

Published in final edited form as:

Org Lett. 2010 December 3; 12(23): 5538–5541. doi:10.1021/ol1024794.

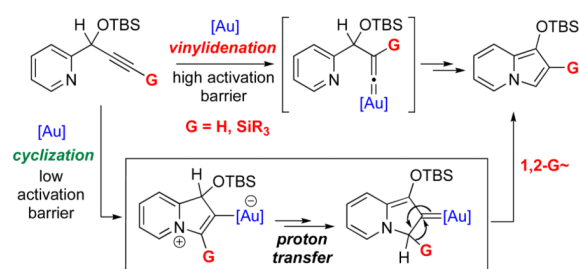
On the Validity of Au-Vinylidenes in the Gold-Catalyzed 1,2-Migratory Cycloisomerization of Skipped Propargylpyridines

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Abstract



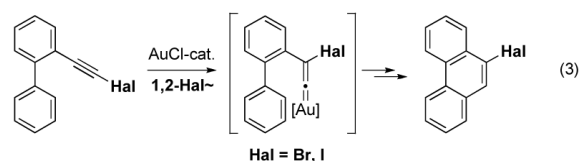
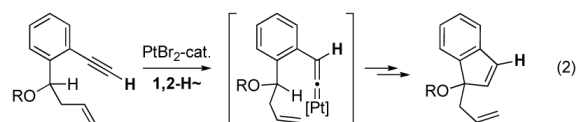
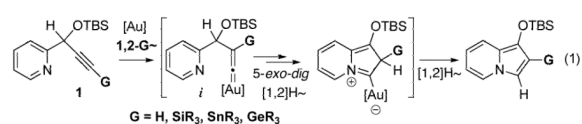
A mechanism of the Au-catalyzed cycloisomerization of propargylpyridines has been investigated. Both DFT computational and experimental results strongly support generation of a Au-carbene via a cyclization/proton transfer sequence over the previously proposed path involving a Au-vinylidene intermediate. For the β -Si-substituted Au-carbene ($G = \text{SiR}_3$), a 1,2-Si migration was shown to be kinetically favored over a 1,2-H shift. This study highlights 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 SiR_3 ,² SnR_3 ,³ SR ,⁴ SeR ,⁵ and I ,⁶ have been shown to undergo the 1,2-migration during this process. Traditionally, generation of metal-vinylidenes from alkynes is well-precedent for W-, Mo-, Ru-, Rh-, Ir-, Co-, Mn-, and Re complexes,¹ however, 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

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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>.

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-,^{8e,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 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 terminal alkyne moiety is provided in Figure 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 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 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 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 decooordination 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 a 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 the 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 DFT calculations. Based on 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 energy (**TS''**). Instead, following the alternative mechanism, **2''** undergoes a more facile irreversible 5-*endo-dig* cyclization via **TS1''** that has only 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 2.0 kcal/mol higher in energy transition state **TS4''** (–14.6 versus –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 a 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 an 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the Natural Science Foundation of China (20872105 and 21002073) and the National Institutes of Health of the US (GM-64444).

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- (18). Computational results for AuBr₃ are similar to those for AuBr.
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- (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.
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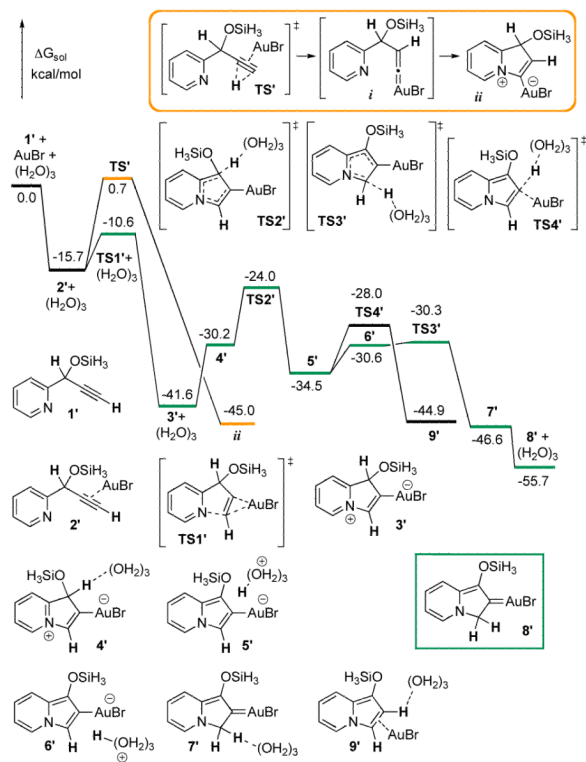


Figure 1.
Potential Energy Surfaces for the AuBr-Catalyzed Cycloisomerization of Terminal Pyridylalkynes **1'**.

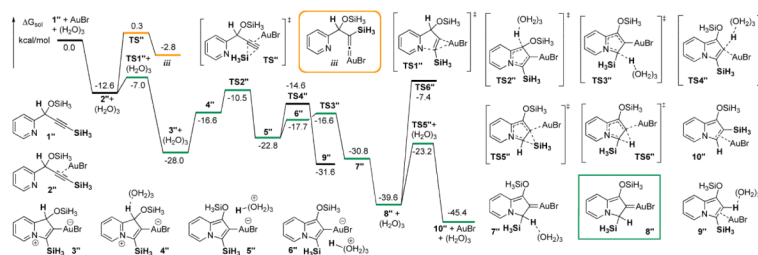
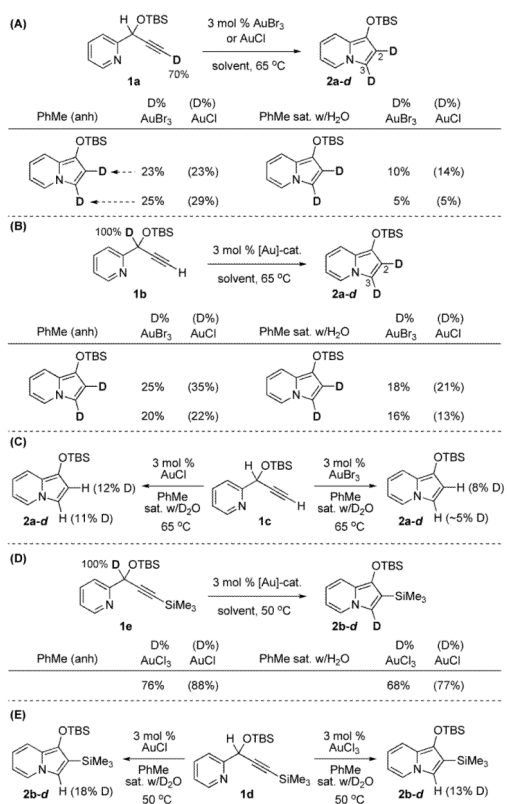


Figure 2.
Potential Energy Surfaces for the AuBr-Catalyzed Cycloisomerization of Silyl-Substituted Pyridylalkynes **1''**.



Scheme 1.
Deuterium-Labeling Studies.