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Divergent Synthesis of Oxa-Cyclic Nitrones through Gold(I)-Catalyzed 1,3-Azaprotio Transfer of Propargylic α-Ketocarboxylate Oximes: Experimental and DFT Studies

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Abstract: 1,3-Azaprotio transfer of propargylic α-ketocarboxylate oximes, a new type of alkynyl oximes featuring an ester tether, has been explored by taking advantage of gold catalysis. The incorporation of an oxygen atom to the chain of alkynyl oximes led to the formation of two different oxa-cyclic nitrones. It was found that internal alkynyl oximes with an *E*-configuration deliver five-membered nitrones, whereas terminal alkynyl oximes with an *E*-configuration afford six-membered nitrones. DFT calculations on four possible pathways supported a stepwise formation of C–N and C–H bonds, in which a 1,3-acyloxy-migration competes with the 1,3-azaprotio-transfer, especially in the case of internal alkynyl oximes. The relative nucleophilic properties of oxygen in the carbonyl group and the nitrogen in the oxime, the electronic effects of alkynes, and the influence of the ring system have been investigated computationally.

Given that cyclic nitrones behave as powerful and versatile N,O-containing building blocks in organic synthesis, a variety of preparative protocols have been developed in the past decades.[1] Among them, 1,3-azaprotio-transfer of oximes is supposed to be a highly atom-economical one, which is free of oxidants and hydroxylamine reagents. It involves an addition of an oxime across a carbon–carbon multiple bond and the straightforward formation of C–N and C–H bonds (Scheme 1 a).[2] In fact, the 1,3-azaprotio transfer of alkenyl oximes towards an electron-deficient alkene, a terminal alkene, and a styrene has been explored and carried out successfully under thermal, acidic, and basic conditions, respectively.[3–6] In contrast, the corresponding alkynyl analogues remain less developed. As independently reported by Grigg and Beauchemin, only a few alkynyl oximes tethered by an all-carbon chain took part in a thermal 1,3-azaprotio-transfer to deliver N-vinyl-substituted cyclic nitrones, which tend to further undergo an isomerization or a N–O bond cleavage.[7–8] Previously, Lewis acids were used instead of Brønsted acids for the 1,3-azaprotio-transfer of allenyl oxime substrates (Scheme 1 b).[9] Inspired by recent progresses in Au activation of alkynes, we envisioned that Au catalysis could be applied for 1,3-azaprotio-transfer of alkynyl oximes.[10] Meanwhile, it was reported that Au^{I} can catalyze 1,3-acyloxy migration of propargylic carboxylate to give an allene–Au complex.[11] We, therefore, expected that the designed substrates, propargylic α-ketocarboxylate oximes, could have such a reaction pattern to give intermediate **I**, which then underwent C1–N bond formation to give five-membered oxa-cyclic nitrones (Scheme 1 c, pathway A). Another possible pathway is the C2–N bond formation to give six-membered products (Scheme 1 c, pathway B). We did not know which pathway would be preferred before we tested the reactions experimentally. To our delight, we found by subsequent experiments that we could tune the reaction selectivity by choosing different R groups, either to give five-membered nitrones when R = alkyl or aryl, or six-membered nitrones when R = H.[12] Herein, we report the results and explain the regiochemistry by DFT calculations.

We commenced the study by using alkynyl oxime **1 a** as a model substrate, which was prepared from undec-4-yn-3-ol and 2-oxopropanoic acid by two steps. Treatment of **1 a** with a catalytic amount of $Ph_3PAuNTf_2$ in toluene at room temperature for three hours gave five-membered oxa-cyclic nitrone **2 a** in 79% yield (Table 1, entry 1). Solvent testing showed that dichloromethane is the best one in terms of both yield and reaction time (entries 1–5). The effects of ligand and counteranion of gold catalyst were further examined (entries 6–9). It was found that the combination of Ph_3PAuCl and $AgSbF_6$ displays the best efficiency, delivering **2 a** in 96% yield. Control experiments revealed that both the gold catalyst and silver additive are indispensable for the formation of this cyclic nitrone.

After obtaining the optimal reaction conditions, we sought to investigate the scope of the internal alkynyl oximes (Scheme 2). Substrates containing ethyl, cyclopropyl, cyclohex-

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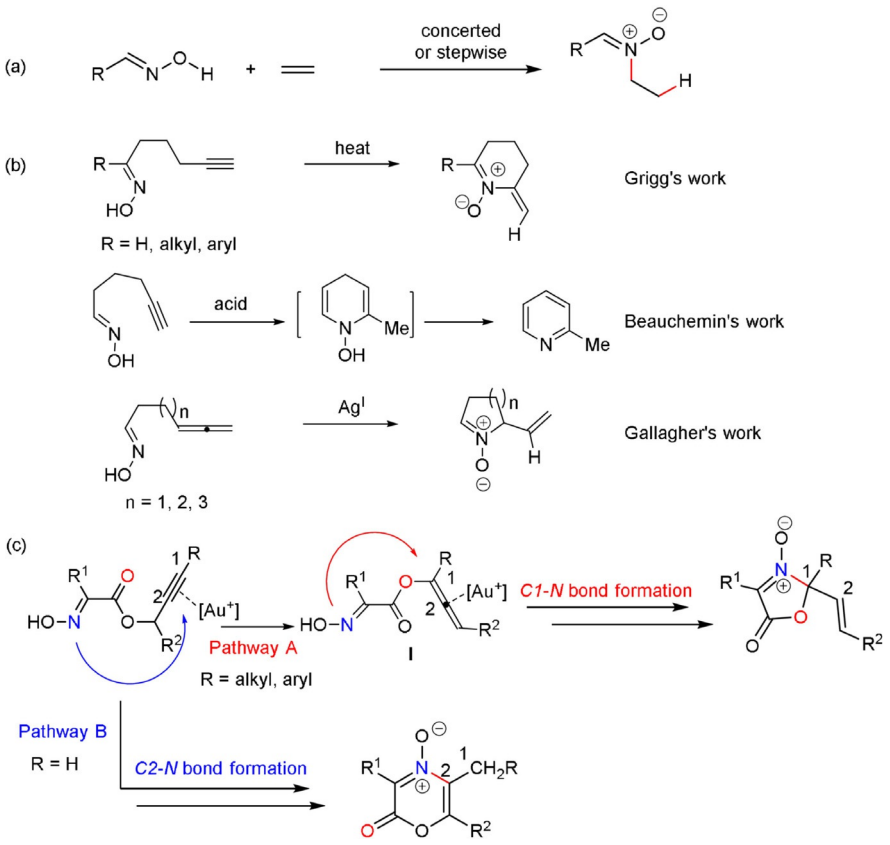
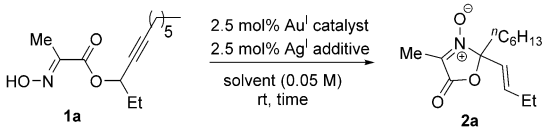


Scheme 1. 1,3-Azaprotio-transfer of oximes.

Table 1. Optimization of gold(I)-catalyzed 1,3-azaprotio-transfer of **1a**.[a]



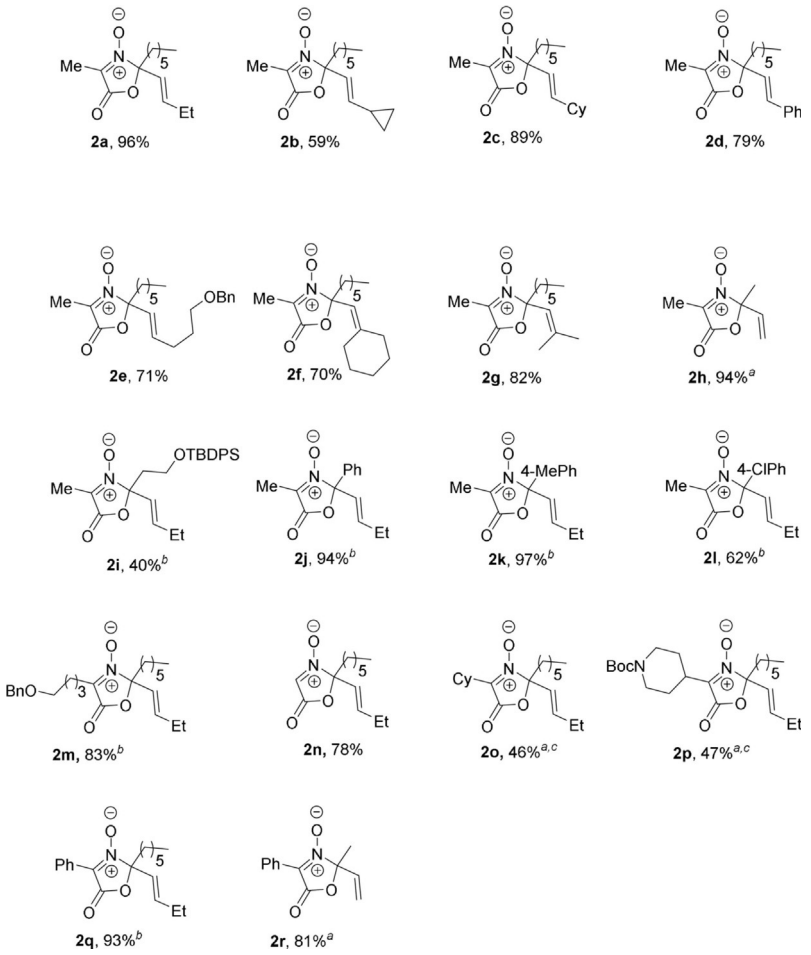
1a **2a**

Entry	Catalyst	Additive	Solvent	*t* [h]	Yield [%][b]
1	Ph_3PAuCl	$AgNTf_2$	PhMe	3	79
2	Ph_3PAuCl	$AgNTf_2$	THF	3	76
3	Ph_3PAuCl	$AgNTf_2$	CH_3CN	12	24
4	Ph_3PAuCl	$AgNTf_2$	acetone	3	92
5	Ph_3PAuCl	$AgNTf_2$	CH_2Cl_2	0.25	94
6	JohnPhosAuCl	$AgNTf_2$	CH_2Cl_2	0.25	88
7	IPrAuCl	$AgNTf_2$	CH_2Cl_2	0.25	86
8	Ph_3PAuCl	AgOTf	CH_2Cl_2	0.25	85
9	Ph_3PAuCl	$AgSbF_6$	CH_2Cl_2	0.25	96

[a] Reaction conditions: alkynyl oxime **1a** (0.1 mmol), gold catalyst (2.5 mol%), silver additive (2.5 mol%) in 2.0 mL solvent at room temperature. [b] Isolated yield. JohnPhos = 2-(di-*tert*-butylphosphino)biphenyl; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

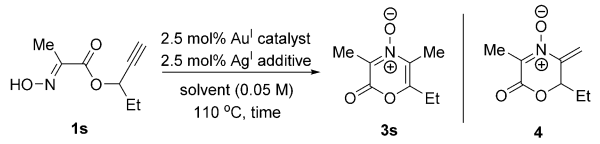
yl, phenyl, 3-benzyloxypropyl groups at the propargylic position participated in the gold(I)-catalyzed 1,3-azaprotio-transfer reaction, giving five-membered cyclic nitrones **2a–e** in yields ranging from 59 to 96%. Cyclic nitrones **2f–h** with cyclohexylidene, *gem*-dimethyl vinylidene and vinyl groups can be generated smoothly from the corresponding *E*-propargylic α-keto carboxylate oximes. The *tert*-butyldiphenylsilyl ether substrate is well tolerated, albeit giving nitrone **2i** in 40% yield. It seems like that the electronic effect of the aromatic substituents on the alkyne terminus significantly affect the formation of cyclic nitrones **2j–l**. The electron-donating group (Me) is more favorable than the electron-withdrawing one (Cl), giving **2k** in a yield higher than that of **2l**. The structure of **2k** was further confirmed by a series of NMR studies (H-H COSY, DEPT-135, HSQC, and HMBC). Oximes derived from 6-(benzyloxy)-2-oxohexanoic acid and 2-oxoacetic acid and 2-phenyl-, 2-cyclohexyl-, and 2-[1-(*tert*-butoxycarbonyl)piperidin-4-yl]-2-oxoacetic acids proceeded with the gold(I)-catalyzed 1,3-azaprotio-transfer as well as their 2-oxopropanoic acid counterparts, which enables a facile installation of diverse substituents (benzyloxybutyl, hydrogen, cyclohexyl, piperidin-4-yl and phenyl) to the C4-position of oxa-cyclic nitrones **2m–r**. It is worth noting that when a mixture containing *E*- and *Z*-oximes was examined, only one of them underwent the 1,3-azaprotio-transfer. To identify which isomer is responsible for the reactivity, we attempted parallel experiments using pure *E*- and *Z*-alkynyl oximes. It was revealed that cyclic nitrones **2q** and **2r** originate from *E*-**1q** and *E*-**1r**, respectively. The *Z*-isomers of **1q** and **1r** did not give any cyclic nitrones or heterocyclic compounds under the identical conditions (see Supporting Information for more details).

When terminal alkynyl oxime **1s** was examined using $Ph_3PAuNTf_2$ as a catalyst, a labile *N*-vinyl nitrone **4** was obtained in 25% yield (Table 2, entry 1). A more stable cyclic ni-



Scheme 2. Five-membered oxa-cyclic nitrones. Reaction conditions: internal alkynyl oxime **1** (0.1 mmol), Ph_3PAuCl (2.5 mol%), $AgSbF_6$ (2.5 mol%) in 2.0 mL dichloromethane at room temperature for 15 min unless otherwise specified. [a] Oxime, Ph_3PAuCl (10 mol%), $AgSbF_6$ (10 mol%) in DCE (0.05 M) at 80 °C for 2 h. [b] Reaction time = 2 h. [c] A mixture of inseparable *E*- and *Z*-oxime isomers was examined.

Table 2. Optimization of gold(I)-catalyzed 1,3-azaprotio-transfer of **1s**.[a]



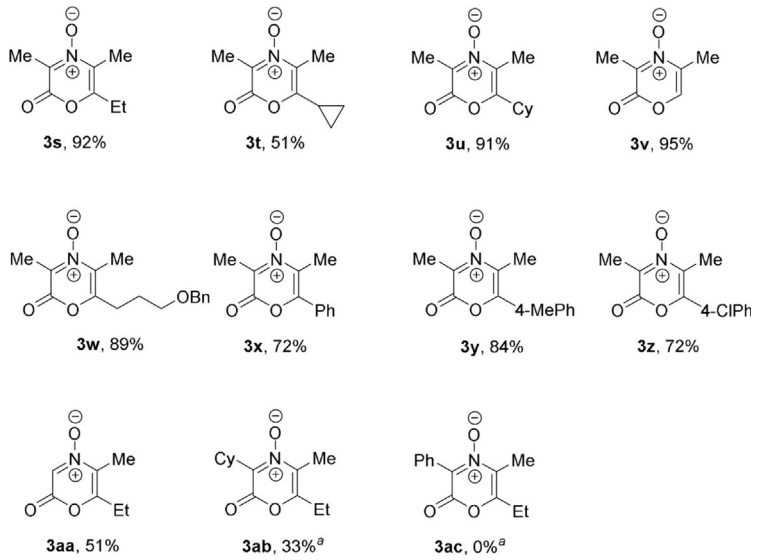
1s **3s** **4**

Entry	Catalyst	Additive	Solvent	*t* [h]	Yield[c] **3s**	**4**
1[b]	Ph_3PAuCl	$AgNTf_2$	DCM	3	0	25
2	Ph_3PAuCl	$AgNTf_2$	PhMe	3	41	5
3	IPrAuCl	$AgNTf_2$	PhMe	2	43	0
4	JohnPhosAuCl	$AgNTf_2$	PhMe	2	53	0
5[d]	JohnPhosAuCl	$AgNTf_2$ MsOH	PhMe	0.2	92	0
6[d,e]	JohnPhosAuCl	$AgNTf_2$ MsOH	PhMe	24	10	0
7	JohnPhosAuCl	–	PhMe	24	0	0
8	–	$AgNTf_2$	PhMe	24	0	0

[a] Reaction conditions: alkynyl oxime **1s** (0.1 mmol), gold catalyst (2.5 mol%), silver additive (2.5 mol%) in 2.0 mL solvent at mentioned temperature. [b] The reaction temperature is 40 °C. [c] Isolated yield. [d] 10 mol% methanesulfonic acid was employed. [e] At room temperature.

trone **3s** was isolated as the major product when the reaction was performed in toluene at elevated temperature (entry 2). Ligand screening revealed that the sterically hindered and electron-rich phosphine (JohnPhos) gave a better yield than triphenylphosphine or N-heterocyclic carbene (entries 2–4). An acidic additive was proven to be beneficial for the formation of **3s**. In the presence of a catalytic amount of methanesulfonic acid (MsOH), the gold(I)-catalyzed 1,3-azaprotio-transfer of **1s** was finished in 10 minutes at 110 °C, giving **3s** in 92% yield (entry 5). The yield dropped drastically when the reaction was performed at room temperature (entry 6). No reaction occurred in the absence of either JohnPhosAuCl or $AgNTf_2$ (entries 7–8).

Under the cooperative catalysis of JohnPhosAuNTf$_2$ and MsOH, the scope of the terminal alkynyl oximes was examined (Scheme 3). Oximes bearing ethyl, cyclopropyl, and cyclohexyl substituents located at the propargylic position underwent the 1,3-azaprotio-transfer smoothly, delivering six-membered oxa-cyclic nitrones **3s–u** in moderate to good yields. 6-Unsubstituted nitrone **3v** was obtained in 95% yield. The benzyl ether was kept untouched, giving nitrone **3w** in 89% yield. Aryl-substituted alkynyl oximes **1x–z** engaged in the 1,3-azaprotio-transfer as their alkylated counterparts, affording arylated nitro-

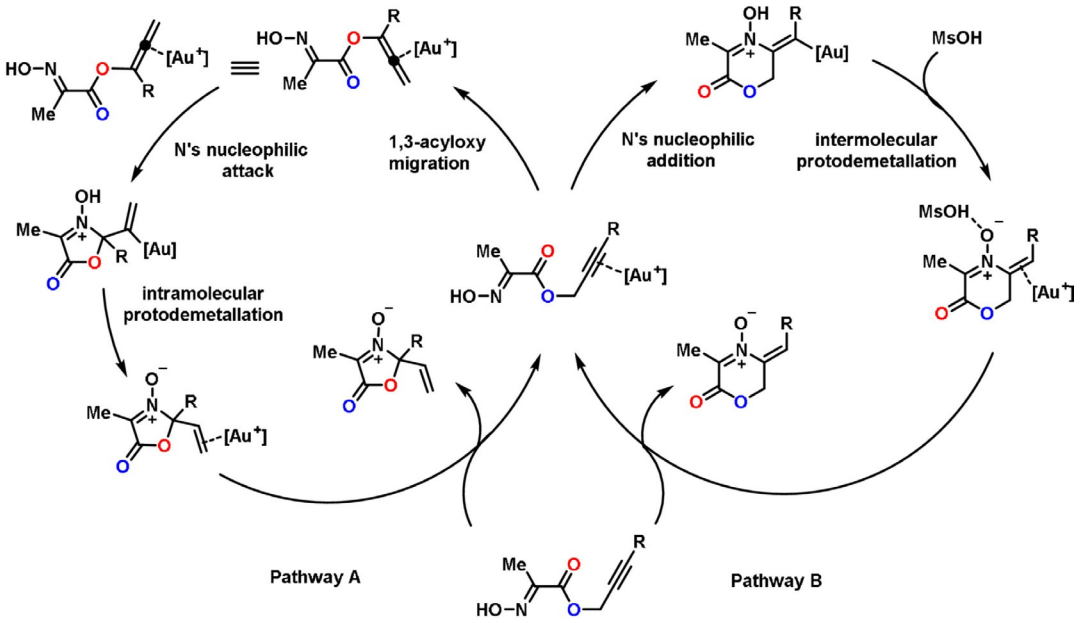


Scheme 3. Six-membered oxa-cyclic nitrones. Reaction conditions: terminal alkynyl oxime (0.1 mmol), JohnPhosAuCl (2.5 mol%), $AgNTf_2$ (2.5 mol%) and MsOH (10 mol%) in 2.0 mL $PhCH_3$ at 110 °C for 10 minutes. [a] A mixture of inseparable *E*- and *Z*-oxime isomers was examined.

nes **3x–z** in good yields. Oximes derived from 2-oxoacetic acid and 2-cyclohexyl-2-oxoacetic acid were converted to nitrones **3aa** and **3ab** in moderate yields, respectively. The incomplete conversion from a mixture containing *E*- and *Z*-**1ab** isomers to **3ab** was observed, further indicating that the configuration of oxime is essential for the 1,3-azaprotio-transfer. To our disappointment, an attempt to attain **3ac** from *E*- and *Z*-**1ac** failed at this stage.

The experimental divergent selectivity drove us to further study the mechanism by DFT calculations. We proposed two possible pathways, which start from Au^I-coordinated substrate (Scheme 4). In pathway A, 1,3-acyloxy migration takes place first, giving the allene–Au intermediate. This is followed by N–OH group's nucleophilic attack to the activated allene, and formation of a 5-membered heterocycle–Au complex, which is then liberated from the catalytic cycle through intramolecular protodemetallation. In pathway B, the substrate–Au complex directly undergoes 6-*exo* cyclization by N–OH group attack to the alkyne–Au moiety, followed by intermolecular protodemetallation mediated by MsOH to give six-membered nitrones (see later discussions). We chose **1h** and **1v** as the model substrates for analyzing the Gibbs free energy surfaces of internal and terminal alkynyl oximes, respectively. To simplify the calculation process, we used PMe_3 as the ligand and ignored the counteranion effect because of the relatively weak coordination ability of SbF_6^- and Tf_2N^- (Scheme 4).

We computed the Gibbs free energy surfaces for pathways A and B of substrates **1h** and **1v** (see Schemes 1c and 4) to understand why the R group can influence the selectivity (Figure 1). There is an equilibrium between **r0-N** (in which Au coordinates to the N atom of the substrate) and **r1** (in which Au coordinates to the alkyne of the substrate). The former complex is more stable and will be transformed to the latter complex, which is the reactive complex for the followed reactions. As demonstrated (in red), when R = Me, the reaction undergoes the 1,3-acyloxy migration via **TS1** from the alkyne coordinated intermediate **r1**, forming the six-membered ring intermediate **INT1**. The following step is a ring-opening reaction via **TS2** (the activation Gibbs free energy of this step is 5.9 kcal mol^{-1}), giving rise to Au^I-coordinated allene complex **INT2**. After that, through the intramolecular attack of nitrogen atom towards Au^I coordinated allene, the five-membered ring intermediate **INT3** is generated. This step needs an activation Gibbs



Scheme 4. Catalytic cycles of pathways A and B.

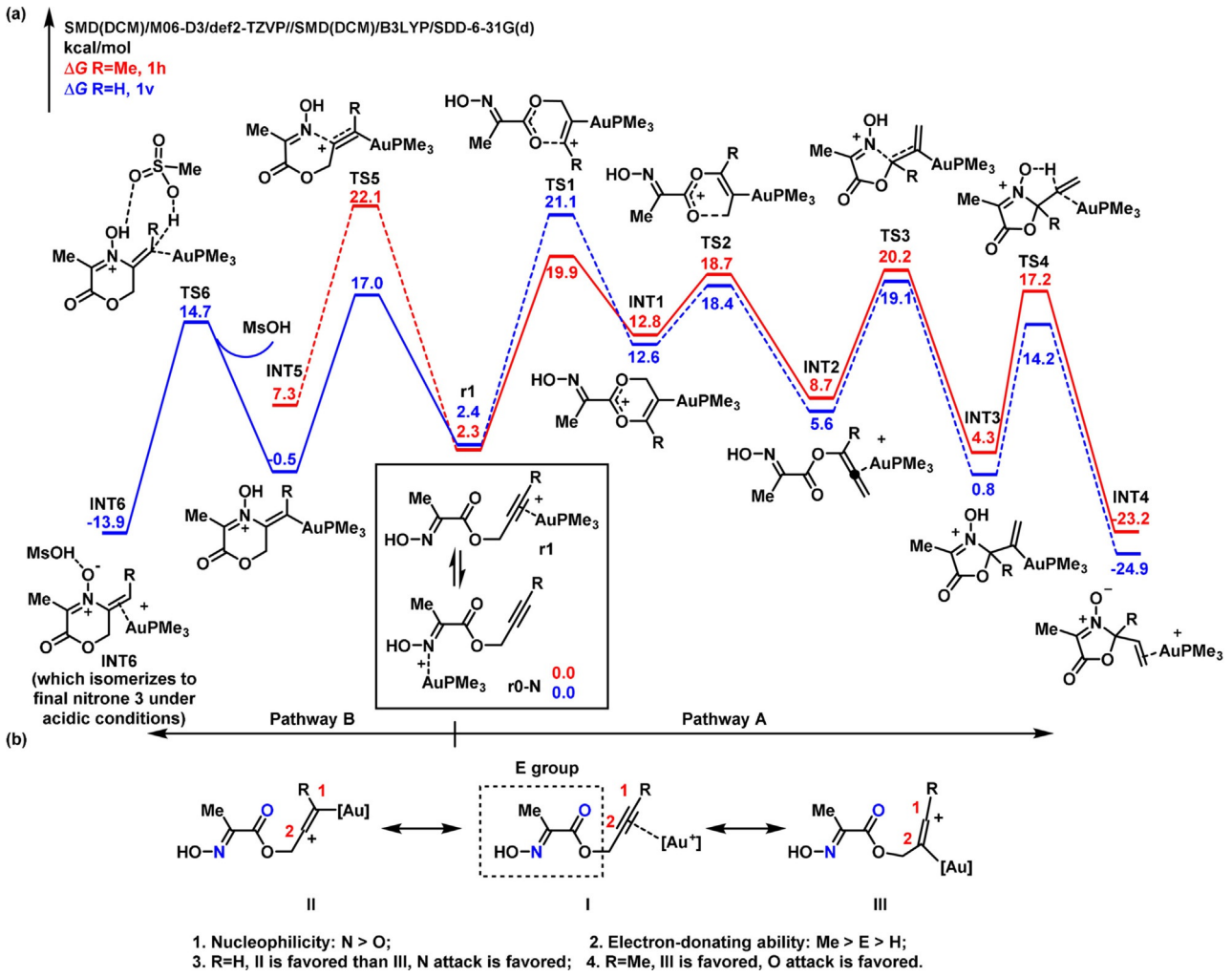


Figure 1. (a) Gibbs free energy surfaces for **1 h** (R = Me) and **1 v** (R = H); (b) Analysis of regiochemistry.

free energy of 11.5 kcal mol^{-1}. The final step is an intramolecular protonation to break Au–C bond via **TS4**, which is relatively easy with an activation Gibbs energy of 12.9 kcal mol^{-1}. In the competition pathway B (the 1,3-azaprotio-transfer process), branching from **r1**, the first step is the C–N bond formation via **TS5**, to give **INT5**. The activation Gibbs free energy of this step is 22.1 kcal mol^{-1}. Therefore, pathway A of forming five-membered nitrones is more favorable for **1 h** (19.9 vs. 22.1 kcal mol^{-1}), which is consistent with experimental observation (the intermolecular protodemetallation of **IN5** by MsOH in pathway B was not further investigated because this pathway is disfavored). However, for substrate **1 v** (R = H, Gibbs free energy surfaces in blue), pathway B is more favorable, which consists of the rate-determining 6-*exo*-cyclization step via **TS5**. The second step in pathway B is an intermolecular MsOH-mediated protodemetallation of the Au–C bond in **INT5** to form **INT6** (intramolecular protodemetallation by OH group in **INT5** is impossible because this OH group and C-Au bond are in a *trans*-configuration). This could explain why acid is required experimentally for the reaction (if acid is not added, we guess that some other proton sources such as a trace amount of water could also facilitate the protodemetallation process). This protodemetallation step is easy with an activation free energy of 15.2 kcal mol^{-1}. Finally **INT6** isomerizes to six-membered oxa-cyclic nitrones under acidic conditions. Pathway B has an activation Gibbs free energy of 17.0 kcal mol^{-1} (**TS5** is the rate-determining transition state), whereas the rate-determining step (via **TS1**) in pathway A has an activation free energy of 21.1 kcal mol^{-1}. This suggests that internal alkynyl oximes lead to five-membered nitrones, which is in agreement with the experimental results.

The above results can be explained by nucleophilicities of N and O, together with the electrophilicities of C1 and C2 in the substrates (Figure 1 b). N is more nucleophilic than O, because the activation barrier difference for their intermolecular attacks to Au-coordinated alkyne is near 5 kcal mol^{-1} (see the Supporting Information). In the intramolecular case, substrate–Au complex has three resonance forms. Form **II** is favored and C2 is more electrophilic than C1 for R=H, whereas form **III** is favored and C1 is more electrophilic than C2 for R = Me, due to the electron-donating abilities of the Me > E group > H (the E group is indicated in Figure 1 b; computational charge and structure analysis are given in the Supporting Information). For **1 v** with R=H, N attack is still favored over O attack (17.0 vs.

21.1 kcal mol^{-1}) for two reasons: 1) N is more nucleophilic than O and 2) C2 is more electrophilic than C1. For **1 h** with R=Me, C1 is more electrophilic than C2; O attack to C1 becomes a little easier than that in **1 v** (19.9 vs. 21.1 kcal mol^{-1}). But the N attack to C2 becomes dramatically sluggish (22.1 vs. 17.0 kcal mol^{-1}) as the electrophilicity of C2 is reduced dramatically. Therefore, the above different regioselectivity changes can be attributed to the different electrophilicitis of C1 and C2 caused by the R group.

To summarize, a gold(I)-catalyzed stepwise 1,3-azaprotio-transfer of propargylic α-ketocarboxylate oximes has been developed. The alkyne substituent effect resulted in the divergent formation of oxa-cyclic nitrones with different ring sizes. It was found that internal alkynyl oximes give five-membered nitrones, whereas terminal alkynyl oximes afford six-membered ones. DFT calculations revealed that in the case of internal alkynyl oximes, an initial 1,3-acyloxy-migration is more favorable than the 1,3-azaprotio-transfer. The factors including the nucleophilic properties of the oxygen atom in the carbonyl group and the nitrogen in oxime, as well as the electronic effects of alkynes, were further investigated based on computational analyses.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,3-azaprotio transfer · DFT calculations · gold catalysis · organic synthesis · oxa-cyclic nitrones

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