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Letter

(Z)- γ -Alkylidenebutenolide Synthesis through Au(I)-Catalyzed 1,3-Acyloxy Migration and the Carbonyl–Ene Reaction

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(Z)- γ -Alkylidenebutenolides are a type of oxygen-containing five-membered heterocycles featuring an α_{β} -unsaturated lactone and an enol ester. This heterocyclic scaffold can be found in numerous naturally occurring bioactive compounds. Previous synthetic approaches toward these compounds engendered different strategies to construct this five-membered ring.¹ The key is how to control the formation of thermodynamically favorable Z-isomer rather than the kinetically favorable E-isomer while keeping flexible substitution patterns, which posed significant challenges to synthetic chemists. For example, the Wittig reaction of furan-2,5-diones or the elimination of the vinylogous Mukaiyama aldol adduct of siloxyfurans was commonly employed to build the exo double bond.^{2,3} However, in most cases, a mixture of Z and E isomers was obtained. Although the formation of 3,4unsubstituted (Z)- γ -alkylidenebutenolides from terminal alkynes and (Z)-3-bromopropenoic acid was achieved in Lu's bimetal-catalyzed Sonogashira coupling and 5-exo-dig hydrocarboxylation, the scope of starting materials limited molecular diversity.⁴ Recent intermolecular lactonizations have also been attempted to generate (Z)- γ -alkylidenebutenolides, though issues on regioselectivity, stereoselectivity, as well as substrate flexibility are still encountered.5-7 Accordingly, development of more general approaches to Z-configured γ -alkylidenebutenolides remains both essential and challenging.

Transitional-metal-catalyzed 1,3-acyloxy of propargyl esters, a class of functionalized alkyne compounds, provides an efficient means to access carbocyclic and heterocyclic ring systems.⁸ The *in situ* generated allenyl esters may perform as nucleophiles,⁹ electrophiles,¹⁰ dienophiles,¹¹ and 1,*n*-dipoles¹² in the cycloisomerization and cycloaddition reactions. Inspired by previous researchers, we envisioned a bimetal catalyzed/ mediated synthesis of (*Z*)- γ -alkylidenebutenolides (Scheme 1).¹³ We proposed that easily accessed substrate propargyl α ketoester, which contains a RCO group and a CH₂R² group, can first undergo M¹-catalyzed 1,3-acyloxy migration to generate an allenyl ester, then the generated intermediate

Scheme 1. Reaction Design



can undergo M^2 -catalyzed ene reaction between RCO group and the allene's CHR² group.^{14,15} Finally, dehydration could then give the butenolide. Here, M^1 could be Au, Pt, Rh, and other catalysts, while M^2 could be the same as M^1 or other Lewis acids. If this can be realized, facile access to the challenging (*Z*)- γ -alkylidenebutenolides from easily prepared substrates might then be readily achieved. Here, we report our realization of this design and DFT understanding of the mechanism for this transformation.

We commenced the study by choosing propargyl α -ketoester **1a** as the model substrate, which was prepared from non-4-yn-3-ol and 2-oxopropanoic acid (for details, see the Supporting Information, SI). To our delight, treatment of **1a** with 5 mol % Ph₃PAuCl and 5 mol % AgNTf₂ in 1,2-dichloroethane at 80 °C for 3 h gave β -alkenylated (Z)- γ -alkylidenebutenolide **2a** in 41% yield (Table 1, entry 1). The compound was identified by a series of NMR studies. The geometry of the olefin and the

 Received:
 May 28, 2021

 Published:
 July 13, 2021



Table 1	. Opti	mization	of the	1,3-Acy	loxy I	Migrati	on/
Carbony	yl-ene	Reaction	of Pro	opargyl (α-Ket	oester	la ^a



entr y	catalyst	additive	solvent	time (h)	yield (%) ^b
1	Ph ₃ PAuCl	0.1 equiv AgNTf ₂	DCE	3	41
2	N CI-Au CI	-	DCE	12	0
3 ^c	PtCl ₂	-	Toluene	16	22
4 ^c	PtCl ₄	-	Toluene	3	13
5 ^c	Ph ₃ PAuCl	0.1 equiv AgNTf ₂	Toluene	1	44
6	Ph ₃ PAuCl	0.1 equiv Cu(OTf) ₂	DCE	1	60
7	Ph ₃ PAuCl	1 equiv Cu(OTf) ₂	DCE	1	82
8	Ph ₃ PAuCl	1 equiv Zn(OTf) ₂	DCE	1	59
9	AuCl	0.05 equiv AgOTf	DCE	1	33

^{*a*}Reaction conditions: a solution of 1a (0.142 mmol), metal catalyst (0.0071 mmol), metal additive (the amount is shown as mentioned) in DCE (1.5 mL) was heated and stirred at 80 or 100 °C. ^{*b*}Isolated yield after column purification. ^{*c*}The temperature was 100 °C. DCE = 1,2-dichloroethane.

enol ester was further confirmed by the single-crystal X-ray analysis of its analogue 2f (see the SI). Attempts to improve the conversion by using dichloro(pyridine-2-carboxylato)gold-(III), PtCl₂, or PtCl₄ as catalyst resulted in inferior results

(Table 1, entries 2–4). The (*Z*)-γ-alkylidenebutenolide was even not formed in the presence of the gold(III) complex.¹⁶ Using the same gold(I) catalyst and silver additive, comparable efficiency was observed in heating toluene (Table 1, entry 5). However, an increased yield was obtained when copper trifluoromethanesulfonate was employed as an additive (Table 1, entry 6). Control experiments demonstrated that an equivalent amount of copper additive gave the butenolide in a yield up to 82% (Table 1, entry 7; for details, see the SI). As a comparsion, zinc salt with the same counteranion afforded **2a** in a lower yield, indicating that a copper effect might be involved (Table 1, entry 8). The *in situ* generated AuOTf gave the butenolide in 33% yield (Table 1, entry 9).¹⁷ It is worth mentioning that no butenolide product was detected in the absence of gold catalysts.

With the optimal condition in hand, we sought to explore the scope of the transformation (Scheme 2). In addition to 1a, propargyl α -ketoesters with a primary chain including a nearby or remote isopropyl, phenyl, chlorine, or cyclohexyl appended on the alkyne terminus participated in the gold-catalyzed 1,3acyloxy migration and the carbonyl-ene cyclization smoothly, delivering (*Z*)- γ -alkylidenebutenolides **2b**-**2g** in yields ranging from 71% to 82%. Of note is that the C-Cl bond was tolerated in the transformation, and butenolide 2g bearing a fully substituted enol ester was obtained without decreasing yield. The secondary propargyl α -ketoesters derived from aldehydes containing chlorine, alkene, phenyl, isopropyl, and cyclohexyl substituents went through the reaction to furnish 2h-2l in variable yields. As shown, styryl butenolide 2j was obtained in 91% yield, while cyclohexylidenemethylbutenolide 2l was isolated only in 47% yield. It means that the electronic and steric effects of substituents located at the homopropargylic position did impact on the formation of the butenolides. A remote isolated terminal alkene did not interrupt the formation of butenolide 2i. The tertiary propargyl α -ketoesters generated from symmetrical ketones such as acetone, cyclopentanone, and tetrahydropyran-4-one gave butenolides 2m-2o in good yields. For the tertiary propargyl esters originated from unsymmetrical ketones including 2-butanone and 3-methylbutan-2-one, butenolides 2p and 2q were obtained selectively.





^{*a*}Reaction conditions: propargyl α -ketoester 1a (0.204 mmol), Ph₃PAuCl (0.01 mmol), Cu(OTf)₂ (0.204 mmol), 1,2-dichloroethane (2 mL), 80 °C, 1 h. Isolated yields after column chromatography.

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Figure 1. (a) Gibbs free energy profile of Au-catalyzed 1,3-acyloxy migration/carbonyl-ene reaction computed at the SMD(DCE)/M06-D3/def2-TZVP//SMD(DCE)/B3LYP/SDD-6-31G(d) level. (b) Gibbs free energy profile of Cu-mediated or nonmetal carbonyl-ene reaction computed at the SMD(DCE)/M06-D3/def2-TZVP//SMD(DCE)/B3LYP/SDD-6-31G(d) level.

Propargyl esters derived from various aliphatic and aromatic α ketoacids engaged in the cycloisomerization in a similar manner as their 2-oxopropanoic acid counterpart, enabling facile installation of diverse substituents involving ethyl, isobutyl, cyclohexyl, *tert*-butyl, phenyl, 4-nitrophenyl, and 4methoxyphenyl on the α -position of $(Z)-\gamma$ -alkylidenebutenolides $2\mathbf{r}-2\mathbf{x}$.

To account for the gold-catalyzed formation of (Z)- γ alkylidenebutenolides as well as to figure out the role of the copper additive in the transformation, we conducted DFT calculations. In order to simplify the calculation process, we changed R¹ to methyl in substrate **1a** and used PMe₃ as the ligand for Au catalyst. Gold cation could be formed with copper salts by chloride abstraction.¹⁸ Considering that the reaction can take place using only gold cation catalyst (Table 1, entry 1), we first analyze how this gold-catalyzed carbonyl-ene reaction occurs (Figure 1a). The DFT-computed potential energy surface suggests that the reaction begins with 1,3acyloxy migration via TS1 from alkyne-coordinated intermediate INT1, giving a six-membered ring intermediate INT2 (the activation Gibbs free energy of this step is 17.1 kcal/mol). The following step is a ring-opening process via TS2 to give allenic intermediate INT3.¹⁹ The first step of the carbonyl-ene reaction is the formation of a C–C bond via TS3-Au. This step needs an activation Gibbs free energy of 16.5 kcal/mol to give a carbocation intermediate, INT4-Au. Then intramolecular hydrogen abstraction via the transition state TS4-Au gives a 1,3-diene intermediate, INT5-Au. Finally, INT5-Au undergoes an exothermic dehydration reaction to form (Z)- γ -alkylidenebutenolide. The Gibbs activation energy of the 1,3-acyloxy migration/carbonyl-ene reaction is 20.0 kcal/mol. When both Au and Cu are used, we proposed that INT3-Au can undergo ligand exchange with INT0 to liberate INT3-0, which is an organic molecule intermediate.²⁰ This intermediate can then form a complex with Cu catalysts to give INT3-Cu. After that, a stepwise carbonyl-ene reaction via TS3-Cu, INT4-Cu, and TS4-Cu gives the final product.²¹ Compared to Au-catalyzed carbonyl-ene reaction, Cu process gives lower Gibbs free energy in TS3 (13.1 kcal/mol vs 20.0 kcal/mol). The overall Gibbs energy barrier of Au-catalyzed 1,3-acyloxy migration/Cu-catalyzed carbonyl-ene reaction is 17.1 kcal/mol (from INT4-Cu to TS4-Cu), lower than that for the Au-catalyzed process with 20.0 kcal/mol in Figure 1a. Nonmetal carbonyl-ene process was also considered. INT3-0 could undergo carbonyl ene reaction, but this is not favored, with an activation Gibbs free energy of 22.2 kcal/mol (via TS3-0, INT4-0, and TS4-0, Figure 1b). Based on these calculation results, we concluded that the copper salt has two effects: one is forming the gold cation as the activated catalyst, another is activating carbonyl moiety in order to promote the carbonyl-ene reaction.

In conclusion, a bimetallic protocol has been developed to construct densely substituted (Z)- γ -alkylidenebutenolide compounds from readily available propargyl α -keto esters. This stereoselective process involves gold-catalyzed 1,3-acyloxy migration of propargyl α -ketoesters and the carbonyl-ene cyclization of *in situ* generated allenyl esters. DFT calculations suggest that the copper additive might play as a chloride abstractor promoting the generation of highly active gold catalyst and a Lewis acid facilitating the stepwise intramolecular carbonyl-ene reaction. Further applications on the tandem 1,3-acyloxy migration/the carbonyl-ene cyclization are underway.

ASSOCIATED CONTENT

1 Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01782.

Experimental procedures, characterizations, copies of ¹H and ¹³C NMR spectra of products, DFT calculations, and single-crystal data (PDF)

Accession Codes

CCDC 1977280 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The work was financially supported by the National Natural Science Foundation of China (21871132, 21572098, 21933003), the National Key Research and Development Program of China (2018YFC0310900) and High-Performance Computing Platform of Peking University.

REFERENCES

(1) For selected reviews on the construction of γ -alkylidenebutenolides, see: (a) Rao, Y. S. Recent advances in the chemistry of unsaturated lactones. *Chem. Rev.* **1976**, 76, 625–694. (b) Ito, M. Recent progress in the synthesis of butenolide, carotenoids and retinoids. *Pure Appl. Chem.* **1991**, 63, 13–22. (c) Negishi, E.-i.; Kotora, M. Regio- and Stereoselective Synthesis of γ -Alkylidenebutenolides and Related Compounds. *Tetrahedron* **1997**, 53, 6707– 6738. (d) Bruckner, R. The β -elimination route to stereodefined γ alkylidenebutenolides. *Chem. Commun.* **2001**, 141–152.

(2) (a) Gara, A. P.; Massy-Westropp, R. A.; Reynolds, G. D. A synthesis of enol lactones. *Tetrahedron Lett.* 1969, *10*, 4171-4172.
(b) Begley, M. J.; Knight, D. W.; Pattenden, G. Regioselective nucleophilic additions to unsymmetrically substituted maleic anhydrides. *Tetrahedron Lett.* 1975, *16*, 4279-4282. (c) Kayser, M. M.; Breau, L. Neighbouring group effects on regioselectivity of wittig reactions with maleic anhydrides. *Tetrahedron Lett.* 1988, *29*, 6203-6206.

(3) (a) Xu, D.; Sharpless, K. B. Synthesis and stereochemical assignments for goniobutenolides A and B. *Tetrahedron Lett.* **1994**, *35*, 4685–4688. (b) Engstrom, K. M.; Mendoza, M. R.; Navarro-Villalobos, M.; Gin, D. Y. Total Synthesis of (+)-Pyrenolide D. *Angew. Chem., Int. Ed.* **2001**, *40*, 1128–1130. (c) Burghart, J.; Bruckner, R. Total Synthesis of Naturally Configured Pyrrhoxanthin, a Carotenoid Butenolide from Plankton. *Angew. Chem., Int. Ed.* **2008**, *47*, 7664–7668.

(4) (a) Lu, X.; Huang, X.; Ma, S. A convenient synthesis of γ -(Z)alkylidenebutenolides. *Tetrahedron Lett.* **1993**, 34, 5963–5966. (d) Liu, F.; Negishi, E.-i. Efficient and Stereoselective Synthesis of Free lingyne via Pd-Catalyzed Cross Coupling and Lactonization. *J. Org. Chem.* **1997**, 62, 8591–8594.

(5) Seo, S.; Willis, M. C. A Copper(I)-Catalyzed Addition/ Annulation Sequence for the Two-Component Synthesis of γ -Ylidenebutenolides. Org. Lett. **2017**, 19, 4556–4559.

(6) Yu, C.; Zhang, J.; Zhong, G. One step synthesis of γ -alkylidenebutenolides from simple vinyl carboxylic acids and alkenes. *Chem. Commun.* **2017**, *53*, 9902–9905.

(7) Bao, M.; Wang, X.; Qiu, L.; Hu, W.; Chan, P. W. H.; Xu, X. Gold-Catalyzed 1,2-Acyloxy Migration/Coupling Cascade of Propargyl Diazoacetates: Synthesis of Isomycin Derivatives. *Org. Lett.* **2019**, *21*, 1813–1817.

(8) For reviews on 1,3-acyloxy of propargyl esters, see: (a) Boyle, J. W.; Zhao, Y.; Chan, P. W. H. Product Divergence in Coinage-Metal-Catalyzed Reactions of π -Rich Compounds. Synthesis 2018, 50,

1402–1416. (b) Day, D. P.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization of 1, n-Diyne Carbonates and Esters. *Adv. Synth. Catal.* **2016**, 358, 1368–1384. (c) Kazem Shiroodi, R.; Gevorgyan, V. Metal-catalyzed double migratory cascade reactions of propargylic esters and phosphates. *Chem. Soc. Rev.* **2013**, 42, 4991–5001. (d) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. Rhodium-catalyzed acyloxy migration of propargylic esters in cycloadditions, inspiration from the recent "gold rush. *Chem. Soc. Rev.* **2012**, *41*, 7698–7711. (e) Wang, S.; Zhang, G.; Zhang, L. Gold-Catalyzed Reaction of Propargylic Carboxylates via an Initial 3,3-Rearrangement. *Synlett* **2010**, 692–706.

(9) (a) Zhao, J.; Hughes, C. O.; Toste, F. D. Synthesis of Aromatic Ketones by a Transition Metal-Catalyzed Tandem Sequence. J. Am. Chem. Soc. 2006, 128, 7436–7437. (b) Cran, J. W.; Krafft, M. E. Regioselective Cyclizations Utilizing a Gold-Catalyzed [3,3] Propargyl Ester Rearrangement. Angew. Chem., Int. Ed. 2012, 51, 9398–9402.

(10) (a) Marion, N.; Dies-Gonzalez, S.; de Fremont, P.; Noble, A. R.; Nolan, S. P. Au¹-Catalyzed Tandem [3,3] Rearrangement— Intramolecular Hydroarylation: Mild and Efficient Formation of Substituted Indenes. *Angew. Chem., Int. Ed.* **2006**, *45*, 3647–3650. (b) Wang, Y.-M.; Kuzniewski, C. N.; Rauniyar, V.; Hoong, C.; Toste, F. D. Chiral (Acyclic Diaminocarbene) Gold(I)-Catalyzed Dynamic Kinetic Asymmetric Transformation of Propargyl Esters. *J. Am. Chem. Soc.* **2011**, *133*, 12972–12975.

(11) (a) Gung, B. W.; Craft, D. T.; Bailey, L. N.; Kirschbaum, K. Gold-Catalyzed Transannular [4 + 3] Cycloaddition Reactions. *Chem.* - *Eur. J.* **2010**, *16*, 639–644. (b) Pirovano, V.; Arpini, E.; DellAcqua, M.; Vicente, R.; Abbiati, G.; Rossi, E. Gold(I)-Catalyzed Synthesis of Tetrahydrocarbazoles via Cascade [3,3]-Propargylic Rearrangement/[4 + 2] Cycloaddition of Vinylindoles and Propargylic Esters. *Adv. Synth. Catal.* **2016**, *358*, 403–409. (c) Chen, X.; Merrett, J. T.; Chan, P. W. H. Gold-Catalyzed Formal [4 + 2] Cycloaddition of 5-(Ethynylamino)pent-2-yn-1-yl Esters to 1,2,3,5-Tetrahydrobenzo[g]-quinolones. *Org. Lett.* **2018**, *20*, 1542–1545.

(12) (a) Zhang, L. Tandem Au-Catalyzed 3,3-Rearrangement-[2 + 2 Cycloadditions of Propargylic Esters: Expeditious Access to Highly Functionalized 2,3-Indoline-Fused Cyclobutanes. J. Am. Chem. Soc. 2005, 127, 16804-16805. (b) Zhang, G.; Catalano, V. J.; Zhang, L. PtCl₂-Catalyzed Rapid Access to Tetracyclic 2,3-Indoline-Fused Cyclopentenes: Reactivity Divergent from Cationic Au(I) Catalysis and Synthetic Potential. J. Am. Chem. Soc. 2007, 129, 11358-11359. (c) Rao, W.; Susanti, D.; Chan, P. W. H. Gold-Catalyzed Tandem 1,3-Migration/ [2 + 2] Cycloaddition of 1,7-Enyne Benzoates to Azabicyclo [4.2.0] oct-5-enes. J. Am. Chem. Soc. 2011, 133, 15248-15251. (d) 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. (e) Chen, C.; Zou, Y.; Chen, X.; Zhang, X.; Rao, W. Gold-Catalyzed Tandem 1,3-Migration/ Double Cyclopropanation of 1-Ene-4,n-diyne Esters to Tetracyclodecene and Tetracycloundecene Derivatives. Org. Lett. 2016, 18, 4730-4733.

(13) For selected papers on bimetallic catalysis involving gold, see: (a) Shi, Y.; Peterson, S. M.; Haberaecker III, W. W.; Blum, S. A. Alkynes as Stille Reaction Pseudohalides: Gold- and Palladium-Cocatalyzed Synthesis of Tri- and Tetra-Substituted Olefins. *J. Am. Chem. Soc.* **2008**, *130*, 2168–2169. (b) Hashmi, A. S.; Lothschutz, C.; Dopp, R.; Rudolph, M.; Ramamurthi, T. D.; Rominger, F. Gold and Palladium Combined for Cross-Coupling. *Angew. Chem., Int. Ed.* **2009**, *48*, 8243–8246. (c) Garcia-Dominguez, P.; Nevado, C. Au-Pd Bimetallic Catalysis: The Importance of Anionic Ligands in Catalyst Speciation. *J. Am. Chem. Soc.* **2016**, *138*, 3266–3269. (d) Alonso, J. M.; Munoz, M. P. Heterobimetallic Catalysis: Platinum-Gold-Catalyzed Tandem Cyclization/C-X Coupling Reaction of (Hetero)-Arylallenes with Nucleophiles. *Angew. Chem., Int. Ed.* **2018**, *57*, 4742– 4746.

(14) For selected reviews on allenes, see: (a) Ma, S. Some Typical Advances in the Synthetic Applications of Allenes. *Chem. Rev.* 2005,

105, 2829–2872. (b) Yu, S.; Ma, S. Allenes in Catalytic Asymmetric Synthesis and Natural Product Syntheses. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074–3112.

(15) For selected reviews on the ene reaction, including the carbonyl-ene reaction, see: (a) Hoffmann, H. M. R. The Ene Reaction. Angew. Chem., Int. Ed. 1969, 8, 556–577. (b) Oppolzer, W.; Snieckus, V. Intramolecular Ene Reactions in Organic Synthesis. Angew. Chem., Int. Ed. 1978, 17, 476–486. (c) Snider, B. Lewis-Acid-Catalyzed Ene Reactions. Acc. Chem. Res. 1980, 13, 426–432. (d) Mikami, K.; Shimizu, M. Asymmetric Ene Reactions in Organic Synthesis. Chem. Rev. 1992, 92, 1021–1050.

(16) (a) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. Gold Catalysis: The Benefits of N and N, O Ligands. Angew. Chem., Int. Ed. **2004**, 43, 6545–6547. (b) Wang, S.; Zhang, L. A Highly Efficient Preparative Method of γ -Ylidene- β -Diketones via Au^{III}-Catalyzed Acyl Migration of Propargylic Esters. J. Am. Chem. Soc. **2006**, 128, 8414–8415. (c) Shapiro, N. D.; Toste, F. D. Synthesis of Azepines by a Gold-Catalyzed Intermolecular [4 + 3] Annulation. J. Am. Chem. Soc. **2008**, 130, 9244–9245.

(17) Kothandaraman, P.; Rao, W.; Foo, S. J.; Chan, P. W. H. Gold-Catalyzed Cycloisomerization Reactions of 2-Tosylaminophenylprop-1-yn-3-ols as a Versatile Approach for Indole Synthesis. *Angew. Chem., Int. Ed.* **2010**, *49*, 4619–4623.

(18) (a) Guerinot, A.; Fang, W.; Sircoglou, M.; Bour, C.; Bezzenine-Lafollee, S.; Gandon, V. Copper Salts as Additives in Gold(I)-Catalyzed Reactions. *Angew. Chem., Int. Ed.* 2013, *52*, 5848–5852.
(b) Motika, S. E.; Wang, Q.; Akhmedov, N. G.; Wojtas, L.; Shi, X. Regioselective Amine-Borane Cyclization: Towards the Synthesis of 1,2-BN-3-Cyclohexene by Copper-Assisted Triazole/Gold Catalysis. *Angew. Chem., Int. Ed.* 2016, *55*, 11582–11586.

(19) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. Golden Carousel in Catalysis: The Cationic Gold/ Propargylic Ester Cycle. *Angew. Chem., Int. Ed.* **2008**, *47*, 718–721.

(20) The ligand-exchange process for allenes was proposed to occur via an associative mechanism, and the experimentally measured activation free energy of ligand exchange was 17 kcal/mol for Au-3-methyl-1,2-butadiene. We propose that in the present system the ligand exchange has a similar process and could be easier than the competing ene reaction steps in Figure 1a,b. For discussions of ligand exchanges for allenes, see: (a) Brooner, R. E. M.; Widenhoefer, R. A. Cationic, Two-Coordinate Gold Complexes. *Angew. Chem., Int. Ed.* **2013**, *52*, 11714–11724. (b) Brown, T. J.; Sugie, A.; Dickens, M. G.; Widenhoefer, R. A. Structures and Dynamic Solution Behavior of Cationic, Two-Coordinate Gold(I)- π -Allene Complexes. *Chem. - Eur. J.* **2012**, *18*, 6959–6971.

(21) Morao, I.; McNamara, J. P.; Hillier, I. H. Carbonyl-Ene Reactions Catalyzed by Bis(oxazoline)Copper(II) Complexes Proceed by a Facile Stepwise Mechansim: DFT and ONIOM (DFT: PM3) Studies. J. Am. Chem. Soc. 2003, 125, 628–629.