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Abstract

Bulk gold powder (~5–50 μm particles) catalyzes the reactions of isocyanides with amines and amine *N*-oxides to produce ureas. The reaction of *n*-butyl isocyanide (*n*Bu–N≡C) with di-*n*-propylamine and *N*-methylmorpholine *N*-oxide in acetonitrile, which was studied in the greatest detail, produced 3-butyl-1,1-dipropylurea (O═C(NH*n*Bu)(N*n*Pr2)) in 99% yield at 60 °C within 2 h. Sterically and electronically different isocyanides, amines, and amine *N*-oxides react successfully under these conditions. Detailed studies support a two-step mechanism that involves a gold-catalyzed reaction of adsorbed isocyanide with the amine *N*-oxide to form an isocyanate (RN═C═O), which rapidly reacts with the amine to give the urea product. These investigations show that bulk gold, despite its reputation for poor catalytic activity, is capable of catalyzing these reactions.
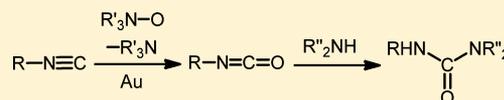
Disciplines

Chemistry

Bulk Gold-Catalyzed Reactions of Isocyanides, Amines, and Amine *N*-Oxides

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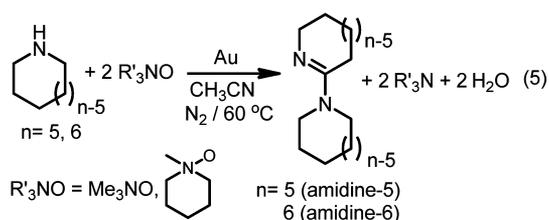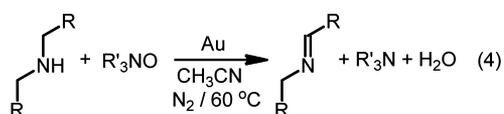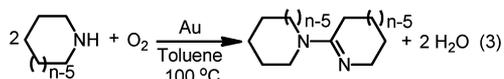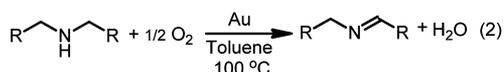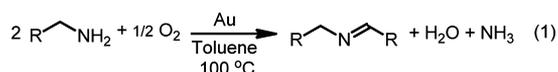
S *Supporting Information*

ABSTRACT: Bulk gold powder ($\sim$5−50 μm particles) catalyzes the reactions of isocyanides with amines and amine *N*-oxides to produce ureas. The reaction of *n*-butyl isocyanide ($^nBu-N\equiv C$) with di-*n*-propylamine and *N*-methylmorpholine *N*-oxide in acetonitrile, which was studied in the greatest detail, produced 3-butyl-1,1-dipropylurea ($O=C(NH^nBu)(N^nPr_2)$) in 99% yield at 60 °C within 2 h. Sterically and electronically different isocyanides, amines, and amine *N*-oxides react successfully under these conditions. Detailed studies support a two-step mechanism that involves a gold-catalyzed reaction of adsorbed isocyanide with the amine *N*-oxide to form an isocyanate ($RN=C=O$), which rapidly reacts with the amine to give the urea product. These investigations show that bulk gold, despite its reputation for poor catalytic activity, is capable of catalyzing these reactions.

$$R-N\equiv C \xrightarrow[\text{Au}]{\overset{R'_3N-O}{\underset{-R'_3N}{}}} R-N=C=O \xrightarrow{R''_2NH} \underset{\underset{O}{\overset{\|}{C}}}{RHN \diagdown \diagup NR''_2}$$
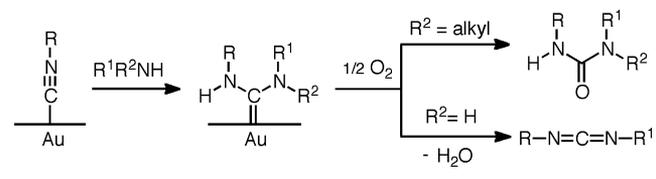
■ INTRODUCTION

Bulk Au has a reputation for having very low catalytic activity. This is in contrast to nanogold particles (<5 nm), which catalyze numerous reactions, including oxidations.[1] However, our group has shown that bulk Au is also an effective catalyst for some oxidations involving O_2, including reactions of carbon monoxide and primary amines to produce ureas[2] and the oxidative dehydrogenation of amines to afford imines (eqs 1−3).[3,4] However, it was not clear whether or not gold could use other oxidizing agents,

$$2\ R\diagup NH_2 + 1/2\ O_2 \xrightarrow[\underset{100\ °C}{\text{Toluene}}]{\text{Au}} R\diagup N \diagdown R + H_2O + NH_3 \quad (1)$$

$$R\diagup N \underset{H}{\diagdown} R + 1/2\ O_2 \xrightarrow[\underset{100\ °C}{\text{Toluene}}]{\text{Au}} R\diagup N \diagdown R + H_2O \quad (2)$$

$$2\ (\text{piperidine NH}) + O_2 \xrightarrow[\underset{100\ °C}{\text{Toluene}}]{\text{Au}} (\text{amidine}) + 2\ H_2O \quad (3)$$

$$\underset{R}{\overset{R}{\diagup}}NH + R'_3NO \xrightarrow[\underset{N_2\ /\ 60\ °C}{\text{CH}_3\text{CN}}]{\text{Au}} \overset{R}{\diagup}N \diagdown R + R'_3N + H_2O \quad (4)$$

$$(\text{piperidine, } n=5,6) + 2\ R'_3NO \xrightarrow[\underset{N_2\ /\ 60\ °C}{\text{CH}_3\text{CN}}]{\text{Au}} (\text{amidine}) + 2\ R'_3N + 2\ H_2O \quad (5)$$

$R'_3NO = Me_3NO,$ (N-methylmorpholine N-oxide)   n= 5 (amidine-5)   6 (amidine-6)

besides O_2, to perform these oxidations. Recently we reported that amine *N*-oxides (R_3NO) were suitable oxidants for the oxidative dehydrogenation of amines to give imines (eqs 4 and 5) and benzyl alcohol to give benzaldehyde.[5] In each of these reactions, the amine *N*-oxide (R_3NO) was the source of the oxygen atom.

We also showed that *bulk* gold powder ($\sim$5−50 μm size) catalyzes reactions of isocyanides with both primary[6] and secondary amines[7] and dioxygen to give carbodiimides and ureas (Scheme 1). Our studies, based on reactions of isocyanide

Scheme 1. Proposed Mechanism for the Bulk Au-Catalyzed Reaction of Isocyanides and O_2 with Primary and Secondary Amines

$$\underset{\text{Au}}{\overset{R}{\underset{\|}{\overset{\|}{N}}}\diagdown C} \xrightarrow{R^1R^2NH} \underset{\text{Au}}{\overset{R}{\underset{H}{N}}\diagdown \underset{C}{\diagup} \overset{R^1}{\underset{R^2}{N}}} \xrightarrow[\text{- }H_2O]{1/2\ O_2} \begin{cases} \overset{R^2 = \text{alkyl}}{\longrightarrow} \underset{H}{\overset{R}{N}}\diagdown \underset{\overset{\|}{O}}{C} \diagup \underset{R^2}{\overset{R^1}{N}} \\ \overset{R^2= H}{\longrightarrow} R-N=C=N-R^1 \end{cases}$$

ligands in organometallic complexes and kinetic investigations, suggested that an isocyanide terminally bonded to one Au atom on the gold surface is attacked by the amine to form a putative diaminocarbene intermediate which then reacts rapidly with oxygen to afford the final product.[6]

In the present studies, we examined amine *N*-oxides as the oxidizing agents, instead of O_2, in the reactions of isocyanides with amines. We sought to determine whether amine oxides give the same products as O_2 and if the reactions are faster or slower with amine oxides. In addition, we sought to determine

whether or not the reaction with amine oxides proceeds through a diaminocarbene intermediate, as proposed for O_2 in Scheme 1, or by way of some other pathway.

■ EXPERIMENTAL SECTION

General Methods. All amines were dried over calcium hydride or potassium hydroxide and then distilled under reduced pressure, according to literature procedures.[8] The isocyanides (n-butyl, tert-butyl, and benzyl) were purchased from Sigma-Aldrich or Strem, stored in a freezer at −20 °C, and used without further purification. Trimethylamine N-oxide dihydrate was dehydrated by sublimation.[9] The other amine N-oxides (N-methylmorpholine N-oxide, N,N-dimethylundecylamine N-oxide, pyridine N-oxide) and triphenyl-methane were purchased from Aldrich and used as received except where otherwise noted. Dry solvents (acetonitrile and hexanes) were obtained by passage through solvent purification columns, similar to those used by Grubbs et al.[10] Stock solutions of the desired isocyanide, amine, and internal standard (2.0 mM isocyanide, 10.0 mM amine, and 0.25 mM Ph_3CH) in solvent were stored in a freezer at −20 °C. Argon (99.996%) was purchased from Linweld and used without further purification.

General Procedure for the Preparation and Cleaning of Gold Powder. The gold powder was prepared from $HAuCl_4$ as described previously.[11] It was then washed with methanol in a Soxhlet extractor for 24 h and allowed to dry in air in an oven at 110 °C overnight. The resulting gold powder was treated with "piranha" solution (3:1 mixture of concentrated H_2SO_4 and 30% H_2O_2), washed with water followed by methanol, and allowed to dry in air in an oven at 110 °C overnight. This dull brown gold powder was then activated by using it in a reaction, which involved treating the gold, in 1.00 g portions, with 5.0 mL of an CH_3CN stock solution of 2.0 mM ^nBuNC, 10.0 mM $^nPr_2NH$, and 40.0 mM NMMO at 60 °C for 24 h. During the reaction, the dull gold powder became shiny, after which it was collected and cleaned as described previously.[11] This gold powder consisted of large particles (∼5–50 μm), which were previously characterized by electron microscopy.[4]

After all of the gold (1.00 g per reaction) was used in a catalytic reaction, it was collected by filtration and then treated with 40 mL of "piranha" solution and stirred for 4 h. The gold was then collected by filtration, washed ten times with 40 mL aliquots of water, followed by five 40 mL methanol washings. It was then dried in air in an oven at 110 °C overnight before use in additional reactions. This gold that was used in another reaction is denoted "second cycle" gold. Gold that was used in subsequent reactions and cleaned as described above was designated "third cycle", "fourth cycle", etc. Since its activity decreased each time the gold was used, comparisons of catalyst activity in this paper were made using gold from the same cycle and therefore having the same usage history. When a significant decrease in catalytic activity was observed (∼5 runs), the gold was dissolved in aqua regia to form $HAuCl_4$, which was then converted back into fresh Au powder according to our standard procedures.[11] Since the Au retains its catalytic activity through all of these purification procedures, which have been performed hundreds of times on the same gold, it is highly unlikely that an impurity in the Au is the actual catalyst.

General Procedure for Gold-Catalyzed Reactions of Iso-cyanides, Amines, and Amine N-Oxides. To 1.0 g of gold powder in a Schlenk tube (2.5 × 17 cm, ∼80 mL volume) was added 5.0 mL of the isocyanide/Ph_3CH stock solution. The reacting amine was then added by a microliter syringe to the tube. A weighed amount of the amine oxide was then added to the tube. The contents of the tube were then degassed by three freeze−pump−thaw cycles, followed by back-filling with argon. After the reaction tube was capped with a septum, the mixture was stirred vigorously with a magnetic stirbar at 60 °C in an oil bath. Aliquots (∼50 μL) of the reaction solution were periodically withdrawn and analyzed by GC (see below).

General Procedure for Mechanistic Studies. Mechanistic studies were performed in NMR tubes (17 × 0.3 cm i.d., ∼1.7 mL volume), which were charged with 0.20 g of Au and then sealed with a

high-vacuum Teflon stopcock. In a glovebox, the NMR tube was loaded with a 0.60 mL CD_3CN solution containing ^nBuNC (10.0 mM), amine or alcohol (30.0 mM), and R_3NO (35.0 mM). The mixture was heated at 60 °C in an oil bath. The reaction progress was monitored by ^1H NMR, or aliquots (∼50 μL) were periodically taken by a syringe and analyzed by GC. As an extra precaution, to reduce the chance of introducing any water into the reaction, the amine N-oxides were sublimed under reduced pressure and subsequently handled in a glovebox. ^nBuNC was brought into the box in a nitrogen-packed ampule.
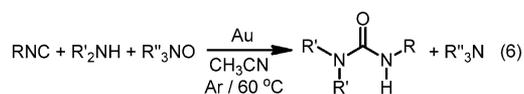
GC and GC-MS Analyses. Gas chromatographic analyses were performed on an HP-6890 instrument equipped with an HP-5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, 5% phenyl, 95% methyl silicone polymer). The GC analysis conditions were as follows: carrier gas, He; mode, constant flow; initial column temperature, 50 °C; temperature program, time at initial temperature, 2 min; heating rate, 15 °C/min; final temperature, 280 °C. Products of the reactions were identified by comparison of their mass spectra and GC retention times with those of authentic samples. Yields were determined by GC integrations using authentic samples of the products as calibrants. GC-MS measurements were made using a Finnegan Magnum GC-MS instrument or a Waters Micromass GCT gas chromatograph.

Preparation of Authentic Samples. Authentic samples of the urea products were prepared from the corresponding amines and isocyanates using published methods.[12] The authentic amidine[13] and imine[4] products were prepared as described previously. All samples were then identified using ^1H NMR and GC-MS.
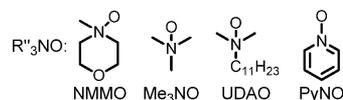
The amidine product from the oxidative dehydrogenation reaction of morpholine was prepared by a previously reported procedure[5] using morpholine (60 mg, 0.69 mmol), O_2 (∼1 L at ∼1 atm), Au (1.00 g), and 5.0 mL of toluene. The mixture was stirred with a magnetic bar at 100 °C for 48 h. Unreacted starting material and solvent were removed under reduced pressure. The amidine product was then recrystallized from dichloromethane/hexanes. ^1H NMR (400 MHz, $CDCl_3$): δ 4.22 (s, 2H, CH_2), 3.69 (t, J_H = 4.8, 4H, CH_2), 3.63 (t, J_H = 4.8, 2H, CH_2), 3.54 (t, J_H = 4.8, 2H, CH_2), 3.20 (t, J_H = 4.8, 4H, CH_2), 1.61 (bs, 0.88H, H_2O). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 150.8, 65.6, 63.2, 63.1, 45.7, 44.1. MS {EI}: 170 [M]$^+$. Anal. Calcd for $C_8H_{14}N_2O_2$·0.44H_2O: C, 53.94; H, 8.42; N, 15.73. Found: C, 53.46; H, 8.37; N 15.51. HRMS (ESI): calculated (M + H) 171.1128, found 171.1132 (2.33 ppm).

■ RESULTS AND DISCUSSION

Reaction of ^nBuNC with $^nPr_2NH$ and NMMO. The reaction of n-butyl isocyanide (^nBuNC), di-n-propylamine ($^nPr_2NH$), and N-methylmorpholine N-oxide (NMMO) in the presence of 1.00 g of gold powder in 5.0 mL of CH_3CN under an argon atmosphere at 60 °C gave 3-butyl-1,1-dipropylurea (eq 6), the same product that was obtained with

$$RNC + R'_2NH + R''_3NO \xrightarrow[\text{Ar / 60 °C}]{\substack{Au \\ CH_3CN}} R' \overset{\displaystyle O}{\underset{R'}{N}}\overset{}{\underset{H}{N}}R + R''_3N \quad (6)$$

RNC: ^nBuNC, ^tBuNC, BnNC

R'$_2$NH: $^nPr_2NH$, $^nBu_2NH$, $^iPr_2NH$, $(CH_2)_5NH$, $O(CH_2CH_2)_2NH$

R''$_3$NO:

NMMO   Me$_3$NO   UDAO   PyNO

O_2 as the oxidant (Scheme 1). As the NMMO concentration was increased from 20.0 to 40.0 mM, an increase in the qualitative rate of urea formation was observed (Figure 1). However, when the NMMO concentration was doubled from 40.0 to 80.0 mM, no additional rate increase was observed. As the concentration of the amine was increased from 10.0 to
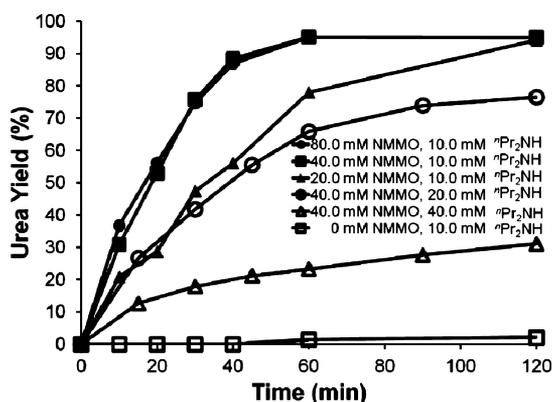
Figure 1. The effect of NMMO and $^{n}Pr_2NH$ concentrations on the rates of reaction (eq 6) of 2.0 mM $^{n}BuNC$ in 5.0 mL CH_3CN catalyzed by 1.00 g of 1st cycle gold at 60 °C.

Figure 2. Effect of various amine oxides in the reaction (eq 6) of 2.0 mM $^{n}BuNC$, 10.0 mM $^{n}Pr_2NH$, and 40.0 mM amine oxide in 5.0 mL of CH_3CN using 1.00 g of first cycle Au at 60 °C.

40.0 mM (Figure 1), the rate of the reaction actually decreased. These dependences of the rate on the NMMO and amine concentrations are very different from those observed for the reactions of isocyanides with amines and O_2 (Scheme 1),[6,7] where the rates of reaction increased as the primary or secondary amine concentration increased and the rates were independent of the O_2 concentration. These results suggest that the mechanisms of the reactions using O_2 and NMMO are different (see the discussion below).

Reactions run in the absence of gold or without amine oxide resulted in little or no reaction. For example, when reaction 6 was run in the absence of amine N-oxide under an Ar atmosphere, using second cycle Au, the total urea yield was only 6% after 8 h (Figure 1). The small amount of urea produced was presumably formed from adventitious oxygen (Scheme 1). In the absence of gold, no urea product was observed even after 24 h at 60 °C, while only unreacted isocyanide, amine, and amine N-oxide remained.

To test for soluble gold species such as gold nanoparticles or Au(I,III) amine complexes as catalysts, reaction 6 was run under standard conditions with second cycle Au. After 30 min of reaction, the yield of urea was 26%. The solution, at 60 °C, was then transferred by cannula to a clean argon-filled Schlenk tube. When the transferred solution was stirred at 60 °C in the absence of the solid gold, no additional urea product was observed after 24 h. This result provides proof that the reaction is not catalyzed by soluble gold complexes or nanogold particles.

Reactions of Different Amine Oxides with $^{n}BuN{\equiv}C$ and $^{n}Pr_2NH$. The reactions of $^{n}BuNC$ and $^{n}Pr_2NH$ with different aliphatic and aromatic amine oxides (eq 6) were investigated in order to determine their effect on the qualitative rates of urea formation. The initial rates of reaction and overall urea yields (Figure 2) were similar, after 2 h, for all three aliphatic amine oxides: NMMO (95%), UDAO (87%), and Me_3NO (85%). A much lower product yield (29% at 2 h) was obtained using pyridine N-oxide (PyNO). The higher rate with the alkyl amine oxides is presumably related to their higher basicities, as reflected in the pK_a's of their conjugate acids: $NMMOH^{+}$ (4.75)[14] > Me_3NOH^{+} (4.56)[15] > $PyNOH^{+}$ (0.79).[16]

Unlike most amine N-oxides, which have a very low solubility in nonpolar solvents,[17] $(C_{11}H_{23})Me_2NO$ (UDAO), with the n-undecyl ($C_{11}H_{23}$) group, was soluble in hexane at 60 °C. Although UDAO (40.0 mM) reacts in acetonitrile with 2.0 mM $^{n}BuNC$ and 10.0 mM $^{n}Pr_2NH$ in the presence of 1.00 g of Au to
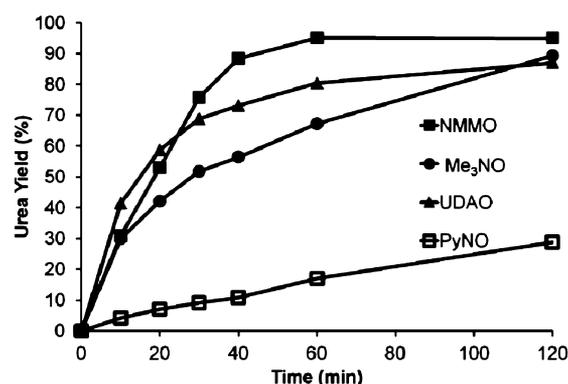
give a 99% yield of the urea within 4 h, the same reaction in hexane solvent proceeds faster initially (58% yield in 25 min) but does not achieve a yield higher than 66% even after 8 h (Figure S1). Since all of the isocyanide was consumed, some of the isocyanide must have reacted to form another product. It has been previously reported that isocyanides are known to polymerize on gold surfaces.[18,19] Since GC analysis of the reaction solutions showed no new products, we analyzed the gold powder surface for isocyanide polymers by diffuse reflectance infrared Fourier transform spectroscopy (DRIFTS). Earlier, McCarley had observed a broad band centered at 1640 cm^{-1},[19] which was assigned to adsorbed polyisocyanide, which was formed when 1,6-diisocyanohexane (DICH) was adsorbed on a gold film. Likewise, the adsorption of DICH on a Cu film resulted in a broad peak, attributed to the N=C double bond of the adsorbed polyisocyanide, at 1650 cm^{-1}.[20] We sought to determine whether or not a similar polymer may be forming on the gold surface during our reactions (eq 6). Therefore, the reaction of 2.0 mM $^{n}BuNC$, 10.0 mM $^{n}Pr_2NH$, and 20.0 mM UDAO with 1.00 g of first cycle Au in 5.0 mL of hexane was performed under Ar at 60 °C. After 2 h of reaction, the isocyanide was no longer detectable, and no additional products were observed in solution by GC. The gold was then separated from the solution by filtration and rinsed for 10 s with fresh hexane to remove any material that was physisorbed on the surface; it was then dried under reduced pressure for 15 min. Analysis of this gold by DRIFTS revealed a broad band at ~1640 cm^{-1}. Since this band did not appear with gold that had not been used in a catalytic reaction or in gold that had been stirred with only 20.0 mM UDAO in hexane under Ar at 60 °C for 2 h, we attribute it to adsorbed polyisocyanide on the surface. It is not obvious why polymer formation occurred in reactions run in hexane but not in acetonitrile.

Reactions of Other Isocyanides and Amines with NMMO. Sterically hindered *tert*-butyl isocyanide ($^{t}BuNC$) and benzyl isocyanide (BnNC) were also investigated with $^{n}Pr_2NH$ (10.0 mM), NMMO (40.0 mM), and 1.00 g of gold (eq 6) under the standard reaction conditions (Figure 3). The urea yield from the reaction of $^{n}BuNC$ with $^{n}Pr_2NH$ was nearly quantitative (99%) within 4 h. In comparison, the reaction with BnNC gave a 94% yield after 24 h, and the reaction with $^{t}BuNC$ gave a yield of only 48% of the corresponding urea even after 3 days. The bulkiness of the isocyanides, which is reflected in their cone angles (^{n}Bu (58°) < Bn (63°) < ^{t}Bu (76°)),[21] was shown previously to affect the amount of isocyanide that can adsorb on a unit of gold surface area: the larger the cone angle,
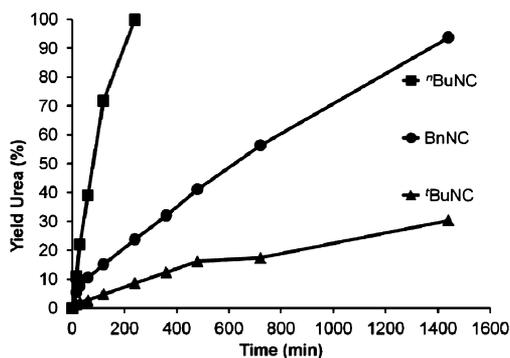
Figure 3. Reaction (eq 6) of 2.0 mM isocyanide, 10.0 mM ^{n}Pr$_2$NH, and 40.0 mM NMMO in acetonitrile and 1.00 g of second cycle Au at 60 °C.

the less isocyanide that can adsorb on a gold surface.[22] Nearly twice as much ^{n}BuNC as ^{t}BuNC adsorbs on the same Au powder surface.[22] As expected, the smaller the cone angle, the more isocyanide that is activated by adsorption and the faster the reaction. The larger cone angle not only results in a reduced amount of isocyanide that binds to the surface but also could make the bulky isocyanides less susceptible to nucleophilic attack for steric reasons. In the case of ^{t}BuNC, the steric bulk is so significant that the isocyanide is much less susceptible to polymerization[23] and in reaction 6 (Figure 3) gives a nearly 48% urea product yield after 72 h, at which point some unreacted ^{t}BuNC remains.

Secondary amines with linear alkyl chains, ^{n}Pr$_2$NH and ^{n}Bu$_2$NH, react with ^{n}BuNC and NMMO in the presence of gold in acetonitrile (eq 6) at 60 °C to give high yields (>97%) of the corresponding ureas within 2 and 4 h, respectively (Figure 4).
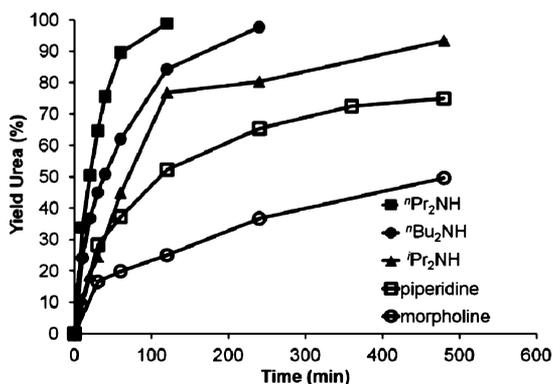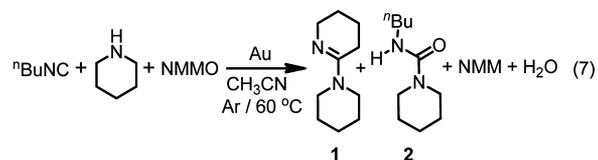

Figure 4. Effect of various secondary amines on the reaction (eq 6) of 2.0 mM ^{n}BuNC, 40.0 mM NMMO, and 10.0 mM amine in acetonitrile with 1.00 g of second cycle Au at 60 °C.
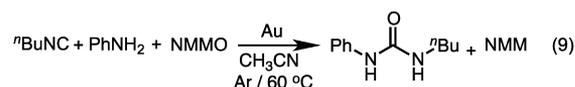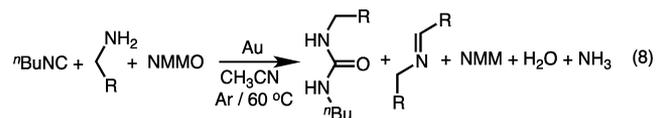
Even the sterically hindered ^{i}Pr$_2$NH gave a very high yield (93%) of the urea. When the cyclic secondary amine piperidine was investigated under the same conditions, urea formation was slower than that with either ^{n}Pr$_2$NH or ^{n}Bu$_2$NH. Over time, the total yield of the piperidinyl urea product did not increase, while the amount of isocyanide in solution decreased. Another product, amidine **1**, resulting from the oxidative dehydrogenation of piperidine (eq 7), formed very slowly at the beginning of the reaction but then increased in rate after 4 h, which corresponded to the time that the isocyanide was no longer observed by GC. Our previous studies of the oxidative dehydrogenation of amines

$$^{n}BuNC + \underset{H}{\overset{H}{N}} + NMMO \xrightarrow[\text{Ar} / 60\,^\circ\text{C}]{\underset{CH_3CN}{Au}} \underset{\mathbf{1}}{N} + \underset{\mathbf{2}}{H} + NMM + H_2O \quad (7)$$

using amine N-oxides as the oxidant showed that piperidine readily undergoes oxidative dehydrogenation to give amidine **1** under conditions similar to those in eq 7.[5] Due to the excess amine present in this reaction, oxidative dehydrogenation may be expected to be a significant competing reaction. Since the isocyanide is ultimately consumed without producing a quantitative yield of the urea product, it is plausible that polymerization of the isocyanide also diminishes the urea yield.

When morpholine was used instead of piperidine in reaction 7, a similar competing oxidative dehydrogenation reaction was also observed to give an amidine product at a faster rate after the isocyanide was completely consumed. As shown in Figure 4, all of the amines have very similar initial rates of reaction within the first 1 h. However, over the course of the reaction, these rates become quite different. For the cyclic amines, it is most likely that the competing oxidative dehydrogenation reactions are responsible for their decreased rates of urea formation over time.

The reactions of primary amines with ^{n}BuNC and NMMO also gave ureas as the predominant product and not carbodiimides, as was observed in the reactions with O$_2$ (Scheme 1).[6] Three primary amines were investigated (eqs 8 and 9): the sterically

$$^{n}BuNC + \underset{R}{\overset{NH_2}{<}} + NMMO \xrightarrow[\text{Ar} / 60\,^\circ\text{C}]{\underset{CH_3CN}{Au}} + NMM + H_2O + NH_3 \quad (8)$$

$$^{n}BuNC + PhNH_2 + NMMO \xrightarrow[\text{Ar} / 60\,^\circ\text{C}]{\underset{CH_3CN}{Au}} Ph\underset{H}{\overset{O}{N}}\underset{H}{N}{}^{n}Bu + NMM \quad (9)$$

hindered cyclohexylamine (CyNH$_2$), the long-chain aliphatic n-hexylamine (^{n}HexNH$_2$), and the arylamine aniline (PhNH$_2$). Like the cyclic secondary amines, oxidative dehydrogenation was observed as a competing reaction when either ^{n}HexNH$_2$ (eq 8) or CyNH$_2$ was used. As for the piperidine and morpholine reactions, oxidative dehydrogenation predominates after about 4 h for both of these amines; the urea product yields reach a maximum of 76% for CyNH$_2$ and 60% for ^{n}HexNH$_2$ (Figure 5), while unreacted
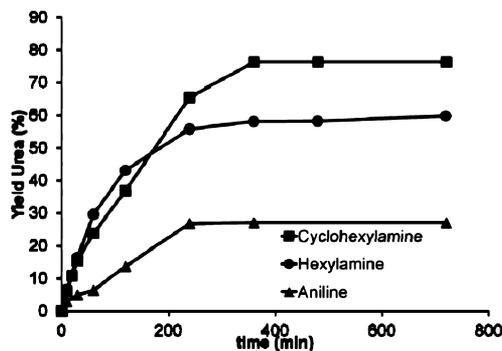

Figure 5. Effect of various primary amines on the reaction (eqs 8 and 9) of 2.0 mM ^{n}BuNC, 40.0 mM NMMO, and 10.0 mM amine in acetonitrile with 1.00 g of second cycle Au at 60 °C.

^{n}BuNC remains in solution. Reaction (eq 9) of the much less basic aniline (pK_a of conjugate acid = 4.76) was much slower than that of either of the two aliphatic amines (pK_a of conjugate acids: ^{n}HexNH$_2$, 10.55; CyNH$_2$, 10.65), and the maximum yield of urea was only 27% after 4 h. Perhaps the slow rate of the reaction with aniline in eq 9 permits the formation of isocyanide polymer which deposits on the gold surface resulting in deactivation. To assess the effect of the ^{n}HexNH$_2$ concentration on the rate of urea formation in eq 8, two reactions were run in which the NMMO concentration was kept constant, while two different concentrations of ^{n}HexNH$_2$ were examined (40.0 and 10.0 mM). The urea yield after 2 h with 40.0 mM ^{n}HexNH$_2$ was only 28%, whereas the yield was 49% when 10.0 mM ^{n}HexNH$_2$ was used (Figure S2). As the ^{n}HexNH$_2$ concentration is increased, it seems probable that its oxidative dehydrogenation to the imine becomes a significant competing reaction.

Recycling the Gold Catalyst. It was previously reported[11,13] in other reactions using a gold powder catalyst that the catalytic activity of the gold decreased each time the gold was reused even though it was cleaned with "piranha" solution and washed between uses. Similar recycling studies were performed for reactions that use amine N-oxides as the oxidant. Freshly prepared gold powder that was obtained through the reduction of HAuCl$_4$ with hydroquinone was initially dull brown, prior to being used in a reaction.[11] When it was used in a reaction with ^{n}BuNC (2.0 mM), ^{n}Pr$_2$NH (10.0 mM), and NMMO (40.0 mM) in acetonitrile under an Ar atmosphere (eq 6, Figure 6), the production of the urea was relatively slow and
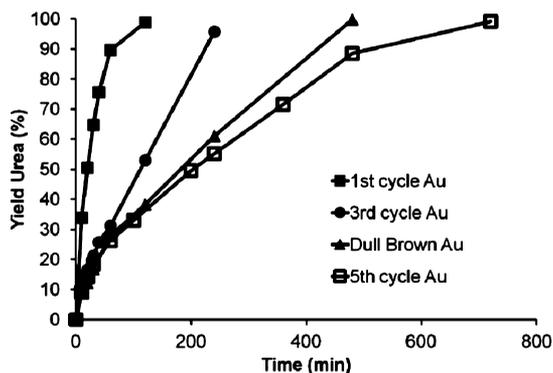

Figure 6. Reaction of 2.0 mM ^{n}BuNC, 10.0 mM ^{n}Pr$_2$NH, and 40.0 mM NMMO in acetonitrile (eq 6) catalyzed by 1.00 g of different cycles of Au at 60 °C.

required 8 h ($t_{1/2} \approx 2.33$ h) to reach completion. After this treatment, the gold became its normal lustrous golden color and also became much more active. After it was recovered by filtration, it was treated with "piranha" solution (H$_2$O$_2$/H$_2$SO$_4$), washed with water, rinsed with methanol, and dried overnight at 120 °C. When this gold was used in the same reaction (first cycle), the yield of urea product was nearly quantitative in only 2 h ($t_{1/2}$ = 0.33 h). By the fifth cycle (Figure 6), the activity of the gold decreased to the point that the rate of formation of the urea was slower than that for the initial dull brown gold. Regeneration of the gold powder by converting it back to HAuCl$_4$ using a literature procedure[11] was typically done at this stage. Previously, it was shown that following regeneration the freshly prepared dull brown gold particles were partially coated with a carbon-containing material that was presumably responsible for its low catalytic activity.[11] After the activating catalytic reaction, the carbon coating and morphology

of the gold particles changed substantially, and it had a much higher catalytic activity in the first cycle reaction (Figure 6). In subsequent uses, the activity decreased, perhaps as a result of the deposition of organic material, possibly polymerized isocyanide, on the gold surface.

Mechanistic Considerations for Au-Catalyzed Reactions of RN≡C, Amines, and Amine Oxides. Two types of mechanisms can be considered for the formation of ureas from the gold-metal-catalyzed reactions of isocyanides, amines, and amine oxides (Scheme 2). It is very likely that the isocyanide

Scheme 2. Possible Mechanisms for the Reaction of Adsorbed Isocyanide with Secondary Amines and Amine Oxides To Form Urea Products
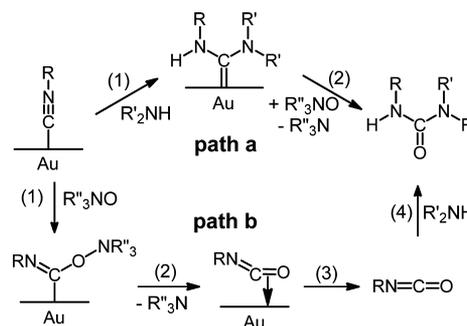
initially adsorbs on the gold surface, as demonstrated by several studies of isocyanide adsorption on gold-metal surfaces.[6,24] In one of these mechanisms (path a), the adsorbed isocyanide is attacked by the amine to give the same diaminocarbene intermediate that was proposed for the O$_2$ oxidations[6,7] (Scheme 1). This intermediate then reacts with the amine N-oxide to give the urea product. The details of this latter step could involve initial transfer of the oxygen from the amine N-oxide to the gold surface followed by reaction with the diaminocarbene, or it could involve direct attack of the amine oxide on the diaminocarbene intermediate. Mechanism b involves gold catalysis of the reaction of isocyanides with amine N-oxides to form isocyanates. In order to test this possibility, an NMR tube reaction mixture of ^{n}BuNC (10.0 mM), 0.60 mL of CD$_3$CN, 0.20 g of Au, and Me$_3$NO (40.0 mM), which was used instead of NMMO to simplify the ^{1}H NMR analysis, was prepared in a glovebox. The sealed NMR tube was then heated in an oil bath at 60 °C and monitored periodically by NMR. Within 3 h, a new product (13%) was observed (Figure 7), which was identified as ^{n}BuNCO (eq 10)
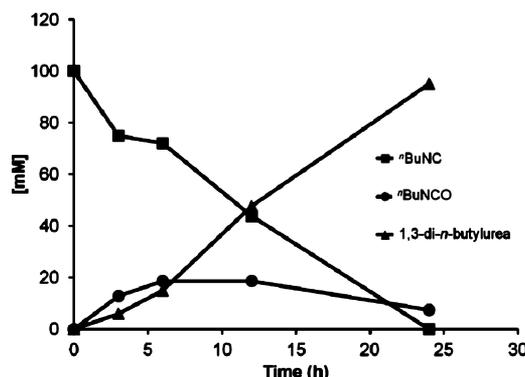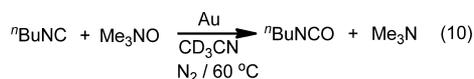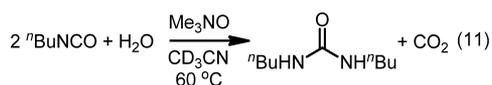

Figure 7. Reaction of 10.0 mM ^{n}BuNC and 40.0 mM NMMO in CD$_3$CN (eq 10) catalyzed by 0.20 g of Au at 60 °C.

$$^{n}\text{BuNC} + \text{Me}_3\text{NO} \xrightarrow[\text{N}_2 / 60\ ^\circ\text{C}]{\overset{\text{Au}}{\underset{\text{CD}_3\text{CN}}{}}} {^{n}\text{BuNCO}} + \text{Me}_3\text{N} \quad (10)$$
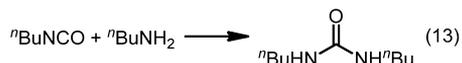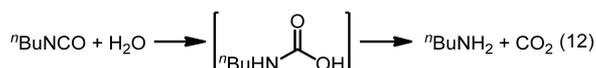
by comparison of its GC and NMR properties with those of an authentic sample of the compound.

The amount of ^{n}BuNCO reached a maximum yield of 20% at 6 h, after which it slowly decreased. The observation of ^{n}BuNCO is consistent with its formation by path b under the conditions of reaction 6. Although ^{n}BuNCO is clearly formed according to eq 10, it is subsequently converted to di-n-butylurea during the reaction; after 24 h, the di-n-butylurea yield was ∼92% (Figure 7). No new products were observed when the reaction was continued further. Even though the reaction mixture (eq 10) was prepared under a nitrogen atmosphere, it is likely that there was sufficient adventitious water to convert the isocyanate to the urea according to eq 11. (When O_2 was used instead of Me_3NO

$$2\ {^{n}\text{BuNCO}} + \text{H}_2\text{O} \xrightarrow[\text{60}\ ^\circ\text{C}]{\overset{\text{Me}_3\text{NO}}{\underset{\text{CD}_3\text{CN}}{}}} {^{n}\text{BuHN}}\overset{\text{O}}{\underset{}{\diagup\!\!\!\diagdown}}\text{NH}^{n}\text{Bu} + \text{CO}_2 \quad (11)$$

in the reaction with ^{n}BuNC and gold, there was no evidence for the formation of ^{n}BuNCO.)

We have observed that ^{n}BuNCO gives di-n-butylurea under the conditions of reaction 10, in the absence of gold (eq 11), presumably involving adventitious water. The reaction of isocyanates with water is well-known.[25,26] Mechanistic studies suggest that it proceeds by initial attack of water on the isocyanate to form a carbamic acid intermediate, which undergoes decarboxylation to generate the primary amine and carbon dioxide (eq 12). The isocyanate then reacts readily with the

$$^{n}\text{BuNCO} + \text{H}_2\text{O} \longrightarrow \left[{^{n}\text{BuHN}}\overset{\text{O}}{\underset{}{\diagup\!\!\!\diagdown}}\text{OH} \right] \longrightarrow {^{n}\text{BuNH}_2} + \text{CO}_2 \quad (12)$$

$$^{n}\text{BuNCO} + {^{n}\text{BuNH}_2} \longrightarrow {^{n}\text{BuHN}}\overset{\text{O}}{\underset{}{\diagup\!\!\!\diagdown}}\text{NH}^{n}\text{Bu} \quad (13)$$

amine to give the urea (eq 13).[25,26] The reaction of isocyanates with water is known to be catalyzed by tertiary amines and other compounds.[26] Since a tertiary amine is produced in our reactions (eq 6), it is plausible that it catalyzes this reaction, with even small amounts of water. As ^{n}BuNCO is not observed during the course of any of the Au-catalyzed reactions of isocyanides with amines and amine oxides (eq 6), the mechanism in path b (Scheme 2) requires that the rate of reaction of ^{n}BuNCO with amine to form the urea be much faster than the rate of ^{n}BuNCO formation from ^{n}BuNC. When a NMR tube containing reactant concentrations of 10.0 mM ^{n}BuNCO and 30.0 mM ^{n}Pr$_2$NH was heated in an NMR instrument at 60 °C, the reaction was complete in less than 90 s. This is much faster than the first step in path b, as $t_{1/2}$ for reaction of ^{n}BuNC with ^{n}Pr$_2$NH and NMMO under the same conditions is approximately 11 h. Total consumption of the isocyanide does not occur for about 24 h. The much faster rate for step 4 in path b in comparison to the rate of formation of ^{n}BuNCO is consistent with this pathway. Since the reaction of ^{n}BuNCO with the amine (step 4 in path b) is fast, the overall rate of reaction is determined by the rate of conversion of ^{n}BuNC to ^{n}BuNCO.

As seen in Figures 4 and 5, the initial rates of reactions of ^{n}BuNC with NMMO and different amines are very similar, which is consistent with mechanism b, in which the amine is not involved in the rate-determining step. However, there are some

modest rate differences which may be attributed to amine competition for gold adsorption sites on which ^{n}BuNC is activated. As is evident in Figures 4 and 5, the rates of the reaction at later stages differ greatly depending on the amine. The reasons for this divergence in rates include the formation of other products and a ^{n}BuNC polymer that reduces the activity of the gold catalyst. These complications were discussed earlier in this paper.

If reaction 6 proceeds by the path b mechanism in Scheme 2, the isocyanate intermediate should also react with other nucleophiles. It is well-known that alcohols react with isocyanates to form carbamates.[26] It was therefore expected that an isocyanide should react with an alcohol and an amine oxide to give a carbamate product. Indeed, the reaction of ^{n}BuNC (10.0 mM), ^{n}PrOH (30.0 mM), and Me_3NO (40.0 mM) in CD$_3$CN at 60 °C gave a 50% yield of the carbamate (eq 14) after 12 h. The rate of this reaction, as shown in Figure 8, is similar to that of the
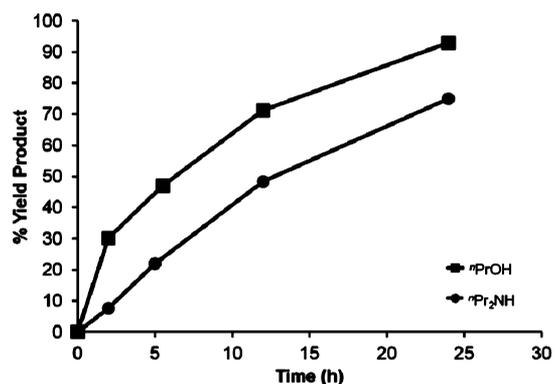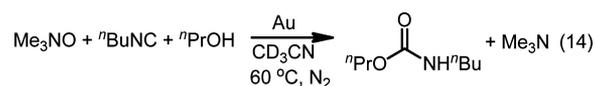
$$\text{Me}_3\text{NO} + {^{n}\text{BuNC}} + {^{n}\text{PrOH}} \xrightarrow[\text{60}\ ^\circ\text{C, N}_2]{\overset{\text{Au}}{\underset{\text{CD}_3\text{CN}}{}}} {^{n}\text{PrO}}\overset{\text{O}}{\underset{}{\diagup\!\!\!\diagdown}}\text{NH}^{n}\text{Bu} + \text{Me}_3\text{N} \quad (14)$$

Figure 8. Reaction of 10.0 mM ^{n}BuNC, 40.0 mM NMMO, and 30 mM ^{n}PrOH or ^{n}Pr$_2$NH in CD$_3$CN (eqs 6 and 14) catalyzed by 0.20 g of Au at 60 °C.

reaction of ^{n}BuNC with ^{n}Pr$_2$NH and NMMO, which is expected if the rate-determining step is the conversion of ^{n}BuNC to ^{n}BuNCO in path b. The slower rate of the amine reaction may be attributed to the adsorption of amine on the Au, which inhibits the adsorption of isocyanide and correspondingly reduces the rate of conversion of the isocyanide to the isocyanate. Although ^{n}BuNCO is not detected during the course of reaction 14, there is evidence to suggest that the putative ^{n}BuNCO intermediate would react with the alcohol to form the carbamate product much more quickly than the overall rate of reaction 14. Indeed, the $t_{1/2}$ value for the reaction of ^{n}BuNCO with ^{n}PrOH in the presence of NMMO is only 9.5 min as compared to a $t_{1/2}$ value of 6 h for reaction 14 under the same conditions. These data are also consistent with path b, in which the formation of ^{n}BuNCO is the rate-determining step. (Semiquantitative rate studies indicate that the reaction of ^{n}BuNCO with ^{n}PrOH is catalyzed by NMMO. Amine oxide catalysis of reactions of isocyanates with alcohols has been previously reported.[27])

When ^{n}BuNC (10.0 mM) and equal concentrations (30.0 mM) of ^{n}PrOH and ^{n}Pr$_2$NH are treated with NMMO (35.0 mM) and 0.20 g Au in acetonitrile at 60 °C, the only observed product is the urea (O=C(NH^{n}Bu)(N^{n}Pr$_2$)), rather than the carbamate. This result is also consistent with path b, as amines are known to react much faster than alcohols with isocyanates.[28]

In addition to the studies described above, there are several other experimental results that provide additional evidence for the mechanism in path b, in which the conversion of ^{n}BuNC to ^{n}BuNCO is the rate-determining step. The rate of reaction 6 increases with the NMMO concentration (Figure 1), which supports a step in which the amine oxide attacks the adsorbed isocyanide; although at high NMMO concentration, the rate does not increase further. Also consistent with amine oxide attack is the higher rate of reaction with the most basic amine oxides (Figure 2), as indicated by the pK_a's of their conjugate acids. Moreover, the rate of the reaction decreases as the size of the isocyanide R group increases (Figure 3), which is consistent with steric resistance to amine oxide attack (path b, step 1); such a decrease in rate with the size of the isocyanide was observed in the bulk gold-catalyzed reactions of isocyanides, secondary amines, and O_2 to form ureas.[7] Furthermore, the rate of reaction 6 decreases as the amine concentration increases (Figure 1), presumably because the amine competes with the isocyanide for adsorption sites, thereby reducing the number of activated, adsorbed isocyanides.

The detailed mechanism for step 1 in path b is proposed to involve nucleophilic attack of the amine oxide on the adsorbed isocyanide. As discussed previously,[6] the carbon of adsorbed isocyanides is electrophilic and therefore susceptible to nucleophilic attack. There are many examples of nucleophilic attack by amines and alcohols on isocyanides coordinated in metal complexes.[29] However, there is only one precedent for the attack of an amine oxide on a coordinated isocyanide ligand, and that is in the first step of the reaction of Fe(C≡NCH$_2$Ph)$_6$$^{2+}$ with Me$_3$NO, which leads to a product in which two isocyanides are oxidized and coupled.[30] In contrast to the few examples of amine oxide attack on coordinated isocyanides, there are many examples of amine oxide attack (eq 15) on

$$ML_x-CO + R_3NO \longrightarrow \underset{ML_x}{\overset{O}{\underset{\Vert}{C}}}-O-NR_3 \longrightarrow L_xM + R_3N + CO_2 \quad (15)$$
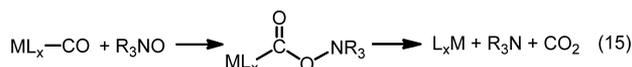
coordinated CO,[9,31] which is pseudo-isoelectronic with isocyanides. Detailed kinetic studies of these reactions, e.g., the reaction of Cr(CO)$_6$ with Me$_3$NO and PPh$_3$, revealed the rate of reaction to be first order in both the metal carbonyl and the amine N-oxide concentrations and zero order in the phosphine concentration. The proposed mechanism (Scheme 3) is very

Scheme 3. Reaction of Cr(CO)$_6$, Me$_3$NO, and PPh$_3$ in CH$_2$Cl$_2$ at 20 °C[9]
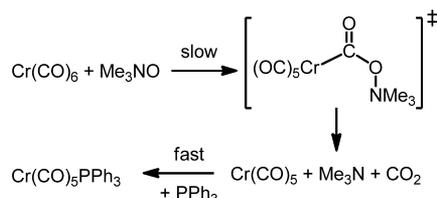
similar to that proposed in step 1 of path b. The CO$_2$ product in eq 15 is also analogous to the RN=C=O intermediate in path b (Scheme 2). Another organometallic reaction that is especially relevant to the mechanism in path b is the reaction of ^{t}BuNC with N$_2$O to form ^{t}BuNCO, which is catalyzed by Cp*Mo[N(^{i}Pr)C-(Me)N(^{i}Pr)](CN^{t}Bu)$_2$ at 25 °C.[32] Detailed studies of this system indicate that the complex initially reacts with the N$_2$O to form an oxo complex which reacts with ^{t}BuNC to form an η^2-^{t}BuNCO

complex, whose structure was established by X-ray crystallography; it is on the basis of this structure that the intermediate resulting from step 2 in path b is proposed to have an η^2-RN=C=O geometry.

CONCLUSIONS

Although both O$_2$ (Scheme 1) and amine oxides (R$_3$NO; eq 6) are able to serve as the oxidizing agent in bulk gold-catalyzed reactions of isocyanides and amines to produce ureas, the studies described herein indicate that they proceed by different mechanisms. In the O$_2$ reaction, attack of the amine on adsorbed C≡NR is the first and rate-determining step. The resulting diaminocarbene intermediate subsequently reacts rapidly with O$_2$ to give the urea product (Scheme 1). In the reaction with amine oxides, attack of R$_3$NO on the adsorbed isocyanide is the initial and rate-determining step to generate an isocyanate (RN=C=O), which rapidly reacts with the amine to give the urea product (Scheme 2, path b). The role of the gold metal in both mechanisms is to activate the adsorbed isocyanide toward nucleophilic attack by either the amine (in the O$_2$ reactions) or the R$_3$NO (in the amine oxide reactions). In the latter reactions, even though both R$_3$NO and R'$_2$NH are present, it is the R$_3$NO that preferentially attacks the adsorbed isocyanide. This faster rate of R$_3$NO attack, as compared with R'$_2$NH attack, is consistent with the observation that reactions using R$_3$NO as oxidant (eq 6) are faster than those using O$_2$ (Scheme 1). It is also consistent with the observation (Scheme 3) that a CO ligand in M(CO)$_6$, where M = Cr, Mo, W,[9] is attacked by Me$_3$NO but not by amines. These results suggest that the pattern of reactivity of isocyanides adsorbed on gold metal with nucleophiles is similar to that of isocyanide ligands in relatively positive metal complexes in solution.

ASSOCIATED CONTENT

S Supporting Information

Figures S1 and S2, showing rates of reactions of ^{n}BuNC with amines and amine oxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

Dedicated to the memory of Prof. F. Gordon A. Stone, one of the original pioneers in organometallic chemistry.

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