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Gold-Catalyzed Oxidative Aminocyclizations of Propargyl Alcohols and Propargyl Amines to form two Distinct Azacyclic Products: Carbene formation versus a 3,3-sigamatropic shift of an initial Intermediate

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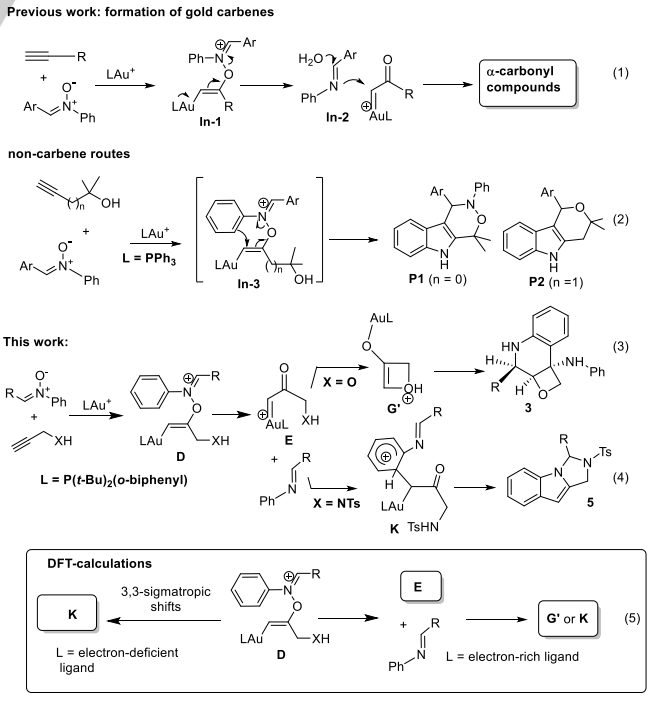
Abstract: Gold catalyzed oxidations of propargyl alcohols with nitrones using P(*t*-Bu)$_2$(*o*-biphenyl)Au$^+$catalyst, afforded bicyclic annulation products from the Mannich reactions of gold enolates. The same reactions of propargylamines with nitrones using the same gold catalyst gave distinct oxoarylation products. Our DFT calculations indicate that oxidation of propargyl alcohols with nitrones using electron-rich gold catalysts lead only to gold carbenes, which can generate gold enolates or oxoarylation intermediates with enolate species having a barrier smaller than that of oxoarylation species.

Introduction

Gold-catalyzed oxidations of pyridine-based oxides[1-2] to form reactive gold carbenes are powerful tools to access α-oxo functionalized molecules. Despite its widespread application, these alkyne oxidations only deliver an oxygen atom on alkynes together with pyridines as chemical waste, thus failing to meet atom economy. We have long interest in gold-catalyzed oxidations of alkynes with nitrones[3-5] to generate electrophilic gold carbenes **In-2** and nucleophilic imines, inducing further chemical reactions to give various α-oxoamination products (eq 1).[4-5] In these nitrone oxidations, we have utilized these gold carbenes **In-2** to enable novel α-oxoamination reactions[4] and oxidative Mannich reactions.[5] However, in our recent work, we noted that catalytic oxidations of 3,3-substituted prop-1-yn-3-ols and but-1-yn-4-ols afforded various indole-fused bicyclic products via a non-carbene route (eq 2),[6] in which intermediates **In-3** undergo an atypical 3,3-sigmatropic rearrangement[6,7] to achieve an oxoarylation process (eq 2). To understand the effects of alkynol substituents on the oxidation chemoselectivity, we investigate gold-catalyzed nitrone oxidations of unsubstituted propargyl alcohols and their amino analogues; interestingly, we discover that the key alcohol intermediates **D** generate gold enolates **G'** whereas the amino derivatives **D** preferably yielded oxoarylation intermediates **K** instead. Notably, the resulting azacyclic products **3** and **5** have complicated frameworks, which are not readily accessible with conventional synthesis. In this work, we employ DFT calculations to confirm that both intermediates **G'** and **K** are generated from gold carbenes **E** with electron-rich P(*t*-Bu)$_2$(*o*-biphenyl)Au$^+$ (eq 5) whereas alcohol substituents are not critical to chemoselectivity.[8,9] When electron-deficient PPh_3Au^+ was used, as depicted in eq 2, the key intermediates **D** will undergo 3,3-sigmatropic shift to form oxoarylation intermediates like **K** directly (eq 5). Accordingly, this 3,3-rearrangement of initial intermediates **In-3** is not the only path to produce oxoarylation species **K,** that can be also attained from gold carbenes **E**.



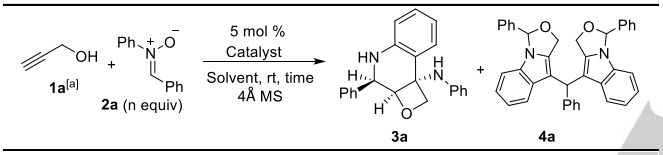
Introduction

Results and Discussion

Table 1 shows our efforts to optimize the nitrone oxidations of proparyl alcohol **1a** using various gold catalysts; the yields of our target **3a** were estimated based on the amount of alcohol **1a** (1 equiv). Herein, compounds **3a** and **4a** represent two products from reactions of gold enolates (eq 3) and oxoarylations (eq 2). Initial trials with LAuCl/AgOTf [L = IPr, PPh_3, $P(OPh)_3$ and P(*t*-Bu)$_2$(*o*-biphenyl)] in CH_2Cl_2 (DCM) gave the desired product **3a** in 0-68% yields with the electron-rich P(*t*-Bu)$_2$(*o*-biphenyl) ligand being the most productive whereas PPh_3 and $P(OPh)_3$ gave oxoarylation product **4a** in small proportions (entries 1-4). A change of the silver salts as in P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgX (X = NTf_2 and SbF_6) increased the yields of **3a** to 72% and 70% respectively (entries 5-6). For LAuCl/NaBARF, the yield of compound **3a** was obtained 61% (entry 7). The use of gold complex $LAuNTf_2$, the yield of desired **3a** in yield 67% (entry 8). For P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$, the yields of compound **3a** were as follows (entries 9-12): THF(40%), DCE (65%), toluene (53%) and CH_3CN (15%). LAuCl as well $AgNTf_2$ alone was catalytically inactive under the same running condition (entries 13- 14). The molecular structure of compound was inferred from x-ray diffraction of its relative **3l**[10] which disclosed the stereochemistry of the structure (*vide infra*).

We assess the substrate scope of various nitrones with standard propargylic alcohol **1a** (Table 2). We first tested the reactions on nitrones **2b-2g**, bearing different *para*-phenyl imines (X = Cl, Me, Br, OMe, *t*-Bu and CF_3), which delivered the desired products **3b-3g** with yields exceeding 61% (entries 1-6).We also tried *meta*-phenyl imine-containing nitrones **2h-2i**, (X = Cl, Br), affording compounds **3h-3i** in 70-75% yields (entries 7-8). Nitrones **2j** and **2k** bearing imine groups with Ar^1 = 2-thienyl and 2-naphthyl were also applicable substrates to deliver compounds **3j** and **3k** in 68-70% yields (entries 9-10). Nitrones **2l-2n** bearing para-substituted anilines (X = Me, F and CO_2Et) yielded the expected **3l-3n** in 0-64% yields, herein true electron-withdrawing ester product **3n** was not obtained (entries 11-13). The molecular structure of compound **3l** was characterized with X-ray diffraction.[10] For nitrones **2o-2q** bearing various *meta*-substituted anilines (X = Me, Cl, Br); their reactions afforded the corresponding products **3o-3q** in 51-63% yield (entries 14–16). We further prepared 1-butyn-3-ol **1b** that afforded a highly substituted heterocyclic compound **3r** bearing four stereogenic center; the yield was 60% yield (entry 17).

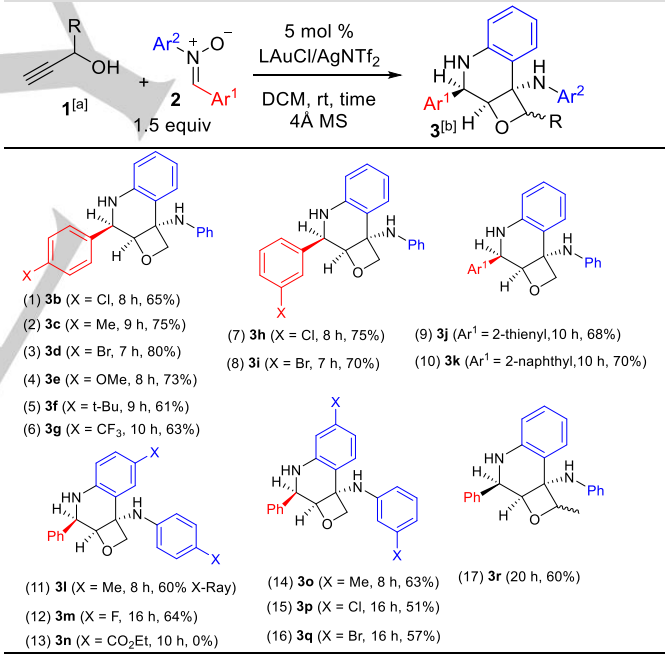
Table 1. Condition for chemical optimizations.



Entries	Catalyst	n eq	Solvent	t (h)	Yield[b] (%)		
					2a	**3a**	**4a**
1	IPrAuCl/AgOTf	1.5	DCM	6	15	58	--
2	PPh_3AuCl/ AgOTf	1.5	DCM	10	51	--	10
3	$(PhO)_3$PAuCl/ AgOTf	1.5	DCM	10	62	--	6
4	LAuCl/AgOTf	1.5	DCM	6	10	68	--
5	LAuCl/$AgNTf_2$	1.5	DCM	8	5	72	--
6	LAuCl/$AgSbF_6$	1.5	DCM	8	8	70	--
7	LAuCl/NaBARF	1.5	DCM	10	10	61	--
8	$LAuNTf_2$	1.5	DCM	8	7	67	--
9	LAuCl/$AgNTf_2$	1.5	THF	8	25	40	--
10	LAuCl/$AgNTf_2$	1.5	DCE	8	10	65	--
11	LAuCl/$AgNTF_2$	1.5	Toluene	10	15	53	--
12	LAuCl/$AgNTf_2$	1.5	CH_3CN	12	66	15	--
13	LAuCl	1.5	DCM	10	68	--	--
14	$AgNTf_2$	1.5	DCM	8	70	--	--

[a] **1a** = 0.20 M, L = P(*t*-Bu)$_2$(*o*-biphenyl), IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2ylidine, [b] The yields were calculated after flash column chromatography on silica gel.

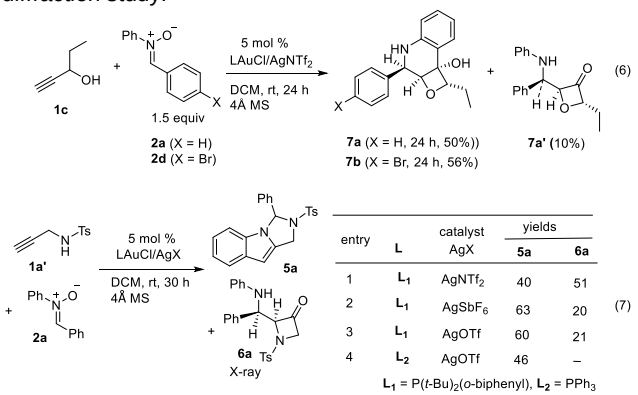
Table 2. Nitrone Substrate scope with Propargylic alcohol.



[a] **1a** = 0.20 M, L = P(*t*-Bu)$_2$(*o*-biphenyl), [b] The product yields were calculated after flash column chromatography on silica gel.

For 1-penty-3-ol **1c**, we noted that its corresponding reactions with nitrones **2a** (X= H) and **2d** (X = Br) gave the expected products **7a** and **7b** bearing a tertiary alcohol. We did not obtain a tertiary amine for compound **7a** because the ethyl group is probably too bulky to allow aniline to attack the neighboring tertiary carbocation. Together with the major product **7a**, we isolated also an oxetan-2-one **7a'** in small proportion (10%, eq 6); this minor product could be converted to compound **7a** with the same gold catalyst in refluxing DCE. The stereochemistry of compounds **7a** and **7a'** were elucidated with

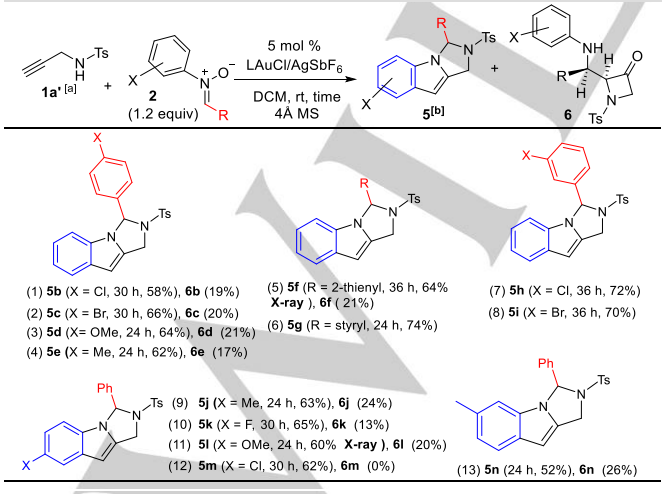
proton NOE spectra. Our next task is to examine the reactions with unsubstituted propargylamine **1a',** which undergoes an oxoarylation reaction preferably. In the case of P(*t*-butyl)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$ in DCM, species **1a'** yielded 2,3-dihydro-1H-imidazo[1,5-a]indole **5a** and azetidin-3-one **6a** in 40% and 51% yields respectively (eq 7). A switch to AgSbF$_6$ and AgOTf, the yields of compound **5a** were increased to 63% and 60% yields respectively. Although only oxoarylation product **5a** was achieved with PPh$_3$AuCl/AgOTf,, but the yield was only 46% yield. The molecular structure of compound **5a** is inferred from X-ray diffraction study of its relatives **5f** and **5l**[10] whereas the stereochemistry of compound **6a** is confirmed from its X-ray diffraction study.[10]



entry	L	catalyst AgX	yields 5a	yields 6a
1	L_1	$AgNTf_2$	40	51
2	L_1	$AgSbF_6$	63	20
3	L_1	AgOTf	60	21
4	L_2	AgOTf	46	–

We assess the reaction generality for the synthesis of 2,3-dihydro-1*H*-imidazo- [1,5-*a*]-indoles **5** with various nitrones; the results are summarized in Table 3. Compounds **5** are separable from the other products **6** on a silica column. Under the optimized conditions, For nitrones 2 bearing various *para*-phenyl imines (X = Cl, Br, OMe, Me), their corresponding fused indole products **5b-5e** were obtained in 58–66% yields along with azetidin-3-ones **6b**-**6e** in 17-21% yields (entries 1-4). Nitrones **2j** and **2r** bearing different imines, Ar^1 = 2-thienyl and 2-styryl,

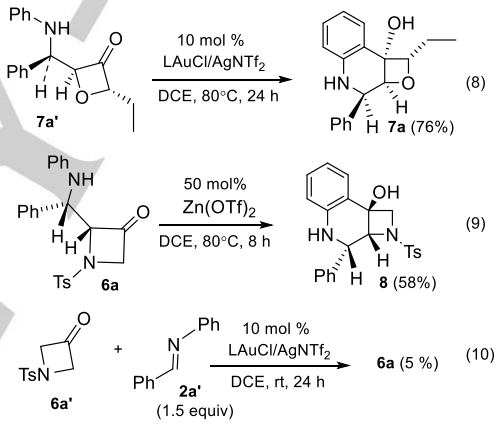
Table 3. Catalytic Oxoarylations of Propargylamines with Nitrones.



[a] **4a** = 0.20 M, L = P(*t*-Bu)$_2$(*o*-biphenyl), [b] The product yields were calculated after flash column chromatography on silica gel.

worked also well to yield the desired products **5f** and **5g** in 64 and 74% yields respectively (entries 5-6). The molecular structure of compound **5f** was characterized with X-ray diffraction study.[10] For nitrones **2p** and **2q** bearing *meta*-substituted imines (X = Cl, Br), similar fused indole compounds **5h-5i** were obtained with yields exceeding 70% (entries 7-8). Nitrones **2l-2m** and **2s-2t** bearing *para*-substituted anilines (X = Me, F, OMe, Cl) afforded the expected fused indoles **5j-5m** with yields exceeding 60% (entries 9-12); herein, azetidin-3-ones **6j-6m** were isolated in small proportions (0-24%)**.** Nitrones **2o** bearing an *meta*-methyl anilines yielded a fused indole **5n** and an azetidin-3-one **6n** in 52% and 26% yields respectively (entries 13).

We conducted intramolecular arylations of a cyclobutanone derivative **7a'** that might be an intermediate for our target **7a**. As we expect, This minor product could be converted to compound **7a** with same gold catalyst in refluxing DCE (eq 8). For azacyclic ketone **6a**, its arylation was also achieved with Zn(OTf)$_2$ in hot DCE to afford a new azacyclic compound **8** (eq 9). We also prepared 1-tosylazetidin-3-one **6a'** that proved to be much less reactive toward the Mannich reaction under the running condition (eq 10). Accordingly, the formation of species **6a** arises from a Mannich reaction of gold enolate of species **6a'**.



We performed DFT calculations[11] to clarify the energy profiles of two possible paths for the key intermediate **D**, including carbene formation versus 3,3-sigmatropic shift. The calculations are based on unsubstituted propargyl alcohol **1a** and P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$ in DCM. As depicted in Figure 1, the reaction of alcohol with nitrone **2a** to form a pre-organized complex **C** is very exothermic to release 16.4 kcal/mol of Gibbs free energy. The barrier for the addition of nitrone at gold-π-alkyne is small (6.2 kcal/mol) to yield the key intermediate **D**. For two possible pathways, we are unable to locate the transition state of a sigmatropic shift, but able to find a viable route to gold carbene **E**. The energy barrier is 7.9 kcal/mol with a release of 14.6 kcal/mol for this carbene route. A dissociation of product pair is favorable with ΔG = - 3.2 kcal/mol due to entropy gain. Our calculation indicates that gold carbene in state **F** have two options, (i) forming C-bound gold enolate **G** or (ii) undergoing an arylation with imine to yield an oxoarylation intermediate **H.** Our DFT calculation predicts the enolate formation **F→G** is more favorable because its barrier is only 1.2 kcal/mol, much smaller than that of 7.1 kcal/mol for an arylation process. This profile suggests that the chemoselectivity is favorable for enolate formation. We also performed the same

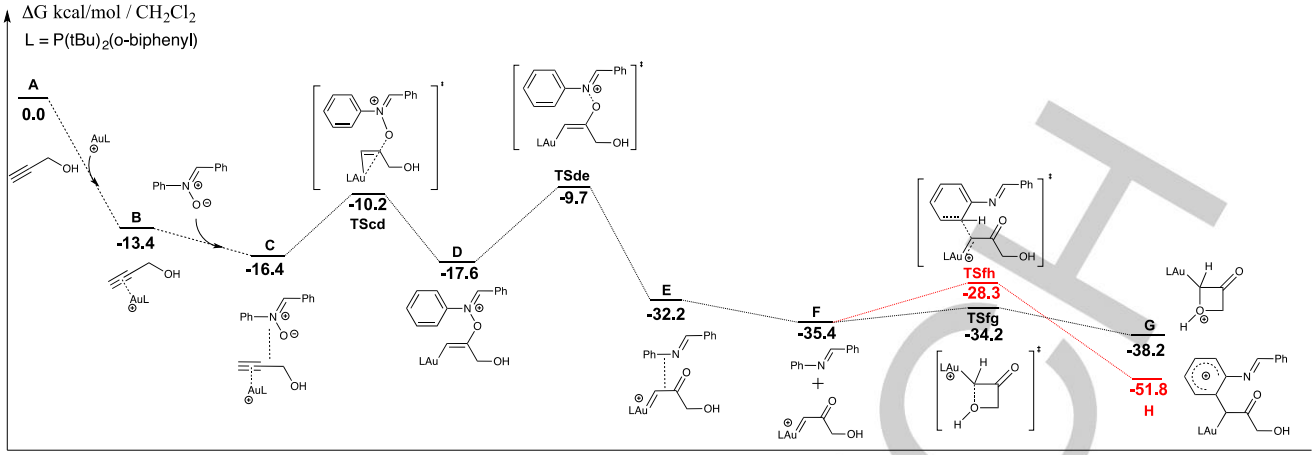
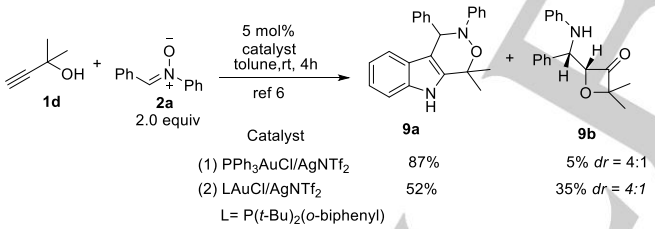


Figure 1. Energy profiles for alcohol **1a** with LAu^+ catalyst.

calculations in toluene (see Figure S1, Supporting Information), and similar energy profiles are attained that intermediate **D** is only feasible to generate gold carbene species **E.** However**,** the energy difference between **TSfh** (-33.1 kcal/mol) and **TSfg** (-37.1/kcal/mol) is decreased to 4.0 kcal/mol**,** still in favor of gold enolates **G**. This model is consistent with our observation (Table 1 entry 9)**.**

Scheme 1 depicts our previous results from the reaction between nitrone **2a**, 3,3-dimethylprop-2-yn-1-ol (**1d**) using $PPh_3AuCl/AgNTf_2$ in toluene; we postulated a 3,3-sigmatropic shift for its key intermediate **D**, giving an oxoarylation product **9a** efficiently. But with P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$, the same reactants in toluene delivered compounds **9a** and **9b** in comparable proportions.



Scheme 1. Chemoselectivities with various gold catalysts.

We hence conducted DFT calculations on key intermediate **D** with alcohols **1a** and **1d** using different ligands; the results are provided in Figure 2. For alcohols **1a** and **1d** with PPh_3Au^+ in toluene, their corresponding intermediates $\mathbf{D_1}$ and $\mathbf{D_3}$ only undergo 3,3-sigmatropic shifts to form oxoaryl intermediates $\mathbf{H_1}$ and $\mathbf{H_3}$. We are unable to find the transition states leading to gold carbenes like **E**. This outcome is rational because PPh_3 ligand is not electron-rich enough to stabilize a gold carbene like **E**. Accordingly propargyl alcohols **1a** and **1d** are expected to give oxoarylation products **9a** and **4a** predominantly using PPh_3Au^+ catalyst, consistent with our observations in Scheme 1 (entries 1) and Table 1 (entry 2). In the case of P(*t*-Bu)$_2$(*o*-biphenyl)Au^+, our DFT calculations indicate that tertiary alcohol **1d**, similar to alcohol **1a**, leads only to gold carbenes **E** and **F** due to the highly electron-rich nature of P(*t*-Bu)$_2$(*o*-biphenyl); we are unable to locate the transition state for a 3,3-sigmatropic shift of the key intermediate $\mathbf{D_2}$. We noted that, due to the zero-point vibrational energy correction, the transition state $\mathbf{TS_{fg}}$ (-40.1 kcal/mol) becomes more stable than gold carbene **F** (-39.5 kcal/mol). This indicates that there is no kinetic barrier for this step. Notably, the two barriers are very small and similar for the transformations of gold carbene **F** to either oxoarylation species $\mathbf{H_2}$ ($\Delta G^‡$ = 1.3 kcal/mol) or gold enolate **G** ($\Delta G^‡$ = 0.0 kcal/mol); we consider their rates to be nearly the same under the running conditions (25 ^{0}C). Accordingly, this energy profile predicts a mixture of two products **9a** (52%) and **9b** (35%) in comparable proportions, in accord with our observation in Scheme 1 (entry 2). We also performed DFT calculations of these three reactions in DCM; the resulting profiles are similar to those in toluene (see Figure S2, Supporting Information). For tertiary alcohol **1d**, the energy barriers for $\mathbf{TS_{fh2}}$ (-33.2 kcal/mol) is higher than that of $\mathbf{TS_{fg}}$ (-36.9 kcal/mol) by a difference $\Delta G^‡$ = 3.7 kcal/mol, in favor of enolate formation. This barrier difference (3.7 kcal/mol) in DCM is larger than that (1.6 kcal/mol) in toluene when tertiary alcohol **1d** is catalyzed with P(*t*-Bu)$_2$(*o*-biphenyl)Au^+.

We performed DFT calculations on propargyl amine **1a'**; we provided the energy profiles in Supporting Information (Figure S3) With P(*t*-Bu)$_2$(*o*-biphenyl)AuNTf$_2$, its pattern bears close resemblance to for propargyl alcohol **1a**. Again, we only located the transition state leading to gold carbenes whereas the transition state of a 3,3-sigmatropic shift can not be found from alkenylgold intermediate **D**.

According to the DFT calculations in Figures 1-2, a 3,3-sigamatropic shift of initial intermediates **D** of alcohols **1a** and **1d** is only feasible with electron-deficient PPh_3Au^+; this route gives only oxoarylation intermediates. In the case of electron-rich P(*t*-Bu)$_2$(o-biphenyl)Au^+, only gold carbenes **E** can be produced to afford, either gold enolates **G** or oxoarylation intermediates $\mathbf{H_2}$; the kinetic barrier of gold enolate **G** is smaller than that of species $\mathbf{H_2}$ with a difference ca. $\Delta G^‡$ = 1.9-6.1 kcal/mol. High selectivity of gold enolates is best achieved with unsubstituted alcohol **1a** using P(*t*-Bu)$_2$(*o*-biphenyl)Au^+ in DCM.

This catalytic system follows gold carbene routes because electron-rich gold catalyst was used. Scheme 2 shows the remaining steps to deliver the two main products **3a** and **5a**. With propargyl alcohol **1a**, *C*-bound gold enolate **G** is kinetically favorable to react with imine via a cyclic transition state, further yielding the Mannich product **I**. A subsequent intramolecular

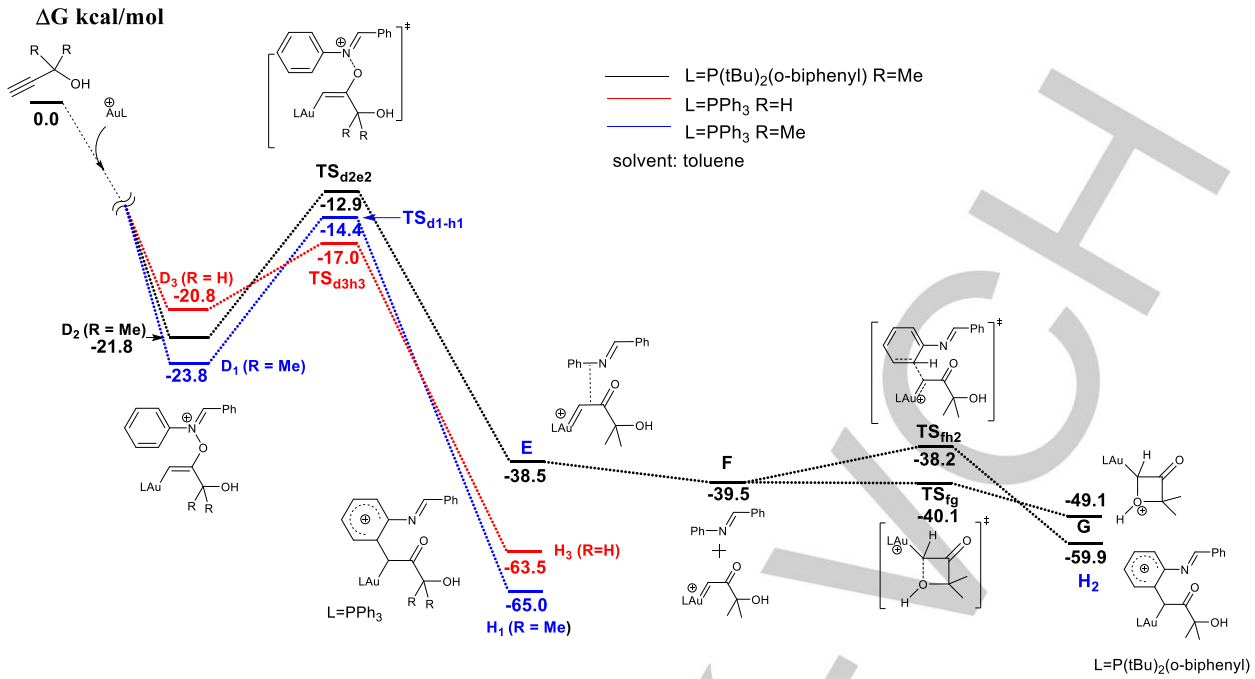
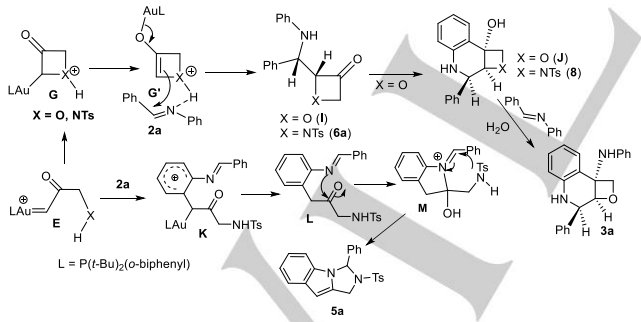


Figure 2. Energy profiles on key intermediate **D** with alcohols **1a** and **1d** using different ligands.

arylation of species **I** affords species **J,** and further the observed product **3a** when aniline is present in the system. We also rationalize the chemoselectivity of propargyl amine **1a'** (eq 7) that its resulting gold carbenes like **E** and **F** afford a mixture of oxoarylation species **K** and **6a,** presumably that their kinetic barriers have small difference**.** A further transformation of species **K** into the observed product **5a** is achievable through a sequential cyclization involving intermediates **L** and **M**.



Scheme 2. A Plausible reaction mechanism.

Conclusion

This work reported gold catalyzed oxidations of propargyl alcohols[12] with nitrones using P(*t*-Bu)$_2$(*o*-biphenyl)Au$^+$catalyst, yielding bicyclic annulation products from gold enolate intermediates. The same reactions of propargylamines with the same gold catalyst gave distinct oxoarylation products. Our DFTcalculations indicate that oxidation of propargyl alcohols with nitrones using electron-rich gold catalysts lead only to gold carbenes, which can generate gold enolates or oxoarylation intermediates with the former has a smaller barrier. If these alcohols were catalyzed with electron-deficient gold catalyst, initial intermediates preferably undergo 3,3-sigmatropic shift to yield oxoarylation products.

Experimental Section

procedure for synthesis of (2a*S*,3*R*,8b*R*)-*N*,3-diphenyl-2a,3,4,8b-tetrahydro-1*H*-oxeto[2,3-*c*]quinolin-8b-amine (3a).

A Schlenk tube was charged with P(*t*-Bu)$_2$(*o*-biphenyl)AuCl (0.0053 g, 0.01 mmol) and $AgNTf_2$ (0.0038 g, 0.01 mmol), and dry DCM (2 mL) was added to that mixture. The resulting mixture was stirred at room temperature for 5 min, and to this mixture was added a dry DCM solution (3 mL) of Propargyl alcohol **1a** (0.0112 g, 0.2 mmol) and (*Z*)-*N*-benzylideneaniline oxide **2a** (0.0591 g, 0.3 mmol) dropwise. After stirring at room temperature for 8 h, the reaction mixture was filtered over a short celite bed and concentrated to crude products **3a**. Flash column chromatography on a silica column (ethyl acetate/hexane = 1:20) afforded the desired (2a*S*,3*R*,8b*R*)-*N*,3-diphenyl-2a,3,4,8b-tetrahydro-1*H*-oxeto[2,3-*c*]quinolin-8b-amine **3a** (0.0505 g, 0.14 mmol, 72%) as white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.2 Hz, 2H), δ 7.36 ~ 3.34 (m, 3H), δ 7.29 (t, *J* = 7.2 Hz, 1H), 7.15 ~ 7.09 (m, 3H), 6.81 (d, *J* = 7.8 Hz, 1H), δ 6.79 (t, *J* = 7.8 Hz, 1H), δ 6.71 (t, *J* = 7.2 Hz, 1H), δ 6.58 (d, *J* = 7.8 Hz, 2H), δ 5.07(d, *J* = 1.8 Hz, 1H), δ 4.60 ~ 4.58 (m, 3H), δ 4.30 (d, *J* = 1.8 Hz, 1H) , δ 4.15 (bs, 1H); ^{13}C NMR (150 MHz, CDCl3): δ 145.6, 144.7, 137.9, 129.1, 128.5, 128.2, 128.1, 128.0, 125.9, 119.9, 124.5, 120.4, 118.2, 115.9, 114.7, 92.1, 82.3, 60.1, 56.8; HRMS-ESI+ calcd for $C_{22}H_{20}N_2O$ (M+Na): 351.1473, found: 351.1469.

Standard procedure for synthesis of 3-phenyl-2-tosyl-2,3-dihydro-1*H*-imidazo[1,5-*a*]indole (5a) and (*S*)-2-((*R*)-phenyl(phenylamino)methyl)-1-tosylazetidin-3-one (6a).

A Schlenk tube was charged with P(*t*-Bu)$_2$(*o*-biphenyl)AuCl (0.0053 g, 0.01 mmol) and $AgSbF_6$ (0.0034g, 0.01 mmol), and to this mixture was added dry DCM (2 mL). The resulting mixture was stirred at room temperature for 5 min, and to this mixture was added a dry DCM solution (3 mL) of 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide **1a'** (0.041 g, 0.2 mmol) and (*Z*)-*N*-benzylideneaniline oxide **2a** (0.0473 g, 0.24 mmol) dropwise. After stirring at room temperature for 30 h, the reaction mixture was filtered over a short celite bed and concentrated to crude products **5a** and **6a**. Flash column chromatography on a silica column (ethyl acetate/hexane = 1:20) afforded the desired 3-phenyl-2-tosyl-2,3-dihydro-1H-imidazo[1,5-*a*]indole **5a** (0.048 g, 0.12 mmol, 63%) as white solid and (*S*)-2-((*R*)-phenyl(phenylamino)methyl)-1-tosylazetidin-3-one **6a** (0.016 g, 0.039 mmol, 20%).

5a. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H), δ 7.48 (d, *J* = 8.4, 1H), δ 7.32 ~ 7.25 (m, 3H), δ 7.15 (d, *J* = 7.2 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), δ 7.01 (t, *J* = 8.4 Hz, 1H), δ 6.94 (t, *J* = 8.4 Hz, 1H), δ 6.75 (d, *J* = 8.4 Hz, 1H), δ 6.67 (s, 1H), δ 6.19 (s,1H), δ 4.80 (d, *J* = 13.8 Hz, 2H), δ 2.30 (s, 3H); ^{13}C NMR (150 MHz, CDCl3): δ 144.0, 137.2, 136.4, 134.4, 132.9, 131.2, 129.7, 129.4, 128.8, 127.3, 121.4, 120.9, 120.2, 109.9, 93.0, 75.3, 46.5, 21.4; FD+ calcd for $C_{23}H_{20}N_2O_2S$: 388.1245, found: 388.1240.

6a. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.4 Hz, 2H), δ 7.35 ~ 7.30 (m, 6H), δ 7.28 ~ 7.26 (m,1H), δ 7.11 (t, *J* = 7.2 Hz, 2H), δ 6.69 (td, *J* = 7.2, 1.2 Hz, 1H), δ 6.59 (dd, *J* = 8.4, 1.2 Hz, 2H), δ 5.05 (d, *J* = 7.2 Hz, 1H), δ 4.99 (dd, *J* = 6.6, 3.6 Hz, 1H), δ 4.82 (t, *J* = 7.2 Hz, 1H), δ 4.4 (d, *J* = 16.2 Hz, 1H) δ 4.28 (dd, *J* = 16.2 Hz, 4.2 Hz, 1H), δ 2.42 (s, 3H). ^{13}C NMR (150 MHz, CDCl3): 193.1, 145.0, 136.4, 129.2, 128.2, 127.7, 127.4, 127.2, 126.6, 117.5, 112.9, 86.1, 70.0, 56.9, 20.6. HRMS-ESI+ calcd for $C_{23}H_{22}N_2O_3S$: 406.1346, found 406.1345.

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Keywords: Aminocyclizations • Azacyclic products • Carbene • Propargyl alcohols • Propargyl amines

[1] Reviews for gold carbenes: a) A. S. K. Hashmi, *Chem. Rev*. **2007**, *107*, 3180−3211; b) L. Zhang, *Acc. Chem. Res.* **2014**, *47*, 877−888; c) H.-S.Yeom, S. Shin, *Acc. Chem. Res.* **2014**, 47, 966−977; d) Z. Zheng, Z. Wang, Y. Wang, L. Zhang, *Chem. Soc. Rev*. **2016**, *45*, 4448−4458; e)Y. Wang, M. E. Muratore, A. M. Echavarren, *Chem. Eur. J.* **2015**, *21*, 7332–7339; f) J. Xiao, X. Li, *Angew. Chem. Int. Ed.* **2011**, *50*, 7226–7236; g) L. Ye, X-Q. Zhu, R. L. Sahani, Y. Xu, P-C. Qian, R.-S. Liu, *Chem. Rev.* **2020**, DOI: 10.1021/acs.chemrev.0c00348.

[2] For the generation of α-oxo gold carbenes with N-O oxides; see selected examples: a) L. Ye, L. Cui, G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2010***, 132*, 3258−3259; b) L. Ye, W. He, L. Zhang, *J. Am. Chem. Soc.***2010**, *132*, 8550−8551; (c) Y. Wang, Z. Zheng and L. Zhang, *J. Am. Chem. Soc*., **2015**, *137*, 5316–5319; (d) G. Zhang, Y. Peng, L. Cui and L. Zhang*, Angew. Chem., Int. Ed*., **2009**, *48*, 3112–3115; (e) Y. Wang, K. Ji, S. Lan, L. Zhang, *Angew. Chem*. **2012**, *124*, 1951–1954; (f) B. Lu, C. Li, L. Zhang, *J. Am. Chem. Soc*., **2010**, *132*, 14070–14072; (g) B. S. Kale, R. S. Liu, *Org. Lett*. **2019**, *21*, 8434−8438; (h) A. P. Jadhav, S. Bhunia, H.-Yi. Liao, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 1769–1771; (i) C. Shu, L. Li, Y.-F. Yu, S. Jiang and L.-W. Ye*, Chem. Commun*., **2014**, *50*, 2522–2525; (j) W. E. Brenzovich, Jr., D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard III and F. D. Toste*, Angew. Chem., Int. Ed*., **2010**, *49*, 5519–5522; (k) T. Wang, S. Shi, P. Daniel, E. Rettenmeier, M. Rudolph, F. Rominger, A. S. K. Hashmi. *Chem. Eur. J.* **2014**, *20*, 292–296; (l) A. S. K. Hashmi, T. Wang, S. Shi, M. Rudolph. *J. Org. Chem.* **2012**, *77*, 7761−7767; (m) A. S. Hashmi, M. Bührle, R. Salathé, J. Bats, *Adv. Synth. Catal*. **2008**, *350*, 2059–2064; (n) A. S. K. Hashmi, T. M. Frost and J. W. Bats, *J. Am. Chem. Soc*., **2000**, *122*, 11553–11554; (o) A. S. K. Hashmi, M. C. Blanco, D. Fischer and J. W. Bats, *Eur. J. Org. Chem*. **2006**, 1387–1389; (p) H. Jin, B. Tian, X. Song, J. Xie, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem., Int. Ed*., **2016**, *55*, 12688–12692; q) Y. Zheng, J. Zhang, X. Cheng, X. Xu, L. Zhang, *Angew. Chem. Int. Ed.* **2019**, *58*, 5241–5245; r) C. Shu, C.-Y.Shi, Q. Sun, B. Zhou, T. -Y.Li, Q. He, X. Lu, R.-S. Liu, L.-W. Ye, *ACS Catal*. **2019**, *9*,1019 –1025. s) J.-M. Yang, Y.-T. Zhao, Z.-Q. Li, X.-S. Gu, S.-F. Zhu, Q.-L. Zhou, *ACS Catal*. **2018**, *8*, 7351–7355.

[3] D. B. Huple, S. Ghorpade, R.-S. Liu, *Adv. Synth. Catal.* **2016**, *358*, 1348−1367.

[4] a) A. Mukherjee, R. B. Dateer, R. Chaudhuri, S. Bhunia, S. N. Karad, R.-S. Liu, *J. Am. Chem. Soc.* **2011**, *133*, 15372–15375; b) Y.-C. Hsu, S.-A. Hsieh, P.-H. Li, R.-S. Liu**,** *Chem. Commun.* **2018**, *54*, 2114-2117.

[5] a) R. L. Sahani, M. D. Patil, S. B. Wagh, R.-S. Liu, *Angew. Chem., Int. Ed.* **2018**, *57*, 14878−14882; (b) H. Wei, M. Bao, K. Dong, L. Qiu, B. Wu, W. Hu, X. Xu, *Angew. Chem., Int. Ed.* **2018**, *57*, 17200−17204.

[6] R. L. Sahani, R.-S. Liu, *ACS Catal.* **2019**, *9*, 5890−5896.

[7] a) B. Sabyasachi, J-C. Chang, R.-S Liu, *Org Lett* **2012**,14, 5522-5525; b) A. B. Cuenca, S. Montserrat, K. M. Hossain, G. Mancha, A. Lledos, M.-S. Mercedes, G. Ujaque, G. Asensio, *Org. Lett.* **2009**, *11*, 4906-4909; c) C.-W. Li, K. Pati, G. Y. Lin, S. M. A. Sohel, H. H. Hung, R.-S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49,* 9891-9894; d) Y. Wang, L. Ye, L. Zhang, *Chem. Commun*. **2011**, *47*, 7815-7817.

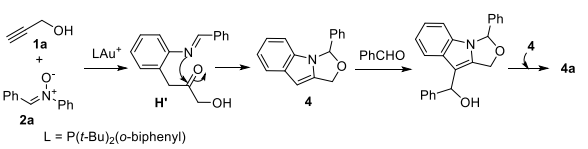
[8] For ligand effects in gold catalysis, see selected review: a) D. J. Gorin, B. D. Sherry, F. D. Toste, *Chem. Rev.* **2008**, *108*, 3351-3378.

[9] a) S. Kramer, F. Gagosz, In Gold Catalysis: An Homogeneous Approach" F. D. Toste and V. Michellet Eds, chapter 1, pp 1-50, Imperial College Press, 2014; b) P. Klahn, S. F. Kirsh, *Chem..Cat. Chem.* **2011**, *3*, 649-652; c) M. R. Luzung, P. Mauleon, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402-12403; d) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, J. L. Mascareñas, *J. Am. Chem. Soc.* **2009,** *131,* 13020-13030; e) I. Alonso, H. Faustino, F. Lopez, J. L. Mascareñas, *Angew. Chem., Int. Ed.* **2011,** *50*, 11496−11500. f) C.-D. Wang, Y.-F. Hsieh, R.-S. Liu, *Adv. Synth. Catal.*, 2014, *356*, 144-152.

[10] Crystallographic data of compounds **3l**, **5f**, **5l** and **6a** were deposited in Cambridge Crystallographic Data Center: **3l** (CCDC 2012689), **5f** (CCDC 2013824), **5l** (CCDC 2023003), **6a** (CCDC 2013420).

[11] The geometry optimizations and zero-point vibrational energy (ZPVE) were carried out using the B3LYP-D3 functional with the LANL2DZ basis set for Au and the 6-31G** basis set for the other atoms (denoted as LACVP**). In order to obtain a more accurate electronic energy, we performed single-point energy calculations based on the same functional, but using a larger basis set, where Au was described with LANL2TZ and the other atoms were described with the 6-311++G**basis set. Solvation energies were calculated using the CPCM implicit solvation model. The solvation calculations used the B3LYP/LACVP** level of theory and the gas-phase optimized structures. All calculations were performed using the Gaussian09 package.

[12] In Table 1, we isolated compound **4a** in several gold catalysts. Formation of **4a** can be rationalized by an initial oxoarylation to form species **H'** that undergoes an intramolecular cyclization to yield product **4**. This step is analogous to that for compound **5a.** A further arylation **of** compound **4** is expected to yield the observed product **4a**.



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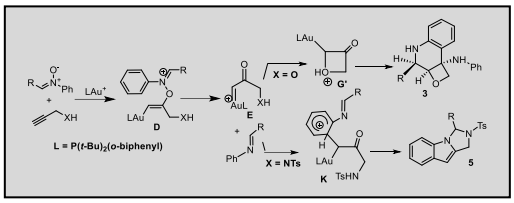
Entry for the Table of Contents



Gold catalyzed oxidations of propargyl alcohols with nitrones using P(*t*-Bu)$_2$(*o*-biphenyl)Au$^+$catalyst, afforded bicyclic annulation products from the Mannich reactions of gold enolates. The same reactions of propargylamines with nitrones using the same gold catalyst gave distinct oxoaylation products.