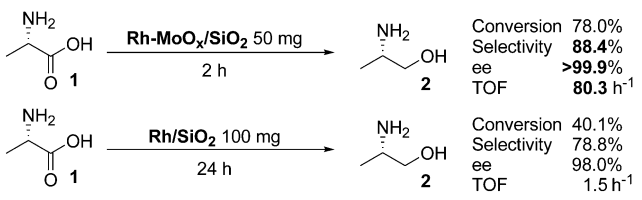
Table 2 Hydrogenation of various amino acids over Rh-MoO_x/SiO_2

Entry	Substrate	Product	Conv./%	Yield/%	ee/%
1	 (1)	 (2)	>99.9	92.8	>99.9
2[a]			99.1	93.7	>99.9
3			>99.9	92.3	—
4[b]			>99.9	92.8	—
5[c]		 [d]	>99.9	92.5	n.d.[d]
6[c]			>99.9	90.5	>99.9
7[c]		 [d]	>99.9	90.6	n.d.[d]
8[c]			99.8	90.0	—
9[c]			>99.9	91.1	—

Reaction conditions: Rh-MoO_x/SiO_2 (Mo/Rh = 1/8) 100 mg ([b]200 mg [c]500 mg), amino acid (4.5 mmol), H_2SO_4 5 mmol, H_2O 20.0 g, H_2 8 MPa 323 K ([a]313 K). [d] The configuration was not determined.

much higher than those of Rh/SiO_2. TOF was calculated using the following equation: TOF = L-alaninol (mmol)/total Rh (mmol)/time (h). Rh-MoO_x/SiO_2 provided fifty times higher TOF than Rh/SiO_2. These results indicate that MoO_x modification of Rh/SiO_2 brings about not only high TOF and high selectivity but also high ee.

The scope of amino acids was examined over Rh-MoO_x/SiO_2 at a lower reaction temperature of 323 K (Table 2). **1** reacted to afford **2** with a high yield of 92.8% and high selectivity and ee (entry 1). Moreover, at 313 K, **2** was obtained with a higher yield of 93.7% (entry 2). Other α-amino acids (entries 3–7) were also converted to the corresponding amino alcohols in high yields (90.5–92.8%) and ee. In addition, the reactions of β-amino acid and γ-amino acid provided the β-amino alcohol and γ-amino alcohol in high yields (entries 8 and 9). It should be noted that Rh-MoO_x/SiO_2 enables high yield synthesis of serinol (entry 4), which is an important intermediate for various useful chemicals such as medicines[16] and X-ray contrast agents.[17] Therefore, Rh-MoO_x/SiO_2 can be applied to various amino acids without loss of the optical purity and is very useful from the practical viewpoint.



Scheme 2 Comparison of performance between Rh-MoO_x/SiO_2 and Rh/SiO_2. Reaction conditions: catalyst (Mo/Rh = 1/8), L-alanine 0.4 g, H_2SO_4 5 mmol, H_2O 20.0 g, H_2 8 MPa, 353 K. TOF = L-alaninol (mmol)/total Rh (mmol)/time (h).

In conclusion, Rh-MoO_x/SiO_2 acts as an efficient heterogeneous catalyst for hydrogenation of amino acids to amino alcohols in water. The synergy between MoO_x and Rh drastically improved the activity, selectivity and ee of the produced amino alcohols. This catalyst can be applied to versatile amino acids to afford the corresponding amino alcohols in high yields (90–94%) without loss of the optical purity of the amino acids.

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