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Gold(I) or Gold(III) as Real Intermediate Species in Gold-Catalyzed Cycloaddition Reactions of Enynal/Enynone?

Caiyun Zhang,^{a,§} Gendi Wang,^{a,§} Licheng Zhan,^{a,§} Xueyan Yang,^a Jiwei Wang,^a Yin Wei,^b Sheng Xu, *,^a Min Shi^{a,b} and Jun Zhang*,^a

^aKey Laboratory for Advanced Materials and Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China

^bState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

KEYWORDS: gold(I) catalysis; gold(III) catalysis; cycloaddition; enynal/enynone; reaction intermediates

ABSTRACT: Metal-bound isobenzopyrylium species are proposed as reactive intermediates in transition metal-catalyzed [3+2] or [4+2] cyclizations of *o*-alkynylbenzaldehydes (enynals) or *o*-alkynylarylketones (enynones). Because of their high reactivity, isolation and structural

characterization of such intermediates has remained elusive. Herein, we report the isolation of such gold(I)- and gold(III)-bound isobenzopyrylium intermediates, and two of them have been characterized by X-ray diffraction analysis. When reacting with reaction partners, such as styrene and phenyl acetylene, Au(I) intermediate exhibited much faster reaction rate than Au(III) species does. A degradation pathway of active Au(III) carbene intermediate was observed, leading to release of Au(I) species and consequent formation of dichloride compound. In other related catalytic reactions, Au(I) intermediate could react well with a range of cyclization partners, while Au(III) intermediate didn't work. The above observations indicate that Au(I) species is probably the real catalyst in such gold-catalyzed transformations of *o*-alkynylbenzaldehydes and *o*-alkynylarylketones.

INTRODUCTION

Gold-catalyzed reactions have been becoming as an important strategy for the preparation of natural products and drug-like scaffolds, featuring mild reaction conditions, good selectivity, and high efficiency.¹ However, although tremendous gold(I)- and gold(III)-catalyzed organic transformations have been developed, some fundamental mechanistic issues remain unresolved, concerning in particular the oxidation states of the active gold intermediate species. Without stabilizing ligands, gold(I) easily undergo disproportionation to gold(III) and gold(0), and gold(III) precatalysts could be reduced in situ to gold(I) due to the high oxidation potential of Au(III) compounds.^{1a} Thus, one would question which one is the real active catalyst, gold(III) or gold(I)?

Scheme 1. Isobenzopyrylium Intermediates A and Target Au(I) and Au(III) Isobenzopyrylium Intermediates B and C

a) Proposed isobenzopyrylium intermediates in the metal-catalyzed reactions of o-alkynylbenzaldehydes (enynals) and o-alkynylarylketones (enynones)



b) An unprecedented degradation of active Au(III) carbene species



Over the past fifteen years, envials and environes have emerged as useful and versatile building blocks in organic transformations.² Among envnals and envnones, *o*-alkynylbenzaldehydes (envnals) and o-alkynylarylketones (envnones) are the most powerful, general and widely used, showing great versatility and high reactivity towards cyclization reactions. Under activation of transition metal catalyst, such as Au,³⁻⁵ Ag,⁶ Cu,⁷ Pd,⁸ In,⁹ Pt,¹⁰ Re,¹¹ Zn,¹² W,¹³ oalkynylbenzaldehydes and o-alkynylarylketones (1) could undergo cyclization to afford intriguing isobenzopyrylium intermediates A in the first place (Scheme 1a), which can further react with a range of reaction partners to construct various polycyclic compounds through [4+2] or [3+2] cycloaddition pathway². Both gold(I)³ and gold(III)⁴ have been employed as efficient catalysts towards these reactions. Interestingly, in some cases, simple gold(I) and gold(III) salts, such as AuCl and AuCl₃, performed equally well for such transformations.⁵ The simplest and most direct way to address the mechanistic issues in these reactions is to isolate and fully characterize the key isobenzopyrylium intermediates, and then directly investigate their reactivities. However, it is generally accepted that isobenzopyrylium intermediate A is too highly reactive to isolate.^{2,14} So far, information regarding the property of intermediates A is limited to *in situ* spectroscopic evidence¹⁴ and computational analysis.¹⁵ By means of NMR, EXAFS and ESI-MS analyses, Nguyen et al. detected a Au(III) intermediate species when reacting equimolar amounts of $AuCl_3$ with o-alkynylarylketone in acetonitrile.^{14a} Spectroscopic evidence indicated that the major complex is a dibenzopyrilium-gold species instead of the commonly proposed monobenzopyrilium-gold species A.

On the other hand, transition-metal mediated intramolecular nucleophilic addition of alkynes has recently emerged as a successful strategy in the direct synthesis of abnormal N-heterocyclic carbene (aNHC) or mesoionic carbene (MIC) metal complexes.¹⁶ We

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previously reported the direct synthesis of a serious of stable aNHC coinage metal complexes through the cyclization of N-propiolic formamidines.¹⁷ The methodology also provides a practical and efficient way to trap active metal species in the metal-promoted transformation of alkynes. In this sense, we envision that by proper choice of suitable substituents in the environment and environment, the corresponding metal-bound benzopyrylium intermediates A may be stable enough to be isolated and structurally characterized. Herein, we report the successful isolation of Au(I)- and Au(III)-bound benzopyrylium intermediates, **B** and **C**, which were structurally characterized by single crystal Xray diffraction analysis (Scheme 1b). To the best of our knowledge, B and C are the first two examples of structurally characterized metal-bound benzopyrylium intermediates A derived from envnals and envnones.¹⁸ Investigation into the reactivities of these intermediates towards reaction partners, such as olefins and alkynes, revealed Au(I)intermediates reacted much easier and faster than did Au(III) intermediates did. Moreover, an unprecedented degradation of active Au(III) carbene species into Au(I) species via chloride migration and reductive elimination steps was observed. In other related Aucatalyzed transformations, Au(I) isobenzopyrylium intermediates could react well with cyclization partners, while Au(III) isobenzopyrylium intermediates didn't work. These findings suggest that Au(I) species is probably the real catalyst in such Au-catalyzed [3+2] or [4+2] cycloaddition of enynals and enynones (Scheme 1b).

RESULTS AND DISCUSSION

First, we examined the reactivities of gold(I) and gold(III) catalysts towards the cyclization of *o*-alkynylbenzaldehydes and *o*-alkynylarylketones, the first step in the cycloaddition of

enynals and enynones. Simple halide precursors, AuCl·Me₂S and AuCl₃ were chosen as gold sources. In the presence of a stoichiometric amount of AuCl·Me₂S, both *o*-alkynylbenzaldehyde **1a**, and *o*-alkynylarylketones, **1b** and **1c** all underwent 6-*endo*-dig cyclizations to form vinyl gold(I) species (benzopyrilium-aurate) **2a**~**2c** at room temperature, respectively (Scheme 2, eqn (1)). Using AuCl₃ instead of AuCl·Me₂S also smoothly led to 6-*endo*-dig cyclization to give the corresponding vinyl gold(III) species **3a**~**3c**, respectively (Scheme 2, eqn (2)). Transformation of **2** into **3** was also investigated. By reacting with AuCl, Au(I) species **2b** easily undergo disproportionation to Au(III) species **3b** and Au(0) (Scheme 2, eqn (3)). Oxidation Au(I) species **2c** with PhICl₂ could also form Au(III) species **3c** (Scheme 2, eqn (4)).

Scheme 2. Synthesis of Gold(I) Complexes 2a~2c and Gold(III) Complexes 3a~3c, and Transformation of 2 into 3. a. NMR yield





Figure 1. Molecular structures of **2c** (left) and **3c** (right) with 20% probability. Selected distances (Å) and angles [°]: For **2c**, Au(1)-C(1) 2.021(4); Au(1)-Cl(1) 2.3175(11); O(1)-C(3) 1.321(5); O(1)-C(2) 1.377(5); C(1)-C(2) 1.355(6); C(1)-C(9) 1.441(6); C(3)-C(4) 1.401(6); C(4)-C(9) 1.420(6); C(1)-Au(1)-Cl(1) 179.52(11); C(2)-C(1)-C(9) 116.0(4); C(1)-C(2)-O(1) 121.7(4); O(1)-C(3)-C(4) 119.7(4). For **3c**, Au(1)-C(1) 2.008(6); Au(1)-Cl(1) 2.275(2) ; Au(1)-Cl(2) 2.3460(19); O(1)-C(3) 1.328(7); O(1)-C(2) 1.394(8); C(1)-C(2) 1.367(9); C(1)-C(9) 1.421(9); C(3)-C(4) 1.410(9); C(4)-C(9) 1.416(9); C(1)-Au(1)-Cl(1) 87.47(18); C(1)-Au(1)-Cl(2) 178.87(18); C(2)-C(1)-C(9) 118.9(6); C(1)-C(2)-O(1) 119.1(6); O(1)-C(3)-C(4) 119.7(6).

The structures of **2c** and **3c** were established by X-ray diffraction analysis (Figure 1). Au(1)– C(1) bond distance (2.021(4) Å) in **2c** is similar to those observed for the gold(I) complex bearing an *a*NHC with a pyrimidin-4-one core $[2.005(8) \text{ Å}]^{17a}$, the abnormal thiazol-5-ylidene gold(I) complex $[2.005(14) \text{ Å}]^{19a}$, and non-heteroatom-stabilized gold carbene complex $[2.039(5) \text{ Å}]^{19b}$. Complex **3c** has square planar geometry about gold(III). The Au(1)–C(1) bond (2.008(6) Å) in **3c** is similar to those in NHC-Au(III) complexes (1.98-2.01 Å),^{20a,20b} shorter than those observed for the Au(III)Cl₃ complex containing an *a*NHC with a isothiochromene core (2.077(7) Å),^{16b} Au(III)

carbene complex (2.120(3) Å),^{20c} and vinyl Au(III)Cl₃ complex (2.2743(9) Å)²¹. It suggests both vinylgold(I) **2a~2c** and vinyl gold(III) **3a~3c** could also be described as *a*NHC or MIC carbene gold complexes of type **A'** (Scheme 1a). Some vinyl gold species were found to be prone to diauration to form *gem*-digold species.²² But such diauration reaction wasn't observed for either vinylgold(I) **2a~2c** or vinyl gold(III) **3a~3c**.

Scheme 3. Control Experiments to Test Different Reactivities of Gold(I) and Gold(III) Complexes 2b and 3b towards Styrene



With vinyl gold(I) and vinyl gold(III) complexes in hand, we first investigated either AuCl- or AuCl₃-catalyzed [4+2] cycloadditon of *o*-alkynylarylketone **1b** with styrene as a model reaction. It has been previously reported, under the catalysis of $Cu(OTf)_2^{7a}$ or NHC-AuCl,^{3c} *o*-alkynylarylketones could react with alkenes to give dihydronaphthalene compounds. We found that in the presence of either 10 mol% AuCl·Me₂S or AuCl₃ [4+2], cycloaddition of **1b** with styrene

at 80 °C afforded the expected dihydronaphthalene **4** as major product, accompanying with minor product, naphthalene **5**, an oxidation product of **4** (Scheme 3, eqn (1)). Au(I) species **2b** and Au(III) species **3b** were then tested for the cycloaddition reaction with styrene. Both **2b** and **3b** proved to be reactive with styrene, offering **4** and **5**, respectively (Scheme 3, eqn (2) and (3)). Au(III) species **3b** led to more oxidation product **5**, probably attributed to the high oxidation property of Au(III). It is rather remarkable that Au(I) species **2b** showed a quite high reaction rate, giving **4** and **5** in a 81% total yield within 0.5 h (Scheme 3, eqn (2)), while Au(III) species **3b** reacted very sluggishly under identical reaction condition, requiring 16 h to obtain complete conversion (Scheme 3, eqn (3)).

Scheme 4. Reactions of 1b with AuCl^{SMe₂} and AuCl₃ in the Presence of Excess Styrene



It is known that alkene could not only induce disproportionation of gold(I), but also reduce gold(III) species.²³ However, even in the presence of excess styrene, **1b** reacted immediately with either AuCl·SMe₂ or AuCl₃, offering **2b** in excellent yield or **3b** in good yield (Scheme 4, eqn (1) and (2)). These observations clearly indicate that gold-mediated cyclization reaction of *o*-alkynylarylketones **1** is fast and should be the first step in both the AuCl- and AuCl₃-catalyzed such tandem cycloaddition reactions, giving active vinyl gold intermediate **2** or **3**.

Scheme 5. Control Experiments to Test Different Reactivities of 2b and 3b towards Phenyl

Acetylene and Formation of Unknown Dicholoride Compound 6



Next, we examined the gold-catalyzed [4+2] cycloaddition of *o*-alkynylarylketones with alkynes. AuCl₃ has been found to be reactive for the transformation.^{4a} In the presence of 10 mol% AuCl·Me₂S or 3 mol% AuCl₃, **1b** reacted with phenyl acetylene to give naphthalene **5** with moderate yield (Scheme 5, eqn (1)). Interestingly, treatment of either **2b** or **3b** with excess phenylacetylene afforded a considerable amount of an unknown dichloride compound **6**, along with **5** (Scheme 5, eqn (2) and eqn (3)). The formation of **6** was confirmed by X-ray crystallography. When reacting with phenyl acetylene, Au(I)

species **2b** also exhibited a faster reaction rate than Au(III) species **3b** did, showing a similar trend in the reaction rate as that in the reactions of **2b** or **3b** with styrene (Scheme 5, eqn (2) and (3)).

Scheme 6. Formation of Dichloride Compound 6 and Its Analogue 7 through Reactions of 1a and 1b with Au(III) Resources in the Presence of Phenyl Acetylene



We further focus on the mechanism of the formation of the dichloride compound **6**. In the presence of equimolar amounts of AuCl₃, one-pot reaction of **1b** with phenyl acetylene could directly afford **6** in 40% yield (Scheme 6, eqn (1)). Dichloride Au(III) complex AuCl₂(Pic) could also work, offering **6** in 33% yield (Scheme 6, eqn (2)). Such transformation is compatible with 2-alkynylbenzaldehyde **1a**, giving the corresponding dichloride compound **7** in 42% yield, along with naphthalene **8** (Scheme 6, eqn (3)).

In the gold-catalyzed cycloaddition of *o*-alkynylbenzaldehydes or *o*-alkynylarylketones with alkynes, the proposed benzopyrilium-aurate intermediate (I) could transform into its resonance structure, a 1,3-dipolar ylide containing a gold carbene complex fragment (II) (Scheme 7a).²⁴ A

DFT study reported by Straub suggests that **II** prefers to undergo the Huisgen-type [3+2] cycloaddition of alkyne substrate to generate gold carbene intermediate **III**, which rearranges to **IV**, leading eventually via the formal [4+2] cycloaddition intermediate **V** to the aromatized naphthyl ketone **VI**.¹⁵ The computational data indicate both AuCl and AuCl₃ feature similar overall barriers for the reaction sequence.

Scheme 7. Generally Accepted Mechanism and a Proposed Mechanism for a Degradation Pathway of Active Gold(III) Species

a) Known mechanism for Au-catalyzed [4+2] cycloaddition of o-alkynylbenzaldehydes and o-alkynylarylketones with alkynes



b) Proposed mechanism for a degradation pathway of active gold(III) species



Then we proposed a plausible reaction mechanism for the formation of dichloride compounds **6** and **7** as shown in Scheme 7b. 1,3-Dipolar Au(III) intermediate **VII** firstly undergoes [3+2]

4 5

6 7

8 9 10

11 12

18 19

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49 50

51 52 53

54 55

60

cycloaddition with alkyne substrate to afford Au(III) carbene VIII, which undergoes chloride migration to give Au(III) species IX, followed by reductive elimination of IX to form dichloride compound X and release of AuCl. Similar chloride migration to the carbene-C atom has been observed for electrophilic Rh-carbene complexes.²⁵ The mechanism involves an unprecedented degradation pathway of active gold(III) species.

Scheme 8. Calculated Reaction Profile for Transformation of Gold(III) Intermediate VIII and its Degradation Pathway.

C

CI-Au TS2

ÌΟ.

C

-0.8

-1.4

Ph

⊖l ... ⊖AuCl₃

44

-9.9

CI-Au-CI

IX

v

Рh

TS4 ⊝[|]_{AuCl₃}

-13.9

-51.5

Ő

Pro2

Pro1 CI-

Ph

Ph

▲G_{298, DCM} (kcal/mol)

C

TS3

CI

CI-Au

ςι

TS1

Ph

11.2

7.1

Ph

Cl₃Au

0.0

Ph

 \cap

VIII

Cl₃Au



from the Au(III) carbene intermediate VIII, and the solvation Gibbs free energy profiles in DCM are shown in Scheme 8. Passing through transition state TS1 with an activation free energy of 7.1 kcal/mol, the chloride migration leads to the formation of an intermediate IX. which is exergonic by 9.9 kcal/mol. The intermediate IX undergoes reductive elimination to afford the dichloride product complex **Pro1** via **TS1** with an activation free energy of 9.1 kcal/mol. The calculation results demonstrate that the proposed mechanism involving the chloride migration and reductive elimination to give dichloride product is reasonable. For comparison, we calculated another reaction pathway starting from the intermediate **VIII** to give naphthalene product. Passing through transition state **TS3** with an activation free energy of 11.2 kcal/mol, the intermediate VIII can undergo an arrangement to produce another intermediate V. The transition state TS3 is located above TS1 by 4.1 kcal/mol, indicating that the chloride migration is kinetically favourable. The C-O bond cleavage takes place via TS4 with an activation free energy of 3.0 kcal/mol to give product complex Pro2. This reaction pathway involving arrangement and C-O bond cleavage is also supported by DFT calculations.

It is known that AuCl₃ and NHC ligand-supported Au(III) catalysts could be reduced by alkenes or alkynes, offering Au(I) species.²⁶ Therefore, we further studied the reactivity of Au(III) intermediate **3b** towards reductive alkenes or alkynes. For comparison, the reaction of non-ligated AuCl₃ with either alkenes or alkynes was first investigated. After mixing AuCl₃ with either phenyl acetylene or styrene and stirring for 20 mins, the resulting mixture was immediately treated with *o*-alkynylarylketone **1b** (Scheme 9, eqn (1) and (2)). As expected, formation of **3b** along with a considerable amount of **2b** was observed in both cases. However, Au(III) species **3b** is quite stable against reduction of either alkenes or phenyl acetylene (Scheme 9, eqn (3) and (4)). These

observations indicate the interaction between Au(III) catalysts and substrates could form more stable Au(III) intermediates, such as **3b**, and thus hamper themselves for reduction.

Scheme 9. Control Experiments to Test the Reactivity of Au(III) Species towards Reductive Alkenes and Alkynes



The above observations indicate that two degradation pathways of active Au(III) species might be present in such gold(III)-catalyzed cycloaddition of *o*-alkynylbenzaldehydes and *o*-alkynylarylketones: (1) reduction of non-ligated Au(III) species, such as AuCl₃, and (2) degradation of Au(III) intermediates through cycloaddition of Au(III) carbene **3** with alkynes. Therefore, considering the degradation processes, combined with the fact that Au(I) species **2** exhibits much faster reaction rate in the reaction with cycloaddition partners than Au(III) species **3** does, we infer that Au(I) species is probably the real catalyst in such AuCl- or AuCl₃-catalyzed transformations of *o*-alkynylbenzaldehydes and *o*- alkynylarylketones. Aiming to obtain more experimental evidences, we finally investigated several known reactions involving the proposed Au-bound isobenzopyrylium intermediates by testing the reactivities of Au(I) intermediates **2** and Au(III) intermediates **3** towards a range of reaction partners.

Scheme 10. Control Experiments to Test the Reactivities of 2a and 3a towards Conjugated Diene *a* Taken from Ref. 5b



Cao and co-workers reported Au-catalyzed reaction of *o*-alkynylarylaldehyde with conjugated diene, 2,3-dimethyl-3-butadiene **9**, generating highly strained tetracyclic bridgehead olefin **10** (Scheme 10, eqn (1)).^{5b} The authors found both AuCl·SMe₂ and AuCl₃ worked well for the reaction. However, when we tested the reactivities of **2a** and **3a** towards conjugated diene **9**, the reaction outcomes are quite different (Scheme 10, eqn (2) and (3)). Au(I) species **2a** reacted with **9** to exclusively give the expected product **10** with good yield in five minutes, while treatment of Au(III) species **3a** with **9** resulted in a trace amount of

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10 over 8 h.

Scheme 11. Control Experiments to Test the Reactivities of 2a and 3a towards Benzofuran *a* NMR Yield



Dyker and co-workers reported in the presence of water, AuCl₃ showed efficient catalytic performance in the tandem reaction of *o*-alkynylarylaldehyde with benzofuran.^{4b} We found that both AuCl·SMe₂ and AuCl₃ are efficient catalysts for the transformation (Scheme 11, eqn (1)). Again, Au(I) species **2a** reacted smoothly with benzofuran to afford the expected product **11** with good yield in 15 minutes, while Au(III) species **3a** resulted in a complex mixture of products with a trace amount of **11** (Scheme 11, eqn (2) and (3)).

Scheme 12. The Stabilities of 2a and 3a towards Trace Water in CDCl₃ and AuCl-

Catalyzed Cyclization of Benzofuran with Benzaldehyde 12



Complex 2a was found to decompose slowly in CDCl₃, and underwent ring opening reaction to give benzaldehyde 12, a hydrolysis product of 1a (Scheme 12, eqn (1)). In contrast, 3a is quite stable in CDCl₃, and no ring open product 12 was detected at room temperature during 8 h (Scheme 12, eqn (2)). Under catalysis of AuCl·SMe₂, 12 can react well with benzofuran to form the desired product 11 (Scheme 12, eqn (3)).

The intrinsic difference in reactivity between 2a and 3a was also observed in their reactions towards MeOH. Yamamoto et al. previously reported the copper-catalyzed domino cyclization/nucleophilic addition of *ortho*-alkynylarylaldehyde.²⁷ We found AuCl·SMe₂ is also an efficient catalyst for the transformation to afford cyclic alkenyl ether **13** in 74% yield (Scheme 13, eqn (1)). However, AuCl₃ doesn't work for the reaction. The observation is also in line with the different reactivities of 2a and 3a towards MeOH. Au(I) species 2a smoothly reacted with MeOH to give **13**, while treatment of Au(III) species 3a

with MeOH led to complex products without producing any of **13** (Scheme 13, eqn (2) and (3)).

Scheme 13. Control Experiments to Test the Reactivities of 2a and 3a towards Methanol



CONCLUSIONS

We report the isolation of key gold(I)- and gold(III)-bound isobenzopyrylium intermediates in the Au(I)-Au(III)-catalyzed cycloaddition of o-alkynylbenzaldehydes and and 0alkynylarylketones. The structures of two representative Au(I) and Au(III) intermediates were confirmed by X-ray diffraction analysis. Au(I) intermediate 2 exhibits much faster reaction rate in the reactions with reaction partners, such as styrene and phenyl acetylene, than Au(III) species 3 does. A degradation pathway of active Au(III) species was observed, involving formation of dichloride compound as degradation product and consequently release of Au(I) species. In other related reactions, Au(I) isobenzopyrylium intermediates could react well with a range of cyclization partners, while Au(III) isobenzopyrylium intermediates didn't work. Based on the above observations, we infer that Au(I) species is probably the real catalyst in such AuCl- and

AuCl₃-catalyzed transformations of *o*-alkynylbenzaldehydes and *o*-alkynylarylketones. Further studies on the reactivities of these isolable Au isobenzopyrylium intermediates would be highly helpful to better understand the mechanisms of Au-catalyzed transformations of both *o*-alkynylbenzaldehydes (enynals) and *o*-alkynylarylketones (enynones).

ASSOCIATED CONTENT

Supporting Information.

Complete experimental procedures, compound characterization, representative NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*zhangj@ecust.edu.cn

*xusheng@ecust.edu.cn

Author Contributions

[§]C.Z., G.W., and L.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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Gold(I) or Gold(III) as Real Intermediate Species in Gold-Catalyzed Cycloaddition Reactions of Enynal/Enynone?



Au(I)- and Au(III)-bound isobenzopyrylium intermediates have been prepared and a degradation pathway of active Au(III) carbene intermediate was revealed, suggesting that Au(I) species is probably the real catalyst in gold-catalyzed cycloaddtion reactions of *o*-alkynylbenzaldehydes and *o*-alkynylarylketones.