Bulk gold catalyzed oxidation reactions of amines and isocyanides and iron porphyrin catalyzed N-H and O-H bond insertion/cyclization reactions of diamines and aminoalcohols

by

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Do not go where the path may lead. Go instead where there is no path and leave a trail.

- **Ralph Waldo Emerson**

Great things are not done by impulse, but by a series of small things brought together.

- **Vincent van Gogh**

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LIST OF ABBREVIATIONS

Bn	benzyl
DRIFTS	diffuse reflectance infrared Fourier transform spectroscopy
EDA	ethyl diazoacetate
EPR	electron paramagnetic resonance
eq	equation
equiv	equivalent
Fe(TPP)Cl	iron(III) tetraphenylporphyrin chloride
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GC-MS	gas chromatography coupled with mass spectrometry
HRMS	high resolution mass spectrometry
m/z	mass/charge density
mg	milligram
mL	milliliter
mM	millimolar
mmol	millimole
MS (EI)	mass spectrometry by electron impact
^{n}BuNC	*normal* butyl isocyanide
NMMO	N-methylmorpholine N-oxide
NMR	nuclear magnetic resonance

ppm	parts per million
RAIRS	reflection absorption infrared spectroscopy
SEM	scanning electron microscopy
TEM	transmission electron microscopy
UDAO	undecyldimethylamine N-oxide

ABSTRACT

Bulk gold catalyzed oxidation reactions of amines and isocyanides and iron porphyrin catalyzed N-H and O-H bond insertion/cyclization reactions of diamines and aminoalcohols

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This work involves two projects. The first project entails the study of *bulk* gold as a catalyst in oxidation reactions of isocyanides and amines. The main goal of this project was to study the activation and reactions of molecules at metal surfaces in order to assess how organometallic principles for homogeneous processes apply to heterogeneous catalysis. Since previous work had used oxygen as an oxidant in bulk gold catalyzed reactions, the generality of gold catalysis with other oxidants was examined. Amine N-oxides were chosen for study, due to their properties and use in the oxidation of carbonyl ligands in organometallic complexes. When amine N-oxides were used as an oxidant in the reaction of isocyanides with amines, the system was able to produce ureas from a variety of isocyanides, amines, and amine N-oxides. In addition, the rate was found to generally increase as the amine N-oxide concentration increased, and decrease with increased concentrations of the amine. Mechanistic studies revealed that the reaction likely involves transfer of an oxygen atom from the amine N-oxide to the adsorbed isocyanide to generate an isocyanate intermediate. Subsequent nucleophilic attack by the amine yields the urea. This is in contrast to the bulk gold-catalyzed reaction mechanism of isocyanides with amines and oxygen. Formation of urea in this case was proposed to proceed through a diaminocarbene

intermediate. Moreover, formation of the proposed isocyanate intermediate is consistent with the reactions of metal carbonyl ligands, which are isoelectronic to isocyanides. Nucleophilic attack at coordinated CO by amine N-oxides produces CO_2 and is analogous to the production of an isocyanate in this gold system.

When the bulk gold-catalyzed oxidative dehydrogenation of amines was examined with amine N-oxides, the same products were afforded as when O_2 was used as the oxidant. When the two types of oxidants were directly compared using the same reaction system and conditions, it was found that the oxidative dehydrogenation of dibenzylamine to N-benzylidenebenzylamine, with N-methylmorpholine N-oxide (NMMO), was nearly quantitative (96%) within 24 h. However, the reaction with oxygen was much slower, with only a 52% yield of imine product over the same time period. Moreover, the rate of reaction was found to be influenced by the nature of the amine N-oxide. For example, the use of the weakly basic pyridine N-oxide (PyNO) led to an imine yield of only 6% after 24 h. A comparison of amine N-oxide and O_2 was also examined in the oxidation of $PhCH_2OH$ to PhCHO catalyzed by bulk gold. In this reaction, a 52% yield of the aldehyde was achieved when NMMO was used, while only a 7% product yield was afforded when O_2 was the oxidant after 48 h.

The bulk gold-catalyzed oxidative dehydrogenation of cyclic amines generates amidines, which upon treatment with Aerosil and water were found to undergo hydrolysis to produce lactams. Moreover, 5-, 6-, and 7-membered lactams could be prepared through a one-pot reaction of cyclic amines by treatment with oxygen, water, bulk gold, and Aerosil. This method is much more atom economical than industrial processes, does not require

corrosive acids, and does not generate undesired byproducts. Additionally, the gold and Aerosil catalysts can be readily separated from the reaction mixture.

The second project involved studying iron(III) tetraphenylporphyrin chloride, Fe(TPP)Cl, as a homogeneous catalyst for the generation of carbenes from diazo reagents and their reaction with heteroatom compounds. Fe(TPP)Cl, efficiently catalyzed the insertion of carbenes derived from methyl 2-phenyldiazoacetates into O-H bonds of aliphatic and aromatic alcohols. Fe(TPP)Cl was also found to be an effective catalyst for tandem N-H and O-H insertion/cyclization reactions when 1,2-diamines and 1,2-alcoholamines were treated with diazo reagents. This approach provides a one-pot process for synthesizing piperazinones and morpholinones and related analogues such as quinoxalinones and benzoxazin-2-ones.

GENERAL INTRODUCTION

Dissertation Organization

The first chapter of this dissertation is a literature review of the catalysts and reactions relevant to this work. Chapters 2-5 are individual papers that are published or submitted to peer-reviewed journals. In Chapter 2, nearly all of the N-H insertion/cyclization reactions with EDA were performed by the author with two exceptions. The reaction of piperidine with EDA and the reaction of 1,2-diamino-4,5-dichlorobenzene with EDA were performed by others. The work in Chapters 3-5 was performed exclusively by the author.

History, Properties, and Industrial Uses of Gold

Gold is one of the longest known and most fascinating elements to mankind. Since ancient times it has been a symbol of wealth and status. It has been described as the most noble of metals and today remains one of the most sought after. The Latin name for gold, *aurum*, means "glowing dawn."[1] The name gold is from 'geolo' the Old English word for yellow.[2]

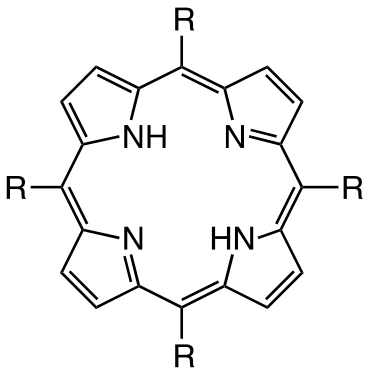
The most malleable and ductile of all metals,[2] gold is also one of the most chemically inert, as it does not tarnish or form a surface oxide with oxygen at room temperature.[3] Moreover, it does not react with any alkaline solutions and most acids.[2] However, gold forms alloys with many metals, including silver, copper, mercury and palladium.[2] These alloys are very important for the jewelry industry, with gold-palladium-silver and gold-nickel-copper-zinc are the two most common alloys used. A unit for measuring the pureness of an alloy is the karat (kt). Pure gold (99.7%) is 24 kt, while 12 kt gold is an alloy that is composed of only 50% gold.

Gold is not only economically valuable, it has many commercial uses. The largest consumers of gold are the jewelry, electronics, weapons, and aerospace industries.[2] The corrosion resistance and high electrical conductivity of gold make it an ideal metal for connectors, printed circuits, relays, and switches.[2] In the aerospace industries, gold is the metal of choice for spacecraft and satellite shielding for radiation protection as it reflects up to 99% of infra-red rays.[2]

The versatility of gold includes uses in modern medicine. From a toxicity standpoint, it is one of the best metals to explore as it is not biologically active. As an x-ray contrast agent, gold nanoparticles have been found to offer advantages over iodine. In preliminary studies with mice, gold nanoparticles were found to have a higher absorption which allows for better contrast with a lower X-ray dose.[4] While gold (I) complexes were first found to treat rheumatoid arthritis in 1929,[5] recent studies of gold (I and III) complexes have shown their ability to inhibit tumor growth in both *in vitro* and *in vivo* studies.[6] This makes them attractive alternatives for platinum antitumor drugs, for which cancer cells oftentimes develop resistance, as well as avoid the harsh side effects of these compounds.

Properties and Biological Applications of Porphyrins

Porphyrins are macrocycles consisting of four pyrrole units that are linked through methine bridges to form a planar, aromatic heterocyclic ring system. They are aromatic molecules with a total of 26 π e^- (Figure 1). Related molecules include corrins and chlorins.



R= Ph (TPP), PhMe (TTP), $PhMe_3$ (TMP)

Figure 1. The structure of a free base porphyrin.

Porphryins complexed to iron are called hemes, and are found in many biological systems. Hemoglobin, a heme protein, is used to carry oxygen through the blood in almost all vertebrates. Myoglobin, which also contains a heme center, is found in muscle tissue where it stores oxygen, which is released into the muscle upon oxygen deprivation, such as during strenuous exercise. Cytochromes A, B, and C, are also heme proteins, and are used in electron transfer reactions in biological systems. Other biologically important porphyrin-type molecules include Vitamin B_{12}, a related cobalt corrin complex that is important for the functioning of the brain and the central nervous system in humans. Chlorophyll is also a related chlorin complex that contains a magnesium center, and is vital for photosynthesis in plants, algae, and cyanobacteria.

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CHAPTER 1: OVERVIEW OF CATALYSIS BY BULK GOLD AND IRON PORPHYRINS

Introduction to Gold Catalysis

Nanogold. The most widely studied heterogeneous gold catalysts are nanosized (<5 nm) gold particles supported on a high-surface area oxide. Understanding the high activity of nano gold catalysts is difficult due to the contributions of a number of potential factors including the size and larger surface area of smaller gold particles, the influence of the support, and the preparation method.[1] For example, previous studies of the oxidation reaction of CO with O_2 catalyzed by supported gold nanoparticles of various sizes showed that the activity of the catalyst generally increased as the particle size decreased for a variety of supports, including Al_2O_3, Fe_2O_3, SiO_2, TiO_2. However, the degree of this increase varied for the individual supports.[2,3,4] Additional complications include the monodispersity range of the small nanoparticles on the support and the potential for particle sintering.[5] Other studies on the effect of the support have shown that the chemical and physical nature of the support influences the structure, the stability, and the catalytic activity of the gold particles.[6,7,8,9] Moreover, the preparative method[1] is responsible for the size of the nanoparticles, their coverage on the support, and the morphology of the gold particles.[10] These different factors make it difficult to reliably compare the catalytic activity of gold nanoparticles, even those that are of the same size on the same support.

The many variables mentioned above also make mechanistic studies very difficult for reactions catalyzed by supported gold nanoparticles. This has been illustrated by several studies of the oxidation of CO with O_2 that utilize different supported gold nanoparticle

catalysts. In addition to the possibility that the reaction takes place entirely on the gold nanoparticles, additional mechanisms have been suggested.[1] One proposal involves activation of the dioxygen by the support, since O_2 does not readily adsorb on gold particles.[1] This activation may occur at oxide vacancies on the surface of the metal oxide support, especially in supports that are readily reduced such as Fe_2O_3 or CeO_2.[1] EPR studies suggest that oxygen may adsorb at these vacancies as the superoxide anion,[11] where it may then migrate to the gold particles, particularly at boundaries. It has also been proposed that the reaction occurs entirely on the support, in which the CO that initially adsorbs on the gold nanoparticles migrates to the support where it then reacts with oxygen species.[12] Another possible mechanism involves cationic gold species as the active sites. For example, reducible supports may undergo reduction when they are treated with the gold precursor, which may result in a positive oxidation state on the supported gold.[13] These issues illustrate the difficulties in identifying the active sites on supported nanogold catalysts, particularly in reactions that involve dioxygen.[1]

Bulk Gold Powder. Unlike supported nanogold particles, bulk gold was thought to be a poor catalyst, until recently.[1] Bulk gold powder used for catalytic reactions was prepared through the reduction of $HAuCl_4$ with hydroquinone, and was found to have a surface area of 0.35 m^2/g.[14] Based on a cubic close-packed structure, the number of gold surface atoms, Au_{surf}, was estimated to be 7.0×10^{-6} mol of atoms per gram of gold or 1 surface atom for every 725 gold atoms. SEM images of the gold powder and at 500x magnification (Figure 1a), showed particles with an average size of ~50 μm.[15] At 50,000x

magnification, the gold was found to have ridges and much smaller gold particles (~100 nm) on the surface of the larger particles (Figure 1b).

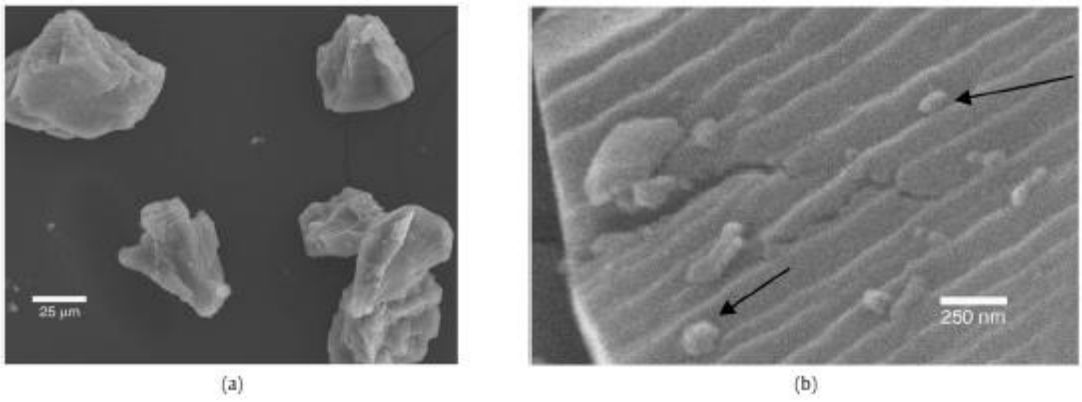


Figure 1. Scanning electron micrographs of gold powder: (a) 500x magnification and (b) 50,000x magnification. Black arrows point to small Au particles on the surface of the much larger Au particles.[15]

When the gold powder is initially prepared, its physical appearance and structure are quite different than the lustrous color usually associated with gold. This freshly-prepared powder is dull brown in color and TEM images at 64,000x revealed a sea urchin-like structure consisting of large particles with attached spines (Figure 2).[16] TEM also revealed its first catalytic application compared to subsequent uses in identical reactions. Along with increased activity after its initial use in a catalytic reaction, the appearance of the gold also changed to its normal color and luster. Additionally, TEM images of this once-used gold showed larger particles with a smoother surface that was devoid of the carbon-containing spines.[16]

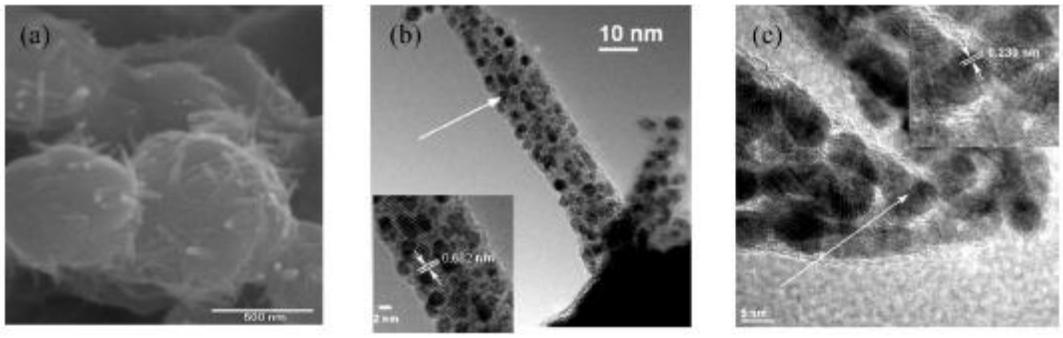


Figure 2. Electron micrographs of dull brown Au particles with sea urchin morphology. (a) Scanning electron microscopy (SEM) image measured at 50,000x magnification; (b) transmission electron microscopy (TEM) image measured at 64,000x magnification with the inset showing an HRTEM image focusing on the lattice fringes; (c) TEM image measured at 440,000x, with the inset showing an HRTEM image focusing on the FCC lattice of the gold nanoparticles. The white arrows in (b) and (c) point to the areas that were modified for the high resolution images (insets).[16]

Adsorption and Reactivity of Molecules on Au Surfaces

In heterogeneous reactions on metal surfaces, the first step often involves adsorption of a molecule at the surface. There are two possible ways for molecules to adsorb to the surface. The first is through physisorption, which is characteristically a very weak interaction between the surface and the molecule, such as through nonspecific dispersion forces. The second is through chemisorption, which involves the formation of a chemical bond between the surface and the molecule.[1] Typically, only chemisorbed molecules are able to undergo reactions on metal surfaces, as physisorbed molecules usually desorb.

Adsorption of Isocyanides on Gold Surfaces

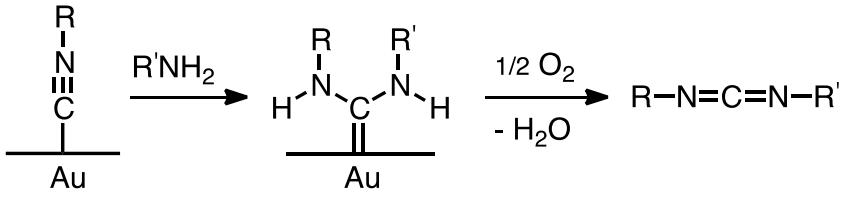
Isocyanides (R-N≡C) and carbon monoxide are isoelectronic and both have been widely studied as ligands in metal complexes. However, CO adsorption on metal surfaces has been more extensively studied.[17] Nonetheless, isocyanides have a high intensity υ(N≡C)

stretching absorption, which provides a useful IR tag. Their adsorption on Au powder was investigated using DRIFTS, in which IR radiation is directed at the surface, after which it is then reflected, refracted, and diffracted to optimize signal intensity at the detector.[18] Upon coordination, the υ(NC) of the isocyanide typically shifts to a higher frequency. In organometallic gold complexes, such as [(RNC)AuCl], terminally bound isocyanide ligands have a υ(NC) frequency that is ca. 100 cm^{-1} higher than that of the free isocyanide.[14] In comparison, isocyanides that are adsorbed on a gold surface typically have a υ(NC) increase of 60-74 cm^{-1}, due to the lower oxidation state of the gold metal. Moreover, the υ(NC) value indicates that the isocyanides are terminally bound to a single Au atom at the surface. The likelihood for the isocyanide to undergo nucleophilic attack can be estimated by the υ(NC) shift of the bound ligand relative to the free molecule. An increase of at least 40 cm^{-1}, which is a general benchmark, indicates that both the isocyanide adsorbed on the gold surface and the isocyanide ligand in the metal complexes have a high susceptibility to undergo reaction with nucleophiles.[19]

Reactions of Isocyanides Adsorbed on Gold Surfaces

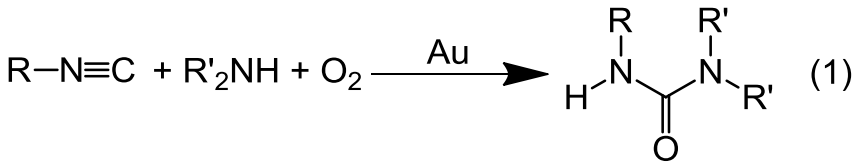
The first example of activation of an isocyanide adsorbed on a gold surface was in a study involving a gold film supported on a glass slide. In this case, isocyanides and primary amines were converted to carbodiimides in the presence of air.[19] This reaction was then investigated using gold powder as a catalyst, with oxygen (~1 L, ~1 atm) and various primary amine concentrations at room temperature. Kinetic studies indicated that the reaction was first order in the amine concentration and zero order in the oxygen concentration.[19] The first step of the reaction involves isocyanide adsorption to the metal surface (η^1). The kinetic

behavior is consistent with a rate-determining nucleophilic attack by the amine on the adsorbed isocyanide to form a diaminocarbene intermediate, analogous to those observed in soluble metal complexes.[20] Subsequent oxidation of the diaminocarbene intermediate afforded the carbodiimide (Scheme 1). This reaction system also tolerated secondary amines, but produced substituted ureas, as carbodiimides are not possible (eq 1).[21] Consistent with a



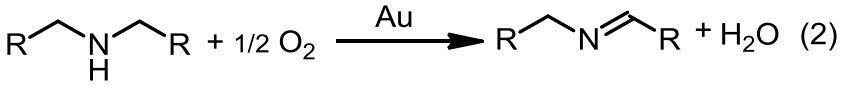
Scheme 1. Mechanism for the Au-Catalyzed Reaction of Isocyanides (R-N≡C) with Primary Amines (R'NH_2) and O_2[19]

rate-determining amine attack on the adsorbed isocyanide, the steric and electronic effects of the amine significantly influenced the rate of reaction.



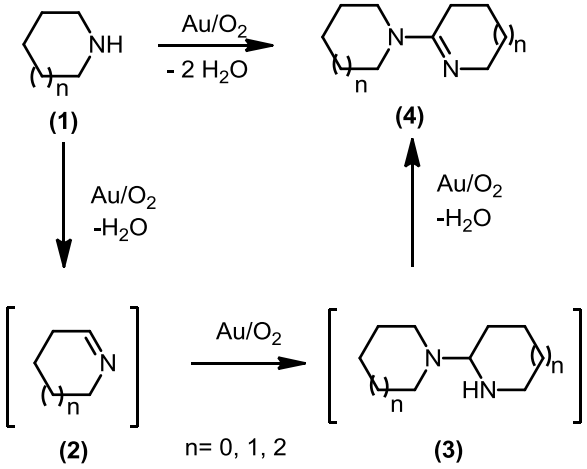
Oxidative Dehydrogenation of Amines Catalyzed by Bulk Gold

Secondary amines were found to undergo oxidative dehydrogenation in the presence of gold powder and O_2 to produce imines (eq 2).[22] These reactions were found to be much



slower than the reactions of isocyanides and amines at 60 °C. In addition, amines in the presence of isocyanides did not undergo oxidative dehydrogenation until all isocyanide was

consumed.[23] The rate of the oxidative dehydrogenation reaction could be increased by using toluene as the solvent and increasing the reaction temperature to 100 °C.[22] The structure of the amine also played a significant role in this reaction, as secondary benzyl amines were far more reactive than the sterically hindered diisopropylamine. When cyclic secondary amines were used as substrates, the final products were amidines. The proposed mechanism (Scheme 2) involves an initial oxidative dehydrogenation of one cyclic amine molecule to

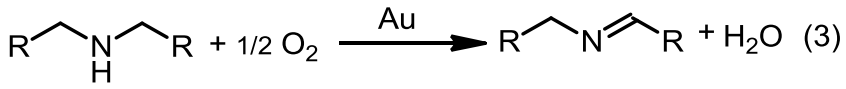


Scheme 2. Proposed pathway for synthesis for gold-catalyzed formation of cyclic imines from cyclic secondary amines.[22]

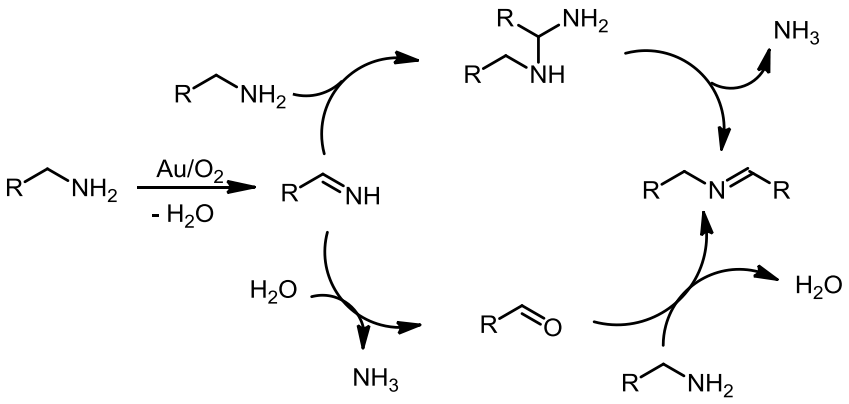
produce a cyclic imine (**2)** intermediate, followed by condensation with another molecule of cyclic amine to generate a 1,3-diamine adduct (**3**). A subsequent oxidative dehydrogenation affords the final amidine product (**4**). Step 1 is likely rate-determining, as intermediates 2 and 3 were not observed over the course of the reaction.[22] Only a few other metals catalyze this type of reaction of cyclic amines, and these include a palladium-black catalyst[24,25] and a Au/C catalyst.[26] However, the versatility of these catalysts is unknown as they have only

been shown to promote the oxidative dehydrogenation of pyrrolidine to its respective amidine.

Primary amines also undergo oxidative dehydrogenation, resulting in an imine product of two coupled amines (eq 3).[15] There are two likely mechanisms for formation of



this product (Scheme 3). The first involves a similar mechanism to that for the oxidation of cyclic amines (Scheme 2), in which one molecule of primary amine is initially oxidized to an imine and subsequently attacked by a second primary amine to generate the coupled imine.



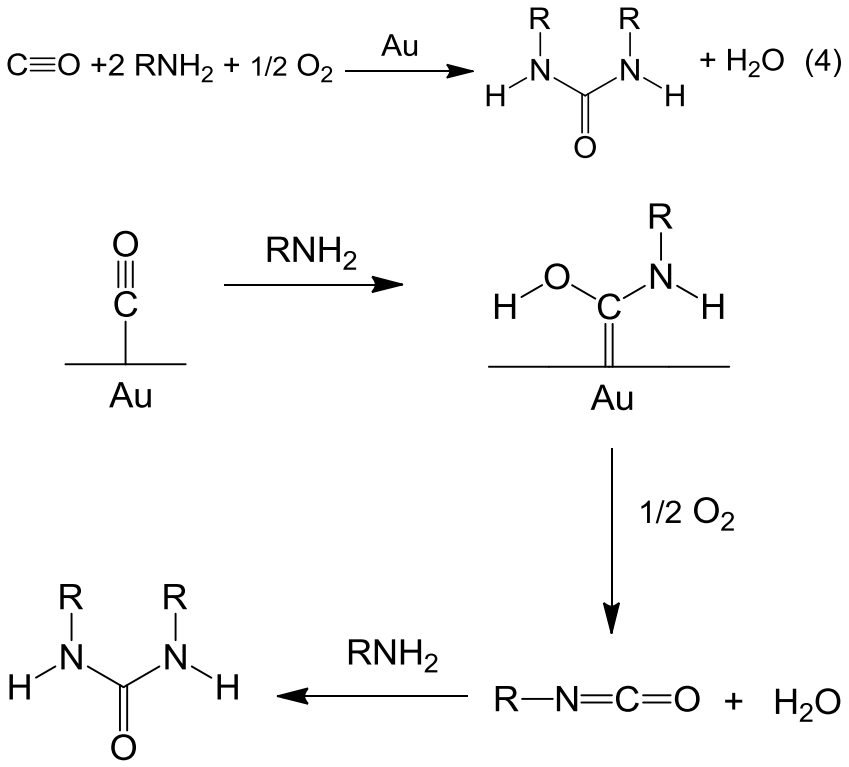
Scheme 3. Possible Mechanisms for the gold-catalyzed aerobic oxidation of primary amines to imines.[15]

In the second mechanism, the imine intermediate reacts with water to produce an aldehyde that is subsequently attacked by another molecule of amine to produce the coupled product.[15]

Oxidative Amination of Carbon Monoxide Catalyzed by Bulk Gold

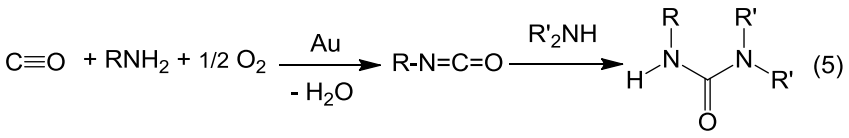
While the oxidation of CO with O_2 to produce CO_2 is the best known reaction catalyzed by supported Au nanoparticles, bulk Au displays no catalytic activity for the same

reaction.[1] However, bulk gold catalyzes the oxidative amination of CO with primary amines to produce ureas (eq 4). Mechanistic studies revealed that the adsorbed CO is likely attacked by a molecule of RNH_2 to generate an isocyanate intermediate (Scheme 4), which undergoes



Scheme 4. Mechanism for the Au-Catalyzed Reaction of Carbon Monoxide (C≡O) with Primary Amines (RNH_2) and O_2.[27]

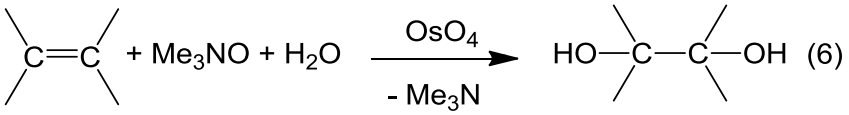
subsequent amine attack to produce a urea.[27] The reaction occurred under one atmosphere of total pressure of CO and O_2 (2.5 CO: 1 O_2) at 45 °C. In some reactions, a small quantity (1-5%) of the isocyanate intermediate was observed by GC during the reaction. Further support for the isocyanate intermediate was found through reactions of equimolar solutions of primary and secondary amines, with excess CO and O_2, in which the final product was a mixed urea (eq 5). In these examples, the secondary amines are not capable of producing



urea due to the presence of only one amine hydrogen.[27] The fact that the final product of the reaction is a mixed urea is consistent with an isocyanate intermediate, as isocyanates react faster with secondary amines, than primary amines.[28]

Properties and Reactivity of Amine N-Oxides

Amine N-oxides are some of the most interesting and versatile oxidants. They were first discovered in 1892 by Pinner and Wolfstein,[29] yet their structure was unknown until an X-Ray diffraction analysis was solved in 1939.[30] The polar N-O bond[31] confers a large molecular dipole moment of 3.6-4.4 D and high reactivity.[32] Amine N-oxides are generally hygroscopic and soluble in water and polar organic solvents. Industrially, N-methylmorpholine N-oxide (NMMO) is used as a solvent in the Lyocell process for the conversion of cellulose to textile fibers.[33] Amine N-oxides are also utilized as stoichiometric oxidants in many transition metal complex-catalyzed reactions.[31] One example is the dihydroxylation reaction of olefins[34] (eq 6) in which the addition of a stoichiometric amount



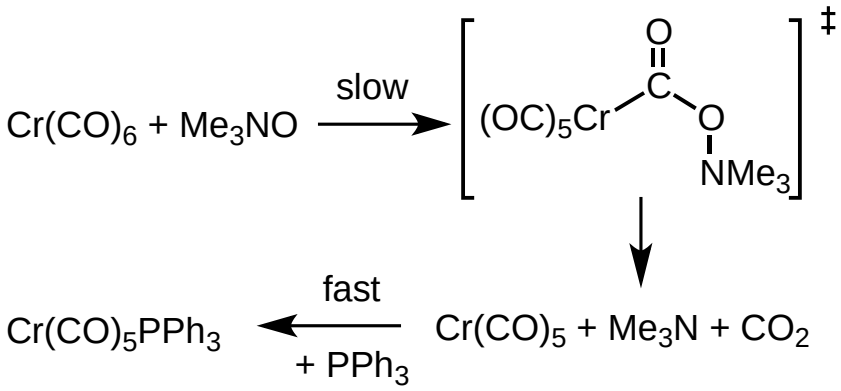
of amine N-oxide regenerates the catalyst, allowing the reaction to utilize a catalytic, rather than stoichiometric amount of osmium tetroxide. Another reaction utilizes a ruthenium porphyrin, which catalyzes the oxygen atom transfer from the amine N-oxide to the olefin to

produce epoxides.[35] Additionally, alcohols can be oxidized to aldehydes utilizing a catalytic amount of a tetralkylammonium ruthenate and a stoichiometric amount of NMMO.[36]

Reactions of Carbonyl Ligands in Metal Complexes

The first known metal carbonyl complex was discovered by Mond et al. by treating nickel particles with CO to produce a substance that was found to be $Ni(CO)_4$.[37] Metal carbonyl complexes exist for most transition metals and undergo a variety of substitution reactions. The reactions of 16 and 18 e^- homoleptic metal carbonyl complexes generally proceed through associative and dissociative mechanisms, respectively.[38] While there are several reports of amine N-oxide attack on coordinated CO ligands,[39,40,41] the attack by amine N-oxides on isocyanide ligands has not been thoroughly studied in metal complexes. The first report of an amine N-oxide attacking a metal carbonyl was a reaction of pyridine N-oxide with iron pentacarbonyl to generate carbon dioxide and iron oxide in 1959, by Hieber.[42] Studies of the rates of the attack of various nucleophiles on homoleptic group 6 metal carbonyl complexes, showed Me_3NO to react faster in most cases, with the following trend: $MeLi > Me_3NO > PhCH_2MgBr >> N_3^- > NCO^- > NCS^- > C1^- > Br^- > I^-$.[39] During studies of metal carbonyls with trimethylamine N-oxide and triphenylphosphine, Basolo and coworkers found that the phosphine substitution reaction was first order in the metal complex and amine N-oxide concentrations, but zero order in the phosphine concentration for both group 6[39] and group 8[43] metals (Scheme 5). Moreover, a study by Basolo and coworkers found that an increase in the basicity of the amine N-oxide led to an increase in the CO substitution rate, providing further support for rate-determining amine N-oxide attack.[40] The reaction of iodosobenzene and acetonitrile with group 6 carbonyls was investigated under the

same conditions, to determine what affect other oxidants would have on the rate of substitution. These reactions also proceeded through a similar pathway, with the rate-determining step being the iodosobenzene attack on the carbonyl. Kinetic data showed that the reaction was first order in the metal carbonyl and iodosobenzene concentrations and zeroth order in the acetonitrile concentration.[44]



Scheme 5. Reaction of $Cr(CO)_6$, Me_3NO, and PPh_3 in CH_2Cl_2 at 20 °C.[40]

Introduction to Metalloporphyrins

The traditional method for synthesizing free-base porphyrins involves a condensation reaction of pyrrole and aldehydes under acidic conditions.[45,46] Metallation of porphyrins is usually achieved by treatment of the free-base form with a metal salt in a high-boiling solvent.[47] The flexibility of the central porphyrin cavity allows chelation with nearly every metal[48] and several nonmetals. If the metal is small, the porphyrin molecule will distort to shrink its cavity to be able to better accommodate the shorter M-N distances. When the metal is large, it can reside above the N_4 core. In addition, porphyrin substituents provide flexibility in tuning properties through modification of the periphery.[49]

Iron Porphyrin Catalyzed Reactions of Carbenes Generated from Diazo Reagents

Diazo compounds are reactive compounds that are used as carbene precursors in many bond forming reactions.[50] Ethyl diazoacetate (EDA), is a commercially available compound that is commonly used to generate carbene complexes. In the absence of any additional substrate, many transition metal complexes, including metalloporphyrins, catalyze the coupling of EDA to produce olefins.[51]. Iron porphyrins have been found to catalyze a variety of reactions with diazo reagents, including the cyclopropanation of olefins,[52] olefination of carbonyl compounds,[53] and C-H bond activation of aryl compounds.[54]

N-H Bond Insertion Reactions

N-H bond insertion reactions utilizing diazo compounds and amines provide a simple route for the formation of important products and synthetic intermediates, such as glycine ethyl ester derivatives, [55] tertiary amines,[56,57] and nitrogen heterocycles.[50] Several metal complexes are reported to catalyze N-H bond insertion reactions. For example, copper(I) chloride,[58] copper(I) cyanide,[58] copper scorpionate complexes,[59] methyltrioxorhenium,[55] and ruthenium porphyrins,[60] have been found to catalyze the N-H bond insertion reactions of primary and secondary amines with EDA to generate glycine ethyl ester derivatives. In addition intermolecular reactions of amines with diazo compounds, $Rh_2(OAc)_4$ catalyzes intramolecular N-H bond insertion reactions, including the reactions of diazocarbonyl compounds to form heterocyclic molecules.[50] One synthetic route to the antibiotic thienamycin includes a step in which $Rh_2(OAc)_4$ catalyzed an intramolecular cyclization of a diazo keto ester to form a β-lactam bicyclic compound.[61]

Recently, iron(III) tetraphenylporphyrin chloride (Fe(TPP)Cl) was found to be a robust catalyst in N-H insertion reactions of amines with ethyl diazoacetate.[56] A very low catalyst loading (<1 mol%) led to high yielding (68-97%) reactions within ten minutes for both aryl and alkyl amines. It was found that in addition to glycine ethyl ester derivatives, tertiary amines could be prepared from primary amines when treated with two equivalents of EDA.

Present study

The first project involved studying amine N-oxides as oxidants in bulk Au catalyzed reactions of isocyanides and amines. Amine N-oxides have previously been shown to oxidize carbonyl ligands, which are isoelectronic with isocyanides, in metal complexes. This study would examine if the principles of organometallic chemistry could be useful in predicting and understanding the reactions that would occur on the gold surface. The findings of this work are presented in Chapter 2. Likewise, since bulk gold also catalyzed the oxidation of amines to imines using oxygen, the next study sought to determine if amine N-oxides could be used as oxidants in the same reactions. Semi-quantitative rate studies were performed to study the rate of reaction with oxygen and with amine N-oxides of different basicity. This work is presented in Chapter 3. It was found that the amidine products from the bulk Au catalyzed oxidative dehydrogenation of amines underwent hydrolysis when treated with Aerosil (fumed silica gel) to produce lactams. A study was undertaken to optimize this reaction and ultimately develop a one-pot system for the production of lactams from cyclic amines. These results are presented in Chapter 4.

The second project involved studying iron(III) tetraphenylporphyrin chloride as a catalyst in the reactions of EDA with diamines and aminoalcohols to give products that result from a N-H bond insertion followed by an ensuing cyclization, in a one-pot reaction. These types of products typically require a multi-step synthesis. Ultimately aryl 1,2-diamines and 1,2-aminoalcohols were studied to expand the versatility of this type of reaction. The results of this study are found in Chapter 5.

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CHAPTER 2: BULK GOLD-CATALYZED REACTIONS OF ISOCYANIDES, AMINES, AND AMINE N-OXIDES

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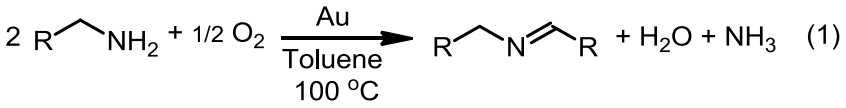
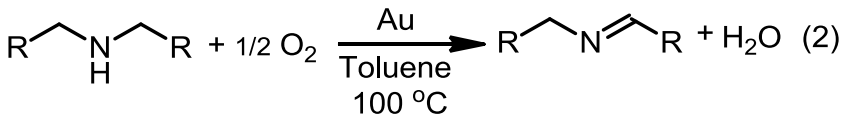
Abstract

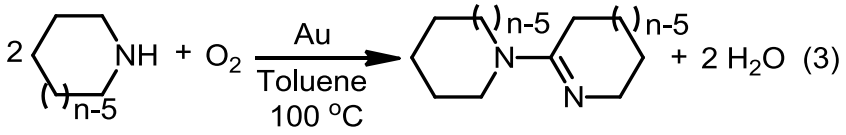
Bulk gold powder (~5-50 μm) catalyzes the reactions of isocyanides with amines and amine N-oxides to produce ureas. The reaction of n-butyl isocyanide (^{n}Bu–N≡C) with di(n-propyl)amine and N-methylmorpholine N-oxide in acetonitrile, which was studied in the greatest detail, produced 3-butyl-1,1-dipropylurea [O=C(NH^{n}Bu)(N^{n}Pr$_2$)] 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 (R–N=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.

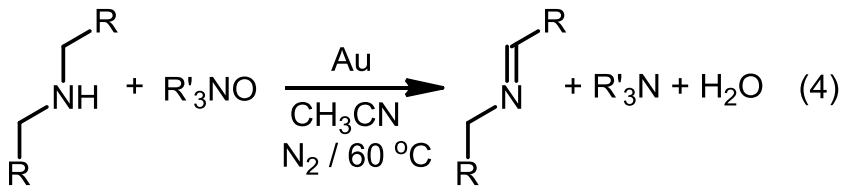
Introduction

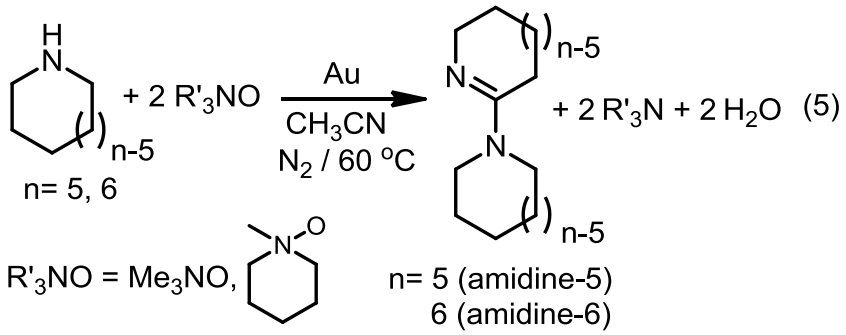
Bulk Au has a reputation for having very low catalytic activity. This is in contrast to nanogold particles (<5 nm), which catalyze numerous reactions, including oxidations.[1] However, our group has shown that bulk Au is also an effective catalyst for some oxidations involving O_2, including reactions 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, besides O_2, to perform these oxidations. Recently we reported that amine N-oxides (R_3N–O) were suitable oxidants for the oxidative dehydrogenation of amines to give imines (eqs 4-5) and benzyl alcohol to give benzaldehyde.[5] In each of these reactions, the amine N-oxide (R_3N–O) was the source of the oxygen atom.



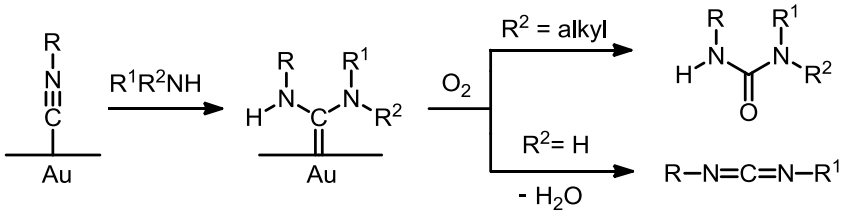








We also showed that *bulk* gold powder (~5-50 μm size) catalyzes reactions of isocyanides with both primary[6] and secondary amines[7] and oxygen (O_2) to give carbodiimides and ureas (Scheme 1). Our studies, based on reactions of isocyanide ligands in organometallic complexes and kinetic investigations, 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]



Scheme 1. Proposed mechanism for the bulk Au-catalyzed reaction of isocyanides and O_2 with primary and secondary amines.

In the present studies, we examined amine N-oxides as the oxidizing agent, 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, *t*-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 triphenylmethane 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 ^{n}BuNC, 10.0 mM $^{n}Pr_2NH$, 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.[4,6]

After all of the gold was used in a catalytic reaction (1.00 g per 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 10 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 "2nd cycle" gold. Gold that was used in subsequent reactions and cleaned as described above were designated "3rd cycle", "4th cycle", etc. Since its activity decreased each time the gold was used, comparisons of catalyst activity in this paper have been made using gold from the same cycle and therefore having the same usage history. When a significant decrease in catalytic activity was observed (~6 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]

General Procedure for Gold-Catalyzed Reactions of Isocyanides, 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 micro 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 backfilling with argon. After capping the reaction tube with a septum, the

mixture was stirred with a magnetic stirbar vigorously 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 ID, ~1.7 mL volume), which were charged with 0.20 g 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 ^{n}BuNC (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 ^{1}H 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. ^{n}BuNC was brought into the box in a nitrogen-packed ampule.

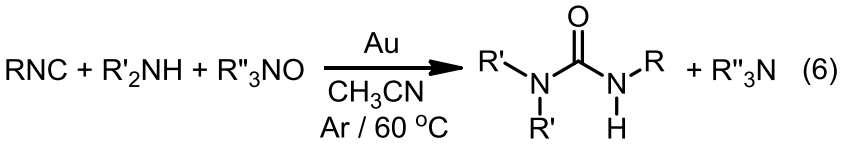
GC and GC-MS Analyses. Gas chromatographic analyses were performed on an HP-6890 instrument equipped with an HP-5 capillary column (30 m length, 0.25 mm internal diameter, 0.25 μm film thickness, 5% phenyl, 95% methyl silicone polymer). The GC analysis conditions were as follows: carrier gas, He; mode, constant flow; initial column temperature, 50 °C; temperature program: time at initial temperature, 2 min; heating time, 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 ^{1}H NMR and GC-MS.

The amidine product from the oxidative dehydrogenation reaction of morpholine was prepared by adding morpholine (60 mg, 0.69 mmol), O_2 (~1 L @ ~1 atm), Au (1.00 g) to 5.0 mL 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. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.22 (s, 2H, C*H*$_2$), 3.69 (t, J_H = 4.8, 4H, C*H*$_2$), 3.63 (t, J_H = 4.8, 2H, C*H*$_2$), 3.54 (t, J_H = 4.8, 2H, C*H*$_2$), 3.20 (t, J_H = 4.8, 4H, C*H*$_2$), 1.61 (bs, 0.88H, *H*$_2$O). ^{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. Calc. for $C_8H_{14}N_2O_2$ •0.44 H_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).

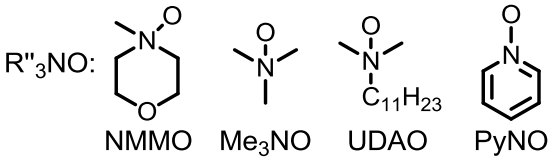
Results and Discussion

Reaction of ^{n}BuNC with $^{n}Pr_2NH$ and NMMO. The reaction of *n*-butylisocyanide (^{n}BuNC), di(*n*-propyl)amine ($^{n}Pr_2NH$), and N-methylmorpholine N-oxide (NMMO) in the presence of 1.00 g gold powder in 5.0 mL CH_3CN under an argon atmosphere at 60 °C gave 3-butyl-1,1-dipropylurea (eq 6), the same product that was obtained with O_2 as the oxidant (Scheme 1). As the NMMO concentration was increased from 20.0 to 40.0 mM, an increase



RNC: ^{n}BuNC, ^{t}BuNC, BnNC

R'$_2$NH: ^{n}Pr$_2$NH, ^{n}Bu$_2$NH, ^{i}Pr$_2$NH, (CH$_2$)$_5$NH, O(CH$_2$CH$_2$)$_2$NH



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

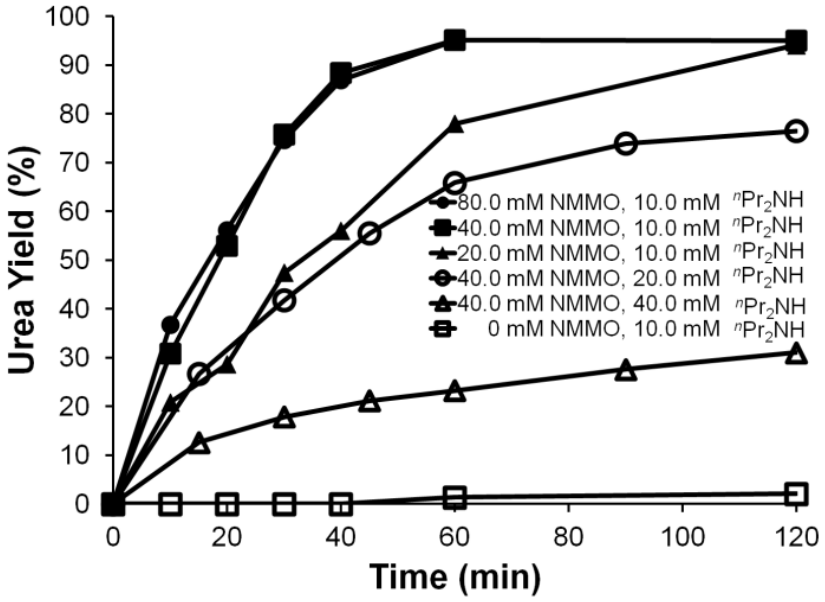


Figure 1. The effect of NMMO and ^{n}Pr$_2$NH concentrations on the rates of reaction (eq 6) of 2.0 mM ^{n}BuNC in 5.0 mL CH$_3$CN catalyzed by 1.00 g of 1st cycle gold at 60 °C.

was observed. As the concentration of the amine was increased from 10.0 to 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 than 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 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 2nd 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 hours 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 or III) amine complexes, as catalysts, reaction 6 was run under standard conditions with 2nd 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 increase in the amount of 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≡C and ^{n}Pr$_2$NH. The reactions of ^{n}BuNC and ^{n}Pr$_2$NH 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 pKa's of their conjugate acids: $NMMOH^+$ (4.75)[14] > Me_3NOH^+ (4.56)[15] > $PyNOH^+$ (0.79).[16]

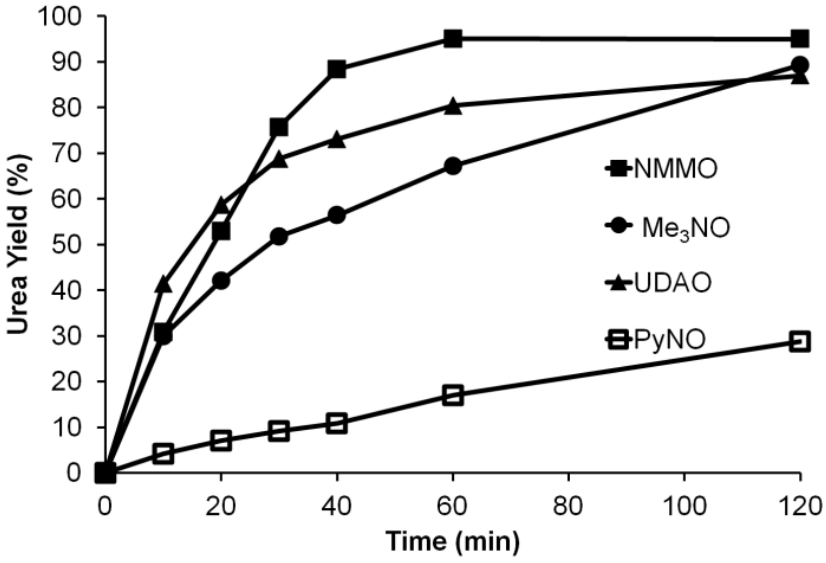


Figure 2. The effect of various amine oxides in the reaction (eq 6) of 2.0 mM ^{n}BuNC, 10.0 mM ^{n}Pr$_2$NH, and 40.0 mM amine oxide in 5.0 mL CH_3CN using 1.00 g 1st cycle Au at 60 °C.

Unlike most amine N-oxides, which have a very low solubility in non-polar solvents,[17] $(C_{11}H_{23})Me_2N$–O, 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$_2$NH in the presence of 1.00 g 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 1st cycle Au in 5.0 mL 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 in 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

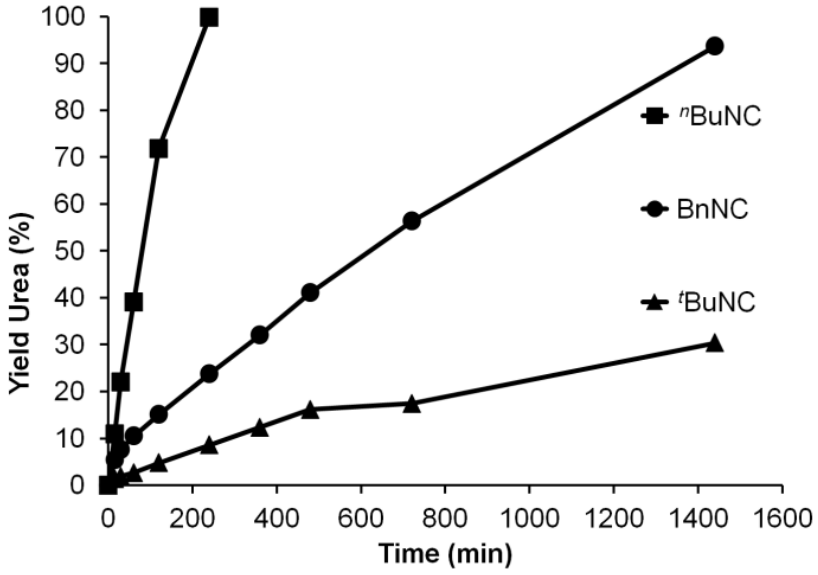


Figure 3. The reaction (eq 6) of 2.0 mM isocyanide, 10.0 mM $^{n}Pr_2NH$, 40.0 mM NMMO in acetonitrile and 1.00 g of 2nd cycle Au at 60 °C.

after 24 h, and the reaction with ^{t}BuNC gave a yield of only 48% of the corresponding urea, even after 3 d. 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 specific gold surface area: the larger the cone angle the less amount of 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 it could also 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 72h.

Secondary amines with linear alkyl chains, $^{n}Pr_2NH$ and $^{n}Bu_2NH$, 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). Even the sterically

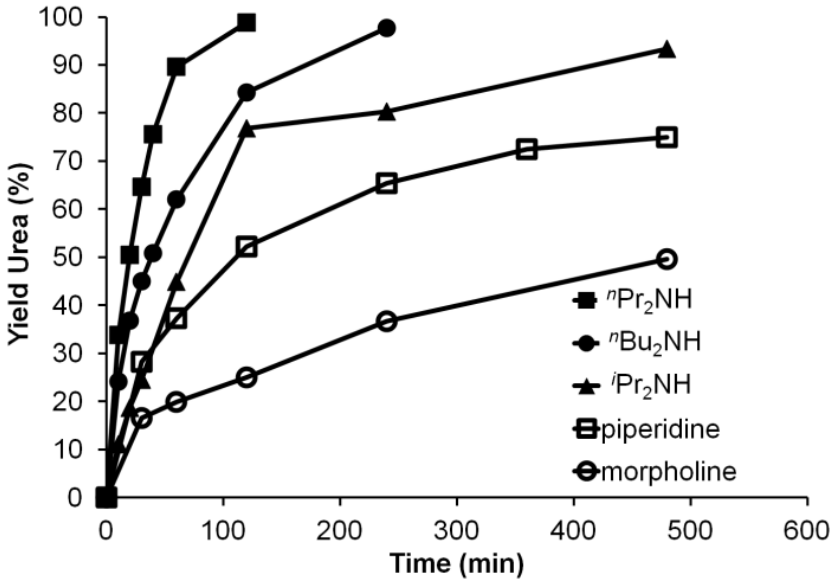
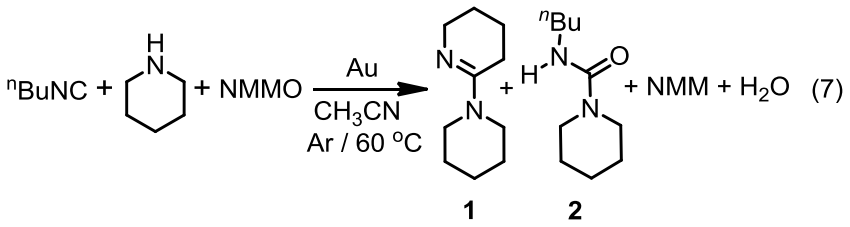


Figure 4. The effect of various secondary amines on the reaction (eq 6) of 2.0 mM ^{n}BuNC, 40.0 mM NMMO, and 10.0 mM amine in acetonitrile with 1.00 g of 2nd cycle Au at 60 °C.

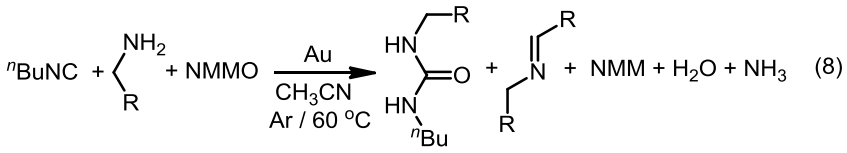
hindered $^{i}Pr_2NH$ gave a very high yield (93%) of the urea. When the cyclic secondary amine, piperidine, was investigated under the same conditions, urea formation was slower than that with either $^{n}Pr_2NH$ or $^{n}Bu_2NH$. Over time, the total yield of the piperidinyl urea product did not increase, 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 at a higher rate after 4 h, which corresponded to the time that the isocyanide was no longer observed by GC. Our previous

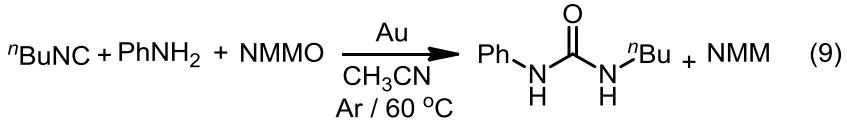


studies of the oxidative dehydrogenation of amines using amine N-oxides as the oxidant showed that piperidine readily undergoes oxidative dehydrogenation to give amidine 1 under conditions similar to those in eq 7.[5] Due to the excess of amine present in this reaction, oxidative dehydrogenation may 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 hour. 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, 9): the sterically hindered cyclohexylamine ($CyNH_2$), the long chain aliphatic n-hexylamine ($^{n}HexNH_2$), and the aryl amine, 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 $^{n}BuNC$ remains in solution.

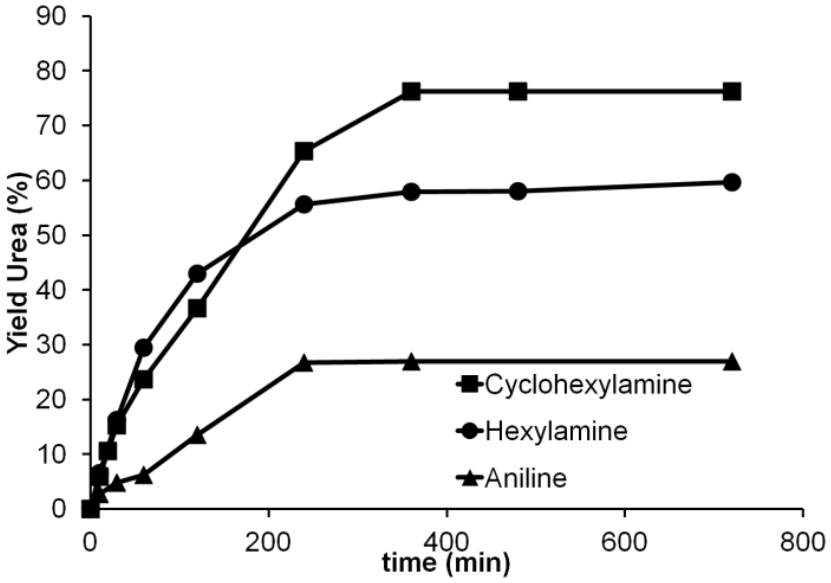


Figure 5. The effect of various primary amines on the reaction (eqs 10 and 11) of 2.0 mM $^{n}BuNC$, 40.0 mM NMMO, and 10.0 mM amine in acetonitrile with 1.00 g of 2nd cycle Au at 60 °C.

Reaction (eq 9) of the much less basic aniline (pKa = 4.76) was much slower than either of the two aliphatic amines (pKa: $^{n}HexNH_2$, 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 its 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 mM 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). Thus, as the amine concentration is increased, the rate of urea formation (eq 8) decreases; this is the same trend that was observed in the reaction with the secondary amine $^{n}Pr_2NH$ (Figure 1). 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 re-used 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. When it was used in a reaction with $^{n}BuNC$ (2.0 mM), $^{n}Pr_2NH$ (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 required 8 h ($t_{1/2}$ = 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_2O_2/H_2SO_4), washed with water, rinsed

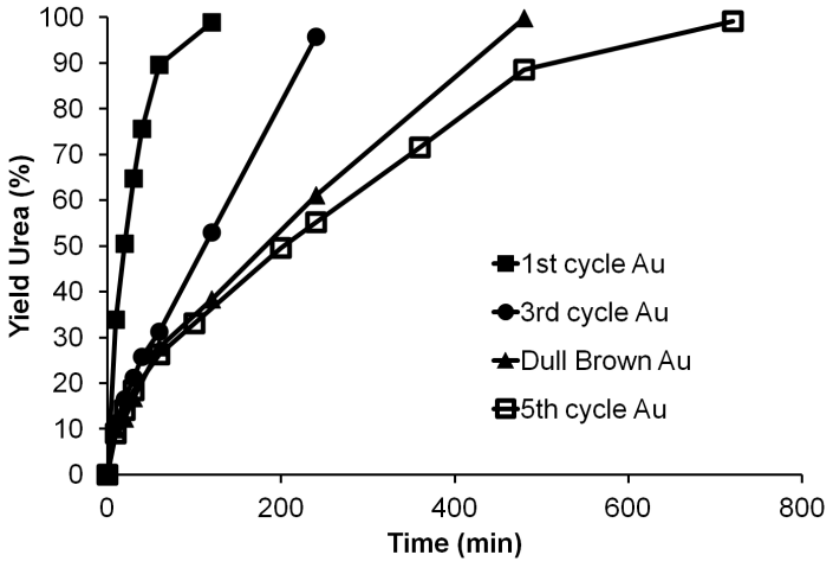
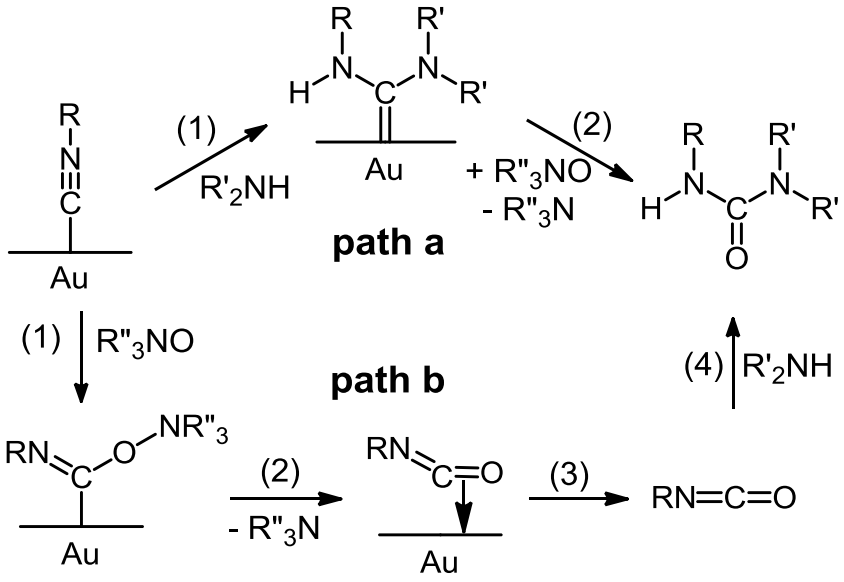


Figure 6. The reaction of 2.0 mM ^{n}BuNC, 10.0 mM $^{n}Pr_2NH$, and 40.0 mM NMMO in acetonitrile (eq 6) catalyzed by 1.00 g of different cycles of Au at 60 °C.

with methanol, and dried overnight at 120 °C. When this gold was used in the same reaction (1st cycle), the yield of urea product was nearly quantitative in only 2 h, ($t_{1/2}$ = 0.33 h). By the 5th cycle, 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 1st 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 R–N≡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 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 (pathway **a**), the adsorbed isocyanide is attacked by the amine to give the



Scheme 2. Possible mechanisms for the reaction of adsorbed isocyanide with secondary amines and amine oxides to form urea products.

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, a NMR tube reaction mixture of ^{n}BuNC (10.0 mM), 0.60 mL CD_3CN, 0.20 g Au, and Me_3NO (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) by comparison of its GC and NMR properties with an authentic sample of the compound.

$$^{n}\text{BuNC} + \text{Me}_3\text{NO} \xrightarrow[\text{CD}_3\text{CN}]{\text{Au}} {}^{n}\text{BuNCO} + \text{Me}_3\text{N} \quad (10)$$
$$\text{N}_2 \,/\, 60\ ^{\circ}\text{C}$$

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

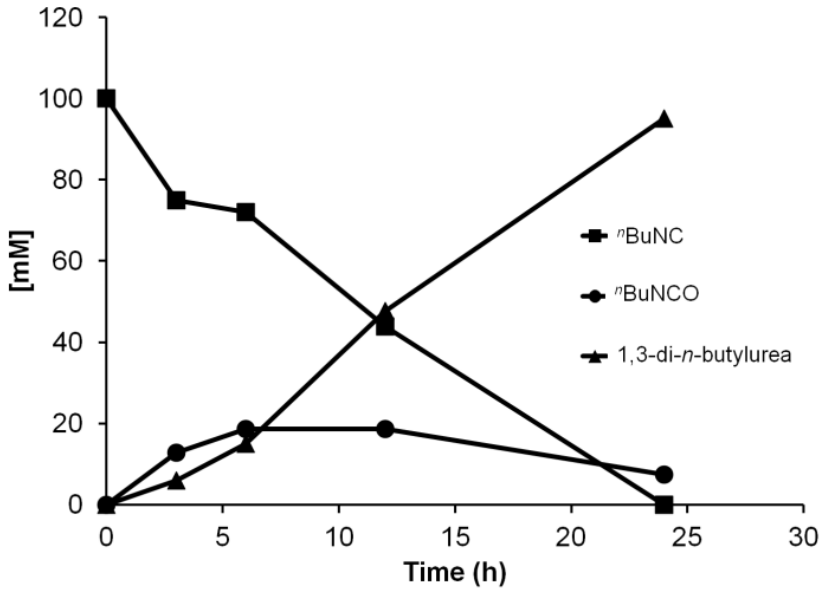
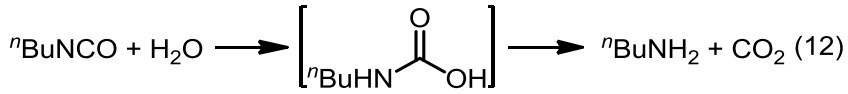


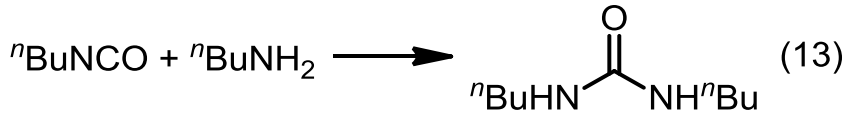
Figure 7. Reaction of 10.0 mM ^{n}BuNC and 40.0 mM NMMO in CD_3CN (eq 10) catalyzed by 0.20 g of Au at 60 °C.

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

$$2\ {}^{n}\mathrm{BuNCO} + H_2O \xrightarrow[CD_3CN,\ 60\ ^{o}C]{Me_3NO} {}^{n}\mathrm{BuHN}\overset{O}{\underset{}{\diagup\!\!\diagdown}}\mathrm{NH}{}^{n}\mathrm{Bu} + CO_2 \quad (11)$$

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 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 pathway **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 $^{n}Pr_2NH$ was heated in an NMR instrument at 60 °C, the reaction was complete in less than 90 seconds. This is much faster than the first step in pathway **b** as $t_{1/2}$ for reaction of ^{n}BuNC with $^{n}Pr_2NH$ 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 pathway **b** than the rate of formation of ^{n}BuNCO is consistent with this pathway. Since the reaction of ^{n}BuNCO with the amine (step 4 in pathway **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 manuscript.

If reaction 6 proceeds by the pathway **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.[27] 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_3CN at 60 °C gave a 50% yield of the carbamate (eq 14) after 12 hours. The rate of this reaction, as shown in Figure 8, is similar to that of the reaction of ^{n}BuNC with $^{n}Pr_2NH$ and NMMO, which is

$$Me_3NO + {}^{n}BuNC + {}^{n}PrOH \xrightarrow[60\ ^{o}C,\ N_2]{Au,\ CD_3CN} {}^{n}PrO\text{-}C(=O)\text{-}NH{}^{n}Bu + Me_3N \quad (14)$$

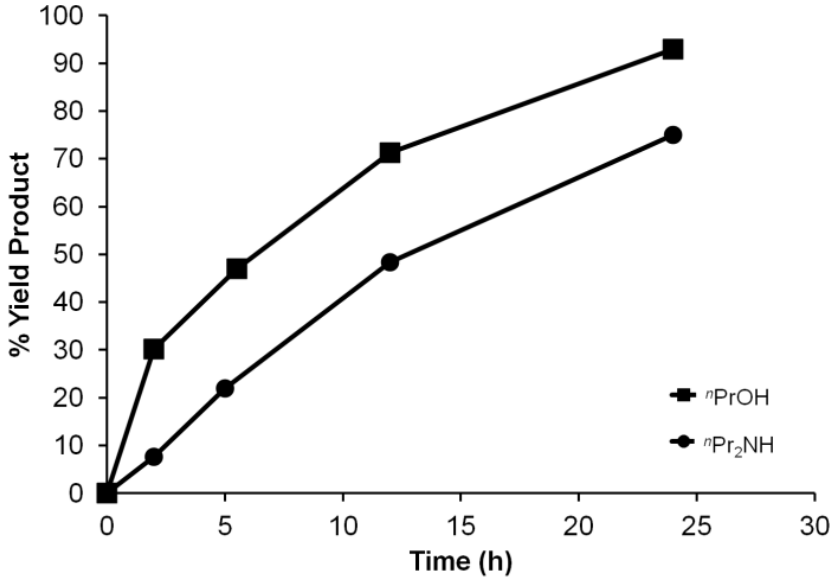


Figure 8. Reaction of 10.0 mM ^{n}BuNC, 40.0 mM NMMO, and 30 mM ^{n}PrOH or $^{n}Pr_2NH$ in CD_3CN (eqs 6 and 14) catalyzed by 0.20 g of Au at 60 °C.

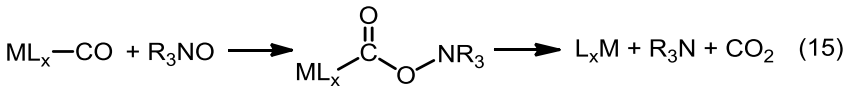
expected if the rate-determining step is the conversion of ^{n}BuNC to ^{n}BuNCO in pathway **b**. The slower rate of the amine reaction may be attributed to the adsorption of amine on the Au, which inhibits the adsorption of isocyanide and correspondingly reduces the rate of conversion of the isocyanide 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 faster than the overall rate of reaction 14. Indeed, the $t_{1/2}$ for the reaction of ^{n}BuNCO with ^{n}PrOH in the presence of NMMO is only 9.5 minutes as compared to a $t_{1/2}$ of 6 h for reaction 14 under the same conditions. These data are also consistent with pathway **b** in which the formation of ^{n}BuNCO is the rate-determining step. (Semi-quantitative 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 $^{n}Pr_2NH$ 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 pathway **b** as amines are known to react much faster than alcohols with isocyanates.[28]

Besides the studies described above, there are several other experimental results that provide additional evidence for the mechanism in pathway **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

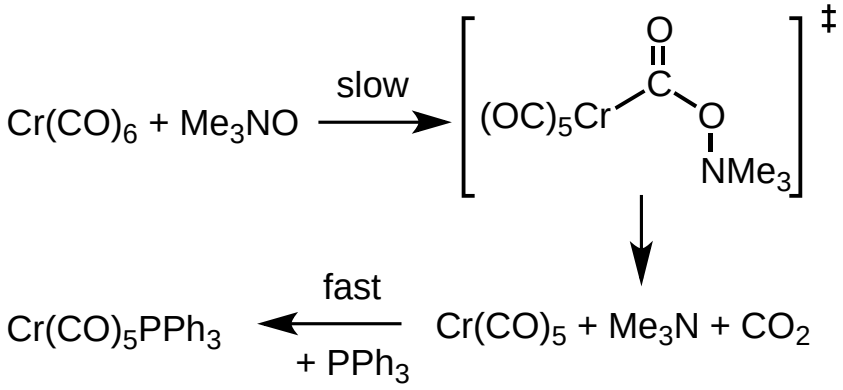
basic amine oxides (Figure 2) as indicated by the pKa's of their conjugate acids. Moreover, the rate of the reaction decreases as the size of the isocyanide R group increases (Figure 3), which is consistent with steric resistance to amine oxide attack (pathway **b**, step 1); such a decrease in rate with the size of the isocyanide was observed in the bulk gold-catalyzed reactions of isocyanides, secondary amines and O_2 to form ureas.[6] 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 pathway **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 $Fe(C{\equiv}NCH_2Ph)_6^{2+}$ with $Me_3N{-}O$ 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



(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_3N-O and PPh_3, revealed the rate of reaction to be first order in both the metal carbonyl and the amine N-oxide concentrations



Scheme 3. Reaction of $Cr(CO)_6$, Me_3NO, and PPh_3 in CH_2Cl_2 at 20 °C.[9]

and zero order in the phosphine concentration. The proposed mechanism is very similar to that proposed in step 1 of pathway **b**. The CO_2 product in eq 15 is also analogous to the R–N=C=O intermediate in pathway **b** (Scheme 2). Another organometallic reaction that is especially relevant to the mechanism in pathway **b** is the reaction of ^{t}BuNC with N_2O 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_2O 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 pathway k is proposed to have an η^2-R–N=C=O geometry.

Conclusions

Although both O_2 (Scheme 1) and amine oxides (R_3N–O, 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≡N–R 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_3N–O on the adsorbed isocyanide is the initial and rate-determining step to generate an isocyanate (R–N=C=O), which rapidly reacts with the amine to give the urea product (Scheme 2). The role of the gold metal in both mechanisms is to activate the adsorbed isocyanide towards nucleophilic attack by either the amine (in the O_2 reactions) or the R_3N–O (in the amine oxide reactions). In the latter reaction, even though both R_3N–O and R'_2NH are present, it is the R_3N–O that preferentially attacks the adsorbed isocyanide. This faster rate of R_3N–O attack, as compared with R'_2NH attack, is consistent with the observation that reactions using R_3N–O 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, or W,[9] is attacked by Me_3NO 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.

Acknowledgement

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Supporting Information

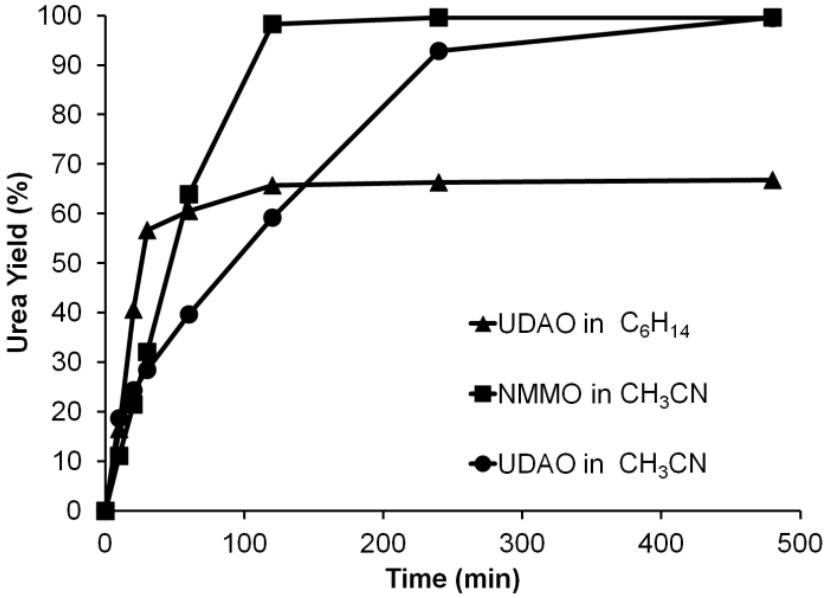

Figure S1: Effect of solvent on the reaction of 2.0 mM ^{n}BuNC, 10.0 mM $^{n}Pr_2NH$, 40.0 mM amine oxide in acetonitrile and 1.00 g 2nd cycle Au at 60 ^{o}C.

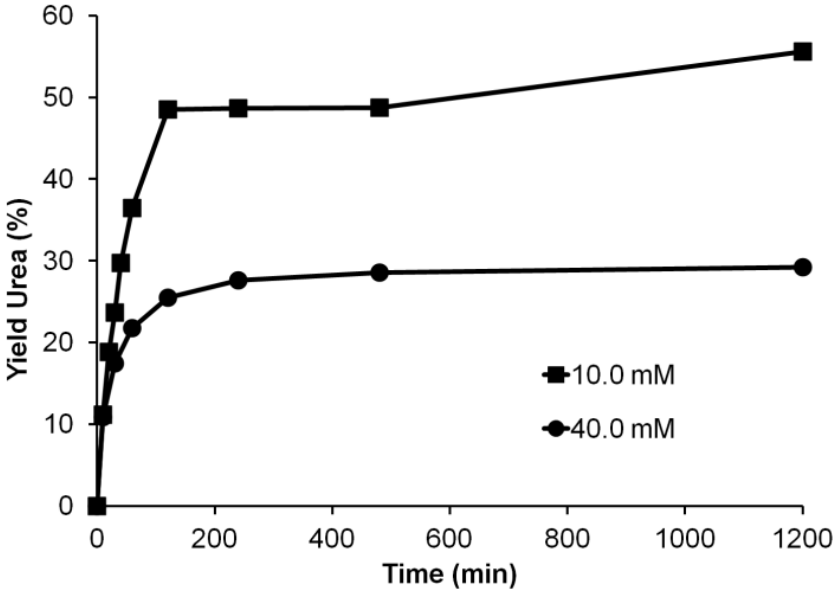

Figure S2: The effect of 80.0 and 10.0 mM hexylamine in the reaction (eq 10) of 2.0 mM ^{n}BuNC, 40.0 mM NMMO, and 1.00 g of third-cycle Au at 60 ^{o}C.

CHAPTER 3: BULK GOLD-CATALYZED OXIDATIONS OF AMINES AND BENZYL ALCOHOL USING AMINE N-OXIDES AS OXIDANTS

A paper submitted to *Catalysis Letters*

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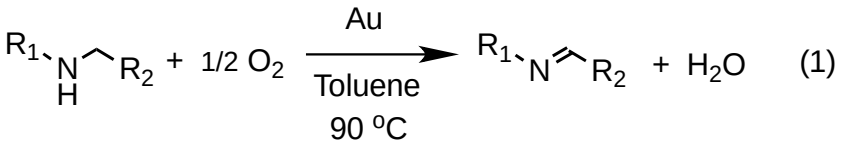
Abstract

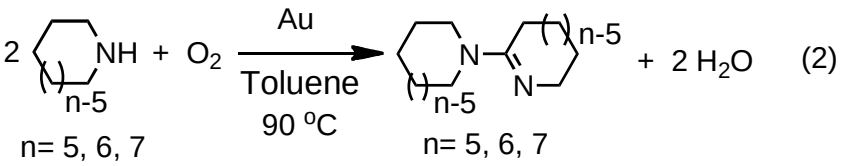
Bulk gold powder (~50 μm) catalyzes the oxidative dehydrogenation of amines and benzyl alcohol using amine N-oxides (R_3N-O) to give imines and benzaldehyde, respectively. Although O_2 was previously shown to oxidize amines in the presence of bulk gold, it is surprising that gold is also capable of catalyzing the oxidation of amines using amine oxides, which are chemically so different from O_2.

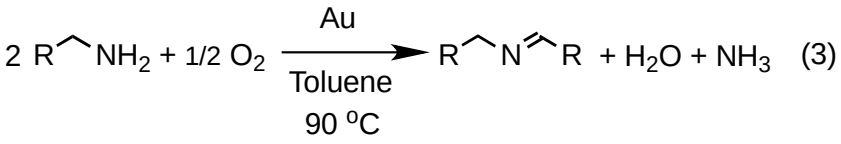
Introduction

Nanogold particles (<5 nm) supported on various oxide supports are known to catalyze numerous reactions,[1,2,3,4,5,6,7] including the oxidation (O_2) of CO, hydrocarbons, and alcohols, while *bulk* gold powder has traditionally been thought to be a poor catalyst.[1] However, our group has recently found that bulk gold also catalyzes several oxidations in which O_2 is the oxidant. These include the reaction of isocyanides with amines to produce

carbodiimides[8] or ureas,[9] reactions of carbon monoxide with primary amines to afford ureas,[10] and reactions of diazoalkanes with amines to give enamines.[11] In addition, we have found that bulk gold catalyzes the oxidative dehydrogenation of amines to imines using O_2 as the oxidant (eqs 1–3).[12, 13] This reaction has drawn much recent interest, as nanogold supported on ceria,[14, 15] polystyrene,[14] alumina,[16] titania,[16] and carbon[16, 17] has also been found to catalyze the oxidative dehydrogenation of amines using O_2.







In expanding the scope of gold catalysis, we examined amine N-oxides (R_3N-O) as the oxidizing agent in the oxidative dehydrogenation of amines. The only other previously reported oxidant in the bulk Au-catalyzed oxidative dehydrogenation of amines is NO_2, which exhibited comparable activity to O_2 in reactions of pyrrolidine and 1,2,3,4-tetrahydroisoquinoline to give their imines.[18] Prior to our studies of amine oxides, we realized that R_3N-O compounds had been used as oxygen atom donors and oxidizing agents in a variety of homogeneous reactions.[19] However, their oxidizing reactivities are typically very different than those of O_2, which is not surprising because of the very different properties of R_3N-O and O_2 molecules. Therefore, the goal of the present investigation was to

assess the effectiveness of bulk gold as a catalyst for the oxidative dehydrogenation of amines using amine oxides. As reported herein, amine oxides do indeed oxidize amines to give the same products as O_2 in the presence of a bulk gold catalyst.

Experimental Section

Dibenzylamine, piperidine, pyrrolidine, 1,2,3,4-tetrahydroisoquinoline (THIQ), and benzyl alcohol were purchased commercially and purified by heating at reflux with CaH_2 for 12 h and distilling under argon before use. N-benzylidenebenzylamine and benzaldehyde were purchased from Sigma-Aldrich and used as received. Amidine-5,[20] amidine-6,[20] and 3,4-dihydroisoquinoline[12] were synthesized as described previously. Acetonitrile-d3 was heated at 80 °C with CaH_2 for 8 h, and then purified by a trap-to-trap distillation under reduced pressure. N-methylmorpholine N-oxide (NMMO), trimethylamine N-oxide (Me_3NO), and pyridine N-oxide (PyNO) were sublimed under reduced pressure. Gold powder was prepared from $HAuCl_4$ as described previously.[21] The powder, which was previously characterized by electron microscopy,[13, 21] consisted of large particles (5-50 μm). The reactions were run in NMR tubes (17 × 0.3 cm ID, ~1.7 mL volume), which were loaded with 0.20 g Au and then sealed with a high-vacuum Teflon stopcock. The tubes were then evacuated and back filled three times with argon, sealed under reduced pressure, and then brought into a nitrogen-atmosphere glove box. After loading the tubes with the desired concentrations of reactants (*vide infra*), they were removed from the glovebox and heated in an oil bath at 60 °C. The reactions were monitored by ^1H NMR on a Varian MR-400 or a Bruker DRX-400 spectrometer with Ph_3CH as the internal standard. ^1H NMR peak positions were referenced against the residual proton signal of CD_3CN (δ = 1.94 ppm). Previous work

showed that the gold powder loses some activity when it is reused in successive reactions.[20,21] In this study we used the most active form of Au in all reactions. This catalyst was prepared from the initial dull brown Au that was produced by reduction of $HAuCl_4$.[21] The dull Au was converted to an active and lustrous golden form by an oxidative dehydrogenation reaction of Bn_2NH and NMMO in CH_3CN for 24 h at 60 °C. After being used in this reaction, the batch of Au powder was collected and cleaned as described previously.[21] This Au powder was used in all of the studies reported herein.

General Procedure for Oxidative Dehydrogenation of Amines Using Amine N-Oxides. In a glove box, an CD_3CN-stock solution was prepared with the desired amine and internal standard (30 mM amine, 18.8 mM Ph_3CH). A second CD_3CN-stock solution of the amine N-oxide (330 mM) was also prepared. The amine/Ph_3CH solution (0.40 mL) and amine N-oxide solution (0.20 mL) were added to an NMR tube containing 0.20 g Au to give a 0.60-mL mixture with the desired amine and amine N-oxide concentrations, 20 and 110 mM, respectively. The tube was sealed with a high-vacuum Teflon stopcock, brought out of the glovebox, and a ^1H NMR spectrum was immediately recorded. The tube was then heated in an oil bath at 60 °C and periodically analyzed by NMR. Products were identified by comparing their ^1H NMR spectra with those of authentic compounds.

General Procedure for Decomposition of Amine N-Oxides. In a glove box, CD_3CN-stock solutions of the amine N-oxide (0.20 mL, 330 mM) and Ph_3CH (0.20 mL, 75 mM) were added to an NMR tube containing 0.20 g Au. Then 0.20 mL CD_3CN was added to give a 0.60-mL mixture with the desired amine N-oxide concentration of 110 mM. The tube was then sealed with a high-vacuum Teflon stopcock, removed from the glovebox, and a

^{1}H NMR spectrum was immediately recorded. The tube was then heated in an oil bath at 60 °C and periodically analyzed by NMR.

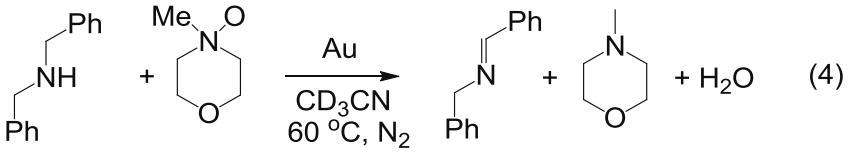
Characterization of 4-methylmorpholine-2,3-dione. Two NMR-tube reactions of the Au-catalyzed decomposition reaction of NMMO (0.20 g Au, 220 mM NMMO, 0.60 mL CD_3CN) were heated at 60 °C. After 48 h, the solutions were transferred from the Au by pipet into a single flask, the volatile components were removed under reduced pressure, and the product was characterized spectroscopically. IR (film on NaCl, ν [cm^{-1}]): 1757 (s, C=O), 1689 (s, C=O), 1354 (m), 1186 (m), 1063 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.53 (t, $^3J_{H,H}$ = 5.2 Hz, 2 H, CH_2), 3.69 (t, $^3J_{H,H}$ = 5.2 Hz, 2 H, CH_2), 3.16 (s, 3 H, CH_3). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.3 (*C*O), 153.7 (*C*O), 65.1 (*C*H_2), 47.0 (*C*H_2), 34.9 (*C*H_3). MS (EI): 128 $[M]^+$. These data match reported values for this compound.[22]

General Procedure for Oxidative Dehydrogenation of Benzyl Alcohol Using NMMO. CD_3CN-stock solutions of benzyl alcohol (BnOH) and Ph_3CH (0.40 mL solution: 30 mM BnOH, 18.8 mM Ph_3CH) and NMMO (0.20 mL, 90-540 mM) were added to an NMR tube containing 0.20 g Au to give a 0.60-mL mixture with the desired alcohol and amine N-oxide concentrations. The tube was sealed with a high-vacuum Teflon stopcock, taken out of the glovebox, and a ^{1}H NMR spectrum was immediately recorded. The tube was then heated in an oil bath at 60 °C and periodically analyzed by NMR.

Results and Discussion

Au-Catalyzed Oxidative Dehydrogenation of Dibenzylamine Using Various Amine N-Oxides or O_2. In previous work, we found that bulk Au powder was an effective

catalyst for the oxidative dehydrogenation of secondary amines using molecular oxygen as the oxidant (eqs 1–3).[12] In the current studies, we initially examined the oxidative dehydrogenation of Bn_2NH, using three different amine N-oxides, NMMO, Me_3NO, and PyNO (Figure 1) in CD_3CN at 60 °C (Figure 1). Within 24 h, a 96% yield of N-benzylidenebenzylamine (100% conversion) was afforded using NMMO as the oxidant (eq 4). A lower yield (77%) of imine product was obtained over the same time period when Me_3NO was used as the oxidant, with a Bn_2NH conversion of only 80%.



(4)

The less basic pyridine N-oxide, PyNO, generated only a 6% yield of the imine product under the same conditions (Figure 1), while the dibenzylamine remained largely unreacted (6% conversion). The reactivities of the amine N-oxides therefore decrease as their basicities decrease as reflected by the pK_as of their conjugate acids: $NMMOH^+$ (4.75)[23] > Me_3NOH^+ (4.56)[24] > $PyNOH^+$ (0.79).[25] To verify that the amine N-oxide and Au were necessary for the transformation, two separate control reactions were run. In one case, the reaction was run without NMMO. After 48 h at 60 °C, less than a 2% yield of the imine was produced. No Au was loaded into the second control reaction, and no conversion of the amine to the imine was observed after heating for 48 h at 60 °C. To test for catalytically active colloidal or soluble gold complexes, a reaction was set up in the glovebox, with the same concentrations of NMMO and Bn_2NH as above, but with a solution volume of 0.80 mL and the tube was sealed with a rubber septum. After 4 h, half (0.40 mL) of the solution at 60

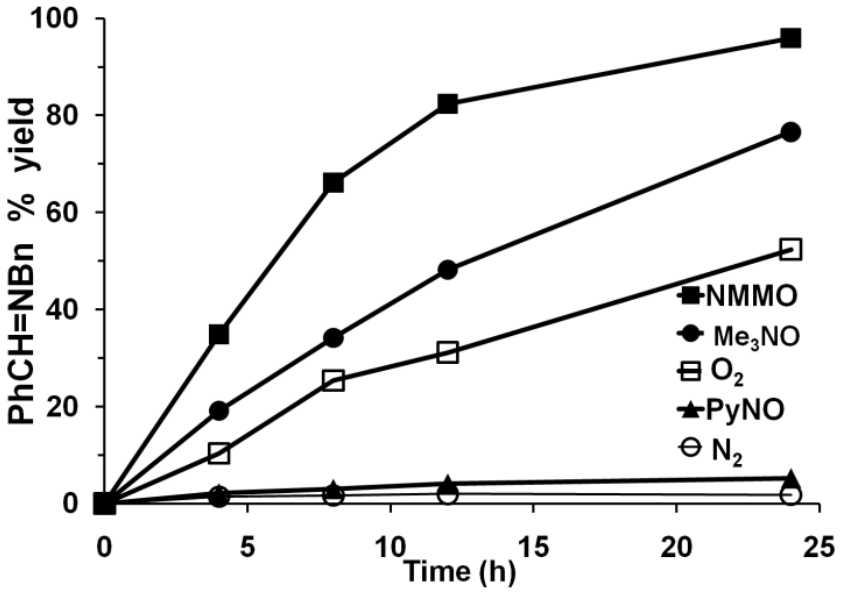


Figure 1. Performance of different oxidants in the catalytic oxidative dehydrogenation of Bn_2NH to PhCH=NBn. Conditions: Bn_2NH (20 mM), oxidant: amine N-oxide (110 mM), O_2 (~1 L, ~1 atm) or N_2 (1 atm), Au (0.20 g), CD_3CN (0.60 mL), 60 °C.

°C was transferred by syringe to another NMR tube. ^{1}H NMR analysis of both tubes showed a 22% yield of the imine product. After heating at 60 ^{o}C for 24 h, an NMR analysis of the tube that contained the gold powder gave a 92% yield of the imine product, while that containing only the reactant solution (with no powdered Au) still showed only 22% of the product. These results clearly show that the bulk Au powder was the active catalyst in this reaction.

To compare the reactivity of O_2 to those of the amine N-oxides, the oxidative dehydrogenation of Bn_2NH was setup in the same manner as above, using O_2 in place of the amine N-oxide. After the NMR tube containing 20 mM Bn_2NH and 0.20 g Au in 0.60 mL

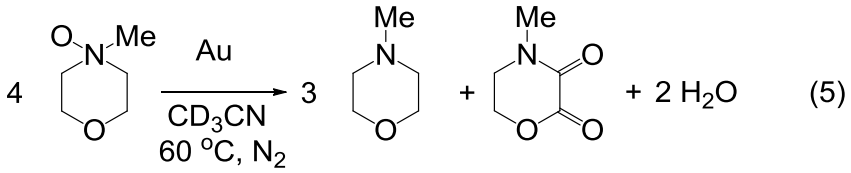
CD_3CN was sealed with a rubber septum, it was removed from the glovebox. After obtaining an initial ^1H NMR spectrum, a syringe needle, attached to a balloon of O_2 (~1 L, ~1 atm), was inserted into the rubber septum of the NMR tube. At 60 °C, the O_2 reaction was found to be much slower than those of both NMMO and Me_3NO, producing only a 52% yield of imine (57% conversion) after 24 h (Figure 1). Extending the reaction time to 48 h increased the yield to 85% (89% conversion).

In an attempt to determine a rate law for the Au-catalyzed oxidative dehydrogenation of Bn_2NH with NMMO, initial rates of the reaction were measured by NMR at different substrate concentrations and a constant initial NMMO concentration. The NMR tube reactions were heated at 50 °C while spinning at 20 Hz in an NMR instrument. Increasing the amine concentration (5-100 mM) had a negligible effect on the rate of the reaction, indicating that the reaction was zero order in amine concentration. The complementary rate studies with increasing NMMO concentrations (16-50 mM), while starting with the same Bn_2NH concentration, always increased the rate. However, it was difficult to generate sufficiently reproducible rates to define a reaction order with respect to NMMO. Thus, it is only possible to state qualitatively that the rate of reaction increases at higher NMMO concentrations. These limited studies suggest that the gold surface is saturated with the amine at all concentrations, which accounts for the zero-order dependence on amine concentration. The increasing rate with an increase in R_3N-O concentration is consistent with a step in the mechanism in which R_3N-O competes with amine for adsorption sites on the gold surface. The faster rates with increasing basicity of the R_3N-O (Figure 1) also supports a step involving competitive adsorption of the R_3N-O. Further mechanistic interpretation is not possible and would be highly speculative.

In reactions that used an amine N-oxide as the oxidant, ^{1}H NMR analysis revealed that the reduction product was the corresponding tertiary amine (e.g., NMM, Me_3N, or pyridine). In the oxidative dehydrogenation reaction of Bn_2NH with NMMO, the yield of tertiary amine (NMM) closely corresponded with the yield of the imine product up to ca. 80% conversion of the Bn_2NH, after which the NMM began to form at a faster rate than the imine. This indicated that NMMO was being consumed by another process that did not involve the oxidation of Bn_2NH (*vide infra*).

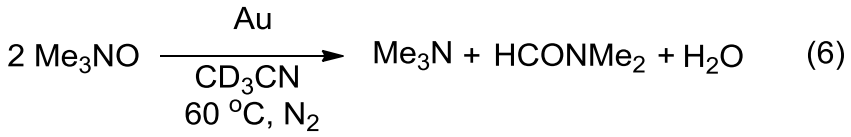
Au-Catalyzed Decomposition of Amine N-Oxides. In a previous study, it was reported that NMMO decomposed above 120 °C, in inert dihalobenzene solvents, to give NMM and morpholine as major products, and formaldehyde as a minor product.[26, 27] We found that no decomposition of NMMO (110 mM in 0.6 mL CD_3CN) occurred at 60 °C, in the absence of Au. We then investigated the gold-catalyzed decomposition of amine N-oxides, under the conditions used for the oxidative dehydrogenation of Bn_2NH. In an NMR-tube reaction, 110 mM NMMO in 0.60 mL CD_3CN and 0.20 g Au powder were heated at 60 °C. After 48 h, NMMO was no longer observable by ^{1}H NMR, and 74% of the starting material was converted to NMM.

In addition to NMM, a new product was identified with ^{1}H NMR peaks at 4.49 (t, $^{3}J_{H,H}$ = 5.2, 2H, CH_2), 3.69, (t, $^{3}J_{H,H}$ = 5.2, 2H, CH_2), and 3.03 (s, 3H, CH_3) ppm in CD_3CN. The isolated compound exhibited IR peaks for ester and amide carbonyl groups at 1757 and 1689 cm^{-1}, respectively, and the mass spectrum exhibited a molecular ion peak at 128 m/z. The IR, ^{1}H NMR, and mass values are in agreement with published data for 4-methyl-morpholine-2,3-dione (eq 5).[22] Approximately 14% of the NMMO was converted to this



dione, as determined by ^{1}H NMR. Since this product contains two carbonyl groups, 28% of the oxygen content of the initial NMMO is incorporated into the dione product. The four hydrogen atoms that are lost during the conversion of NMMO to the dione are most likely consumed by another two oxygen atoms to produce two equivalents of water, which would account for an additional 28% of the oxygen content from the NMMO. Although the fate of a majority of the oxygen (56%) in the initial NMMO was determined, the mass balance was less than quantitative, indicating that unidentified oxygen-containing products must also be formed. Unfortunately, quantification of water by ^{1}H NMR was not possible due to overlapping peaks with NMM. GC-MS analysis of the reaction mixture also showed the presence of a trace product with a mass of 115 m/z. Compounds of this mass could be either N-methylmorpholinone or 4-formylmorpholine.

The decomposition of Me_3NO was also investigated under the same conditions as those for NMMO (0.20 g Au, 110 mM Me_3NO, 0.6 mL CD_3CN, 60 °C). In addition to the expected Me_3N, dimethylformamide (DMF)[28] was also formed (eq 6, Figure 2). After 72 h,



all of the Me_3NO was consumed, resulting in the formation of DMF (39%) and Me_3N (26%). The non-stoichiometric Me_3N/DMF ratio is likely due to the volatility of Me_3N (BP = 3 °C).

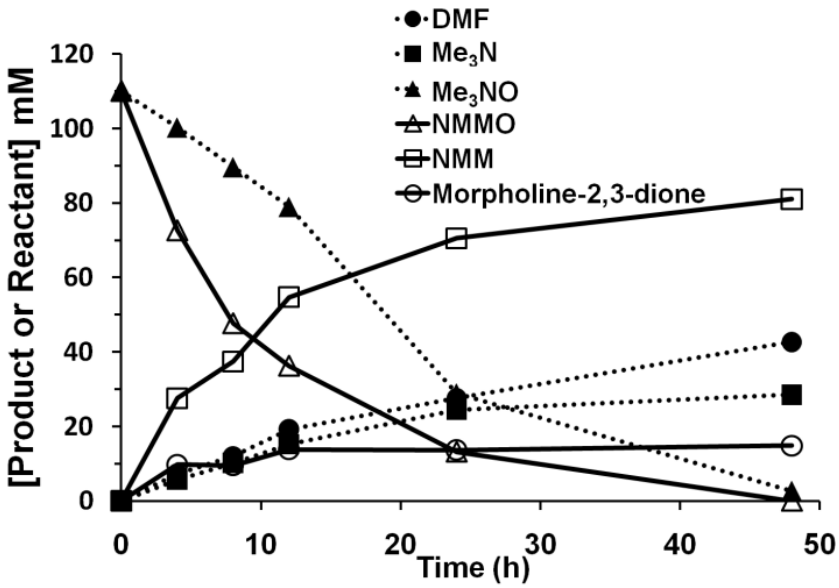


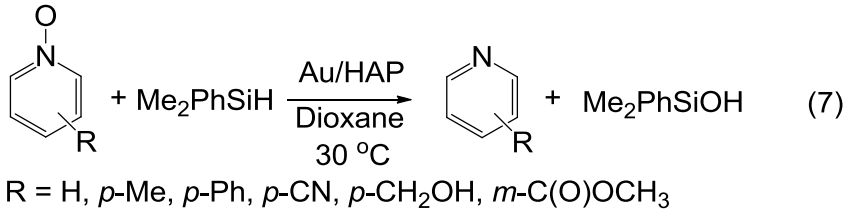
Figure 2. Au-catalyzed deoxygenation reactions of amine N-oxides. Conditions: Amine N-oxide (110 mM), Au (0.20 g), CD_3CN (0.60 mL), 60 °C.

The production of DMF involves the consumption of an equivalent amount of oxygen atoms (eq 6), which would utilize 78% of the oxygen in the original Me_3NO. Therefore, other unidentified oxygen-containing products must also form. ^{1}H NMR integration of a semi-broad water peak at 2.19 ppm (partially overlapped with the Me_3N peak), accounted for less than 46% of the oxygen content, with a large uncertainty in the integration due to the overlapping signals.

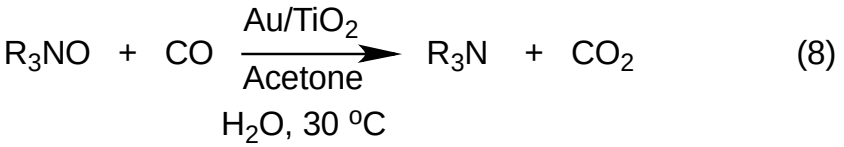
Qualitative rates of the decomposition of NMMO and formation of the NMM product were compared in the presence and absence of Bn_2NH. As shown in Figure 3, NMM and PhCH=NBn form in about a 1:1 ratio up to 8 h (80% conversion). At this time (8 h), the production of 4-methylmorpholine-2,3-dione was first observed and the production of NMM began to occur at a faster rate than the formation of the imine. The formation of the dione is

consistent with the increased rate of decomposition of NMMO (eq 5) under conditions of low Bn_2NH concentration.

The only previous studies of Au-catalyzed deoxygenation reactions of amine N-oxides were those using gold nanoparticles supported on hydroxyapatite (HAP) or titania (TiO_2) in reactions with either dimethylphenylsilane (eq 7)[29] or CO/H_2O (eq. 8).[30]



R = H, *p*-Me, *p*-Ph, *p*-CN, *p*-CH_2OH, *m*-$C(O)OCH_3$



R_3NO= PyNO, Et_3NO

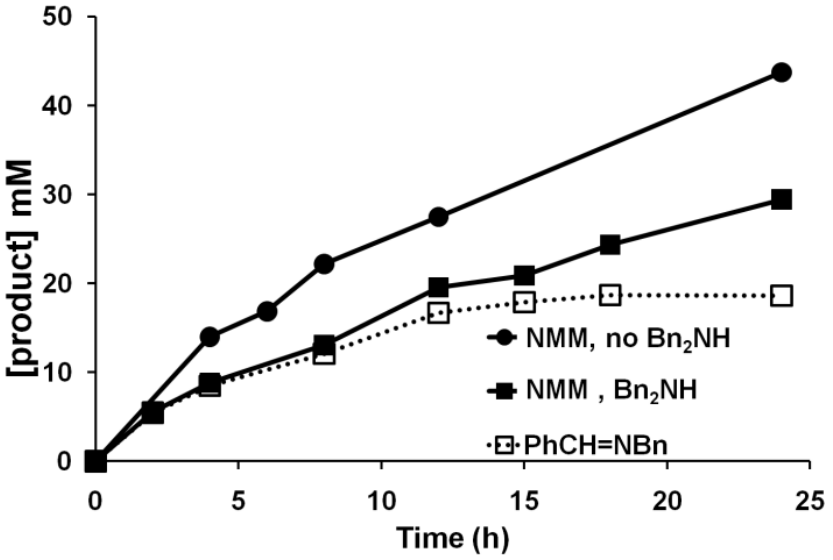
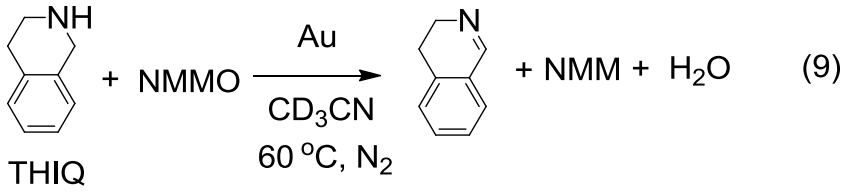
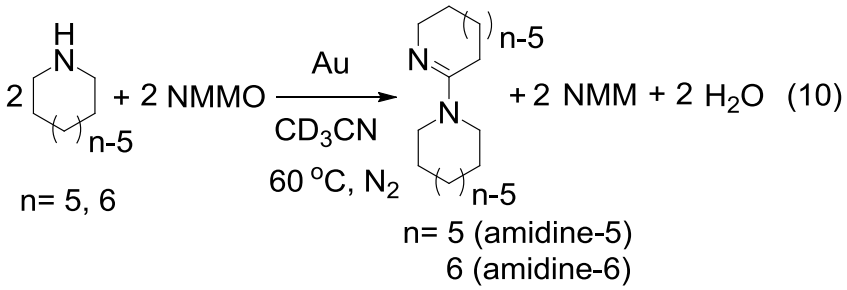


Figure 3. Effect of the presence of Bn_2NH on the deoxygenation of NMMO. Conditions: amine N-oxide (110 mM), Bn_2NH (20 mM, if applicable), Au (0.20 g), CD_3CN (0.60 mL), 60 °C.

Au-Catalyzed Oxidative Dehydrogenation of Other Amines Using NMMO. The oxidative dehydrogenations of THIQ, pyrrolidine [$(CH_2)_4NH$], and piperidine [$(CH_2)_5NH$] were investigated using the same conditions that were used for Bn_2NH. The overall product yields for each of these amines were lower than that for Bn_2NH (Figure 4). The same imine products (eqs. 9–10)[12] were obtained as when molecular oxygen was used as the oxidant (eqs 1–2). When the reaction time was extended from 24 to 48 h in the oxidative

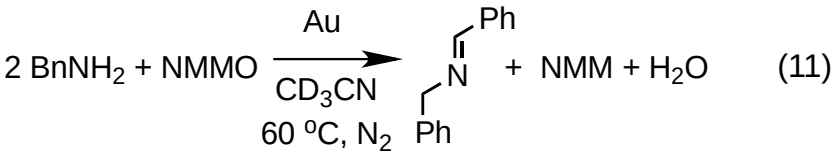




dehydrogenation of THIQ (eq 9), the yield of imine increased from 61% (85% conversion) to 70% (100% conversion), while the yield of the amidine-5 product from the pyrrolidine reaction (eq 10) increased from 65 to 91% over the same time period.

The reaction of the primary amine benzylamine ($BnNH_2$) and NMMO was studied under the same conditions as those used for the secondary amines. N-benzylidenebenzylamine was the only product that resulted from the oxidative dehydrogenation of the amine (eq 11), as was also observed when molecular oxygen was used as the oxidant (eq 3).[13] The yield of PhCH=NBn after 24 h, was 33% (34% conversion), while the yield increased further to 45% (46% conversion) after 48 h. The

reaction most likely involves an initial oxidation of the amine to an imine intermediate which is attacked by an additional molecule of $BnNH_2$ to give the final PhCH=NBn product, as previously proposed for the bulk gold catalyzed reaction using O_2 as the oxidant.[13]



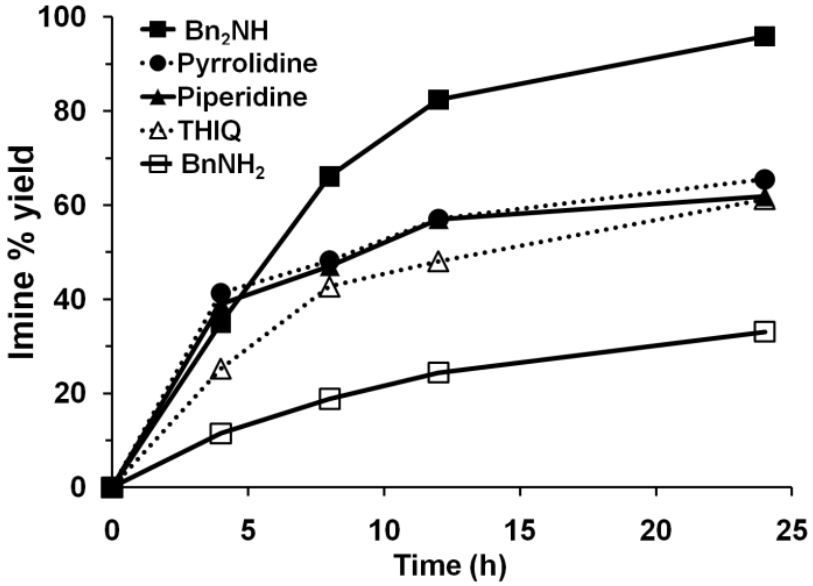


Figure 4. Percent yield of imine products (eqs. 4, 9–11) from various amines using NMMO as the oxidant. Conditions: amine (20.0 mM), NMMO (110 mM), Au (0.20 g), CD_3CN (0.60 mL), 60 °C.

Au-Catalyzed Oxidative Dehydrogenation of Benzyl Alcohol Using NMMO and O_2

The oxidation of BnOH (20 mM) with NMMO (110 mM) in CD_3CN was also investigated using Au powder as the catalyst (eq 12) at 60 °C. This afforded benzaldehyde (PhCHO) in 42% yield (65% conversion) after 24 h. When the reaction time was extended from 24 to 48

h, the yield of PhCHO increased to only 52% (77% conversion). In an attempt to optimize the aldehyde yield, the NMMO concentration was first decreased from 110 mM to 30 mM,

$$\text{BnOH + NMMO} \xrightarrow[\text{CD}_3\text{CN}]{\text{Au}} \text{PHCHO + NMM + H}_2\text{O} \quad (12)$$

$$60\ ^{o}\text{C, N}_2$$

which led to a decrease in the aldehyde yield (47%, 50% conversion) after 48 h (Figure 5). Increasing the NMMO concentration to 180 mM improved the PhCHO yield to 57%, (69% conversion) after 48 h. An increase in temperature also had a positive effect on the reaction. At 85 °C (110 mM NMMO), the reaction rate was fastest and the highest yield of PhCHO (63%, 76% conversion) was afforded after 48 h.

To verify that the gold catalyst was necessary for this oxidation, a control reaction was performed under identical conditions (20 mM BnOH, 110 mM NMMO, 0.6 mL CD_3CN, 60 °C), but without gold powder. No conversion of benzyl alcohol was observed. As compared to NMMO, O_2 was a far inferior oxidant in this reaction, as the oxidative dehydrogenation of benzyl alcohol using O_2 (~1 L, ~1 atm) at 60 °C, resulted in a substantially slower rate with only a 7% yield of PhCHO, while 91% BnOH remained unreacted after 48 h (Figure 5). Although many supported nanogold catalysts[7] including Hydrotalcite,[31] titania,[32] ceria,[32] and gallia[33] catalyze this reaction with O_2 more efficiently than Au powder, this is the first report of bulk Au showing any activity in alcohol oxidation.

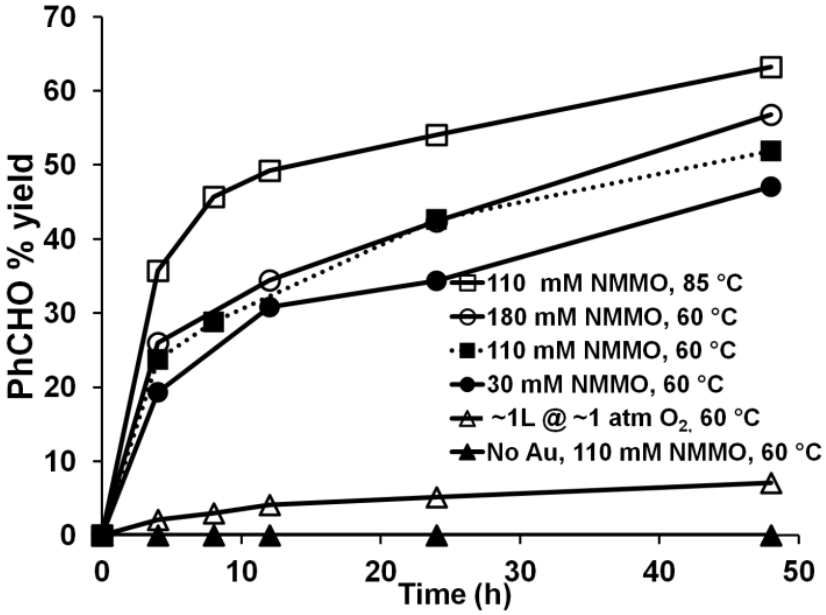


Figure 5. Percent yield of benzaldehyde in the Au-catalyzed reaction of benzyl alcohol with NMMO and O_2. Conditions (unless otherwise noted): BnOH (20 mM), NMMO (30–180 mM), Au (0.20 g), CD_3CN (0.60 mL).

Conclusions

The results described in this manuscript show that aliphatic amine N-oxides are effective oxidants in bulk Au-catalyzed oxidative dehydrogenation reactions of both amines and benzyl alcohol. Although details of the mechanisms have not been established for the reactions of either R_3N-O or O_2, they are undoubtedly different because of the very dissimilar natures of these oxidants. However, it important to note that bulk gold is capable of catalyzing reactions using both oxidants. The basicity of the amine N-oxide strongly influences the oxidative dehydrogenation of Bn_2NH, as the reactions were much faster with the most basic amine N-oxides (NMMO and Me_3NO) than with the less basic PyNO. The

discoveries reported in this manuscript further expand the range of reactions that are catalyzed by bulk gold.

Acknowledgment

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CHAPTER 4: CONVERSIONS OF CYCLIC AMINES TO NYLON PRECURSOR LACTAMS USING BULK GOLD AND FUMED SILICA CATALYSTS

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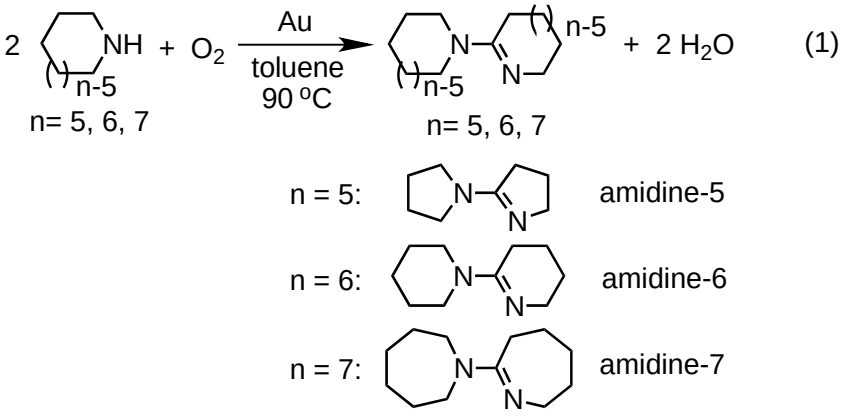
Abstract

Bulk gold powder (~50 μm) and alumina-supported gold catalyzed the oxidative dehydrogenation of 5-, 6-, and 7-membered cyclic amines to amidines. These amidines were hydrolyzed upon treatment with Aerosil 200 (fumed silica gel) and water to produce lactams and amines in yields from 42 to 73%. The gold and Aerosil 200 catalysts could also be combined in a one-pot reaction to catalyze the conversion of cyclic amines to lactams in yields up to 51%.

Introduction

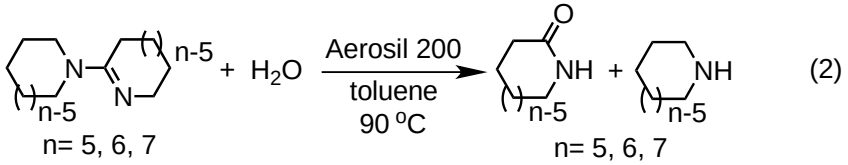
While supported nanogold particles (< 5 nm) have attracted much interest due to their ability to catalyze several different types of reactions,[1,2,3,4,5,6,7] *bulk* Au powder (~50 μm) has a reputation as a poor catalyst.[1] However, we have shown it to be an effective catalyst in a

number of different reactions, such as the reaction of isocyanides with amines and O_2 to form carbodiimides[8] or ureas,[9] the reaction of CO with amines and O_2 to give ureas,[10] the coupling of carbene precursors to olefins,[11] and the reaction of diazoalkanes with amines and O_2 to give enamines.[12] In addition, we have demonstrated that bulk Au and 5% Au/Al_2O_3 catalyze the oxidative dehydrogenation of cyclic amines with O_2 to form amidines (eq 1).[13,14]

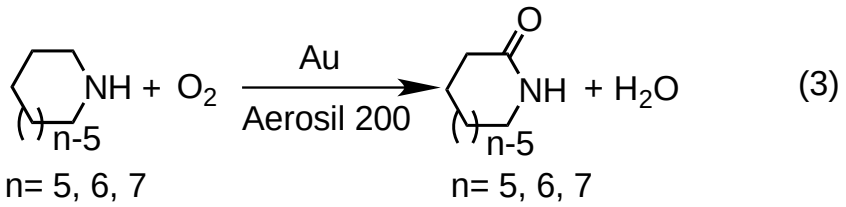


To the best of our knowledge, only two other examples have been reported in which cyclic amines are catalytically converted to amidines, and these both involved pyrrolidine. One used Pd black to catalyze the dehydrogenation of pyrrolidine under an Ar atmosphere at 80 °C to give amidine-5 in 65% yield.[15,16] The other catalyst for this conversion is carbon-supported nanogold, which catalyzed the oxidative dehydrogenation of pyrrolidine to amidine-5 in 99% yield.[17]

We have now found that cyclic amidines undergo hydrolysis to form lactams upon heating with Aerosil 200 and water (eq 2). In addition, we report that these lactams can be



produced directly by treating cyclic amines with Au, Aerosil, oxygen, and water in one pot (eq 3). This represents a potentially significant improvement for the multistep production



(3)

of industrially important nylon precursors such as caprolactam.[18,19] This compound is traditionally prepared from cyclohexane using harsh conditions in a process that generates substantial waste ammonium sulfate.[20] The large-scale manufacture of caprolactam and its subsequent polymerization to nylon-6 is driven by the low cost of benzene and its conversion to cyclohexane.[19,21] The analogous polymerization of butyrolactam and valerolactam to nylons-4 and -5, respectively,[22,23] has tremendous potential for use in textile fibers as these nylons are able to absorb more moisture and generate less static buildup compared to nylon-6.[24] Despite these advantages, nylons-4 and -5 are a minor component of the polyamide fiber industry. However, improved syntheses of butyro- and valerolactam may enhance the market viability of nylons-4 and -5. Details of the hydrolysis of amidines (eq 2) and the overall conversion of cyclic amines (eq 3) to lactams are described in this paper.

Experimental Section

All amines were dried over calcium hydride, distilled under reduced pressure according to literature procedures,[25] and stored over type 4A molecular sieves, prior to use. All other solvents and compounds were used as received, unless otherwise noted. Toluene, *p*-xylene, decane, dodecane, triphenylmethane, γ-butyrolactam, δ-valerolactam, ε-

caprolactam, and oxygen (99.9%) were purchased commercially. Alumina (Basic Brockman Activity I, 150 m^2/g, particle size = 44-250 μm, pore volume = 0.25 mL/g, pore diameter= 60 Å) was purchased from Fisher, and Amberlyst-15, a porous sulfonated crosslinked polystyrene (40-50 m^2/g, particle size = 300-1150 μm, pore volume = 0.24-0.40 mL/g, pore diameter= 300 Å), was acquired from Sigma- Aldrich. Aerosil 200 (nonporous silica gel, 200 m^2/g, average primary particle size = 12 nm), hereafter referred to as Aerosil, was a gift from the Evonik Degussa Corporation, and silica gel (500-600 m^2/g, particle size = 40-63 μm, pore volume = 0.65-0.85 mL/g, pore diameter = 60 Å) was purchased from Sorbent Technologies. Hydrotalcite (82 m^2/g, pore diameter = 250 Å) was prepared using a published procedure.[26]

General Procedure for the Preparation and Cleaning of Gold Powder. Gold powder was prepared from $HAuCl_4$ and cleaned as described previously.[11] The powder consists of large particles (5-50 μm), which were previously characterized by electron microscopy.[8,11] Due to gradual loss of activity with each run, comparisons of catalytic results were restricted to those with batches of gold powder that had previously undergone the same number and type of reactions. Once a batch was used for the comparative studies, it was recycled for the next cycle of experiments using the following multistep treatment: the gold was collected by filtration from a catalytic reaction mixture, rinsed with 50 mL acetonitrile, washed with 50 mL methanol, stirred with 40 mL of "piranha" solution[11] for 4 h, diluted with 200 mL water, filtered on filter paper, washed ten times with 40-mL volumes of water, rinsed with five 40-mL methanol aliquots, and oven-dried overnight in air at 110 °C.

General Procedure for Separation of Aerosil and Au. Following a one-pot reaction using both gold powder and Aerosil, the solution was filtered and the solid residues

were transferred to a beaker containing 25 mL H_2O. The Aerosil was removed by agitating the mixture and removing the suspended particles with a pipet. Additional fresh water was added, until all of the Aerosil was removed by pipetting. The gold was then cleaned and dried as described above.

Preparation of 5% Au/Al_2O_3. Au/Al_2O_3 was prepared by an incipient wetness impregnation method similar to that used previously[14] with the following modification: Alumina (γ-Al_2O_3) was purchased from Alfa Aesar (200 m^2/g, particle size = 40 μm). Au/Al_2O_3 was characterized by STEM, TEM, and EDX. The Au particle shapes were irregular and the sizes were in the 20-700 nm range.

Au-Catalyzed Reaction of Amines and O_2. A glass tube (2.0 × 17 cm, ~65 mL volume) was loaded with 1.00 g Au powder or 100. mg 5% Au/Al_2O_3. Stock solutions, in toluene, of the desired amine (1.0 mL, 200.0 mM) and decane or dodecane internal standard (4.0 mL, 4.5 mM) were then added to the tube to produce a 5.0 mL solution with the desired substrate concentration (40.0 mM). The vessel was capped with a rubber septum through which oxygen gas was delivered by the insertion of a syringe needle that was attached to a balloon of oxygen (~1.0 L at ~1 atm). The reaction was stirred with a magnetic stirbar at 90. °C in an oil bath. Aliquots (~50 μL) were withdrawn periodically by a syringe and analyzed by GC (see below).

Aerosil-Catalyzed Hydrolysis of Amidines. A glass tube (2.0 × 17 cm, ~65 mL volume) was charged with 5.0 mL of a solution containing the desired concentration of amidine (20.0 mM) and internal standard (decane or dodecane) in a given solvent, after which 50. mg of Aerosil and 200. μL water were added. The tube was then capped with a

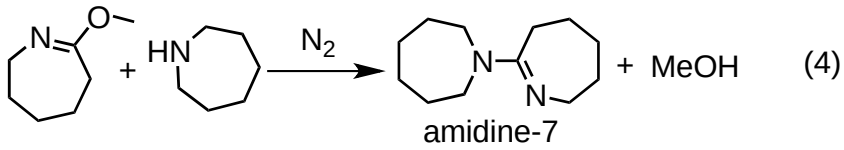
septum and the mixture was stirred at 90. °C in air in an oil bath. Aliquots were periodically extracted with a syringe and analyzed by GC (see below).

Combined Au Powder/Aerosil-Catalyzed Conversion of Amines to Lactams. A 5.0 mL solution with the desired concentrations of the amine (40.0 mM) and internal standard was prepared by the addition and subsequent dilution of stock solutions. To a Schlenk tube (2.5 × 17 cm, ~80 mL volume) was added 1.0 mL of a 200.0 mM solution of the amine, followed by 4.0 mL of a stock solution of internal standard in the same solvent. The contents of the tube were then shaken to mix the solution together. Gold powder (1.00 g) or 5% Au/Al_2O_3 (100. mg), 50. mg of Aerosil, and 200. μL of deionized water were then added to the prepared solution. A 28-cm water-cooled condenser was fitted with a rubber septum and attached to the Schlenk tube. Oxygen was supplied to the reaction system with a balloon of O_2 (~1.0 L @ ~1 atm) attached to a syringe needle inserted into the septum at the top of the condenser. The reaction was then stirred at 90 °C in an oil bath. Aliquots were taken periodically and analyzed by GC (see below). Prior to GC analysis, the aliquots were filtered through a cotton plug to remove suspended Aerosil particles.

Preparation of Authentic Amidine Samples. The amidines (amidine-5 and amidine-6) that are generated from the oxidative dehydrogenation of pyrrolidine and piperidine, were prepared using larger scale reaction conditions.[13] The ^{1}H NMR and GCMS results for these compounds matched reported values for amidine-5[15] and amidine-6.[13] Amidine-5: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.67 (t, ^3J(H,H) = 6.9 Hz, 2H; CH_2), 3.37 (t, ^3J(H,H) = 7.8 Hz, 4H; CH_2), 2.19 (t, ^3J(H,H)=7.8 Hz, 2H; CH_2), 2.00-1.86 ppm (m, 6H; CH_2). Amidine-6: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.50 (t, ^3J(H,H)=5.6 Hz,

2H; CH_2), 3.26 (t, ^3J(H,H)=5.6 Hz, 4H; CH_2), 2.19 (t, ^3J(H,H) = 6.4 Hz, 2H; CH_2), 1.70 (m, 2H; CH_2), 1.54 ppm (m, 8H; CH_2).

Authentic amidine-7 was prepared through an independent synthesis using a modified procedure involving the addition of hexamethyleneimine (211 mg, 2.11 mmol) to neat caprolactim methyl ether (250 mg, 1.97 mmol) (eq 4).[27] The reaction was stirred under



(4)

nitrogen for 8 h at 100 °C, and then for 8 h at 70 °C. Unreacted reagents and volatile components were removed under reduced pressure to afford amidine-7 (159 mg, 42% yield). The ^{1}H NMR spectrum matched reported literature values.[13] Caprolactim methyl ether was prepared according to a published procedure.[28] Amidine-7: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 3.41 (m, 6H; CH_2), 2.49 (m, 2H; CH_2), 1.73-1.48 ppm (m, 14H; CH_2)

GC and GC-MS Analyses. GC 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: He carrier gas; constant flow mode; initial column temperature, 50 °C for 2 min; heating rate, 15 °C/min; final temperature, 280 °C.

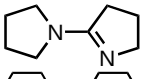
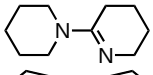
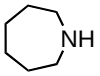
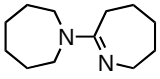
Reaction products were identified by comparison of their mass spectra and GC retention times with those of authentic samples. Yields were determined by GC integrations using authentic samples of the products for response factors. GC-MS measurements were obtained from a Finnegan Magnum GC-MS or a Waters Micromass GCT instrument.

Results and Discussion

Au-catalyzed reaction of cyclic amines and O_2. We reported previously that both bulk Au[13] and 5% Au/Al_2O_3[14] catalyzed the oxidative dehydrogenation reaction of the cyclic amines, pyrrolidine, piperidine, and hexamethyleneimine to amidines (eq 1, Table 1). In the present work, the 5% Au/Al_2O_3 catalyst was prepared using a different commercially available γ-alumina as the support. When used in the oxidative dehydrogenation of cyclic amines under the same conditions as the previous studies, the new 5% Au/Al_2O_3 showed the same trend in decreasing product yield as the size of the amine ring increased. However, this batch of catalyst was not as active as the previously reported Au/Al_2O_3[14] (Table 1).

While the previously synthesized 5% Au/Al_2O_3 consisted primarily of smaller Au particles (50-150 nm), the new supported catalyst contained Au particle sizes in the 20-700 nm range. The size and broad Au particle distribution in the new supported catalyst may explain its reduced activity, as compared with that for the previously reported 5% Au/Al_2O_3.

Table 1: Product yields for the Au-catalyzed oxidative dehydrogenation reaction (eq 1) of various cyclic amines[a]

		Yield (%)		
Amine	Product	Au powder[b]	Au/Al_2O_3[c]	New Au/Al_2O_3[c]
		93[d]	98[d]	58
		87	95[d]	54
		20	33[d]	24

[a] Reaction conditions: 40.0 mM amine, O_2 (~1.0 L @ ~1 atm) in 5.0 mL toluene solvent at 100 °C for 24 h. [b] 1.00 g Au powder catalyst. [c] 100. mg 5% Au/Al_2O_3 catalyst. [d] Ref 14.

Aerosil-catalyzed hydrolysis of amidines. Amidines generally undergo hydrolysis with water[29] under both homogenous base[30,31] and acid[32] catalysis. However, the hydrolysis of the amidines in Table 1 has not been studied. Thus, we sought to determine the optimum conditions for the hydrolysis (eq 2) of our cyclic amidines in the presence of various heterogeneous catalysts. Both acidic and basic oxides were tested, as well as a solid acid catalyst. The materials examined included Aerosil, basic alumina, silica gel, hydrotalcite, and Amberlyst-15. Treatment of amidine-6 with all oxide catalysts led to hydrolysis and gave valerolactam and piperidine as the only observable products (eq 2). As described below, Aerosil was the most effective catalyst (Table 2).

When a solution of amidine-6 (20.0 mM) in 5.0 mL of toluene at 90 ^{o}C was treated with 50 mg of nonporous fumed silica Aerosil in the absence of added water, it underwent hydrolysis to form valerolactam in 26 % yield after 36 h. When more than 50 mg of Aerosil was used as the catalyst, the mixture became a gel that was difficult to separate and analyze. An important factor in this process is the amount of water present. Although Aerosil contains adsorbed water, the addition of extra water to the reaction mixture, up to 200 μL, was observed to increase the rate and yield of hydrolysis. The addition of 400 μL water resulted in no additional hydrolysis beyond that produced by 200 μL water. Moreover, the addition of 1.5 mL water drastically inhibited the reaction, reducing the yield to <5% valerolactam after 36 h (Figure 1). Optimized conditions, using 50 mg Aerosil with water (200 μL, 2.2 M) in toluene resulted in a 60% yield of valerolactam. It should be noted that the use of *p*-xylene as the solvent gave essentially the same yield of lactam as toluene in this reaction. Other catalysts hydrolyzed amidine-6 to valerolactam in considerably lower yields when studied using the optimized conditions (Table 2).

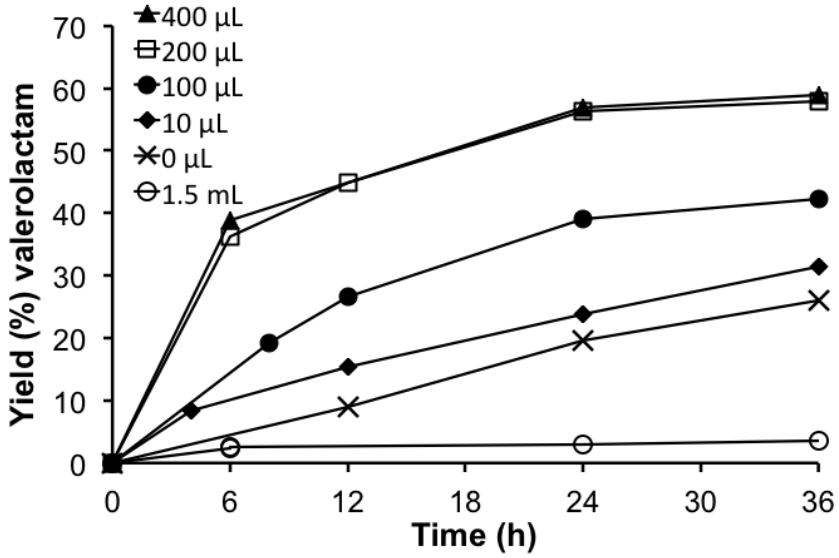


Figure 1. Effect of the addition of various amounts of water to the Aerosil-catalyzed hydrolysis (eq 2) of amidine-6 (20.0 mM) at 90 °C in 5 mL toluene.

Using the optimized conditions, amidine-7 was hydrolyzed to caprolactam (73%) and hexamethyleneimine (63%), while amidine-5 was hydrolyzed under the same conditions to produce butyrolactam (42%) along with pyrrolidine (36%) (Figure 2). At reaction times greater than 24 h, the lactam yield increased only slightly and after 24 h, very little amidine was detected by GC (Figure 3).

In seeking to improve yields, we sought to determine if some of the valerolactam and piperidine products remained adsorbed on the Aerosil. Using quantities similar to those in our reaction conditions, 5.0 mL of a 20.0 mM toluene solution of valerolactam was stirred with 200 µL of water and 50 mg Aerosil for 48 h at 90 °C. GC analysis of the resulting solution showed that about 30% of the lactam had adsorbed on the Aerosil. After the solution was removed by filtration, the Aerosil was stirred in 5.0 mL methanol at ambient temperature with an internal standard for 48 h in a capped tube; GC analysis showed that approximately 33% of the adsorbed valerolactam was extracted into the methanol. The remaining 67% of the

Table 2: Catalyst performance in the hydrolysis reaction of amidine-6 (eq. 2)[a]

Entry	Catalyst	% Conversion	% Yield
1	Aerosil	100 (100)[b]	60 (29)[b]
2	Alumina	85 (67)[b]	35 (16)[b]
3	Hydrotalcite	48 (27)[b]	20 (6)[b]
4	Silica Gel	100	19
5	Amberlyst-15	100	0
6	None	16	16

[a] Reaction conditions: amidine-6 (20.0 mM), catalyst (50 mg), H_2O (200 μL) in 5.0 mL toluene at 90 °C for 48 h.
[b] Numbers in parentheses were from runs in which no water was added.

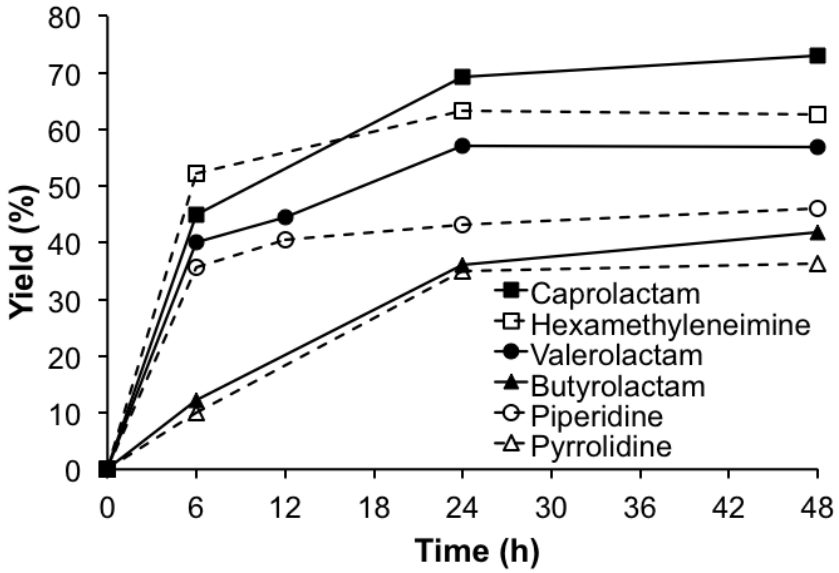


Figure 2. Aerosil-catalyzed hydrolysis (eq 2) of amidines. Conditions: 20.0 mM amidine, 50 mg Aerosil, and 200 μL H_2O in 5.0 mL toluene at 90 °C. Amidine-6 hydrolysis was run in *p*-xylene.

valerolactam may be strongly adsorbed to the Aerosil or may have undergone hydrolysis or polymerization under the conditions of the adsorption (90 ^oC and 200 μL water) and would

not have been detected by GC. In a separate experiment using *p*-xylene as the solvent so that the amount of piperidine product could be quantified by GC analysis, the Aerosil-catalyzed hydrolysis of amidine-6 was run for 48 h at 90 ^{o}C, after which GC analysis of the solution showed a 57% conversion of amidine-6 to valerolactam and a 46% yield of piperidine. The Aerosil was recovered by filtration and then stirred for 48 h at ambient temperature in 5.0 mL

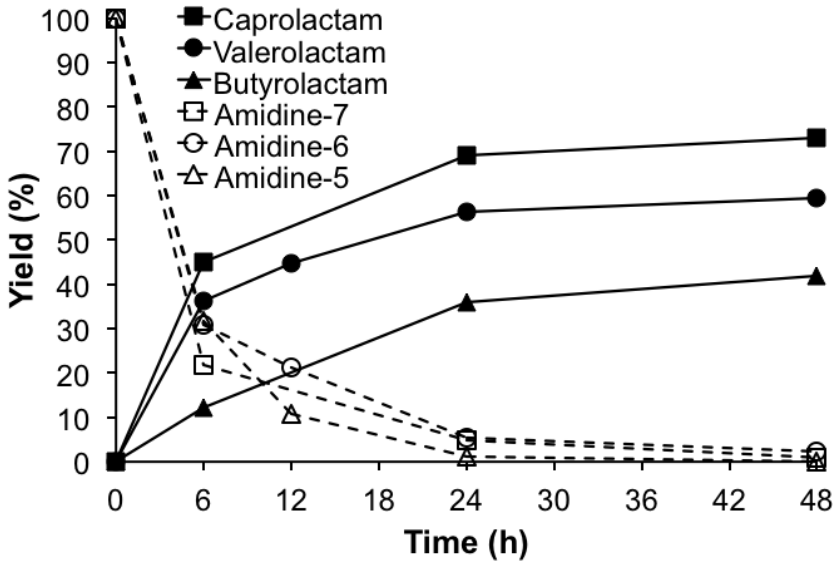


Figure 3. Aerosil-catalyzed hydrolysis (eq 2) of amidines. Conditions: 20.0 mM amidine-6, 50 mg Aerosil, and 200 μL H_2O in 5.0 mL toluene at 90 °C. Dashed lines indicate disappearance of amidines and solid lines show formation of lactams.

methanol with triphenylmethane as an internal standard. GC analysis of the methanol solution detected additional amounts of valerolactam and piperidine which increased the overall yields of these products to 65% and 51%, respectively. Since all of the amidine-6 is consumed under the conditions of the hydrolysis reaction (90 ^{o}C, 48 h), 35% of the amidine is not converted to detectable lactam product. Some of the valerolactam could have undergone hydrolysis or polymerization, as suggested by the previous experiment in which valerolactam

is converted on Aerosil at 90 ^{o}C to compounds that could not be extracted from the Aerosil and/or were not sufficiently volatile to be detected by GC.

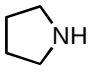
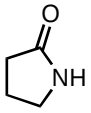
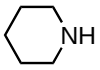
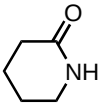
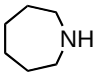
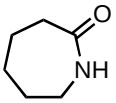
The low yield of the piperidine product (51%) from the hydrolysis (eq. 3) of amidine-6 suggests that it also is either strongly adsorbed on the Aerosil and/or reacts (perhaps with the lactam) to give a non-volatile product. Previous studies showed that piperidine is strongly adsorbed on hydrated silica due to protonation to form the piperidinium cation;[33] this may account for the low quantity of detected piperidine product.

Combined Au powder/Aerosil-catalyzed conversion of amines to lactams (eq 3). As an alternative to running the oxidative dehydrogenation and hydrolysis processes as separate batch reactions, we examined a one-pot, tandem catalyst system that combines both the Au and the Aerosil. We chose reaction conditions (90 °C, in toluene, 1.00 g Au, 50 mg Aerosil, ~1.0 L at ~1 atm O_2) that were suitable for both steps. When no additional water was added, the yield of valerolactam from piperidine was only 21%, according to the stoichiometry in eq 3. However, under the same conditions but with 200 μL of water added, the lactam yield improved to 51%. The same conditions were used in directly converting the other cyclic amines. Piperidine is converted to the corresponding lactam in the highest yield of all of the cyclic amines that were tested (Table 3).

The amount of lactam produced is a net result of contributions from the two steps (oxidative dehydrogenation and hydrolysis, eqs 1, 2) involved in the overall transformation (eq 3). The most favorable oxidative dehydrogenation step occurs with pyrrolidine and piperidine which gave amidines in 93% and 87% yields, respectively (Table 1). On the other hand, the hydrolysis step gives the highest yield (73%) of lactam with amidine-7 (Figure 2).

When the new Au/Al_2O_3 was used as the catalyst, the valerolactam yield was much lower (24% vs. 51%) as compared with gold powder, presumably due to its decreased efficiency in

Table 3: Lactam yields (eq 3) for the combined Au/Aerosil- catalyzed oxidative dehydrogenation and subsequent hydrolysis reactions of various cyclic amines[a]

Entry	Amine	Product	Conversion (%)	Yield (%)	TON[e]
1			100[b]	35[b]	12
2			100[b]	51[b] (24)[c] (21)[bd]	16[b] (1600)[c]
3			100[b]	11[b]	4

[a] Reaction conditions: 40.0 mM amine, O_2 (~1.0 L @ ~1 atm), 50. mg Aerosil, 200. µL H_2O in 5.0 mL toluene solvent at 90 °C for 96 h. [b]1.00 g Au powder. [c]100 mg Au/Al_2O_3 in place of Au powder. [d] No water added. [e] Estimated TONs were based on the number of surface atoms[34] and assuming all were active sites.

producing amidine-6 in the oxidative dehydrogenation of the amine (Table 1). In contrast, the very low overall yield of caprolactam reflects the low yield of amidine-7 in the Au-catalyzed oxidative dehydrogenation of hexamethyleneimine.

Catalyst Recycling. After each combined Au/Aerosil catalyzed reaction of amines to lactams, the solid catalyst was recovered by filtration. Removal of the Aerosil catalyst from the Au powder was accomplished by utilizing density differences as described in the experimental section. The gold was then treated with "piranaha" solution (see experimental

section). This recycled Au catalyst together with fresh Aerosil was used again in a reaction of piperidine with oxygen and water (Figure 4).

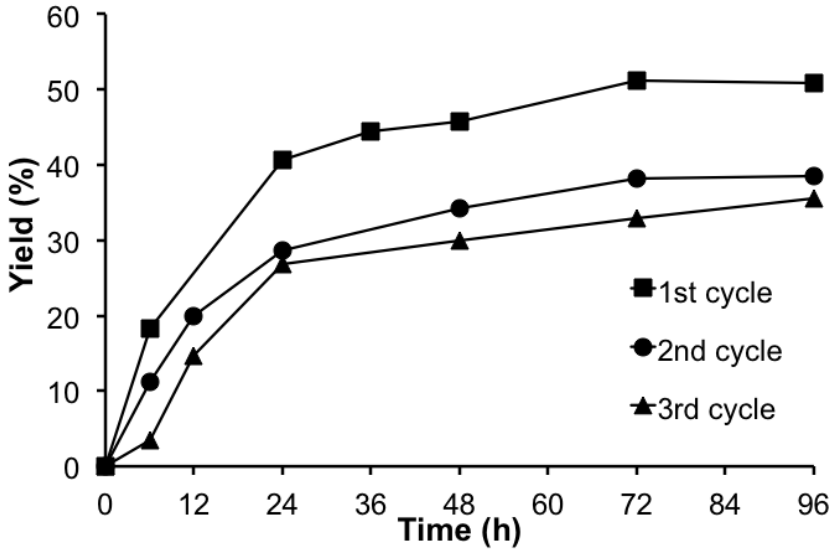


Figure 4. Product Yields for the Au/Aerosil-catalyzed conversion of piperidine to valerolactam (eq 3). Conditions: amine (0.2 mmol), O_2 (~1.0 L @ ~1 atm), Au powder (1.00 g), Aerosil (50. mg), H_2O (200 μL) in 5.0 mL toluene at 90 °C.

The first use of the Au/Aerosil catalyst produced the highest yield of valerolactam (51%). When this batch of gold was cleaned and used in a second reaction, the valerolactam yield decreased to 39%. On reuse of the Au a third time, the decrease in activity was less pronounced (36% yield). The loss of activity is most likely due to the incomplete removal of organic material on the Au surface, even after piranha treatment. A similar loss in activity was observed in self-coupling reactions of diazoalkanes catalyzed by bulk Au.[11]

Conclusions

Both bulk gold powder (~50 μm) and 5% gold supported on alumina catalyzed the oxidative dehydrogenation of cyclic amines to amidines (eq 1) in yields up to 98% (Table 1).

Subsequent conversion of the amidines to lactams was most effectively accomplished with Aerosil 200 (fumed silica gel) as a hydrolysis catalyst (eq 2). The hydrolysis rate could be enhanced by adding an optimal amount of water to the solution. A convenient one-pot process using a tandem catalyst system of bulk gold or 5% Au/Al_2O_3 with Aerosil 200 was developed for the overall catalytic conversion of amines to lactams. In the case of piperidine, valerolactam was produced in >50% yield. In summary, we have developed a heterogeneous catalytic system that is able to perform a tandem process involving oxidative dehydrogenation of cyclic amines, followed by a subsequent hydrolysis of the resulting amidine to form lactams. This is a novel route for the synthesis of industrially important nylon precursors from readily available cyclic amines using oxygen, water and commercially available catalysts.

Acknowledgements

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Supporting Information

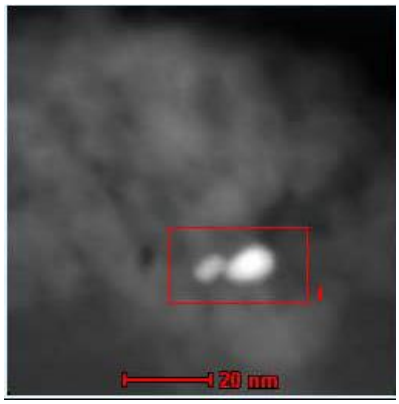

Figure S1: Scanning transmission electron micrographs of the 5% Au/Al_2O_3. Red rectangle represents the area of the EDX analysis.

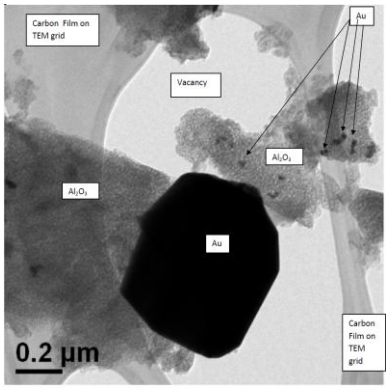

Figure S2: Transmission electron micrographs of Au/Al_2O_3 catalyst. The black arrows point to small Au particles on the alumina surface. The large black shape is an ~0.7 µm Au particle.

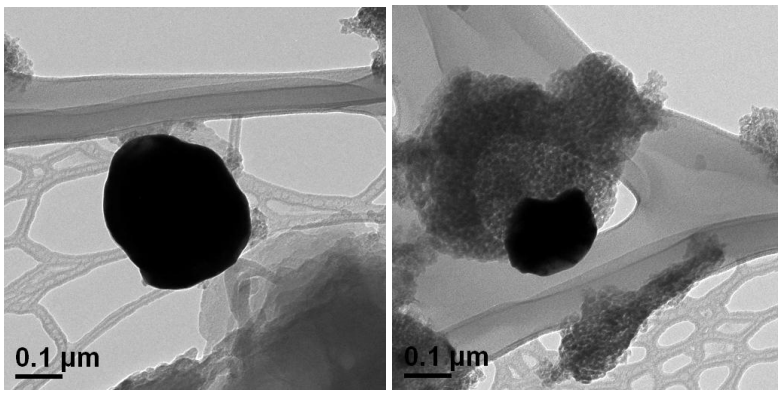

Figure S3: Transmission electron micrograph of an Au particle supported on alumina.

CHAPTER 5: O-H INSERTION AND TANDEM N-H INSERTION/CYCLIZATION REACTIONS USING AN IRON PORPHYRIN AS CATALYST WITH DIAZO COMPOUNDS AS CARBENE SOURCES

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Abstract

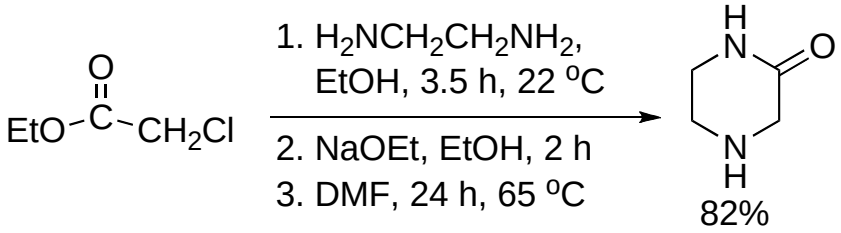
Iron(III) tetraphenylporphyrin chloride, Fe(TPP)Cl, efficiently catalyzed the insertion of carbenes derived from methyl 2-phenyldiazoacetates into O-H bonds of aliphatic and aromatic alcohols with yields generally above 80%. Although the analogous N-H insertions are rapid at room temperature, the O-H insertion reactions are slower and required heating in refluxing methylene chloride for about 8 hours using 1.0 mol% catalyst. Fe(TPP)Cl was also found to be effective for tandem N-H insertion/cyclization reactions when 1,2-diamines and 1,2-alcoholamines were treated with diazo reagents to give piperazinones and morpholinones and related analogues such as quinoxalinones and benzoxazin-2-ones. This approach provides a new one-pot route for synthesizing these classes of heterocyclic compounds.

Introduction

The synthesis of α-hydroxy and α-alkoxy carboxylic acid derivatives is of considerable importance since these compounds are useful synthetic intermediates for the construction of natural products and biologically active molecules. Diazocarbonyl compounds are useful reagents for the synthesis of these types of derivatives, due to their ready availability, relative kinetic stability, and facile decomposition under thermal, photochemical, and metal-catalyzed conditions. Transition-metal-catalyzed procedures are often the method of choice, taking place under relatively mild conditions. The original catalytic reactions with diazo reagents were based on copper metal or simple copper(II) salts.[1] Rhodium(II) carboxylates were introduced later by Teyssie and co-workers in the early 1970's.[2] In recent years, new transition-metal catalysts have been developed that are now widely used since they mediate a broad range of carbenoid transformations such as cyclopropanation, C-H insertion, addition to aromatic rings, and ylide formation.[3] Consequently, synthetic uses of diazocarbonyl compounds have increased dramatically.

Our recent interest in iron porphyrin reactions with diazo reagents centers on C-H and N-H insertion reactions,[4] which despite their potential in synthesis, have not been widely utilized.[5] Earlier work done by our group established that iron tetraphenylporphyrin chloride, Fe(TPP)Cl, is one of the most effective catalysts for the insertion of carbenes from diazo esters into N-H[6] and C-H bonds.[7] The present study sought to extend the use of iron porphyrins to O-H insertion reactions and also determine if the highly efficient N-H insertion process could be coupled with subsequent cyclization reactions to give products that contain piperazinone or morpholinone moieties. A typical multistep synthesis of piperazinone is shown in Scheme 1.[8] Improved synthetic methods for 2-piperazinone intermediates could

lead to important applications, such as the production and use of peptide nucleic acids (PNAs).[9] This has the potential for rapid identification of PNA oligomers for use in therapeutics, diagnostics and gene characterization tools. Derivatives of 2-piperazinones are known to have therapeutic properties and generally act by controlling or inhibiting cell-adhesion.[10]

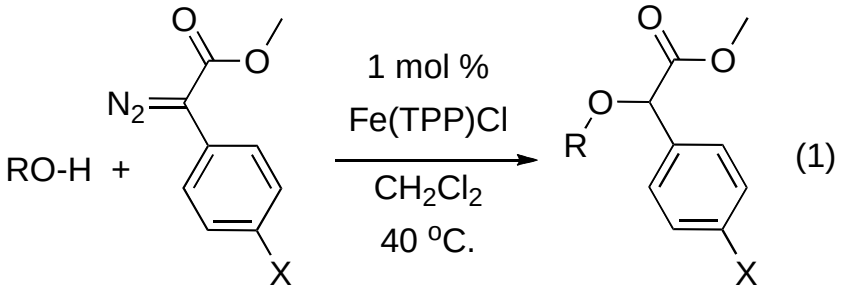


Scheme 1.

Results and Discussion

Substituted methyl 2-phenyldiazoacetates (MPDAs) were found to be useful carbene sources for O-H insertion reactions with alcohols when Fe(TPP)Cl was used as the catalyst (eq 1). However, when ethyl diazoacetate (EDA) was tried as the carbene source for O-H insertion reactions using Fe(TPP)Cl as a catalyst, only maleates and fumarates were formed. This is in contrast to analogous N-H insertions reactions where EDA was shown to be an excellent carbene source.[6] Treating an alcohol with 1-2 equiv of substituted methyl 2-phenyldiazoacetate in refluxing methylene chloride using 1.0 mol% catalyst efficiently produced O-H insertion products. The yields obtained were as high as 88% (Table 1). No aromatic C-H insertion products[7] were detected by GC when phenol was used as the substrate. These products were readily characterized by mass spectrometry and ^{1}H and ^{13}C NMR spectroscopy. For example, methyl 2-phenoxy-2-(*p*-tolyl)acetate, 1a, produced from

phenol and methyl 2-(*p*-tolyl)-diazoacetate, gave a characteristic methine singlet ^{1}H NMR signal at 5.63 ppm while the methine carbon exhibited a ^{13}C NMR signal at 78.5 ppm. Both the ^{1}H and ^{13}C NMR spectra were found to match literature values.[11] This reaction was extended to aliphatic alcohols. Treatment of ethanol with *p*-MeO-MPDA in refluxing methylene chloride and 1.0 mol% Fe(TPP)Cl produced methyl 2-ethoxy-2-(*p*-methoxy-phenyl)acetate, 3b. This product was purified by elution through a silica gel column using 20:1 hexanes/ethyl acetate, resulting in an isolated yield of 74%. The product exhibited a ^{1}H NMR singlet for the new methine proton at 4.84 ppm while the two α-methylene hydrogens gave diastereotropic multiplets at 3.53 ppm.



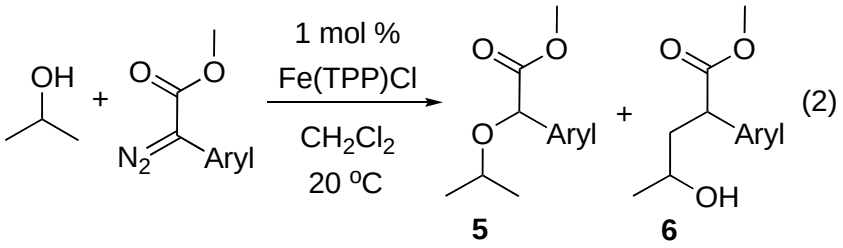
R = Ph (**1**), cyclohexyl (**2**), Et (**3**), *n*-Pr (**4**), *i*-Pr (**5**) X = Me (**a**), OMe (**b**)

Isopropanol was found to react with p-MeO-MPDA to give a mixture of O-H insertion product **5b** and C-H insertion product **6b** in a ratio of 6:1, respectively (eq 2). The O-H insertion product **5b** exhibited characteristic NMR signals for the two types of methine protons. The isopropyl methine hydrogen appeared at 3.67 (1H, m) and a singlet at 4.95 ppm was assigned to the methine hydrogen alpha to the ester group. The diastereotropic nature

Table 1. Summary of catalytic reactions of *para*-substituted methyl 2-phenyldiazoacetate compounds with various alcohols[a]

alcohol	MPDA *p*-X	product	% yield[b]
phenol	CH_3-	**1a**	80
phenol	CH_3O-	**1b**	83
cyclohexanol	CH_3-	**2a**	86
cyclohexanol	CH_3O-	**2b**	88
ethanol	CH_3O-	**3b**	74
n-propanol	CH_3-	**4a**	71
2-propanol	CH_3O-	**5b**	56[c]

[a] Conditions: CH_2Cl_2 used as solvent, 40 °C for 8 hours, alcohol:diazo reagent ratio of 2:1, 1.0 mol% Fe(TPP)Cl catalyst. [b] Isolated yield. [c] Methyl C-H insertion product also detected by NMR.



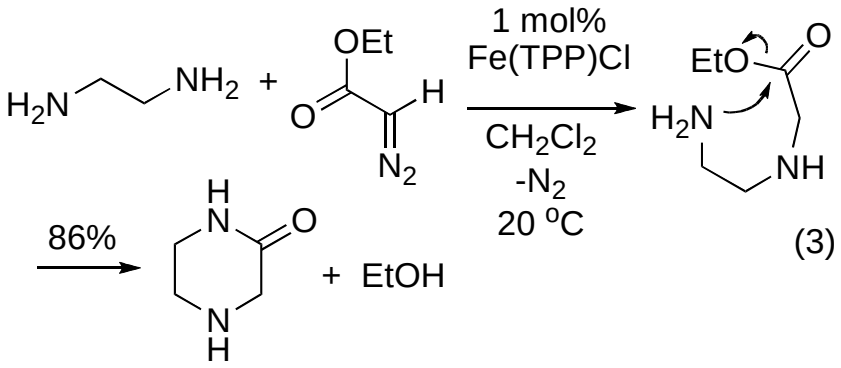
(2)

of the isopropyl methyl groups is manifested by distinct doublets at 1.24 and 1.19 ppm, each integrating as three protons. Although it was not possible to isolate a pure sample of the C-H insertion product, the presence of doublets for the terminal CH_3 proton signal at 0.96 ppm (3H) and multiplets at 3.65 (2H) and 4.03 ppm (1H) for the methylene and methine protons, respectively, suggested that an insertion into the terminal C-H group occurred to give **6b**. These results illustrate that Fe(TPP)Cl is an effective catalyst for O-H insertion reactions and is more efficient than typical rhodium catalysts that produce lower O-H insertion yields under similar conditions.[12]

The mechanism for catalytic O-H insertion is likely to be similar to that proposed for the analogous N-H process.[6] This involves reaction of the iron porphyrin with the diazo reagent to form a transient carbene complex. Subsequent attack of the alcohol oxygen at the electrophilic carbene carbene ligand produces the insertion product. The need to heat the O-H insertion reactions is consistent with the lower nucleophilicity of alcohols relative to amines. In contrast, N-H insertion reactions catalyzed by Fe(TPP)Cl typically occurred within minutes at ambient temperature.

Tandem Insertion/Cyclization Reactions

Ethylenediamine reacted rapidly with ethyl diazoacetate in the presence of 1.0 mol% catalyst at ambient temperature to give 2-piperazinone in yields above 80% (eq 3, Table 2). This was confirmed by the absence of the ^{1}H NMR methine signal for EDA that appears at 4.72 ppm. The absence of ^{1}H NMR signals around 4.2 (q) and 1.2 (t)



(3)

indicated that the ethyl group of the ester had been lost. The highly polar 2-piperazinone was found to be soluble in water and insoluble in organic solvents and could not therefore be purified by silica gel chromatography. However, it was extracted from methylene chloride with a 1:1 mixture of methanol and water to give a 90%-pure product. This product

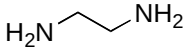
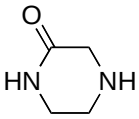
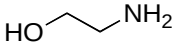
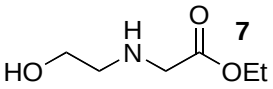
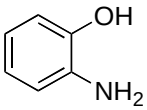
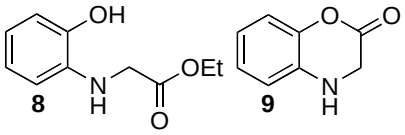
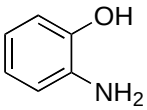
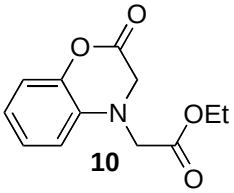
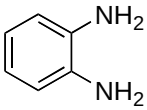
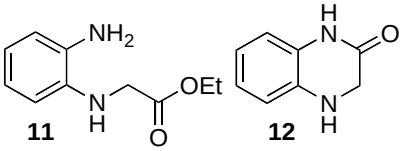
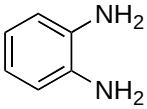
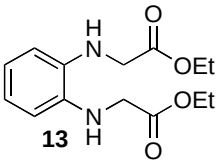
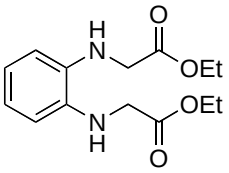
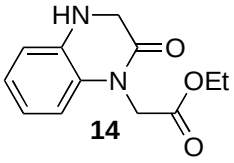
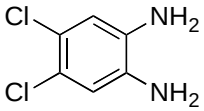
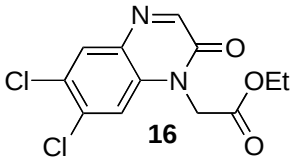
exhibited a proton NMR singlet at 3.53 ppm for the two hydrogens at C3, a triplet of doublets at 3.38 ppm for the two protons at C6, and a triplet at 3.04 for the two hydrogens at C5. The amide N-H proton was detected as a broad peak at 6.47 ppm while the amine proton was not observed. These NMR data compare well with spectra of other 2-piperazinone nucleoside analogs substituted at the amine nitrogen.[13]

In contrast, ethanolamine reacted with one equiv of EDA to give a single product, **7**, that resulted from an insertion at the amino group. Unlike the reaction of ethylenediamine with EDA, this product did not undergo an ensuing cyclization, even after reaction times greater than one day and elevated temperature or with added acid. This linear product was purified by flash column chromatography using 10:1 methylene chloride/methanol as the eluent. No product derived from O-H insertion was observed. This is consistent with earlier observations that have clearly shown that N-H insertion reactions are more facile than O-H insertions.[6] Slow addition of 2 equiv of EDA to ethanolamine resulted only in maleates and fumarates as determined by GC/MS analysis.

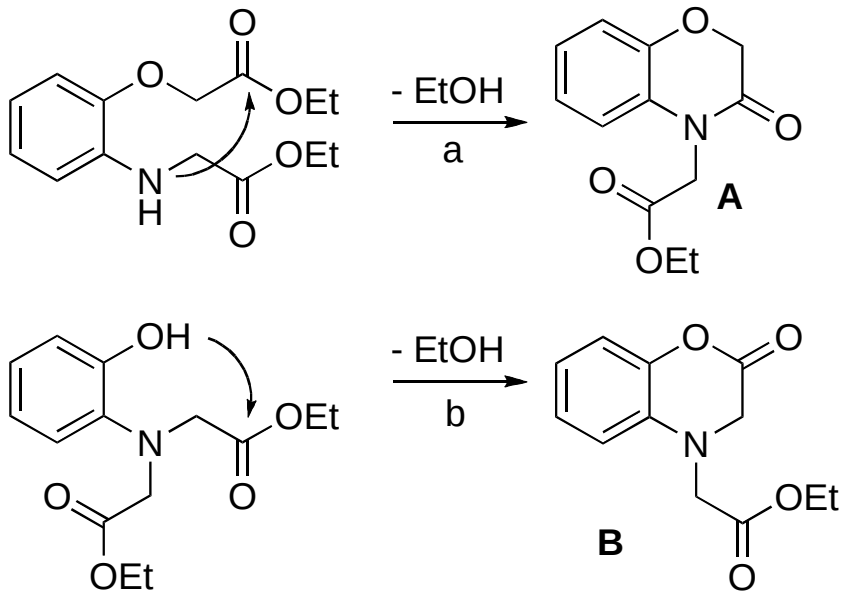
Geometrically constrained 1,2-aminoalcohols and phenylene diamines were found to undergo partial cyclization after N-H insertion with 1 equiv EDA (Table 2). For example, the reaction of 2-aminophenol with one equiv of EDA afforded a mixture of products. The major species was a N-H insertion product **8** which exhibited a characteristic glycyl methylene proton singlet at 3.91 ppm [6a] GC-MS analysis revealed the formation of about 10% of another minor product. Although the minor product could not be isolated, its molecular ion peak of 150 *m/z* reflected loss of an ethoxy group and was consistent with the cyclization product **9**. When 2 equiv of EDA were added slowly to 2-aminophenol, three different insertion products were detected by GC-MS along with maleates and fumarates.

However, when the mixture was separated by SiO_2 chromatography, cyclized product **10** was obtained in 42% yield. Two isomers are possible for the benzomorpholinone product as shown in Scheme 2. Pathway (a) involves a double OH/NH insertion intermediate and produces 3-keto product **A** via amine attack at the O-bound ester. Given the lower propensity for carbene insertion at the OH position, this is the less likely pathway. Alternatively, 2-keto isomer **B** arises from phenol attack (pathway b) at one of the N-bound diesters. The structure of compound **10** was initially assigned by a comparison of its ^{13}C NMR spectrum with those of two similar compounds, 2*H*-1,4-benzoxazin-3(4H)-one (benzomorpholin-3-one),[14] and 3,4-dihydro-1,4-benzoxazin-2-one (benzomorpholin-2-one).[15] The methylene carbon (C2) on the aliphatic ring appears at 67 ppm for the 3-keto isomer, while the methylene carbon (C3) on the aliphatic ring appears at 45 ppm for the 2-keto analog. In compound **10**, the methylene carbon on the aliphatic ring appears at 51 ppm. This value is more consistent with a 2-keto product, **B**. The structure of **10** was confirmed spectroscopically through 2D $^{13}C–^{1}H$ HSQC, ^{13}C-^{1}H HMBC, and $^{15}N–^{1}H$ HMBC experiments. The ^{13}C-^{1}H HSQC showed no direct C-H couplings to the two carbonyl peaks (169.2 and 164.3 ppm) nor to the two aromatic carbons (141.7 and 133.4 ppm). The ^{13}C-^{1}H HMBC spectrum exhibited cross peaks between the carbonyl signal at 169.2 ppm and the methylene resonances at 4.00 (s, 2H) and 4.24 (q, 2H) ppm. These 2- and 3-bond couplings definitively allow the assignment of these signals to the carbonyl and methylene units of the ester side chain. In addition, an HMBC cross peak between the ring carbonyl (164.3 ppm) and the CH_2 signal at 4.13 ppm (s, 2H) definitively assigned this proton resonance to the methylene unit in the morpholinone ring. Both methylene singlets (4.01 and 4.13 ppm) also showed cross peaks with the quaternary aromatic carbon at 133.4 ppm. These 3-bond

Table 2. Summary of products from 1,2-disubsituted substrates.

Substrate	Eq. EDA	Product	% yield[a]
	1		86
	1	 **7**	62
	1	 **8** **9**	71 (**8**)
	2	 **10**	42
	1	 **11** **12**	40 (**12**)
	2	 **13**	68
	0	 **14**	88[b]
	2	 **16**	44[c]

[a]Typical conditions: 0.500 mmol substrate, 1.0 mol% Fe(TPP)Cl, 5.0 mL CH_2Cl_2, 22 ^oC, stirring for 10-30 min. [b]Heating substrate neat for 12 h at 60 ^oC under N_2. [c]See experimental section for details.



Scheme 2.

correlations can only occur with the ring junction carbon at C5 in the 2-keto structure. It is not possible for both methylene singlets to correlate to the same quaternary aromatic carbon in the 3-keto isomer. Further support for the 2-keto isomer was derived from the ^{15}N–^{1}H HMBC data in which the ^{15}N resonance (243 ppm) showed 2-bond correlations to both methylene singlets at 4.13 and 4.01 ppm. This correlation is only possible if both these units are adjacent to the nitrogen. The observed product **10** is most likely formed through a double insertion at the amine nitrogen followed by an ensuing cyclization (Scheme 1).

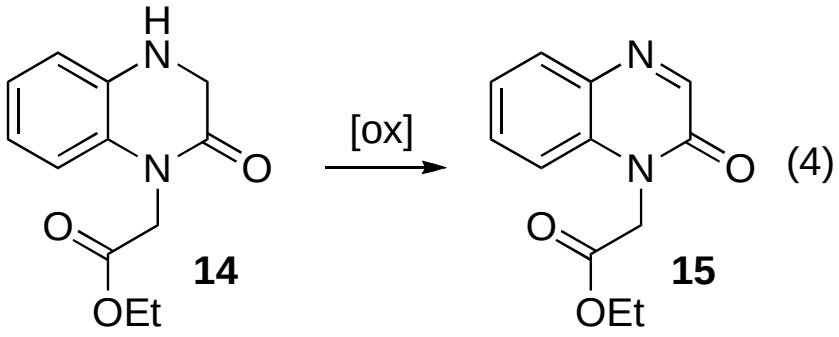
Treatment of 1,2-phenylenediamine with one equiv of EDA in methylene chloride and 1.0 mol% catalyst afforded three products as detected by GC-MS. The two major products had molecular ion peaks of 191 m/z, **11**, and 148 m/z, **12**, in about a 3:1 ratio. The third product was a bisinsertion product, **13**, observed in small amounts. The main product

exhibited a molecular ion peak at 191 m/z suggesting that it was a product in which one of its amino groups has undergone a single insertion of EDA. However, separation by silica gel chromatography using hexanes/ethyl acetate (1:1) as the eluent resulted in the isolation of only product **12**. The ^{1}H NMR spectrum of the product showed no ^{1}H NMR peaks around 4.2 (q) or 1.2 (t), indicating that the ethyl unit of the ester group had been lost, most likely following a cyclization pathway similar to that involved in the reaction of ethylenediamine and EDA (eq 3). This suggested that subsequent cyclization occurred on the column.

Treatment of 1,2-phenylenediamine with 2 equiv of EDA resulted in clean formation of product **13** in which both the amine groups had undergone N-H insertions. This double insertion product gave a four-proton ^{1}H NMR doublet at 3.90 ppm for the new methylene hydrogens of the two *N*-acetate groups. Heating solid **13** under nitrogen at 60 °C for 12 h produced bicyclic compound **14** in an 88% isolated yield in analytically pure form. The increased complexity in the ^{1}H NMR spectrum relative to that of the diester **13** indicated a reduction of symmetry in the product. Moreover, the loss of an ethoxy group indicated that the molecule had undergone a cyclization.

Over time, compound **14** converted to a new product **15** in solution (eq 4). The new aromatic protons of **15** shifted strongly downfield relative to **14** by an average of 0.7 ppm to 7.93 (1H, dd), 7.58 (1H, td), 7.39 (1H, td), and 7.12 (1H, d). Proton signals at 4.26 (2H, q) and 1.28 (3H, t) indicated that the ethyl ester group was retained. New downfield signals at 8.36 (1H, s) and 5.03 (2H, s) were observed. These NMR data are consistent with quinoxalin-3-one structure **15** in which the imine proton is assigned to the downfield resonance at 8.36 ppm and the methylene protons are assigned to the 5.03-ppm singlet. The quinoxalinone product was prepared independently by treatment of **14** with DDQ. Heating

this mixture in benzene for 30 minutes at 60 °C resulted in clean oxidation to produce **15** in a 79% isolated yield.



In general, the addition of one equiv of EDA to a 1,2-diamine or aminoalcohol substrate led to mixtures that typically contained an N-H insertion product and a subsequent partial cyclization to a piperazinone or morpholinone structure. Under various conditions, it was not possible to cleanly cyclize all of the initial N-H insertion product. However, using 2 equiv of EDA allowed the isolation of a clean product as illustrated by the preparation of compounds **10** and **14**. As further demonstration of the utility of this approach, 1,2-diamino-4,5-dichlorobenzene was treated with 2 equiv of EDA and 1 mol% Fe(TPP)Cl. The intermediate N,N' bisinsertion product was subsequently heated under N_2 at 60 ^{o}C for 12 h to produce cyclized, dehyrogenated imine compound **16** in 44% yield.

Conclusions

Fe(TPP)Cl is an effective catalyst for the O-H insertion reactions of alcohols when substituted MPDAs are used as carbene sources. Aromatic and normal aliphatic alcohols gave O-H insertion as the only product. Treatment of isopropanol with p-MeO-MPDA and Fe(TPP)Cl yielded O-H insertion as the major product and a minor C-H insertion at the

terminal position. This catalyst was also found to be very efficient in the syntheses of 2-piperazinone and 2-morpholinone through a tandem N-H insertion/cyclization process using EDA as the carbene source. The tandem N-H insertion/cyclization process provides an easy one-pot procedure for the syntheses of novel piperazinones, and their substituted analogues.

Experimental Section

Fe(TPP)Cl was obtained from Aldrich and used without further purification. Substituted methyl 2-phenyldiazoacetates were prepared as outlined in the literature.[11] All reactions were performed under an atmosphere of nitrogen. Proton NMR and ^{13}C NMR spectra were run in $CDCl_3$ and recorded on a Varian VXR 300 or a Bruker DRX400 spectrometer. Two dimensional NMR experiments were run on a Bruker 700 MHz Avance II 700 spectrometer with a Bruker Z-gradient inverse TXI $^{1}H/^{13}C/^{15}N$ 5mm cryoprobe at 25 ^{o}C. ^{1}H NMR peak positions were referenced against residual proton resonances of $CDCl_3$ (δ, 7.27). Gas chromatographic analyses were performed on a HP 5890 series II or a Finnigan GC-MS instrument. IR data was collected on a Bruker IFS-66V FT-IR using samples that were prepared as a thin film on NaCl plates. Elemental analyses were performed on a Perkin-Elmer Model 2400 CHN/S elemental analyzer by Iowa State University Chemical Instrument Services.

General procedure for O-H insertion reactions. The alcohol (0.32-0.64 mmol) was accurately weighed, placed in a 50-mL round bottom flask containing a stir bar and dissolved in 5.0 mL of methylene chloride. A condenser, fitted with a rubber septum, was attached to the round bottom flask and the contents thoroughly flushed with nitrogen. The catalyst (1.0 mol%) and 1.0 equiv diazo reagent were added and the contents bubbled with

dry nitrogen for 5 min. The mixture was then heated for 8 h at reflux while stirring. The products were purified by eluting on a flash silica gel column (4 cm diameter, 30 cm height, hexane/ethyl acetate; 20:1).

General procedure for N-H insertion reactions. About 0.500 mmol of the amine were accurately weighed, placed in a 50-mL round bottom flask containing a stir bar and dissolved in 5.0 mL of methylene chloride. A condenser, fitted with a rubber septum, was attached to the round bottom flask and the contents thoroughly flushed with nitrogen. The catalyst (1.0 mol %) and the desired amount of the diazo reagent was then added over a period of forty minutes by syringe pump. When substituted MPDAs were used as the diazo reagent, the addition took place at the same time that the catalyst was added. The mixture was then stirred until the diazo reagent was consumed, as monitored by TLC or GC. The products were purified using a flash column as above.

Methyl 2-(p-tolyl)diazoacetate insertion with phenol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), phenol (30.0 mg, 0.320 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-phenoxy-2-(4-methylphenyl)acetate, **1a**, (66.2 mg, 0.257 mmol, 80% yield) was obtained. The proton NMR and ^{13}C NMR spectra matched literature values [11]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, 2H, J_H = 7.9, aryl-H), 7.29 (d, 2H, J_H = 7.9, aryl-H), 7.22 (d, 2H, J_H = 7.9, aryl-H), 6.97 (m, 3H, aryl-H), 5.63 (s, 1H, methine C-H), 3.75 (s, 3H, OCH_3), 2.37 (s, 3H, Ar-CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 170.6, 157.4, 139.0, 132.5, 129.6, 129.5, 127.1, 121.8, 115.5, 78.5, 52.6, 21.3. MS{EI}: 258 $[M]^+$.

Methyl 2-(p-methoxyphenyl)diazoacetate insertion with phenol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), phenol (30.0 mg, 0.320 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-phenoxy-2-(4-methoxyphenyl)acetate, **1b**, (72.2 mg, 0.265 mmol, 83% yield) was obtained. The proton NMR and ^{13}C NMR spectra matched literature values [11]. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, 2H, J_H = 8.4, aryl-H), 7.36 (d, 2H, J_H = 8.4, aryl-H), 6.95 (m, 5H, aryl-H), 5.61 (s, 1H, methine C-H), 3.82 (s, 3H, $ArOCH_3$), 3.75 (s, 3H, OCH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 170.7, 160.2, 157.3, 129.6, 128.6, 127.5, 121.8, 115.5, 114.3, 78.2, 55.4, 52.6. MS{EI}: 272 $[M]^+$.

Methyl 2-(p-tolyl)diazoacetate insertion with cyclohexanol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), cyclohexanol (48.0 mg, 0.480 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-cyclohexanoxy-2-(4-methylphenyl)acetate, **2a**, (72.2 mg, 0.276 mmol, 86% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, 2H, J_H = 8.0, aryl-H), 7.17 (d, 2H, J_H = 8.0, aryl-H), 5.03 (s, 1H, methine C-H), 3.71 (s, 3H, OCH_3), 3.34 (m, 1H, cyclo-methine C-H), 2.35 (s, 3H, $ArCH_3$), 1.99 (m, 1H), 1.88 (m, 1H), 1.74 (m, 2H), 1.53 (m, 1H) 1.41 (m, 2H), 1.23 (m, 3H). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 172.3, 138.3, 134.4, 129.3, 127.1, 78.0, 52.2, 32.3, 32.2, 25.7, 24.2, 21.2. MS{EI}: 262 $[M]^+$.

Methyl 2-(p-methoxyphenyl)diazoacetate insertion with cyclohexanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), cyclohexanol (48.0 mg, 0.480 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-cyclohexanoxy-2-(4-methoxyphenyl)acetate, **2b**, (78.3 mg, 0.282 mmol, 88% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, 2H, J_H = 8.4, aryl-H), 6.89 (d, 2H, J_H = 8.4, aryl-H), 5.00 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, OCH_3), 3.32 (m, 1H, cyclo-methine C-H), 1.99 (m, 1H), 1.87 (m, 1H), 1.73 (m, 2H), 1.53 (m, 1H) 1.39 (m, 2H), 1.22 (m, 3H). ^{13}C NMR (100.5, $CDCl_3$) δ: 172.3, 159.7, 129.5, 128.5, 114.0, 77.6, 55.3, 52.2, 32.3, 32.2, 25.7, 24.2. MS{EI}: 278 $[M]^+$. Anal. Calc. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.70; H, 7.40.

Methyl 2-(p-methoxyphenyl)diazoacetate insertion with ethanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl) diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), ethanol (29.4 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-ethoxy-2-(4-methoxyphenyl)acetate, **3b**, (53.0 mg, 0.237 mmol, 74% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, 2H, J_H = 8.8, aryl-H), 6.90 (d, 2H, J_H = 8.8, aryl-H), 4.84 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.72 (s, 3H, OCH_3), 3.53 (m, 2H, OCH_2), 1.27 (t, 3H, J_H = 8.8, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 170.3, 159.2, 128.8, 128.6, 114.1, 80.5, 65.1, 55.3, 52.3, 15.2. MS{EI}: 224 $[M]^+$.

Methyl 2-(p-tolyl)diazoacetate insertion with n-propanol. The general procedure was used with methyl 2-(*p*-tolyl)diazoacetate (60.8 mg, 0.320 mmol), (TPP)FeCl (2.20 mg, 1.0 mol%), *n*-propanol (39.7 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-propanoxy-2-(4-methoxyphenyl)acetate, **4a**, (50.4 mg, 0.227 mmol, 71% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, 2H, J_H = 8.0, aryl-H), 7.18 (d, 2H, J_H = 8.0, aryl-H), 4.85 (s, 1H, methine C-H), 3.71 (s, 3H, OCH_3), 3.48 (m, 1H, OCH_2), 3.40 (m, 1H, OCH_2), 2.35 (s, 3H, $ArCH_3$), 1.67 (m, 2H, CH_2), 0.94 (t, 3H, J_H = 7.6, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 171.7, 138.5, 133.8, 129.3, 127.2, 80.9, 71.5, 52.2, 22.8, 21.2, 10.5. MS{EI}: 222 $[M]^+$.

Methyl 2-(p-methoxyphenyl)diazoacetate insertion with isopropanol. The general procedure was used with methyl 2-(*p*-methoxyphenyl)diazoacetate (65.9 mg, 0.320 mmol), (TPP)FeCl (2.2 mg, 1.0 mol%), isopropanol (39.4 mg, 0.640 mmol) and 5.0 mL of methylene chloride. The mixture was heated at reflux for 8 h. The product was purified by eluting through a silica gel column using a 20:1 hexane/ethyl acetate mixture. The product methyl 2-isopropanoxy-2-(4-methoxyphenyl)acetate, **5b**, (42.6 mg, 0.179 mmol, 56% yield) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (d, 2H, J_H = 8.6, aryl-H), 6.89 (d, 2H, J_H = 8.6, aryl-H), 4.95 (s, 1H, methine C-H), 3.81 (s, 3H, $ArOCH_3$), 3.71 (s, 3H, OCH_3), 3.65 (m, 1H, OCH), 1.24 (d, 3H, J_H = 6.2, RCH_3), 1.19 (d, 3H, J_H = 6.2, RCH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 171.3, 159.4, 128.7, 115.6, 114.4, 78.2, 70.8, 55.5, 52.4, 22.4, 22.1. MS{EI}: 238 $[M]^+$.

EDA insertion with ethylenediamine. Ethylenediamine (30.0 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in

5.0 mL of methylene chloride. The mixture was flushed with nitrogen and ethyl diazoacetate (57.0 mg, 0.500 mmol), dissolved in 3.0 mL of methylene chloride, was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 10 minutes. The product was extracted using distilled water and dried under reduced pressure to obtain 2-piperazinone (43.1 mg, 0.431 mmol, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.47 (bs, 1H, NH), 3.53 (s, 2H, CH_2), 3.38 (td, 2H, J_H = 5.4, J_H = 2.4, CH_2), 3.01 (t, 2H, J_H = 5.4, CH_2). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 170.1, 49.9, 43.0, 42.3. MS{EI}: 100 $[M]^+$. Spectral results match reported values.[16]

EDA insertion with ethanolamine. Ethanolamine (30.0 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen after which ethyl diazoacetate (57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was done within 15 minutes. The product was purified by eluting through a silica gel column using a 10:1 methylene chloride/methanol mixture. The product N-(2-hydroxyethyl)glycine ethyl ester, **7**, (45.6 mg, 0.310 mmol, 62% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.21 (q, 2H, J_H = 7.2, CH_2), 3.63 (t, J_H = 5.1, 2H, CH_2), 3.44 (s, 2H, CH_2), 2.82 (t, J_H =5.1, 2H, CH_2), 2.14 (bs, 2H, OH, NH), 1.29 (t, J_H = 7.2, 3H, CH_2). ^{13}C NMR: (100.5 MHz, $CDCl_3$) δ: 172.5, 60.8, 60.7, 51.0, 50.3, 14.1. MS{EI}: 148 $[M+1]^+$. Spectral data matched literature values.[17]

EDA reaction with 2-aminophenol (1:1). 2-Aminophenol (54.2 mg, 0.500 mmol) and (TPP)FeCl (3.5 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen after which ethyl

diazoacetate (57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 20 minutes. The products were purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product N-(2-hydroxyphenyl)glycine ethyl ester, **8**, (69.3 mg, 0.355 mmol, 71% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.57-6.86 (m, 4H, aryl-H) 4.27 (q, J_H = 7.2, 2H, CH_2), 3.95 (s, 2H, CH_2), 1.31 (t, J_H = 7.2, 3H, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 172.4, 153.6, 127.9, 126.4, 120.4, 116.0, 61.7, 56.4, 14.5. MS{EI}: 195 $[M]^+$. Anal. Calc. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.02; H, 6.60; N, 6.96.

EDA reaction with 2-aminophenol (2:1). 2-Aminophenol (54.2 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen after which ethyl diazoacetate (114 mg, 1.00 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was finished within 30 minutes. The product was purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product, **10**, ethyl (2-oxo-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl) acetate (49.4 mg, 0.210 mmol, 42% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.07 (m, 2H, aryl-H), 6.89 (td, 1H, J_H = 7.8, J_H = 1.5, aryl-H), 6.63 (dd, 1H, J_H = 7.8, J_H = 1.5, aryl-H), 4.24 (q, 2H, J_H = 7.2, CH_2), 4.13 (s, 2H, CH_2), 4.01 (s, 2H, CH_2), 1.59 (bs, 0.4H, H_2O), 1.29 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 169.2, 164.3, 141.7, 133.4, 125.2, 120.5, 117.2, 112.5, 61.4, 51.1, 50.8, 14.2. MS{EI}: 236 $[M+1]^+$. Anal. Calc. for $C_{12}H_{13}NO_4$•0.2 H_2O: C, 60.35; H, 5.66; N, 5.86. Found: C, 60.56; H, 5.40; N, 6.02.

EDA insertion on 1,2 phenylenediamine (1:1). 1,2-Phenylenediamine (54.4 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen after which ethyl diazoacetate (57.0 mg, 0.500 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was complete within 20 minutes. The products were purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product, 3,4-dihydroquinoxalin-2(1H)-one, **12**, (29.5 mg, 0.199 mmol, 40% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.84 (bs, 1H, NH), 6.90 (m, 1H, aryl-H), 6.77 (m, 2H, aryl-H), 6.68 (d, 1H, J_H = 7.8, aryl-H), 4.01 (s, 2H, CH_2), 3.88 (bs, 1H, NH). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 167.1, 133.6, 125.4, 123.9, 119.5, 115.7, 114.0, 47.1. MS{EI}: 148 $[M]^+$. IR(NaCl): $\nu_{C=O}$ 1680 cm^{-1}. Spectral results match reported values.[18]

EDA insertion on 1,2 phenylenediamine (2:1). 1,2-Phenylenediamine (54.3 mg, 0.500 mmol) and (TPP)FeCl (3.50 mg, 1.0 mol%) were placed in a 50-mL round bottom flask and dissolved in 5.0 mL of methylene chloride. The mixture was flushed with nitrogen after which ethyl diazoacetate (114 mg, 1.00 mmol) dissolved in 3.0 mL of methylene chloride was added dropwise using a syringe pump while continuously stirring the flask contents. The reaction was finished within 20 minutes. The product was purified by eluting through a silica gel column using a 1:1 hexane/ethyl acetate mixture. The product N,N-bis(2-aminophenyl)glycine ethyl ester, **13**, (95.2 mg, 0.340 mmol, 68% yield) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.82 (m, 2H, aryl-H), 6.60 (m, 2H, aryl-H), 4.26 (q, J_H = 7.2, 4H, CH_2), 4.09 (bt, 2H, J_H = 6.0, NH), 3.90 (d, 4H, J_H = 6.0, CH_2), 1.31 (t, 6H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 171.3, 136.5, 120.0, 112.6, 61.2, 46.5, 14.2. MS{EI}: 280

$[M]^+$. IR(NaCl): $\nu_{C=O}$ 1741 cm^{-1}. Anal. Calc. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.04; H, 6.91; N, 9.98.

Cyclization of Diester Compound 13. Upon heating at 60 °C, under nitrogen for twelve hours, solid compound **13** (70.1 mg, 0.250 mmol) cyclized to product **14**, ethyl (2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetate and was obtained in 88% yield (51.4 mg, 0.220 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.94 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 6.83 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H) 6.73 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 6.70 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 4.66 (s, 2H, CH_2), 4.25 (q, 2H, J_H = 7.2, CH_2), 4.01 (s, 2H, CH_2), 3.96 (bs, 1H, N-H), 1.29 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 168.2, 166.1, 135.5, 128.1, 123.9, 119.9, 114.5, 114.4, 61.6, 47.5, 43.7, 14.1. MS{EI}: 234 $[M]^+$. IR (NaCl): $\nu_{C=O}$ 1742, 1675 cm^{-1}. Anal. Calc. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.50; H, 5.95; N, 11.63.

Oxidation of 14 with DDQ. Ethyl (2-oxo-3,4-dihydroquinoxalin-1(2H)-yl) acetate (50.2 mg, 0.215 mmol) and 2,3-dichloro-5,6-dicyano-p-benzoquinone (50.0 mg, 0.218 mmol) were placed in a 50-mL round bottom flask and dissolved in 10.0 mL of benzene. The flask was then stirred and heated at 60 ºC. Complete conversion of the starting material was seen after 30 minutes. The grayish precipitate that formed ($DDQH_2$) was removed by vacuum filtration. The desired product **15**, ethyl (2-oxoquinoxalin-1(2H)-yl) acetate (39.3 mg, 0.169 mmol) was obtained in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H, CH), 7.93 (dd, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.58 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.39 (td, 1H, J_H = 8.0, J_H = 1.2, aryl-H), 7.12 (d, 1H, J_H = 8.0, aryl-H), 5.03 (s, 2H, CH_2), 4.26 (q, 2H, J_H = 7.2, CH_2), 1.28 (t, 3H, J_H = 7.2, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$) δ: 166.8, 154.5, 149.9, 133.4, 132.3, 131.2, 130.8, 124.1, 113.2, 62.2, 43.1, 14.1. MS{EI}: 232 $[M]^+$.

IR(NaCl): $\nu_{C=O}$ 1737, 1664 cm^{-1}. Anal. Calc. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.68; H, 5.08; N, 11.72.

EDA insertion on 4,5-dichloro-1,2-phenylenediamine (2:1) and cyclization. Using Schlenk techniques under N_2, Fe(TPP)Cl (1 mol%) and 4,5-dichloro-1,2-phenylenediamine (305 mg, 1.78 mmol) were transferred to a 50-mL flask and 15 mL of dry, deoxygenated CH_2Cl_2 was added via syringe. A 2.09 M solution of EDA (1.79 mL, 427 mg, 3.74 mmol) in dry, air-free CH_2Cl_2 was added to the flask dropwise over an hour. Immediate N_2 evolution was noticed as EDA was added. The reaction was stirred for 16 h, producing three products as detected by GC. The solution was subsequently concentrated under vacuum and purified on a silica gel column. Unreacted EDA was removed with 10:1 hexanes/EtOAc, and the products eluted with 1:1. The solid double insertion product was dried in vacuo overnight and and converted to the pyrazinone form by heating N_2 at 60^o C for approximately 12 h. The resulting brown solid was suspended in CH_2Cl_2, filtered, and washed with CH_2Cl_2. Recrystallization from ethyl acetate resulting in a white hydrate, **16**, containing one equiv of water (228 mg, 44.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (s, 1H, aryl-H), 8.00 (s, 1H, aryl-H), 7.20 (s, 1H, N=C-H), 4.95 (s, 2H, N-CH_2), 4.29 (q, 2H, J_H = 8.0, OCH_2CH_3), 1.32 (t, 3H, J_H = 8.0, OCH_2CH_3), 1.58 (s, 2H, H_2O). MS{EI}: 301 $[M]^+$. Anal. Calc. for $C_{12}H_{10}N_2O_3Cl_2 \cdot H_2O$: C, 45.16; H, 3.79; N, 8.78. Found: C, 44.98; H, 2.91; N, 8.59.

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GENERAL CONCLUSIONS

This dissertation focuses on original research involving projects in both heterogeneous and homogeneous catalysis. The heterogeneous catalysis project involved studying *bulk* gold powder as a catalyst in oxidation reactions. One goal of the heterogeneous studies was to investigate molecules that adsorb on a metal surface and examine the subsequent reactions. An additional objective was to assess which organometallic reaction principles for homogeneous complexes would be useful guides in predicting and explaining the reactions of molecules adsorbed on the gold surface. Although previous work with bulk gold as the catalyst in the reactions of isocyanides and amines utilized molecular oxygen, it was unknown if other oxidants could be used in these reactions. Since amine N-oxides were previously studied in oxidizing metal carbonyls, they were investigated as alternative oxidants in reactions with isocyanides.

The gold catalyzed reactions of isocyanides with amines and amine N-oxides produced ureas. The rates for these reactions were found to generally increase as the concentration of the amine N-oxide was increased. In addition, qualitative rates were negatively dependent on the amine concentration. Likewise, it was also found that amine N-oxides with a higher basicity, as reflected by the pKa's of their conjugate acids, led to an increased rate of reaction. Mechanistic studies suggest that the first step involves a rate-limiting nucleophilic amine N-oxide attack on the isocyanide to form an isocyanate, which then reacts with the amine. These results are consistent with the reactions of carbonyl ligands in metal complexes upon treatment with amine N-oxides that result in a carbon dioxide product. However this proposed mechanism is in contrast to the reactions that used

O_2 as the oxidant. The oxygen-based reactions were found to be first order in the amine concentration and proposed to proceed through a diaminocarbene intermediate.

When amine N-oxides were studied in oxidative dehydrogenation reactions of amines, the same imine products were observed that were found when oxygen was used as the oxidant. This was true for each of the structurally very different dialkyl secondary, cyclic, and primary amines. Rate studies revealed that the oxidative dehydrogenation reaction of dibenzylamine was faster when NMMO was used as the oxidant, as opposed to O_2. Additional rate studies of the same reaction found that an increase in the basicity of the amine N-oxide led to faster rates. Unlike dioxygen, amine N-oxides were also found to be suitable reagents for the oxidation of benzyl alcohol to benzaldehyde. The reaction was substantially faster with NMMO, as benzaldehyde was present in a 52% yield after 48 h, while the product yield was only 7% with O_2 over the same time period.

A new green route to lactams with a high atom economy was discovered. This process avoids corrosive acids and does not generate undesired byproducts. Amidine products from the oxidative dehydrogenation reaction of cyclic amines underwent hydrolysis when treated with Aerosil and water to produce industrially important lactams. These lactams could be prepared in a one pot synthesis by treating 5-, 6-, and 7-membered cyclic amines with gold, Aerosil, water, and O_2. Other advantages are that the gold and Aerosil catalysts can readily be separated from the reaction mixture, after which the gold could be cleaned and reused in multiple reactions, without a significant loss of activity.

Iron metalloporphyrins were used as homogeneous catalysts in a one-pot synthesis of morpholinones, piperazinones, and related derivatives. These heterocyclic products form by an N-H insertion and subsequent cyclization reaction of diamines or aminoalcohols with

carbenes generated by an iron(III) tetraphenylporphyrin chloride catalyst. Typically, these types of products require multi-step syntheses. However this one-pot system, which can be run at room temperature, also utilizes commercially available reactants, solvents, and catalyst.

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