VIP One-Pot Synthesis Very Important Paper

International Edition: DOI: 10.1002/anie.201507134
German Edition: DOI: 10.1002/ange.201507134

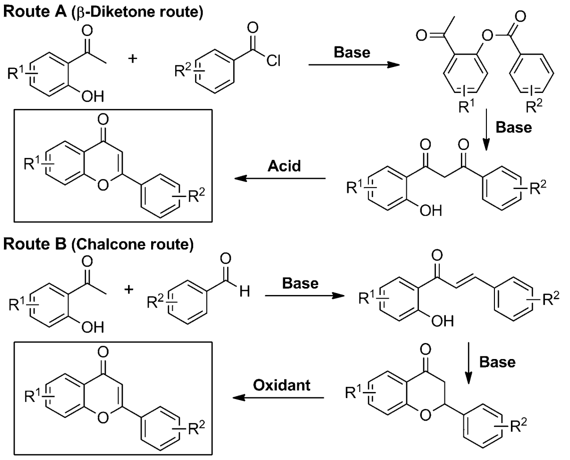
# Gold Nanoparticles Supported on a Layered Double Hydroxide as Efficient Catalysts for the One-Pot Synthesis of Flavones

*Takafumi Yatabe, Xiongjie Jin, Kazuya Yamaguchi, and Noritaka Mizuno**

***Abstract:*** *Flavones are a class of natural products with diverse biological activities and have frequently been synthesized by step-by-step procedures using stoichiometric amounts of reagents. Herein, a catalytic one-pot procedure for the synthesis of flavone and its derivatives is developed. In the presence of gold nanoparticles supported on a Mg-Al layered double hydroxide (Au/LDH), various kinds of flavones can be synthesized starting from 2′-hydroxyacetophenones and benzaldehydes (or benzyl alcohols). The present one-pot procedure consists of a sequence of several reactions, and Au/LDH can catalyze all these different types of reactions. The catalysis is shown to be truly heterogeneous, and Au/LDH can be readily recovered and reused.*

Flavones are a class of flavonoids with a 2-phenylchromen-4-one skeleton and present in many fruits and vegetables.[1] They possess a variety of biological activities that are due to the basic skeleton and have especially been found to be effective for several diseases related to oxidative stress, such as arteriosclerosis, diabetes, cancer, Alzheimer's disease, and Parkinson's disease.[1] Their activities and targets are largely dependent on their substitution patterns.[1] Therefore, to discover flavone-based prominent lead compounds for various diseases, it is very important to not only investigate their structure–activity relationships in detail but also develop new efficient procedures for their synthesis and structural modification.

Thus far, various kinds of flavones have been synthesized by utilizing two major routes (routes A and B in Scheme 1).[1–4] Route A (the β-diketone route) is the traditional and most frequently utilized choice. The Baker–Venkataraman reaction and the Allan–Robinson reaction belong to this category.[2] The reaction typically proceeds through the condensation of 2′-hydroxyacetophenones with acid chlorides (or anhydrides) followed by rearrangement to produce the β-diketone intermediates in the presence of strong bases. Then, acid-catalyzed cyclodehydration of the β-diketones gives the corresponding flavones. Route A is intrinsically a step-by-step procedure, and strong acids, strong bases (typically in superstoichiometric amounts), and preactivated substrates are required.[2] Route B (the chalcone route) is an attractive procedure because the 2′-hydroxychalcone intermediates can be readily synthesized by a base-catalyzed Claisen–Schmidt condensation of readily available 2′-hydroxyacetophenones and benzaldehydes.[3] However, the oxidative dehydrogenation step in route B is still problematic, and halogen-based, organic, or metal-based oxidants, such as $Br_2$, $I_2$, $I_2$/dimethyl sulfoxide (DMSO), 2,3-dichloro-5,6-dicyano-*para*-benzoquinone (DDQ), and $SeO_2$, have generally been utilized.[3] Although a homogeneous copper-catalyzed aerobic oxidative cyclization of 2′-hydroxychalcones to flavones promoted by ionic liquids has recently been developed, their direct synthesis from 2′-hydroxyacetophenones and benzaldehydes has not been reported, and the 2′-hydroxychalcones thus have to be separately prepared.[3k]



***Scheme 1.*** Synthetic procedures for flavones.

Recently, heterogeneous catalysts have been increasingly used for liquid-phase fine-chemical synthesis, and numerous powerful catalytic systems have been developed to date.[5,6] Despite the advantages of heterogeneous catalysts, most of the previously reported systems for the synthesis of flavones are homogeneous.[1–4] Therefore, if the above-mentioned route B could be realized as a heterogeneously catalyzed one-pot procedure using molecular oxygen as the terminal oxidant, it would be one of the greenest and most powerful procedures for the synthesis of flavones.

Herein, we have developed the first efficient heterogeneously catalyzed one-pot synthesis of flavones starting directly from 2′-hydroxyacetophenones and benzaldehydes (or benzyl alcohols) in the presence of gold nanoparticles supported on a Mg-Al layered double hydroxide (Au/LDH).[7] The present one-pot process consists of a Claisen–Schmidt condensation (base catalysis), an intramolecular oxa-Michael addition (base catalysis), and an aerobic oxidative dehydrogenation of chromanones (gold catalysis; route B in

---

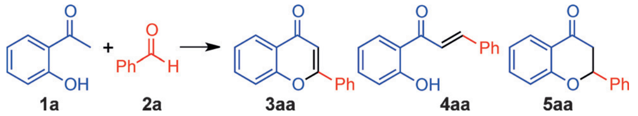
[*] T. Yatabe, Dr. X. Jin, Dr. K. Yamaguchi, Prof. Dr. N. Mizuno
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201507134.

Scheme 1).[8–10] When benzyl alcohols are used as the starting materials, the sequence begins with aerobic oxidation of the alcohol (gold catalysis).[7] The Au/LDH catalyst plays multiple roles in this process, catalyzing all the different types of reactions included in this sequence. The catalysis is shown to be truly heterogeneous, and the Au/LDH catalyst can be reused without a severe loss of catalytic performance. The present procedure possesses several noteworthy features, for example, 1) the use of a reusable heterogeneous catalyst, 2) simple one-pot operation and avoidance of tedious isolation steps, 3) the use of the greenest oxidant, namely molecular oxygen (in air), as the terminal oxidant, 4) readily available starting materials, 5) no need for additives, and 6) the formation of water as the theoretically only by-product.

To begin with, we prepared various kinds of supported metal catalysts (referred to as metal/support, see the Supporting Information),[11] and they were tested for the direct one-pot synthesis of flavone (**3aa**) starting from 2′-hydroxyacetophenone (**1a**) and benzaldehyde (**2a**). The reactions were carried out in mesitylene at 130 °C in open air (1 atm) using an equimolar mixture of **1a** and **2a**. Under these reaction conditions, the desired compound **3aa** was not produced at all in the absence of catalyst (Table 1, entry 11).

***Table 1:*** Synthesis of flavone (**3aa**) using various catalysts.[a]



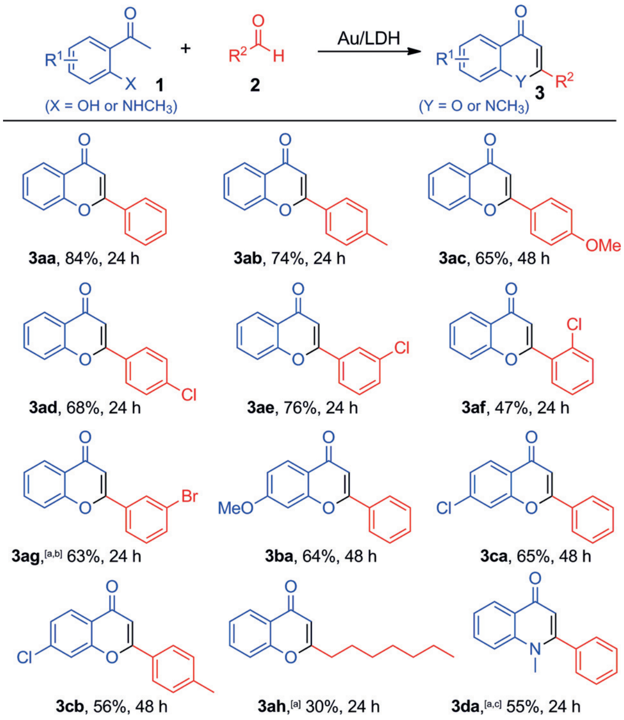
| Entry | Catalyst | Conv. [%] | | Yield [%] | | |
|---|---|---|---|---|---|---|
| | | **1a** | **2a** | **3aa** | **4aa** | **5aa** |
| 1 | Au/LDH | >99 | 97 | 76 | <1 | <1 |
| 2 | Ru/LDH | 70 | 78 | <1 | 5 | 16 |
| 3 | Rh/LDH | 79 | 74 | <1 | 20 | 39 |
| 4 | Pd/LDH | 84 | >99 | 2 | 2 | 22 |
| 5 | Pt/LDH | 91 | 96 | <1 | 20 | 44 |
| 6 | Au/$Al_2O_3$ | 79 | 83 | 58 | 2 | 3 |
| 7 | Au/$TiO_2$ | 46 | 56 | 34 | <1 | <1 |
| 8 | Au/$CeO_2$ | 40 | 78 | 3 | <1 | <1 |
| 9[b] | Au/LDH | >99 | >99 | 24 | 15 | 34 |
| 10 | LDH | >99 | 90 | <1 | 31 | 59 |
| 11 | – | 9 | 65 | <1 | <1 | <1 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (130 mg), mesitylene (2 mL), 130 °C, open air (1 atm), 24 h. Benzoic acid (formed by the oxidation of **2a**) was formed as a side product. When supported gold catalysts were used, aurone (possibly by dehydrogenation of the 5-*exo*-trig oxa-Michael adduct) was formed as a side product (<5 %). Yields were determined by GC analysis using biphenyl as an internal standard. [b] Ar atmosphere (1 atm).

Although the Claisen–Schmidt condensation product **4aa** and the oxa-Michael addition product **5aa** were formed when using just LDH,[12] the oxidative dehydrogenation of **5aa** to **3aa** did not take place at all (entry 10). In the presence of Ru/LDH, Rh/LDH, Pd/LDH, or Pt/LDH, **3aa** was barely produced even though the Claisen–Schmidt condensation and the oxa-Michael addition proceeded (entries 2–5), thus indicating that these supported metals are intrinsically inactive for the oxidative dehydrogenation. Fortunately, the desired product **3aa** was obtained in 76 % yield when the Au/LDH catalyst was used (entry 1). When the reaction was carried out with Au/LDH under an argon atmosphere, the yield of **3aa** decreased to 24 % (entry 9). In this case, the hydrogenation of the C=C bond of **4aa** also proceeded to some extent. Therefore, molecular oxygen (in air) acted as the terminal oxidant in the present system.[13] The effect of the gold supports was significant, and LDH showed the best performance among the supports examined (entries 1 and 6–8). The basicity of LDH possibly plays an important role for not only catalyzing the Claisen–Schmidt condensation and the oxa-Michael addition,[12] but also promoting the oxidative dehydrogenation of **5aa** (see below).

To determine whether the active catalyst was solid Au/LDH or a leached metal species (gold, magnesium, and/or aluminum), Au/LDH was removed by hot filtration during the reaction when **3aa** had been formed in approximately 50 % yield; then the reaction was repeated with the filtrate under the same reaction conditions. As shown in the Supporting Information, Figure S1, the production of **3aa** was completely stopped by removal of Au/LDH. Furthermore, we confirmed by inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis that gold, magnesium, and aluminum species were hardly present in the filtrate (Au: <0.003 %, Mg: <0.02 %, Al: <0.4 %). The above experimental results rule out that metal species that had leached into the reaction solution contribute to the observed catalysis, which is thus truly heterogeneous.[14] After the reaction of **1a** and **2a** was completed, the Au/LDH catalyst could be readily retrieved from the reaction mixture by simple filtration. It could then be reused for the same reaction without a severe loss of catalytic performance (Table S1).[15]

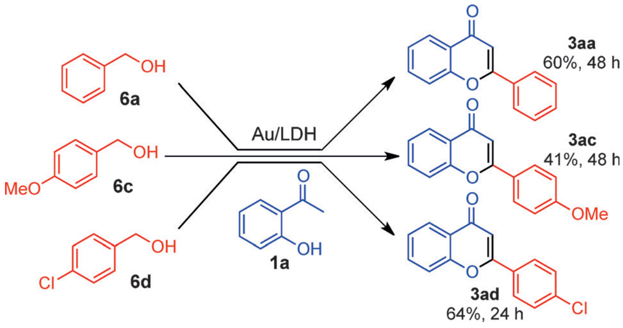
Next, we examined the scope of the present Au/LDH-catalyzed one-pot procedure. Under the optimized reaction conditions, various structurally diverse flavones could be synthesized starting directly from 2′-hydroxyacetophenones and benzaldehydes.[16] The products were readily isolated by simple column chromatography on silica gel (see the Supporting Information), and the yields of isolated products are given in Scheme 2. The reaction of **1a** with benzaldehydes with either electron-donating or electron-withdrawing substituents at various positions of the aryl rings efficiently produced the corresponding flavones (**3aa**–**3ag**). In the case of *para*-tolualdehyde, the undesirable oxidation of the benzylic methyl group hardly proceeded (**3ab**). Furthermore, various substituted 2′-hydroxyacetophenones were suitable reaction partners for benzaldehydes (**3ba**, **3ca**, and **3cb**). By utilizing the present Au/LDH-catalyzed one-pot procedure, various halogen-substituted flavones could be efficiently synthesized. These halide functional groups could then be used for further derivatization of these flavone molecules. Aside from benzaldehydes, aliphatic aldehydes could be employed; for example, the reaction of **1a** with *n*-octanal afforded the corresponding chromone (**3ah**). Furthermore, by using 2′-(methylamino)acetophenone and **2a** as the starting materials, the present Au/LDH-catalyzed one-pot procedure could successfully construct the corresponding 4-quinolone skeleton (**3da**). It is known that Au/LDH can act as an efficient heterogeneous catalyst for the aerobic oxidation of



*Scheme 2.* Substrate scope. Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), Au/LDH (100 mg), mesitylene (2 mL), 130 °C, open air (1 atm). Yields (based on **1**) of isolated products are given. [a] Au/LDH (200 mg). [b] **3aa** was also formed (8%). [c] The product was isolated as a monohydrate.

alcohols.[7] Therefore, we expected that benzyl alcohols (instead of benzaldehydes) could also be utilized as the starting materials for the present Au/LDH-catalyzed one-pot flavone synthesis. As shown in Scheme 3, several substituted flavones could indeed be synthesized directly from **1a** and benzyl alcohols. To the best of our knowledge, such a heterogeneously catalyzed direct one-pot flavone synthesis was hitherto unknown.

The reaction profile for the Au/LDH-catalyzed transformation of **1a** and **2a** revealed that **4aa** and **5aa** are initially produced followed by the formation of **3aa** (Figure S2). Furthermore, it was confirmed by separate experiments that **3aa** can be synthesized starting from **4aa** (Scheme S1) or **5aa** (Table S2) in the presence of Au/LDH. Therefore, the present one-pot procedure consists of a Claisen–Schmidt condensation of the 2′-hydroxyacetophenones (**1**) with the benzaldehydes (**2**) to yield 2′-hydroxychalcones (**4**), an intramolecular oxa-Michael addition of intermediates **4** to form chromanones (**5**), and the oxidative dehydrogenation of **5**, which affords the desired flavones (**3**). The LDH can act as a solid base catalyst of the Claisen–Schmidt condensation and the oxa-Michael addition.[12] When benzyl alcohols are used as the starting materials, the sequence begins with aerobic alcohol oxidation by a typical alkoxide formation/hydride elimination mechanism.[7,17]



*Scheme 3.* One-pot synthesis of flavones starting from **1a** and benzyl alcohols. Reaction conditions: **1a** (0.5 mmol), **6** (0.5 mmol), Au/LDH (130 mg), mesitylene (2 mL), 130 °C, open air (1 atm). Yields were determined by GC analysis using biphenyl as an internal standard.

To elucidate the roles of the catalyst in the oxidative dehydrogenation step in more detail, several experiments were carried out. First, the oxidative dehydrogenation of **5aa** to **3aa** was performed with various supported metal catalysts. Ru/LDH, Rh/LDH, Pd/LDH, and Pt/LDH were inactive for the dehydrogenation, whereas supported gold catalysts gave **3aa** in significant yields (Table S2). These results are consistent with those described in Table 1. The effect of the gold support was also significant; the catalytic performance depended on the kind of support and was independent of the specific surface area (Table S2).[18] Therefore, we conclude that the basicity of LDH assists the gold-catalyzed oxidative dehydrogenation likely by promoting the deprotonation of **5aa**. The oxidative dehydrogenation of **5aa** was not influenced by the presence of an equimolar amount of the radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) with respect to **5aa** (Figure S3), indicating that radical species are not involved in the present transformation. Next, the oxidative dehydrogenation of **5aa** was carried out with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). TEMPO is also a radical scavenger and known to be an effective hydrogen atom abstractor. Furthermore, it has been reported that TEMPO can abstract a hydrogen atom (one electron and one proton) from a Au−H species with concomitant formation of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPOH).[17] When the Au/LDH-catalyzed oxidative dehydrogenation of **5aa** was carried out in the presence of an equimolar amount of TEMPO with respect to **5aa**, the reaction was somewhat faster than without TEMPO, and the formation of TEMPOH was observed (Figure S3). This result clearly supports the formation of a Au−H species during the catalytic cycle.

Based on the above-mentioned experimental results, we now propose a possible mechanism for the gold-catalyzed oxidative dehydrogenation of **5** (Scheme S2). The direct hydrogen atom abstraction pathway can be excluded because the reaction rates did not decrease in the presence of radical scavengers such as BHT and TEMPO. Therefore, we believe that the dehydrogenation possibly proceeds by a deprotonation/hydride elimination mechanism. The relatively acidic hydrogen atom at the 3-position of **5** is abstracted as a proton in a process that is promoted by the LDH, and the proton is temporarily stored on the basic LDH surface. The hydrogen at the 2-position is eliminated as a hydride to form a transient Au−H species. As mentioned above, molecular oxygen (in air) acts as the terminal oxidant in the present system[13] and regenerates the active gold species by removing the hydrogen atom from the Au–H species via the formation of a hydroperoxide.[17] The proton stored on LDH is consumed for the production of water.

In conclusion, we have described the first heterogeneously catalyzed synthesis of flavones in a one-pot process from 2′-hydroxyacetophenones and benzaldehydes (or benzyl alcohols). Gold nanoparticles supported on a layered double hydroxide catalyzed all three (four) steps of the overall process. Owing to the practical reaction conditions, we hope that this transformation will find wide application for the synthesis of flavone derivatives and related compounds.

## Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

**Keywords:** flavones · gold catalysis · heterogeneous catalysis · layered double hydroxides · one-pot synthesis

**How to cite:** *Angew. Chem. Int. Ed.* **2015**, *54*, 13302–13306
*Angew. Chem.* **2015**, *127*, 13500–13504

---

[1] a) E. Middleton, Jr., C. Kandaswami, T. C. Theoharides, *Pharmacol. Rev.* **2000**, *52*, 673; b) A. K. Verma, R. Pratap, *Tetrahedron* **2012**, *68*, 8523; c) M. Singh, M. Kaur, O. Silakari, *Eur. J. Med. Chem.* **2014**, *84*, 206, and references therein.

[2] a) J. Allan, R. Robinson, *J. Chem. Soc.* **1924**, *125*, 2192; b) T. S. Wheeler, *Org. Synth.* **1952**, *32*, 72; c) D. Nagarathnam, M. Cushman, *Tetrahedron* **1991**, *47*, 5071; d) M. Kucukislamoglu, M. Nebioglu, M. Zengin, M. Arslan, N. Yayli, *J. Chem. Res.* **2005**, *9*, 556; e) C. Jin, F. He, H. Wu, J. Chen, W. Su, *J. Chem. Res.* **2009**, *1*, 27.

[3] a) T. Emilewicz, S. von Kostanecki, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 696; b) H. S. Mahal, K. Venkataraman, *J. Chem. Soc.* **1936**, 569; c) W.-H. Huang, P.-Y. Chien, C.-H. Yang, A.-R. Lee, *Chem. Pharm. Bull.* **2003**, *51*, 339; d) S. Alam, *J. Chem. Sci.* **2004**, *116*, 325; e) P. D. Lokhande, S. S. Sakate, K. N. Taksande, B. Navghare, *Tetrahedron Lett.* **2005**, *46*, 1573; f) N. Yao, A. Song, X. Wang, S. Dixon, K. S. Lam, *J. Comb. Chem.* **2007**, *9*, 668; g) M. M. Naik, S. G. Tilve, V. B. Kamat, *Tetrahedron Lett.* **2014**, *55*, 3340; h) Y. Hoshino, N. Takeno, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4468; i) Y. K. Rao, S.-H. Fang, Y.-M. Tzeng, *Bioorg. Med. Chem.* **2005**, *13*, 6850; j) H. S. Mahal, H. S. Rai, K. Venkataraman, *J. Chem. Soc.* **1935**, 866; k) Z. Du, H. Ng, K. Zhang, H. Zeng, J. Wang, *Org. Biomol. Chem.* **2011**, *9*, 6930.

[4] For other synthetic procedures towards flavones, see: a) Q. Yang, H. Alper, *J. Org. Chem.* **2010**, *75*, 948; b) G. Maiti, R. Karmakar, R. N. Bhattacharya, U. Kayal, *Tetrahedron Lett.* **2011**, *52*, 5610; c) M. Yoshida, Y. Fujino, K. Saito, T. Doi, *Tetrahedron* **2011**, *67*, 9993; d) X.-F. Wu, H. Neumann, M. Beller, *Chem. Eur. J.* **2012**, *18*, 12595; e) K. V. Sashidhara, M. Kumar, A. Kumar, *Tetrahedron Lett.* **2012**, *53*, 2355.

[5] a) R. A. Sheldon, H. van Bekkum, *Fine Chemicals through Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2001**; b) *Liquid Phase Oxidation via Heterogeneous Catalysis: Organic Synthesis and Industrial Applications* (Eds.: M. G. Clerici, O. A. Kholdeeva), Wiley, Hoboken, **2013**.

[6] For excellent reviews on one-pot syntheses using heterogeneous catalysts, see: a) M. J. Climent, A. Corma, S. Iborra, *Chem. Rev.* **2011**, *111*, 1072; b) H. Miyamura, S. Kobayashi, *Acc. Chem. Res.* **2014**, *47*, 1054.

[7] For the use of Au/LDH for aerobic alcohol oxidation, see: a) T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Adv. Synth. Catal.* **2009**, *351*, 1890; b) T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa, K. Kaneda, *Green Chem.* **2009**, *11*, 793; c) P. Liu, Y. Guan, R. A. van Santen, C. Li, E. J. M. Hensen, *Chem. Commun.* **2011**, *47*, 11540; d) J. Feng, C. Ma, P. J. Miedziak, J. K. Edwards, G. L. Brett, D. Li, Y. Du, D. J. Morgan, G. J. Hutchings, *Dalton Trans.* **2013**, *42*, 14498; e) S. Nishimura, Y. Yakita, M. Katayama, K. Higashimine, K. Ebitani, *Catal. Sci. Technol.* **2013**, *3*, 351; f) J. Wang, X. Lang, B. Zhaorigetu, M. Jia, J. Wang, X. Guo, J. Zhao, *ChemCatChem* **2014**, *6*, 1737.

[8] For selected examples of recently reported efficient functional-group transformations using supported gold catalysts and related reviews, see: a) H. Sun, F.-Z. Su, J. Ni, Y. Cao, H.-Y. He, K.-N. Fan, *Angew. Chem. Int. Ed.* **2009**, *48*, 4390; *Angew. Chem.* **2009**, *121*, 4454; b) Y. Wang, D. Zhu, L. Tang, S. Wang, Z. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 8917; *Angew. Chem.* **2011**, *123*, 9079; c) J.-F. Soulé, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2011**, *133*, 18550; d) T. Mitsudome, K. Kaneda, *Green Chem.* **2013**, *15*, 2636; e) K. Yamaguchi, Y. Wang, T. Oishi, Y. Kuroda, N. Mizuno, *Angew. Chem. Int. Ed.* **2013**, *52*, 5627; *Angew. Chem.* **2013**, *125*, 5737; f) K. Taniguchi, S. Itagaki, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2013**, *52*, 8420; *Angew. Chem.* **2013**, *125*, 8578; g) B. S. Takale, M. Bao, Y. Yamamoto, *Org. Biomol. Chem.* **2014**, *12*, 2005; h) X. Liu, H.-Q. Li, S. Ye, Y.-M. Liu, H.-Y. He, Y. Cao, *Angew. Chem. Int. Ed.* **2014**, *53*, 7624; *Angew. Chem.* **2014**, *126*, 7754; i) A. Corma, A. Leyva-Rérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657; j) X. Liu, L. He, Y.-M. Liu, Y. Cao, *Acc. Chem. Res.* **2014**, *47*, 793, and references therein.

[9] Although supported gold catalysts have been utilized for various oxidative functional-group transformations,[7,8] to the best of our knowledge, they have not been used for the oxidative dehydrogenation of saturated carbonyl compounds except for in our recent work; see: X. Jin, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2014**, *53*, 455; *Angew. Chem.* **2014**, *126*, 465.

[10] Recently, several excellent oxidative dehydrogenation systems for saturated carbonyl compounds using palladium- or iridium-based homogeneous catalysts have been reported; see: a) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566; b) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209; c) Y. Moon, D. Kwon, S. Hong, *Angew. Chem. Int. Ed.* **2012**, *51*, 11333; *Angew. Chem.* **2012**, *124*, 11495; d) Y. Izawa, C. Zheng, S. S. Stahl, *Angew. Chem. Int. Ed.* **2013**, *52*, 3672; *Angew. Chem.* **2013**, *125*, 3760; e) T. Diao, T. J. Wadzinski, S. S. Stahl, *Chem. Sci.* **2012**, *3*, 887; f) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci.* **2012**, *3*, 883; g) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851; h) T. Diao, D. Pun, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8205; i) D. Pun, T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 8213; j) S. Kusumoto, M. Akiyama, K. Nozaki, *J. Am. Chem. Soc.* **2013**, *135*, 18726; k) N. Gigant, J.-E. Bäckvall, *Chem. Eur. J.* **2014**, *20*, 5890.

[11] The detailed procedure for the preparation of Au/LDH is given in the Supporting Information. The gold content in Au/LDH was 2.4 wt %, and the average particle size of gold was 4.2 nm (standard deviation, $\sigma = 1.2$ nm; Figure S4).

[12] a) F. Cavani, F. Trifirò, A. Vaccari, *Catal. Today* **1991**, *11*, 173; b) M. J. Climent, A. Corma, S. Iborra, J. Primo, *J. Catal.* **1995**, *151*, 60; c) B. M. Choudary, M. L. Kantam, C. R. V. Reddy, K. K. Rao, F. Figueras, *J. Mol. Catal. A* **1999**, *146*, 279; d) K. Kaneda, K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, *Catal. Surv. Jpn.* **2000**, *4*, 31.

[13] The Au/LDH-catalyzed oxidative dehydrogenation of **5aa** under the conditions described in Table S2 gave **3aa** in 66 % yield. Under an argon atmosphere, the yield of **3aa** decreased to 4 %,

and the hydrogenation of **4aa** (formed by a retro-Michael addition) was observed.

[14] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485.

[15] The yield of **3aa** gradually decreased for each reuse experiment (Table S1). The average particle size of gold in the fresh Au/LDH sample was 4.2 nm ($\sigma = 1.2$ nm) and was unchanged after the second reuse experiment (4.3 nm, $\sigma = 1.2$ nm; Figure S4). It was confirmed by X-ray photoelectron spectroscopy (XPS) analysis that the oxidation state of gold was still zero after the reaction (Figure S5). X-ray diffraction (XRD) analysis revealed that the structure of LDH had been almost preserved after the reaction (Figure S6). The IR spectrum of Au/LDH after the second reuse experiment showed a band around 1600 $\mathrm{cm^{-1}}$, which was attributed to carboxylate species, suggesting the adsorption of carboxylic acids (formed by oxidation of the aldehyde substrates and/or mesitylene) on the basic LDH surface (Figure S7). Therefore, the deactivation of Au/LDH is not caused by a change in the size of the gold nanoparticles but by the adsorption of carboxylic acids.

[16] A larger (5 mmol) scale synthesis was also effective and gave **3aa** in 64% yield under the conditions described in Scheme S3.

[17] M. Conte, H. Miyamura, S. Kobayashi, V. Chechik, *J. Am. Chem. Soc.* **2009**, *131*, 7189.

[18] The influence of the particle size of the gold nanoparticles was also studied (Table S2). In our previous study, we had observed that the gold-catalyzed oxidative dehydrogenation of such compounds tends to become slower as the average gold particle size increases.[9]

Received: July 31, 2015
Revised: August 21, 2015