

On the Validity of Au-vinylidenes in the Gold-Catalyzed 1,2-Migratory Cycloisomerization of Skipped Propargylpyridines

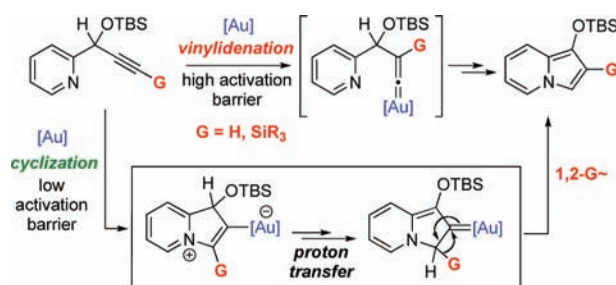
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ABSTRACT



A mechanism of the Au-catalyzed cycloisomerization of propargylpyridines has been investigated. Both DFT computational and experimental results strongly support generation of a Au-carbene via a cyclization/proton transfer sequence over the previously proposed path involving a Au-vinylidene intermediate. For the β -Si-substituted Au-carbene (G = SiR₃), a 1,2-Si migration was shown to be kinetically favored over a 1,2-H shift. This study highlights the importance of alternative pathways that could explain reactivities commonly attributed to an alkyne–vinylidene isomerization in Au catalysis.

Catalytic transformations featuring metal-vinylidene intermediates are powerful C–C and C–heteroatom bond forming strategies in organic synthesis.¹ In one of the commonly accepted scenarios, metal-vinylidenes can be generated from

terminal alkynes upon the alkyne–vinylidene isomerization, involving an initial coordination of the metal to a triple bond of the alkyne followed by a direct [1,2]-H shift.¹ Besides hydrogen, other groups, such as SiR₃,² SnR₃,³ SR,⁴ SeR,⁵

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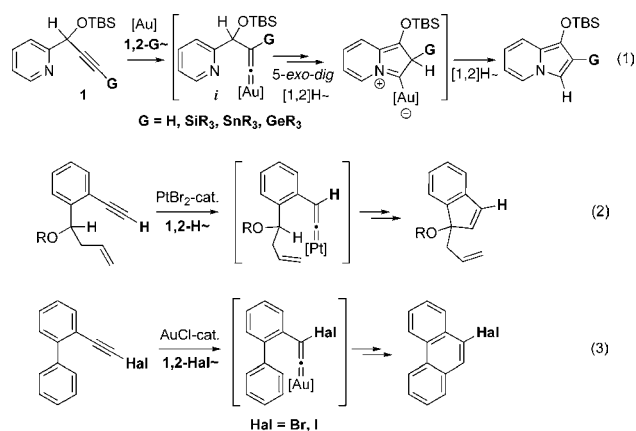
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and I,⁶ have been shown to undergo the 1,2-migration during this process. Traditionally, generation of metal-vinylidenes from alkynes is well-precedented for W, Mo, Ru, Rh, Ir, Co, Mn, and Re complexes;¹ however, it has recently been evidenced to play a key role in Pt-⁷ and Au-catalyzed⁸ transformations. Along this line, we recently reported the Au-catalyzed cycloisomerization of propargylpyridines **1** into indolizines, featuring the 1,2-shifts of H- and Si-, Sn-, and Ge-containing groups via a putative Au-vinylidene intermediate *i* (eq 1).^{8a,b} Besides, based on the DFT-computational and labeling experiments, formation of Pt-vinylidene species was established by Yamamoto in the synthesis of indenes (eq 2).^{7a} Furthermore, Fürstner observed a 1,2-halogen shift in the phenanthrene synthesis, proceeding through the Au-vinylidene (eq 3),^{8c} intermediacy of which was later validated by the DFT calculations.^{8d} Nonetheless, evidence was accumulated in support of alternative pathways in Au-,^{8c,9} Pt-,^{2d,10} and even “classical” W-¹¹ and Ru-catalyzed¹² processes that could account for the reactivities commonly attributed to the alkyne–metal-vinylidene isomerization. This prompted us to investigate the validity of the proposed Au-vinylidene species *i* in the Au-catalyzed cycloisomerization of **1** (eq 1). Herein, we report our theoretical and experimental results on the mechanism of this transformation. Our studies indicate that the observed 1,2-H and 1,2-Si shifts are, indeed, outcomes of a sequence of elementary steps alternative to the formation of the Au-vinylidene.



To shed light on a mechanism of the above-mentioned cycloisomerization, DFT calculations¹³ have been performed first. Considering the fact that a basic pyridine moiety of a substrate may play a significant role in possible H-migration steps during the cycloisomerization of **1**, we decided to

simulate such a base with a simple three-water molecule cluster.¹⁴ Employment of pyridine or the substrate molecules as proton shuttles in place of the water cluster in DFT calculations did not affect the overall energetic profile of the reaction.¹⁵ The computed energy surface for the AuBr-catalyzed¹⁶ cycloisomerization of propargylpyridine **1'** possessing a terminal alkyne moiety is provided in Figure 1.

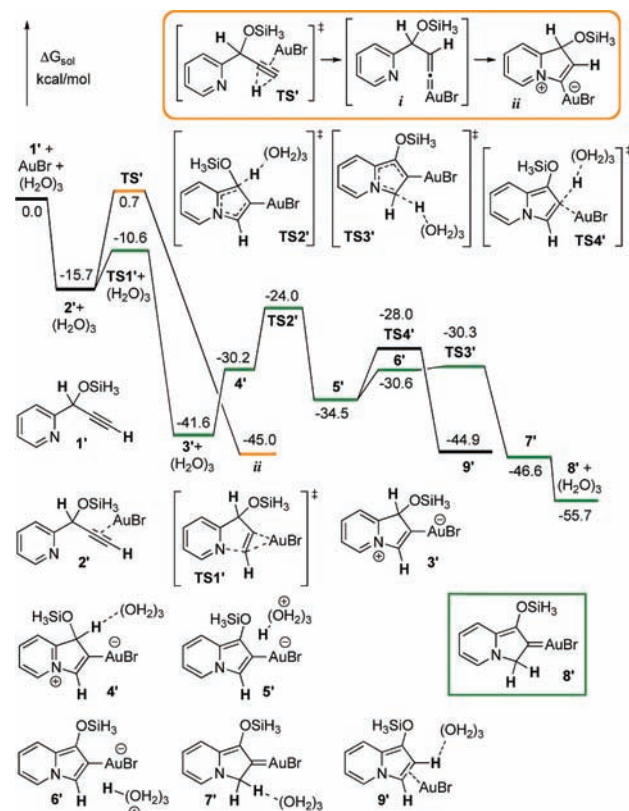


Figure 1. Potential energy surfaces for the AuBr-catalyzed cycloisomerization of terminal propargylalkynes **1'**.

According to it, coordination of AuBr to the alkyne moiety of **1'** gives the π -complex **2'** with the free energy decreased by 15.7 kcal/mol in toluene solution. A subsequent alkyne–vinylidene isomerization of **2'** should occur via the transition

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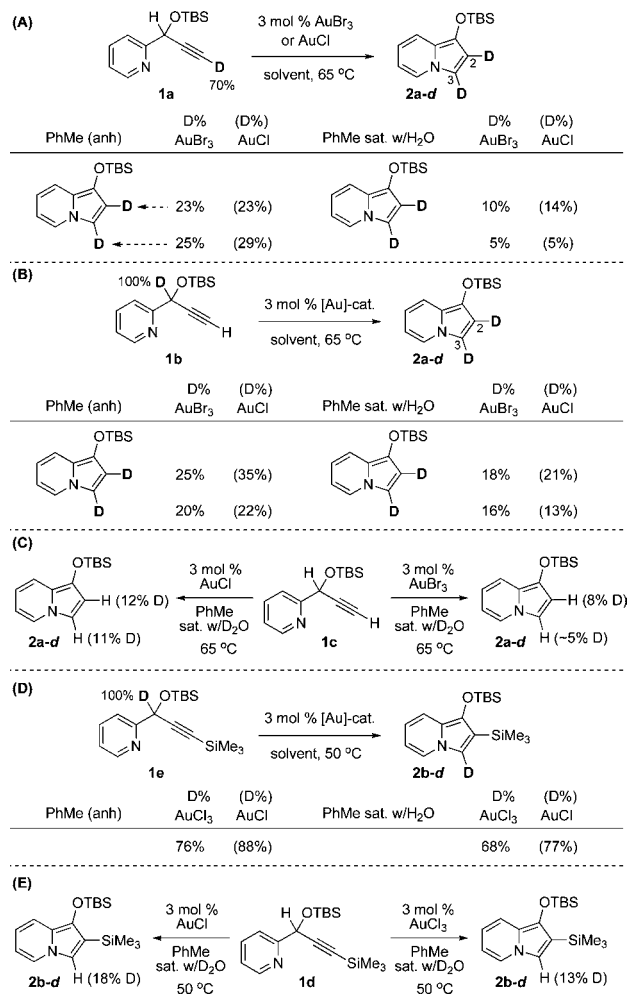
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state **TS'**. However, the corresponding vinylidene structure *i* could not be located, probably due to its instability. Instead, the 1,2-H migration via **TS'** leads to a cyclic intermediate *ii* directly, and this process has a high 16.4 kcal/mol activation free energy barrier. In contrast, according to an alternative mechanism, a highly exergonic direct 5-*endo-dig* cyclization of **2'** into **3'** via **TS1'** needs only a 5.1 kcal/mol activation barrier. Next, coordination of the water cluster to the H-atom in **3'** endergonic by 11.4 kcal/mol (**4'**) is followed by a proton abstraction via **TS2'** with 6.2 kcal/mol activation free energy to give the Au-indolizine species **5'**. A facile β -protonation of the vinyl-Au moiety in **5'** via **6'** and **TS3'** leads to **7'** and requires 4.2 kcal/mol free energy. An exergonic decoordination of the water cluster from **7'** furnishes the Au-carbene **8'**. The formal 1,3-H shift from **3'** through **5'** to give **8'** via a stepwise H-abstraction-donation is a reversible process. An alternative α -protonation of the vinyl-Au moiety in **5'** via **TS4'** (6.5 kcal/mol activation energy) gives indolizine **9'**. Overall, formation of the product **9'** from **3'** and **8'** via a water-assisted formal 1,2-H shift needs 17.6 and 27.7 kcal/mol free energy, respectively. Barriers for the direct 1,2-H shift to the Au center in **3'** or **8'** are as high as 23.9 and 34.6 kcal/mol, respectively.¹⁷

To validate the above computational results, D-labeling studies have been performed. The results are outlined in Scheme 1. We find them in complete agreement with the results of the DFT calculations. Accordingly, a reversible formation of the Au-carbene **8'** explains the distribution of a D-label between the C2 and C3 positions in indolizine **2a-d** upon the cycloisomerization of a terminally labeled **1a** (Scheme 1, A). The scrambling of the D-label was observed for both AuBr₃¹⁸ and AuCl catalysts. A partial loss of the D-label at both the C2 and C3 in **2a-d** (18–22% out of 70) was observed when reaction was performed in anhydrous toluene. The loss of the D-label becomes even more severe with the employment of H₂O-saturated toluene solvent (Scheme 1, A). These observations fully support the involvement of a stepwise water- or base-assisted H-abstraction–donation process established by the DFT calculations. Furthermore, the DFT-predicted reversible formation of the Au-carbene **8'** suggests that an analogous distribution and loss of the D-label should be observed in the Au-catalyzed cycloisomerization of the isotopomer **1b**. Indeed, these predictions have been confirmed experimentally (Scheme 1, B).

Furthermore, almost equal incorporation of the D-label at C2 and C3 positions was achieved upon the cycloisomerization of the H-isotopomer **1c** in D₂O-saturated toluene media (Scheme 1, C), which is expected according to the

Scheme 1. Deuterium-Labeling Studies



DFT calculations. On the basis of these results, the originally proposed reaction pathway featuring the alkyne–vinylidene isomerization is considered to be less likely.^{19,20}

Having established a mechanism for terminal alkynes (eq 1, **G** = H), DFT calculations have been performed for the AuBr-catalyzed cycloisomerization of the silyl-substituted propargylpyridine **1''** (Figure 2). The computed potential energy surfaces are analogous to that for **1'** (Figure 1). Thus, a coordination of AuBr to the alkyne moiety of **1''** leads to the π -complex **2''**. Formation of the Au-vinylidene *iii* upon the alkyne–vinylidene isomerization of **2''** with a 1,2-Si shift is possible; however, it requires 12.9 kcal/mol activation free

(15) See Supporting Information for details.

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(19) In addition, DFT calculations showed that another alternative prototropic isomerization of the alkyne **1** into an allene is a reversible process requiring 18.5 kcal/mol activation free energy. No loss of the D-label was observed in **1b** recovered from the Au-catalyzed cycloisomerization reaction at 50% conversion. On the basis of this, the allenization route can be ruled out. See Supporting Information for details.

(20) The initially proposed mechanism (eq 1), involving two [1,2]-H shifts, could account for the equal distribution of the D-label between the C-2 and C-3 positions in **2a-d** upon the Au-catalyzed cycloisomerization of **1a-d** under anhydrous conditions (see ref 8a). However, the observed significant loss of the D-label during the cycloisomerization of **1a-d** in the presence of H₂O contradicts the concerted nature of the 1,2-H migrations suggested in the previous mechanistic rationale.

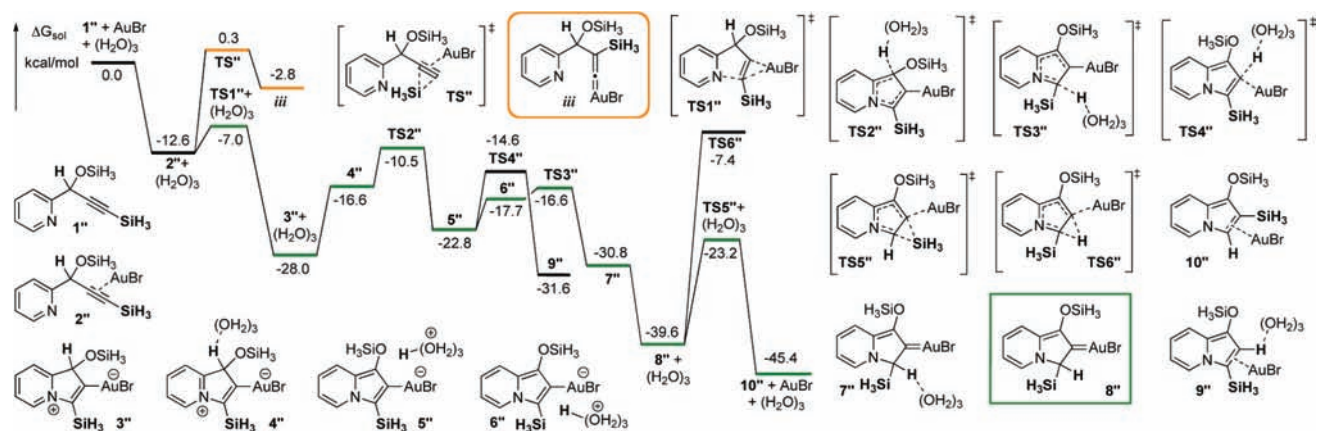


Figure 2. Potential energy surfaces for the AuBr-catalyzed cycloisomerization of silyl-substituted pyridylalkynes **1''**.

energy (**TS''**). Instead, following the alternative mechanism, **2''** undergoes a more facile irreversible *5-endo-dig* cyclization via **TS1''** that has only a 5.6 kcal/mol activation barrier. Coordination of the water cluster (**4''**) followed by the water-assisted proton abstraction (**TS2''**) furnishes the Au-indolizine species **5''**. The β -protonation of the vinyl-Au moiety in **5''** through the intermediate **6''** and the corresponding **TS3''** affords the Au-carbene **7''** reversibly, requiring a total of 6.2 kcal/mol free energy for two steps. An alternative α -protonation of **5''** leading to indolizine **9''** has a 2.0 kcal/mol higher in energy transition state **TS4''** (−14.6 vs −16.6 kcal/mol for **TS3''**) and, thus, is less favorable. Decoordination of the water cluster from **7''** gives the Au-carbene **8''** exergonically. A subsequent direct 1,2-Si shift²¹ (**TS5''**, 16.4 kcal/mol activation free energy) produces indolizine **10''**, which is in complete agreement with the experimentally observed formation of the C2-silyl-substituted products. A direct 1,2-H shift in **8''** via **TS6''** is kinetically not feasible owing to its very high, over 30 kcal/mol, barrier.

Supporting the above DFT predictions, a notable loss (Scheme 1, **D**) and incorporation (Scheme 1, **E**) of the D-label were observed in the Au(I)- and Au(III)-catalyzed cycloisomerizations of the silyl-substituted alkynes **1d** and **1e**, analogously to that for the terminal alkynes **1a–c**.

In summary, the mechanism of the Au-catalyzed cycloisomerization of propargylpyridines into indolizines was investigated using DFT computational and experimental studies.²² It was found that this transformation occurs via a sequence of steps consisting of (a) formation of the vinyl-

Au species upon irreversible *5-endo-dig* cyclization, (b) β -protonation of the vinyl-Au, and (c) the [1,2]-Si- or a base-assisted stepwise 1,2-H migration to the generated Au-carbene center. This route constitutes a feasible, yet hard to envision, alternative to the originally proposed alkyne–vinylidene isomerization path. In the case of the Si-substituted alkynes, the cycloisomerization proceeds via a formation of the β -Si-Au-carbene intermediate, wherein the 1,2-Si migration is kinetically favored over the 1,2-H shift. Finally, the present study highlights the importance of the alternative mechanistic pathways that could mimic reactivities typically explained by the intermediacy of metal-vinylidenes. In addition, this work provides a better understanding of the existing reactions of alkynes activated by Au complexes and may guide design of new transformations in the future.

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Supporting Information Available: Computational and experimental details as well as full citation of computational methods. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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