OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Controlling the Selectivity Patterns of Au-Catalyzed Cyclization−Migration Reactions

Mo Chen,[†] Naijing Su,[‡] Tianning Deng,[‡] Donald J. Wink,[‡] Yingwei Zhao,[‡,§] and Tom G. Driver*[,‡]

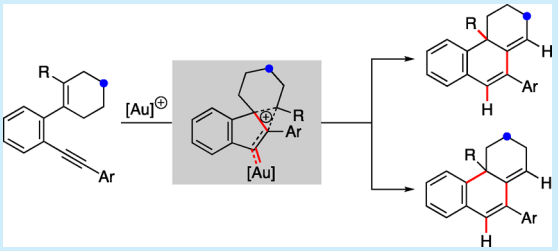
[†]College of Chemistry, Nankai University, 94 Weijin Road, Tianjin 30007, People's Republic of China

[‡]Department of Chemistry, University at Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States

[§]College of Chemical Engineering, Huaqiao University, 668 Jimei Boulevard, Xiamen, Fujian 361021, People's Republic of China

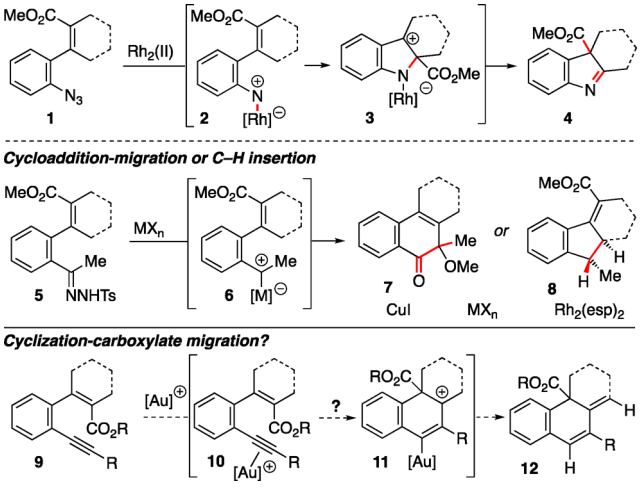
Supporting Information

ABSTRACT: As little as 2 mol % of (XPhos)AuNTf$_2$ catalyzes the transformation of a broad range of *o*-acetylene-substituted styrenes into 1,2-dihydronaphthalenes. Our data suggests that this transformation occurs via a gold-stabilized cyclopropyl carbinyl cation, which triggers either a [1,2] carboxylate shift or a less favorable [1,2] aryl shift. The relative rates of these migrations can be controlled by the identity of the ligand or by stabilizing the mesomeric cation.



Accessing electrophilic gold reactive intermediates from internal acetylenes has spurred significant reaction discovery.[1] The reactivity embedded in these carbenoid or cationic intermediates has been exploited in reactions that are often mechanistically distinct from traditional transition-metal-catalyzed reactions even though they proceed via similar intermediates.[2] Although gold-catalyzed tandem reactions are common,[3] sequences involving a [1,2] alkyl- or aryl group shift are scarce and limited to alleviating ring strain or establishing aromaticity.[4] Our laboratory has investigated the reactivity patterns of aryl-substituted metal carbenes and nitrenes (Scheme 1). Our investigations established that rhodium *N*-aryl nitrenes such as **2** reacted with the proximal olefin to initiate an electrocyclization [1,2] carboxylate migration to construct 3*H*-indoles.[5] In contrast, electron-rich aryl,alkyl-disubstituted metal carbenes **6** generated from *N*-tosylhydrazones reacted with either the carbon oxygen double bond to create *α*-methoxy 2*H*-naphthalenone **7** or the allylic C−H bond to furnish **8** using either CuI or Rh$_2$(esp)$_2$ as the catalyst.[6] Because the identity of the metal controlled the site selectivity of reaction, we were curious if a gold catalytic intermediate generated from an internal acetylene would react with a proximal electron-deficient olefin in a cyclization−migration reaction or if this reactivity pattern was limited to rhodium nitrenoids.[7] Despite their potential to form quaternary carbon stereocenters, the only tetrasubstituted olefins reported to capture the gold acetylene intermediate have either been cyclopropylidenes or enoxysilanes,[4e,f,8] and [1,2] carboxylate migrations in these tandem reactions are unprecedented.[9] Herein, we demonstrate that carboxylate migrations are not limited to metal nitrenes but are a reactivity pattern of electron-rich metal divalent catalytic intermediates that can be accessed using cationic gold complexes.

Scheme 1. Deconvoluting the Reactivity Patterns of Metal Divalent Intermediates

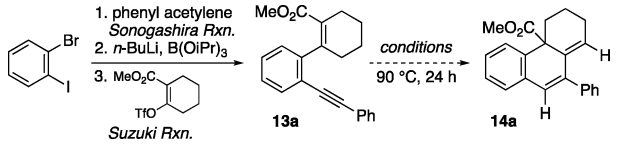


Our investigation into examining the reactivity of *o*-acetylene-substituted trisubstituted styrenes toward gold complexes was initiated using **13a** (Table 1). This substrate was chosen to determine the optimal conditions because it was readily available from 2-bromoiodobenzene through a three-step Sonogashira Suzuki−Miyaura sequence. After a survey of transition-metal complexes that had been reported to catalyze related cycloisomerization reactions,[10] we discovered that 5 mol % of (Ph$_3$P)AuNTf$_2$ produced a new product whose structure was confirmed to be **14a** by X-ray crystallography (entry 1). Salt metathesis was required: in the absence of AgNTf$_2$ no reaction was obtained. Changing the ligand on gold

Received: December 5, 2018

DOI: 10.1021/acs.orglett.8b03888
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Cycloisomerization Reaction



entry	catalyst (mol %)	AgX (mol %)	solvent	yield[a] (%)
1	$(Ph_3P)AuCl$ (5)	$AgNTf_2$ (6)	PhMe	20
2	(iPrNHC)AuCl (5)	$AgNTf_2$ (6)	PhMe	dec
3	$[(dppf)(AuCl)_2]$ (5)	$AgNTf_2$ (12)	PhMe	<5
4	(XPhos)AuCl (5)	$AgNTf_2$ (6)	PhMe	22
5	(XPhos)AuCl (5)	$AgNTf_2$ (6)	DCE	99
6	(XPhos)AuCl (2)	$AgNTf_2$ (2.4)	DCE	95
7	(XPhos)AuCl (1)	$AgNTf_2$ (1.5)	DCE	88
8	(XPhos)AuCl (5)	AgOTf (6)	DCE	12
9	(XPhos)AuCl (5)	$AgPF_6$ (6)	DCE	20
10	(XPhos)AuCl (5)	$AgSbF_6$ (6)	DCE	70
11	(XPhos)$AuNTf_2$ (5)		DCE	96
12		$AgNTf_2$	DCE	nr
13[b]		$AgNTf_2$	DCE	nr

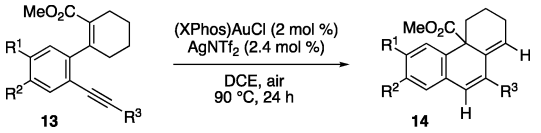
[a]Determined using ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard. [b]2 μL of H_2O added.

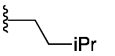
also affected the yield with the best outcome obtained using XPhos (entries 2−4). The reaction conditions were further explored using this gold complex (entries 6−10). The yield was increased when the solvent was changed. While no reaction or low yields were obtained in THF, MeOH, or MeCN, switching to DCE improved the yield to 99% (entry 5). While lowering the catalyst loading to 2 mol % had a negligible effect, the reaction yield was attenuated when only 1 mol % of catalyst was used (entries 6 and 7). Changing the identity of the counterion to triflate, hexafluorophosphate, or hexafluoroantimonate also produced lower yields (entries 8−10). Control experiments were performed to determine that the reaction was catalyzed by gold and not by either silver or proton (entries 11−13).

Using the optimal conditions, the scope and limitations of the tandem reaction were investigated using substrates that varied the electronic nature of the acetylenic substituents (Table 2). First, we found that the reaction could be scaled to 1 mmol without negatively affecting the yield of the tandem reaction (entry 1). Next, the reaction was found to be immune to changing the electronic nature of the R^1 and R^2 substituent with only an attenuation of yield observed with a CF_3 group (entries 2−7). Changing the identity of the terminal R^3 group had a larger effect on the reaction outcome (entries 8−12). While electron-rich and electron-poor aryl groups were tolerated, no reaction was observed with an R^3-cyclopentyl group. To our surprise, **13l** bearing a cyclopropyl R^3 group was smoothly converted to 1,2-dihydronaphthalene **14l**. The lack of ring-opening byproducts suggests that no radical intermediates are formed during the transformation. While no reaction was observed when the acetylenic substituent was an alkyl group (**13m**), only decomposition was observed when the substrate contained an isopropenyl R^3 substituent (**13n**).

Next, the scope and limitations of this reaction were examined by varying the identity of the alkenyl portion of substrate **15** (Table 3). First, the identity of the ester substituent could be changed to ethyl without negatively impacting the reaction outcome (entry 1). Next, we found that the size of cycloalkenyl could be changed without affecting the

Table 2. Exploration of the Scope and Limitations



entry	#	R^1	R^2	R^3	%, yield[a]
1	a	H	H	Ph	99 (70)[b]
2[c]	b	OMe	H	Ph	81
3	c	Me	H	Ph	99
4	d	F	H	Ph	90
5	e	CF_3	H	Ph	75
6	f	H	OMe	Ph	84
7	g	H	Me	Ph	94
8	h	H	H	$(4\text{-MeO})C_6H_4$	99
9	i	H	H	$(4\text{-}F_3C)C_6H_4$	61
10	j	H	H	*o*-Tol	65
11	k	H	H		n.r.[d]
12	l	H	H		90
13	m	H	H		n.r.
14	n	H	H		dec

[a]Isolated yield of **14** after silica gel chromatography. [b]1 mmol scale. [c]5 mol % of (XPhos)AuCl and 6 mol % of $AgNTf_2$ used. [d]100% of **13k** recovered.

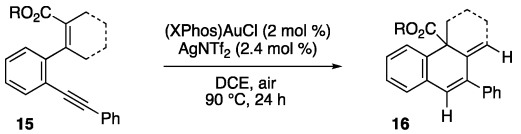
reaction outcome (entries 2−4). A cyclic *o*-alkenyl substituent was not required: irrespective of the geometry, *Z*-**15e** or *E*-**15f** was smoothly transformed to product (entries 5 and 6). Exposure of **15g** to reaction conditions revealed that in the absence of the β-carboxylate only cyclization occurred to afford naphthalene **16g** (entry 7).

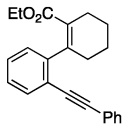
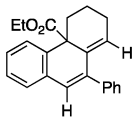
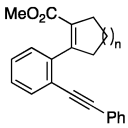
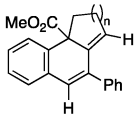
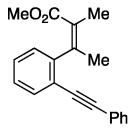
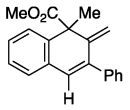
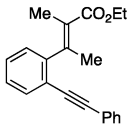
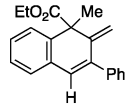
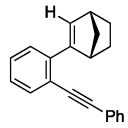
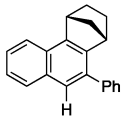
Our investigations into substrate control of the stereoselectivity of the reaction provided insight into the possible mechanisms for product formation (Scheme 2). To test if diastereoselectivity could be obtained, 4-*tert*-butyl-substituted **17a** was submitted to the reaction conditions. To our surprise, two isomers **18a** and **19a** were obtained in 72:28 ratio. While **18a** was obtained as a single diastereomer, **19a** was formed in a 3:1 ratio. The formation of both isomers provides insight into the mechanism of the isomerization−migration reaction: coordination of the cationic gold complex to the acetylene triggers a cyclization to form cyclopropylcarbinyl cation **21**. Dihydronaphthalene cation **24** is formed either from a [1,2] carboxylate shift or a [1,2] aryl shift.[11−13] These [1,2] shifts can be visualized as occurring via mesomers **22** or **23** of the cyclopropyl carbinyl cation. Elimination of the gold cation then produces the product. The product ratio observed from the reaction of **17a** suggests that the [1,2] carboxylate migration reaction is preferred.

Next, we were curious if the relative rates of migration could be modified to favor carboxylate migration by stabilizing mesomer **22**.[14] To test this hypothesis, substrates **17b−e** were synthesized (Table 4). We anticipated that as the R substituent became more electron-rich that the [1,2] carboxylate migration

DOI: 10.1021/acs.orglett.8b03888
Org. Lett. XXXX, XXX, XXX−XXX

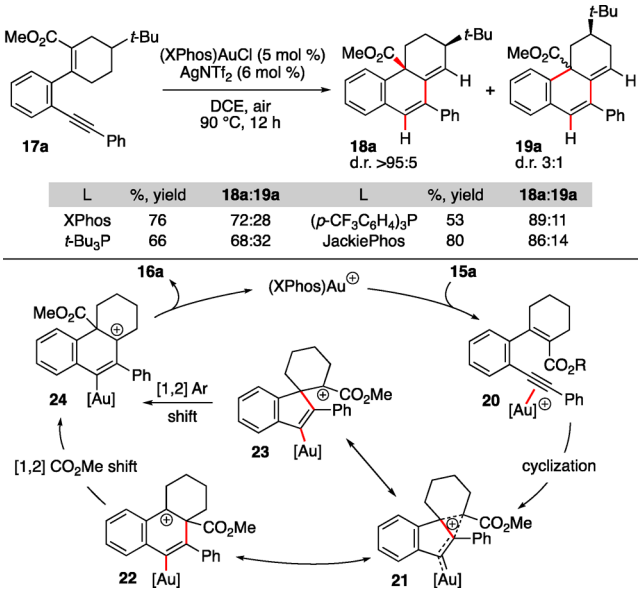
Table 3. Investigation of the Effect of Changing the *Ortho*-Substituent



entry	#	15	16	%, yield[a]
1	a			99
2	b			n = 1, 99
3	c			n = 3, 99
4	d			n = 4, 94
5	e			99
6	f			80
7	g			quant.

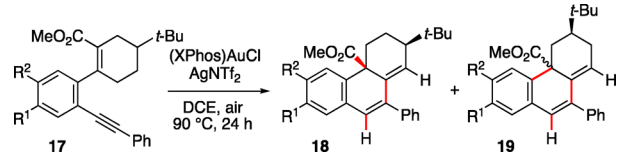
[a]Isolated yield of **16** after silica gel chromatography.

Scheme 2. Competing Mechanisms for 1,2-Dihydronaphthalene Formation



would become more favorable. In line with our assertion, we found that the amount of **18** increased as the R substituent became more electron-donating. Comparing the reaction outcome between **17b** and **17d** underscores the importance of stabilizing the positive charge in **21** (or the partial positive charge formed in the cyclization): positioning the methoxy group in the 4-position resulted in an 88:12 mixture of **18b** and **19b**, while placing it in the 5-position, where it cannot stabilize **21**, produced a 59:41 mixture of isomers. To determine if this electronic effect could be maximized by changing the phosphine ligand, the reactivity of **17b** was explored using JackiePhos as the ligand to produce an 89:11 mixture of **18b** and **19b**.

Table 4. Electronic Control of the Relative Rates of Cyclization



entry[a]	no.	R^1	R^2	yield[b] (%)	18/19
1	**b**	MeO	H	74	88:12[c]
2	**c**	Me	H	82	73:27
3	**a**	H	H	76	72:28
4	**d**	H	MeO	74	59:41
5	**e**	F_3C	H	56	54:46

[a]5 mol % of (XPhos)AuCl and 6 mol % of $AgNTf_2$ were used. [b]As determined using ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]Use of 5 mol % of (JackiePhos)AuCl resulted in an 89:11 mixture of **18b** and **19b**.

In conclusion, we discovered that (XPhos)$AuNTf_2$ catalyzes the transformation of *o*-(alkynyl)styrenes into 1,2-dihydronaphthalenes. This transformation occurs through a gold-stabilized cyclopropyl carbinyl cation that triggers either a [1,2] carboxylate shift or a less favorable [1,2] aryl shift. The relative rates of migration can be controlled by the phosphine ligand or by stabilizing the mesomeric cation to illustrate the effect that substitution has on the mechanism. Our future experiments are aimed at further understanding and controlling the relative rates of cyclization to develop an enantioselective variant of this transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03888.

Experimental procedures and analytical data (PDF)

Accession Codes

CCDC 1874905 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: tgd@uic.edu.

ORCID

Donald J. Wink: 0000-0002-2475-2392

Tom G. Driver: 0000-0001-7001-342X

DOI: 10.1021/acs.orglett.8b03888
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Science Foundation CHE-1564959, University of Illinois at Chicago, Office of the Vice-Chancellor for Research, Huaqiao University Xiamen, the Fujian Hundred Talents Plan, Nankai University, and the Chinese Academy of Science for their generous financial support. We thank Mr. Furong Sun (UIUC) for HRMS data.

■ REFERENCES

(1) (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Qian, D.; Zhang, J. *Chem. Soc. Rev.* **2015**, *44*, 677. (c) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (d) Pflasterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331. (e) Zi, W.; Dean Toste, F. *Chem. Soc. Rev.* **2016**, *45*, 4567. (f) Li, Y.; Li, W.; Zhang, J. *Chem. - Eur. J.* **2017**, *23*, 467.

(2) (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (c) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (d) Joost, M.; Amgoune, A.; Bourissou, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 15022.

(3) (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Zhang, D.-H.; Tang, X.-Y.; Shi, M. *Acc. Chem. Res.* **2014**, *47*, 913.

(4) (a) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708. (b) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315. (c) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633. (d) García-García, P.; Martínez, A.; Sanjuán, A. M.; Fernández-Rodríguez, M. A.; Sanz, R. *Org. Lett.* **2011**, *13*, 4970. (e) Pitaval, A.; Leboeuf, D.; Ceccon, J.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 4580. (f) Zheng, H.; Felix, R. J.; Gagné, M. R. *Org. Lett.* **2014**, *16*, 2272. (g) Sanjuán, A. M.; Rashid, M. A.; García-García, P.; Martínez-Cuezva, A.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Chem. - Eur. J.* **2015**, *21*, 3042.

(5) (a) Kong, C.; Driver, T. G. *Org. Lett.* **2015**, *17*, 802. (b) Kong, C.; Su, N.; Zhou, F.; Jana, N.; Driver, T. G. *Tetrahedron Lett.* **2015**, *56*, 3262.

(6) (a) Su, N.; Theorell, J. A.; Wink, D. J.; Driver, T. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 12942. (b) Su, N.; Deng, T.; Wink, D. J.; Driver, T. G. *Org. Lett.* **2017**, *19*, 3990.

(7) For related metal-catalyzed cyclizations of *o*-acetylene mono- and disubstituted styrenes, see the following. W: (a) Maeyama, K.; Iwasawa, N. *J. Org. Chem.* **1999**, *64*, 1344. Pd, Pt, Rh: (b) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809. W: (c) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 518. Pt: (d) Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757. Ru: (e) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762. Pt: (f) Mamane, V.; Hannen, P.; Fürstner, A. *Chem. - Eur. J.* **2004**, *10*, 4556. Ru: (g) Madhushaw, R. J.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560. Au: (h) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, *2006*, 411. Pd, Au: (i) Aziz, J.; Frison, G.; Le Menez, P.; Brion, J.-D.; Hamze, A.; Alami, M. *Adv. Synth. Catal.* **2013**, *355*, 3425. Ru: (j) Watanabe, T.; Abe, H.; Mutoh, Y.; Saito, S. *Chem. - Eur. J.* **2018**, *24*, 11545.

(8) (a) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236. (b) Felix, R. J.; Weber, D.; Gutierrez, O.; Tantillo, D. J.; Gagné, M. R. *Nat. Chem.* **2012**, *4*, 405. (c) Huwyler, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13066. (d) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679.

(9) For seminal reports of acyl migration reactions that proceed through C−O bond cleavage in Au-catalyzed cycloisomerizations, see: (a) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (b) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442. (c) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274. (d) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868.

(10) See the Supporting Information for more details.

(11) For monomeric cationic phosphine Au(I) internal acetylene crystal structures, see: (a) Review: Brooner, R. E. M.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 11714. (b) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 2779. (c) Hooper, T. N.; Green, M.; Russell, C. A. *Chem. Commun.* **2010**, *46*, 2313. (d) Celik, M. A.; Dash, C.; Adiraju, V. A. K.; Das, A.; Yousufuddin, M.; Frenking, G.; Dias, H. V. R. *Inorg. Chem.* **2013**, *52*, 729. (e) Zhu, D.; Cao, X.; Yu, B. *Org. Chem. Front.* **2015**, *2*, 360.

(12) Cyclopropylcarbinyl cations have been proposed as reactive intermediates in Au(I)-catalyzed reactions. For leading reports, see: (a) Mauleón, P.; Krinsky, J. L.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 4513. (b) Garayalde, D.; Gómez-Bengoa, E.; Huang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 4720. (c) Wang, G.; Zou, Y.; Li, Z.; Wang, Q.; Goeke, A. *J. Org. Chem.* **2011**, *76*, 5825.

(13) 5-*Endo-dig* cyclizations are a rare phenomenon in metal-catalyzed isomerization reactions of *o*-(alkynyl)styrenes. For the only two examples, see: (a) Referenec 4g. (b) Fang, W.; Wei, Y.; Shi, M. *Chem. Commun.* **2017**, *53*, 11666.

(14) In contrast to the recent report by Sanz and co-workers (ref 4g), the addition of alcohol did not change the reaction outcome.

DOI: 10.1021/acs.orglett.8b03888
Org. Lett. XXXX, XXX, XXX−XXX