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Gold nanoparticles on OMS-2 for heterogeneously catalyzed aerobic oxidative α,β-dehydrogenation of β-heteroatom-substituted ketones†

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Daichi Yoshii,[a] Xiongjie Jin,[a] Takafumi Yatabe,[a] Jun-ya Hasegawa,[b] Kazuya Yamaguchi*[a] and Noritaka Mizuno*[a]

In the presence of Au nanoparticles supported on manganese oxide OMS-2 (Au/OMS-2), various kinds of β-heteroatom-substituted α,β-unsaturated ketones (heteroatom = N, O, S) can be synthesized through α,β-dehydrogenation of the corresponding saturated ketones using O_2 (in air) as the oxidant. The catalysis of Au/OMS-2 is truly heterogeneous, and the catalyst can be reused.

A C=C double bond formation by selective dehydrogenation of ubiquitous C–C saturated bond is very important transformation in both bulk and fine chemicals productions.[1] In industrial alkene productions, the dehydrogenation has frequently been performed using heterogeneous catalysts, such as supported metals and metal oxides.[2] For laboratory scale fine chemicals synthesis, homogeneous complexes, *e.g.*, Ir PCP-pincer-type complexes, have been utilized for dehydrogenation.[3] However, most of the previously developed catalytic systems have several shortcomings; limited substrate scopes, harsh reaction conditions, and/or needs for stoichiometric hydrogen acceptors, *e.g.*, *tert*-butylethylene (TBE). Therefore, the development of efficient catalytic oxidative dehydrogenation using molecular oxygen (O_2) as the hydrogen acceptor (oxidant) has attracted much attention.[4]

β-Heteroatom-substituted α,β-unsaturated ketones (heteroatom = N, O, S) are very important compounds especially for fine chemicals and pharmaceuticals productions. For example, enaminones (β-*N*-substituted ketones) are versatile synthetic intermediates for various natural products.[5] Chromones, flavones, and thiochromones, a class of cyclic β-*O*- and β-*S*-substituted ketones, are key structural motifs in a variety of biologically active compounds, and widely utilized as pharmaceutical ingredients.[6] β-Heteroatom-substituted α,β-unsaturated ketones have frequently been synthesized *via* the reaction of amines, alcohols, or thiols with β-diketones or propargyl ketones.[5,6] Meanwhile, selective α,β-dehydrogenation of β-substituted ketones provides one of the most straightforward methods, considering the easy accessibility of the various starting materials by the Mannich reaction or hetero-Michael addition.[7] α,β-Dehydrogenation of saturated ketones[8] has typically been carried out by using stoichiometric oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[9] *o*-iodoxybenzoic acid (IBX),[10] and Pd(II) salts[7,11] (Scheme S1, a, ESI†). Recently, several efficient homogeneous Pd[12]- or Ir[13]-based catalytic systems have been developed using O_2 or alkenes as the hydrogen acceptor, or under acceptorless conditions (Scheme S1, a, ESI†). Considering the easy recovery and reuse of heterogeneous catalysts compared to their homogeneous counterparts, the development of efficient heterogeneous catalytic systems for the oxidative dehydrogenation using O_2 as the terminal oxidant is highly desirable. With regard to heterogeneous systems, supported Pd nanoparticles have been reported to show high catalytic performance for the dehydrogenation of cyclohexanone derivatives to the corresponding phenols.[14] However, as far as we know, heterogeneously catalyzed selective α,β-dehydrogenation of β-heteroatom-substituted ketones to the corresponding α,β-unsaturated ketones has never been reported so far.

Quite recently, we have developed heterogeneous supported Au nanoparticles-catalyzed one-pot synthesis of enaminals[15a] and flavones[15b] in which the respective α,β-dehydrogenation reactions of β-aminoaldehydes[15a] and flavanones[15b] were the key steps. With our continuing interest in the dehydrogenation catalysis of Au nanoparticles, herein we report for the first time that Au nanoparticles supported on manganese oxide octahedral molecular sieve OMS-2 (KMn_8O_{16})[16] (Au/OMS-2) could act as an efficient reusable heterogeneous catalyst for aerobic oxidative α,β-dehydrogenation of various kinds of structurally diverse β-heteroatom-substituted ketones to the corresponding α,β-unsaturated ketones (Scheme S1, b, ESI†). OMS-2 not only worked as the support to highly disperse Au nanoparticles, but

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[a] *Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.*
E-mail: kyama@appchem.t.u-tokyo.ac.jp, tmizuno@mail.ecc.u-tokyo.ac.jp;
Fax: +81-3-5841-7220
[b] *Institute for Catalysis, Hokkaido University, Kita 21 Nishi 10, Kita-ku, Sapporo 001-0021, Japan.*

† Electronic Supplementary Information (ESI) available: Experimental details, plausible explanation for the promotion effect of Br^-, spectral data of β-heteroatom-substituted α,β-unsaturated ketones, Tables S1–S4, Figs. S1–S7, Schemes S1–S2. See DOI: 10.1039/x0xx00000x

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also played a pivotal role as the electron transfer mediator between Au nanoparticles and O_2.

Initially, various supported metal catalysts were applied to the oxidative dehydrogenation of 1-methyl-4-piperidone (**1a**) to 2,3-dihydro-1-methyl-4(1*H*)-pyridinone (**2a**). The reactions were carried out in water at 50 °C under an air atmosphere (1 atm) for 4 h. Under the present reaction conditions, **2a** was not obtained at all in the absence of the catalysts or in the presence of just OMS-2 (Table S1, entries 10 and 11, ESI†). Au/OMS-2 and Pd/OMS-2 gave **2a** in 78% and 24% yields, respectively, whereas the reaction did not proceed at all in the presence of Ag/OMS-2, Cu/OMS-2, and Ru/OMS-2 (Table S1, entries 1–5, ESI†). When prolonging the reaction time to 8 h, the yield of **2a** reached up to 90% when using Au/OMS-2 (Table S1, entry 1, ESI†). Among various supported Au nanoparticles catalysts examined, such as Au/OMS-2, Au/Al_2O_3, Au/CeO_2, and Au/TiO_2, Au/OMS-2 showed the highest catalytic performance for the transformation (Table S1, entries 1 and 6–8, ESI†), indicating that OMS-2 is the best support. In addition, a physical mixture of Au/Al_2O_3 and OMS-2 gave almost the same **2a** yield as Au/Al_2O_3 alone (Table S1, entry 9 *vs*. entry 6, ESI†), which indicates that the OMS-2 support plays an important promoting role in the present reaction. Among various solvents examined, such as water, ethanol, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, acetonitrile, toluene, 1,4-dioxane, and tetrahydrofuran, water showed the best performance (Table S2, ESI†).

To verify whether the observed catalysis was truly heterogeneous or not, the following several experiments were performed. For the transformation of **1a**, Au/OMS-2 was removed from the reaction mixture by hot filtration during the reaction at approximately 45% yield of **2a**. After that, the reaction was performed using the filtrate. In this case, no further production of **2a** was observed (Fig. S1, ESI†). Moreover, we confirmed by the inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that Au and Mn species were hardly present in the filtrate (Au: 0.02%, Mn: 0.02%).[17] These results revealed that the catalysis did not derive from the leached metal species, and thus the observed catalysis was truly heterogeneous.

After the oxidative dehydrogenation of **1a** to **2a** was completed, Au/OMS-2 was easily retrieved from the reaction mixture by simple filtration (>95% recovery). The retrieved catalyst, which was washed with ethanol and acetone, and then calcined at 300 °C before being used for each reuse experiment, could be reused for the reaction of **1a** at least four times keeping its high catalytic performance; 90% yield of **2a** using the fresh Au/OMS-2 catalyst, and 91%, 91%, 90%, and 91% yields for the 1st, 2nd, 3rd, and 4th reuse experiments, respectively (Fig. S2, ESI†). On the other hand, the X-ray diffraction (XRD) analysis revealed that the OMS-2 support gradually changed to Mn_3O_4 as the reuse experiment was repeated (Fig. S3, ESI†).[17] This is likely due to the reduction of manganese species and the elimination of the tunnel K^+ species in the OMS-2 support.[17] In addition, the transmission electron microscopy (TEM) analysis exhibited that the average particle size of Au increased from 3.9 nm (fresh catalyst) to 4.8 nm after the use for the oxidative dehydrogenation of **1a** (Fig. S4, ESI†).

With the optimized reaction conditions in hand, we next examined the scope of the present Au/OMS-2-catalyzed oxidative dehydrogenation. As shown in Table 1, various kinds of structurally diverse β-heteroatom-substituted α,β-unsaturated ketones were successfully obtained starting from the corresponding saturated ketones. Various cyclic enaminones could be synthesized by the present Au/OMS-2-catalyzed oxidative dehydrogenation (Table 1, entries 1–3). In the case of the dehydrogenation of 1,3-dimethyl-4-piperidone (**1b**), which is possibly converted into two regioisomers, the isomer possessing a more substituted C=C double bond (**2b**) was preferentially generated (more substituted **2b**/less substituted **2b’** = 4:1) (Table 1, entry 2). Moreover, various electron-withdrawing or electron-donating groups-substituted chromone and flavone derivatives could effectively be produced by the present Au/OMS-2-catalyzed oxidative dehydrogenation (Table 1, entries 4–9).[18] It was revealed that the addition of a small amount of LiBr (1 mol%) to the reaction mixture significantly promoted the oxidative dehydrogenation of chromanone derivatives (Table S3; Fig. S5, ESI†).[19] Thiochroman-4-one (**1j**), a cyclic β-*S*-substituted ketone, could selectively be converted into thiochromen-4-one (**2j**) without oxygenation of the S groups (Table 1, entry 10). A linear β-*N*-substituted ketone was also effectively converted into the corresponding α,β-unsaturated ketone (Table 1, entry 11). The oxidative dehydrogenation of β-*N*-substituted ester and nitrile proceeded to some extent using Au/OMS-2, whereas the yields of the desired products were not satisfactory. For example, the reaction of ethyl 3-(dimethylamino)propionate (**1l**) gave the desired ethyl 3-(dimethylamino)acrylate (**2l**) in 41% yield with the undesirable occurrence of the *N*-methyl group oxygenation (Table 1, entry 12).[19] In the case of 3-(methylphenylamino)propanenitrile (**1m**), the demethylation mainly proceeded, and the yield of the desired 3-(methylphenylamino)-2-propenenitrile (**2m**) was only 13% (Table 1, entry 13). In contrast with the Pd-based catalysts,[12] the oxidative dehydrogenation of cyclohexanones hardly proceeded when using Au/OMS-2.

In order to investigate the reaction mechanism and the role of catalysts for the present oxidative α,β-dehydrogenation, the following several experiments were carried out using “Au/Al_2O_3”. The oxidative dehydrogenation of **1a** to **2a** using Au/Al_2O_3 hardly proceeded under an Ar atmosphere (1 atm) (Table S4, entry 3, ESI†). This result indicates that O_2 (in air) is the terminal oxidant for the Au/Al_2O_3-catalyzed oxidative dehydrogenation. The Au/Al_2O_3-catalyzed dehydrogenation of **1a** was significantly accelerated by the addition of a stoichiometric amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) with respect to **1a** even under an air atmosphere, and the yield of **2a** increased from 31% to 40% (Table S4, entry 1 *vs.* entry 2, ESI†). Therefore, TEMPO is the better oxidant than O_2 for the Au/Al_2O_3-catalyzed dehydrogenation. When the Au/Al_2O_3-catalyzed dehydrogenation was carried out using TEMPO as the oxidant under an Ar atmosphere, **2a** was obtained in 33% yield (Table S4, entry 4, ESI†). In this case,

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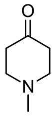
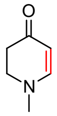
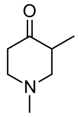
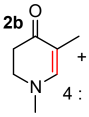
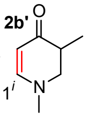
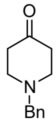
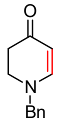
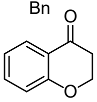
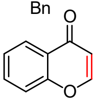
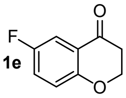
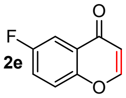
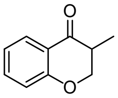
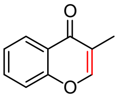
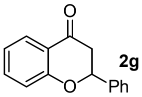
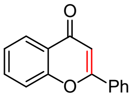
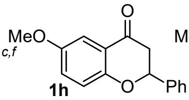
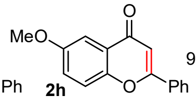
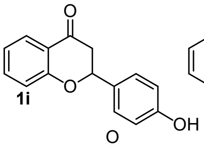
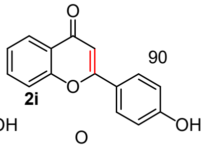
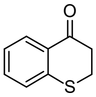
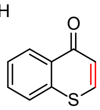
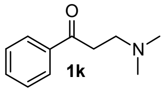
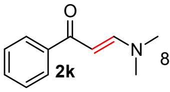
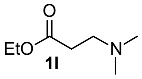
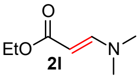
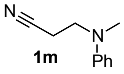
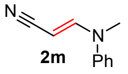
Table 1 Scope of the Au/OMS-2-catalyzed oxidative α,β-dehydrogenation[a]

Entry	Substrate	Product	Temp (°C)	Time (h)	Conv. (%)	Yield (%)
1	**1a** 	**2a** 	50	8	94	90
2	**1b** 	**2b**  + **2b'**  4 : 1[i]	50	16	86	86(78[i])
3	**1c** 	**2c** 	70	24	98	70[j](64)
4[b,c,d]	**1d** 	**2d** 	80	8	99	97
5[b,c,d]	**1e** 	**2e** 	90	20	99	93(72)
6[c,e]	**1f** 	**2f** 	90	24	>99	76
7[b,c,e]	**1g** 	**2g** 	90	24	99	95
8[b,c,f]	**1h** 	**2h** 	90	24	>99	90
9[b,c,e]	**1i** 	**2i** 	90	24	97	85(68)
10[b,c,e,h]	**1j** 	**2j** 	90	24	71	60(54)
11[b,c]	**1k** 	**2k** 	80	0.5	93	93
12[g,h]	**1l** 	**2l** 	90	24	82	41[k]
13[b,g]	**1m** 	**2m** 	110	12	74	13[l]

[a] Reaction conditions: **1** (0.5 mmol), Au/OMS-2 (Au: 3.6 mol%), H_2O (2 mL), air (1 atm). Conversions and yields were determined by GC analysis. The values in parentheses are the yields of isolated products. [b] O_2 (1 atm). [c] LiBr (1 mol%). [d] H_2O/1,4-dioxane (1.9 mL/0.1 mL). [e] H_2O/1,4-dioxane (1 mL/1 mL). [f] H_2O/*N*, *N*-dimethylacetamide (1 mL/1 mL). [g] *N*,*N*-dimethylacetamide. (2 mL) [h] Au/OMS-2 (Au: 7.2 mol%). [i] Isolated as a mixture of regioisomers. The isomer ratio was determined by ^1H NMR analysis. [j] Yield was determined by HPLC analysis. [k] Ethyl 3-(folmylmethylamino)propionate was formed in 36% yield. [l] 3-(Phenylamino)propanenitrile was formed in 19% yield.

1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPOH) was formed in 60% yield (based on TEMPO). This 1:2 **2a**/TEMPO stoichiometry indicates that TEMPO can work as a one-electron oxidant for the dehydrogenation. Moreover, the control experiment showed that TEMPO itself could not promote the reaction (Table S4, entry 8, ESI†). It has been reported that TEMPO can act as a one-electron oxidant to abstract a hydrogen atom from Au–H species and then TEMPO itself is converted into TEMPOH.[21] Therefore, Au–H species is likely formed during the present oxidative dehydrogenation and that the oxidation of the Au–H species to regenerate active Au species[22] is included in the catalytic cycle. The above-mentioned promotional effects of TEMPO suggest that the oxidation of the Au–H species by O_2 is likely rate-determining step for the Au/Al_2O_3-catalyzed dehydrogenation of **1a**.

Next, the oxidative dehydrogenation of **1a** was carried out in the presence of "Au/OMS-2". To our surprise, even under an Ar atmosphere, **2a** was still produced in 91% (Table S4, entry 7, ESI†). This result is in sharp contrast to the above-mentioned result using Au/Al_2O_3; **2a** was hardly obtained under an Ar atmosphere when using Au/Al_2O_3 (Table S4, entry 3, ESI†). It was confirmed by the XRD analysis that the OMS-2 support completely reduced to Mn_3O_4 after the reaction of **1a** under an Ar atmosphere (Fig. S6, c, ESI†). In contrast, the structure of OMS-2 remained almost unchanged when the same reaction was performed under an air atmosphere (Fig. S6, b, ESI†). These results suggest that OMS-2 can act as the oxidant to promote the oxidation of the Au–H species to regenerate active Au species[22] and that the reduced OMS-2 can be reoxidized by O_2 (in air).[16] However, it is likely that the reoxidaiton of OMS-2 by O_2 is somewhat slower than the oxidation of the Au–H species by OMS-2; hence, OMS-2 was gradually reduced to Mn_3O_4 in the above-mentioned repeated reuse experiments (Fig. S3, ESI†).[17] Furthermore, TEMPO did not accelerate the oxidative dehydrogenation of **1a** when using Au/OMS-2 as the catalyst (Table S4, entry 5 *vs.* entry 6, ESI†). One of the possible explanations for this is that OMS-2 is the better oxidant for the oxidation of the Au–H species than TEMPO. Based on the aforementioned results, we consider that OMS-2 can act as an electron-transfer mediator between Au nanoparticles and O_2. Consequently, Au/OMS-2 exhibited higher catalytic performance than other supported Au nanoparticles catalysts, such as Au/Al_2O_3, Au/TiO_2 and Au/CeO_2, and this is likely derived from the ability of the OMS-2 support to effectively oxidize the Au–H species.

Here, we propose a possible reaction mechanism for the Au/OMS-2-catalyzed oxidative α,β-dehydrogenation of β-heteroatom-substituted ketones (Scheme 1). Initially, supported Au nanoparticles oxidize the C–X (X = N, O, S) bond in a substrate to produce a cation (iminium, oxonium, or sulfonium) intermediate;[23] the β-hydrogen is eliminated as a hydride species possibly through the consecutive two electrons and one proton transfer, and Au–H species is formed (Scheme 1, step 1). As above-mentioned, the OMS-2 support oxidizes the Au–H species, and then O_2 reoxidizes the reduced OMS-2. The cation intermediate is converted into the desired α,β-unsaturated ketone *via* hydration followed by E1cB elimination (Scheme 1, step 2 and step 3), or *via* direct tautomerization (Scheme 1, step 2'). This reaction mechanism is

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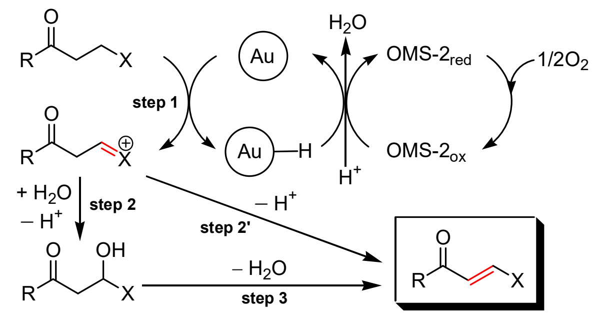

Scheme 1 Possible reaction mechanism for the Au/OMS-2-catalyzed oxidative α,β-dehydrogenation of β-heteroatom-substituted saturated ketones. X = NR'R', OR', SR'; R, R' = alkyl, aryl.

completely different from that for the homogeneous Pd-catalyzed oxidative dehydrogenation of saturated ketones; in the homogeneous Pd-catalyzed system, it has been postulated that the dehydrogenation proceeds *via* deprotonative coordination of a ketone substrate at the α-position to the Pd center followed by β-hydride elimination, and then the Pd–H species is reoxidized by O_2.[12] Thus, in the previously reported Pd-catalyzed systems, cyclohexanones are also oxidized well to the corresponding cyclohexenones or phenols.[12] The ineffectiveness of Au/OMS-2 for the oxidative dehydrogenation of cyclohexanones indicates the importance of β-heteroatom substituents, and supports the mechanistic difference between Pd- and Au-catalyzed dehydrogenation.

In conclusion, we have successfully developed for the first time an efficient system for the heterogeneously Au/OMS-2-catalyzed aerobic oxidative α,β-dehydrogenation of β-heteroatom-substituted ketones to produce various kinds of structurally diverse β-heteroatom-substituted α,β-unsaturated ketones. Owing to the practical and environmentally friendly conditions, we hope that this transformation will find wide application for the synthesis of various β-heteroatom-substituted α,β-unsaturated ketones and their related compounds.

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18 Under the reaction conditions described in Table 1, the oxidative dehydrogenation of aliphatic β-*O*-substituted ketones, such as tetrahydro-4*H*-pyran-4-one and 4-ethoxy-2-butanone, hardly proceeded.
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