# Gold(I) or gold(III) as active species in AuCl₃-catalyzed cyclization/cycloaddition reactions? A DFT study†

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In a B3LYP mechanistic study, AuCl and AuCl₃ catalysts feature similar overall barriers for a reaction sequence of 2-ethynyl benzaldehyde and ethyne to 1-naphthyl carbaldehyde, comprising cyclization, [3+2] cycloaddition, and two rearrangements.

The development of homogeneous gold catalysis for synthetic reactions, particularly for alkyne transformations, is gaining increasing attention.[1,2] The use of gold catalysts in natural product syntheses reflects the growing importance of gold chemistry.[3] Many gold(I) as well as gold(III) compounds are powerful catalysts and both oxidation states I and III have been proposed for the active species.[1,2] Due to the high oxidation potential of gold(III) compounds,[4] their rapid reduction in the reaction mixture would be no surprise. Indeed, the reduction of high oxidation state pre-catalysts to the active catalyst is mandatory in several late transition metal-catalyzed reactions.[5] Thus, the question arises whether both gold oxidations states are potentially active.[1d] In this DFT study, the mechanisms of Yamamoto and co-workers' gold-catalyzed benzannulation reaction is modelled (Scheme 1).[1]
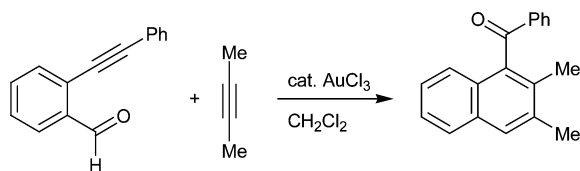


**Scheme 1** Yamamoto and co-workers' gold-catalyzed benzannulation.

Pathways of both the proposed AuCl₃ catalyst as well as of AuCl were investigated. Ethynyl benzaldehyde and ethyne were used as simplified quantum-chemical model substrates. The main challenge is to predict the influence of the gold oxidation state on the overall reaction barrier. For geometry optimizations and frequency analyses,[6] the B3LYP functionals[7] were combined with the LANL2DZ effective core potential and basis set for gold[8] and the 6-31G(d) basis set for C, H, O, and Cl.[9] For single point calculations, a triple-zeta Los Alamos basis set for gold and the 6-311G(d,p) basis set for C, H, O, and Cl were used.[10] Gibbs free energies are based on unscaled frequency calculations for gas phase conditions at 298.15 K and 1 atm. The pathways for AuCl and AuCl₃ are structurally very similar. Thus, the AuClₓ complexes will be given the same numbers: gold(I) species obtain the suffix **a** ($x = 1$), gold(III) compounds obtain the suffix **b** ($x = 3$).

AuCl complexes of strained alkynes have already been structurally characterized.[11] For AuCl₃, the coordination of a carbonyl oxygen to the gold(III) center is more favoured by 21.3 kJ mol⁻¹ than alkyne coordination. For both gold oxidation states, however, the nucleophilic attack of the carbonyl oxygen of **1a** or **1b** at the terminal alkynyl carbon C1 proceeds rapidly *via* **2a** or **2b** subsequent to gold coordination at the C≡C moiety of the ethynyl benzaldehyde substrate (Fig. 1). The resulting complexes **3a** and **3b** can be regarded as mesomeric structures of an oxonianaphthalene aurate and a 1,3-dipolar ylide with a gold carbene complex

fragment (Fig. 2 and 3). An NBO analysis[12] reveals that the p orbital of **3a** at the former carbonyl carbon C9 has an electron occupation of only 0.88. The natural charge of this carbon is +0.29. The corresponding p orbital at the former terminal alkyne carbon C1 has a higher electron occupation of 0.97 and a less positive natural charge of +0.15. In the analogous gold(III) complex **3b**, the electron occupations (0.85 and 0.95) and natural charges (+0.31, +0.17) are very similar. Accordingly, the largest coefficient of the LUMOs are located on C9, respectively. In the literature, a direct [4+2] cycloaddition of the alkyne substrate (such as 2-butyne or phenylethyne) has been assumed.[1a,b] Surprisingly, all attempts to locate hetero-Diels–Alder [4+2] cycloaddition transition states failed and led to the Huisgen-type[13] [3+2] cycloaddition transition states **4a** and **4b**. Scans of the energy hypersurface of the carbonyl ylides **3a** or **3b** plus ethyne with constrained C2–C11-distances also
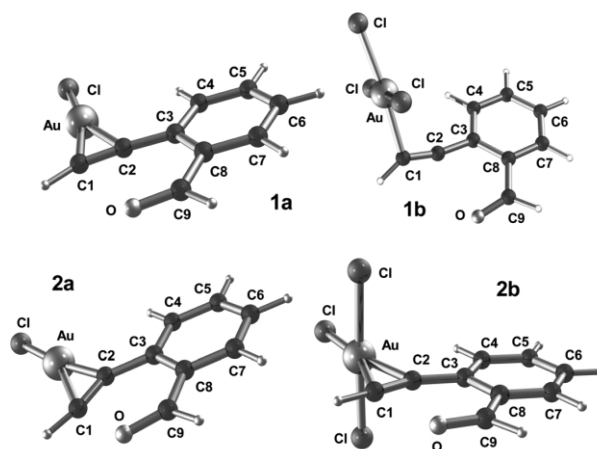


**Fig. 1** Ball and stick models of **1a**, **1b**, **2a**, and **2b**. Selected distances [Å] in **1a**: C1–O, 3.009. **1b**: C1–O, 3.173. **2a**: C1–O, 2.173. **2b**: C1–O, 2.535.
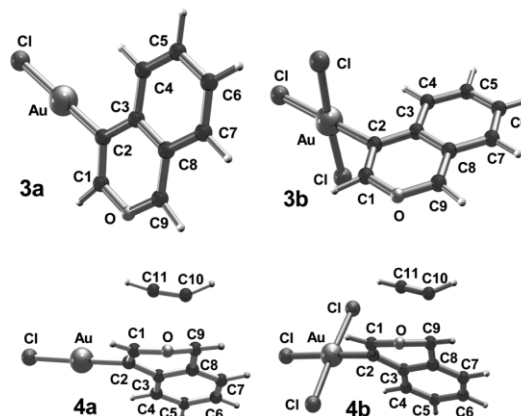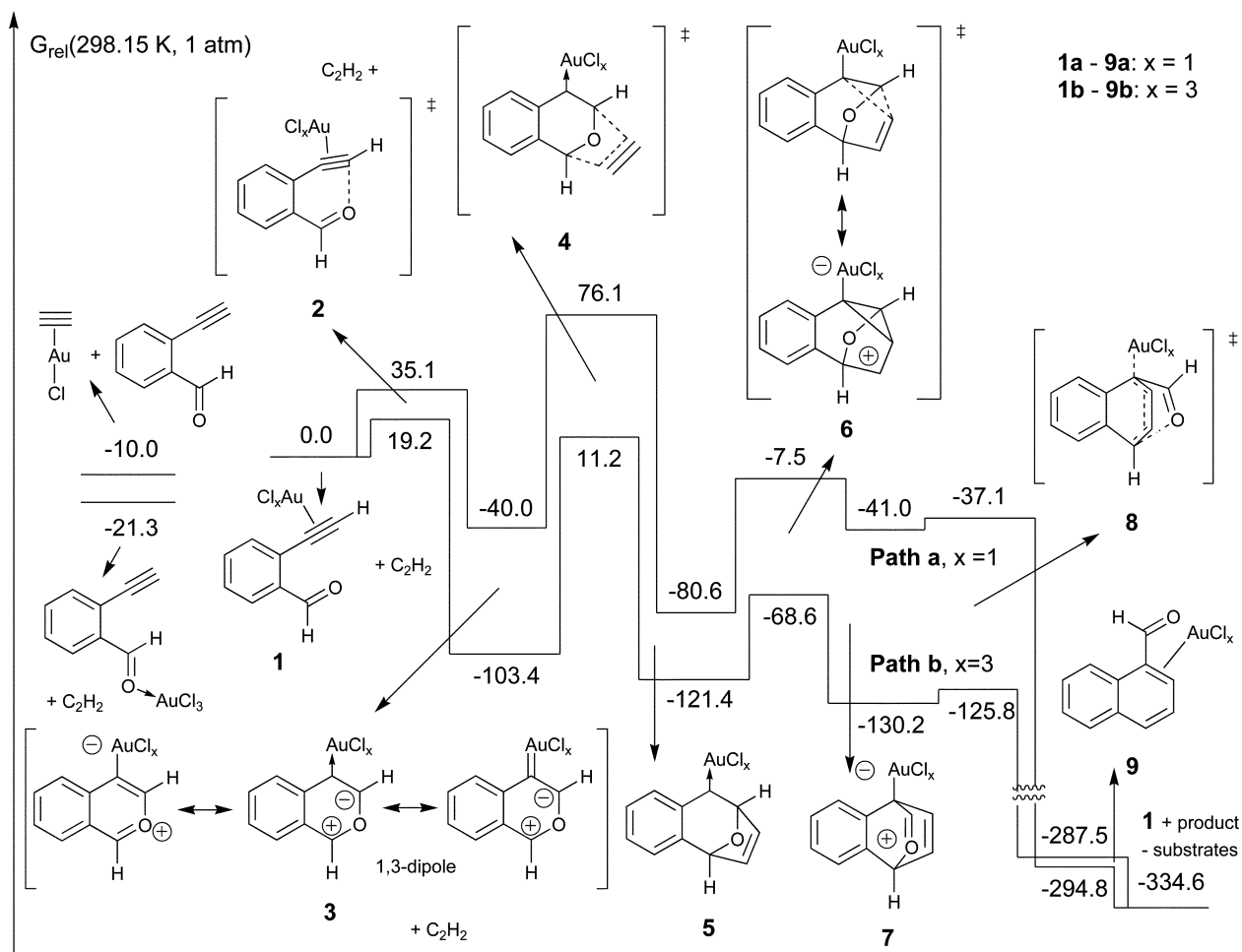


**Fig. 2** Ball and stick models of **3a**, **3b**, **4a**, and **4b**. Selected distances [Å] in **3a**: C9–O, 1.311; O–C1, 1.370; C1–C2, 1.373. **3b**: C9–O, 1.312; O–C1, 1.366; C1–C2, 1.362. **4a**: C9–O, 1.344; O–C1, 1.354; C1–C2, 1.393; C9–C10, 2.070; C1–C11, 2.511; C2–C11, 2.758; C10–C11, 1.240. **4b**: C9–O, 1.351; O–C1, 1.350; C1–C2, 1.375; C9–C10, 1.983; C1–C11, 2.691; C2–C11, 2.819; C10–C11, 1.242. Free C₂H₂: C10–C11, 1.205.

$G_{rel}$(298.15 K, 1 atm)

$C_2H_2$ +

**1a** - **9a**: x = 1
**1b** - **9b**: x = 3

76.1

35.1

19.2

0.0

11.2

-40.0

-7.5

-41.0

-37.1

-10.0

-21.3

-103.4

-80.6

-68.6

**Path a**, x =1

**Path b**, x=3

-121.4

-130.2

-125.8

-287.5

-294.8

-334.6

**1** + product
- substrates

1,3-dipole

+ $C_2H_2$

**1**  **2**  **3**  **4**  **5**  **6**  **7**  **8**  **9**

**Fig. 3** Energy diagram of the computed multistep cyclization–cycloaddition–double rearrangement mechanisms. Gibbs free energies are normalized to the energies of **1a** and **1b**, respectively, since these are the first structurally equivalent intermediates in the reaction sequence. The contribution of the Au=C mesomeric structure in the catalyst resting state **3** is of course much more pronounced for gold(I) than for gold(III).

underline the preference for Huisgen-type reactivity. [3+2] cycloaddition reactions of carbonyl ylides and alkynes are known for more than 30 years.[14] The charge distributions in **3a** and **3b** are responsible for the electrophilic attack of C9 at C10 of the alkyne in the transition states **4a** and **4b** (Fig. 2). In **4a**, the ethyne fragment has a net positive charge of +0.11. In **4b**, the charge transfer is even larger (0.19). The cycloaddition proceeds concerted, but highly asynchronous.[15] The formation of the C1–C11-bond is retarded by 0.441 Å in **4a** and by 0.703 Å in the more electrophilic **4b**.

Our non-finding of a [4+2] pathway does of course not strictly prove its non-existence. However, the obvious tendency for a dipolar carbonyl ylide plus alkyne cycloaddition to **5a** and **5b**, and the feasible rearrangements **6a** and **6b** to the formal [4+2] cycloaddition products **7a** and **7b** strongly support a stepwise process. The rearrangement transition states **6a** and **6b** are mesomeric structures of a Wagner–Meerwein-type shift of a vinyl group and a cyclopropyl carbenium aurate (Fig. 3 and 4).

The C–O bond ruptures in **7a** and **7b** *via* the transition states **8a** and **8b** result in the highly exergonic formation of the AuClₓ-coordinated naphthalene derivatives **9a** and **9b** (Fig. 3 and 5). Finally, a ligand exchange can release the naphthyl ketone product, transfer the gold chloride fragment to an ethynyl benzaldehyde substrate, thereby forming complexes **1a** or **1b** and closing the catalytic cycle. A Gibbs free energy of $\Delta G = -334.6$ kJ mol$^{-1}$ is predicted for the overall reaction. For both gold oxidation states, the rate-determining steps **4a** and **4b** feature a predicted Gibbs activation energy of about 115 kJ mol$^{-1}$. Though a significant part of the Gibbs free reaction energy is released earlier in the gold(III) pathway **b** than in the gold(I) pathway **a**, the predicted catalytic activities of AuCl$_3$ and AuCl are indistinguishable within the reliability of the chosen level of theory.

The proposed [3+2] cycloaddition at a 1,3-dipolar carbonyl ylide is in accordance with the experimentally observed regioselectivities (Scheme 2). π electron-donating substituents at the C11 position of the alkyne support the charge donation of C10 to C9. As a consequence, alkyl and aryl π donor groups are guided to the *ortho*
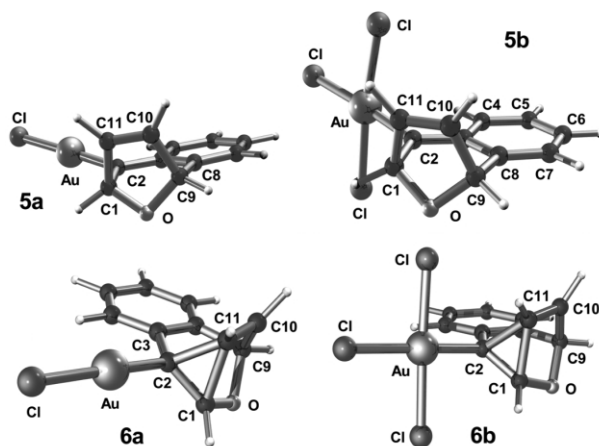
**Fig. 4** Ball and stick models of **5a**, **5b**, **6a**, and **6b**. Selected distances [Å] in **5a**: C1–C2, 1.511; C9–C10, 1.538; C1–C11, 1.548; C2–C11, 2.398; C10–C11, 1.331; C9–O, 1.431; O–C1, 1.426. **5b**: C1–C2, 1.502; C9–C10, 1.539; C1–C11, 1.551; C2–C11, 2.398; C10–C11, 1.330; C9–O, 1.431; O–C1, 1.422. **6a**: C1–C2, 1.429; C9–C10, 1.531; C1–C11, 1.862; C2–C11, 1.724; C10–C11, 1.340; C9–O, 1.460; O–C1, 1.351. **6b**: C1–C2, 1.423; C9–C10, 1.529; C1–C11, 1.774; C2–C11, 1.766; C10–C11, 1.341; C9–O, 1.450; O–C1, 1.364.
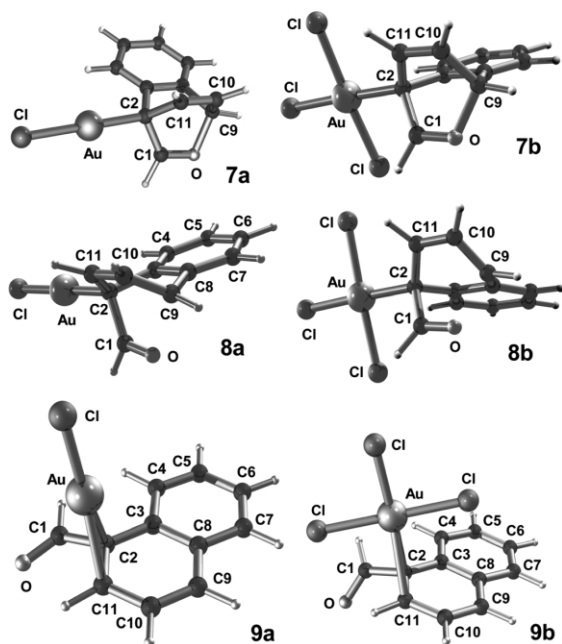
**Fig. 5** Ball and stick models of **7a**, **7b**, **8a**, **8b**, **9a**, and **9b**. Selected distances [Å] in **7a**: C1–C2, 1.485; C1–O, 1.275; O–C9, 1.546; C9–C10, 1.506; C10–C11, 1.335; C2–C11, 1.547. **7b**: C1–C2, 1.497; C1–O, 1.270; O–C9, 1.552; C9–C10, 1.509; C10–C11, 1.336; C2–C11, 1.540. **8a**: C1–C2, 1.552; C1–O, 1.236; O–C9, 1.887; C9–C10, 1.458; C10–C11, 1.349; C2–C11, 1.518. **8b**: C1–C2, 1.557; C1–O, 1.234; O–C9, 1.885; C9–C10, 1.459; C10–C11, 1.348; C2–C11, 1.512. **9a**: C1–C2, 1.507; C1–O, 1.213; C9–C10, 1.371; C10–C11, 1.427; C2–C11, 1.418. **9b** C1–C2, 1.519; C1–O, 1.209; C9–C10, 1.376; C10–C11, 1.412; C2–C11, 1.422.
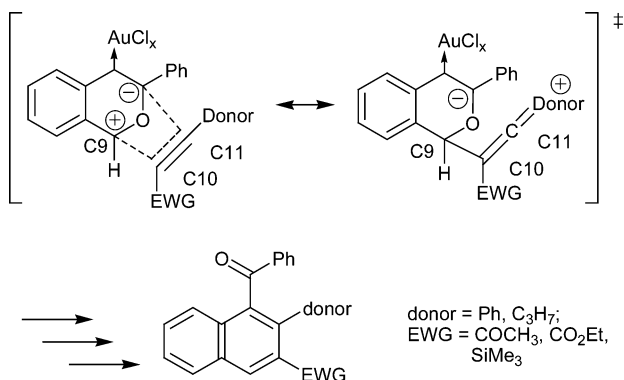


**Scheme 2** Rationalization of the electronic influence of alkyne substituents in the [3+2] cycloaddition step.

position of the 1-acyl naphthalene product, while π electron-withdrawing groups are guided to the *meta* position.

In summary, the benzannulation mechanism proposed by the Yamamoto group is mostly confirmed by quantum-chemical calculations. However, both gold(I) as well as gold(III) lead to essentially identical predicted overall reaction barriers. Thus, the question whether Au(III) is a better catalyst or oxidizing reagent under the reaction conditions remains unclear. With the present data at hand, even the simultaneous catalysis by gold(I) and gold(III) cannot be ruled out. Secondly, the formal [4+2] cycloaddition between the oxonianaphthalene and the alkyne substrate proceeds stepwise *via* a rate- and selectivity-determining [3+2] cycloaddition with a subsequent rearrangement.

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