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Computational study on the mechanism of transition metal-catalyzed formation of highly substituted furo [3,4-d] [1,2] oxazines

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The mechanism of gold(III)-catalyzed 1,3-dipolar [3 + 3] cycloaddition reactions of 2-(1-alkynyl)-2-alken-1-ones with nitrones to afford highly-substituted furo [3,4-d] [1,2] oxazines, which are useful as structural skeletons in biologically active compounds and as synthetic building blocks in organic synthesis, have been studied computationally. The results show that the reaction proceeds via the formation of a π-complex in which the gold moiety coordinates to the triple bond of the 2-(1-alkynyl)-2-alken-1-ones, resulting in an intramolecular cyclization of the gold intermediate to generate a carbocation intermediate which is trapped by the nucleophilic oxygen of the nitrone to form a furanyl–gold complex, which upon subsequent cyclization affords the furo [3,4-d] [1,2] oxazine as well as regenerates the gold catalyst. The highest activation barrier in the entire cycle is 19.5 kcal/mol which accompanies the intramolecular cyclization step. The activation barriers for the reactions of 2-(1-alkynyl)2-alken-1-ones with electron-donating and cyclic substituents are generally lower compared to those of the parent 2-(1-alkynyl)2-alken-1-one while the reactions of 2-(1-alkynyl)2-alken-1-ones with electron-withdrawing substituents have higher activation barriers. Preliminary exploratory calculations on the possibility of replacing gold, an expensive and rare metal, with a copper-based catalyst for the reaction, show that for the key elementary steps, the Cu (III) catalyst is at least as active as the Au (III) complex, thus providing a cheaper route to furo [3,4-d] [1,2] oxazine.

Keywords: Furo [3,4-d] [1,2] oxazine; 2-(1-alkynyl)2-alken-1-one; nitrone; 1,3-dipolar cycloaddition; density functional theory; gold catalysis.

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1. Introduction

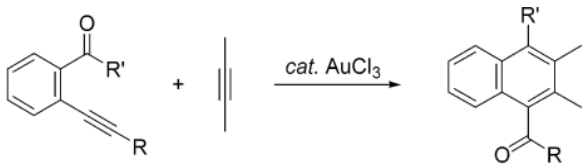
Catalysis of organic reactions by transition metals represents a new frontier in synthetic organic chemistry.[1a] Organometallic reactions have received an ever-growing attention because of their selectivity and reactivity. The use of transition metal complexes for the catalytic activation of carbon–carbon π-bonds has been greatly explored.[1b]

Gold complexes have emerged as outstanding catalysts for the catalysis of novel types of cycloaddition reactions, which mostly employ unsaturated systems such as alkenes, alkynes, 1,3-dienes, and allenes. Gold complexes tend to activate alkynes, alkenes or allenes in a highly chemoselective manner; activation that opens interesting reaction pathways that usually involve carbocationic intermediates.[2] Homogenous catalysis employing gold complexes has experienced a remarkable growth, specifically for alkyne transformations.[3] Gold catalysts are found to be of soft and carbophilic character, and have high π-acidity and high tolerance of functional groups due to the strong relativistic effect of gold.[4] Gold-catalyzed reactions are convenient and are usually accomplished under remarkably mild conditions. In addition to high-level control of chemo-, regio- and diastereoselectivity of many reactions, highly enantioselective gold catalysis has also emerged.[5] Gold-catalyzed transformations have been elaborated in numerous heterocycles and carbocycles.

Gold catalysis has been extensively employed in 1,3-dipolar cycloaddition reactions which play a significant role in the synthesis of a great variety of heterocycles.[6] 1, 3-dipolar compounds are versatile synthetic tools for the formation of five-membered rings by $[2+3]$ cycloadditions with dipolarophiles and a corresponding $[3+3]$ cycloaddition for the formation of six-membered heterocyclic compounds.[7]

Gold complexes have been found to promote the formation of highly substituted 3,4-fused bicyclic furans through 1,3-dipolar $[3+3]$ cycloaddition reactions of 2-(alkynyl)-2-alken-1-ones with nitrone. Highly substituted 3,4 bicyclic furans are useful as structural skeletons in biologically active compounds and as synthetic building blocks in organic synthesis. The construction of furan skeletons has attracted considerable attention due to their occurrence in numerous natural products.[8] Highly substituted furans are found as structural components in many biologically active natural products such as pinguisone, furodysinin and methyl vouacapenate and synthetic compounds[9] which are structural units in many natural products such as keloids, combranolides, pheromones, and polyether antibiotics and have also found applications in many pharmaceuticals, fragrances and dyes. Furan subunits are often employed as important precursors in the preparation of acyclic, carbocyclic and heterocyclic compounds.[10,11] Furans are used as commercial pharmaceutical agents, flavor and fragrance compounds, insecticides and anti-leukemic agents.[12]

Asao *et al.*[13] communicated a $AuCl_3$-catalyzed formal $[4+2]$ benzannulation between o-alkynyl(oxo)benzenes and alkyne to produce naphthyl ketones in good to high yield as illustrated in Scheme 1.

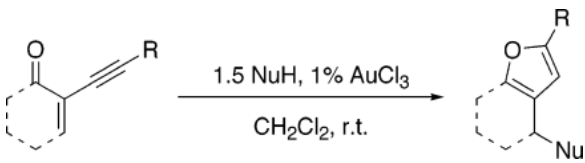


Scheme 1. $AuCl_3$-catalyzed formal [4 + 2] benzannulation between *o*-alkynyl(oxo)benzenes **1** and alkynes.[13]

Straub[14] conducted a DFT study on the mechanism proposed by Asao *et al.*[13] to investigate the influence of the oxidation state of gold on the reaction barrier of ethynyl bezaldehyde and ethyne. The results showed a minimal difference between the reaction barriers for gold (I) and gold (III)-complexes, indicating that both catalysts are potentially active enough to catalyze a cyclization reaction to the same extent provided the reaction conditions are the same.

Larock *et al.*[15] communicated a gold (III)-catalyzed approach leading to highly substituted furans through the cyclization of 2-(1-alkynyl)-2-alken-1-ones with methanol and other nucleophiles under very mild reaction conditions as shown in Scheme 2. They reported that alcohols and 1, 3-diketones, as well as various electron-rich aromatics, serve as efficient nucleophiles in this process. Their results indicated that AgO_2CCF_3 (10 h, 87%), Cu $(O_3SCF_3)2$ (9 h, 81%), $AuCl_3$ (0.5 h, 88%), and Hg $(O_2CCF_3)_2$ (8 h, 86%) all afford good yields of furan. Among these salts, however, $AuCl_3$ is the most effective catalyst based on reaction time; hence, $AuCl_3$ was employed as the catalyst for the cyclization of several other substrates.

Zhang and Schmalz[16] found out from the experiment that $(Ph_3P)AuOTf$ is an effective catalyst for the reaction of cyclopropyl ketones with nucleophiles such as MeOH. They predicted that the reaction will not take place in the absence of a nucleophile. Zhang *et al.*[17] reported a DFT study on the use of catalytic amounts of Au(I) to form a highly substituted furan from 1-(1-alkynyl)-cyclopropyl ketone with nucleophile (MeOH) as proposed earlier by Zhang and Schmalz *et al.*[16] Their theoretical study revealed that nucleophiles such as MeOH are important for the formation of highly subsbtitued furans. Fang *et al.*[10] reported a DFT study on the detailed mechanism and regioselectivity of the gold (I)-catalyzed synthesis of highly substituted furans, focusing on the factors that control the activation barriers. They also investigated the effects of solvent, and thermodynamic and kinetic properties of



Scheme 2. Transition metal-catalyzed cyclization to highly substituted furans.[15]

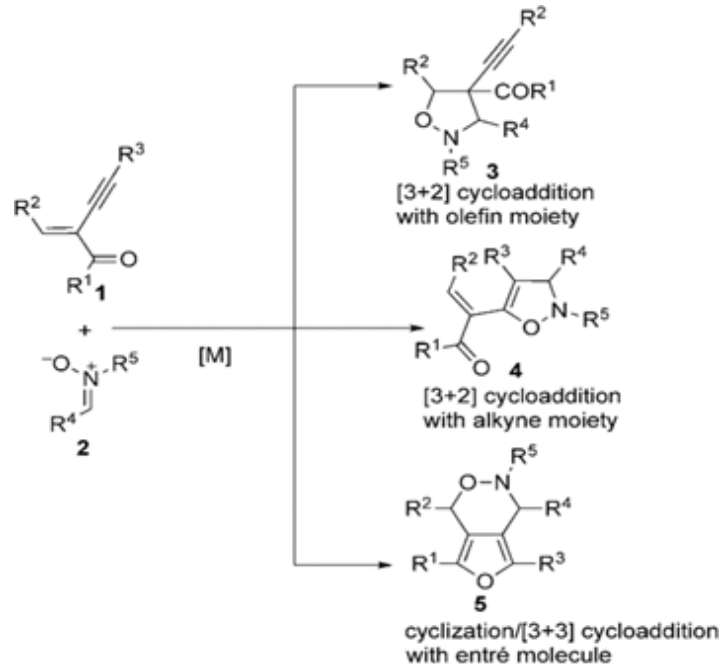
the reactions. Their proposed plausible mechanistic channels were based on their findings and experimental evidence reported earlier by Zhang and Schmalz.[16]

Yang *et al.*[18] performed a DFT study that showed that gold(III) catalyzed cyclization of cyclic 2-(1-alkynyl)-2-alken-1-ones with nucleophiles affords highly substituted furans based on experimental evidence illustrated by Larock *et al.*[15] in Scheme 2. The reaction was proposed to take place via the formation of a carbocation intermediate that reacts with nucleophiles to yield the corresponding products. Fu *et al.*[12] demonstrated that 2-(alkynyl)-2-alken-1-ones could be employed as starting materials for the formation of 3-chloro- and 3-bromofurans derivatives due to the structural similarity with 1-(1-alkynyl)-cyclopropyl ketones. Yaun *et al.*[11] reported that CuBr-catalyzed reaction of 2-(1-alkynyl)-2-alken-1-ones with nucleophile MeOH (excess) in DMF affords highly substituted furans.

Liu *et al.*[19] predicted that the metal-catalyzed cycloaddition reaction of the alkyne moiety in reactant **1** with nitrone **2** might provide three types of adducts; isoxazolidines **3** by a 1,3-dipolar $[3 + 2]$ cycloaddition of nitrones with the olefin moiety of **1**, 2,3-dihydroisoxazoles **4** by a 1,3-dipolar $[3 + 2]$ cycloaddition of nitrones with the alkyne moiety of **1**; and novel heterobicyclic furo [3,4-d] [1,2] oxazines **5** by a 1,3-dipolar $[3 + 3]$ cycloaddition (tandem double cyclizations) of nitrone with **1**. Liu *et al.*[19] examined the cycloaddition reaction of 2-(1-alkynyl)-2-alken-1-one and nitrone in the presence of different metal complexes. When the reaction was carried out in the presence of a catalytic amount of metal complexes such as $Sc(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Y(OTf)_3$, In-$(OTf)_3$, and $Ni(ClO_4)_2{\cdot}6H_2O$ there was almost no catalytic activity. The reaction proceeded very well in CH_2Cl_2 at room temperature in the presence of $Ph_3PAuOTf$. However, after reaction time of 20 min, 95% of furo [3,4-d] [1,2] oxazine was isolated at room temperature in the presence of the gold complex and in the CH_2Cl_2 which was determined by the ^1H NMR analysis. Changing to solvents such as MeCN, THF or toluene failed to improve the reaction. The $[3 + 2]$ cycloadduct was not formed, indicating that this transformation is regiospecific and chemospecific.[19]

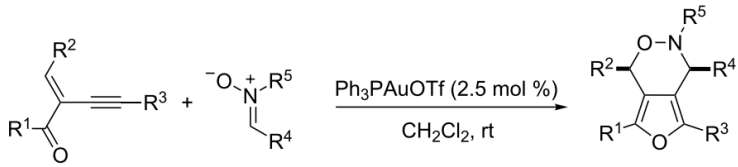
Despite the numerous methods developed for the synthesis of highly substituted furan compounds from various cyclic precursors, it still remains a grand challenge to effectively assemble novel 3,4-fused bicyclic furans especially from acyclic precursors. Liu *et al.*[19] reported a catalytic approach to the synthesis of 1, 2 oxazines from 2-(1-alkynyl)-2-alken-1-ones with nitrone under gold catalysis. Even though the synthetic utility of the reaction of 2-(1-alkynyl)-2-alken-1-ones with nitrones to form highly substituted furo [3,4-d]-[1,2] oxazines is widely known and exploited, to date no work has attempted to confirm the existence of these adducts and to elucidate the mechanism of the reaction, making it difficult to define the factors affecting product outcome. Scheme 5 has been proposed as the plausible mechanistic pathway for the gold (III)-catalyzed cycloaddition of 2-(1-alkynyl)-2-alken-1-ones with nitrones to afford furo [3,4-d]- [1,2] oxazines based on the experimental work of Liu *et al.*[19]

Even though Liu *et al.*[19] established that 2-(1-alkynyl)-2-alken-1-ones and nitrones proceed via the $[3 + 3]$ π-addition pathway to yield highly substituted

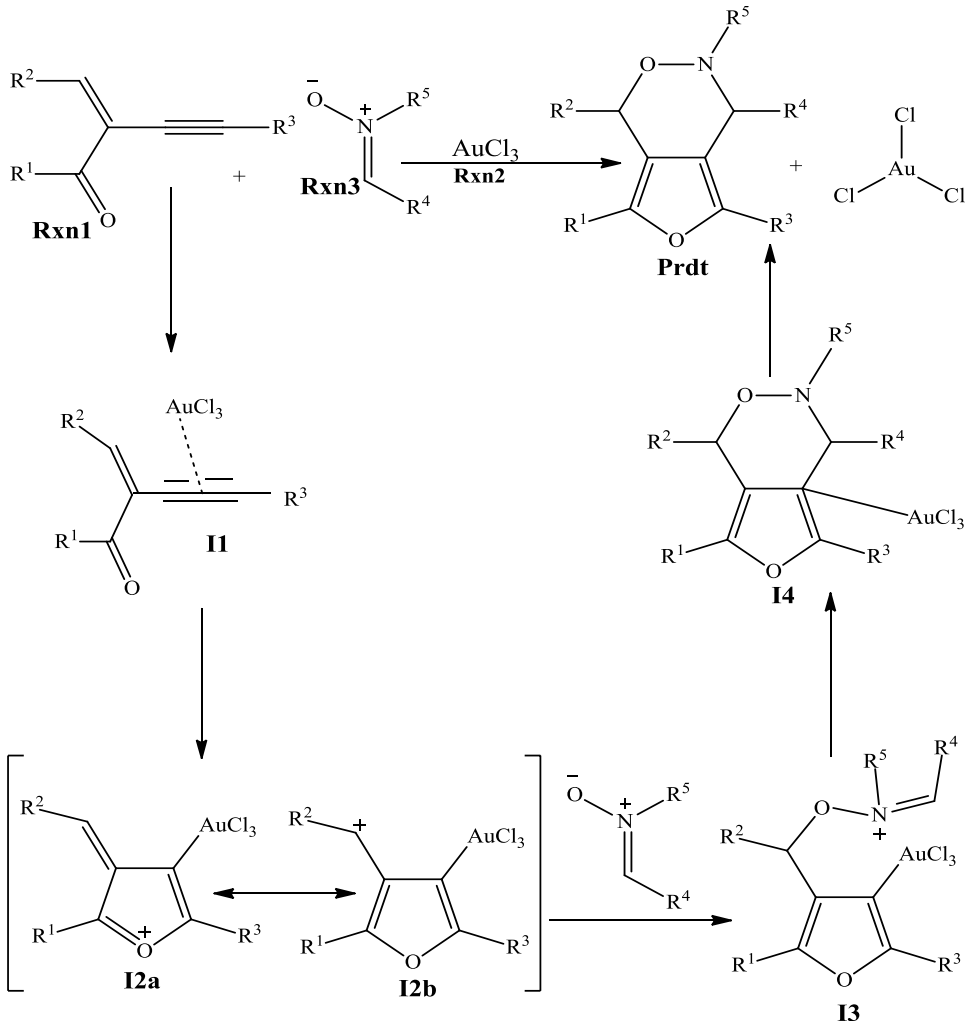


Scheme 3. Metal-catalyzed cycloaddition of 2-(1-alkynyl)-2-alken-1-ones 1 with nitrones 2.[19]

furo [3,4-d] [1,2] oxazines, the elementary mechanistic details remain unknown. Moreover, substituent effects (electronic and steric) on the mechanism of the reaction is unknown. Also, the effects of changing the metals in the same group on the reaction mechanism has not been explored.[19] This work therefore aims at exploring the [3 + 3] cycloaddition of substituted 2-(1-alkynyl)-2-alken-1-ones and nitrones catalyzed by gold. The electronic and steric effects of substituents on the reaction mechanism is also investigated at positions R^1, R^3 and R^4, R^5 for the 2-(1-alkynyl)-2-alken-1-ones and nitrone, respectively except for methyl substituted which involves substitutions at all positions of the substrates (Scheme 5). The geometries and relative energies of the relevant structures (reactants, transition states, intermediates, and products) along the proposed reaction pathway (Scheme 5) are computed to provide insight into the plausible mechanistic channel(s) of the formation of 1, 2-oxazines. The catalytic property of a cheaper



Scheme 4. Liu's proposed mechanism for the formation of 1,2-oxazine.[2]



Scheme 5. Proposed scheme for the [3 + 3] cycloaddition reaction for the formation of furo [3,4-d] [1,2] oxazines.

metal such as Cu is also investigated to explore the possibility of replacing the more expensive gold complexes with cheaper copper complexes.

2. Computational Details and Methodology

All calculations were carried out with Spartan 10 and Spartan 14 Molecular Modeling program[20,21] at the DFT MO6/6-31G* level of theory augmented with a quasi-relativistic pseudopotential, Lanl2dz for the metal centers. The LANL2DZ basis set uses the all-electron valence double zeta basis set (D95V), developed by

Dunning, for first row elements[22] and the Los Alamos ECP plus double zeta basis set developed by Wadt and Hay for the atoms Na–La, Hf–Bi.[23,24]

The starting geometries of the molecular systems were constructed using Spartan's graphical model builder and minimized interactively using the sybyl force field.[25] All geometries were fully optimized without any symmetry constraints.

The optimized geometries were subjected to full frequency calculations to verify the nature of the stationary points. Equilibrium geometries were characterized by the absence of imaginary frequencies. The transition state structures were located by a series of constrained geometry optimizations in which the forming-bonds and breaking-bonds were fixed at various lengths while the remaining internal coordinates were optimized. The approximate stationary points located from such a procedure were then fully optimized using the standard transition state optimization procedure in Spartan. All first-order saddle-points were shown to have a Hessian matrix with a single negative eigenvalue, characterized by an imaginary vibrational frequency along the reaction coordinate.[26]

3. Results and Discussion

3.1. *Gold-catalyzed reaction of the parent alkenynone and nitrone*

Figure 1 shows the optimized geometries and relative Gibbs free energies of the relevant stationary points involved in the gold (III) chloride (**Rxt 2**)-catalyzed [3 + 3] addition reaction of alkenynone (**Rxt 1**) with nitrone (**Rxt 3**). In the reactions of the unsubstituted 2-(1-alkynyl)-2-alken-1-ones and unsubstituted nitrones ($R^1 = R^2 = R^3 = R^4 = R^5 = H$) the results show that, in the first step of the catalytic cycle, the gold moiety coordinates to the triple bond (C^1–C^2) of the alkyne to generate a pi-complex intermediate **I1** which is 17.1 kcalmol^{-1} more stable than the separated reactants. In **I1**, the lengths of the two Au-C bonds are 2.60 Å and 2.24 Å, respectively, and the terminal C–C triple bond which was 1.21 Å in **Rxt 1** has lost a little of its triple bond character and is now 1.24 Å in **I1**. (In Fig. 1 the C–C triple bond in II appears longer than the C–C single bonds). Again, in **I1**, the coordination of the triple bond of **Rxt 1** to the $AuCl_3$ enhances the electrophilicity of the alkyne, and subsequent nucleophilic attack of the carbonyl oxygen to the electron-deficient alkyne forms structure **I2** through transition state **TS1-P** (square planar) or **TS1-T** (tetrahedral). The square planar transition state is 26.2 kcalmol^{-1} lower in energy than the tetrahedral transition state and this is consistent throughout all the reactions of the substituted systems. The higher activation barrier in the tetrahedral organogold trichloride could be attributed to the greater distortion in the tetrahedral geometry. **Rxt 1** reacts with $AuCl_3$ in a [3 + 3] addition fashion through transition state **TS1-P** to form carbocation intermediate **I2** and an oxonium ion (which seem to exist as resonance hybrids of each other), a step that has an activation barrier of 5.8 kcalmol^{-1} and is exergonic with relative energies of −30.9 kcalmol^{-1} and −31.0 kcalmol^{-1} for the carbocation and oxonium, ion respectively with respect to

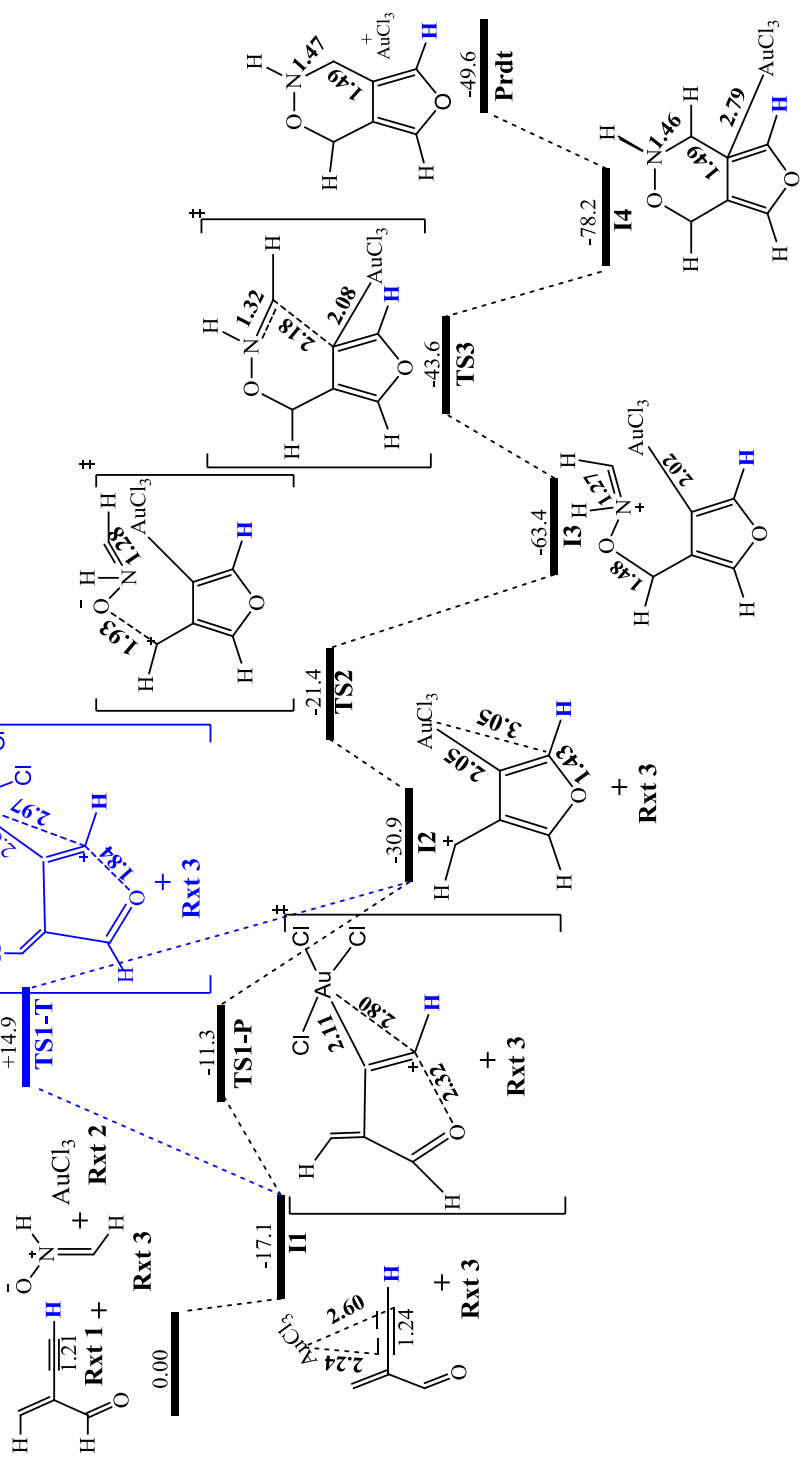


Fig. 1. Free energy profile for the [3 + 3] gold (III) catalyzed reaction of unsubstituted alkenynone with nitrone. Relative energies in kcal/mol. All bond distances are measured in Å.

the reactants. Carbocationic intermediate **I2** is rapidly attacked by the nucleophilic oxygen of the nitrone (**Rxt 3**) via transition state **TS2** to form intermediate **I3** which is 63.4 kcalmol^{-1} below the reactants, with an activation barrier of 9.5 kcalmol^{-1}. In going to intermediate **I3** via transition state **TS2**, the C–O bond length in the furanyl-gold intermediate **I3** decreases by 0.45 Å. Intermediate **I3** further goes through transition state **TS3** to form intermediate **I4**, with an activation barrier of 19.5 kcalmol^{-1} and the process is 78.2 kcalmol^{-1} exergonic. The rate-determining step is the cyclization of the fused furanyl-gold and the nitrone complex through transition state **TS3** which has a barrier of 19.5 kcalmol^{-1}. In the formation of intermediate **I4** through transition state **TS3**, the C–C bond decreases by 0.69 Å indicating bond formation, and the C–N bond increases by 0.14 Å which indicates the breaking of the C=N bond. Further cyclization leads to intermediate **I4**, the furo oxazine precursor which undergoes reductive elimination to afford the observed product. In intermediate **I4** the Au–C bond length increases from 1.27 Å in **I3** to 2.79 Å in **I4**, a clear indication that the Au–C is breaking to release the furo oxazine and re-generated the catalyst. Even though the transition state for this step could not be located, the relative energies of **I4** and **Prdt** shows that the minimum energy required to form the final product is 28.6 kcalmol^{-1}. The final product is exergonic with a reaction energy of 49.6 kcalmol^{-1} with respect to the starting reactants.

3.2. *Investigating the effects of substituents on the alkeynone*

3.2.1. *The effects of electron-donating and ring substituents on 2-(1-alkynl)-2-alken-1-ones*

This section explores the effects of electron-donating and ring substituents on alkenynone reacting with the parent nitrone. The energetics are shown in the profile in Fig. 2 and tabulated in Table 3. The results show that the reactions of 2-(1-alkynl)-2-alken-1-ones substituted with electron-donating and ring systems (R^3 = ethyl, hydroxy, amino, cyclopropane; $R^1 = R^2 = R^4 = R^5 = H$) with the unsubstituted nitrone generally affords thermodynamically less stable adducts than the parent substrate except hydroxy as depicted in Fig. 2. The intermediates formed for electron-donating and ring-substituted alkenynone and the parent nitrone are generally more stable compared to the intermediates generated from the parent substrates, this effect being much more pronounced in the case of amino and hydroxy substituents. This trend could be attributed to the strongly activating electron-donating nature of amino and hydroxy. It is important to note that the organogold intermediate **I3** and the furo-oxazine precursor **I4** for ethyl- and cyclopropane-substituted alkenynone, respectively are slightly less stable than the parent substrate while the corresponding adduct for amino and hydroxy substituted alkenynone are more stable compared to the unsubstituted substrates.

The Au–C bond length in ethyl intermediate $\mathbf{I4_{Et}}$ increases to 2.77 Å (Fig. S1) analogous to the increase in the Au–C bond distance of the parent substrates to 2.79

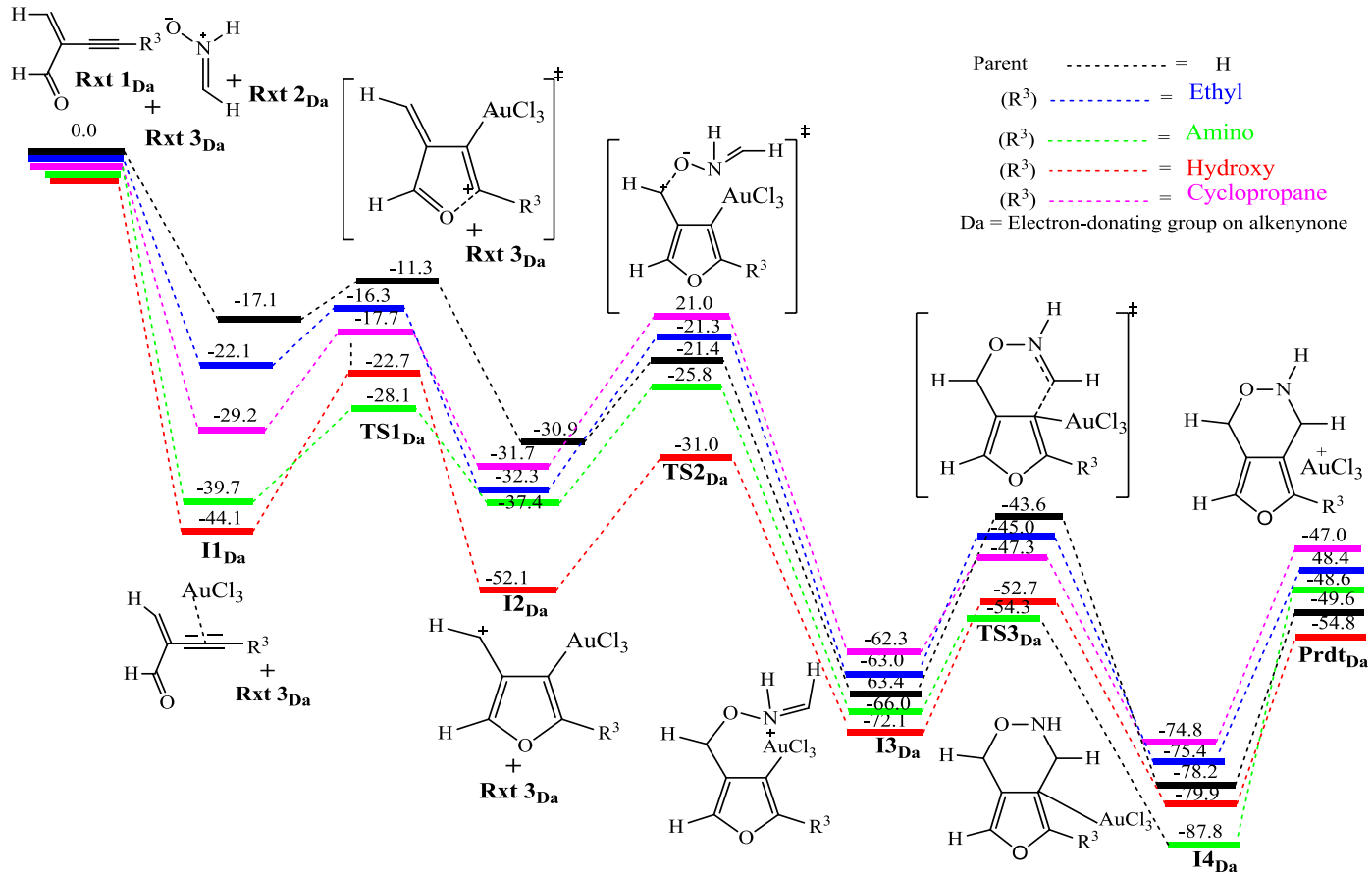


Fig. 2. Free energy profile for the [3 + 3] gold (III) catalyzed reaction of electron-donating substituted (R^3 = ethyl, amino, hydroxy, cyclopropane; $R^1 = R^2 = R^4 = R^5 = H$) alkenynone with nitrone. Relative energies in kcal/mol.

(Fig. 1) which reveals that the $AuCl_3$ catalyst cleaves from intermediate **I4** leading to the formation of the final product. However, in the study of strongly activating electron-donating groups such as OH and NH_2 and cyclopropane moiety at position R^3 of the alkenynone, the cleavage of the Au–C bond is less feasible compared to the situation in the parent cycloadduct **I4** and other substituents employed in the study which shows the elongation of the Au–C bond in the furo-oxazine cycloadduct. The difficulty in the recovery of the catalyst in the cyclopropane substituted alkenynone could be due to steric hindrance, electronic effects and ring strain in the cyclopropane moiety which makes the Au–C bond is difficult. The furo-oxazine precursor **I4** for hydroxy, amino, cyclopropane forms with a C–Au bond distance of 2.30, 2.23 and 2.42 Å, respectively between the gold and the carbon atom (Figs. S2–S4).

It has been observed that there is an increase in the activation barriers of the first and second steps for electron-donating and ring-substituted alkenynones and a decrease in the activation energies of the third step. The rate-determining step of the reactions of alkenynones with electron-donating, ring substituents is the third step which is the cyclization of the fused furanyl-gold and the nitrone complex through transition state **TS3**. The exception is hydroxyl-substituted alkenynone in which the rate-determining step shifts to the first step through transition state **TS1** which involves the cyclization of the carbonyl oxygen onto the triple bond to form the five-membered carbocation intermediate. The minimum activation energy required to form the observed products for the ethyl-, hydroxyl- and cyclopropane-substituted alkenynones are +27.0, +25.1 and +27.8 $kcalmol^{-1}$ respectively which are lower than those of the unsubstituted substrates which have a minimum activation energy of +28.6 while minimum barrier for amino substituted alkenynone is +10.6 $kcalmol^{-1}$ higher in comparison the parent substrates.

The stability of the product decrease in the order: cyclopropane < ethyl < amino < parent < hydroxy substituted alkenynone.

3.2.2. *The effects of electron-withdrawing substituents on 2-(1-alkynl)-2-alken-1-ones*

This section explores the energetics of the reactions of electron-withdrawing-substituted 2-(1-alkynl)-2-alken-1-ones (R^3 = cyano, bromo and nitro) with unsubstituted nitrone substrate. The energetics are shown in the profile in Fig. 3. It is observed that the intermediates formed are thermodynamically unstable compared to the adducts generated from the parent substrate. The rate-determining step in the reactions of electron-withdrawing-substituted alkenynones is the third step, i.e. the step involving the cyclization of the fused furanyl-gold and the nitrone complex which is the same as the rate-determining step for the parent substrate. The energies of formation of the cyano-, bromo- and nitro-substituted products are −48.5, −52.2 and −65.0 $kcalmol^{-1}$ which makes them thermodynamically stable compared to the adducts generated from the unsubstituted substrates (−49.6 $kcalmol^{-1}$) while the cyano-substituted system is comparatively less stable than the adduct generated

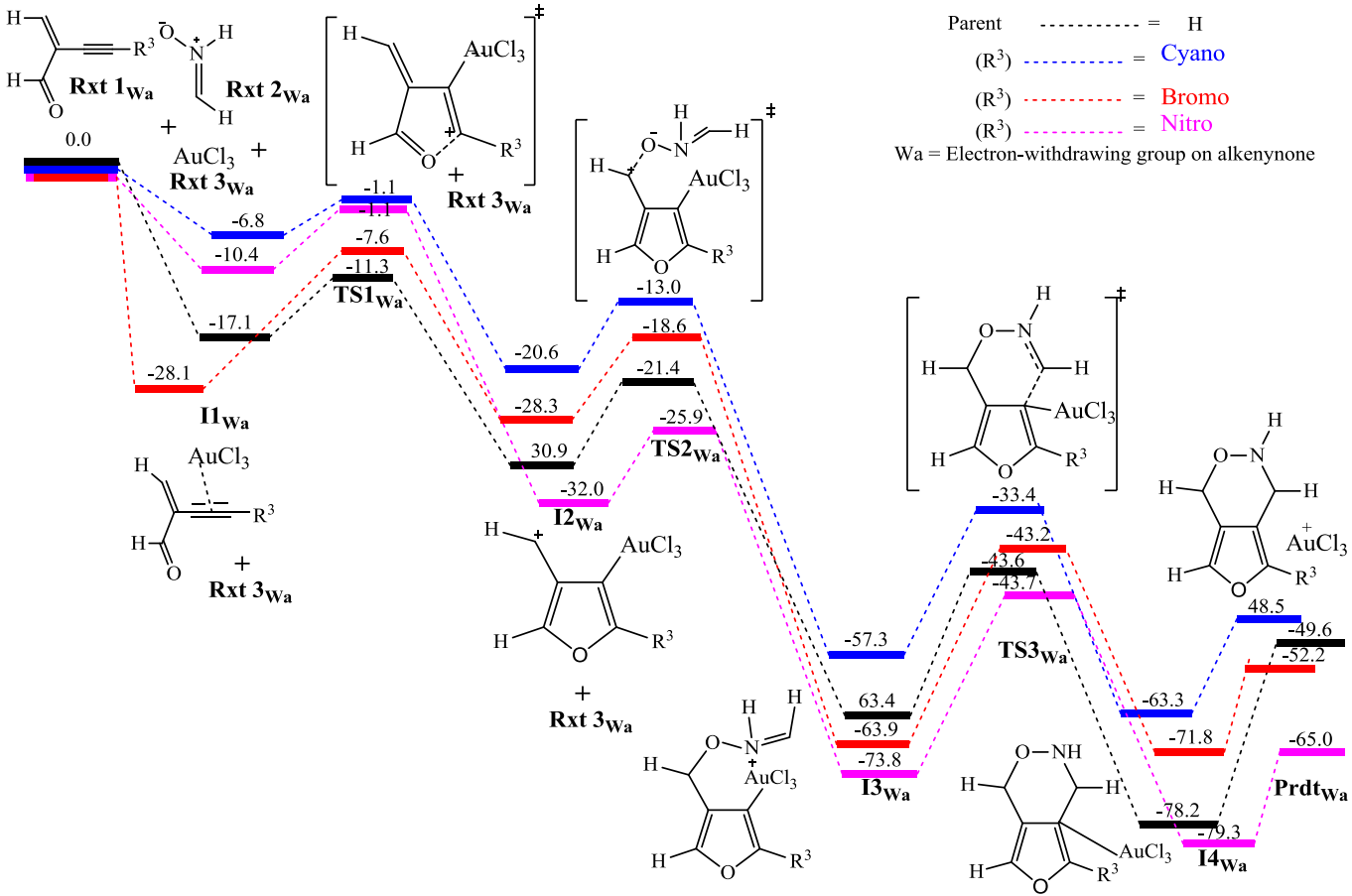


Fig. 3. Free energy profile for the [3 + 3] gold catalyzed reaction of electron-withdrawing substituted (R^3 = cyano, bromo and nitro; $R^1 = R^2 = R^4 = R^5 = H$) alkenynone with nitrone compared with parent substrate. Relative energies in kcal/mol.

Table 1. Activation barriers and reaction energies of the reactions of gold catalyzed substituted 2-(1-alkynyl)2-alken-1-ones and the nitrone. Energies in kcal/mol.

Substituent; R_3 (alken-1-ones)	I1-Au	Ea [1] P-Au	Ea [1] T-Au	I2-Au	Ea [2]-Au	I3-Au	Ea [3]-Au	I4-Au	Prdt
H	−17.1	+5.8	+32.0	−30.9	+9.5	−63.4	+19.5	−78.2	−49.6
Et	−22.1	+5.8	+36.3	−32.3	+11.0	−63.0	+18.0	−75.4	−48.4
OH	−44.5	+21.8	+48.8	−44.6	+21.1	−72.1	+19.4	−79.9	−54.8
NH_2	−39.7	+11.6	+38.1	−37.4	+11.6	−66.0	+11.7	−87.8	−48.6
(R_1–R_5) Me	−20.6	+9.6	+36.0	−40.0	+15.6	−69.1	+14.5	−74.4	−45.3
C_3H_6	−29.2	+11.5	+46.1	−31.7	+10.7	−62.3	+15.0	−74.8	−47.0
CN	−6.8	+5.7	+36.7	−20.6	+7.6	−57.3	+23.9	−63.3	−48.5
Br	−28.1	+20.5	+53.9	−28.3	+9.7	−63.9	+20.7	−71.8	−52.2
NO_2	−10.4	+9.3	+37.0	−32.0	+6.1	−73.8	+30.1	−79.3	−65.0

from the parent substitute with relative energy of $-49.2\,\text{kcalmol}^{-1}$. Thus, electron-withdrawing substituents employed in the study gives more stable products compared to the parent except CN substituted alkenynone (Table 1).

3.2.3. *Investigating the effect of electron-donating and electron-withdrawing substituents on the* 2-(1-*alkynl)*-2-*alken*-1-*one substrate* (*Mono Substitution*)

The section explores the activation barriers and reaction energies of electron-donating-substituted 2-(1-alkynl)-2-alken-1-ones and unsubstituted nitrones (R1 = R, R2 = R3 = R4 = R5 = H), and from the results, thermodynamically stable adducts compared to those of the unsubstituted substrates are obtained. This stability could be used as a result of the electron-donating nature of the substituents. R1 = $NHCH_3$ results in a less stable intermediate **C**, which has a relative energy of 13.3 kcal/mol higher than the corresponding unsubstituted intermediate (Table 2). Also, the first two activation barriers of $NHCH_3$ (**T. S1 A-B** and **T.S2 B-C**) are higher than all the other electron-donating substituents and the unsubstituted substrate. All the electron-donating substituents give furo-oxazine adducts that are less stable compared with the unsubstituted 2-(1-alkynl)-2-alken-1-one and unsubsutituted nitrones, with the exception of vinyl (–$CHCH_2$)-substituted furo-oxazine adduct which has an energy of 3.3 kcal/mol lower than the unsubstituted. Some of these trends may be due to steric as opposed to electronic effects of the substituents.

Though electron-withdrawing substituted 2-(1-alkynl)-2-alken-1-one gives thermodynamically stable adducts than the electron-donating substituted 2-(1-alkynl)-2-alken-1-one adducts the cycloaddduct **D**, the furo-oxazine precursors are less stable than the electron-donating substituted adducts. Although electron-withdrawing substituents afford thermodynamically stable adducts, the activation barriers required for the adduct formation are relatively high compared to the unsubstituted and electron-donating substituted adducts, and hence are kinetically not feasible. The rate-determining step for both electron-donating and electron-withdrawing

Table 2. Activation barriers and reaction energies of the reactions of mono-substituted 2-(1-alkynl)-2-alken-1-ones (electron-donating and electron-withdrawing) with unsubstituted nitrones. Energies in kcal/mol.

Substituents	A	T.S1 A-B	B	T.S2 B-C	C	T.S3 C-D	D	E
R1=R2=R3=R4=R5=H	−17.01	5.73	−31.16	9.71	−62.93	11.16	−77.47	−50.41
R1 = R2 = R3 = R4 = R5 = CH_3	−23.99	12.87	−43.21	19.05	−65.10	12.82	−71.25	−41.13
R1 = $NHCH_3$, R2 = R3 = R4 = R5 = H	−20.37	9.29	−39.48	25.47	−49.63	10.74	−82.78	−33.06
R1 = $CHCH_2$, R2 = R3 = R4 = R5 = H	−19.02	5.21	−40.65	14.66	−67.10	10.89	−85.96	−53.71
R1 = CHO, R2 = R3 = R4 = R5 = H	−17.09	7.3	−48.50	19.59	−67.84	12.38	−78.79	−60.79
R1 = COCl, R2 = R3 = R4 = R5 = H	−15.67	7.81	−53.53	25.08	−71.44	17.14	−78.20	−62.15

substituents involves the addition of nitrone onto the furanyl–gold complex through transition state **T.S2 B-C** (Table 2).

3.2.4. *The effect of electron-donating and electron-withdrawing substituents on the* 2-(1-*alkynl*)-2-*alken*-1-*one substrate* (*di-substitution*)

The energetics of the di-substituted 2-(1-alkynl)-2-alken-1-ones with electron-donating groups (R1 = R3 = R, R2 = R4 = R5 = H) and the unsubstituted nitrone follow the pattern of the mono-substituted 2-(1-alkynl)-2-alken-1-ones with the unsubstituted nitrone and affords far more stable adducts than the unsubstituted substrates and even the mono-substituted adducts (Figs. S6 and S7 in the supporting information). Also, the adducts obtained from the electron-withdrawing-substituted 2-(1-alkynl)-2-alken-1-ones (R1 = R3 = X, R2 = R4 = R5 = H) are generally as stable as the di-substituted electron-donating adducts. Though adducts with electron-withdrawing substituents are more stable than adducts with electron-donating substituents in terms of kinetics, the formation of adducts with electron-donating substituents are more feasible (Figs. S6 and S7). Also, the rate-determining step for the electron-donating and electron-withdrawing substituents is the step where the nitrone is added onto the furanyl–gold complex, **T.S2 B-C**. All attempts to locate the various transition states for a $NHCH_3$-substituted 2-(1-alkynl)-2-alken-1-one were not possible. Table 3 shows a comparison between the energies of electron-donating and electron-withdrawing substituted adducts as well as their activation barriers with the adducts and activation barriers of the unsubstituted reactants.

Table 3. Activation barriers and reaction energies of the reactions of substituted 2-(1-alkynl)-2-alken-1-one and unsubstituted nitrones (electron-donating and electron-withdrawing) with unsubstituted nitrones. Energies in kcal/mol.

Substituents	A	T.S1 A-B	B	T.S2 C-D	C	T.S3 D-E	D	F
R1 = R2 = R3 = R4 = R5 = H	−17.01	5.73	−31.16	9.71	−62.93	11.16	−77.47	−50.41
R1 = R3 = $NHCH_3$, R2 = R4 = R5 = H	−37.65	—	−46.73	—	−49.50	—	−77.42	−29.79
R1 = R3 = C = CH_2, R2 = R4 = R5 = H	−21.78	7.04	−42.25	16.42	−67.34	8.62	−76.32	−54.21
R1 = R3 = CHO, R2 = R4 = R5 = H	−13.11	13.04	−44.32	18.44	−70.29	17.71	−74.00	−62.72
R1 = R3 = COCl, R2 = R4 = R5 = H	−9.21	9.16	−47.53	23.13	−73.24	21.48	−72.24	−65.55

3.3. *Investigating the effects of substituents on nitrone*

Both electron-donating and electron-withdrawing substituents at position R^5 of the nitrone generally decrease the activation barriers of the reactions. For reactions of electron-donating substituted nitrones with the parent alkenynone, the rate-determining step is the third step through transition state **TS3** which involves the cyclization of the fused furanyl-gold and the nitrone complex and this is the same as the rate-determining step for substituted alkenynone and the parent nitrone. It is noteworthy that the rate-determining step shifts to the second transition state for methoxy-substituted nitrone which is in contrast to the trend in electron-donating substituents on the nitrone. This could be attributed to the strongly activating electron-donating nature of methoxy directly on the nitrone. The rate-determining step for electron-withdrawing substituents on nitrone with the unsubstituted alkenynone is the second step through transition state **TS2** which is the addition of the nitrone to the furanyl–gold complex. Nitrones with electron-withdrawing substituents generally have higher product stability while nitrone with electron-donating substituents having lower product stability.

The reaction between the substituted nitrone at R^4 and the unsubstituted 2-(1-alkynyl)-2-alken-1-ones afforded adducts with lower stability than the unsubstituted reactants (except OCH_3 and CH_2CH which have higher adduct stability for product C), and have activation barriers higher than the unsubstituted reactants, except for OCH_3 at **T.S2 B-C** as shown in Table 4. The rate-determining step for the electron-withdrawing substrates is the step where nitrone is added onto the furanyl–gold complex, **T.S2 B-C** whereas the rate-determining step for the electron-donating substituent is the cyclization of fused furanyl–gold and nitrone complex, **T.S3 C-D**.

The optimized geometries and free energy profiles for the reactions of nitrones with electron-withdrawing and electron-donating substituents studied in this work are shown in the Supplementary Material attached as Figs. S8–S10.

Table 4. Energetics of the reactions of nitrones with electron-donating and electron-withdrawing substituents at positions R^5 and R^4. Energies in kcal/mol.

Substituent; R_5 (nitrone)	I1	Ea [1] P	I2	Ea [2]	I3	Ea [3]	I4	Prdt
Ph	−17.1	+5.8	−30.9	+12.7	−65.7	+19.0	−76.4	−48.6
NH_2	−17.1	+5.8	−30.9	+18.1	−61.8	+20.5	−77.3	−49.2
NO_2	−17.1	+5.8	−30.9	+25.5	−43.6	+9.6	−71.6	−50.2
COOH	−17.1	+5.8	−30.9	+13.7	−62.3	+11.3	−92.7	−54.2
CHO	−17.1	+5.8	−30.9	+14.1	−61.3	+11.3	−89.8	−63.8
Substituent; R_4 (nitrone)	A	Ea [1] A-B	B	Ea [2] B-C	C	Ea [3] C-D	D	E
OCH_3	−17.0	+5.7	−31.2	4.02	−78.0	20.7	−76.4	−48.7
$CHCH_2$	−17.0	+5.7	−31.2	11.39	−68.1	20.7	−68.6	−39.0
CHO	−17.0	+5.7	−31.2	19.43	−52.8	10.4	−66.6	−43.0
COCl	−17.0	+5.7	−31.2	16.3	−52.0	11.9	−70.9	−48.4

3.4. *Investigating the catalytic activity of Cu (III) chloride for the formation of Furo* [3,4-*d*] [1,2] *Oxazine and its derivatives*

Extending these studies, the catalytic property of copper (III) catalyst which is a cheaper metal is explored to see the energetics compared with that of the gold catalyst. Consistently, the intermediates formed from the Cu (III)-catalyzed reaction of the parent 2-(1-alkynl)-2-alken-1-one with nitrone are less stable compared to the intermediates formed in the Au (III)-catalyzed reaction of the parent substrates. The pi-complex in the gold (III) system is $-7.1\,\text{kcalmol}^{-1}$ lower in energy than the copper pi-complex intermediate in the Au (III) system hence the copper intermediates may decompose more easily to facilitate the reaction. The five-membered carbocation intermediate **I2** for the gold and copper catalyzed reactions have relative energies of $-30.9\,\text{kcalmol}^{-1}$ and $-21.4\,\text{kcalmol}^{-1}$ respectively. The organogold intermediate **I3** for the copper-catalyzed reaction is less stable compared to the gold-catalyzed reaction. The relative energies of the intermediate **I3** for the gold- and copper-catalyzed reaction are $-63.4\,\text{kcalmol}^{-1}$ and $-57.5\,\text{kcalmol}^{-1}$, respectively. The gold-catalyzed furo-oxazine intermediate **I4** is more stable than that of the corresponding copper cycloadduct **I4**. It has been observed that the first step transition state $\mathbf{TS1_{Cu}}$ involved in copper-catalyzed pathway has a marginally lower activation barrier than that of the gold-catalyzed pathway. It is seen that the third transition state in which the cyclization of the fused furanyl-gold and the nitrone complex occurs, copper has an activation energy of $+22.0\,\text{kcalmol}^{-1}$ which is slightly higher than the gold catalyzed-reaction which has an activation barrier of $+19.5\,\text{kcalmol}^{-1}$. The formation of the final products for both the gold- and copper-catalyzed reactions are exergonic by $49.6\,\text{kcalmol}^{-1}$. This results show that the Cu (III) catalyst is at least as active as the Au (III) complex, thus providing a cheaper route to furo [3,4-d] [1,2] oxazine.

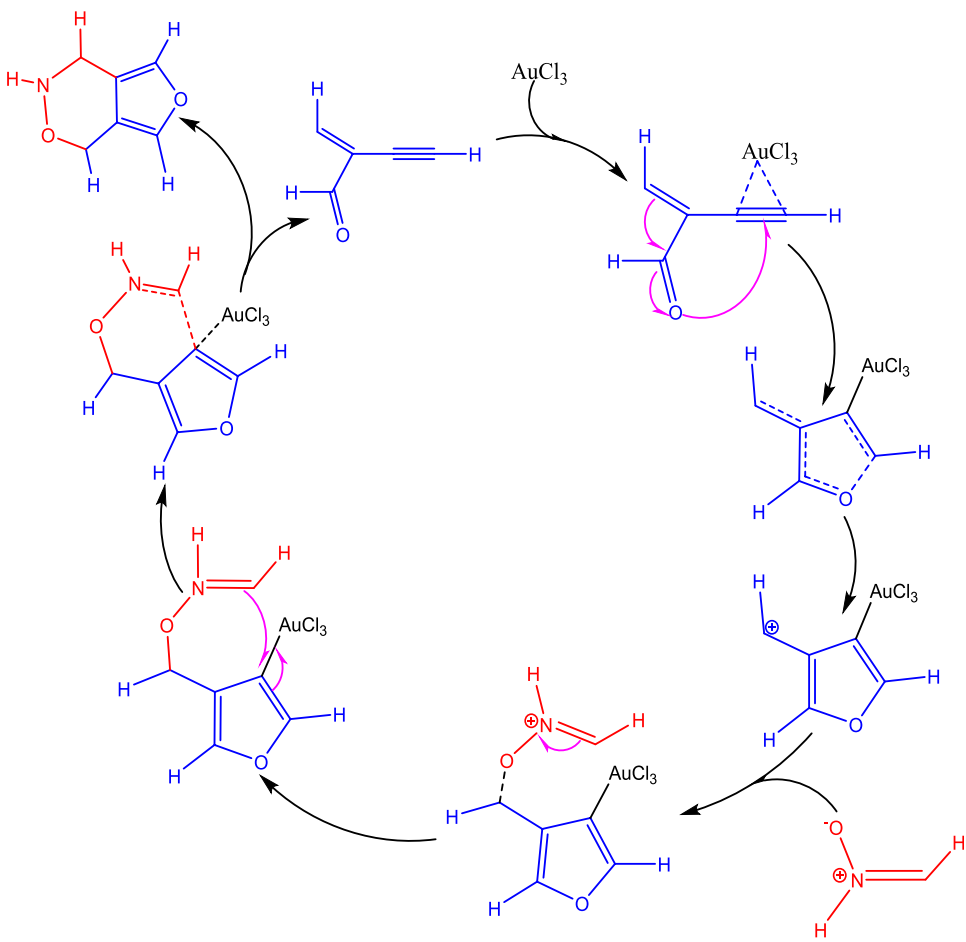
Table 5. Activation energies, reaction energies of intermediates and products formed from gold and copper catalyzed reaction of 2-(1-alkynyl)2-alken-1-ones and the nitrone. Energies in kcal/mol.

Substituent; R_3	I1		Ea [1]		I2		Ea [2]		I3		Ea [3]		I4		Prdt	
(alken-1ones)	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au
H	−10.0	−17.1	+3.4	+5.8	−22.2	−30.9	−1.3	+9.5	−57.5	−63.4	+22.0	+19.5	−69.8	−78.2	−49.6	−49.6
Et	−16.1	−22.1	+6.1	+5.8	−24.3	−32.3	+0.5	+11.0	−58.1	−63.0	+22.6	+18.0	−67.0	−75.4	−48.4	−48.4
OH	−34.9	−44.5	+48.6	+21.8	−34.6	−44.6	+0.2	+21.1	−61.7	−72.1	+18.9	+19.4	−71.0	−79.9	−54.8	−54.8
C_3H_6	−22.1	−29.2	+10.1	+11.5	−25.2	−31.7	+1.3	+10.7	−57.4	−62.3	+20.1	+15.0	−65.2	−62.3	−47.0	−47.0
NO_2	−5.10	−10.4	+8.5	+9.3	−29.1	−32.0	−3.5	+6.1	−69.6	−73.8	+34.4	+30.1	−72.9	−79.3	−65.0	−65.0
Br	−8.9	−28.1	+7.1	+20.5	−21.0	−28.3	−1.9	+9.7	−58.0	−63.9	+24.8	+20.7	−62.7	−71.8	−52.2	−52.2
CN	−0.9	−6.8	+5.2	+5.7	−14.0	−20.6	−3.3	+7.6	−53.6	−57.3	+28.1	+23.9	−55.7	−63.3	−48.5	−48.5
Substituent; R_3	I1		TS [1]		I2		TS [2]		I3		TS [3]		I4		Prdt	
(alken-1ones)	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au	Cu	Au
OCH_3	−10.0	−17.1	+3.4	+5.8	−22.2	−30.9	+4.9	+21.6	−44.9	−47.3	+19.6	+21.6	−62.2	−70.6	−42.9	−42.9
Ph	−10.0	−17.1	+3.4	+5.8	−22.2	−30.9	−5.2	+12.7	−57.7	−65.7	+18.9	+19.0	−68.4	−76.4	−48.6	−48.6
NH_2	−10.0	−17.1	+3.4	+5.8	−22.2	−30.9	−6.5	+18.1	−54.2	−61.8	20.9	+20.5	−68.8	−77.3	−49.2	−49.2
COOH	−10.0	−17.1	+3.4	+5.8	−22.2	−30.9	−6.9	+13.7	−57.1	62.3	+15.1	+11.3	−84.4	−89.8	−54.2	−54.2

As seen in Table 5, some of the activation barriers are slightly negative. This may be due to the basis set supposition error as was seen in the works of Frenking and Haunschild.[27,28]

4. Summary and Conclusions

Molecular-level understanding has been provided in support of the Liu-proposed mechanism in the gold-catalyzed 1,3-dipolar [3 + 3] cycloaddition reactions of 2-(1-alkynyl)-2-alken-1-ones with nitrones to afford highly substituted furo [3,4-d] [1,2] oxazines. The reaction has been shown to proceed via the formation of a π-complex in which the gold moiety coordinates to the triple bond of the 2-(1-alkynyl)-2-alken-1-ones, resulting in an intramolecular cyclization of the gold intermediate to generate a carbocation intermediate which is trapped by the nucleophilic oxygen of the nitrone



Scheme 6. Mechanism of gold-catalyzed formation of substituted furo [3,4-d] [1,2] oxazines.

to form a furanyl–gold complex, which upon subsequent cyclization affords the furo [3,4-d] [1,2] oxazine as well as regenerates the gold catalyst (Scheme 6).

The highest activation barrier in the entire cycle is 19.5 kcal/mol which accompanies the intramolecular cyclization step. The activation barriers for the reactions of 2-(1-alkynyl)2-alken-1-ones with electron-donating and cyclic substituents (ethyl, hydroxy, amino, methyl, and cyclopropane) are generally lower compared to those of the parent 2-(1-alkynyl)2-alken-1-one, while those of 2-(1-alkynyl)2-alken-1-ones with electron-withdrawing substituents (cyano, bromo and nitro) have higher activation barriers. Also, the mono-substituted 2-(1-alkynyl)2-alken-1-one at R1 and disubstituted 2-(1-alkynyl)2-alken-1-one at R1 and R3 with either electron-donating ($NHCH_3$ and $CHCH_2$) or electronwithdrawing (CHO and COCl) substituents have higher activation barriers than the unsubstituted reactants.

Substituents on the nitrone, whether electron-donating or withdrawing tend to decrease the activation barrier except amino group. Nitrones with electron-withdrawing substituents generally have higher product stability while nitrone with electron-donating substituents have lower product stability.

Preliminary exploratory calculations on the possibility of replacing gold, an expensive and rare metal, with a copper-based catalyst for the reaction, show that for the key elementary steps, the Cu (III) catalyst is at least as active as the Au (III) complex, thus potentially providing a cheaper route to the formation of furo [3,4-d] [1,2] oxazines.

Competing Interests

The authors declare no competing interests.

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