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Experimental and Computational Evidence for Gold Vinylidenes: Generation from Terminal Alkynes via a Bifurcation Pathway and Facile C−H Insertions

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Supporting Information

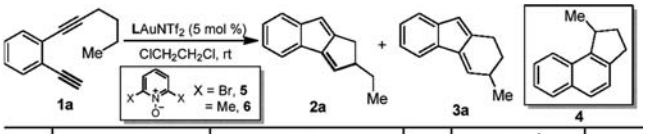
ABSTRACT: Facile cycloisomerization of (2-ethynylphenyl)alkynes is proposed to be promoted synergistically by two molecules of BrettPhosAuNTf$_2$, affording tricyclic indenes in mostly good yields. A gold vinylidene is most likely generated as one of the reaction intermediates on the basis of both mechanistic studies and theoretical calculations. Different from the well-known Rh, Ru, and W counterparts, this novel gold species is highly reactive and undergoes facile intramolecular C(sp^3)−H insertions as well as O−H and N−H insertions. The formation step for the gold vinylidene is predicted theoretically to be complex with a bifurcated reaction pathway. A pyridine *N*-oxide acts as a weak base to facilitate the formation of an alkynylgold intermediate, and the bulky BrettPhos ligand in the gold catalyst likely plays a role in sterically steering the reaction toward formation of the gold vinylidene.

As a result of intense efforts by many research groups in the past decade, various initially novel aspects of homogeneous gold catalysis[1] have now been well-accepted and increasingly applied in synthesis of complex structures.[2] Further development of gold chemistry likely hinges on the discovery of novel gold intermediates and the application of their new reactivities.

Vinylidene complexes[3] of various metals such as Ru, Rh, and W are versatile intermediates that promote the formation of various carbon−heteroatom and carbon−carbon bonds in a range of powerful catalytic reactions. Little is known, however, about gold vinylidenes. Several studies have invoked their intermediacy,[4] but later calculations have suggested alternative pathways.[5] The only exception is the formation of gold *β*-halovinylidene intermediates via AuCl-promoted [1,2]-halo migration of terminally halogenated alkynes (i.e., haloalkynes),[4d] which was later supported by density functional theory (DFT) calculations.[6] For synthetic usefulness, terminal alkynes are ideal, simple starting materials to access metal vinylidenes. To date, no proven case of gold vinylidene formation from terminal alkynes has been reported. Herein we report a gold-catalyzed cycloisomerization of (2-ethynylphenyl)alkynes, where a gold vinylidene is the most likely intermediate on the basis of both mechanistic studies and theoretical calculations; importantly, this novel gold intermediate, in contrast to its Ru, Rh, and W counterparts, which often can be isolated,[3] is highly reactive and undergoes facile C(sp^3)−H insertions to form tricyclic indenes.

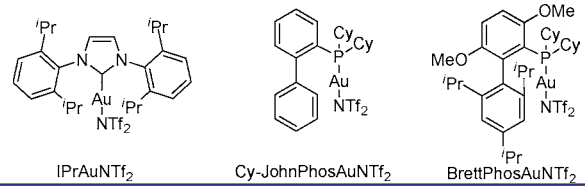
During our continuing study of gold-catalyzed intermolecular alkyne oxidation,[7] we subjected diyne **1a** to various combinations of gold catalysts and pyridine/quinoline *N*-oxides. While complex mixtures often resulted, a clean transformation was noticed when BrettPhosAuNTf$_2$[7a,8] (5 mol %) and 2,6-dibromopyridine *N*-oxide (**5**, 1.1 equiv) were used. To our surprise, the oxidant **5** was not consumed at all, and the major product (92% NMR yield) was a hydrocarbon whose structure was assigned as 1,2-dihydrocyclopenta-[*a*]indene **2a** (Table 1, entry 1).[9] Notably, this reaction involved an apparent C(sp^3)−H insertion leading to a tricyclic structural motif found in natural products such as pallidol[10] and sporolides[11] and patented compounds of medical interest.[12] A minor product, also involving C−H insertion, was assigned as the six-membered structural isomer **3a.**

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	time	yield[b]	2a/3a
1	BrettPhosAuNTf$_2$	**5** (1.1 equiv)	2 h	92%[c]	21/1
2	BrettPhosAuNTf$_2$	**5** (0.5 equiv)	4 h	82%	21/1
3	BrettPhosAuNTf$_2$	**5** (0.2 equiv)	10 h	66%	21/1
4	BrettPhosAuNTf$_2$	-	24 h	64%	21/1
5	BrettPhosAuNTf$_2$	**6** (1.1 equiv)	4 h	91%	21/1
6	BrettPhosAuNTf$_2$	**6** (0.5 equiv)	6 h	88%	21/1
7	BrettPhosAuNTf$_2$	**6** (0.2 equiv)	24 h	88%	21/1
8	BrettPhosAuNTf$_2$	2,6-Br$_2$Py (0.5 equiv)	24 h	70%	20/1
9	BrettPhosAuNTf$_2$	lutidine (0.5 equiv)	48 h	15% (75% **1a**)	20/1
10	BrettPhosAuNTf$_2$	TsNa (0.5 equiv)	12 h	79%	21/1
11	Cy-JohnPhos	**6** (0.5 equiv)	48 h	55% (20% **1a**)	10/1
12[d]	IPrAuNTf$_2$	**6** (0.5 equiv)	24 h	35% (40% **1a**)	3/1
13	Ph$_3$PAuNTf$_2$	**6** (0.5 equiv)	48 h	3% (92% **1a**)	-
14	Et$_3$PAuNTf$_2$	**6** (0.5 equiv)	20 h	9% (84% **1a**)	-
15	PtCl$_2$	toluene, 100 °C	10 h	45% of **4**	-

[a]Reaction run in vials using regular DCE as the solvent; [**1a**] = 0.1 M. [b]Measured by ^{1}H NMR analysis using diethyl phthalate as the internal standard. [c]90% isolated yield. [d]Reaction temperature: 60 °C.



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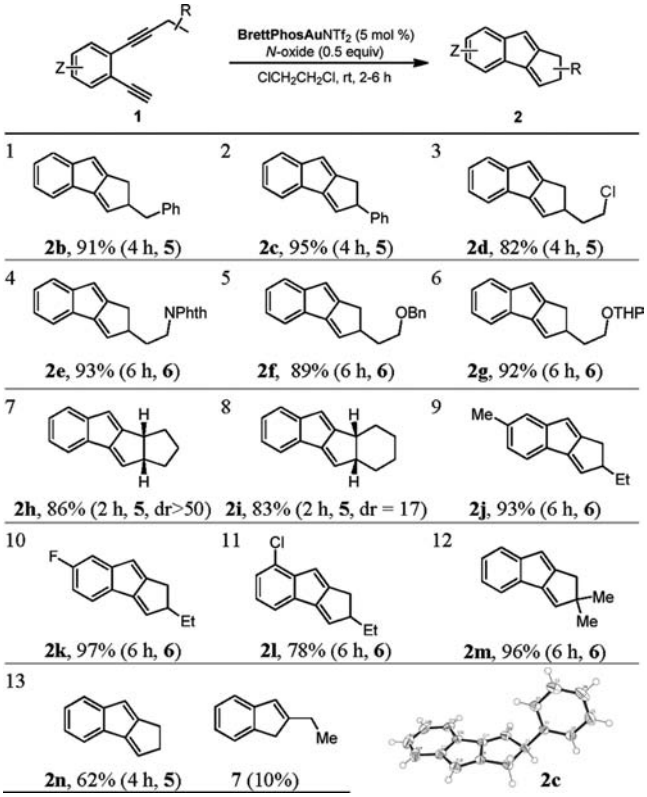
We were rather curious about the role of **5** and first probed the impact of its quantity on the reaction outcome. As shown in Table 1, entries 1−4, the reaction became slower and less efficient as the amount of the *N*-oxide was decreased. Lutidine *N*-oxide (**6**) also worked well as an additive, though the reactions were a bit slower (entries 5−7). We suspected that the *N*-oxides might simply function as bases. Indeed, 2,6-dibromopyridine offered a small improvement to the reaction (entry 8 vs 4), whereas lutidine was deleterious (entry 9), perhaps because of its strong basicity (conjugate acid pK_a = 6.77). Sodium toluenesulfinate, with moderate basicity (conjugate acid pK_a = 1.99[13]), led to an acceptable reaction rate and 79% yield (entry 10). Subsequent catalyst screening (entries 11−14) revealed that bulky BrettPhos was uniquely effective as the Au(I) ligand, rendering both a high yield and excellent chemoselectivity (i.e., **2a** vs **3a**). Contrary to BrettPhosAuNTf$_2$, PtCl$_2$ promoted selective formation of **4** (entry 15), consistent with Liu's previously published results.[14]

The reaction scope for this rapid construction of 1,2-dihydrocyclopenta[*a*]indenes was then studied. As shown in Table 2, zthe aliphatic substituent on the internal alkyne tolerated a range of functional groups, including phenyl (entries 1 and 2),

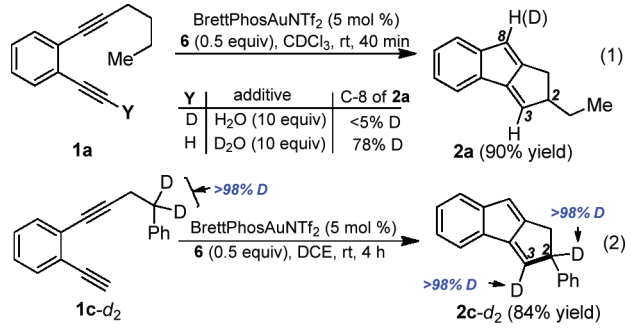
Table 2. Reaction Scope and X-ray Crystal Structure of 2c[a,b]



[a]Reactions were run in vials; isolated yields are reported. [b]The yields of the six-membered ring isomer **3** were <5%.

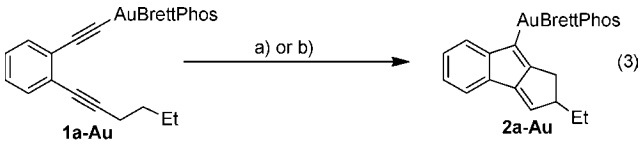
chloro (entry 3), protected amino (entry 4), and protected hydroxyl (entries 5 and 6). Moreover, cycloalkyl groups such as cyclopentyl (entry 7) and cyclohexyl (entry 8) were allowed, leading to tetracyclic products. Substitutions on the benzene ring (entries 9−11) at different positions were readily allowed. In addition to efficient insertion into methylene C−H bonds, the insertion into a methine C−H bond proceeded equally well (entry 12). Insertion into a methyl C−H bond was less efficient (entry 13), and a small amount of 2-ethyl-1*H*-indene (**7**) was isolated in addition to **2n**. X-ray diffraction studies of product **2c** confirmed our structural assignments.

To probe the reaction mechanism, we performed deuterium-labeling studies. The results shown in eq 1 indicated that the hydrogen isotope at C-8 of **2a** came mostly from the added H_2O or D_2O and little from the alkyne terminus in the substrate. Labeling the aliphatic side chain with deuteriums



(eq 2) allowed the origin of the C-3 H/D in the products to be firmly established, consistent with the formation of the C-2 and C-3 bond via an intramolecular carbene C−H insertion.

Equation 1 further suggested that the C-8 hydrogen in **2a** might be installed via protodeauration and that the alkyne terminal hydrogen in **1a** might become labile in the course of the reaction. Using phenylacetylene as the model alkyne, we indeed observed facile exchange of its alkyne terminal hydrogen with added D_2O (10 equiv) in $CDCl_3$ in the presence of BrettPhosAuNTf$_2$ and *N*-oxide **6** (50% conversion in 5 min); an alkynylgold species is the most likely intermediate.[15] Importantly, without **6**, the exchange was much slower (50% conversion after 1.5 h). This result suggests that **5** or **6** acts as a base to facilitate the removal of the alkyne terminal hydrogen to form alkynylgold **1a-Au** (see eq 3). Fortunately, this intermediate could be prepared in its pure form. When we treated **1a-Au** with 5 mol % BrettPhosAuNTf$_2$, the reaction



a) BrettPhosAuNTf$_2$ (5 mol %), ClCH$_2$CH$_2$Cl (anhydrous), rt, 5 min; quantitative yield
b) Ph$_3$PAuNTf$_2$ (7.5 mol %), CD$_2$Cl$_2$, rt, 5 h; 72% NMR yield (90% conversion)

proceeded to completion in 5 min, and 8-aurated-1,2-dihydrocyclopenta[*a*]indene **2a-Au** was formed in a quantitative yield (eq 3). To confirm the uniquely effective nature of BrettPhosAuNTf$_2$, Ph$_3$PAuNTf$_2$ was used as the catalyst instead, and the reaction was much slower and less efficient (eq 3) The use of Ph$_3$P in place of BrettPhos in **1a-Au** with either BrettPhosAuNTf$_2$ or Ph$_3$PAuNTf$_2$ as the catalyst led to even slower reactions and little desired products.[16]

A mechanism consistent with the above results is proposed in Scheme 1. First, the *N*-oxide acts as a base to abstract the proton from the terminal alkyne, which is activated by BrettPhosAu$^+$. This affords the alkynylgold complex **1-Au**. The reverse process (i.e., protodeauration) may occur, but the presence of a base should help shift the equilibrium toward **1-Au**. A strong base such as lutidine, however, would bind to the gold catalyst and therefore hinder the overall reaction. Another BrettPhosAu$^+$ can then activate the other C−C triple

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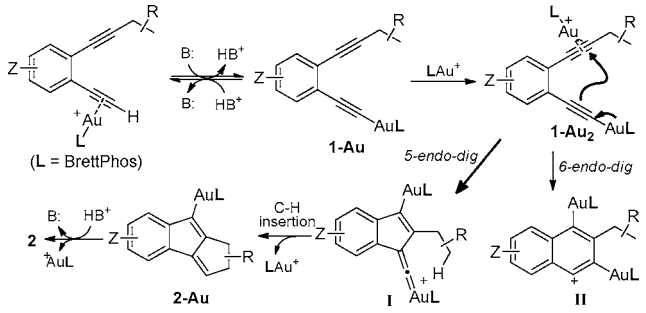
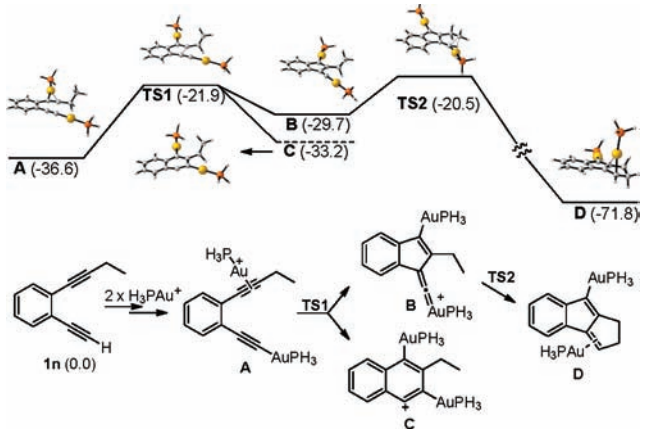
Scheme 1. Proposed Reaction Mechanism



bond of **1-Au** via the intermediacy of **1-Au$_2$**, which undergoes a 5-endo-dig cyclization that we believe leads to gold vinylidene intermediate **I**.[17] This novel species is apparently highly reactive and may undergo facile C−H insertion[18] leading to **2-Au**, which is followed by protodeauration to form the observed product. The formation of the six-membered structural isomer (e.g., **3a**, Table 1) could be readily explained by a competing 1,6-C−H insertion by the gold vinylidene. A likely competing 6-endo-dig cyclization by **1-Au$_2$** could lead to intermediate **II**, which is somewhat analogous to that leading to **4** with platinum catalysis;[14] however, no naphthalenic products were observed. The preference for the 5-endo-dig cyclization over the 6-endo-dig cyclization might be attributed on one hand to the bulky BrettPhosAu moiety at the alkyne end, as its bulk[19] might help steer the approach of the other C−C triple bond to the less hindered distal alkyne end, and on the other hand to back-bonding of the Au center to the adjacent carbocation in the form of a gold vinylidene (i.e., **I**).

DFT calculations of the reaction energy surface of a model reaction (Scheme 2) at the M06/6-31+G(d,p)/LANL2DZ(Au)(SMD) in $CHCl_3$ level have shown that this is a reasonable mechanism, supporting the hypothesis that a gold vinylidene intermediate would be stable enough to form yet

Scheme 2. Free Energy Diagram for the Reaction in Chloroform at 298 K Calculated at the M06/aug-cc-pVTZ-PP(SMD)//M06/6-31+G(d,p)/LANL2DZ(Au) Level (All Values in kcal/mol Relative to 1n)



reactive enough to carry out the required C−H insertion reaction readily. The energetics for the expected proton abstraction by pyridine *N*-oxides is favorable (uphill by only 2.2 kcal/mol in chloroform[16]), and the 5-endo-dig ring closure was found to occur with a free energy barrier in chloroform of only 14.7 kcal/mol in single-point calculations at the M06/aug-cc-pVTZ/aug-cc-pVTZ-PP(Au)(SMD) level. This reaction step forms the novel gold vinylidene intermediate **B**, with a predicted $\Delta G^{\circ}_{CHCl_3}$ of 6.9 kcal/mol from **A**. The calculated bond lengths and charges clearly support the vinylidene character of **B**.[16] This intermediate is highly reactive and can rapidly undergo an intramolecular C−H insertion reaction with a calculated free energy barrier of 9.2 kcal/mol for primary C−H bonds to form the tricyclic intermediate **D**. The corresponding energy barrier for insertion into the secondary C−H bonds of a pendent *n*-propyl group was calculated to be 4.9 kcal/mol.[16] The observed product is formed from **D** following sequential decomplexation and protodeauration steps.

The theoretical energy surface for the critical 5-endo-dig cyclization step to give **B** shows a most interesting situation in which the alternative 6-endo-dig cyclization to form **C** actually forms from the *same* transition state, **TS1**. This constitutes a bifurcated reaction pathway with a ridge−valley inflection point on a relatively flat energy surface, as shown in Figure 1. A second transition state structure, **TS1a**, that is 0.89 kcal/mol lower in electronic energy than the first, was found for

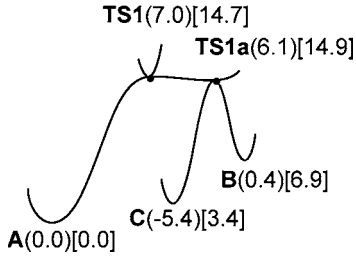


Figure 1. Energy diagram showing a bifurcation at a ridge−valley inflection, calculated at the M06/aug-cc-pVTZ-PP(SMD)//M06/6-31+G(d,p)/LANL2DZ(Au) level. Relative electronic energies are given in parentheses and relative free energies in chloroform in brackets, all in kcal/mol at 298 K. For pictures of typical 3D surfaces, see ref 20.

interconversion of the five- and six-membered ring intermediates **B** and **C**. In situations of this sort, the choice between **B** and **C** is made on the basis of dynamical factors along the ridge (between **TS1** and **TS1a**) separating the valleys for **B** and **C**, and the product ratios must be predicted by dynamical effects in trajectory calculations rather than classical transition state theory.[20,21] Preliminary atom-centered density matrix propagation (ADMP) molecular dynamics calculations for a simplified model reaction with PH_3 ligands, a methyl substituent, and no benzo fusion gave reaction trajectories starting from the first transition state and going to both the five- and six-membered ring products within 150−300 fs with no intermediate formation. The trajectories predicted that the five-membered ring product should prevail, as observed, but not overwhelmingly. It was expected that the stronger selectivity toward the 5-endo-dig cyclization observed experimentally might be attributed to the steric bulk of one of the BrettPhos ligands. The bulky BrettPhos ligand on the gold vinylidene moiety in **B** is held a C═C bond length further away from the ring and pendant ethyl group than in **C**. This steric preference for **B** with a BrettPhos ligand was confirmed with calculations on structures optimized at the B3LYP/6-31G(d)/LANL2DZ(Au) level that showed a steric shift in the free energy differences toward the five-membered ring intermediate of 5.1 kcal/mol.[16] The calculation was performed on a model with the full BrettPhos structure for the relavent ligand and PMe_3 for the other ligand. The conformation

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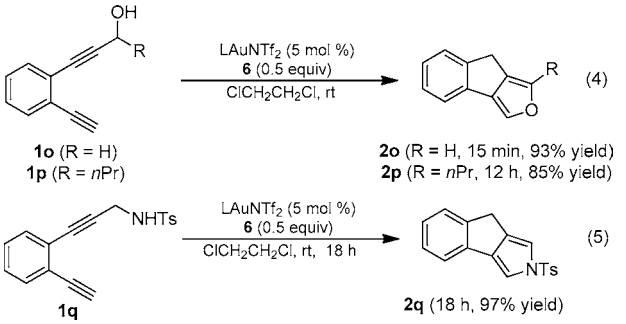
chosen for the BrettPhos ligand was the same as that found in the crystal structure of BrettPhosAuNTf$_2$.[7a] Interestingly, such bifurcation pathways are still very rare in organometallic chemistry but have recently been seen for gold-catalyzed reactions.[22]

The gold vinylidene intermediate of type **I** was also found to insert readily into O−H (eq 4) and N−H bonds (eq 5), leading to highly efficient formation of useful tricyclic furan and pyrrole structures, respectively. Interestingly, when there was a



competition between O−H and C−H bonds (i.e., in the case of **1p** in eq 4), the gold vinylidene preferred the O−H bond, and no C−H insertion product was found.

In summary, we have reported a gold-catalyzed cycloisomerization of benzene-1,2-dialkynes in which two molecules of BrettPhosAuNTf$_2$ are proposed to work synergistically and a gold vinylidene is the most likely intermediate on the basis of both mechanistic studies and theoretical calculations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) While Scheme 2 suggests the possibility that **B** and **C** might equilibrate through **TS1a**, this equilibration was calculated to be somewhat slower than the competing C−H insertion reaction for a secondary C−H bond. The possible fate of any **C** formed in the reaction was predicted computationally. It was found to undergo an exothermic gold migration and C−H insertion with a barrier as low as that for **B** and to be faster than equilibration of **B** and **C**. This insertion product would lead to 2,3-cyclopentano-fused naphthalenes rather than the 1,2-fusion seen in **4** from Pt. See the SI for details.

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