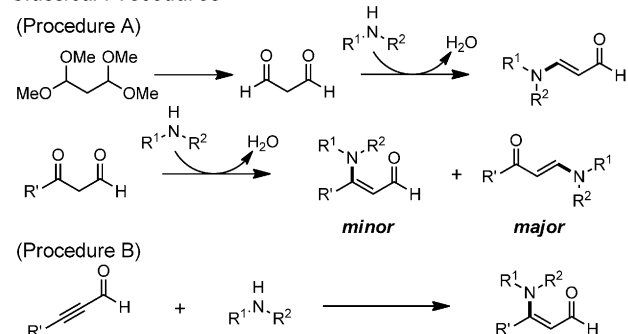**Heterogeneous Gold Catalysis**

Gold-Catalyzed Heterogeneous Aerobic Dehydrogenative Amination of α,β-Unsaturated Aldehydes to Enaminals**

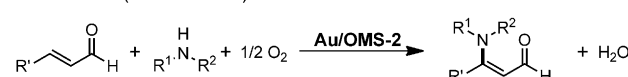*Xiongjie Jin, Kazuya Yamaguchi, and Noritaka Mizuno*

Abstract: *Although enaminals (β-enaminals) are very important compounds and have been utilized as useful synthons for various important compounds, they have been synthesized through non-green and/or limited procedures until now. Herein, we have successfully developed a green synthetic procedure using a heterogeneous catalyst. In the presence of gold nanoparticles supported on manganese-oxide-based octahedral molecular sieves OMS-2 (Au/OMS-2), dehydrogenative amination of α,β-unsaturated aldehydes with amines proceeded efficiently, with the corresponding enaminals isolated in moderate to high yields (50–97%). The catalysis was truly heterogeneous, and Au/OMS-2 could be reused. Furthermore, the formal Wacker-type oxidation of α,β-unsaturated aldehydes to enaminones has been realized.*

Scheme 1. Synthesis of enaminals.

Enaminals (β-enaminals) are important compounds that have been utilized for the synthesis of various heterocyclic compounds such as furans, pyrans, pyrroles, pyridines, pyrazoles, isothiazoles, and isoxazoles.[1,2] In addition, they are key synthons for several bioactive compounds, including noeuromycin, AKT (protein kinase B) inhibitor-IV, and AZD4877 (a kinesin spindle protein inhibitor and potential anticancer agent).[1,2] To date, several synthetic procedures for enaminals have been developed,[2,3] and the following two procedures have most commonly been utilized: 1) Dehydrative condensation of amines with malondialdehyde generated in situ by the hydrolysis of 1,1,3,3-tetramethoxypropane (Procedure A in Scheme 1). 2) Hydroamination of propargylic aldehydes (Procedure B in Scheme 1). Procedure A is limited to the synthesis of β-aminoacroleins; β-substituted enaminals cannot be synthesized by the dehydrative condensation of ketoaldehydes with amines, owing to the higher reactivity of aldehyde functional groups to the condensation, consequently giving enaminones as the major products.[3e] Although procedure B is efficient for the synthesis of a wide variety of enaminals, the development of alternative synthetic procedures for enaminals would be of great significance considering the limitation in availability (synthesis) of starting propargylic aldehydes. Direct dehydrogenative amination of

readily available α,β-unsaturated aldehydes would be a candidate for an efficient synthetic route to enaminals (Procedure C in Scheme 1).

Dehydrogenative amination or amidation of alkenes, namely aza-Wacker-type oxidation, is a valuable method for the construction of C(sp²)−N bonds.[4–6] To date, there have been several reports of palladium-catalyzed amidation, and less-basic amides, such as sulfonamides, carbamates, and lactams, have been utilized as amide nucleophiles in most cases.[4] In comparison with amidation, amination using simple amines as nucleophiles is a relatively less-developed reaction,[5,6] likely because of the severe deactivation of homogeneous metal-based catalysts by the strong coordination of amines. With regard to the amination of α,β-unsaturated carbonyl compounds, the groups of Ishii[5e,h] and Ying[5g] have recently reported excellent palladium-catalyzed procedures. However, α,β-unsaturated carbonyl compounds suitable for these systems are limited to α,β-unsaturated esters and ketones,[7] and the scope of amines is also limited to only aniline derivatives.[5e,g,h] Thus, the dehydrogenative amination of α,β-unsaturated aldehydes to enaminals has never been previously reported. To realize dehydrogenative amination to synthesize structurally diverse enaminals, the design of efficient catalysts is required. We focused on heterogeneous catalysts in particular because of their easy separation and reusability. More importantly, we envisaged that heterogeneous catalysts would possess higher durability against oxidative conditions, heating, and strong coordination of nitrogen nucleophiles in comparison with their homogeneous counterparts.

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Herein, we disclose for the first time a gold-catalyzed dehydrogenative amination of α,β-unsaturated aldehydes to enaminals using air (molecular oxygen) as the sole oxidant (Procedure C in Scheme 1). In the presence of gold nanoparticles on manganese-oxide-based octahedral molecular sieves OMS-2[8] (Au/OMS-2; average particle size of gold = 4.1 nm; see the Supporting Information, Figure S1), the amination of various combinations of α,β-unsaturated aldehydes and amines proceeded efficiently, with the corresponding enaminals isolated in moderate to high yields (50–97%). The catalysis in the present amination was truly heterogeneous, and the Au/OMS-2 catalyst could be reused several times. The procedure developed herein provides a highly efficient synthetic route to enaminals and reveals new oxidation catalysis of gold.[9,10]

Initially, the dehydrogenative amination of cinnamaldehyde (1a) with pyrrolidine (2a) to 3-phenyl-3-(1-pyrrolidinyl)-2-propenal (3aa) was carried out in the presence of various kinds of supported metal catalysts (such as gold, palladium, ruthenium, rhodium, and copper on various supports; given in the format: metal/support). The reaction was carried out at 50°C in air (1 atm). The amination barely proceeded in the absence of catalysts or in the presence of Pd/Al$_2$O$_3$, Cu/Al$_2$O$_3$, Ru/Al$_2$O$_3$, or Rh/Al$_2$O$_3$ (Table S1, entries 1–4 and 13).[7] In contrast, 44% yield (as determined by GC analysis) of the desired amination product 3aa was obtained when using Au/Al$_2$O$_3$ (Table S1, entry 5). Among the supports examined, OMS-2 was the best support; the yield of 3aa increased up to 83% (as determined by GC analysis) using Au/OMS-2 (Table S1, entry 8).[11] Amination with a physical mixture of Au/TiO$_2$ and OMS-2 gave almost the same yield of 3aa as with Au/TiO$_2$ (Table S1, entry 11), and OMS-2 alone could not promote the amination (Table S1, entry 12). Thus, highly dispersed gold nanoparticles on the surface of OMS-2 would play an important role on the present amination.[12]

To verify whether the observed catalysis was derived from solid Au/OMS-2 or leached metal species (gold and/or manganese), the Au/OMS-2 catalyst was removed by hot filtration, and the reaction was carried out with the filtrate under the same reaction conditions described in Table S1. The amination was completely stopped by removal of the catalyst (Figure S2). Furthermore, it was confirmed by inductively coupled plasma atomic emission spectroscopic (ICP-AES) analysis that gold and manganese species were hardly present in the filtrate (Au: < 0.002%, Mn: < 0.00001%). These results can rule out any contribution to the observed catalysis from metal species that had leached into the reaction solution, and the observed catalysis for the present amination is intrinsically heterogeneous.[13] After the amination of 1a with 2a, the Au/OMS-2 catalyst could be easily retrieved from the reaction mixture by simple filtration with > 97% recovery. The retrieved catalyst could be reused at least five times for the same reaction without a significant loss in its high catalytic performance. Even at the fifth reuse experiment, 76% yield (as determined by GC analysis) of 3aa was still obtained, although decreases in the reaction rates for the reuse experiments were observed (for example, 0.20 mm h^{-1} for the fifth reuse experiment vs. 0.27 mm h^{-1} for the first run with the fresh catalyst; Figure S3).

Next, we investigated the scope of the present Au/OMS-2-catalyzed dehydrogenative amination of α,β-unsaturated carbonyl compounds. Under the optimized reaction conditions, various structurally diverse enaminals could be synthesized from α,β-unsaturated aldehydes and amines (Schemes 2 and S1). All products could be readily isolated (see the Supporting Information), and the yields of isolated products are summarized in Scheme 2.
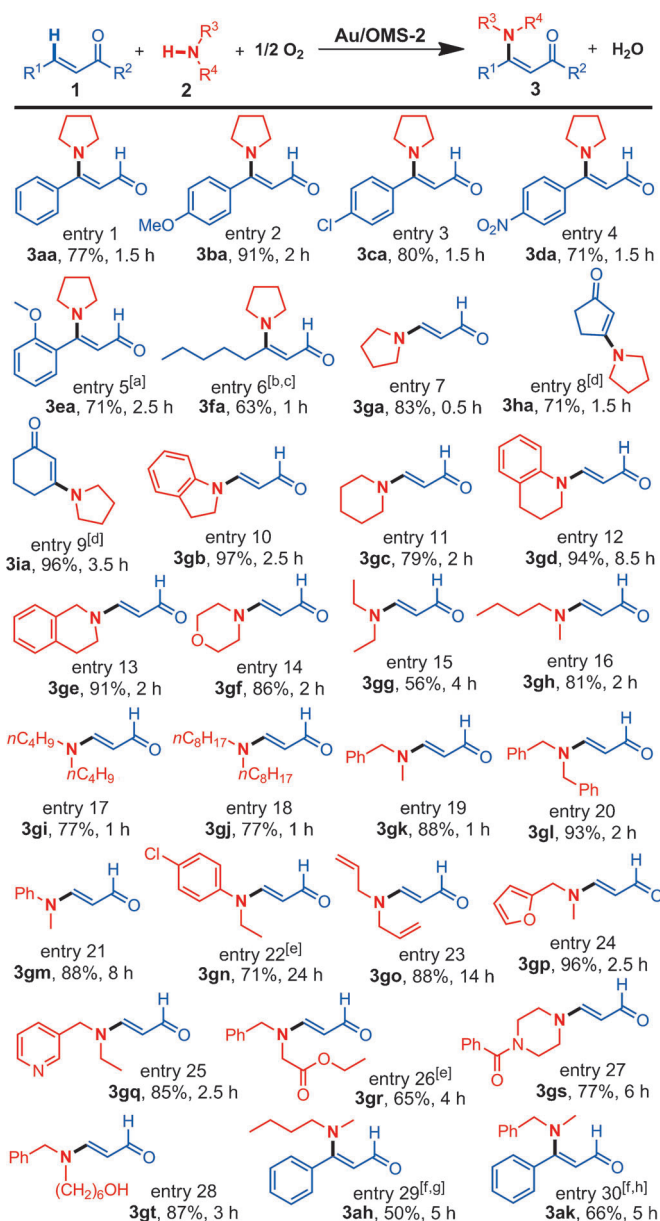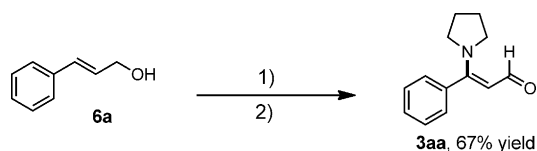

Scheme 2. Aerobic dehydrogenative amination of α,β-unsaturated aldehydes. Reaction conditions: 1 (0.5 mmol), 2 (1.0 mmol), Au/OMS-2 (3.6 mol%), THF (1.9 mL), H$_2$O (0.1 mL), 50°C, air (1 atm). Yields (based on 1) of isolated products are shown. Major byproducts were amidation products 4 (< 5% yield, except for 4ea). See the Supporting Information for the E/Z ratios of products. [a] 4ea was obtained as an amidation byproduct (24% yield). [b] THF (2 mL), without addition of H$_2$O. [c] 5fa (see Scheme 4) was obtained as a byproduct (28% yield). [d] 2 (2.0 mmol), THF (1.8 mL), H$_2$O (0.2 mL). [e] THF (1.8 mL), H$_2$O (0.2 mL). [f] Toluene (2 mL). [g] 60°C. [h] 70°C.

Various substituted cinnamaldehydes efficiently reacted with **2a** to give the corresponding enaminals (Scheme 2, entries 1–5). An aliphatic α,β-unsaturated aldehyde was also useful for the present amination (Scheme 2, entry 6). In this case, a moderate yield of **5fa** (enaminone), derived from the isomerization of the corresponding enaminal, was formed as a byproduct (see below; see also Scheme 4). Gratifyingly, acrolein, which is susceptible to both polymerization and oxidation under oxidative conditions, could be utilized as a substrate for the present amination (Scheme 2, entries 7 and 10–28). Aside from aldehydes, α,β-unsaturated ketones could be efficiently aminated at the β-position, although four equivalents of **2a** were required (Scheme 2, entries 8 and 9).

Considering the significant utility of β-aminoacrolein moieties in organic synthesis,[1,2] we mainly used acrolein as a coupling partner to examine the amine scope. Various aliphatic amines efficiently reacted with acrolein to give the corresponding β-aminoacroleins (Scheme 2, entries 10–18). Benzylic amines and aniline derivatives were excellent amination reagents for acrolein (Scheme 2, entries 19–22). With regard to diallylamine, the allyl group remained intact after the reaction (Scheme 2, entry 23). Furan and pyridine derivatives were also compatible with the present amination (Scheme 2, entries 24 and 25). Ester and amide groups survived under the reaction conditions (Scheme 2, entries 26 and 27). A secondary amine containing an alcohol group also reacted well with acrolein (Scheme 2, entry 28). The amination of **1a** with aliphatic and benzylic amines also gave the corresponding enaminals (Scheme 2, entries 29 and 30).

Notably, we could successfully synthesize **3aa** in 67% yield (as determined by GC analysis) starting from cinnamylalcohol (**6a**) by a one-pot sequential reaction of the oxidative dehydrogenation of **6a** to **1a**, followed by amination with **2a** (Scheme 3). Thus, Au/OMS-2 could act as an efficient heterogeneous catalyst for both the oxidative dehydrogenation of alcohols and the amination of α,β-unsaturated aldehydes.

As described above, the corresponding enaminone **5fa**, which can be regarded as a Wacker-type oxidation product, was formed as a byproduct for the reaction of 2-octenal (**1f**) with **2a**. We found that enaminones (Wacker-type oxidation products) could be synthesized from α,β-unsaturated aldehydes and amines. The overall conversion of α,β-unsaturated aldehydes to enaminones was accomplished as a one-pot procedure by simply adding amines and water to the reaction solution after the Au/OMS-2 catalyzed amination was completed. For example, enaminones **5aa** and **5fa** could be efficiently synthesized from **1a** and **1f**, respectively
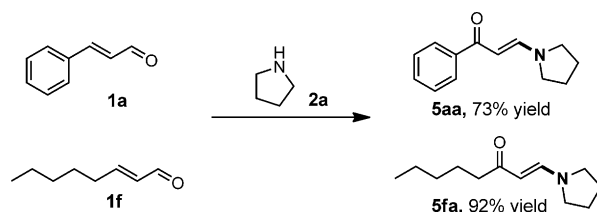
Scheme 4. One-pot synthesis of enaminones from α,β-unsaturated aldehydes and **2a**. Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), Au/OMS-2 (3.6 mol%), THF (1.9 mL), H₂O (0.1 mL), 50°C, 1.5 h, air (1 atm). Then, the catalyst was filtered off, followed by the addition of **2a** (2.0 mmol) and H₂O (0.1 mL) to the filtrate. For **1a**, the filtrate was stirred at 60°C for an additional 24 h. For **1f**, 50°C for an additional 3 h. Yields (based on **1**) of isolated products are shown.

(Scheme 4). To the best of our knowledge, this is the first example of (formal) Wacker-type oxidation of α,β-unsaturated aldehydes.[14]

For the amination of **1a** with **2a**, the reaction rate and the final yield of **3aa** were almost unchanged, even in the presence of stoichiometric amounts of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) or 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO; Figure S4), which indicates that radical species were not involved in the present amination. The reaction profiles for the present Au/OMS-2-catalyzed amination showed that a β-aminoaldehyde (aza-Michael addition product) was initially produced, followed by formation of the corresponding enaminal (Figure S5). In addition, we confirmed that Au/OMS-2 could catalyze the dehydrogenation of 1-methyl-4-piperidone (β-aminoketone) to the corresponding enaminone (Scheme S2).

These experimental results indicate that the present Au/OMS-2-catalyzed amination of α,β-unsaturated aldehydes possibly proceeds through the following sequential reactions: Initially, aza-Michael addition of a secondary amine to an α,β-unsaturated aldehyde proceeds to give a β-aminoaldehyde (step 1 in Scheme 5). Then, the oxidative dehydrogenation of the β-aminoaldehyde takes place to give the corresponding enaminal (step 2 in Scheme 5),[6,15] which is efficiently promoted by Au/OMS-2. This mechanism is completely different from the traditional palladium-catalyzed amination, which is supposed to proceed through migratory insertion of an amine into a palladium–alkene complex, followed by β-hydride elimination.[5e,g,h]

Scheme 3. One-pot synthesis of **3aa** from **6a** and **2a**. Reaction conditions: 1) **6a** (0.5 mmol), Au/OMS-2 (3.6 mol%), toluene (2 mL), 100°C, 1 h, O₂ (1 atm). Then, 2) **2a** (1.0 mmol) was added to the reaction mixture followed by stirring at 50°C for an additional 6 h. Yield was determined by GC analysis.
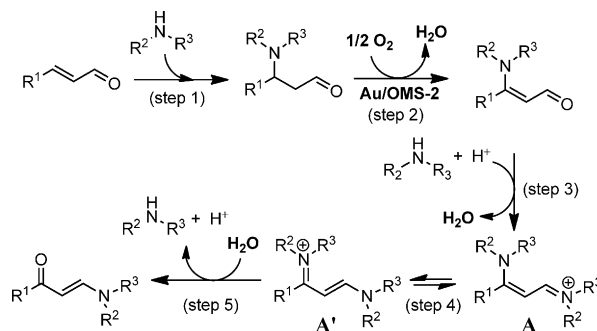

Scheme 5. Proposed reaction path for the present Au/OMS-2 catalyzed dehydrogenative amination of α,β-unsaturated aldehydes and formal Wacker-type oxidation.

In the presence of excess amounts of amine, an enaminal could react further with the amine to form transient iminium species **A** (step 3 in Scheme 5), which can isomerize to species **A′** (step 4 in Scheme 5). The hydrolytic decomposition of species **A′** affords the corresponding enaminone as a final Wacker-type oxidation product (step 5 in Scheme 5).

In summary, we have successfully developed a novel heterogeneous dehydrogenative amination of α,β-unsaturated aldehydes catalyzed by Au/OMS-2. Various structurally diverse enaminals could be synthesized. Furthermore, formal Wacker-type oxidation of α,β-unsaturated aldehydes to enaminones has been realized for the first time. The present system provides a convenient approach to synthetically important enaminals and enaminones, starting from readily available α,β-unsaturated aldehydes and amines.

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[12] Au/OMS-2 showed high catalytic activity, even under Ar atmosphere (Table S1, entry 9), which suggests that step 2 in Scheme 5 is efficiently promoted by the presence of OMS-2.[8b]

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