Article

Selective Vinylogous Reactivity of Carbene Intermediate in Gold-Catalyzed Alkyne Carbocyclization: Synthesis of Indenols

Cheng Zhang, Hongli Li, Chao Pei, Lihua Qiu, Wenhao Hu, Xiaoguang Bao, and Xinfang Xu

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.8b04144 • Publication Date (Web): 01 Feb 2019

Selective Vinylogous Reactivity of Carbene Intermediate in Gold-Catalyzed Alkyne Carbocyclization: Synthesis of Indenols

Cheng Zhang,[†,‡,§] Hongli Li,[‡,§] Chao Pei,[‡] Lihua Qiu,[‡] Wenhao Hu,[*,†] Xiaoguang Bao,[*,‡] and Xinfang Xu[*,†,‡]

[†]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China

[‡]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

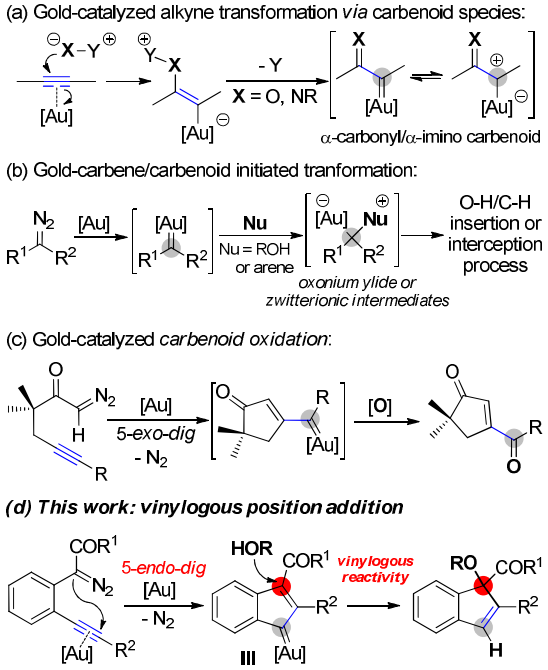
ABSTRACT: A gold-catalyzed carbocyclization of alkynes with a pendant diazo group that is completed by reaction with a protic nucleophile for the synthesis of indenol derivatives with a tertiary center is described. Mechanistic studies and DFT calculations indicate that the transformation is initiated by a gold-promoted 5-*endo-dig* carbocyclization to form the key intermediate vinyl gold-carbene, which is intercepted by an unprecedented vinylogous addition and followed by external protic nucleophile assisted protodeauration. Furthermore, in this catalytic alkyne transformation, various nucleophiles, including water, commercially available 1°, 2° and 3° alcohols, menthol, D-galactose, cholesterol, steroid, *etc.*, all perform well under these mild conditions to produce the corresponding indenol derivatives in high yields with structural diversity.

KEYWORDS: gold-catalysis, 5-endo-dig carbocyclization, diazo compound, gold carbene, indenol

INTRODUCTION

Indenols are important structural motifs found in a number of natural compounds[1] and biologically active molecules.[2-4] For example, these compounds show antiproliferative activity[2a] and antimycobacterial activity;[2b] some are used as antitumor antibiotics,[2c] molecular probes,[3] and for the treatment of chronic obstructive pulmonary disease (COPD)[4a,4b] and CNS disorders.[4c] Consequently, the development of effective methods for the construction of indenol skeletons with structural diversity is an attractive subject in organic synthesis.[5-8] Of these approaches, transition-metal-catalyzed carbocyclization of alkynes with carbonyl group has been established as a powerful synthetic method for the direct construction of indenols with a tertiary carbon center.[6] For example, advances in this direction *via* C-H bond activation are reported by Cheng,[7a] Glorius,[7b] and Zhao,[7c] independently. However, the methods for the straightforward synthesis of the ether and ester variants, which are difficult to prepare from corresponding tertiary indenols, are quite limited.[8] Thus, the development of efficient, diversity-oriented approaches is a useful endeavor and remains a challenge.

Recently, gold-catalyzed alkyne transformations have experienced explosive development for the effective construction of C-C and C-X bonds. Intermediates possessing carbene/carbenoid character have been postulated and verified experimentally,[9,10] including both the α-carbonyl[11] and α-imino[12] gold carbene species (Scheme 1a). In comparison with Rh[13] and Cu[14] catalyzed metal carbene transformations, most of the gold-catalyzed reactions of diazo compounds proceed through carbene reactivity,[15] including cyclopropanation and cyclopropenation,[16] X-H insertion,[17] and others.[18] However,



Scheme 1. Carbenoid *vs* Vinylogous Reactivity in Gold-Catalysis

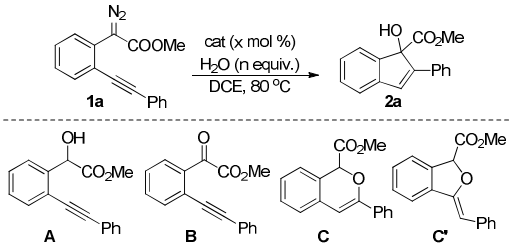
the formation of a distinct Au=C bond has been demonstrated to have dramatic differences in both reactivity and selectivity.[19] For example, X. Shi and J. Zhang have observed an exclusive electrophilic aromatic substitution of arenes with α-

diazoesters, independently.[20] Moreover, the ylide or zwitterionic intermediates, which were generated from gold carbenoid species with corresponding nucleophiles, have been successfully intercepted in various tandem processes (Scheme 1b),[21] such as dihydrofuran[21a] and indene[21b] synthesis. On the other hand, Toste has disclosed a gold-catalyzed oxidative rearrangement of alkyne-tethered diazoketone, and a vinyl gold-carbenoid intermediate was proposed in this report which was formed *via* a gold-catalyzed 5-*exo*-*dig* carbocyclization (Scheme 1c).[22] Inspired by these milestone works on the gold-catalyzed carbenoid reactions and as the continuation of our interest in the carbene/alkyne metathesis (CAM) transformations,[23] we are intrigued by the possibility that using the nucleophilic carbon of a diazo compound addition with a gold-activated alkyne to form the vinyl gold carbene species **III** (Scheme 1d), instead of an *N*-oxide or azide to generate the α-carbonyl and α-imino carbenoid intermediates, respectively (Scheme 1a). New transformations *via* interception of this intermediate **III**, especially the vinylogous reactivity that hasn't been reported in gold-carbenoid transformations,[24] could be envisioned.[25] However, preferential activation of the carbon-carbon triple bond with the gold catalyst could be highly challenging because the competitive direct carbenoid formation with the coexisting diazo group shows priority according to previous reports (Scheme 1a, and 1b).[15-21] Herein, we present our recent results in this direction, the gold-catalyzed 5-*endo*-*dig* carbocyclization of *o*-alkynylphenyl diazoacetates **1** occurs in the presence of a protic nucleophile, which is found to be the key factor to selectively facilitate the catalytic transformation. This unprecedented reaction not only provides a direct and efficient access for the synthesis of indenol derivatives in high to excellent yields with structural diversity, but also presents the first example of selective vinylogous reactivity in comparison with the disclosed gold carbenoid reactions. Functional groups, especially alkenyl and azide, which are described as reactive toward the metal carbenoid or in gold-promoted alkyne transformations,[12] remain untouched in this work, and the synthetic utility of these products with a remaining azide group for the construction of tetracyclic frameworks is also demonstrated.

RESULTS AND DISCUSSION

Following our initial hypothesis (Scheme 1d), a variety of gold complexes were initially evaluated for the carbocyclization reaction of **1a**, which could be easily prepared from *o*-bromophenyl acetates through Sonogashira coupling and diazo transfer reactions in high yields.[26] It is surprising that, in anhydrous dichloroethane (DCE) at 80 °C, JohnPhosAu(CH_3CN)SbF_6 (**3**) did not catalyze any transformation of **1a**, and a majority of the material was recovered after 3 hours under these conditions (Table 1, entry 1). However, when the commercially available DCE was directly used as the solvent, the indenol product **2a** was isolated in 45% yield (entry 2). Water was found to have a considerable impact on the catalytic activity in this gold-catalyzed reaction, which not only acted as a reagent but was also essential to promoting the catalytic transformation. The reaction gave comparable results in the presence of 5-10 equivalents of water (entries 3 and 4) at 60-80 °C (entries 3 and 5), and the best results were obtained in the presence of 5 equivalents of water at 80 °C in DCE (entry 3, 92% isolated yield). Decreasing the catalyst loading resulted in moderate yields (entry 6). Varying the counterion of gold catalyst from NTf_2^- to SbF_6^- shown little effect (entry 7). Notably, this reaction was performed without slow addition of the diazo compound *via* syringe pump, and the observed chemoselectivity is unique for gold catalysis because no indenol product **2a** was generated in the presence of silver, dirhodium, or copper catalysts (entries 10-12). By-products **A**, **B**, **C**, and **C'** were generated in these cases *via* the corresponding metal carbene reaction pathway.[27]

Table 1. Condition Optimization[a]

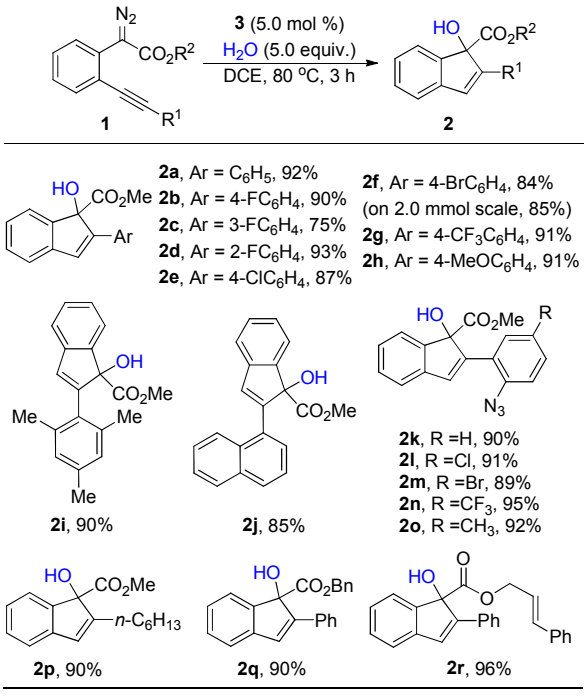


entry	cat (x mol %)	H_2O (n equiv.)	yields (%)[b] **2a/A/B/C**
1[d]	JohnPhosAu(CH_3CN)SbF_6 **3** (5.0)	-	-/-/-/-
2[e]	**3** (5.0)	-	45[f]/-/-/-
3	**3** (5.0)	5	92[f]/-/-/-
4	**3** (5.0)	10	85[f]/< 5/-/-
5[g]	**3** (5.0)	5	87[f]/-/-/-
6	**3** (2.0)	5	60[f]/-/-/-
7	JohnPhosAuCl (5.0) + $AgNTf_2$ (5.0)	5	89[f]/-/-/-
8	JohnPhosAuCl (5.0)	5	16/< 10/30[f]/18[c]
9	$AuCl_3$ (5.0)	5	< 10/75[f]/11/-
10	$AgSbF_6$ (5.0)	5	-/32[f]/35[f]/-
11	$Rh_2(OAc)_4$ (2.0)	5	-/75[f]/11/0
12	$Cu(hfacac)_2 \cdot H_2O$ (5.0)	5	-/-/30[f]/60[c]

[a]Reaction conditions: to a solution of the catalyst in dry DCE (2.0 mL), was added the solution of **1a** (0.2 mmol) in DCE (2.0 mL) at the indicated temperature under argon atmosphere and the reaction was stirred for 3 h under these conditions. [b]Yields were determined by proton NMR of the crude reaction mixture based on the yields of isolated products. [c]Isolated as a mixture of **C** and **C'**. [d]Most of **1a** was recovered. [e]Commercially available DCE was used as solvent and partial of **1a** was reserved. [f]Isolated yields. [g]The reaction was carried at 60 °C. DCE = dichloroethane.

SCOPE

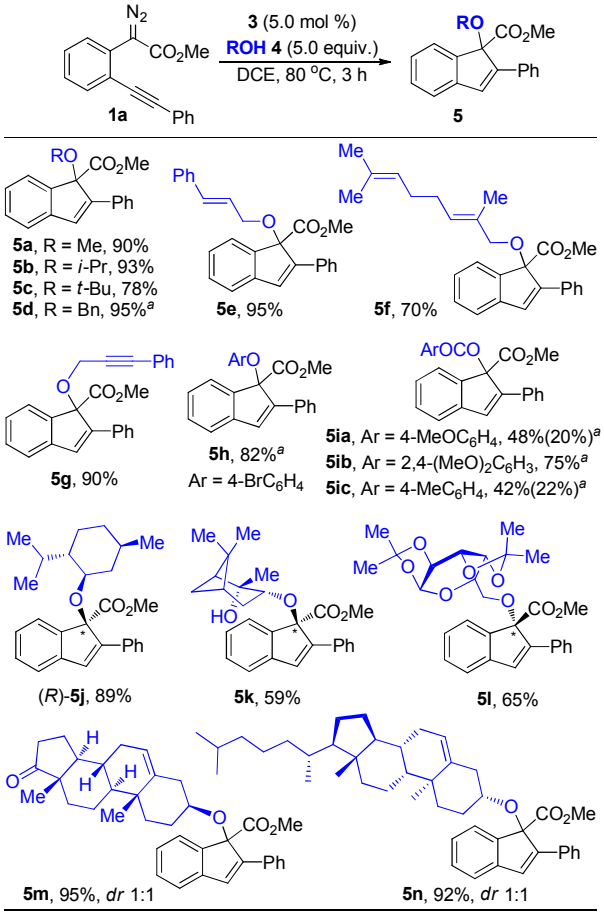
Under the optimal reaction conditions, a wide variety of 2-substituted indenols have been generated with this method (Scheme 2). The impact of substituents on the alkyne motifs of **1a** was initially investigated (R^1), Electron-neutral, electron-withdrawing, electron-donating, and bulky groups were all tolerated in this transformation, and provided the corresponding products in high to excellent yields (**2a**-**2i**, 75-93%). Moreover, comparable results were obtained when the reaction was carried out on a 2.0 mmol scale (**2f**, results in parenthesis). The naphthyl- and alkyl-substituted substrates also underwent



Scheme 2. Scope of Diazo Compounds 1. The reactions were carried out on a 0.2 mmol scale in DCE at 80 °C for 3 h.

the reaction smoothly, leading to indenols **2j** and **2p** in 85% and 90% yields, respectively. Notably, the azide group, which was reported to form the α-imino gold carbene with alkyne in the presence of gold catalyst,[12] remained untouched under these conditions, and corresponding products were isolated in > 89% yields (**2k**-**2o**). These results not only showed the preferential reactivity of diazo group over the azide, but also offered the potential synthetic utility of these products with a remaining azide group. Subsequently, the ester part of the diazoacetates was investigated. It is worth mentioning that diazoacetates bearing the groups, including benzyl and alkenyl groups which were described as reactive toward the metal carbene for C-H insertion and cyclopropanation reactions, respectively, were also well-tolerated in this reaction and afforded indenol products in > 90% yields (**2q** and **2r**). The structures of products **2f** and **2n** were unambiguously confirmed by signal-crystal X-ray analysis.[28]

Encouraged by the above promising results of this gold-catalyzed reaction in the presence of water, we envisioned that the catalytic system may also facilitate the carbocyclization of alkyne with other challenging substrates (Scheme 3). To our delight, the reaction showed broad substrate generality, including alkyl alcohol, cinnamyl alcohol, geraniol, and phenylpropargyl alcohol all promoted the reaction smoothly and provided the corresponding ether products **5a**-**5g** with a tertiary carbon center in > 70% yields. It is worth mentioning that with the *tert*-butyl alcohol, the reaction provided the corresponding product **5c** with an ethereal bond flanked by two quaternary centers in 78% yields. Phenol was well-tolerated under these reaction conditions, giving the cyclization product **5h** in 82% yield at room temperature. Notably, benzoic acid derivatives, which are more acidic than water or alcohol, were also compatible, giving the corresponding cyclization products



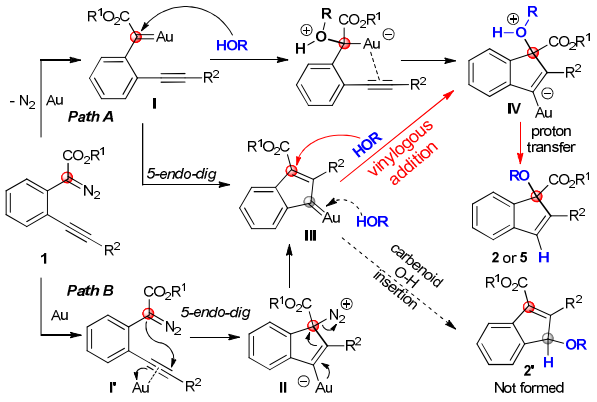
Scheme 3. Scope of Protic Nucleophiles 4. The reactions were carried out on a 0.2 mmol scale in DCE at 80 °C for 3 h. [a] The reactions were carried out at room temperature for 5 h, and the data in parentheses are yields of corresponding carbene O-H insertion products, see SI for details.

5ia-**5ic** in fairly good yields contaminated with the direct O-H insertion product in the cases with **5ia** and **5ic**. Lower reaction temperature was necessary to ensure the high yield in the cases with phenol and benzoic acids to avoid the direct O-H insertion. Furthermore, chiral protic nucleophiles, including L-menthol, (+)-2,3-pinanediol, and even sugar derivative diacetone-D-galactose, all proceeded smoothly and selectively to afford the ether products **5j**, **5k**, and **5l**, each as a signal enantiomer in 89%, 59%, and 65% yields, respectively. The competition experiment has been carried out in the presence of equal amount of isopropanol and *tert*-butanol, and only selective addition product with secondary alochol was formed (see Figure S4 in the SI for details). And the chiral alcohol itself contributed to the high stereoselectivity in this transformation. The stereochemistry of the newly formed chiral center in **5j** was unambiguously determined to be *R* by single-crystal X-ray analysis,[28] and the structure **5l** of **5l** and was tentatively assigned by the comparison of optical rotations.[26] It is worth mentioning that this is the first example that provided the direct access for the synthesis of optical pure indenol ethers with a tertiary center.[8] In addition, two biomolecules, dehydroepiandrosterone and cholesterol, were also tested in

this reaction, and the indene moiety was successfully linked to these compounds and the products were obtained in > 92% yields with 1:1 *dr* (**5m** and **5n**). These results showed significant potential of this underexplored pattern of reactivity for the selective modification of bioactive molecules which possess a hydroxyl group, especially for the *late-stage modification* of natural products or pharmaceuticals.

MECHANISTIC DISCUSSION

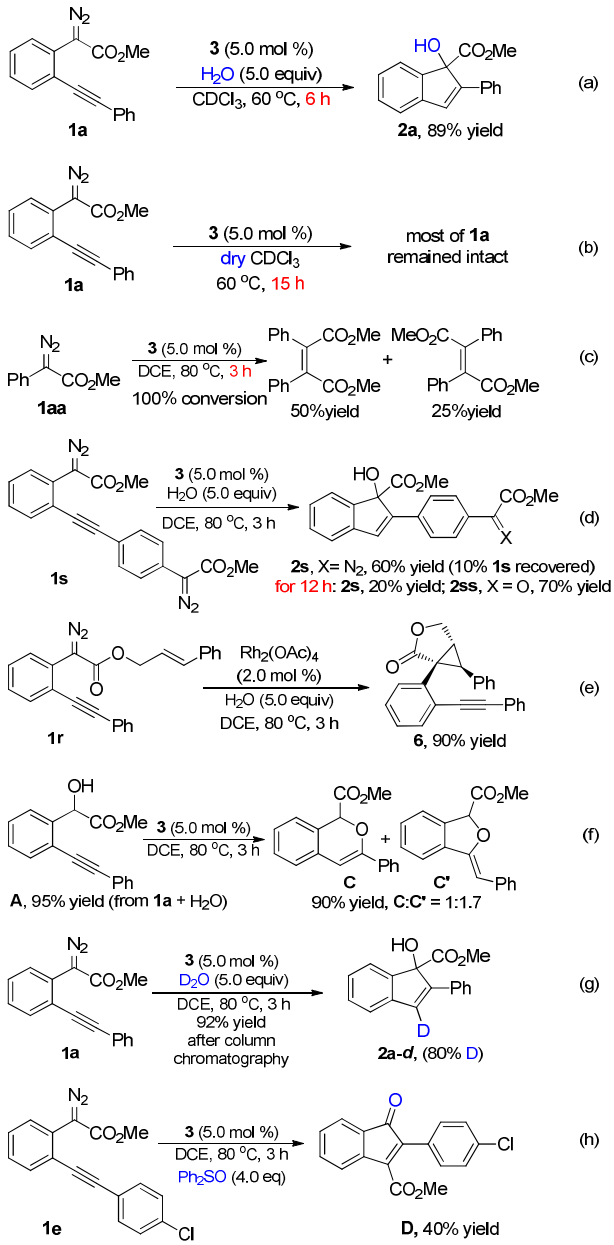
According to the previously reported gold-catalyzed transformations, two potential catalytic pathways may be involved in this reaction, including direct gold-carbene formation of the diazo group,[15-21] and classic alkyne activation with the π-acidic carbophilic gold catalyst (Scheme 4, Path A and B).[9-12] To



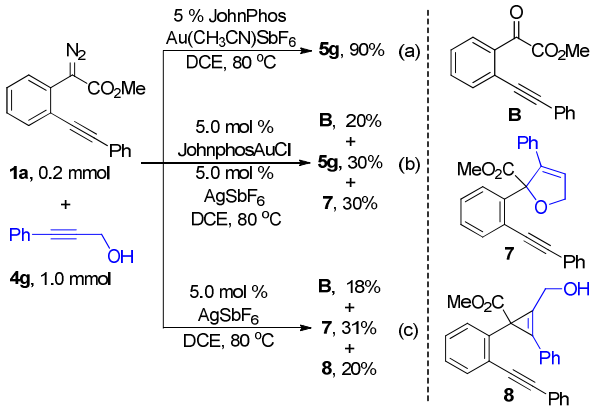
Scheme 4. Proposed Mechanism

gain insight into the initial step, control reactions of **1a** and **1aa** were conducted individually in the presence of gold catalyst **3** Although **2a** was isolated in 89% yield when the reaction was conducted at 60 °C in the presence of water (Scheme 5a), the majority of **1a** was recovered after 15 hours at 60 °C in dry $CDCl_3$ (Scheme 5b and Figure S1). On the other hand, complete decomposition of **1aa** occurred within 3 hours in DCE, leading to the formation of dimerized products as a *Z*/*E* mixture (Scheme 5c and Figure S2). Interestingly, the additional diazo group on the substrate **1s** survives under these reaction conditions, and affords the cyclized product **2s** in 60% yields with 10% of material recovered (Scheme 5d, decomposition of **2s** occurs slowly under these reaction conditions to give the corresponding carbonyl product **2ss**, see SI for details).[26] These results suggest that the activation of the alkyne has priority in this case compared with the gold-catalyzed diazo group decomposition, and similar preferential reactivity was observed by Doyle and co-authors in gold-catalysis.[29] On the other hand, in the presence of $Rh_2(OAc)_4$ instead of gold catalyst **3**, the cyclopropanation product **6** is formed from **1r** in 90% yield *via* a corresponding metal carbene intermediate, which is distinctly different from the product formed in the gold catalysis (Scheme 5e *vs* **2r** in Scheme 2). Furthermore, the O-H insertion product **A** is produced as the only product from **1a** in the presence of degassed water catalyzed by $Rh_2(OAc)_4$, and the cyclization products **C** and **C'** could be obtained from **A** when catalyzed by **3** (Scheme 5f).[27] All these results lead to the conclusion that direct formation of the gold carbenoid intermediate **I** (Scheme 4, Path A) was not the initial step in this reaction. The deuterated product **2a-*d*** was isolated in 92% yields in the presence of D_2O after column chromatography (Scheme 5g). In addition, the carbenoid oxidation product **D** was isolated in 40% yield in the presence of diphenylsulfoxide instead of water (Scheme 5h),[22] which indicated the possibility of the formation of corresponding vinyl gold carbenoid species **III** in this transformation (Scheme 4, Path B). And the remaining question is the preferential addition between the vinylogous position (Scheme 4, red arrows) to give the product **2** and the carbenoid O-H insertion to produce the regioisomer **2'** which is not detected in this transformation (dashed arrows).

To further understand the reaction mechanism, comparison experiments of **1a** with phenylpropargyl alcohol **4g** catalyzed by gold and silver separately or in combination are carried out (Scheme 6). Under the standard conditions, which means with



Scheme 5. Control Experiments



Scheme 6. Comparison Experiments of Au- and/or Ag-Catalysis

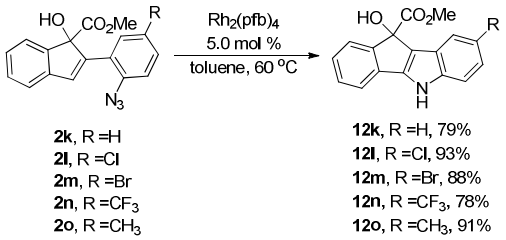
the gold catalyst **3** alone, the reaction forms the indenol derivate **5g** as the only product in 90% yield (Scheme 6a). However, by combining of gold with silver, which is supposed to form **3** *in situ*, only resulted in the formation of product **5g** in 30% yield, and contaminated with compounds **B** and **7** in 20% and 30% yields, respectively (Scheme 6b). And these two by-products are generated through the metal carbene intermediate.[21] Additionally, when the reaction is catalyzed by $AgSbF_6$ alone, three identifiable products **B**, **7**, and **8** are isolated in combined high yields, instead of **5g** (Scheme 6c). These results clearly illustrate that the current reaction goes through a reaction pathway that is different from the reported transformations, which does not involve the direct formation of metal carbene intermediate at the diazo group (Scheme 4, Path A).

Density functional theory (DFT) calculations were carried out to gain a mechanistic insight on the formation of indenol derivatives.[26] The formation of Au(I)-carbenoid intermediate (**I**) could be achieved by the gold catalyzed activation of the diazo moiety of **1a** and synchronously release N_2 (Figure S5, Path A).[19,30] The predicted energy barrier for Path A is 29.6 kcal/mol relative to separated **1a** and the catalyst. Alternatively, Path B leading to the cyclized Au(I)-carbenoid intermediate (**III**) *via* the alkyne activation with the π-acidic carbophilic gold catalyst was explored. The calculated $\Delta G^{\neq}$ for the cyclization step is 27.1 kcal/mol, which is 2.5 kcal/mol lower in energy than that of the direct activation of diazo moiety to form the gold carbenoid **I** (Figure S5 Path B). Therefore, the computational results suggest that it is more feasible for **1a** to undergo the Au(I) promoted *5-endo-dig* carbocyclization followed by N_2 dissociation to afford the gold carbenoid intermediate **III**. After the generation of **III**, the predicted energy barrier for the vinylogous position addition step is 19.5 kcal/mol relative to separated **III** and methanol (Figure S6). The proton transfer step could be facilitated by another molecule of methanol to complete the proton migration with a lower energy barrier (see Figure S6 *vs* S7).[26]

Based on the above experimental studies and DFT calculations, a possible reaction mechanism was proposed (Scheme 4, Path B). Initially, the gold-promoted *5-endo-dig* carbocyclization of **1** leads to the key intermediate vinyl gold carbenoid **III** *via* **II**, followed by preferential vinylogous position addition and external protic nucleophile assisted protodeauration through **IV** to deliver the indenol derivatives **2** or **5**. Moreover, the ^{31}P NMR analysis results by combination of gold catalyst **3** (0.02 mmol) and **1a** (0.02 mmol) in the absence of protic nucleophile suggested the formation of a relative stable complex(s) under these conditions (see Figure S3 in SI), and the reaction could not complete a catalytic cycle in the absence of the protic nucleophile under current conditions. It should be noted that other possible reaction pathway(s), such as combination of path A and B, couldn't be totally ruled out so far.

UTILITY

To demonstrate the synthetic utility of the current method, further transformations of carbocyclization products **2** were conducted. For example, **2a** was readily converted into the indanone product under basic aqueous conditions followed by treatment with HCl.[26] Notably, with the azide product **2k-2o**, the C-N bond formation occurred in the presence of a rhodium(II) carboxylates catalyst, and the tetracyclic fused indole products **12** precipitated out as solid and obtained after filtration in 78-93% isolated yields without further purification (Scheme 7).[31] Other derivations, including reduction and



Scheme 7. Derivatization of Indenol Products 2

Sonogashira coupling reaction with bromo-substituted product **2f** were also conducted, and the corresponding products were obtained in 69% and 89% yields, respectively.[26]

CONCLUSIONS

In summary, we have disclosed an unprecedented gold-catalyzed carbocyclization reaction of alkyne-tethered diazo compounds with protic nucleophiles, which provides a direct access for the synthesis of indenol derivatives under mild reaction conditions with broad substrate scope in high to excellent yields. Various protic nucleophiles, including water, commercially available alcohols, menthol, steroid, etc., are all well tolerated under these conditions to produce the corresponding indenol derivatives with structural diversity. Mechanistic studies and DFT calculations suggest that the vinyl gold carbenoid is the key intermediate in this transformation, and the following selective interception of this intermediate with protic nucleophile presents the first example of vinylogous reactivity in comparison with the disclosed gold carbenoid reactions. This underexplored pattern of reactivity shows significant untapped potential in selective modification of privileged bioactive molecules with a hydroxyl group, and its innovative applications beyond organic synthesis could be expected.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedure, the ^{1}H and ^{13}C NMR spectra of all the products (PDF), crystallographic data for **2f**, **2n** and **5j** (CIF), and computational details.

AUTHOR INFORMATION

Corresponding Author

* E-mail: huwh9@mail.sysu.edu.cn
xgbao@suda.edu.cn
xinfangxu@suda.edu.cn

Author Contributions

§C.Z. and L.H. contributed equally to this work.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Support for this research from the National Natural Science Foundation of China and NSFC of Jiangsu (NSFC21602148, NSFC21642004); and the Program for Guangdong Introducing Innovative and Entrepreneurial Teams (No. 2016ZT06Y337) are greatly acknowledged. We also thank the reviewers for their insightful comments on the reaction mechanism.

REFERENCES

(1) (a) Namdaung, U.; Aroonreek, N.; Suksamrarn, S.; Danwisetkanjana, K.; Saenboonrueng, J.; Arjchomphu, W.; Suksamrarn, A. Bioactive Constituents of the Root Bark of Artocarpus Rigidus Subsp. Rigidus. *Chem. Pharm. Bull.* **2006**, *54*, 1433-1436. (b) Abdelfattah, M. S.; Rohr, J. Premithramycinone G, an Early Shunt Product of the Mithramycin Biosynthetic Pathway Accumulated upon Inactivation of Oxygenase MtmOII. *Angew. Chem., Int. Ed.* **2006**, *45*, 5685-5689. (c) Oh, D.-C.; Williams, P. G.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. Cyanosporasides A and B, Chloro- and Cyano-cyclopenta[*a*]indene Glycosides from the Marine Actinomycete "Salinispora Pacifica". *Org. Lett.* **2006**, *8*, 1021-1024. (d) Lee, I.-K.; Kim, Y.-S.; Jang, Y.-W.; Jung, J.-Y.; Yun, B.-S. New Antioxidant Polyphenols from the Medicinal Mushroom Inonotus Obliquus. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6678-6681. (e) Eea, G. C. L.; Teoa, S. H.; Rahmania, M.; Limb, C. K.; Limc, Y. M.; Go, R. Artomandin, a New Xanthone from Artocarpus Kemando (Moraceae). *Nat. Prod. Res.* **2011**, *25*, 995. (f) Lane, A. L.; Nam, S.-J.; Fukuda, T.; Yamanaka, K.; Kauffman, C. A.; Jensen, P. R.; Fenical, W.; Moore, B. S. Structures and Comparative Characterization of Biosynthetic Gene Clusters for Cyanosporasides, Enediyne-Derived Natural Products from Marine Actinomycetes. *J. Am. Chem. Soc.* **2013**, *135*, 4171-4174.

(2) (a) Alonso, C.; Fuertes, M.; Gonzalez, M.; Rubiales, G.; Tesauro, C.; Knudsen, B. R.; Palacios, F. Synthesis and Biological Evaluation of Indeno[1,5]naphthyridines as Topoisomerase I (TopI) Inhibitors with Antiproliferative Activity. *Eur. J. Med. Chem.* **2016**, *115*, 179-190. (b) Upadhayaya, R. S.; Shinde, P. D.; Kadam, S. A.; Bawane, A. N.; Sayyed, A. Y.; Kardile, R. A.; Gitay, P. N.; Lahore, S. V.; Dixit, S. S.; Földesi, A.; Chattopadhyaya, J. Synthesis and Antimycobacterial Activity of Prodrugs of Indeno[2,1-*c*]quinoline Derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 1306-1324. (c) Jiang, Z.-H.; Hwang, G.-S.; Xi, Z.; Goldberg, I. H. Formation and Structure of a Novel Enediyne-RNA Base Covalent Adduct. *J. Am. Chem. Soc.* **2002**, *124*, 3216-3217.

(3) (a) Xi, Z.; Hwang, G.-S.; Goldberg, I. H.; Harris, J. L.; Pennington, W. T.; Fouad, F. S.; Qabaja, G.; Wright, J. M.; Jones, G. B. Targeting DNA Bulged Microenvironments with Synthetic Agents: Lessons from a Natural Product. *Chem. Biol.* **2002**, *9*, 925-931. (b) Xiao, Z.; Kappen, L. S.; Goldberg, I. H. Development of New Simple Molecular Probes of DNA Bulged Structures. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2895-2899. (c) Lin, Y.; Jones, G. B.; Hwang, G.-S.; Kappen, L.; Goldberg, I. H. Convenient Synthesis of NCS-Chromophore Metabolite Isosteres: Binding Agents for Bulged DNA Microenvironments. *Org. Lett.* **2005**, *7*, 71-74. (d) Ma, D.; Lin, Y.; Xiao, Z.; Kappen, L.; Goldberg, I. H.; Kallmerten, A. E.; Jones, G. B. Designed DNA Probes from the Neocarzinostatin Family: Impact of Glycosyl Linkage Stereochemistry on Bulge Base Binding. *Bioorg. Med. Chem.* **2009**, *17*, 2428-2432.

(4) (a) Prat, M.; Fernández, D.; Buil, M. A.; Crespo, M. I.; Casals, G.; Ferrer, M.; Tort, L.; Castro, J.; Monleón, J. M.; Gavaldà, A.; Miralpeix, M.; Ramos, I.; Doménech, T.; Vilella, D.; Antón, F.; Huerta, J. M.; Espinosa, S.; López, M.; Sentellas, S.; González, M.; Albertí, J.; Segarra, V.; Cárdenas, A.; Beleta, J.; Ryder, H. Discovery of Novel Quaternary Ammonium Derivatives of (3*R*)-Quinuclidinol Esters as Potent and Long-Acting Muscarinic Antagonists with Potential for Minimal Systemic Exposure after Inhaled Administration: Identification of (3*R*)-3-{[Hydroxy(di-2-thienyl)acetyl]oxy}-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane Bromide (Aclidinium Bromide). *J. Med. Chem.* **2009**, *52*, 5076-5092. (b) Prata, M.; Buila, M. A.; Fernándezb, M. D.; Torta, L.; Monleóna, J. M.; Casalsa, G.; Ferrera, M.; Castroa, J.; Gavaldàa, A.; Miralpeixa, M.; Ramosa, I. Discovery of Novel Quaternary Ammonium Derivatives of (3*R*)-Quinuclidinyl Amides as Potent and Long Acting Muscarinic Antagonists. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1736-1741. (c) Kerscher-Hack, S.; Renukappa-Gutke, T.; Höfner, G.; Wanner, K. T. Synthesis and Biological Evaluation of a Series of *N*-Alkylated Imidazole Alkanoic Acids as mGAT3 Selective GABA Uptake Inhibitors. *Eur. J. Med. Chem.* **2016**, *124*, 852-880.

(5) (a) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. $PtBr_2$-Catalyzed Transformation of Allyl(*o*-ethynylaryl)carbinol Derivatives into Functionalized Indenes. Formal sp^3 C-H Bond Activation. *J. Org. Chem.* **2006**, *71*, 6204-6210. (b) Teng, T.-M.; Das, A.; Huple, D. B.; Liu, R.-S. Gold-Catalyzed Stereoselective Synthesis of 9-Oxabicyclo[3.3.1]nona-4,7-dienes from Diverse 1-Oxo-4-oxy-5-ynes: A Viable Formal [4 + 2] Cycloaddition on an s-trans-Heterodiene Framework. *J. Am. Chem. Soc.* **2010**, *132*, 12565-12567. (c) Chen, Y.; Chen, M.; Liu, Y. Gold-Catalyzed Cascade Cyclizations of 1,6-Diynyl Carbonates to Benzo[*b*]fluorenes Involving Arylation of Oxocarbenium Ion Intermediates and Decarboxylative Etherification. *Angew. Chem., Int. Ed.* **2012**, *51*, 6493-6497. (d) Morán-Poladura, P.; Rubio, E.; González, J. M. Intramolecular C-H Activation through Gold(I)-Catalyzed Reaction of Iodoalkynes. *Angew. Chem., Int. Ed.* **2015**, *54*, 3052-3055. (e) Rao, W.; Koh, M. J.; Kothandaraman, P.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization of 1,7-Diyne Benzoates to Indeno[1,2-c]azepines and Azabicyclo[4.2.0]octa-1(8),5-dines. *J. Am. Chem. Soc.* **2012**, *134*, 10811-10814.

(6) Pioneering report: (a) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. Intramolecular Nucleophilic Addition of Vinylpalladiums to Aryl Ketones. *J. Am. Chem. Soc.* **1999**, *121*, 3545-3546. Selected recent advances: (b) Shimamoto, Y.; Sunaba, H.; Ishida, N.; Murakami, M. Regioselective Construction of Indene Skeletons by Palladium-Catalyzed Annulation of Alkynylborates with *o*-Iodophenyl Ketones. *Eur. J. Org. Chem.* **2013**, 1421-1424. (c) González, J.; Santamaría, J.; Ballesteros, A. Gold(I)-Catalyzed Addition of Silylacetylenes to Acylsilanes: Synthesis of Indanones by C-H Functionalization through a Gold(I) Carbenoid. *Angew. Chem., Int. Ed.* **2015**, *54*, 13678-13681.

(7) (a) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. Regioselective Synthesis of Indenols by Rhodium-Catalyzed C-H Activation and Carbocyclization of Aryl Ketones and Alkynes. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169-4172. (b) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. Diverse Strategies toward Indenol and Fulvene Derivatives: Rh-Catalyzed C-H Activation of Aryl Ketones Followed by Coupling with Internal Alkynes. *J. Am. Chem. Soc.* **2011**, *133*, 2154-2156. (c) Zhang, J.; Ugrinov, A.; Zhao, P. Ruthenium(II)/N-Heterocyclic Carbene Catalyzed [3+2] Carbocyclization with Aromatic N-H Ketimines and Internal Alkynes. *Angew. Chem., Int. Ed.* **2013**, *52*, 6681-6684.

(8) (a) Tsukamoto, H.; Ueno, T.; Kondo, Y. Palladium(0)-Catalyzed Regioselective and Multicomponent Synthesis of 1,2,3-Trisubstituted 1*H*-Indenes. *Org. Lett.* **2007**, *9*, 3033-3036. (b) Clarke, C.; Incerti-Pradillos, C. A.; Lam, H. W. Enantioselective Nickel-Catalyzed anti-Carbometallative Cyclizations of Alkynyl Electrophiles Enabled by Reversible Alkenylnickel *E*/*Z* Isomerization. *J. Am. Chem. Soc.* **2016**, *138*, 8068-8071. (c) Myers, A. G.; Proteau, P. J.; Handel, T. M. Stereochemical Assignment of Neocarzinostatin Chromophore. Structures of Neocarzinostatin Chromophore-methyl Thioglycolate Adducts. *J. Am. Chem. Soc.* **1988**, *110*, 7212-7214. (d) Marion, N.; Díez-González, S.; Frémont, P.; Noble, A. R.; Nolan, S. P. Au^{I}-Catalyzed Tandem [3,3] Rearrangement-Intramolecular Hydroarylation: Mild and Efficient Formation of Substituted Indenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647-3650. (e) Thummanapelli, S. K.; Hosseyni, S.; Su, Y.; Akhmedova, N. G.; Shi, X. Ligand-Controlled Gold-Catalyzed Cycloisomerization of 1,*n*-Enyne Esters Toward Synthesis of Dihydronaphthalene. *Chem. Commun.* **2016**, *52*, 7687-7690.

(9) Pioneering works: (a) Teles, J. H.; Brode, S.; Chabanas, M. Cationic Gold(I) Complexes: Highly Efficient Catalysts for the Addition of Alcohols to Alkynes. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415-1418. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. Highly Selective Gold-Catalyzed Arene Synthesis. *J. Am. Chem. Soc.* **2000**, *122*, 11553-11554. (c) Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. Cationic Gold(I) Complexes: Highly Alkynophilic Catalysts for the *exo*- and *endo*-Cyclization of Enynes. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402-2406. (d) Gorin, D. J.; Davis, N. R.; Toste, F. D. Gold(I)-Catalyzed Intramolecular Acetylenic Schmidt Reaction. *J. Am. Chem. Soc*. **2005**, *127*, 11260-11261.

(10) For reviews: (a) Gorin, D. J.; Toste, F. D. Relativistic Effects in Homogeneous Gold Catalysis. *Nature* **2007**, *446*, 395-403. (b) Hashmi, A. S. K. Gold-Catalyzed Organic Reactions. *Chem. Rev.* **2007**, *107*, 3180-3211. (b) Li, Z.; Brouwer, C.; He, C. Gold-Catalyzed Organic Transformations. *Chem. Rev.* **2008**, *108*, 3239-3265. (c) Zhang, L. A Non-Diazo Approach to α-Oxo Gold Carbenes via Gold-Catalyzed Alkyne Oxidation. *Acc. Chem. Res.* **2014**, *47*, 877-888. (d) Dorel, R.; Echavarren, A. M. Gold(I)-Catalyzed Activation of Alkynes for the Construction of Molecular Complexity. *Chem. Rev.* **2015**, *115*, 9028-9072. (e) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. Au-Catalysed Oxidative Cyclisation. *Chem. Soc. Rev.* **2016**, *45*, 4448-4458.

(11) Selected recent advances: (a) Gronnier, C.; Kramer, S.; Odabachian, Y.; Gagosz, F. Cu(I)-Catalyzed Oxidative Cyclization of Alkynyl Oxiranes and Oxetanes. *J. Am. Chem. Soc.* **2012**, *134*, 828-831. (b) Henrion, G.; Chavas, T. E. J.; Goff, X. L.; Gagosz, F. Biarylphosphonite Gold(I) Complexes as Superior Catalysts for Oxidative Cyclization of Propynyl Arenes into Indan-2-ones. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277-6282. (c) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. Rapid Access to Chroman-3-ones through Gold-Catalyzed Oxidation of Propargyl Aryl Ethers. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915-1918. (d) Ji, K.; Zhao, Y.; Zhang, L. Optimizing *P*,*N*-Bidentate Ligands for Oxidative Gold Catalysis: Efficient Intermolecular Trapping of α-Oxo Gold Carbenes by Carboxylic Acids. *Angew. Chem., Int. Ed.* **2013**, *52*, 6508-6512. (e) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. Tempering the Reactivities of Postulated α-Oxo Gold Carbenes Using Bidentate Ligands: Implication of Tricoordinated Gold Intermediates and the Development of an Expedient Bimolecular Assembly of 2,4-Disubstituted Oxazoles. *J. Am. Chem. Soc.* **2012**, *134*, 17412-17415. (f) Ji, K.; Zheng, Z.; Wang, Z.; Zhang, L. Enantioselective Oxidative Gold Catalysis Enabled by a Designed Chiral P,N-Bidentate Ligand. *Angew. Chem., Int. Ed.* **2015**, *54*, 1245-1249. (g) Wang, Y.; Zheng, Z.; Zhang, L. Intramolecular Insertions into Unactivated $C(sp^3)$-H Bonds by Oxidatively Generated β-Diketone-α-Gold Carbenes: Synthesis of Cyclopentanones. *J. Am. Chem. Soc.* **2015**, *137*, 5316-5319.

(12) Selected recent advances: (a) Yan, Z.-Y.; Xiao, Y.; Zhang, L. Gold-Catalyzed One-Step Construction of 2,3-Dihydro-1*H*-Pyrrolizines with an Electron-Withdrawing group in the 5-position: A Formal Synthesis of 7-Methoxymitosene. *Angew. Chem., Int. Ed.* **2012**, *51*, 8624-8627. (b) Wetzel, A.; Gagosz, F. Gold-Catalyzed Transformation of 2-Alkynyl Arylazides: Efficient Access to the Valuable Pseudoindoxyl and Indolyl Frameworks. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354-7358. (c) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. Umpolung Reactivity of Indole through Gold Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 8358-8362. (d) Li, N.; Wang, T.-Y.; Gong, L.-Z.; Zhang, L. Gold-Catalyzed Multiple Cascade Reaction of 2-Alkynylphenylazides with Propargyl Alcohols. *Chem. Eur. J.* **2015**, *21*, 3585-3588. (e) Li, N.; Lian, X.-L.; Li, Y.-H.; Wang, T.-Y.; Han, Z.-Y.; Zhang, L. Gong, L.-Z. Gold-Catalyzed Direct Assembly of Aryl-Annulated Carbazoles from 2-Alkynyl Arylazides and Alkynes. *Org. Lett.* **2016**, *18,* 4178-4181.

(13) For reviews: (a) Davies, H. M. L.; Mortona, D. Guiding Principles for Site Selective and Stereoselective Intermolecular C-H Functionalization by Donor/Acceptor Rhodium Carbenes. *Chem. Soc. Rev.* **2011**, *40*, 1857-1869. (b) Padwa, A. The Interaction of Rhodium Carbenoids with Carbonyl Compounds as a Method for the Synthesis of Tetrahydrofurans. *J. Organomet. Chem.* **2005**, *690*, 5533-5540. (c) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev.* **2015**, *115*, 9981-10080. (d) Deng, Y.; Qiu, H.; Srinivas, H. D.; Doyle, M. P. Chiral Dirhodium(II) Catalysts for Selective Metal Carbene Reactions. *Curr. Org. Chem.* **2016**, *20*, 61-81.

(14) For reviews: (a) Zhu, S.-F.; Zhou, Q.-L. Transition-Metal-Catalyzed Enantioselective Heteroatom-Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365-1377. (b) Zhao, X.; Zhang, Y.; Wang, J. Recent Developments in Copper-Catalyzed Reactions of Diazo Compounds. *Chem. Commun.* **2012**, *48*, 10162-10173. (c) Díaz-Requejo, M. M.; Pérez, P. J. Copper, Silver and Gold-based Catalysts for Carbene Addition or Insertion Reactions. *J. Organomet. Chem.* **2005**, *690*, 5441-5450.

(15) For reviews: (a) Qian, D.; Zhang, J. Gold-Catalyzed Cyclopropanation Reactions Using a Carbenoid Precursor Toolbox. *Chem. Soc. Rev.* **2015**, *44*, 677-698. (b) Liu, L.; Zhang, J. Gold-Catalyzed Transformations of α-Diazocarbonyl Compounds: Selectivity and Diversity. *Chem. Soc. Rev.* **2016**, *45*, 506-516. (c) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. Gold and Diazo Reagents: a Fruitful Tool for Developing Molecular Complexity. *Chem. Commun.* **2016**, *52*, 7326-7335.

(16) (a) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. Highly Stereoselective Olefin Cyclopropanation of Diazooxindoles Catalyzed by a C_2-Symmetric Spiroketal Bisphosphine/Au(I) Complex. *J. Am. Chem. Soc.* **2013**, *135*, 8197-8200. (b) Zhou, Y.; Trewyn, B. G.; Angelici, R. J.; Woo, L. K. Catalytic Reactions of Carbene Precursors on Bulk Gold Metal. *J. Am. Chem. Soc.* **2009**, *131*, 11734-11743. (c) Briones, J. F.; Davies, H. M. L. Gold(I)-Catalyzed Asymmetric Cyclopropenation of Internal Alkynes. *J. Am. Chem. Soc.* **2012**, *134*, 11916-11919.

(17) Fructos, M. R.; Belderrain, T. R.; Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. A Gold Catalyst for Carbene-Transfer Reactions from Ethyl Diazoacetate. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284-5288.

(18) (a) Xu, G.; Zhu, C.; Gu, W.; Li, J.; Sun, J. Gold(I)-Catalyzed Diazo Cross-Coupling: A Selective and Ligand-Controlled Denitrogenation/Cyclization Cascade. *Angew. Chem., Int. Ed.* **2015**, *54*, 883-887. (b) Pagar, V. V.; Liu, R.-S. Gold-Catalyzed Cycloaddition Reactions of Ethyl Diazoacetate, Nitrosoarenes, and Vinyldiazo Carbonyl Compounds: Synthesis of Isoxazolidine and Benzo[*b*]azepine Derivatives. *Angew. Chem., Int. Ed.* **2015**, *54*, 4923-4926. (c) Lonzi, G.; López, L. A. Regioselective Synthesis of Functionalized Pyrroles viaGold(I)-Catalyzed [3+2] Cycloaddition of Stabilized Vinyl Diazo Derivatives and Nitriles. *Adv. Synth. Catal.* **2013**, *355*, 1948-1954. (d) Yu, Z.; Qiu, H.; Liu, L.; Zhang, J. Gold-Catalyzed Construction of Two Adjacent Quaternary Stereocenters *via* Sequential C-H Functionalization and Aldol Annulation. *Chem. Commun.* **2016**, *52*, 2257-2260. (e) Pagar, V. V.; Jadhav,

A. M.; Liu, R.-S. Gold-Catalyzed Formal [3+3] and [4+2] Cycloaddition Reactions of Nitrosobenzenes with Alkenylgold Carbenoids. *J. Am. Chem. Soc.* **2011**, *133*, 20728-20731. (f) Pawar, S. K.; Wang, C.-D.; Bhunia, S.; Jadhav, A. M.; Liu, R.-S. Gold-Catalyzed Formal Cycloaddition of 2-Ethynylbenzyl Ethers with Organic Oxides and α-Diazoesters. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559-7563. (g) Briones, J. F.; Davies, H. M. L. Enantioselective Gold(I)-Catalyzed Vinylogous [3+2] Cycloaddition between Vinyldiazoacetates and Enol Ethers. *J. Am. Chem. Soc.* **2013**, *135*, 13314-13317. (h) Rao, S.; Prabhu, K. R. Gold-Catalyzed [2,3]-Sigmatropic Rearrangement: Reaction of Aryl Allyl Alcohols with Diazo Compounds. *Org. Lett.* **2017**, *19*, 846-849.

(19) (a) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. A Bonding Model for Gold(I) Carbene Complexes. *Nat. Chem.* **2009**, *1*, 482-486. (b) Seidel, G.; Fürstner, A. Structure of a Reactive Gold Carbenoid. *Angew. Chem., Int. Ed.* **2014**, *53*, 4807-4811. (c) Wang, Y.; Muratore, M. E.; Echavarren, A. M. Gold Carbene or Carbenoid: Is There a Difference?. *Chem. Eur. J.* **2015**, *21*, 7332-7339.

(20) (a) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. Chemoselective Carbophilic Addition of α-Diazoesters through Ligand-Controlled Gold Catalysis. *Angew. Chem., Int. Ed.* **2014**, *53*, 9817-9821. (b) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. Highly Site-Selective Direct C-H Bond Functionalization of Phenols with α-Aryl-α-diazoacetates and Diazooxindoles *via* Gold Catalysis. *J. Am. Chem. Soc.* **2014**, *136*, 6904-6907. (c) Ma, B.; Chu, Z.; Huang, B.; Liu, Z.; Liu, L.; Zhang, J. Highly *para*-Selective C-H Alkylation of Benzene Derivatives with 2,2,2-Trifluoroethyl α-Aryl-α-Diazoesters. *Angew. Chem., Int. Ed*. **2017**, *56*, 2749-2753.

(21) (a) Wang, J.; Yao, X.; Wang, T.; Han, J.; Zhang, J.; Zhang, X.; Wang, P.; Zhang, Z. Synthesis of 2,5-Dihydrofurans *via* a Gold(I)-Catalyzed Formal [4+1] Cycloaddition of α-Diazoesters and Propargyl Alcohols. *Org. Lett.* **2015**, *17*, 5124-5127. (b) Ma, B.; Wu, Z.; Huang, B.; Liu, L. Zhang, J. Gold-Catalysed Facile Access to Indene Scaffolds *via* Sequential C-H Functionalization and 5-*endo-dig* Carbocyclization. *Chem. Commun.* **2016**, *52*, 9351-9354. (c) Shi, T.; Guo, X.; Teng, S.; Hu, W. Pd(II)-Catalyzed Formal [4+1] Cycloaddition Reactions of Diazoacetates and Aryl Propargyl Alcohols to form 2,5-Dihydrofurans. *Chem. Commun.* **2015**, *51*, 15204-15207. (d) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. Scope and Mechanistic Analysis of the Enantioselective Synthesis of Allenes by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Propargylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 15497-15504.

(22) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. Gold(I)-Catalyzed Oxidative Rearrangements. *J. Am. Chem. Soc.* **2007**, *129*, 5838-5839.

(23) Selected recent advances: (a) Jansone-Popova, S.; May, J. A. Synthesis of Bridged Polycyclic Ring Systems *via* Carbene Cascades Terminating in C-H Bond Insertion. *J. Am. Chem. Soc.* **2012**, *134*, 17877-17880. (b) Cambeiro, F.; López, S.; Varela, J. A.; Saá, C. Vinyl Dihydropyrans and Dihydrooxazines: Cyclizations of Catalytic Ruthenium Carbenes Derived from Alkynals and Alkynones. *Angew. Chem., Int. Ed.* **2014**, *53,* 5959-5963. (c) González-Rodríguez, C.; Suárez, J. M.; Varela, J. A.; Saá, C. Nucleophilic Addition of Amines to Ruthenium Carbenes: *ortho*-(Alkynyloxy)benzylamine Cyclizations towards 1,3-Benzoxazines. *Angew. Chem., Int. Ed.* **2015**, *54*, 2724-2728. (d) Chen, P.; Setthakarn, K.; May, J. A. A Binaphthyl-Based Scaffold for a Chiral Dirhodium(II) Biscarboxylate Ligand with α-Quaternary Carbon Centers. *ACS Catal.* **2017**, *7*, 6155-6161. (e) Torres, Ó.; Parella, T.; Solà, M.; Roglans, A.; Pla-Quintana, A. Enantioselective Rhodium(I) Donor Carbenoid-Mediated Cascade Triggered by a Base-Free Decomposition of Arylsulfonyl Hydrazones. *Chem. Eur. J.* **2015**, *21*, 16240-16245. (f) Qian, Y.; Shanahan, C. S.; Doyle, M. P. Templated Carbene Metathesis Reactions from the Modular Assembly of Enol-diazo Compounds and Propargyl Acetates. *Eur. J. Org. Chem.* **2013**, 6032-6037. (g) Ni, Y.; Montgomery, J. Synthetic Studies and Mechanistic Insight in Nickel-Catalyzed [4+2+1] Cycloadditions. *J. Am. Chem. Soc.* **2006**, *128*, 2609-2614. Our works: (h) Zheng, Y.; Mao, J.; Weng, Y.; Zhang, X.; Xu, X. Cyclopentadiene Construction via Rh-Catalyzed Carbene/Alkyne Metathesis Terminated with Intramolecular Formal [3+2] Cycloaddition. *Org. Lett.* **2015**, *17*, 5638-5641. (i) Yao, R.; Rong, G.; Yan, B.; Qiu, L.; Xu, X. Dual-Functionalization of Alkynes *via* Copper-Catalyzed Carbene/Alkyne Metathesis: A Direct Access to the 4-Carboxyl Quinolines. *ACS Catal.* **2016**, *6*, 1024-1027. (j) Wang, X.; Zhou, Y.; Qiu, L.; Yao, R.; Zheng, Y.; Zhang, C.; Bao, X.; Xu, X. Enantioselective Carbene Cascade: An Effective Approach to Cyclopentadienes and Applications in Diels-Alder Reactions. *Adv. Synth. Catal.* **2016**, *358*, 1571-1576. (k) Dong, K.; Pei, C.; Zeng, Q.; Wei, H.; Doyle, M. P.; Xu, X. Selective C(sp^3)-H Bond Insertion in Carbene/Alkyne Metathesis Reactions. Enantioselective Construction of Dihydroindoles. *ACS Catal.* **2018**, *8*, 9543-9549.

(24) Xu, X.; Zavalij, P. Y.; Doyle, M. P. Synthesis of Tetrahydropyridazines by a Metal-Carbene-Directed Enantioselective Vinylogous N-H Insertion/Lewis Acid-Catalyzed Diastereoselective Mannich Addition. *Angew. Chem., Int. Ed.* **2012**, *51*, 9829-9833.

(25) For reviews: For reviews: (a) Xu, X.; Doyle, M. P. The [3+3]-Cycloaddition Alternative for Heterocycle Syntheses: Catalytically Generated Metalloenolcarbenes as Dipolar Adducts. *Acc. Chem. Res.* **2014**, *47*, 1396-1405. (b) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427-2440. (c) Davies, H. M. L.; Lian, Y. The Combined C-H Functionalization/Cope Rearrangement: Discovery and Applications in Organic Synthesis. *Acc. Chem. Res.* **2012**, *45*, 923-935.

(26) See Supporting Information for details.

(27) Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. Sequential Au(I)-Catalyzed Reaction of Water with *o*-Acetylenyl-Substituted Phenyldiazoacetates. *Beilstein J. Org. Chem.* **2011**, *7,* 631-637.

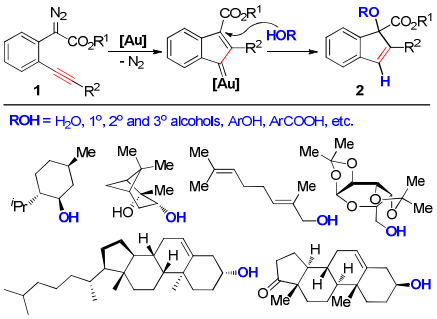
(28) CCDC 1551665, CCDC 1556423, and CCDC 1556770 contain the supplementary crystallographic data for **2f**, **2n**, and **5j**, respectively. These data can be obtained free of charge from the Cambridge crystallographic data centre via www.ccdc.cam.ac.uk/data_request/cif.

(29) Qiu, H.; Srinivas, H. D.; Zavalij, P. Y.; Doyle, M. P. Unprecedented Intramolecular [4+2]-Cycloaddition between a 1,3-Diene and a Diazo Ester. *J. Am. Chem. Soc.* **2016**, *138*, 1808-1811.

(30) For selected examples of computational studies on the formation of gold carbenoid intermediates *via* diazo compounds, see (a) Liu, Y.; Yu, Z.; Zhang, J. Z.; Liu, L.; Xia, F.; Zhang, J. Origins of Unique Gold-Catalysed Chemo- and Site-Selective C-H Functionalization of Phenols with Diazo Compounds. *Chem. Sci.* **2016**, *7*, 1988-1995. (b) Duan, A.; Yu, P.; Liu, F.; Qiu, H.; Gu, Doyle, M. P.; F. L.; Houk, K. N. Diazo Esters as Dienophiles in Intramolecular (4+2) Cycloadditions: Computational Explorations of Mechanism. *J. Am. Chem. Soc.* **2017**, *139*, 2766-2770. (c) Seidel, G.; Gabor, B.; Goddard, R.; Heggen, B.; Thiel, W.; Fürstner, A. Gold Carbenoids: Lessons Learnt from a Transmetalation Approach. *Angew. Chem., Int. Ed.* **2014**, *53*, 879-882.

(31) Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. Rh_2(II)-Catalyzed Synthesis of Carbazoles from Biaryl Azides. *J. Org. Chem.* **2009**, *74*, 3225-3228.

TOC


N2
CO2R1
[Au]
- N2
1
R2
CO2R1
HOR
[Au]
RO
CO2R1
R2
H
2
ROH = H2O, 1°, 2° and 3° alcohols, ArOH, ArCOOH, etc.
Me
iPr
OH
Me
Me
Me
HO
OH
Me
Me
Me
OH
Me
O
O
O
O
Me
OH
H
H
OH
H
H
H
O
Me
Me
OH