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Mechanism of Gold(I)-Catalyzed Rearrangements of Acetylenic Amine-*N*-Oxides: Computational Investigations Lead to a New Mechanism Confirmed by Experiment

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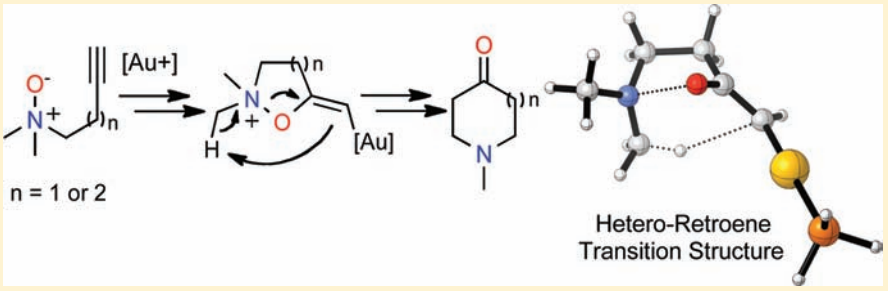
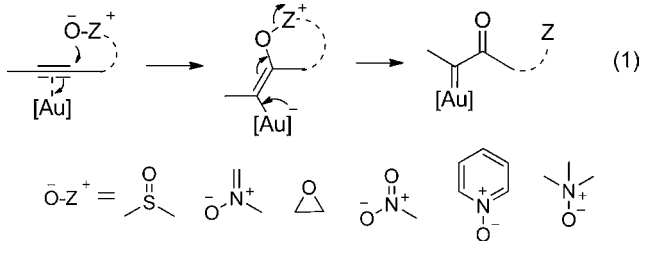
Supporting Information



ABSTRACT: Quantum mechanical studies of the mechanism of gold-catalyzed rearrangements of acetylenic amine-*N*-oxides to piperidinones or azepanones have revealed a new mechanism involving a concerted heteroretroene reaction, formally a 1,5 hydrogen shift from the *N*-alkyl groups to the vinyl position of a gold-coordinated methyleneisoxazolidinium or methyleneoxazinanium. Density functional calculations (B3LYP, B3LYP-D3) on the heteroretroene mechanism reproduce experimental regioselectivities and provide an explanation as to why the hydrogen is transferred from the smaller amine substituent. In support of the proposed mechanism, new experimental investigations show that the hydrogen shift is concerted and that gold carbenes are not involved as reaction intermediates.

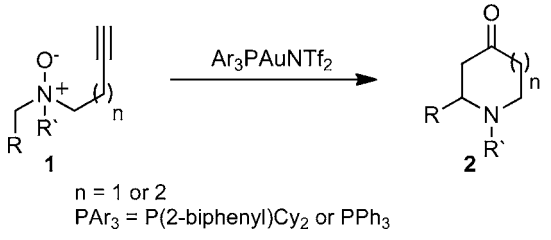
INTRODUCTION

Cationic gold catalysts activate π bonds for reactions with a range of nucleophiles, leading to sigmatropic rearrangements, migrations, and cycloisomerizations.[1] A particularly important class of nucleophiles is an oxidant that possesses a nucleophilic oxygen and can formally deliver the oxygen atom during the reaction, and this type of gold-catalyzed alkyne oxidation has been proposed to generate a reactive α-oxo gold carbene intermediate, which would undergo an array of versatile transformations



(eq 1).[2] Early studies in this area use tethered oxidants such as sulfoxide,[3] nitrone,[4] epoxide,[5] nitro,[6] and amine *N*-oxide,[7] and recently one of us has used pyridine/quinoline *N*-oxides as external oxidants to achieve intermolecular alkyne oxidation.[8] While α-oxo gold carbenes have been invoked as reactive intermediates in many of these studies, studies using external arylsulfoxides[9] argue against such intermediacy. Here we present computational and experimental studies to suggest that gold carbene intermediates are not involved in two intramolecular cases; moreover, we disclose the first example of a gold-catalyzed reaction involving a heteroretroene reaction.

One of our groups reported the gold-catalyzed annulation to form piperidin-4-ones or azepan-4-ones (eq 2).[7] These reactions



were hypothesized to proceed via the mechanism in Scheme 1. The amine oxides, **1**, are prepared by reactions of amines with butynyl or pentynyl tosylates followed by oxidation with *m*CPBA. Coordination of **1** with gold(I) catalyst is proposed to form **3**. Nucleophilic attack on the gold-activated alkyne, **3**, forms **4**.

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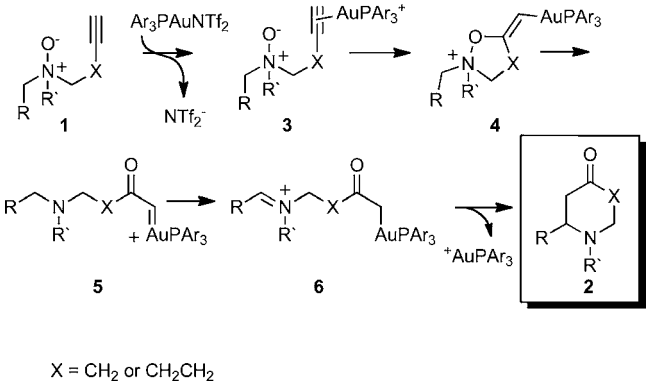
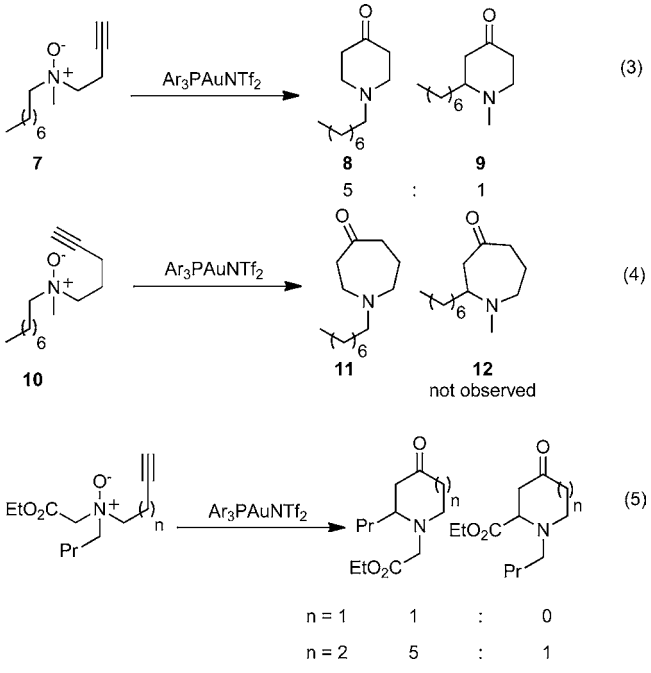
Scheme 1. Proposed Mechanism[7] for the Rearrangements of Acetylenic Amine-*N*-oxides to Piperidinones and Azepanones[a]



[a]When n = 1, piperidinones are formed, and when n = 2, azepanones are formed.

Intermediate **4** was thought to ring-open to form a gold carbenoid intermediate, **5**. This intermediate undergoes a 1,6-hydride shift or 1,7-hydride shift to form the iminium intermediate **6**, which leads to the product, **2**. While the proposed mechanism accounts for the formation of the major product, it fails to explain the selective hydride migration from one of the *N*-alkyl substituents.

That is, when the amine oxide has two different substituents, the hydrogen shift occurs selectively from the smaller group. The transformation shown in eq 3[7a] yielded a 5:1 ratio of products (**8**:**9**). The longer chain substrate, **10**, in eq 4,[7b] yielded a single product, **11**. Acidic hydrogens α to an ester group appear



to migrate either less effectively (n = 2) or not at all (n = 1) (eq 5).[7] We now present computational evidence for a different mechanism that accounts for the selection observed in these reactions. A novel heteroretroene reaction is identified.

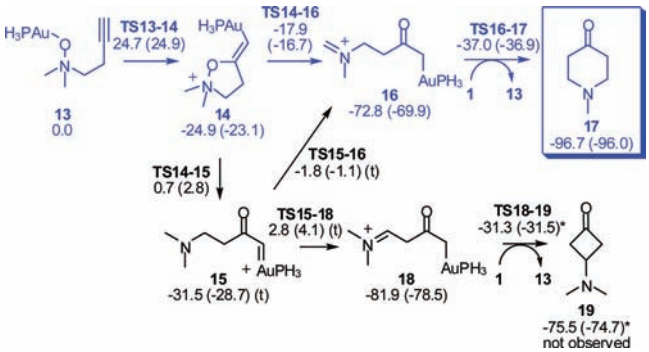
■ COMPUTATIONAL METHODS

Calculations were performed with Gaussian09[10] with a hybrid density functional (B3LYP and B3LYP-D3[11]) with LANL2DZ and 6-31G(d) basis sets for gold and for all other atoms, respectively. Structures were optimized with the CPCM model for dichloromethane (DCM) solvent. The gold catalyst ligand, PPh_3 or P(2-biphenyl)Cy_2, was modeled by PH_3. The coordination of the gold to either the *N*-oxide or alkyne as well as the *syn* addition to the alkyne were additionally modeled with PPh_3 and gave comparable results to that of the PH_3 ligand. Modeling PPh_3 with PH_3 is very common[12] because it gives good structures and approximates reaction barriers.[12c,13] B3LYP has recently been shown to give reasonable energy and geometry predictions for homogeneous gold catalysis.[14]

■ RESULTS AND DISCUSSION

Two different mechanisms for the conversion of **13** to **17** were investigated; the original proposal is shown in black and the lowest energy path described here is shown in blue in Scheme 2.

Scheme 2. B3LYP/6-31G(d)/CPCM(DCM) (B3LYP-D3) Energetics for the Conversion of the Gold-Coordinated *N*-Oxide, 13, to Cyclic Ketones 17 and 19[a]



[a]Compound **19** is not observed experimentally. (t) indicates the species is a ground-state triplet. *gas phase optimization with a single point solvation correction.

The cationic gold catalyst preferentially coordinates to the *N*-oxide to give **13**. The alkynyl-gold complex, **20**, is 15.6 kcal/mol higher in energy than **13** (Scheme 3). Calculations with PPh_3 as the gold ligand predict that coordination of gold to the *N*-oxide is favored by 15.4 kcal/mol over coordination to the alkyne. The *syn* addition to the alkyne from **13** has a barrier of 24.7 kcal/mol (**TS13−14**). The reaction is exothermic by 24.9 kcal/mol and gives intermediate **14**. *Anti* addition has been established for a variety of nucleophilic additions to alkynes;[15] however, here the *N*-oxide strongly coordinates to the cationic gold, and no transition structure for the *anti* addition could be located (Scheme 3).[16]

If the *N*-oxide were protonated by *m*-chlorobenzoic acid (*m*-CBA), the gold cation would be less likely to coordinate to the OH group. However, calculations indicate that proton transfer from *m*-CBA to the *N*-oxide, **1**, is endothermic by 7.3 kcal/mol in DCM.

Along the proposed mechanistic path, the ring opening of **14** has a barrier of 25.6 kcal/mol and leads to a triplet carbenoid, **15**. This triplet acyl carbenoid is stabilized by conjugation with the carbonyl, while the singlet (5.9 kcal/mol higher in energy) is less stabilized.[17] α-Carbonyl carbenes are ground state triplets and adopt a planar geometry.[18] Alkyl gold carbenoids have been involved in other gold(I)-catalyzed reactions and are predicted to be singlets.[12c,19]

Intermediate **15** can undergo a 1,6-hydride shift with a barrier of 29.6 kcal/mol (**TS15−16**) to form **16**. The barrier

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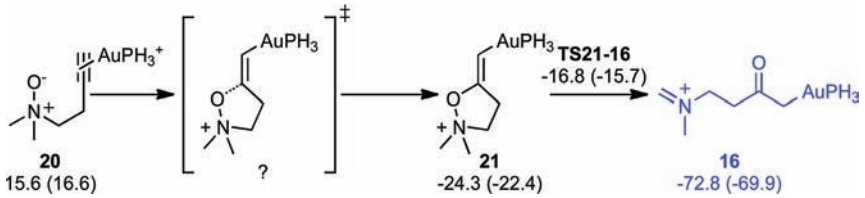
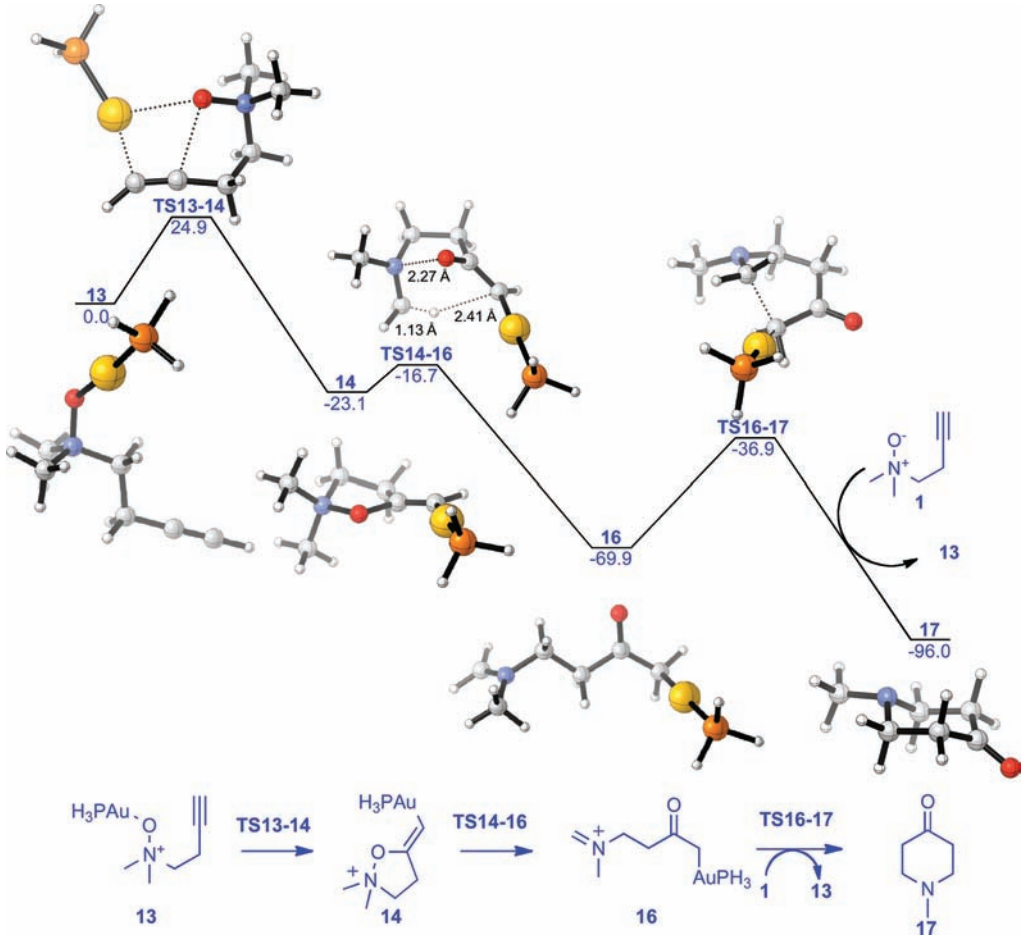
Scheme 3. *Anti* Addition Pathway to 16



Scheme 4. B3LYP-D3 Free Energy Diagram for the Lowest Energy Path from 13 to 17[a]



[a]Carbon is grey; nitrogen is blue; oxygen is red; gold is gold; and phosphorus is orange.

for the 1,4-hydride shift (**TS15−18**) is 4.6 kcal/mol higher in energy than that for the 1,6-hydride shift.

An alternative to the mechanism involving the sequential ring opening and 1,6-hydride shift was found to be energetically much more favorable. This new mechanism involves a hetero-retroene reaction and leads directly from **14** to **16**, thus avoiding the gold-carbenoid intermediate, **15**, altogether. This step is favored over ring opening by 18.6 kcal/mol. Cyclization of **16** forms the product, **17**, and regenerates the catalyst. This final step was calculated to have a barrier of 35.8 kcal/mol. This barrier should be lowered by the presence of an NTf_2^- counterion or the coordination to a molecule of the *N*-oxide starting material, **1**.[20] Also, the actual aryl phosphine ligands used experimentally are more electron-rich than our model phosphine, which should facilitate the dissociation of the gold catalyst. This step is exothermic by 23.9 kcal/mol.

Scheme 4 summarizes the lowest energy path from **13** to **17**. In this path, the first step is the *syn* addition of the gold-coordinated *N*-oxide, **13**, to form **14**. Intermediate **14** undergoes the heteroretroene reaction and forms **16**. The final step is the cyclization of **16** to yield the piperidine product, **17**, and regenerate the catalyst. This cyclization is calculated to be the rate-determining step. The overall transformation is exothermic by 96.7 kcal/mol.

The role of the gold catalyst in the heteroretroene reaction was probed by comparing the gold-catalyzed reaction to one without the $AuPH_3$ group. Figure 1 shows the transition structures for the reaction of **14** and of **22**. In **22** $AuPH_3$ is replaced by H. While the reactions are equally exothermic, the barrier is 9.5 kcal/mol lower in energy with the gold catalyst than without. In **14** the cationic gold-phosphine makes the adjacent carbon more negative compared to **22**. Because the carbon in **14** is more nucleophilic, the hydrogen transfer is favored, resulting in a lower energy transition structure.

As indicated earlier, experiments showed that the hydrogen is transferred from the smaller amine substituent.[7] This

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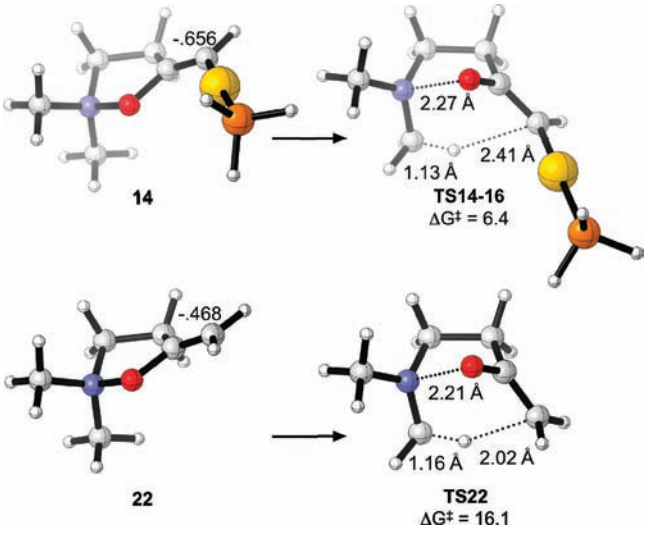

Figure 1. Comparison of the heteroretroene reaction with and without gold including bond distances and Mulliken charges. The ΔG_{rxn} is −46.9 and −48.4 kcal/mol with and without gold, respectively. Free energies determined by B3LYP-D3.

observation is consistent with the newly proposed mechanism. Figure 2 shows the heteroretroene transition structure, **TS14−16**. The least sterically hindered position on the amine substituent (highlighted in green) is not involved in the heteroretroene reaction. A quantitative study of this phenomenon was undertaken as well. The acetylenic amine-*N*-oxide, **7**, under experimental conditions afforded **8** and **9** in a 5:1 ratio (eq 3). This product distribution corresponds to the heteroretroene reaction preferentially involving hydrogen shift from the methyl group rather than the octyl substituent. Calculations on the *N*-methyl, *N*-ethyl substrate gave a 1.0 kcal/mol preference for **TS7−8**, corresponding to a 5.4:1 product ratio (Figure 3).

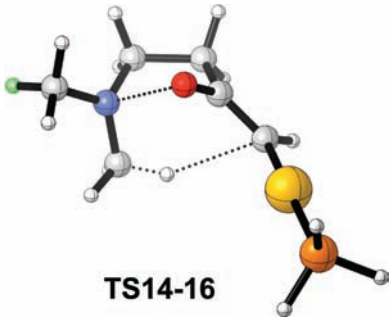

Figure 2. The heteroretroene transition structure, **TS14−16**. The highlighted (green) hydrogen is at the least sterically hindered position on the N substituents.

Similar mechanistic and regioselectivity studies were carried out for the annulation to azepanones. The mechanism for the conversion of **23** to **27**, including competing pathways, is shown in Scheme 5. Again, the gold preferentially coordinates to the *N*-oxide rather than the alkyne, and no transition structure corresponding to the *anti* addition could be located (Scheme 6). When PPh_3 is used, calculations predict that coordination of gold to the *N*-oxide is favored by 10.0 kcal/mol and the barrier for the *syn* addition is 11.1 kcal/mol. The heteroretroene mechanism is favored over the mechanism involving stepwise ring opening followed by a hydride shift.

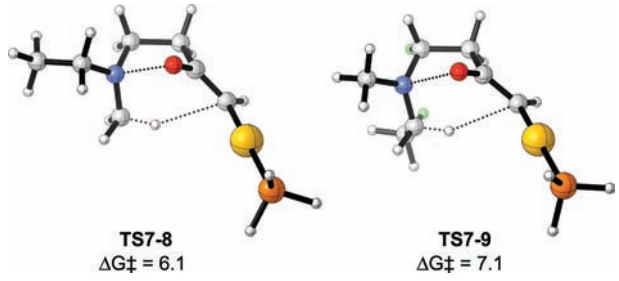

Figure 3. Heteroretroene reaction transition structures dictating the product distribution of **8** and **9**. Highlighted hydrogens in **TS7−9** are 2.28 Å apart. Free energies are determined by B3LYP-D3.

From the gold coordinated *N*-oxide intermediate, **23**, the *syn* addition to the alkyne forms **24**. Intermediate **24** can either ring-open or undergo a heteroretroene reaction. Analogous to the annulation to piperidinones, the heteroretroene transition structure, **TS24−26**, is favored, but only by 1.7 kcal/mol over the ring opening. This indicates that a small amount of the gold carbenoid, **25**, could be formed, although the necessity for intersystem crossing will disfavor this pathway. Intermediate **25** undergoes a 1,7-hydride shift, rather than a 1,5-hydride shift ($\Delta\Delta G^{\ddagger}$ = 17.8 kcal/mol). An iminium intermediate, **26**, leads to the product **27**. Again, the barrier for the cyclization is overestimated by our calculations. The transformation from **23** to **27** is exothermic by 85.9 kcal/mol. The free energy diagram for the lowest energy pathway is shown in Scheme 7.

Calculations are in good agreement with the experimental regioselectivity observed in this transformation as well. The heteroretroene transition structure, **TS24−26**, is in a chair conformation with the substituent involved in the rearrangement in an axial position (Figure 4). This is consistent with the experimental observation that smaller groups are involved in the hydrogen shift. The acetylenic amine-*N*-oxide, **10**, under experimental conditions afforded only **11** (eq 4). As shown in Figure 5, the activation energy of the heteroretroene reaction involving the methyl group is 2.2 kcal/mol lower in energy than that involving the ethyl substituent. The prediction is that a 43:1 ratio of products should occur.

The annulation to azapanones is more regioselective than the annulation to piperidinones (eqs 3 and 4), because the axial/equatorial difference is larger in the chairlike transition structure (**TS10−12**, Figure 5) than in the envelope transition structure (**TS9−11**, Figures 3). The distances between the ethyl substituent and the nearest hydrogen (both highlighted in green) in **TS10−12** and in **TS9−11** are 2.10 and 2.28 Å, respectively.

■ EXPERIMENTAL STUDIES

These computational studies indicate that the hydrogen migration is intramolecular and the intermediacy of gold carbene intermediates of type **5** (Scheme 1) is unlikely. Experiments were performed to provide further support for these conclusions and thereby the calculated heteroretroene mechanism.

To examine the hydrogen migration, the α-methylene group in the tertiary amine **30**-d_2 was fully labeled by deuterium. When compound **30**-d_2 was subjected to the oxidation and gold catalysis sequence, little deuterium loss was detected in the *N*-benzylazepanone product **31**-d_2 (eq 6), suggesting that the hydrogen/deuterium migration is intramolecular.[21] As more than 1 equiv of *m*-CBA was present in the reaction mixture during the gold catalysis, an intermolecular ionic

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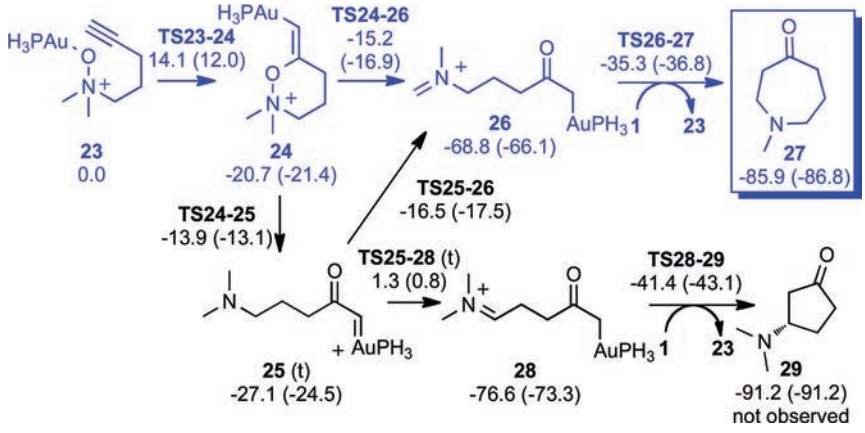
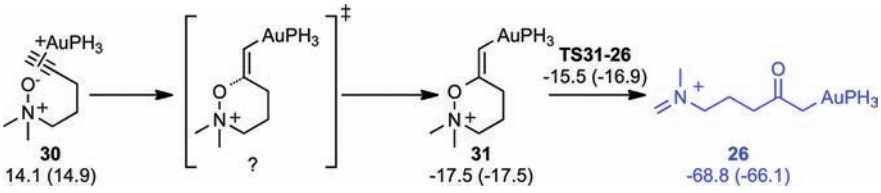
Scheme 5. B3LYP/6-31G(d)/CPCM(DCM) (B3LYP-D3) Energetics for the Conversion of the Gold-Coordinated *N*-Oxide, 23, to Piperidinone 27 and Cyclopentanone 29[a]

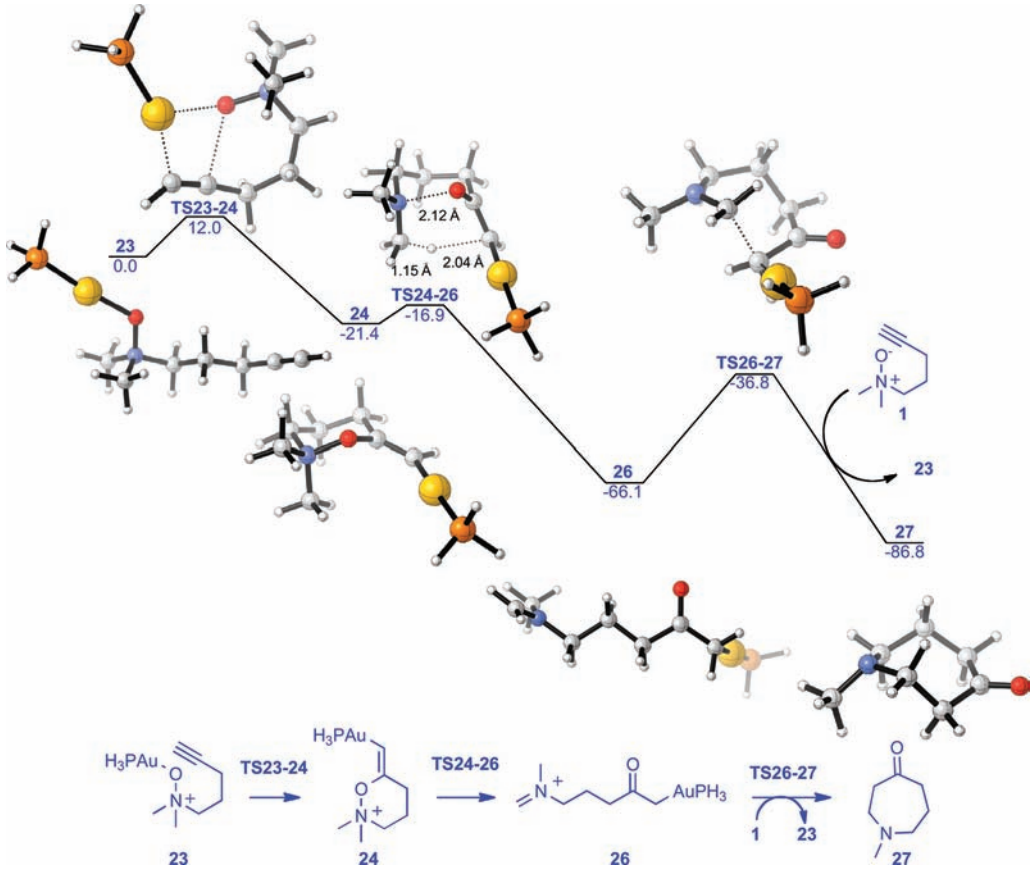


[a]Compound **29** is not observed experimentally. (t) indicates the species is a ground-state triplet.

Scheme 6. *Anti* Addition Pathway to 26



Scheme 7. B3LYP-D3 Free Energy Diagram for the Lowest Energy Path from 23 to 27



process would most likely lead to substantial loss of deuterium. This result is consistent with the heteroretroene mechanism.

To offer evidence against the intermediacy of gold carbene **5** or related carbenoid intermediates, the diazo ketone **33** was prepared[22] and treated with $Ph_3PAuNTf_2$ in 1,2-dichloroethane.

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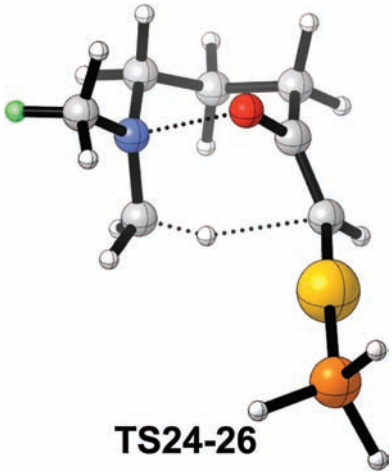


Figure 4. The heteroretroene transition structure, **TS24−26**, for the transformation from **24** to **26**. The highlighted hydrogen is at the least sterically hindered position on the N substituents.

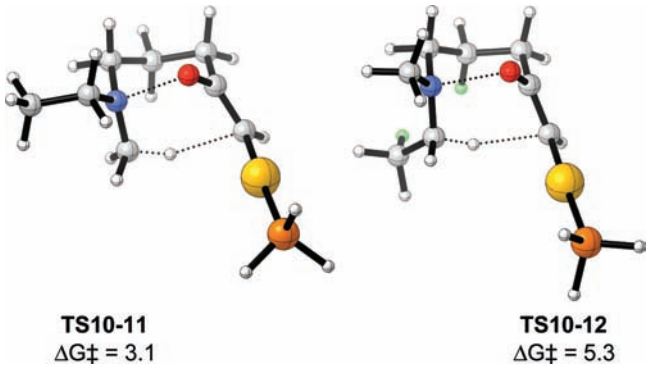
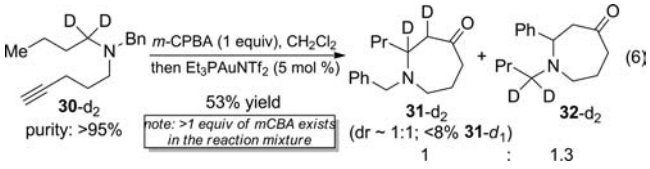
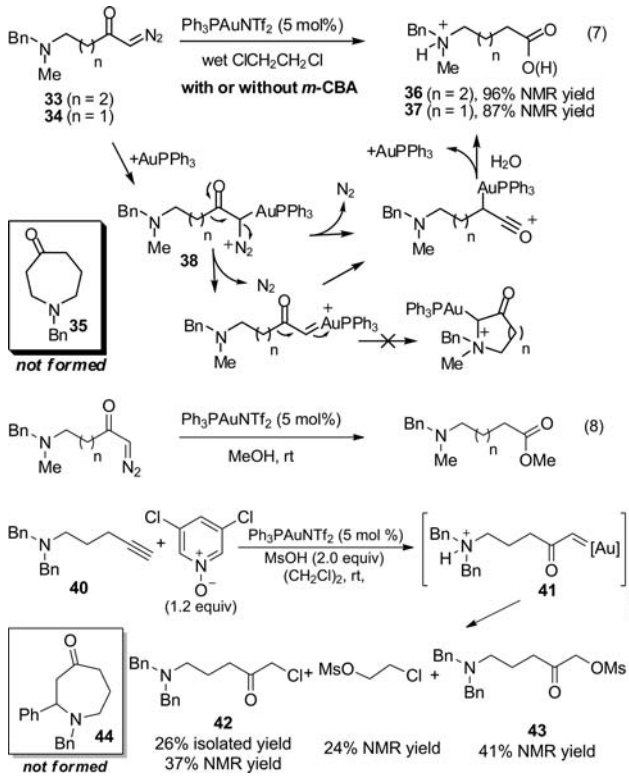


Figure 5. The heteroretroene reaction transition structures for the formation of **11** and **12**. The highlighted hydrogens in **TS10−12** are 2.10 Å apart. Free energies are determined by B3LYP-D3.



The expected azepan-4-one product **35** was not formed (eq 7); instead, the Wolff rearrangement[23] product, amino acid **36**, was formed in 96% NMR yield. The addition of a stoichiometric amount of *m*-CBA did not alter the reaction outcome. With **34**, similar results were observed; amino acid **36**, but not the piperidine-4-one product, was observed. When MeOH was used as solvent, the corresponding methyl ether was isolated in 70% yield (eq 8). While there is no previous report on gold-catalyzed Wolff rearrangements, the related Ag catalysis[24] is known, but the mechanistic role of the metal is not well understood. It is commonly assumed, though, a carbene or carbenoid intermediate might be involved. In these clean Wolff rearrangements, either gold carbenoid **38** or gold carbene **39** is the mostly likely intermediate, and the 1,2-alkyl migration could either be in concert with or follow the expulsion of N_2. This migration was seemingly highly facile as the tethered tertiary amine moiety did not cyclize to the electrophilic carbene/carbenoid center. Since the gold carbene **39** would be



highly electrophilic (vide infra), this unexpected preference for the Wolff rearrangement suggests that concerted 1,2-alkyl migration and nitrogen expulsion from carbenoid **38** are more likely.

An alternative approach to access a gold carbene of type **39** was then pursued. One of us has recently developed a facile access to putative *α*-oxo gold carbenes via gold-catalyzed intermolecular oxidations of alkynes using pyridine/quinoline *N*-oxides as oxidants.[8] By using this strategy, intermediate **41**, with its gold carbene moiety similar to that of **39**, was most likely formed from the substrate **40** in the presence of MsOH (2 equiv, eq 9). The reaction, however, did not afford azepan-4-one **44** but instead *α*-chloro ketone **42** and *α*-methanesulfonyloxy ketone **43**. The formation of **42** is a strong indication of the formation of a highly electrophilic intermediate such as gold carbene **41** as it abstracts a chloride from the solvent, dichloroethane.[25] This chloride abstraction is supported by the observation of 2-chloroethyl mesylate, which accounts for the remaining part of the solvent molecule. When *m*-CBA (1.2 equiv) replaced MsOH, no oxidation of the C−C triple bond occurred.

These studies argue against the intermediacy of gold carbene **5** (Scheme 1) and are fully consistent with the concerted heteroretroene reaction predicted computationally.

■ CONCLUSION

A heteroretroene mechanism for the rearrangements of acetylenic amine-*N*-oxides to piperidinones and azapanones has been identified. The experimental regioselectivities are reproduced by the computations of activation barriers for the heteroretroene reaction. Experimental studies support the proposed mechanism. This is the first case in which a retroene reaction of a gold-coordinated intermediate has been identified. This type of mechanism may be important in other gold-catalyzed alkyne oxidations.

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■ ASSOCIATED CONTENT

Supporting Information

Full ref 10, molecular orbitals for carbenoids **15** and **25**, C−O bond distance scan for the trans addition to the alkyne, Cartesian coordinates, and experimental methods and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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