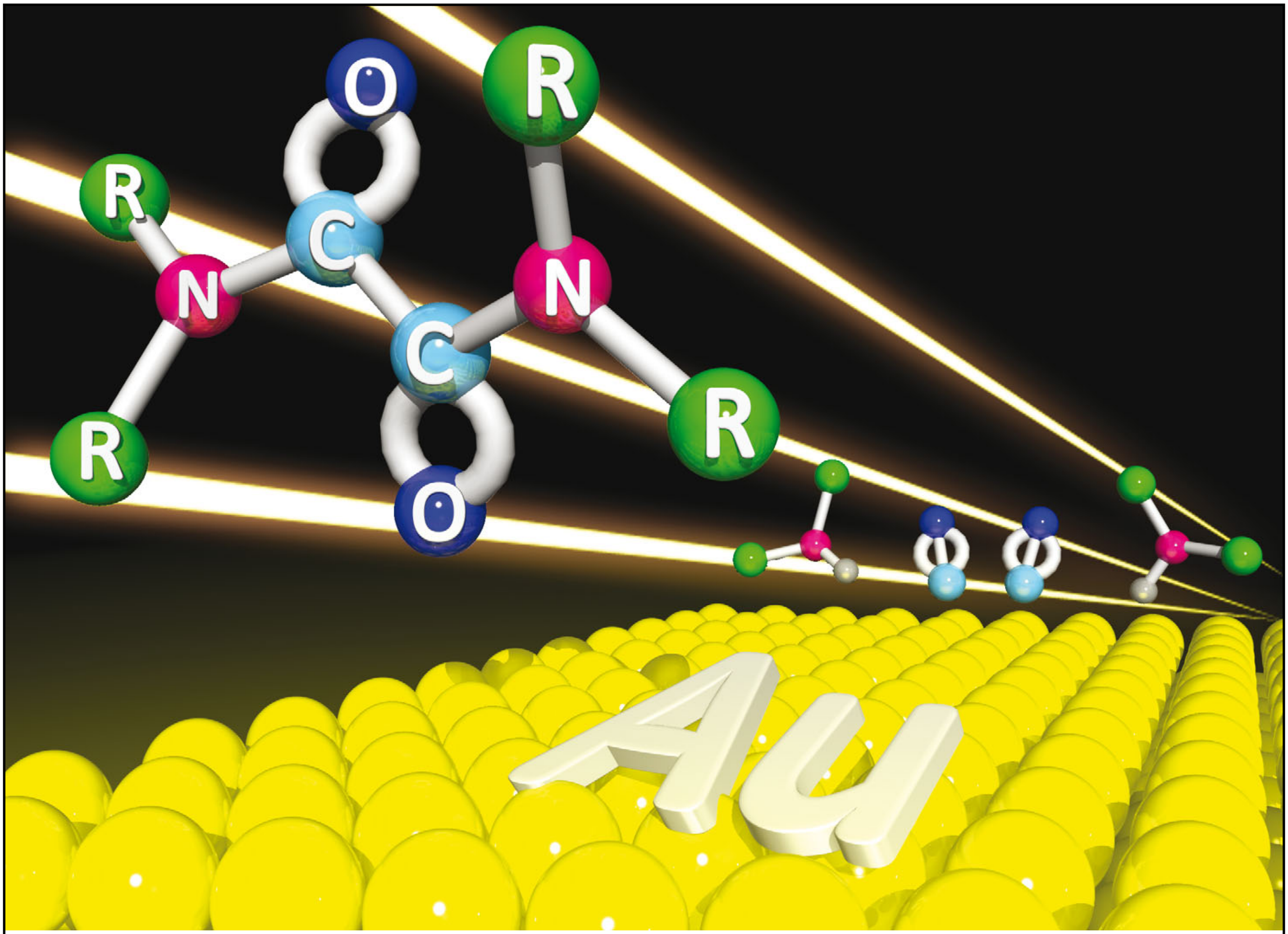

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Highly efficient double-carbonylation of amines to oxamides using gold nanoparticle catalysts

Supported gold nanoparticles catalyzed the double-carbonylation of various amines to the corresponding oxamides with high efficiency under mild reaction conditions. The cooperation between gold nanoparticles and basic sites of supports plays a key role in the carbonylation.

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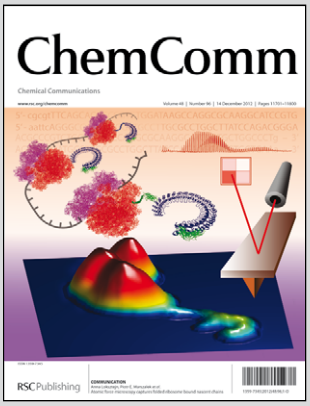

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COMMUNICATION

Highly efficient double-carbonylation of amines to oxamides using gold nanoparticle catalysts†

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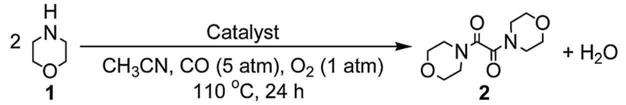
Hydrotalcite-supported gold nanoparticles (Au/HT) catalyzed the highly efficient double-carbonylation of amines to oxamides under mild reaction conditions. Various amines were selectively converted to the corresponding oxamides. The cooperation between gold nanoparticles and basic sites of HT plays a key role in the reaction.

Carbonylations of nitrogen-containing compounds have attracted much attention in both academic and industrial chemistry.[1] In this content, *mono*-carbonylations of amines to the corresponding *N,N′*-disubstituted urea derivatives with carbon monoxide have been achieved using various metal complex catalysts.[2] On the other hand, catalytic *double*-carbonylations of amines are considerably rare despite their straightforward approach to the synthesis of oxamides which are important precursors to carboxylic acids and amides as well as key components of anticancer drugs and HIV inhibitors.[3] To date, there are a few homogeneous catalysts involving Pd or Ni complexes for the double-carbonylation.[4] These catalytic systems, however, suffer from the requirement of a high pressure of CO (> 50 atm), inorganic halide promoters such as KI and CuI as well as stoichiometric amounts of hazardous oxidants such as 1,4-dichloro-2-butene and $FeCl_3(OPPh_3)_2$. Tedious workup procedures for the separation of the catalysts from the reaction mixtures and the reuse of the catalysts are also significant drawbacks. Therefore, the development of alternative and highly efficient catalytic systems for the double-carbonylation of amines remains a challenging objective.

Herein, we present a new catalytic system using supported gold nanoparticles (Au NPs) for highly efficient double-carbonylation of amines to oxamides. Small Au NPs on basic supports such as hydrotalcite (HT) and Al_2O_3 showed high catalytic activity and selectivity for the double-carbonylation of various amines to oxamides without any additives under a lowered pressure of CO (5 atm) with air (1 atm). The present supported Au catalysts were reusable without any loss of activity or selectivity. This is the first example of the use of Au NP catalysts for the double-carbonylation of amines.

Morpholine (**1**) was added to acetonitrile solvent in the presence of inorganic materials-supported Au NPs with similar particle sizes of Au NPs and then the mixture was heated for 24 h at 110 °C under CO/O_2 (5/1 atm) (Table 1, entries 1, 7–9 and 11).[5] When using Au NPs supported on basic materials such as HT and Al_2O_3, **1** was converted efficiently to afford the corresponding oxamide 1,1′-oxalyldimorpholine (**2**) (entries 1 and 7). Notably, HT-supported Au NPs (Au/HT) showed high catalytic activity, providing 94% yield of **2** with 99% selectivity. On the other hand, non-basic supports such as TiO_2, hydroxyapatite (HAP) and SiO_2 were not effective (entries 8, 9 and 11). The addition of Na_2CO_3 as a base in the ineffective

Table 1 Double-carbonylation of **1** to the corresponding oxamide (**2**)[a]



Entry	Catalyst	*d* (nm)	Yield[b] (%)	Sel.[b] (%)
1	Au/HT	2.7	94	99
2[c]	Au/HT	2.7	93	99
3[d]	Au/HT	2.7	1	99
4[c,e]	Au/HT	3.0	91	99
5[c,f]	Au/HT	3.0	91	99
6[c,g]	Au/HT	3.0	91	99
7	Au/Al_2O_3	3.6	75	99
8	Au/TiO_2	3.7	25	99
9	Au/HAP	3.0	2	99
10[h]	Au/HAP	3.0	55	99
11	Au/SiO_2	2.2	2	99
12	Au/HT	5.8	76	99
13	Au/HT	7.9	66	99
14	Au/HT	12	51	99
15	Au/HT	20	38	99
16	Rh/HT		6	99
17	Pt/HT		0	—
18	Pd/HT		0	—
19	Ru/HT		0	—
20	Ag/HT		0	—
21	$PdCl_2$		< 1	—
22	$Pd(OAc)_2$		< 1	—

[a] Reaction conditions: catalyst (M: 0.9 mol%), CH_3CN (5 mL), **1** (0.5 mmol). [b] Determined by GC using an internal standard technique. [c] Using 1 atm of air in place of pure O_2. [d] In the absence of O_2. [e] Reuse 1. [f] Reuse 2. [g] Reuse 3. [h] 1.5 mmol of Na_2CO_3 was added.

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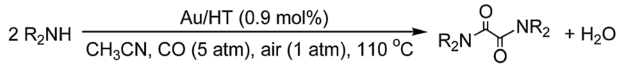
† Electronic supplementary information (ESI) available: Experimental details, EXAFS analysis, TEM images, kinetic studies and FT-IR spectra. See DOI: 10.1039/c2cc36636c

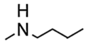
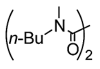
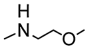
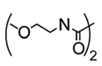
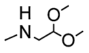
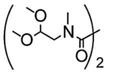
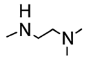
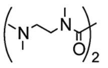
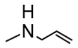
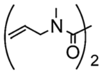
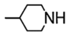
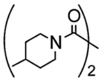
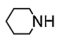
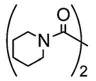
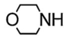
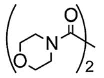
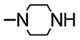
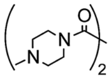
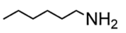
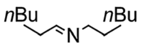
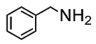
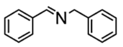
HAP-supported Au NP catalyst system significantly enhanced the yield of **2**, confirming the necessity of bases for promoting the reaction (entries 9 *vs.* 10). The double-carbonylation of **1** successfully proceeded even when using 1 atm of air in place of pure O_2 (entry 2).[6] O_2 was found to be essential; when O_2 was absent, Au/HT produced only a trace amount of **2** (entry 3). The size effect of Au NPs was also investigated using Au/HTs with different particle sizes (entries 1 and 12–15).[7] The yields of **2** increased with decreasing particle sizes, indicating that small Au NPs were more effective for the high catalytic activity. The highest yield of **2** was obtained by the use of Au/HT with a mean diameter of 2.7 nm (entry 1). Next, various metal NPs on HT were synthesized and tested in the reaction under similar conditions. Only Rh/HT gave a low yield of **2** (Entry 16), while other metal NPs such as Pt, Pd, Ru and Ag did not show any catalytic activities (entries 17–20).[8] It has been reported that homogeneous catalytic systems such as $PdCl_2$[4e] and $Pd(OAc)_2/K_2CO_3/KI$[4c] promoted the double-carbonylation of amines. However, the use of $PdCl_2$ and $Pd(OAc)_2$ in place of Au/HT in our reaction system resulted in the formation of only trace amounts of **2** (entries 21 and 22). These results clearly reveal that Au NPs have unique and significantly superior catalytic activity compared to those of other metal NPs, and that the combination of Au NPs and bases in the presence of O_2 is vital for the efficient double-carbonylation. In a separate experiment, we carried out CO oxidation under the conditions similar to those given in entry 2 in the absence of **1**. Only 0.2% yield of CO_2 based on initial amounts of CO was obtained.[9] This result shows both CO and O_2 are high-selectively used for the oxidative double-carbonylation, which is consistent with the high efficiency of our Au/HT catalyst system.

At 40% conversion of **1**, Au/HT was removed by filtration and further treatment of the resulting filtrate under similar reaction conditions did not afford any products. The absence of Au ions in the filtrate was also confirmed by inductively coupled plasma analysis (the detection limit is below 0.1 ppm).[10] These phenomena demonstrate that the double-carbonylation takes place on the Au/HT solid surface. Kinetic studies also support heterogeneous catalysis in the double-carbonylation (*vide infra*). Furthermore, after the reaction, Au/HT was easily recoverable by filtration from the reaction mixture and reusable without any loss of efficiency (Table 1, entries 4–6). TEM analysis of the used Au/HT catalyst revealed that the size of the Au NPs did not significantly differ from those of the fresh Au/HT (Fig. S2, ESI†), supporting the above excellent reusability of Au/HT.

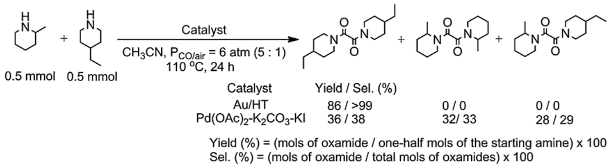
Under the optimized conditions using Au/HT, the substrate scope of amines was investigated (Table 2). Aliphatic and alicyclic secondary amines were converted to the corresponding oxamides in high yields with excellent selectivities (entries 1–11). Diverse functional groups on the amines such as ether, acetal, amine and allyl groups were compatible under the present reaction conditions. Primary aliphatic and benzylic amines were not suitable for the double-carbonylation; the corresponding imines were mainly formed (entries 12 and 13). Interestingly, when 2-methyl- and 4-ethyl-piperidines were used as a mixture of substrates, 4-ethyl piperidine reacted exclusively to afford the corresponding double-carbonyl compound in an excellent yield while 2-methyl piperidine remained intact. The above phenomenon is in sharp contrast with the result obtained using previously reported homogeneous catalyst $Pd(OAc)_2$ where a mixture of symmetric and asymmetric double-carbonylation products was formed (Scheme 1). These differences can be explained by the specific property of the solid catalysis; the steric hindrance by the substituent on the *ortho* position of piperidine prevents the coordination of the N atom to Au/HT.

Table 2 Double-carbonylation of various amines to oxamides[a]

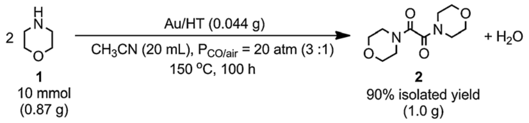


Entry	Substrate	Product	Time (h)	Yield[b] (%)	Sel.[b] (%)
1	Me_2NH	$(Me_2NCO)_2$	12	73	99
2	Et_2NH	$(Et_2NCO)_2$	12	87	99
3			12	92	99
4			12	87	99
5[c]			24	80	99
6[c]			24	87	99
7[c]			24	86	99
8			24	85	99
9			24	90	99
10			24	93	99
11[c]			24	85	99
12			12	43	81
13			12	49	99

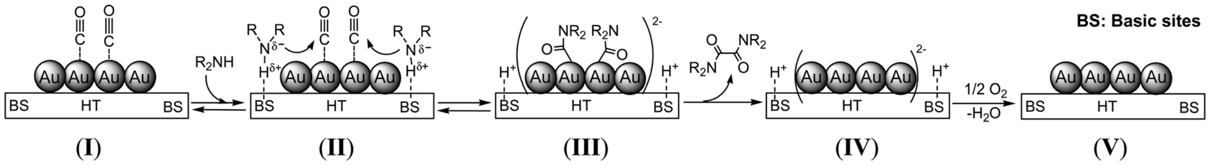
[a] Reaction conditions: Au/HT (0.1 g), amine (0.5 mmol), CH_3CN (5 mL). [b] Determined by GC using an internal standard technique. [c] Amine (0.2 mmol).



Scheme 1 Competitive reaction of 2-methyl- and 4-ethyl-piperidine.



Scheme 2 10 mmol-scale double-carbonylation of **1** using Au/HT.



Scheme 3 Plausible reaction mechanism.

Au/HT was also applicable to scale-up conditions (Scheme 2). Lowering the catalyst loading to 0.02 mol% gave a turnover frequency (TOF) of 45 h^{-1} and a turnover number (TON) of 4500 upon prolonged heating at elevated temperatures, which demonstrated the high activity and stability of Au/HT. These values for TOF and TON of Au/HT are much greater than those of previously reported catalytic systems such as $PdCl_2(PPh_3)_2$/1,4-dichloro-2-butene:[4a] TOF = 11 h^{-1}, TON = 192; $Pd(OAc)_2/K_2CO_3/KI$:[4c] TOF = 5 h^{-1}, TON = 15; $PdCl_2$:[4e] TOF = 0.3 h^{-1}, TON = 7; $PdCl_2(MeCN)_2/CuI/O_2$:[4d] TOF = 0.44 h^{-1}, TON = 8.8; $NiBr_2(NH_2Bu)_4/FeCl_3(OPPh_3)_2$:[4b] TOF = 2 h^{-1}, TON = 12.

To obtain insight into the Au/HT-catalyzed double-carbonylation, the dependency of reaction rates in the double-carbonylation of **1** was investigated.[11] The initial rates (R_0) were linearly proportional to the amount of Au/HT and independent of the O_2 pressure. The R_0 increased with increasing CO pressure and concentration of **1**, and approached an asymptotic plateau at high pressures and high concentrations, respectively, suggesting that the reaction proceeds through the Langmuir–Hinshelwood mechanism. A small kinetic isotope effect (k_H/k_D = 1.2) was observed in the double-carbonylation of 1-(D)-morpholine. Fourier transform infrared (FT-IR) studies of Au/HT were also carried out. When Au/HT was treated with 1-(*H*)- and 1-(D)-morpholine vapor at 353 K, new bands appeared at 3234 and 2512 cm^{-1}, corresponding to the O–H and O–D stretching bands of Mg–O(*H*-morpholine)–Al and Mg–O(D-morpholine)–Al, respectively, on the surface of HT. This reveals the activation of morpholine by the strong adsorption on basic sites of HT.[11]

Based on the above results, a plausible reaction mechanism is proposed as shown in Scheme 3. First, CO is adsorbed on Au NPs on HT (**I**). Next, a H atom on the N–H group of an amine (R_2NH) is withdrawn by a basic site of HT to promote the nucleophilic attack of the $R_2N^{\delta-}$ to the CO adsorbed on Au NPs (**II**),[12] affording the formation of H^+ and $[Au\text{-}CONR_2]^-$ species (**III**). Subsequent coupling of $[Au\text{-}CONR_2]^-$ species occurs to produce an oxamide $[(CONR_2)_2]$ accompanied by negatively charged Au NPs and H^+ (**IV**). The resulting hydrogen species are treated by O_2 to afford H_2O, thereby completing the catalytic cycle (**V**). The results obtained from our kinetic experiments also support the above mechanism.[13]

In conclusion, we discovered a highly efficient double-carbonylation of amines to the corresponding oxamides using Au NPs without any additives under mild reaction conditions. Au/HT showed outstanding catalytic activity compared to those of other metal NPs and previously reported catalyst systems. Furthermore, the solid Au/HT catalyst was recoverable and reusable without any loss of its activity or selectivity. The experimental results combined with kinetic and spectroscopic studies also establish that Au NPs and basic supports promote the double-carbonylation in a concerted fashion.

Supports of this work were provided by JSPS KAKENHI (23686116 and 10J01438). We thank Dr Uruga and Dr Nitta (SPring-8) for XAFS measurements. The TEM experiments were carried out at a facility of the Research Center for Ultrahigh Voltage Electron Microscopy, Osaka University.

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5 Au NPs on various supports were synthesized by our previously reported method. See: T. Mitsudome, A. Noujima, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Green Chem.*, 2009, **11**, 793.

6 The flammability range of CO in air is 13.5–73.0% at 200 °C. See: C. M. Bartish and G. M. Drissel, *"Carbon monoxide" in Kirk-Othmer Encyclopedia of Chemical Technology*, Wiley, New York, 3rd edn, 1984, vol. 4, p. 774. The concentration of CO (83%) in air under our reaction conditions (CO (5 atm) and air (1 atm) at 110 °C) is out of the flammability range, showing the practical advantage of the present Au/HT catalytic system.

7 Au/HTs with different particle sizes were prepared by our previously reported method. See: A. Noujima, T. Mitsudome, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Angew. Chem., Int. Ed.*, 2011, **50**, 2986.

8 The preparation of Pt/HT, Pd/HT, Rh/HT, Ag/HT, and Ru/HT was reported in our previous study. See: T. Mitsudome, A. Noujima, Y. Mikami, T. Mizugaki, K. Jitsukawa and K. Kaneda, *Chem.–Eur. J.*, 2010, **16**, 11818.

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10 For a recent report of ICP measurements being crucial for gold catalysis, see: A. S. K. Hashmi, C. Lothschütz, R. Dőpp, M. Ackermann, J. De Buck Becker, M. Rudolph, C. Scholz and F. Rominger, *Adv. Synth. Catal.*, 2012, **354**, 133.

11 See ESI† for details.

12 It has been known that solid bases abstract H atoms from amines on their basic sites to catalyze the addition of amines to dienes. See: (*a*) Y. Kakuno and H. Hattori, *J. Catal.*, 1984, **85**, 509; (*b*) H. Hattori, *Appl. Catal., A*, 2001, **222**, 247.

13 The proposed mechanism agreed well with the kinetic data showing that the rate-determining step is coupling of the carbamoyl species adsorbed on Au NPs (**III** → **IV** in Scheme 3). See ESI† for details.