Heterogeneous Gold Catalysis

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Supported Gold Nanoparticles for Efficient α-Oxygenation of Secondary and Tertiary Amines into Amides

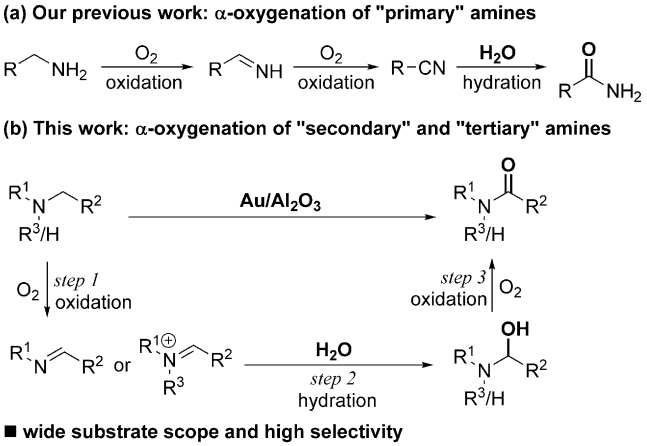
*Xiongjie Jin, Kengo Kataoka, Takafumi Yatabe, Kazuya Yamaguchi, and Noritaka Mizuno**

Abstract: *Although the α-oxygenation of amines is a highly attractive method for the synthesis of amides, efficient catalysts suited to a wide range of secondary and tertiary alkyl amines using O_2 as the terminal oxidant have no precedent. This report describes a novel, green α-oxygenation of a wide range of linear and cyclic secondary and tertiary amines mediated by gold nanoparticles supported on alumina (Au/Al_2O_3). The observed catalysis was truly heterogeneous, and the catalyst could be reused. The present α-oxygenation utilizes O_2 as the terminal oxidant and water as the oxygen atom source of amides. The method generates water as the only theoretical by-product, which highlights the environmentally benign nature of the present reaction. Additionally, the present α-oxygenation provides a convenient method for the synthesis of ^{18}O-labeled amides using $H_2{}^{18}O$ as the oxygen source.*

Amides are very important compounds in both bulk and fine chemical industries given their widespread applications as intermediates in organic synthesis, raw materials for engineering plastics, intensifiers for perfumes, color pigments for ink, anti-block reagents, detergents, and lubricants.[1] Among the various synthetic methods developed for amide preparation to date, nucleophilic substitution of carboxylic acid derivatives (such as acid chlorides, anhydrides, and esters) with amines (including NH_3) is one of the most commonly utilized methods.[2] Hydration of nitriles and the Beckmann rearrangement have found utility in the production of large scale industrial chemicals, such as acrylamide[3] and ε-caprolactam.[4] However, these traditional methods often employ stoichiometric amounts of toxic reagents and/or produce large amounts of waste. Therefore, the development of novel, green procedures for amide synthesis with high atom economy is of paramount importance. An approach pioneered by Milstein and co-workers, involving acylation of primary and secondary amines using alcohols or aldehydes instead of carboxylic acid derivatives, and with generation of H_2 or water as the sole by-product, has recently emerged as an attractive environmentally friendly alternative for amide synthesis .[5] Although this method provides a powerful tool for accessing linear amides, synthesis of cyclic amides with a wide variety of substituted patterns is somewhat problematic.

Selective α-oxygenation of amines using O_2 as the terminal oxidant would provide another powerful green synthetic method for amides, given 1) the easy accessibility of amines through a wide variety of chemical transformations, 2) use of O_2 as the green terminal oxidant, and 3) generation of water as the sole by-product. However, the α-oxygenation of amines has generally been carried out using stoichiometric organic or inorganic oxidants, such as *t*BuOOH,[6] RuO_4 (generated in situ by reaction of RuO_2 and $NaIO_4$),[7] iodosobenzene,[8] and $PhCO_3tBu$.[9] Therefore, the α-oxygenation of amines using O_2 as the terminal oxidant is a highly attractive, yet challenging task.

Recently, we developed an efficient method for α-oxygenation of primary amines into primary amides by alumina supported ruthenium hydroxide, $Ru(OH)_x/Al_2O_3$,[10a] and manganese oxide-based octahedral molecular sieves, OMS-2 (Scheme 1 a).[10b] Although these procedures are highly efficient for the α-oxygenation of primary amines, secondary and tertiary amines cannot be converted into the corresponding secondary and tertiary amides. As a continuation of our interest in the development of efficient amide synthetic methods,[10,11] we have focused on the development of a method for α-oxygenation of secondary and tertiary amines. To date, several homogeneous[12,13] and heterogeneous catalysts[14] are reported to catalyze α-oxygenation of secondary and tertiary amines using O_2 as the terminal oxidant. However, substrate scope for these procedures is generally limited to tetrahydro(iso)quinoline or aniline derivatives. Quite recently, Milstein and co-workers reported



Scheme 1. α-Oxygenation of amines.

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an "acceptorless" homogeneous ruthenium-catalyzed oxygenation of secondary amines into amides.[15] However, in this case the substrate scope was limited to cyclic secondary amines. To the best of our knowledge, there is no precedent for the α-oxygenation of aliphatic linear secondary and tertiary amines using O_2 as the terminal oxidant. Therefore, the development of novel catalysts for amine α-oxygenation with wide substrate scope; especially for the selective α-oxygenation of unsymmetrical secondary and tertiary amines; is highly desirable.

Herein, we disclose for the first time a highly selective and widely applicable route for heterogeneous α-oxygenation of secondary and tertiary amines. The method uses O_2 as the oxidant and is catalyzed by gold nanoparticles supported on alumina (Au/Al_2O_3, with an average particle size of Au = 4.9 nm; see the Supporting Information, Figure S1; Scheme 1b). The present reaction proceeds through the following oxidation/hydration/oxidation sequence; 1) oxidation of secondary/tertiary amines into imine/iminium intermediates (Scheme 1b, step 1), 2) hydration of the imine/iminium intermediates to form hemiaminals (Scheme 1b, step 2), and 3) oxidation of the hemiaminals into the desired amide products (Scheme 1b, step 3). In the presence of Au/Al_2O_3, a wide range of cyclic and linear secondary and tertiary amines could be converted into the corresponding amides in moderate to high yields. The catalysis in the present reaction was truly heterogeneous, and the Au/Al_2O_3 catalyst could be reused several times. This reaction is an efficient green method for the α-oxygenation of secondary and tertiary amines when it is considered that 1) water is used as the oxygen atom source in the amide group, 2) O_2 is employed as the terminal oxidant, and 3) water is the only theoretical by-product. Additionally, ^{18}O-labeled amides were readily synthesized using $H_2{}^{18}O$ as the oxygen source.

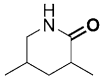
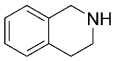
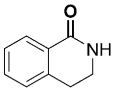
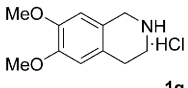
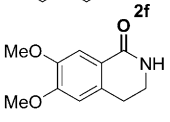
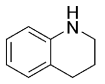
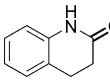
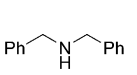
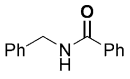
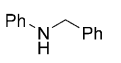
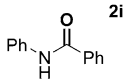
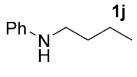
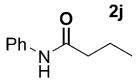
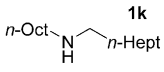
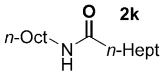
Initially, various supported metal catalysts (designated as metal/support) were prepared (Supporting Information, Table S1) and applied to the α-oxygenation of piperidine (**1a**) into 2-piperidone (**2a**) (Supporting Information, Table S2). The reaction was carried out in water at 100 °C in O_2 (1 atm). Under these conditions, we confirmed that **2a** was not obtained in the presence of pure Al_2O_3 or in the absence of catalysts (Supporting Information, Table S2, entries 14 and 15). In the presence of Pd/Al_2O_3, only a trace amount of **2a** was obtained (Supporting Information, Table S2, entry 1). Other supported metal catalysts, such as Ru/Al_2O_3, Rh/Al_2O_3, and Cu/Al_2O_3 did not show any catalytic activity for the present transformation (Supporting Information, Table S2, entries 2–4). Notably, Au/Al_2O_3 promoted the reaction significantly (Supporting Information, Table S2, entry 5), and a quantitative yield of **2a** was obtained after 24 h (Supporting Information, Table S2, entry 6). Among the various supports examined, Al_2O_3 was the best (Table S2, entries 5–10). The reaction using Au/Al_2O_3 in air (1 atm) only gave a trace amount of **2a** (Supporting Information, Table S2, entry 11), while a 57% yield of **2a** was obtained in pressurized air (5 atm; Supporting Information, Table S2, entry 12). The reaction did not proceed at all under Ar atmosphere (Supporting Information, Table S2, entry 13), which indicates that O_2 is the terminal oxidant in the oxygenation reaction.

To verify whether the observed catalysis for the present reaction was truly heterogeneous, Au/Al_2O_3 was removed by hot filtration when the yield of **2a** reached approximately 60%, and the reaction then carried out with the filtrate under the same reaction conditions. As shown in Figure S2 (Supporting Information), the reaction completely stopped upon removal of Au/Al_2O_3. Furthermore, analysis of the filtrate by inductively coupled plasma atomic emission spectroscopy (ICP-AES) revealed that gold species were hardly present in the filtrate (that is, gold was not present in quantities above the instrumental detection limit: Au < 0.008%). These experimental results indicate that catalysis did not originate from gold species leached from the catalyst, and thus, the described catalyst is deemed intrinsically heterogeneous.[16] After the reaction, Au/Al_2O_3 could be easily retrieved by simple filtration, achieving > 95% recovery. The retrieved catalyst could be reused several times, though the yields of the desired product gradually decreased after repeated reuse experiments (Supporting Information, Figure S3). This is likely because of the aggregation of gold nanoparticles; the average particle size of gold increased from 4.9 nm (fresh catalyst) to 9.9 nm after the third recycling experiment (Supporting Information, Figure S1).

With the optimized reaction conditions in hand, we subsequently examined the substrate scope for α-oxygenation. As shown in Table 1, various secondary cyclic and linear amines could be oxygenated to produce the corresponding amides in moderate to high yields. The α-oxygenation of five-, six-, and seven-membered cyclic amines efficiently proceeded to give the corresponding lactams (Table 1, entries 1–8). When morpholine (**1e**) was used as a substrate, it was exclusively oxygenated in the 3-position to give the corresponding amide, and oxygenation did not occur at the 2-position (Table 1, entry 5). Furthermore, the α-oxygenation of tetrahydroisoquinoline derivatives (**1f** and **1g**) effectively proceeded at the benzylic positions (Table 1, entries 6 and 7). Although tetrahydroquinoline (**1h**) was oxygenated to afford the corresponding amide (34%), quinoline (51%) was a major product in this case (Table 1, entry 8). Various linear amines were oxygenated to give the corresponding amides in moderate yields (Table 1, entries 9–12).[17]

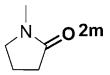
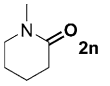
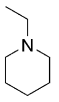
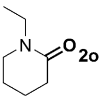
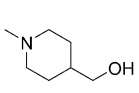
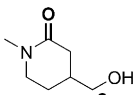
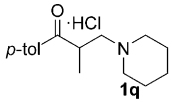
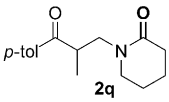
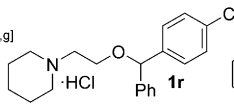
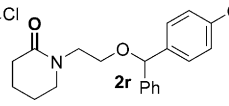
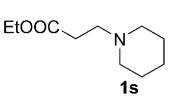
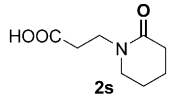
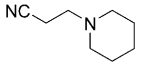
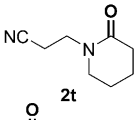
The present catalytic system was also applicable to the α-oxygenation of tertiary amines. As shown in Table 2, various kinds of cyclic and linear tertiary amines were efficiently oxygenated to give the corresponding amides. The present α-oxygenation method was especially powerful for the selective synthesis of lactams from cyclic tertiary amines. The five- and six-membered tertiary cyclic amines were all exclusively oxygenated at ring positions to give the corresponding lactams in high yields (Table 2, entries 1–8). A cyclic tertiary amine with an alcohol group reacted well, and the hydroxy group in **2p** remained intact (Table 2, entry 4). Tolperisone, a well-known muscle relaxant,[18] was also a suitable substrate, and selectively oxygenated at the ring position (Table 2, entry 5). Cloperastine, a cough suppressant,[19] was also selectively oxygenated to give the corresponding amide, leaving chloride and ether functional

Table 1: Scope of the α-oxygenation of secondary amines.[a]

Entry	Substrate	Product	Conv. [%]	Yield [%]
1	 1a	 2a	>99	>99(80)
2	 1b	 2b	>99	>99
3	 1c	 2c	>99	52
4[b,c]	 1d	 2d	98	40(41)
5[b,c]	 1e	 2e	52	51
6	 1f	 2f	>99	94(77)
7[d]	 1g	 2g	>99	>99
8[e]	 1h	 2h	85	34
9[c,f,g]	 1i	 2i	>99	63
10[f,g]	 1j	 2j	>99	51
11[b,c,f,g]	 1k	 2k	>99	57
12[b,c,f,h]	 1l	 2l	99	75

[a] Reaction conditions: **1** (0.5 mmol), Au/Al_2O_3 (4 mol%), H_2O (2 mL), O_2 (1 atm), 100°C, 24 h. Conversions and yields were determined by GC analysis. The values in parentheses are the yields of isolated products. For entry 6, the average isolated yield for two runs (containing ±4% error) is shown. By-product information and a likely formation pathway are provided in Table S3 and Scheme S1 (Supporting Information). [b] 80°C. [c] Au/Al_2O_3 (8 mol%). [d] NaOH (1.5 mmol). [e] Quinoline was formed in 51% yield. [f] 1,4-dioxane/H_2O (0.1 mL/1.9 mL). [g] NaOH (1.0 mmol). [h] 48 h.

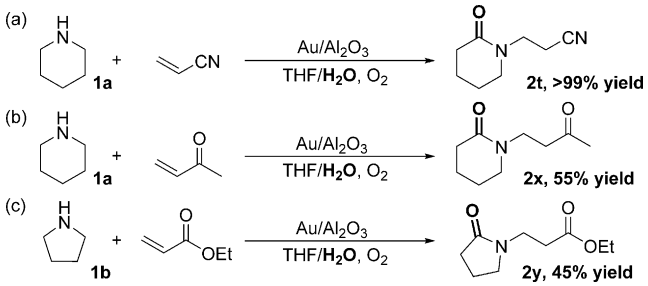
Table 2: Scope of the α-oxygenation of tertiary amines.[a]

Entry	Substrate	Product	Conv. [%]	Yield [%]
1	 1m	 2m	>99	>99
2	 1n	 2n	>99	96
3[b]	 1o	 2o	>99	86(75)
4[c]	 1p	 2p	99	73(72)
5[b,d,e]	 1q	 2q	98	85(66)
6[c,f,g]	 1r	 2r	99	99(93)
7[b,d,f]	 1s	 2s	>99	94(91)
8[c]	 1t	 2t	>99	>99(98)
9[b,c,h]	1u	2u	99	87(78)
10[b,c,h]	1v	2v	>99	71
11[b,c,h,i]	1w	2w	95	49(45)

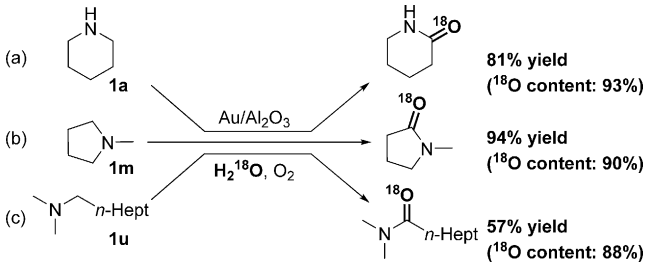
[a] Reaction conditions: **1** (0.5 mmol), Au/Al_2O_3 (4 mol%), H_2O (2 mL), O_2 (1 atm), 80°C, 24 h. Conversions and yields were determined by GC analysis. The values in parentheses are the yields of isolated products. For entry 9, the average isolated yield for two runs (containing ±3% error) is shown. By-product information and a likely formation pathway are provided in Table S3 and Scheme S1 (Supporting Information). [b] Au/Al_2O_3 (8 mol%). [c] 60°C. [d] 1,4-dioxane/H_2O (0.1 mL/1.9 mL). [e] NaOH (1.5 mmol). [f] NaOH (1.0 mmol). [g] THF/H_2O (0.5 mL/1.5 mL). [h] THF/H_2O (1.7 mL/0.3 mL). [i] 48 h.

groups intact (Table 2, entry 6). As for the ester group substituted amine **1s**, the oxygenation proceeded efficiently, although the ester group was hydrolyzed into the corresponding carboxylic acid functional group (Table 2, entry 7). A cyclic tertiary amine substituted with a nitrile group reacted smoothly without hydrolysis or hydration of the nitrile group (Table 2, entry 8). Linear tertiary amines were also oxygenated, albeit in moderate yields (Table 2, entries 9–11).[17] It should be noted that the aforementioned α-oxygenation of tertiary amines proceeded in a highly regioselective manner and exclusively gave one regioisomer. Such high regioselectivity is likely derived from the stability of iminium and/or hemiaminal intermediates (Scheme 1, step 1).[20] Furthermore, we successfully synthesized **2t** starting from **1a** and acrylonitrile through an aza-Michael addition/α-oxygenation one-pot sequential reaction (Scheme 2a). Methylvinylketone[21] and ethylacrylate could also be applied to the sequential reaction (Scheme 2b and 2c).

When the oxidation of dibenzylamine (**1i**) by Au/Al_2O_3 was performed in 1,4-dioxane in the absence of water,



Scheme 2. Sequential aza-Michael addition/α-oxygenation reactions. Reaction conditions: **1** (0.5 mmol), acrylonitrile, methylvinylketone, or ethylacrylate (0.5 mmol), Au/Al_2O_3 (4 mol%), THF/H_2O (1 mL/1 mL), O_2 (1 atm), 50°C, 24 h. Yields were determined by GC analysis.



Scheme 3. Syntheses of ^{18}O-labeled amides. Reaction conditions for: a) **1a** (0.5 mmol), Au/Al_2O_3 (4 mol%), $H_2{}^{18}O$ (0.9 mL), O_2 (1 atm), 100°C, 24 h; b) **1m** (0.5 mmol), Au/Al_2O_3 (4 mol%), THF (0.5 mL), $H_2{}^{18}O$ (0.5 mL), O_2 (1 atm), 60°C, 24 h; c) **1u** (0.5 mmol), Au/Al_2O_3 (8 mol%), THF (1.7 mL), $H_2{}^{18}O$ (0.3 mL), O_2 (1 atm), 60°C, 24 h. Yields were determined by GC analysis.

N-benzylidenebenzylamine (**3i**) was obtained in 46% yield (Supporting Information, Scheme S2a). Additionally, the reaction of **3i** in water afforded the corresponding amide **2i** in 63% yield. These results suggest the involvement of imines as intermediates in the α-oxygenation of secondary amines (Supporting Information, Scheme S2b). Similarly, for the α-oxygenation of tertiary amines, iminium intermediates are likely formed through the oxidation of tertiary amines by Au/Al_2O_3 (Scheme 1, step 1). We observed that aldehydes, carboxylic acids, and amines were formed as by-products during the reaction (Supporting Information, Table S3).[17] Consequently, we questioned whether the present α-oxygenation reaction proceeds through an initial hydrolysis of imine or iminium intermediates into aldehydes and amines, followed by the reaction of these decomposed intermediates to afford the amide products.[5] To confirm this hypothesis, the reaction of benzylamine and benzaldehyde was carried out. In this case, **2i** was indeed formed in 33% yield, together with 54% of benzoic acid (Supporting Information, Scheme S2c). The oxygenation of **3i** in the presence of $[D_5]$benzaldehyde gave a 66% yield of **2i**, and the $[D_5]$phenyl group content in the product was 36% (Supporting Information, Scheme S2c). Therefore, the present α-oxygenation reaction mainly proceeds through the pathway shown in Scheme 1, but partly through the aforementioned hypothetical pathway.

The α-oxygenation of **1a** in $H_2{}^{18}O$, using $^{16}O_2$ (1 atm) as the oxidant, resulted in a 93% ^{18}O incorporation at the amide carbonyl group (Supporting Information, Table S4, entry 2). This high labeling ratio of ^{18}O in **2a** demonstrates the potential utility of the present α-oxygenation method for the preparation of ^{18}O-labeled amides. Indeed, several ^{18}O-labeled amides were successfully synthesized by the present method using $H_2{}^{18}O$ (Scheme 3). In contrast, the α-oxygenation of **1a** in $H_2{}^{16}O$ using $^{18}O_2$ (1 atm) as the oxidant gave **2a** with only 1% ^{18}O labeling at the amide carbonyl group (Supporting Information, Table S4, entry 3). These results suggest that the oxygen atom in the amide group was derived from water rather than O_2, thus supporting the involvement of hemiaminal intermediates formed by hydration of imine or iminium intermediates (Scheme 1, step 2). Finally, the oxidation of the hemiaminal intermediates by Au/Al_2O_3 gave the corresponding amide products (Scheme 1, step 3).[5]

The oxygenation of **1n** in the presence of a stoichiometric amount of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) in O_2 (1 atm) was 2.4 times faster than the oxygenation without TEMPO, and the formation of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPOH) was observed (Figure 1). The reaction in the presence of TEMPO in O_2 without Au/Al_2O_3 did not give **2n**. Furthermore, the acceleratory effect of TEMPO was also observed for the oxygenation of a secondary amine **1a** (Supporting Information, Scheme S3). Additionally, the oxygenation of **1n** using 1 equiv of TEMPO (with respect to **1n**) as the terminal oxidant in Ar (1 atm), proceeded to give **2n** in 25% yield together with TEMPOH (96% yield based on TEMPO; Figure 1). Under the same

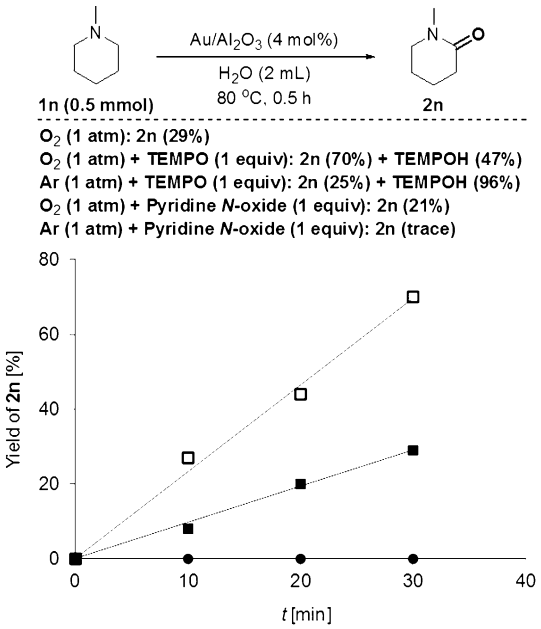


Figure 1. Effect of various oxidants on the present α-oxygenation. Reaction conditions: **1n** (0.5 mmol), Au/Al_2O_3 (4 mol%), H_2O (2 mL), 80°C. Yields were determined by GC analysis. Reaction profile in the presence of TEMPO (——□——; 0.5 mmol) in O_2 (1 atm); line fit, Yield = 2.32*t* (R^2 = 0.99). Reaction profile without TEMPO in O_2 (——■——; 1 atm); line fit, Yield = 0.96*t* (R^2 = 0.99). Reaction profile in the presence of TEMPO (——●——; 0.5 mmol) in O_2 (1 atm) without Au/Al_2O_3.

reaction conditions, the oxygenation of **1a** also gave **2a** in 11% yield, concomitant with TEMPOH (41% yield; Supporting Information, Scheme S3). This 1:4 amide/TEMPOH stoichiometry is consistent with that of the overall reaction shown in Scheme S4 (Supporting Information). It has been reported that TEMPO can work as a one-electron oxidant to abstract a hydrogen atom from Au–H species, where TEMPO itself is reduced to TEMPOH.[22] Thus, the above experimental results strongly indicate the involvement of Au–H species during the reaction, and suggest that an Au–H species is likely formed during the oxidation of amines and the hemiaminal intermediates. Specifically, β-H elimination after coordination of amines and hemiaminals to gold would generate Au–H species. TEMPO acts as a one-electron oxidant to effectively regenerate the active gold species through the oxidation of Au–H species. In contrast, two-electron oxidants, such as pyridine *N*-oxide, hardly promoted the oxygenation of **1n** and **1a** (Figure 1; Supporting Information, Scheme S3), suggesting that this type of oxidant is not suitable for the oxidation of Au–H species. The experimental results described above suggest the formation of radical-like oxygen species (the superoxide anion for example) on the surface of gold during oxygenation using O_2.

The substantial promotional effect of TEMPO on the reaction indicates that the oxidation of Au–H species is likely involved in the rate-determining step. The aforementioned reaction is faster in O_2 (1 atm) than in air (1 atm), which also supports the involvement of the oxidation of Au–H species by O_2 in the rate-determining step. The slow oxidation of Au–H species retards the oxidation of hemiaminal intermediates (Scheme 1, step 3), which results in the competing hydrolytic decomposition of imine or iminium intermediates (Supporting Information, Scheme S1).[17]

In summary, we have successfully developed for the first time an efficient heterogeneously Au/Al_2O_3-catalyzed α-oxygenation of secondary and tertiary amines using O_2. Additionally, this reaction provides a convenient method for the synthesis of ^{18}O-labeled amides. Owing to the practicality of the reaction conditions, we hope that this α-oxygenation method will find wide application in the synthesis of amide derivatives and related compounds.

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