Computational Exploration of Counterion Effects in Gold(I)-Catalyzed Cycloisomerization of ortho-(Alkynyl)styrenes

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ABSTRACT: A detailed theoretical analysis of the mechanism and chemoselectivity for gold(I)-catalyzed reaction of o-(alkynyl)styrene containing an isopropyl and a methyl at the terminal position of the alkene has been reported in this work. Two different counterions (SbF$_6^-$ and OTs$^-$) were studied as model catalysts. According to our calculation, for SbF$_6^-$, the reaction pathway is more prone to direct 1,2-H shifts (isopropyl H) than the elimination and ring expansion pathway. However, an elimination pathway affords the indenyl derivative by forming p-toluenesulfonic acid (HOTs), which may be the main pathway in the presence of OTs$^-$. The chemoselectivity for the title reaction is mainly determined by the electronic effect of the counterion and the substituent rather than the steric effect. In other words, less basic SbF$_6^-$ mainly provides the charge separation effect rather than assisted proton elimination. However, the more basic OTs$^-$ mainly assist proton elimination through the formation of HOTs. In addition to the good agreement with the experimental data, the density functional theory results also provide a significant contribution to the understanding of the reaction mechanism.

1. INTRODUCTION

Gold(I) catalysis is currently recognized as one of the hot topics in organic synthesis. New methods based on gold catalysis has not only become an experimental research field but also a major field of theoretical research. For gold-mediated transformations of alkynes, the cationic gold system is a commonly used type of catalyst that is primarily prepared by the metathesis reaction between the simple gold complex LAuCl and the silver salt AgX (X: “noncoordinating” counterion). Various anions (such as SbF$_6^-$, NTf$_2^-$, OTs$^-$, and OT$^-$) can be applied in the gold catalytic system. Compared with a large number of effort on understanding the effects of ligands, it is only recently that chemists have begun to study the effect of counterions on determining the reaction pathway in the gold-catalyzed reactions. In fact, counterions often play an important role in reactions involving cationic species. The counterion was generally considered to be an important factor in the regioselectivity and stereoselectivity of the reaction. For example, several groups reported the skeletal rearrangement reaction of several metal-catalyzed α-substituted and mono- or non-β-substituted o-(alkynyl)styrenes. In these studies, the more common examples are the 6-endo cyclization with only a small amount of 5-exo adducts. In addition, 5-endo adduct was also detected. Recently, a series of gold-catalyzed reaction of ortho-(alkynyl)styrenes to form different products has been reported by the Sanz group. These experimental results show that the olefin substitution pattern is crucial for the ring isomerization of ortho-(alkynyl)styrenes. Among these studies, the recent reaction of o-(alkynyl)styrenes from the Sanz group envisioned that naphthalene derivatives (6-endo-cyclization) are isolated in high yield for α-substituted (R$^1$ = Me) o-(phenylethynyl)styrenes under the conditions of [AuCl(Ph$_3$P)]/AgSbF$_6$ catalysis. However, β, β-disubstituted (R$^2$ = R$^3$ = Me) o-(phenylethynyl)styrenes give indenyl derivatives in very high yields. Under the conditions of [AuCl(Ph$_3$P)]/AgSbF$_6$ catalysis, a new reaction pathway was successfully achieved for o-(alkynyl)styrene containing an isopropyl and a methyl at the terminal position of the alkene. Interestingly, changing the catalyst to [AuCl(Ph$_3$P)]/AgOTs will result in the formation of the indenyl derivative product (Scheme 1). According to the experiment results, Sanz et al. proposed three possible pathways including elimination, ring expansion, and 1,2-H shift to explain experimental facts (Scheme 2). In our previous work, the regioselectivity in the [AuCl(Ph$_3$P)]/AgSbF$_6$-catalyzed cycloisomerization of α-substituted and β, β-disubstituted o-(phenylethynyl)styrenes has been employed by density functional theory (DFT) calculations. In addition, a novel reaction pathway for elimination of protons involving the four-center-three-electron intermediate is located from our...
In this work, our aim is mainly focused on the effect of counterions in the chemoselectivity. Experimental facts show that the chemoselectivity of o-(alkynyl)styrene containing an isopropyl and a methyl at the terminal position of the alkene is entirely controlled by the counterion. That is, under the conditions of [AuCl(Ph3P)]/AgSbF6 catalysis, 1,2-H shift is the main reaction pathway. An elimination pathway for the formation of the indenyl derivative may be the main pathway in the presence of [AuCl(Ph3P)]/AgOTs. In the present work, we will pursue a detailed DFT investigation of the title reaction to explore the different role of SbF6− and OTs− in the determination of the chemoselectivity. We believe that the calculation results provided in this study are very

**Scheme 1. Gold(I)-Catalyzed Cycloisomerization of o-(Phenylethynyl)styrene**

**Scheme 2. Plausible Pathway Proposed by Sanz et al.**

**Figure 1.** Full energy profile calculated of the first step for series A and B with selected structures (selected bond lengths are in Å). Relative energies are expressed in kcal/mol.
important for a better understanding of the gold(I)-catalyzed reaction of o-(alkynyl)styrene containing an isopropyl and a methyl at the terminal position of the alkene. In addition, it also offers some new insights into the generation of chemoselectivity under different counterions.

2. RESULTS AND DISCUSSION

In our DFT calculations, o-(alkynyl)styrene containing an isopropyl and a methyl at the terminal position of the alkene were used as model substrates. H$_3$PAuSbF$_6$ (series A) and H$_3$PAuOTs (series B) were selected as model catalysts.

Figures 1, 2, 3, and 4 show the energy profiles for series A and B along with selected structures and key geometry parameters (e.g., bond lengths). The detailed structural parameters and energies for the structures determined here are given in the Supporting Information.

2.1. Computational Results for H$_3$PAuSbF$_6$-Catalyzed Reaction (Series A). The first step of the series A forms a stable intermediate A-1 in which the Au atom is coordinated with the $\pi$-bond of the alkyne moiety. The bond lengths of the two Au–C bonds in A-1 are 2.370 and 2.346 Å. In fact, the C=C coordination to gold enhances the electrophilicity of the...
C≡C bond. The next step for intramolecular nucleophilic attack of the olefin will form a cationic intermediate A-2 through A-TS1. The free energies of activation for this step is 8.9 kcal/mol for A-TS1 (Figure 1). In addition, the 5-exo-dig can also provide another possible reaction pathway. The free energies of activation for this pathway are 22.9 kcal/mol. Higher activation energy indicates that 5-exo-dig cyclization is unfavorable. After formation of A-2, without the assistance of SbF$_6^-$, the next step would afford enyne intermediates A-2a or A-2d via the direct 1,4-H shift (H on methyl or isopropyl) process. The calculated free energy barrier of the direct 1,4-H shift process was as high as 30.3 and 31.8 kcal/mol for A-TSe1 (H on isopropyl) and A-TSf1 (H on methyl), respectively (Figure S2, Supporting Information). These values indicated that the direct proton transfer pathway is not possible under experimental conditions. However, experimental results obviously revealed that minor (10%) products of the indenyl derivative would be generated from the elimination pathway. Following our previous work, the reaction pathway for elimination of protons assisted by SbF$_6^-$ was also located in our present calculation. The calculated free energy barriers for A-TSa1 (H on isopropyl) and A-TSd1 (H on methyl) are 12.9 kcal/mol.

Figure 3. Full energy profile calculated for series A via path b with selected structures (selected bond lengths are in Å). Relative energies are expressed in kcal/mol.
and 13.8 kcal/mol, respectively (Figure 2). This calculation shows that A-TSa1 and A-TSd1 have relatively lower free energy, which makes elimination pathways possible. Subsequently, indene A-3a and A-3d would be generated via protodemetalation and 1,2-H shift, in addition to the regeneration of the gold catalyst. The activation free energies of these steps are 1.4 and 11.1 and −0.4 and 11.3 kcal/mol for A-TSa2 and A-TSa3 and A-TSd2 and A-TSd3, respectively. For A-TSd2, the activation free energy is negative, which may be mainly because A-1d is stabilized by π···H···F weak interactions and is more inclined to form more stable intermediates. The complete catalytic processes are exothermic by −23.6 and −19.9 kcal/mol lower than A-1. Apart from the elimination pathways, intermediate A-2 could also undergo a direct 1,2-H shift, Friedel−Crafts-type alkylation and protodemetalation furnishes final product (pathway b). First, the direct 1,2-H (H on methyl) shift was performed. Consistent with previous results,9 the activation energy for this pathway is as high as 31.8 kcal/mol (Figure S2, Supporting Information), which revealed that the formation of the product via pathway b is not favorable. Subsequently, we turn our attention to the direct 1,2-H shift on isopropyl groups. Because of the different migration directions, two different chiral products (Syn or Anti) would be formed in this pathway. Figure 3 shows that the calculated free energy barriers for the direct 1,2-H (H on isopropyl) shift are 11.8 and 12.9 kcal/mol for Syn-A-TSb1 and Anti-A-TSb1, respectively. In addition, the free energies of the reaction for Syn-A-1b and Anti-A-1b are 4.2 and 7.1 kcal/mol with respect to A-2, respectively. Subsequent Friedel−Crafts-type alkylation reaction of Syn-A-1b and Anti-A-1b would afford the dihydrobenzo[α]fluorene derivative Syn-A-2b and Anti-A-2b through Syn-A-TSb2 and Anti-A-TSb2. The calculated free activation energies for Friedel−Crafts-type alkylation reaction are 4.8 and 3.0 kcal/mol for Syn and Anti, respectively. Next, Syn-A-2b and Anti-A-2b undergoes protodemetalation, affording the final product Syn-A-3b and Anti-A-3b with a barrier of 8.6 and 9.8 kcal/mol for Syn and Anti, respectively. In addition, the formation of Syn-A-3b and Anti-A-3b is strongly exergonic by 37.0 and 35.4 kcal/mol for Syn and Anti, respectively. For pathway c, the corresponding 6-endo-cyclization products will be formed by ring expansion. The calculated free activation energy for ring expansion is 19.9 kcal/mol (Figure S2, Supporting Information). Higher activation energies observed for this step indicate that the pathway for 6-endo is unfavorable.9

An overview of all the reaction pathways of the series A reveals that the final product is determined by A-TSa1, A-TSB1 (Syn and Anti), and A-TSd1. The calculated free energies of activation are 12.9, 11.8, 12.9, and 13.8 kcal/mol for A-TSa1, Syn-A-TSB1, Anti-A-TSB1, and A-TSd1, respectively. Relatively lower free energies of activation observed for Syn-A-TSB1 compared with those of A-TSa1, Anti-A-TSB1, and A-TSd1 indicated that the direct 1,2-H (H on isopropyl) shift pathway would predominantly take place to finally produce Syn-A-3b. Furthermore, relatively small free energies of activation difference (1.1, 1.1, and 2.0 kcal/mol) between Syn-A-TSB1 and A-TSa1 and Anti-A-TSB1 and A-TSd1 means that the Anti-A-3b and indenyl derivatives A-3a and A-3d would be generated as byproducts. Our calculations are completely consistent with the experimental observations.8e

In addition, the lower barriers are found for direct 1,2-H shift (H on isopropyl), mainly because of the following reasons.
First, in the presence of less basic SbF$_6^-$, the elimination pathway is an abnormal reaction pathway through a four-center-three-electron structure instead of forming HSBF$_6^-$, which makes SbF$_6^-$-assisted migration efficiency relatively low. The second and most important reason is that the structure of the direct 1,2-H shift transition state can be stabilized by the presence of two methyl groups in the isopropyl group, which can greatly reduce the free energies of activation. This conclusion can also be proved from the high free energies of activation of 1,2-H shift (H on methyl). Third, because of the presence of ions, the charge separation effect in the solution is more obvious, and it also contributes to the reduction of the free energies of activation of 1,2-H shift.

2.2. Computational Results for H$_2$PaAuOTs-Catalyzed Reaction. Similar to series A, the first step for series B also led to the formation of B-1 in which the Au atom is coordinated with the $\pi$-bond of the alkyne moiety. Next, cationic intermediate B-2 will be formed by intramolecular nucleophilic attack of the olefin (B-TS1). This step requires free energies of activation of 8.1 kcal/mol (Figure 1). The relatively small difference in free energies of activation between A-TS1 and B-TS1 indicates that the counterion has almost no effect on this step. For 5-exo-dig cyclization pathway of series B, the calculated free energy of activation is 24.3 kcal/mol. This value also disclosed that 5-exo-dig cyclization is unfavorable. After the formation of B-2, three basic possible pathways can also be envisioned. Because the free energies of activation for direct 1,4-H shift are very high, only the counterion-assisted proton elimination pathway is considered. Unlike SbF$_6^-$, OTs$^-$-assisted proton elimination is a classic elimination reaction that forms p-toluenesulfonic acid (HOTs). Figure 4 shows that the calculated free energy barriers are 11.9 and 11.0 kcal/mol for B-TSa1 (H on isopropyl) and B-TSd1 (H on methyl), respectively. The formation of B-1a and B-1d is an exothermic process, and the energies of the reaction are $-$12.0 and $-$14.7 kcal/mol with respect to B-2, respectively. The subsequent protodemetalation and regeneration of the gold catalyst require activation energies of 3.7 and 9.4 kcal/mol, respectively. Similarly, intermediate B-2 could also undergo a direct 1,2-H shift pathway (pathway b). Because of the high free energies of activation of 1,2-H shift (H on methyl), only 1,2-H (H on isopropyl) shift was calculated in our calculation. Figure 4 shows that the calculated free energy barriers for the direct 1,2-H shift on isopropyl groups are 15.6 and 17.7 kcal/mol for Syn-B-TSb1 and Anti-B-TSb1, respectively. Relatively higher free activation energies observed for this step indicate that the direct 1,2-H shift (H on isopropyl) is not favorable. For pathway c, the calculated free activation energies for the ring expansion pathway is as high as 22.4 kcal/mol for B-TSc1, which revealed that the 6-endo is also unfavorable. The overall analysis of the potential energy surface of the series B shows the final product would evolve through the elimination pathway to afford mixed indenyl derivative B-2a and B-2d. On the basis of our calculation results, in the presence of more basic OTs$^-$, the elimination pathway is a classic reaction pathway to form HOTs and is a strongly exothermic process with relatively low activity energy. In addition, the direct 1,2-H shift transition state can also be stabilized by the presence of two methyl groups in the isopropyl group, and the charge separation ability of OTs$^-$ in solution is weaker than that of SbF$_6^-$, resulting in higher free activation energies for direct 1,2-H shift of series B.

2.3. Role of SbF$_6^-$ and OTs$^-$ . According to our calculated results, the chemoselectivity of o-(alkynyl)styrilene containing an isopropyl and a methyl at the terminal position of the alkene is mainly controlled by the electronic effect of the counterion and substituent rather than the steric effect. In the presence of less basic SbF$_6^-$, the elimination path through the four-center-three-electron intermediate indeed can be observed in our calculation. However, the elimination pathway is an abnormal reaction pathway, which makes SbF$_6^-$-assisted migration efficiency relatively low. In contrast, because of the presence of two methyl groups in the isopropyl group and strong charge separation effects, the direct 1,2-H shift would be the most favorable pathway. In other words, SbF$_6^-$ mainly provides the charge separation effect rather than assisting proton elimination. Under the presence of more basic OTs$^-$, a classic reaction pathway to form HOTs was located and was a strongly exothermic process with relatively low activity energy. Although the direct 1,2-H shift transition state can also be stabilized by the presence of two methyl groups in the isopropyl group, the charge separation ability of OTs$^-$ in solution is weaker than that of SbF$_6^-$, resulting in relatively higher free activation energies for direct 1,2-H shift of series B. This fact can also be confirmed by the NBO charge of A-2 and B-2. The NBO charges for the F and O atoms are $-$0.498 and $-$0.669 au for A-2 and B-2, respectively. Larger negative charges found for the O atom of A-2 suggest that it is easier for OTs$^-$ to eliminate protons. Furthermore, because of the extremely high acidity of HSbF$_6$, the formation of HSBF$_6^-$ is not possible; only the elimination path through the four-center-three-electron can be located. However, the more basic OTs$^-$ easily assist proton elimination through the formation of HOTs. Our calculations are completely consistent with the experimental observations.

3. CONCLUSIONS

In summary, the mechanism and chemoselectivity for gold(I)-catalyzed reaction of o-(alkynyl)styrilene containing an isopropyl and a methyl at the terminal position of the alkene are employed by the DFT calculations. On the basis of our calculations, we can draw the following conclusions:

1. Calculation results clearly show that the direct 1,2-H shift (H on isopropyl) is more favorable than the elimination and ring expansion pathway for SbF$_6^-$.

2. An elimination pathway affords the indenyl derivative by forming HOTs, which is possibly the major pathway in the presence of OTs$^-$.

3. In the presence of less basic SbF$_6^-$, the product has a relatively high stereoselectivity and the major product was Syn-A-3b. The Anti-A-3b and indenyl derivative A-3a and A-3d would be generated as the byproduct.

4. The chemoselectivity for the model reaction is mainly controlled by the electronic effect of the counterion and substituent rather than the steric effect. In other words, SbF$_6^-$ mainly provides the charge separation effect rather than assisted proton elimination. However, the more basic OTs$^-$ mainly assist proton elimination through the formation of HOTs.

5. For the direct 1,2-H shift, the presence of two methyl groups in the isopropyl group would play a crucial role in stabilizing the transitional structure. It can greatly reduce the free energies of activation. This finding
provides important results on the effect of counterions in other gold(I) catalytic systems.

3.1. Computational Details. All calculations were performed with the Gaussian 09 programs.11 In the calculation, the geometries of all structures were fully optimized by using DFT12 of the M06-2X method.13 In addition, the 6-31G (d,p) basis set was selected for all atoms except for Au and Sb, for which the cc-pVDDZ-PB14 basis set (BSI) containing an effective core relativistic pseudopotential was employed. Vibrational frequency calculations done at the same level were used to characterize all of the stationary points as either minima [the number of imaginary frequencies (NIMAG = 0) or transition states (NIMAG = 1)]. Furthermore, the solvent effect was considered by single-point calculations with the integral equation formalism polarizable continuum model (IEFPCM) in dichloromethane (ΔGsol). The 3D molecular structures are generated using CYL-view.18

ASSOCIATED CONTENT

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b01131. Additional calculated energy profile, optimized cartesian coordinates with the self-consistent field energies, and the imaginary frequencies of transition states, as described in the text (PDF)

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ADDITIONAL NOTES

“All in the discussions in the main text, Z-type reactants are used as calculation models.

b To maintain low computational cost, the PPh3 ligand of gold is replaced with PH3. In the systems studied herein, PH3 is a model for PPh3 because of minimal steric effects, related to the low number of ligands around the gold metal center (vide infra). To further consider the effect of the ligand, the key step for all of the reaction pathways of PPh3 was calculated. Figure S1 in the Supporting Information shows the energy profile for this process. Calculation results revealed a marginal difference between PPh3 and PH3, for the systems studied herein.

“The attempt to locate the structures IIA (Scheme 2) was unsuccessful. Only the structures IIB (named A-2 and B-2) were obtained in our calculation.

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