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Keywords
Lactams, Nanogold, Ceria, Cyclic amines, Oxidation, Amine oxidation

Aerobic oxidation of cyclic amines to lactams catalyzed by ceria-supported nanogold

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Abstract The oxidative transformation of cyclic amines to lactams, which are important chemical feedstocks, is efficiently catalyzed by CeO_2-supported gold nanoparticles (Au/CeO_2) and Aerosil 200 in the presence of an atmosphere of O_2. The complete conversion of pyrrolidine was achieved in 6.5 hours at 160 ^oC, affording a 97% yield of the lactam product 2-pyrrolidone (γ-butyrolactam), while 2-piperidone (δ-valerolactam) was synthesized from piperidine (83% yield) in 2.5 hours. Caprolactam, the precursor to the commercially important nylon-6, was obtained from hexamethyleneimine in 37% yield in 3 hours. During the oxidation of pyrrolidine, two transient species, 5-(pyrrolidin-1-yl)-3,4-dihydro-2*H*-pyrrole (amidine-5) and 4-amino-1-(pyrrolidin-1-yl)butan-1-one, were observed. Both of these compounds were oxidized to 2-pyrrolidone under catalytic conditions, indicating their role as intermediates in the reaction pathway. In addition to the reactions of cyclic secondary amines, Au/CeO_2 also efficiently catalyzes the oxidation of N-methyl cyclic tertiary amines to the corresponding lactams at 80 ^oC and 100 ^oC.

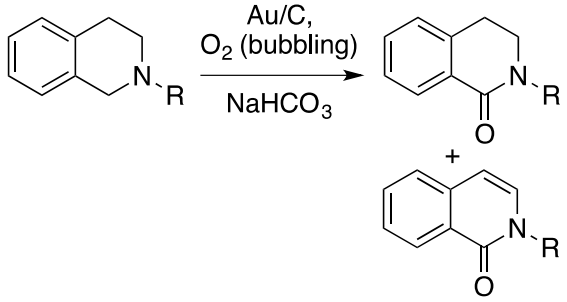
Keywords Lactams, nanogold, ceria, cyclic amines, oxidation, amine oxidation

1 Introduction

Lactams have important uses as feedstocks in many chemical processes, particularly in the plastics and pharmaceutical industries [1-13]. For example, N-methyl-2-pyrrolidone is widely-used as a solvent [4, 6], and the lactams 2-pyrrolidone (butyrolactam) and 2-piperidone (valerolactam) can be polymerized into nylon-4 and nylon-5, respectively [3, 14, 15]. Furthermore, caprolactam is reported to have biological activity [16] and is polymerized on a large scale into the widely-used nylon-6 [2, 17-20]. Despite their commercial importance, lactams are manufactured by methods that have significant shortcomings, such as multiple reaction steps and substantial waste generation [5, 6, 21]. Following earlier reports of the Gif system (Fe, Zn, O_2)-catalyzed oxidation of tertiary amines to the corresponding lactams, albeit in low yields [22, 23], the development of efficient catalysts for the syntheses of lactams remains an active area of research [24]. An example, recently reported by Milstein and co-workers, employs a ruthenium complex with a pincer ligand that was capable of homogeneously catalyzing the oxidation of cyclic secondary amines to the corresponding lactams, with water as the source of oxygen [25]. For that catalyst, reaction times ranged from 48 to 89 hours at 150 ^{o}C. Another type of catalyst, supported nanogold, was shown to catalyze the aerobic oxidation of benzo-fused cyclic amines. For example, Au nanoparticles supported on graphite catalyzed the oxidation of benzo-fused cyclic tertiary amines, resulting mostly in the formation of both the corresponding amides and the enamides (Scheme 1) [26]. Also, Sakurai and co-workers showed that nanogold supported on polyvinylpyrrolidone (PVP) catalyzes the oxidation of 1,2,3,4-tetrahydroisoquinoline and other benzo-fused cyclic secondary amines [27]. However, a large amount of NaOH additive (1 – 2 equiv) was required, and

the reactions often led to mixtures of products. Additionally, the oxidation of a derivative of tetrahydroisoquinoline to the corresponding amide and enamide was catalyzed by polymer-confined Au nanoclusters [28].

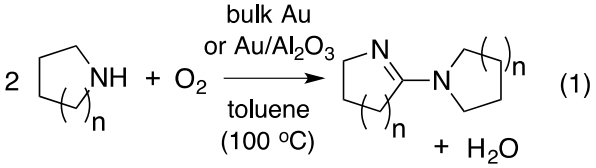
Scheme 1 Aerobic oxidation of cyclic tertiary amines to amides and enamides, catalyzed by graphite-supported gold nanoparticles [26].



Following the discovery of the catalytic activity of nanoparticulate CeO_2 and CeO_2-supported nanogold for the oxidation (O_2) of aromatic amines and alcohols [29-31], the number of reports has surged on the use of Au supported on CeO_2 as well as mixed CeO_2-metal oxides for amine oxidation reactions. For example, CeO_2-supported nanogold catalyzes the high-pressure (5 bars of O_2) oxidation of benzylamine to N-benzylidenebenzylamine [32, 33]. Also, the catalytic activity of *in situ* generated CeO_2-supported nanogold in the oxidation of benzylamine, indoline, dibenzylamine, and N-*t*-butylbenzylamine into the corresponding imines was reported [33-35]. Furthermore, nanogold supported on CeO_2-Fe_2O_3 catalyzed the oxidation of benzylamine to the imine [36].

Very recently, after the present work was completed, Mizuno and co-workers described the Au/Al_2O_3-catalyzed aerobic oxidation of a range of secondary and tertiary amines to amides [37]. Their reactions were conducted in water solvent under 1 atm of O_2 at 80-100 ^oC.We previously reported that bulk Au and alumina-supported Au catalyzed the oxidation of cyclic secondary amines to amidines (eq. 1) [38, 39]. We also showed

that Aerosil 200 (amorphous fumed silicon dioxide) catalyzed the hydrolysis of amidine-5, amidine-6, or amidine-7 into 2-pyrrolidone (42% yield), 2-piperidone (60% yield) or caprolactam (73% yield), respectively, in the presence of H_2O (eq. 2). Subsequently, we



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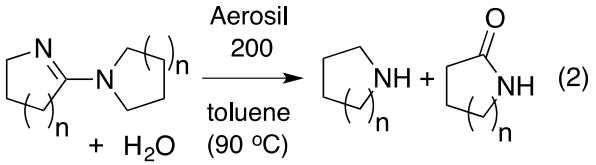

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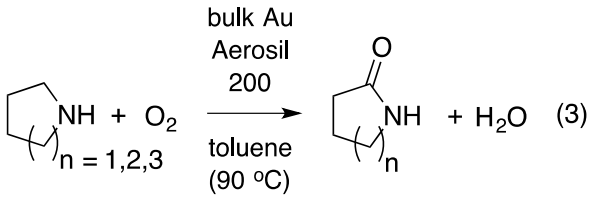
demonstrated that a one-pot combination of bulk Au powder and Aerosil 200 catalyzed the conversion of cyclic secondary amines (eq. 3) directly to lactams [40]. Although our one-pot procedure is a novel method for the preparation of lactams, it suffers from the use of a large amount of bulk Au powder (1.00 g per 0.20 mmol of substrate) and gives only low to medium product yields (caprolactam: 11%, 2-pyrrolidone: 35%, and 2-piperidone: 51%). The ability of CeO_2 to facilitate oxidation reactions [29, 30] and the improved



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efficiency of Au when supported on high surface area metal oxides [38, 39], including CeO_2 [32], prompted us to explore the activity of Au/CeO_2 in the oxidation of cyclic amines to lactams. We report herein that Au/CeO_2 efficiently catalyzes the oxidation of both cyclic secondary and N-methyl cyclic tertiary amines to the corresponding lactams.

The reaction times are much shorter, product yields are higher, and the amount of catalyst loading is much lower than the bulk gold-catalyzed reactions.

2 Experimental Section

All reagents were obtained from commercial sources (Sigma-Aldrich, Fisher Scientific, and Acros Organics) and used without further purification. Toluene, THF, and CH_2Cl_2 were dried and deoxygenated by passage through columns of alumina and reduced copper. Ultra pure water was obtained from a Milli-Q® UV plus water purification system. Aerosil 200 was a gift from the Evonik Degussa Corporation. NMR spectra were obtained using Varian MR 400 MHz and Bruker AVIII 600 MHz spectrometers. NMR peak positions were referenced against residual proton (δ 7.26 ppm) or ^{13}C (77.36 ppm) resonances in $CDCl_3$. HRMS data were collected on an Agilent 6540 QTOF accurate mass MSMS instrument.

2.1 GC and GC-MS analyses

GC analyses of reaction mixtures were performed on an HP-6890 instrument equipped with an HP-5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, 5% phenyl, 95% methyl silicone polymer). Reaction products were identified by comparing their GC retention times with those of authentic samples and yields were determined by GC integrations relative to dodecane as an internal standard. Yields of products were reproducible within ± 6% as determined by two or more runs of representative reactions. GC-MS analyses were carried out using an Agilent 7890A-5975C instrument, equipped with an HP-5MS column.

2.2 Electron Microscopy

Transmission electron microscopy (TEM) was carried out on a FEI Tecnai G2 F20 field emission microscope and a scanning transmission electron microscope (STEM) operating at 200kV (point-to-point resolution <0.25 nm and a line-to-line resolution of < 0.10 nm). TEM samples were prepared by placing 2-3 drops of dilute ethanol suspensions onto lacey-carbon-coated copper grids. The compositions of the Au/CeO_2 structures were characterized by elemental mapping and energy dispersive X-ray spectroscopy (EDS) in the STEM mode.

2.3 Surface Area and Porosimetry

Textural properties of the CeO_2 support and Au/CeO_2 catalysts were measured by nitrogen sorption isotherms at -196 ^oC in a Micromeritics Tristar analyzer. Surface areas were calculated using the Brunauer-Emmett-Teller method, and the pore size distribution was calculated by the Barrett-Joyner-Halenda (BJH) method. Prior to surface area measurements, samples were pretreated under flowing N_2 gas for 6 h at 100 ^oC.

2.4 ICP-OES analyses

The Au loadings on the CeO_2 support were determined using a PerkinElmer Optima 2100 DV inductively coupled plasma-optical emission spectroscope (ICP-OES). Catalyst samples (5 mg) were digested for 24 h in an aqueous solution containing a mixture of HF and HCl (0.18 and 5.0 v/v %, respectively). A 1-mL aliquot was then diluted to 10 mL with a 10 v/v % aqueous aqua regia solution.

2.5 X-ray Photoelectron Spectroscopy (XPS)

The XPS analysis was carried out using a PHI 5500 multitechnique system with a standard Al X-ray source. Charge correction was done by setting the Ce 3d binding

energy peak to 882.66 eV [41].

2.6 Preparation of ceria-supported nanogold (Au/CeO_2) catalysts

The synthesis and characterization of the CeO_2 support (169 – 203 m^2/g) was published earlier [42]. The supported catalysts was prepared according to a procedure reported by Pérez et al. [32]. $HAuCl_4 \bullet 3H_2O$ (213 mg, 0.541 mmol) was dissolved in ultra pure water (390 mL). The solution was then added to a CeO_2 suspension (1.00 g in 13 mL water). Following pH adjustment to 10, using 0.2 M aqueous NaOH, the resulting suspension was stirred for 18 h at room temperature. After filtration, the supported catalyst was washed with water (400 mL in 40-mL aliquots) until the wash was free of chloride ions, as indicated by the absence of a AgCl precipitate when the tenth 40-mL wash was treated with 0.001 M aqueous $AgNO_3$. After being washed, the solid was dried under reduced pressure at room temperature. Thereafter, the supported catalyst was treated with sec-phenethyl alcohol at 160 ^oC for 20 min. After filtration, the resulting powder was washed with water and acetone, then dried overnight under reduced pressure at room temperature. The gold loading was found to be 5.4 ± 0.1 wt% (by ICP-OES).

2.7 General procedure for the Au/CeO_2-catalyzed conversion of cyclic secondary amines to lactams, in the presence of O_2, as illustrated with pyrrolidine

A 100-mL Schlenk flask, equipped with a high-vacuum Teflon stopcock, was charged with a stir bar and 70 mg of 5.4 wt% Au/CeO_2 catalyst (3.78 mg, 0.0192 mmol of Au). This was followed by the addition of 111 mg of Aerosil 200 (amorphous fumed silicon dioxide), 0.45 mL of ultra-pure water, 1.11 mL of a 400. mM stock solution of pyrrolidine (0.444 mmol) in diglyme solvent, and 3.33 mL of a 23.8-mM dodecane stock solution (0.0793 mmol internal standard) in diglyme. The reaction flask was purged

through the side arm with oxygen for 1 min and sealed with the stopcock. (A pure oxygen atmosphere, achieved by a more rigorous exclusion of air, led to lower lactam yields and the formation of a variety of unidentified products, in addition to the lactam. None of the by-products were identified). The contents of the sealed flask were stirred at 160 ^{o}C in an oil bath. The mole ratio of gold atoms to substrate was 1:23. To monitor the course of the reaction, the mixture was cooled periodically to ambient temperature and an aliquot was withdrawn for GC analysis. Then the reaction flask was purged again with O_2, re-sealed, and re-heated to 160 ^{o}C. After 6.5 h of reaction time, 100% substrate conversion was achieved, with a 97% yield of 2-pyrrolidone. No peroxides (Indigo Instruments peroxide test strips) were detected in the final reaction mixture. Catalytic conversions of the intermediates amidine-5 (**I**) and [4-amino-1-(pyrrolidin-1-yl)butan-1-one)] (**II**) into 2-pyrrolidone followed the same procedure. When the reaction of pyrrolidine was carried out under an air atmosphere, the same procedure was followed as above, but without the oxygen gas purge.

2.8 Treatment of pyrrolidine with Au/CeO_2 under an argon atmosphere

After a 100-mL Schlenk flask was charged with a stir bar, 70 mg of 5.4 wt% Au/CeO_2 catalyst, 111 mg of Aerosil 200, 0.45 mL of ultra-pure water, pyrrolidine in diglyme, and dodecane (internal standard) as described above (section 2.7), the reaction vessel was degassed with three freeze-pump-thaw cycles, back-filled with argon, and sealed. Stirring and heating the reaction mixture at 160 ^{o}C produced an 8% GC yield of 2-pyrrolidone after 6.5 h.

2.9 Catalyst reusability

An initial catalytic run was set up as described in Section 2.7 with 70 mg of 5.4 wt%

Au/CeO_2 catalyst, 111 mg of Aerosil 200, 0.45 mL of ultra-pure water, 0.444 mmol of pyrrolidine, and 0.0793 mmol of dodecane (internal standard) in diglyme. After periodic GC analysis of the reaction solution during the first catalytic run (6.5 h of heating at 160 ^oC), the Au/CeO_2-Aerosil catalyst was recovered by filtration of the reaction mixture. The recovered catalyst was rinsed repeatedly with 5-mL aliquots of diglyme, until the catalyst was free of the lactam, as determined by GC analysis of the rinse. The catalysts were further rinsed with two 5-mL aliquots of acetone. The rinsed and air-dried catalyst was then used in subsequent catalytic runs, as described in section 2.7 above.

2.10 Procedure for the Au/CeO_2-catalyzed conversion of N-methyl cyclic tertiary amines into lactams, in the presence of O_2, as illustrated with N-methylpyrrolidine

A 100-mL Schlenk flask, equipped with a high-vacuum Teflon stopcock was charged with a stir bar and 70 mg of 5.4 wt% Au/CeO_2 catalyst (3.78 mg, 0.0192 mmol Au). This was followed by the addition of 0.45 mL of ultra-pure water, 2.66 mL of 1,4-dioxane, 1.21 mL of a 404-mM stock solution of N-methylpyrrolidine (0.488 mmol) in 1,4-dioxane, and 0.67 mL of a dodecane (internal standard) stock solution (120. mM) in 1,4-dioxane. The reaction flask was purged through the side arm with oxygen for 1 min and sealed with the stopcock. The contents of the flask were stirred at 80 ^oC in an oil bath. The mole ratio of gold atoms to substrate was 1:25. GC analysis was performed as described in Section 2.7. At 3.5 h of reaction time, a 100% substrate conversion was achieved with a 97% yield of N-methyl-2-pyrrolidone. When the reaction of N-methylpyrrolidine was carried out under an air atmosphere, the same procedure was followed as above, but without the purge with oxygen gas. Periodic GC analysis of the reaction solution revealed a 97% yield of N-methyl-2-pyrrolidone after 10 hours of

heating at 80 °C. When the reaction was carried out under an argon atmosphere, using the procedure outlined in section 2.8, GC analysis of the reaction solution after 3.5 hours of heating at 80 °C revealed a 4% yield of N-methyl-2-pyrrolidone.

2.11 Preparation and characterization of amidine-5 (I)

Amidine-5 was synthesized by treating 221 mg (3.09 mmol) of pyrrolidine in 75 mL of toluene with O_2 in the presence of 1.135 g of bulk gold catalyst, according to a published procedure [38]. The oily product was isolated by filtration of the reaction mixture and removal of the toluene solvent under reduced pressure (190 mg, 1.37 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.86 (m, 4H, C*H*$_2$), 1.93 (m, 2H, C*H*$_2$), 2.47 (t, 2H, *J* = 8.0 Hz, C*H*$_2$), 3.35 (t, 4H, *J* = 8.0 Hz, C*H*$_2$), 3.64 (t, 2H, *J* = 8.0 Hz, C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.15, 25.82, 32.86, 47.78, 56.95, 166.85. HRMS (+ESI): calcd for $[MH]^+$ $(C_8H_{15}N_2)^+$ *m/z* 139.1235; found *m/z* 139.1230.

2.12 Synthesis and characterization of [4-amino-1-(pyrrolidin-1-yl)butan-1-one)] (II)

Intermediate **II** was synthesized and obtained as a light yellow oil (53% yield) from pyrrolidine and Boc-protected γ-aminobutyric acid (see Supporting Information for experimental details). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (br, 2H, N*H*$_2$), 1.81 (m, 4H, C*H*$_2$), 1.90 (m, 2H, C*H*$_2$), 2.29 (t, 2H, *J* = 8.0 Hz, C*H*$_2$), 2.72 (t, 2H, *J* = 8.0 Hz, C*H*$_2$), 3.40 (m, 4H, C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 24.68, 26.39, 29.00, 32.35, 42.19, 45.91, 46.88, 171.61 (N*C*O). HRMS (+ESI): calcd for $[MH]^+$ ($[C_8H_{17}N_2O]^+$) *m/z* 157.1341; found *m/z* 157.1334.

3 Results and Discussion

3.1 Catalyst characterization

The Au/CeO_2 catalyst was synthesized from $HAuCl_4 \bullet 3H_2O$ and CeO_2 as described in

section 2.6 above. Nitrogen physisorption studies were used to determine the surface areas of the support and catalyst. The surface area for the 5.4 wt% Au/CeO_2 catalyst was 146 m^2g^{-1} (Table S1, Fig. S13), which is lower than that for the support (180 m^2g^{-1}), likely due to the blockage of pores.

Powder X-ray diffraction (PXRD) analysis of Au/CeO_2 showed peaks that were indexed to the cubic fluorite phase of ceria. These peaks were broad, suggesting small ceria crystallites and/or lattice strain. The small crystallite size is consistent with the high surface areas observed. Also present were very low intensity, broad peaks observed around 38°, corresponding to the reflections of fcc-Au. This indicates the presence of small (<5 nm) gold crystallites. Furthermore, STEM images (Fig. 1a) showed the presence of spherical Au particles with an average size of 6.5 ± 1.1 nm (Fig. S19b),

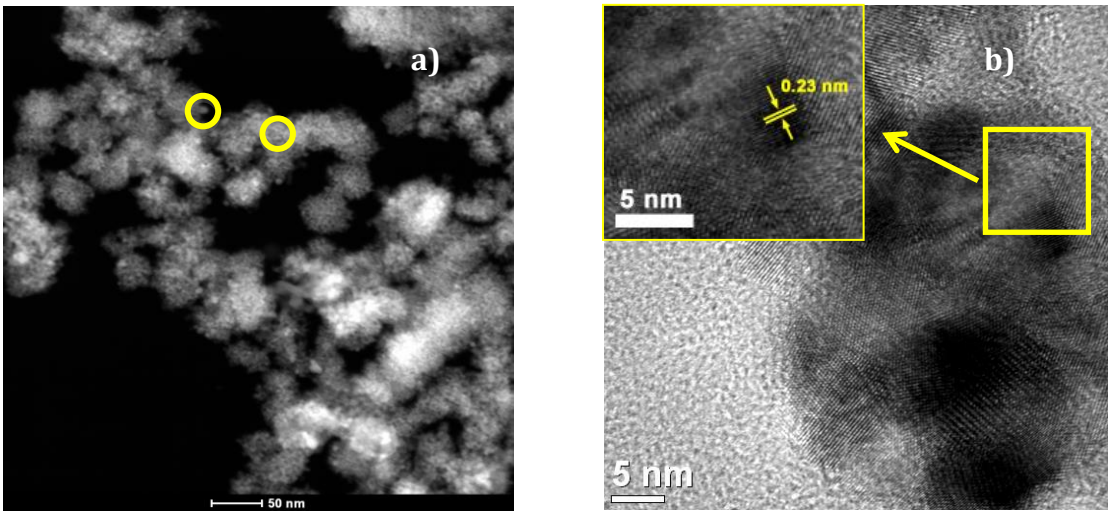


Figure 1. (a) Scanning transmission electron microscopy (STEM) image of the unused 5.4 wt% Au/CeO_2 catalyst. Circles indicate representative Au nanoparticles. (b) High-resolution transmission electron microscopy (HR-TEM) image showing the presence of Au particles on the surface of CeO_2 for the unused 5.4 wt% Au/CeO_2 catalyst.

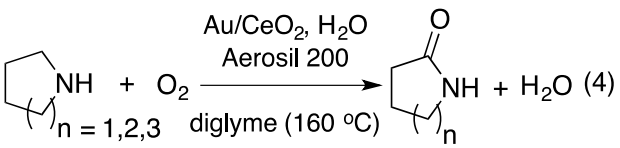
consistent with the PXRD data. High-resolution transmission electron microscopy (HR-TEM) of the gold particles showed a 0.23 nm d spacing, which agrees well with the (111)

surface termination for Au particles (Fig. 1b) [43, 44]. The STEM image (Fig. 1a) also illustrates the porous nature of the catalyst support, consistent with the high surface areas from nitrogen physisorption analysis. The CeO_2 support surface termination is predominantly the (111) plane, as previously reported [42].

X-ray photoelectron spectroscopic studies were undertaken in order to probe the oxidation state of Au in the supported catalyst. The XPS spectrum (Fig. S18) of a fresh sample of 5.4 wt% Au/CeO_2 showed two peaks in the Au 4f core level region (83 – 93 eV). The spectrum was fitted with the two spin-orbit $4f_{7/2}$ and $4f_{5/2}$ components of Au separated by 3.6 eV [45, 46]. Deconvolution of the spectrum suggests the catalyst consists mainly of metallic Au^0 (84.0 eV for $4f_{7/2}$ and 87.6 eV for $4f_{5/2}$, 93 %) but also contains a small fraction of oxidized Au^{+1} (85.8 eV for $4f_{7/2}$ and 89.4 eV for $4f_{5/2}$, 7 %). These results are consistent with the report by Casaletto and co-workers, who obtained a 90:10 atomic ratio of Au^0 to Au^{+1} for Au/CeO_2 also prepared by deposition-precipitation. Importantly, they observed high CO oxidation activity for this catalyst compared to other supports and attributed it to the presence of Au^{+1} and its stabilization as AuO^- by the cerium oxide support [46].

3.2 Au/CeO_2-catalyzed oxidation of cyclic secondary amines to lactams

Gold nanoparticles supported on high surface area (169 – 203 m^2/g) CeO_2 (Au/CeO_2), together with Aerosil 200 as a co-catalyst, efficiently catalyze the oxidation of cyclic secondary amines into lactams (eq. 4). Product yields were maximized by varying the temperature, reaction time, and the amounts of water, oxygen, and co-catalyst (Table 1).



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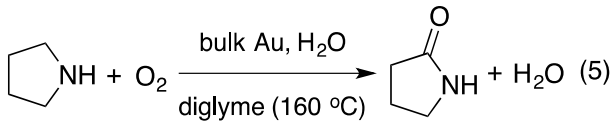
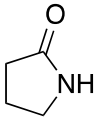
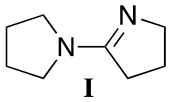
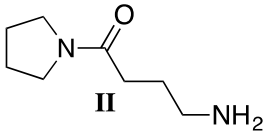
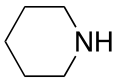
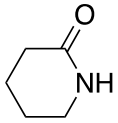
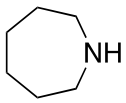
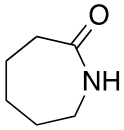
For pyrrolidine (100 mM), the optimized reaction conditions involved heating a diglyme solution with 5.4 wt% Au/CeO_2, Aerosil and H_2O (56 equiv relative to pyrrolidine) under one atmosphere of O_2 at 160 ^oC for 6.5 h. This resulted in complete substrate conversion to give a 97% yield of 2-pyrrolidone (Table 1, entry 1, Fig. 2). When the catalytic oxidation of pyrrolidine to 2-pyrrolidone was carried out under the same conditions, but without the Aerosil co-catalyst, a product yield of 75% (Table 1, entry 3) was achieved. If the reaction was performed under air (1 atm) rather than O_2 (1 atm) keeping all other parameters at optimized reaction conditions, a 93% yield of the lactam product was achieved in a reaction time of 6.5 h (Table 1, entry 6). Under an atmosphere of argon gas, only an 8% yield of 2-pyrrolidone was obtained (Table 1, entry 5). The small amount of observed product was presumably due to the presence of adventitious O_2 [47]. Varying the amount of added H_2O from 56 equiv, while keeping all other parameters at optimized values, resulted in lower yields of 2-pyrrolidone as follows (Fig. S10): 18% (0 equiv), 34% (10 equiv), 55% (28 equiv), 80% (90 equiv), and 77% (112 equiv). Moreover, under optimized conditions but with only CeO_2 (no deposited nanogold) and Aerosil as catalysts, no lactam formation was observed.

To demonstrate the superiority of Au/CeO_2 over bulk gold powder in the catalytic oxidation of amines into lactams, 1.00 g of Au powder with Aerosil 200 (111 mg) was used under conditions optimized for 5.4 wt% Au/CeO_2, in the catalytic oxidation of pyrrolidine. This reaction gave a 27% yield of 2-pyrrolidone after 6.5 h (Table 1, entry 2, eq. 5), as compared with a 97% product yield obtained with Au/CeO_2 (Table 1, entry 1), which shows that 3.78 mg of Au in Au/CeO_2 is more effective as a catalyst than 1.00 g of bulk gold powder.



With Aerosil 200, lactam yield = 27% at 6.5 h
Without Aerosil 200, lactam yield = 18% at 6.5 h

Table 1. Catalytic conversion of cyclic secondary amines, amidine-5 (I), or 4-amino-1-(pyrrolidin-1-yl)butan-1-one) (II) to lactams in diglyme solvent, under O_2 (1 atm, unless stated otherwise), at 160 °C[a]

Entry	Substrate	Product	Time (h)	Product Yield (%)	TON[i]
1			6.5	97[a]	22.4
2	"	"	6.5	27[a,b]	0.0236
3	"	"	6.5	75[c]	17.4
4	"	"	6.5	18[b,c]	0.0157
5	"	"	6.5	8[d]	1.85
6	"	"	6.5	93[e]	21.5
7	 **I**	"	6.5	95[f,j]	23.3
8	 **II**	"	6.5	96[g,j]	21.8
9			2.5	83[a]	19.2
10			3	37[h]	3.43
11	"	"	4	19[a]	4.40

[a]0.444 mmol (100 mM; 1 eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 111 mg of Aerosil (4.2 eq), 0.45 mL H_2O (56 eq), 4.44 mL diglyme. [b]1.00 g of bulk Au powder used instead of Au/CeO_2. [c]Aerosil not added. [d]Under argon atmosphere. [e]Under air atmosphere (1 atm). [f]0.235 mmol (100 mM; 1 eq) substrate, 36.6 mg of 5.4 wt% Au/CeO_2, 59 mg of Aerosil (4.2 eq), 0.236 mL of H_2O (56 eq). [g]0.218 mmol (100 mM; 1 eq) substrate, 34 mg of 5.4 wt% Au/CeO_2, 55 mg of Aerosil (4.2 eq), 0.22 mL of H_2O (56 eq). [h]0.20 mmol (40

mM; 1 eq) substrate, 78.8 mg of 5.4 wt% Au/CeO_2, 50 mg of Aerosil (4.2 eq), 0.20 mL of H_2O (56 eq). [i]TON is defined as the number of moles of product per mole of Au. [j]Yield assumes that intermediates **I** and **II** give 2 moles of 2-pyrrolidone.

Furthermore, the use of bulk gold without Aerosil under the same conditions produced only 18% of 2-pyrrolidone from the oxidation of pyrrolidine (Table 1, entry 4, eq. 5), as compared with a 75% yield in the Au/CeO_2-catalyzed reaction without Aerosil (Table 1, entry 3). Notably, the oxidation of pyrrolidine catalyzed by bulk gold at a lower temperature (100 ^oC in toluene), without Aerosil, gave 93% yield of amidine-5 (eq. 1, n = 1), and not 2-pyrrolidone [40].

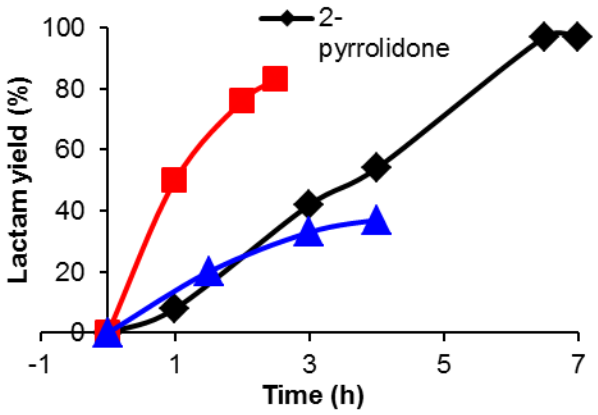


Fig. 2. Lactam product yields during the Au/CeO_2-Aerosil-catalyzed oxidation of cyclic amines in diglyme at 160 ^oC under optimized conditions. (a) pyrrolidine to 2-pyrrolidone: 0.444 mmol (100 mM) pyrrolidine, 70 mg of 5.4 wt% Au/CeO_2, 111 mg of Aerosil (4.2 eq), 0.45 mL H_2O (56 eq), 4.44 mL diglyme; (b) piperidine to 2-piperidone: 0.444 mmol (100 mM) piperidine, 70 mg of 5.4 wt% Au/CeO_2, 111 mg of Aerosil (4.2 eq), 0.45 mL H_2O (56 eq), 4.44 mL diglyme; (c) hexamethyleneimine to caprolactam: 0.20 mmol (40 mM) hexamethyleneimine, 78.8 mg of 5.4 wt% Au/CeO_2, 50 mg of Aerosil (4.2 eq), 0.20 mL of H_2O (56 eq), 5.0 mL diglyme.

The scalability of the reaction was demonstrated by increasing the pyrrolidine concentration 10-fold, from 0.100 M (0.444 mmol) to 1.06 M (4.76 mmol), in diglyme but using the same amount of Au/CeO_2 catalyst and Aerosil. The reaction solution was

heated under an O_2 atmosphere at 160 ^oC with 70 mg of 5.4 wt% Au/CeO_2, 111 mg of Aerosil and 2.38 mL of H_2O (28 equiv. relative to pyrrolidine). After 10 h of heating, GC analyses revealed a 99% amine substrate conversion and an 84% yield of 2-pyrrolidone, representing a TON of 207, based on the moles of Au in the Au/CeO_2 catalyst (TON = mol of product per mole of Au).

A heterogeneity test of the catalyst was performed using a hot filtration technique. First, a reaction was run using a mixture containing 100 mM pyrrolidine in diglyme together with the Au/CeO_2-Aerosil catalyst, H_2O and dodecane (internal standard) at 160 ^oC under optimized conditions. After 40 min of reaction, a 22% yield of 2-pyrrolidone was obtained. At this point, the hot mixture was filtered and the solution phase was heated again at 160 ^oC under an O_2 atmosphere. After 5 h, no further conversion of the remaining pyrrolidine occurred, demonstrating that the catalytically active species is not in the solution phase of the reaction and that the Au/CeO_2-Aerosil solid is the active catalyst.

In assessing the recyclability of the catalyst, the Au/CeO_2-Aerosil solids recovered from an optimized pyrrolidine oxidation reaction that produced a 98% yield of 2-pyrrolidone were washed with diglyme until no lactam was detected by GC in the rinsate (see experimental section). The washed and air-dried catalyst used in a second catalytic cycle produced an 88% yield of 2-pyrrolidone. However, when the recovered catalyst was washed, dried, and used in a third catalytic cycle, only a 14% yield of 2-pyrrolidone was obtained.

After the Au/CeO_2 catalyst sample had been used in 3 catalytic runs, its XPS spectrum remained unchanged from that of the freshly prepared material (Figs S18a and

S18b). However, powder x-ray diffraction (PXRD) analysis of the Au/CeO_2 catalyst recovered from the third catalytic cycle showed that the Au crystallite size had grown from around 5 nm (for the fresh catalyst; Fig. S14a) to 29 nm (for the used catalyst; Fig. S14b). Also, TEM and STEM images (Fig. S15b and S16b, respectively) of the used catalyst revealed aggregated gold of about 200 nm in size. Such an increase in gold particle size would lead to a reduction in the number of catalytically active sites on the Au surface, which could be the reason for the decreased activity upon recycling. A sharp drop in catalytic activity was also observed during the Au/TiO_2-catalyzed oxidation of glycerol to lactic acid at 90 ^oC after 5 catalytic runs; this loss of activity was attributed to an increase in the size of the gold particles [44].

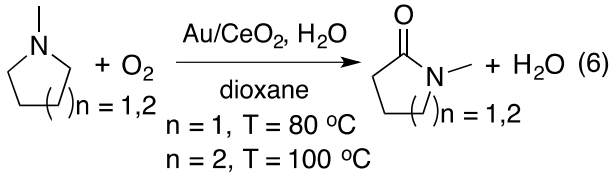
The scope of the reaction was expanded to additional cyclic secondary amines. Treatment of piperidine (eq. 4, n = 2) under the optimized conditions for the catalytic oxidation of pyrrolidine (100. mM, 0.444 mmol) afforded an 83% yield of 2-piperidone in 2.5 h, with a 100% conversion of the piperidine substrate (Table 1, entry 9). Thus, the optimized reaction conditions for the oxidation of both pyrrolidine and piperidine were the same.

The optimized conditions for the oxidation of the 7-membered cyclic amine, hexamethyleneimine, into caprolactam (eq. 4, n = 3) involved a 40 mM solution of hexamethyleneimine (0.200 mmol) in diglyme, 78.8 mg of 5.4 wt% Au/CeO_2, 50 mg of Aerosil 200, and 0.20 mL of H_2O (56 equiv relative to substrate), resulting in a 37% yield of the product (100% substrate conversion) in 3 h (Table 1, entry 10). Doubling the amount of H_2O under these conditions gave only a 16% product yield. When the catalytic oxidation of hexamethyleneimine was carried out under the optimized conditions used for

the oxidation of pyrrolidine and piperidine, a 19% yield of caprolactam (100% conversion of the substrate) was obtained in 4 h (Table 1, entry 11). Thus, a lower substrate concentration (40 mM) was more effective than a higher concentration (100 mM) for the catalytic oxidation of hexamethyleneimine to caprolactam. The use of 5 mol% of NaOH or K_2CO_3 as additives [25, 48, 49] in the reaction, while keeping all other parameters optimized, resulted in a 17% yield of caprolactam in each case, with 100% substrate conversion. It is noteworthy that prolonged heating after complete substrate conversion generally resulted in the appearance of several unidentified GC peaks.

3.3 Au/CeO_2-catalyzed oxidation of cyclic tertiary amines to lactams

The N-methyl derivatives of pyrrolidine, piperidine, and morpholine were also oxidized by O_2 in the presence of the Au/CeO_2 catalyst to give the corresponding lactams (eq. 6 and 7) without the need for Aerosil 200 as a co-catalyst, and at lower reaction temperatures (80 ^oC and 100 ^oC) than that required for the secondary amine analogs (160



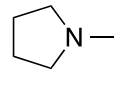
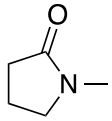
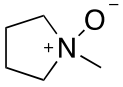
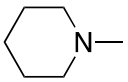
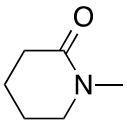
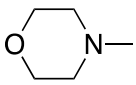
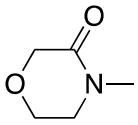
^oC). For example, under optimized conditions, N-methyl-2-pyrrolidone was obtained in 97% yield after heating a 108 mM dioxane-solution of N-methylpyrrolidine (0.488 mmol) with 5.4 wt% Au/CeO_2 and 0.45 mL H_2O (51 equiv relative to the amine) under O_2 (1 atm) at 80 ^oC for 3.5 h (Table 2, entry 1; Fig. 3); this represents a TON of 24.7 and a TOF of 7.04 h^{-1}. Under the same reaction conditions, but in the presence of Aerosil 200, a 90% lactam yield was obtained at a longer reaction time (10.5 h) from a 101 mM amine solution (Table 2, entry 2). Thus, catalytic efficiency is reduced in the presence of

Aerosil, at 80 ^{o}C. However, at 100 ^{o}C with or without Aerosil, the lactam yields (Table 2, entries 3 – 4: 94 – 98%) were similar to that for the optimized reaction.

Under optimized conditions, but without the addition of H_2O, the oxidation of N-methylpyrrolidine gave only an 8% yield of N-methyl-2-pyrrolidone with a 66% conversion of the amine substrate (Table 2, entry 5). Furthermore, only a 4% yield of N-methyl-2-pyrrolidone was obtained after 3.5 h of heating a dioxane-solution of N-methylpyrrolidine with 5.4 wt% Au/CeO_2 and H_2O at 80 ^{o}C under an atmosphere of argon (Table 2, entry 6). In addition, when the catalytic oxidation of N-methylpyrrolidine was carried out in air, rather than an O_2 atmosphere, a 49% yield of N-methyl-2-pyrrolidone was obtained after 3.5 h, as compared with the 97% yield obtained after 3.5 h when the reaction was carried out in an O_2 atmosphere. However, when the air reaction was allowed to proceed for a total of 10 h, a 97%-yield of the lactam product was obtained. (Table 2, entry 7). When only CeO_2 (no deposited nanogold) was used as a catalyst, but all other conditions optimized, no lactam formation was observed.

N-methyl-2-piperidone was also synthesized by the catalytic oxidation of N-methylpiperidine with O_2 (eq. 6, n = 2). The optimized conditions for this reaction involve heating a 95 mM dioxane solution of N-methylpiperidine (0.423 mmol) with 70 mg of 5.4 wt% Au/CeO_2 and 1.80 mL H_2O (236 equiv relative to the amine) at 100 ^{o}C for 4 h resulting in a 97% yield of N-methyl-2-piperidone and a 100% conversion of the substrate (Table 2, entry 9; Fig. 3); this represents a TON of 21.4 and a TOF of 5.35 h^{-1}. Halving the amount of added H_2O (i.e. 118 equiv relative to the amine), but keeping all other conditions optimized, resulted in a 76% yield of N-methyl-2-piperidone (100% substrate conversion) in 3 h (Table 2, entry 10). A further decrease in the amount of H_2O

Table 2. Catalytic conversion of N-methyl cyclic tertiary amines to lactams in 1,4-dioxane solvent, under O_2 (1 atm unless stated otherwise).

Entry	Substrate	Product	Temp (ºC)	Time (h)	Product yield (%)	TON[n]
1			80	3.5	97[a]	24.7
2	"	"	80	10.5	90[b]	21.1
3	"	"	100	3.5	94[b,c]	22.0
4	"	"	100	3.5	98[b]	22.9
5	"	"	80	3.5	8[a,d]	2.03
6	"	"	80	3.5	4[a,e]	1.02
7	"	"	80	10	97[a,f]	24.7
8		"	80	3.5	9[a]	2.29
9			100	4	97[g]	21.4
10	"	"	100	3	76[h]	16.8
11	"	"	100	3	56[i]	12.3
12	"	"	80	18	79[i]	17.4
13			100	10	72[j]	17.0
14	"	"	100	13.5	60[k]	14.1
15	"	"	100	24	34[l]	8.01
16	"	"	100	24	1[m]	0.236

[a]0.488 mmol (108 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.45 mL H_2O (51 eq), 4.54 mL 1,4-dioxane. [b]0.449 mmol (101 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 111 mg of Aerosil (4.1 eq), 0.45 mL H_2O (56 eq), 4.48 mL 1,4-dioxane. [c]Aerosil not added. [d] H_2O not added. [e]Under argon atmosphere. [f]Under air atmosphere. [g]0.423 mmol (95 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 1.80 mL H_2O (236 eq), 4.45 mL 1,4-dioxane. [h]0.423 mmol (95 mM; 1 eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.90 mL H_2O (118 eq), 4.45 mL 1,4-dioxane. [i]0.423 mmol (95 mM; 1eq)

substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.45 mL H_2O (59 eq), 4.45 mL 1,4-dioxane. [j]0.452 mmol (101 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.90 mL H_2O (110 eq), 4.48 mL 1,4-dioxane. [k]0.452 mmol (101 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 1.80 mL H_2O (220 eq), 4.48 mL 1,4-dioxane. [l]0.452 mmol (101 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.45 mL H_2O (55 eq), 4.48 mL 1,4-dioxane. [m]0.452 mmol (101 mM; 1eq) substrate, 70 mg of 5.4 wt% Au/CeO_2, 4.48 mL 1,4-dioxane. [n]TON is defined as the number of moles of product per mole of Au.

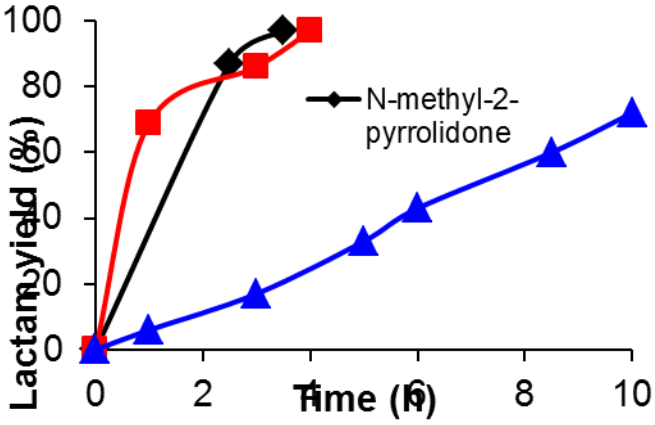
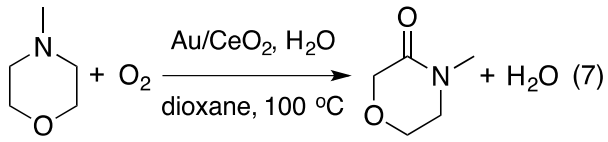


Fig. 3. Lactam product yields during the Au/CeO_2-catalyzed oxidation of tertiary cyclic amines under optimized conditions. (a) 0.488 mmol (107.5 mM) N-methylpyrrolidine substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.45 mL H_2O (51 eq), in 4.54 mL of 1,4-dioxane at 80 ^oC; (b) 0.423 mmol (95 mM) N-methylpiperidine substrate, 70 mg of 5.4 wt% Au/CeO_2, 1.80 mL H_2O (236 eq), in 4.45 mL of 1,4-dioxane at 100 ^oC; (c) 0.452 mmol (101 mM) N-methylmorpholine substrate, 70 mg of 5.4 wt% Au/CeO_2, 0.90 mL H_2O (110 eq), in 4.48 mL of 1,4-dioxane at 100 ^oC.

(59 equiv relative to the amine) led to only a 56% yield of N-methyl-2-piperidone in 3h (100% conversion of substrate, Table 2, entry 11). When this reaction (with 59 equiv of added H_2O) was carried out at 80 ^oC, a 79% product yield and a 97% substrate conversion were achieved after 18 h (Table 2, entry 12), indicating that the catalytic oxidation of N-methylpiperidine to N-methyl-2-piperidone proceeded much faster (3 h versus 18 h) but with a lower product yield (56% versus 79%) at a higher temperature (100 ^oC versus 80 ^oC).

N-methylmorpholine was also oxidized by O_2 in the presence of 5.4 wt% Au/CeO_2 (eq. 7) to give N-methylmorpholin-3-one. The ^1H and ^{13}C NMR data (see supporting information) of the isolated product were different from those reported for the



lactone 4-methylmorpholin-2-one [50, 51]. Furthermore, 2D NMR analysis confirmed that the lactam, and not the lactone, was formed from the Au/CeO_2-catalyzed oxidation reactions of N-methylmorpholine. For example, HMBC revealed a strong 3-bond heteronuclear coupling between the N-methyl protons and the CO carbon (Fig. S9). In the lactone 4-methylmorpholin-2-one, the related coupling would be across 4 bonds, and would be too weak to be observed. Under optimized conditions, a 72% yield of N-methylmorpholin-3-one (100% substrate conversion) was obtained after 10 h, when a 101 mM dioxane solution of the amine substrate (0.452 mmol) was heated at 100 °C with 5.4 wt% Au/CeO_2 in the presence of 0.90 mL (110 equiv relative to substrate) of H_2O (Table 2, entry 13; Figs. 3 and S11). In addition, doubling the amount of H_2O under optimized conditions (220 equiv instead of 110 equiv) led to a slightly lower (60%) yield of N-methylmorpholin-3-one and 99% substrate conversion after a longer reaction time of 13.5 h (Table 2, entry 14, Fig S11). Under the same conditions, but using only 0.45 mL of H_2O (55 equiv relative to the substrate), only a 34% yield of N-methylmorpholin-3-one was obtained from an 81% conversion of the N-methylmorpholine, after 24 h (Table 2, entry 15, Fig S11). Furthermore, when H_2O was eliminated from the optimized conditions, the yield of N-methylmorpholin-3-one was only 1% (56% conversion of N-methylmorpholine) after a reaction time of 24 h (Table 2, entry 16, Fig. S11).

3.4 Reaction pathways for the formation of lactams from cyclic secondary and tertiary amines

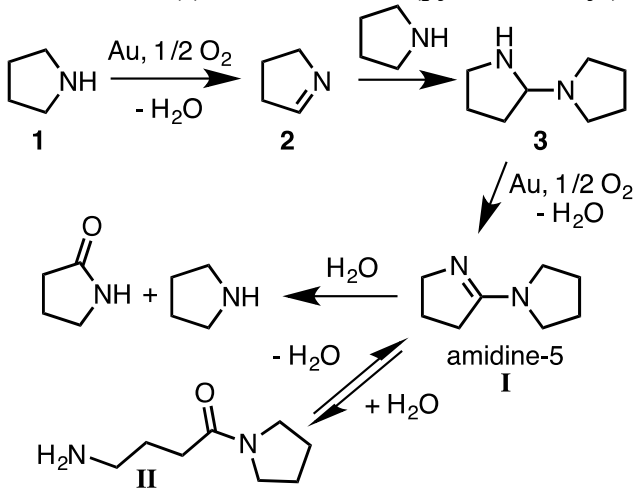
a) Mechanism for the Oxidation of cyclic secondary amines to lactams

In the optimized catalytic Au/CeO_2-Aerosil system, GC monitoring during the oxidation of pyrrolidine to 2-pyrrolidone revealed the appearance of two new GC peaks, at 9.18 and 10.98 min, during the course of the reaction. These two peaks gradually disappeared as the product peak (6.50 min) continued to grow in intensity, suggesting the involvement of reaction intermediates. Analysis of the reaction mixture by GC-MS led to the assignment of these two transient peaks to 5-(pyrrolidin-1-yl)-3,4-dihydro-2*H*-pyrrole (amidine-5, **I**, Scheme 2) and 4-amino-1-(pyrrolidin-1-yl)butan-1-one) (**II**). Additional support for the role of amidine-5 (**I**) and compound **II** as intermediates was derived from their independent syntheses and conversion to 2-pyrrolidone, under the optimized conditions for pyrrolidine oxidation. Specifically, under the optimized conditions for the catalytic oxidation of pyrrolidine, 0.235 mmol of amidine-5 (**I**) produced 0.447 mmol of 2-pyrrolidone (95% yield, Table 1, entry 7), which is close to the 2:1 stoichiometry expected for the conversion of **I** to 2-pyrrolidone. Similarly, treatment of compound **II** (0.218 mol) under catalytic conditions produced 0.419 mmol of 2-pyrrolidone (96% yield, Table 1, entry 8).

A likely pathway for the catalytic oxidation of pyrrolidine (**1**) is shown in Scheme 2. Previous evidence from the bulk gold powder-catalyzed reaction suggested that the first step involved the oxidative dehydrogenation of the amine substrate to give the imine (**2**) [38, 39]. In this and subsequent oxidation steps, it is assumed that H_2O is the co-product because H_2O_2 was not detected in the final reaction mixture; moreover, H_2O_2

would likely decompose to H_2O and O_2 under the conditions of the reaction [52]. Reaction of the imine with pyrrolidine [38] would give diamine **3**, which subsequently undergoes oxidative dehydrogenation to afford amidine-5 (**I**). The formation of **II** presumably results from the reversible hydrolysis of the C=N bond of amidine-5 (**I**) (Scheme 2). The formation of compound **II** is nonproductive towards the production of 2-pyrrolidone, but it re-enters the pathway by reconverting to **I**.

Scheme 2 Possible pathway for the Au/CeO_2-Aerosil-catalyzed oxidation of pyrrolidine via amidine-5 (**I**) and 4-amino-1-(pyrrolidin-1-yl)butan-1-one (**II**).



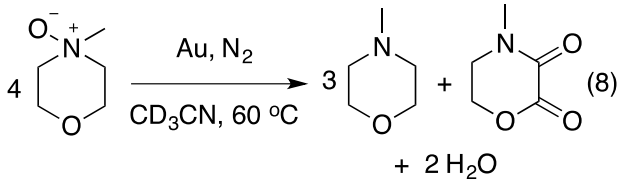
Water clearly plays a role in the mechanism, as the yield of 2-pyrrolidone is only 18% when water is not added to the reaction mixture, as compared with a 97% yield when 56 equivalents, relative to pyrrolidine, of water are added. Since the amidine-5 intermediate (**I**) is present during the reaction, it appears that its hydrolysis to give 2-pyrrolidone is the rate-determining step, which may account for the effect of water on the overall rate of reaction. However, when more than 56 equiv of water is added, the yield decreases to 80 and 77% (Fig. S10), perhaps due to ring-opening hydrolysis of the 2-pyrrolidone to give the zwitterionic 4-aminobutyric acid.

In contrast to the reaction of pyrrolidine, in which amidine-5 (**I**) was identified as an intermediate, amidine-6 or amidine-7 were not observed as intermediates during the Au/CeO_2-Aerosil-catalyzed oxidation of piperidine or hexamethyleneimine, respectively. The 6- or 7-membered analogs of intermediate **II** were also not observed. However, amidine-6 and amidine-7 were formed when bulk gold catalyzed the oxidation (O_2) of the cyclic amines, as previously reported [38, 40]; this result suggests that the oxidations of the 6- and 7-membered ring amines (eq. 4) also proceed through amidine intermediates. In the previously reported bulk gold/Aerosil-catalyzed oxidation of hexamethyleneimine, the low yield of caprolactam was attributed to the relatively low production of amidine-7 [40]. Thus, the lower yields of 2-piperidone (83%) and caprolactam (37%) from piperidine and hexamethyleneimine, respectively, are a likely consequence of smaller amounts of amidine-6 and 7 formed from the oxidative dehydrogenation step.

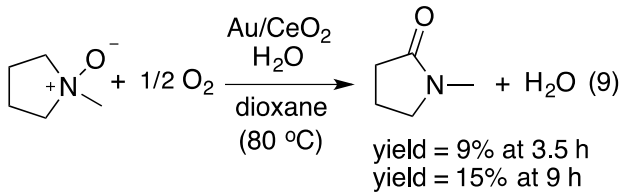
b) Oxidation of N-methyl cyclic tertiary amines to lactams

Because of the presence of the N-methyl group in the N-methyl cyclic amines, it is not possible for these amines to be oxidized to imines as proposed in the first step (Scheme 2) for the cyclic secondary amines. No intermediates that might suggest a mechanism for the oxidation of N-methylpyrrolidine to its lactam (eq. 6, n = 1) were detected by GC during the reaction. However, a previous report demonstrated that tertiary amines, such as triethylamine and pyridine, are converted to their N-oxides in the presence of a carbon-supported Au catalyst and O_2 (1 - 2 atm) in H_2O at 70 and 90 ^oC [53]. In addition, we previously reported that bulk Au catalyzes the conversion of N-methylmorpholine-N-oxide into N-methylmorpholine (74% yield) and N-methyl-morpholine-2,3-dione (14% yield) after 48 h of heating at 60 ^oC (eq. 8) [54]. Thus, it

seemed plausible that an N-methylmorpholine-N-oxide intermediate would convert to the N-methylpyrrolidone product in the presence of a Au catalyst. However, when N-methylpyrrolidine-N-oxide was treated with O_2 under the optimized conditions used for



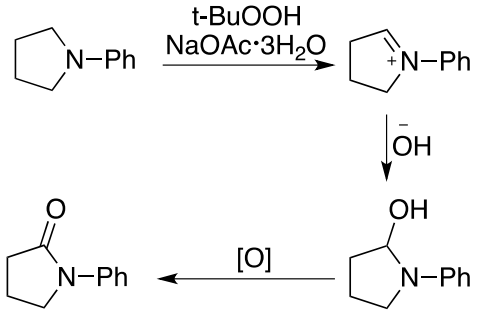
the catalytic oxidation of N-methylpyrrolidine, only a 9% yield of N-methyl-2-pyrrolidone was obtained (Table 2, entry 8) after the optimized reaction time (3.5 h). The yield increased to 15% after a total reaction time of 9 h (eq. 9). The low yield of N-methyl-2-pyrrolidone obtained from N-methylpyrrolidine-N-oxide (as compared to a 97% lactam yield from N-methylpyrrolidine; Table 2, entry 1) under the same optimized conditions suggests that amine N-oxides represent a minor pathway, or are not involved, in the catalytic oxidation of the cyclic tertiary amines studied here. A possible alternate intermediate in the catalytic oxidation of the cyclic tertiary amines is an iminium ion.



Such species have been generated from tertiary amines in the presence of molecular oxygen as well as other oxidants [26, 55-59]. For example, during the oxidation (O_2) of N-phenyl tetrahydroisoquinoline, catalyzed by graphite-supported Au nanoparticles, Che and co-workers proposed the generation of a cationic iminium intermediate, which was subsequently trapped by nucleophiles [26]. Furthermore, an iminium intermediate was proposed to have been generated during the copper-catalyzed oxidative cross-

dehydrogenative-coupling of N-phenyl tetrahydroisoquinoline with nitroalkanes and malonates in the presence of atmospheric pressure of O_2 [59]. In addition, a cationic iminium species was suggested as an intermediate during the $NaClO_2$ oxidation of tertiary allylamines into 2,3-epoxyamides [57]. More recently, Rao and Periasamy reported the oxidation of N-phenyl and N-(*p*-tolyl)pyrrolidine to the corresponding amides in the presence of *t*-butyl hydroperoxide as an oxidant and *t*-BuOK as a base. In that report, an N-phenyl pyrrolidinium intermediate was proposed (Scheme 3) [55].

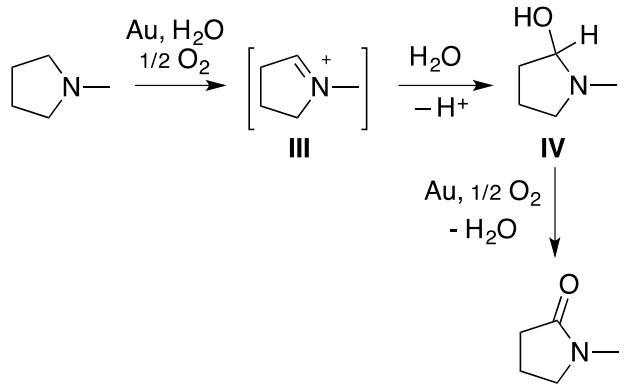
Scheme 3 Proposed generation of N-phenylpyrrolidinium during the oxidation of N-phenylpyrrolidine [55].



Under the optimized conditions for the current Au/CeO_2-catalyzed oxidation of N-methylpyrrolidine into N-methyl-2-pyrrolidone, it is conceivable that the N-methylpyrrolidinium cation **III** is generated, which then undergoes addition of water to produce the hemiaminal compound **IV** (Scheme 4). The resulting hemiaminal could then undergo oxidation to give the N-methylated lactam product. Although this is a plausible mechanism, none of the proposed intermediates have been detected or identified. However, the high yield (97%, Table 2, entry 1) of N-methyl-2-pyrrolidone when 110 equiv of water, relative to N-methylpyrrolidine, is added to the reaction mixture, as compared with only an 8% yield of the lactam product when no water is added (Table 2, entry 5) suggests that nucleophilic addition of water to the ionic intermediate **III** is a key

step. A similar mechanism was proposed for the Au/Al_2O_3-catalyzed oxidation of tertiary amines to amides [37].

Scheme 4. Proposed pathway for the Au/CeO_2-catalyzed oxidation of N-methylpyrrolidine to N-methyl-2-pyrrolidone via an iminium intermediate.



4 Conclusions

Nanogold (6.5 ± 1.1 nm) supported on high surface area (169 – 203 m^2/g) CeO_2 nanoparticles is active in the oxidation (1 atm O_2) of pyrrolidine, piperidine, and hexamethyleneimine to give 2-pyrrolidone (97% yield; eq 4, n = 1), 2-piperidone (83% yield; eq. 4, n = 2), and caprolactam (37% yield; eq. 4, n = 3). Studies suggest that these conversions proceed in two distinguishable steps (Scheme 2). The first involves a gold-catalyzed reaction of the amine with oxygen to give an amidine (eq. 1). This reaction is also catalyzed by bulk gold [38] and Au/Al_2O_3 [39, 40]. The second step involves hydrolysis of the amidine to give the lactam and the cyclic amine (eq. 2). This reaction occurs to some extent at 160 ^oC even without a hydrolysis catalyst, as pyrrolidine gives a 27% yield of 2-pyrrolidone using only a bulk gold catalyst. However, at 100 ^oC, bulk gold gives only amidine-5, indicating that amidine-5 is not hydrolyzed at the lower temperature [38-40]. The addition of Aerosil 200 to the bulk gold-catalyzed reaction does give 2-pyrrolidone (35%), even at 90 ^oC, because Aerosil catalyzes the hydrolysis of the

amidine. It appears that the CeO_2 support in the present study also catalyzes the amidine hydrolysis to give a 97% yield (at 6.5 h) of the lactam using Au/CeO_2 under optimized conditions.

The N-methyl cyclic tertiary amines are also oxidized (O_2) to the corresponding lactams at temperatures (80 - 100 ^oC) that are milder than those (160 ^oC) used for the cyclic secondary amines. Using the Au/CeO_2 catalyst (eq. 6,7) under optimized reaction conditions, N-methylpyrrolidine, N-methylpiperidine, and N-methylmorpholine are converted to N-methyl-2-pyrrolidone (97% yield; eq. 6, n = 1), N-methyl-2-piperidone (97% yield; eq. 6, n = 2), and N-methylmorpholin-3-one (72% yield; eq. 7). The mechanism of the Au/CeO_2-catalyzed oxidation of N-methylated cyclic tertiary amines to their lactams (eq. 6 and 7) is clearly different from that for the oxidation of cyclic secondary amines (eq. 4), since the N-methyl substituent prevents oxidative dehydrogenation to form the initial imine (Scheme 2).

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