

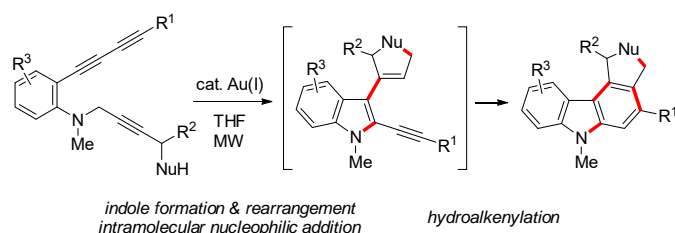
Title	Synthesis of Fused Carbazoles by Gold-Catalyzed Tricyclization of Conjugated Diynes via Rearrangement of an N-Propargyl Group
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Synthesis of Fused Carbazoles by Gold-Catalyzed Tricyclization of Conjugated Diynes via Rearrangement of an *N*-Propargyl Group

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Supporting Information Placeholder

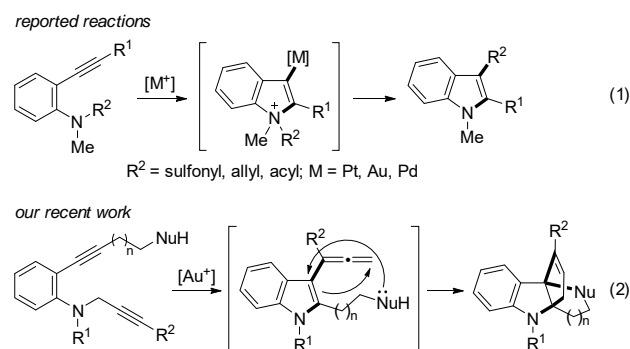


ABSTRACT: Various *N*-propargylanilines bearing a conjugated diyne moiety at the 2-position were converted to tetracyclic fused carbazoles by treatment with a homogeneous gold(I) catalyst. This cascade reaction proceeds through indole formation with concomitant rearrangement of the *N*-propargyl group, intramolecular nucleophilic addition toward the resulting allene moiety, and subsequent hydroalkenylation. This transformation enables a one-pot synthesis of fused carbazoles from readily accessible substrates with 100% atom economy.

The carbazole scaffold is frequently found in natural products and synthetic compounds with attractive bioactivities¹ and interesting electrochemical properties.² Fused carbazoles are particularly known for their diverse biological activities, including antibacterial, anti-inflammatory, and antitumor effects.³ Traditional methods for the synthesis of fused carbazoles rely on a stepwise introduction/construction of the pyrrole and benzene rings.⁴ More recently, cascade reactions catalyzed by transition metals such as palladium and gold have emerged as efficient approaches for the direct construction of fused carbazoles.⁵

Intramolecular nucleophilic addition of 2-alkynylanilines is a well-established strategy for the construction of indole rings,⁶ including those in fused carbazoles.⁷ Reactions involving a rearrangement of one of the substituents on an aniline nitrogen are highly attractive as they directly provide 2,3-disubstituted indole derivatives in a single operation (Scheme 1, eq 1). In 2005, Yamamoto et al. reported the first example of this type of rearrangement for synthesis of 3-acylindoles.⁸ Some other substituents, including sulfonyl,⁹ allyl,¹⁰ and acyl groups,¹¹ have also been used as the migrating group.¹² Quite recently, we have demonstrated that rearrangement of a propargyl group provides efficient access to fused indolines (eq 2).¹³ Thus, treatment of 2-alkynyl-*N*-propargylanilines with a cationic gold catalyst induces formation of 3-allenylindoles via rearrangement of the propargyl group, followed by nucleophilic cyclizations under the same reaction conditions.

Scheme 1. Rearrangement of *N*-Substituents in Transition-Metal-Catalyzed Indole Formation from 2-Alkynylanilines



Considering that an allene is the highly reactive functional group in gold-catalyzed nucleophilic reactions,¹⁴ we envisioned that the indole formation–propargyl rearrangement cascade would have great potential for the construction of other complex heterocycles, including fused carbazoles. Our concept is shown in Scheme 2. The indole formation–rearrangement cascade from conjugated diyne-substituted aniline **1**, bearing a nucleophilic functional group (NuH) in the migrating propargyl group, would form allenylindole intermediate **A** (pathway a). A second nucleophilic cyclization toward the allene moiety (pathway b) would then give **B**, and a subsequent third cyclization (pathway c) would produce fused carbazoles **C**. The key to success for this strategy is to ensure that the desired cyclizations are predominant over other pathways. For example, 4-*endo-dig* cyclization from **1** (pathway d) will produce **D**, while nucleophilic cyclization of the indole from **A**

(pathway e, a similar pathway to that shown in eq 2) will afford cationic intermediate **E**. Our expectation was that the usually fast indole formation of the 2-alkynylaniline (pathway a) and 5-*endo-trig* cyclization (pathway b) would be favored over the pathways that lead to a strained ring (system) in compounds **D** and **E**. Herein, we report a novel direct approach to tetracyclic fused carbazoles based on tricyclization of conjugated diynes via rearrangement of a propargyl group.¹⁵

Scheme 2. Our Concept: Fused Carbazole Synthesis via Rearrangement of a Propargyl Group

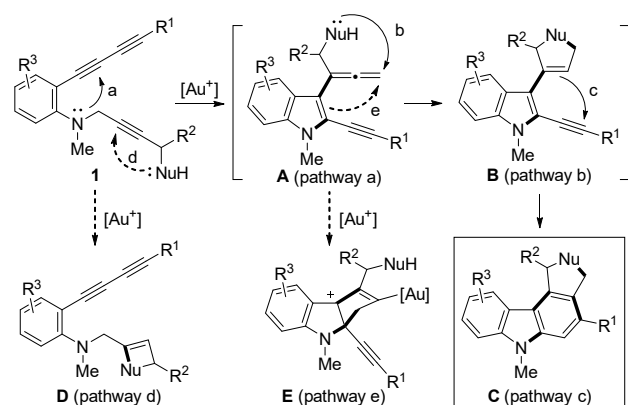
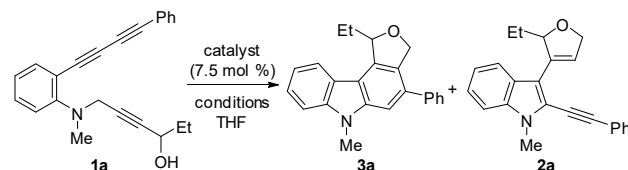
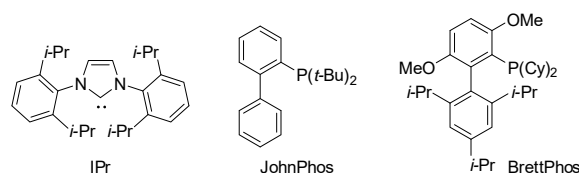


Table 1. Optimization of Catalyst and Reaction Conditions



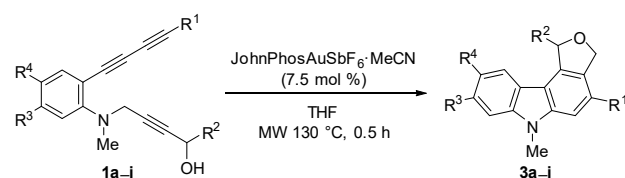
entry	catalyst	conditions		yield (%) ^d	
		temp (°C)	time (h)	3a	2a
1	BrettPhosAuCl/AgSbF ₆	70	2	-	70
2	BrettPhosAuCl/AgSbF ₆	130 ^d	0.5	35	46
3	PPh ₃ AuCl/AgSbF ₆	130 ^d	0.5	-	-
4	IPrAuCl/AgSbF ₆	130 ^d	0.5	63	-
5	JohnPhosAuSbF ₆ ·MeCN	130 ^d	0.5	86	-
6	JohnPhosAuCl/AgNTf ₂	130 ^d	0.5	68	-
7	JohnPhosAuCl/AgOTf	130 ^d	0.5	38	17
8	AuCl·DMS	130 ^d	0.5	20	55
9	PtCl ₂	130 ^d	0.5	-	-
10	JohnPhosAuSbF ₆ ·MeCN ^b	130 ^d	0.5	75	-
11	JohnPhosAuSbF ₆ ·MeCN ^c	130 ^d	0.5	65	-
12	JohnPhosAuSbF ₆ ·MeCN	70	2	78	-

^a The yields were determined by the combined isolated yields and ¹H NMR analyses of the mixtures of **2a** and **3a**. ^b Using 5 mol % of the catalyst. ^c Using 2.5 mol % of the catalyst. ^d Under microwave irradiation in a sealed tube.



We chose triyne **1a** as the model substrate for screening catalysts and optimizing the reaction conditions. The results are summarized in Table 1. The reaction of **1a** with 7.5 mol % of BrettPhosAuCl activated by AgSbF₆ (BrettPhosAuCl/AgSbF₆) in THF under reflux gave only the biscyclization product **2a** (entry 1), the anticipated intermediate for the tricyclization. Treatment of **1a** with the same catalyst at 130 °C under microwave irradiation partially promoted the third cyclization, affording the desired fused carbazole **3a** in 35% yield, along with intermediate **2a** (46%, entry 2). The structure of carbazole **3a** was confirmed by X-ray crystallography (see the Supporting Information). Although the use of PPh₃AuCl/AgSbF₆ led to the decomposition of triyne **1a** (entry 3), IPrAuCl/AgSbF₆ improved the yield of **3a** to 63% (entry 4). To our delight, the use of JohnPhosAuSbF₆·MeCN (prepared in advance) provided 86% yield of **3a** (entry 5). The effect of the counterion was also significant, as using AgNTf₂ and AgOTf resulted in lower yields of **3a** (entries 6 and 7). Neutral catalysts including AuCl·DMS and PtCl₂ (entries 8 and 9) and solvents such as CH₃NO₂, CH₂Cl₂, EtOH, CH₃CN, and toluene (Table S1, Supporting Information) were less effective. It is worth mentioning that JohnPhosAuSbF₆·MeCN showed good activity even at lower catalyst loadings (5 and 2.5 mol %; entries 10 and 11, respectively). Moreover, the reaction proceeded efficiently at 70 °C to furnish **3a** in slightly lower yield (78%, entry 12) than that under microwave irradiation (86%, entry 5).

Table 2. Substrate Scope



entry	R ¹	R ²	R ³	R ⁴	yield (%) ^a
1	Ph	Et	H	H	86 (3a)
2	<i>n</i> -Hex	Et	H	H	71 (3b)
3	(CH ₂) ₂ OBn	Et	H	H	69 (3c)
4	Ph	Ph	H	H	62 (3d)
5	Ph	Bn	H	H	53 (3e)
6	Ph	Et	Me	H	76 (3f)
7	Ph	Et	Cl	H	77 (3g)
8	Ph	Et	H	OMe	57 (3h)
9	Ph	Et	H	Br	81 (3i)

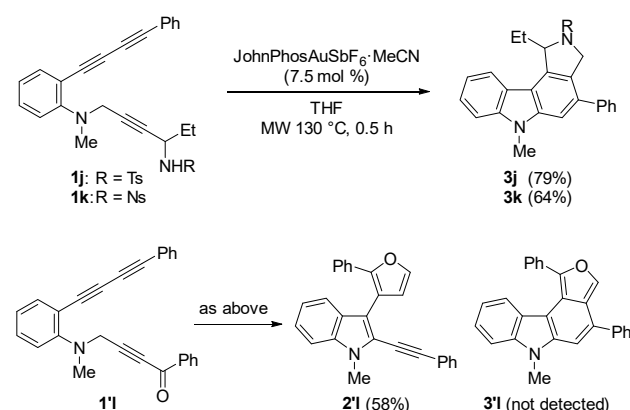
^a Isolated yields.

With the optimized conditions in hand (Table 1, entry 5), we examined the substrate scope of the reaction (Table 2). When the substituent R¹ at the alkyne terminus was changed from a

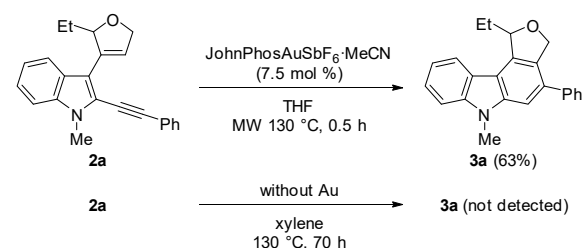
phenyl group to an alkyl group (*n*-hexyl or benzyloxyethyl group), small decreases in the yield of **3** were observed (entries 2 and 3). Phenyl and benzyl groups as propargylic substituents (R^2) were also tolerated, resulting in moderate yields of **3d** (62%) and **3e** (53%) (entries 4 and 5, respectively). The electronic effect of the aniline moiety did not significantly affect the reaction efficiency. Substrates bearing an electron-donating (methyl or methoxy) or -withdrawing group (chloro or bromo) at the 5- or 4-position (R^3 or R^4) were transformed smoothly to the corresponding carbazoles **3f–i** (entries 6–9). A slightly lower yield of **3h** (R^4 = OMe) was obtained, along with formation of unidentified byproducts. This can be rationalized by the highly electron-rich nature of the 5-methoxy-substituted indole ring leading to decreased stability of the product or competitive nucleophilic attack of indole (e.g., pathway e) resulting in formation of undesired products.

The reaction using nucleophiles other than a hydroxy group was examined next (Scheme 3). Tosyl and nosyl amides were effective nucleophiles, and produced the corresponding carbazoles **3j** and **3k**, fused with a 3-pyrroline ring, in good yields (79% and 64%, respectively). However, reaction of ketone **1l** did not result in the formation of furan-fused carbazole **3l**. Instead, furan-substituted indole **2l** was obtained in 58% yield,¹⁶ presumably due to the low nucleophilicity of the 4-position of the furan ring.

Scheme 3. Reaction of Sulfonamide and Ketone Nucleophiles



Scheme 4. Reaction of the Biscyclization Intermediate 2a

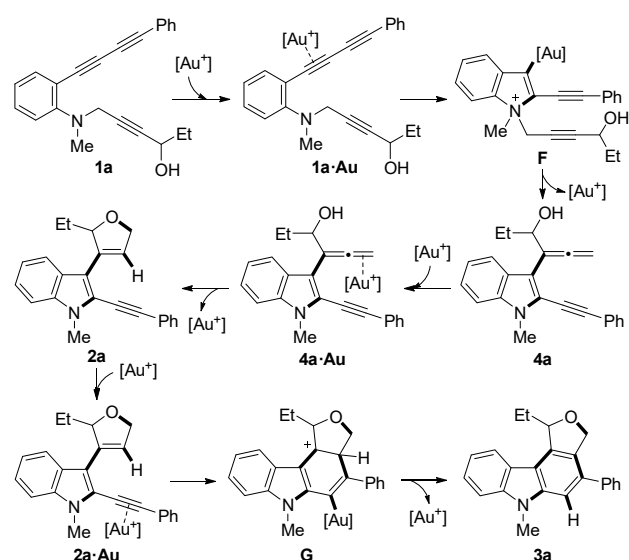


To gain insight into the reaction mechanism, we investigated the reaction of the intermediate **2a** (Scheme 4). Under the optimized reaction conditions using JohnPhosAuSbF₆·MeCN (7.5 mol %), complete consumption of **2a** was observed within

0.5 h to produce the fused carbazole **3a** in 63% yield. This result suggests that the dihydrofuran **2a** is an intermediate of the tricyclization, as we expected. A lower yield compared with the one-pot reaction can be attributed to the relatively unstable nature of **2a**. In contrast, heating **2a** at 130 °C in the absence of any catalysts led to complete decomposition after 70 h. Thus, we have demonstrated that both the formation and cyclization of **2a** are catalyzed by the cationic gold species.¹⁷

A postulated reaction mechanism is shown in Scheme 5. First, the triple bond adjacent to the aniline benzene ring of conjugated diyne **1a** is activated by a cationic gold catalyst (**1a·Au**) to facilitate nucleophilic attack of the aniline nitrogen and furnish indolylgold species **F**. Rearrangement of the propargyl group on the indole nitrogen¹⁸ then leads to the formation of allenylindole **4a**. A 5-*endo-trig* cyclization toward the allenic moiety and subsequent protodeauration then take place to give dihydrofurylindole **2a**. Finally, 6-*endo-dig* cyclization from **2a**, via gold complexes **2a·Au** and **G**, results in the formation of carbazole **3a**.¹⁹

Scheme 5. Postulated Reaction Mechanism



In conclusion, we have developed a gold-catalyzed tricyclization cascade of *N*-propargylanilines bearing conjugated diynes at the 2-position. The key feature of this reaction is the rearrangement of the *N*-propargyl group, which allows the second and third cyclizations to proceed through the allenylindole and dihydrofurylindole intermediates, respectively. This catalytic system provides direct access to carbazoles fused with a dihydrofuran or 3-pyrroline ring with 100% atom economy.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03254.

X-ray data for compound **3a** (CIF)

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193.
- (2) For recent reviews, see: (a) Lellouche, J.-P.; Koner, R. R.; Ghosh, S. *Rev. Chem. Eng.* **2013**, *29*, 413. (b) Venkateswararao, A.; Thomas, K. R. *J. Solar Cell Nanotechnology* **2014**, 41. For our recent papers, see: (c) Suzuki, T.; Tokimizu, Y.; Sakano, Y.; Katoono, R.; Fujiwara, K.; Naoe, S.; Fujii, N.; Ohno, H. *Chem. Lett.* **2013**, *42*, 1001. (d) Suzuki, T.; Sakano, Y.; Tokimizu, Y.; Miura, Y.; Katoono, R.; Fujiwara, K.; Yoshioka, N.; Fujii, N.; Ohno, H. *Chem. Asian J.* **2014**, *9*, 1841.
- (3) For recent reviews, see: (a) Sherer, C.; Snape, T. J. *Eur. J. Med. Chem.* **2015**, *97*, 552. (b) Głuszynska, A. *Eur. J. Med. Chem.* **2015**, *94*, 405. For our recent study, see: (c) Takeuchi, T.; Oishi, S.; Watanabe, T.; Ohno, H.; Sawada, J.; Matsuno, K.; Asai, A.; Asada, N.; Kitaura, K.; Fujii, N. *J. Med. Chem.* **2011**, *54*, 4839.
- (4) For recent reviews, see: (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099. (c) Yoshikai, N.; Wei, Y. *Asian J. Org. Chem.* **2013**, *2*, 466. See also, ref 1.
- (5) (a) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (b) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2007**, 4516. (c) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368.
- (6) For selected reviews, see: (a) Platon, M.; Amardeil, R.; Djakovitch, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (b) Abbiati, G.; Marinelli, F.; Rossi, E.; Arcadi, A. *Isr. J. Chem.* **2013**, *53*, 856.
- (7) (a) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368. (b) Hirano, K.; Inaba, Y.; Takahashi, N.; Shimano, M.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 1212. (c) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068.
- (8) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546.
- (9) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 2284.
- (10) (a) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (b) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1881. (c) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (d) Majumdar, K. C.; Hazra, S.; Roy, B. *Tetrahedron Lett.* **2011**, *52*, 6697.
- (11) (a) Li, G.; Huang, X.; Zhang, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 346. (b) Nakamura, I.; Sato, Y.; Konta, S.; Terada, M. *Tetrahedron Lett.* **2009**, *50*, 2075. (c) Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. *Org. Lett.* **2014**, *16*, 5124.
- (12) For related reactions, see: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473. (b) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081. (c) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron*, **2007**, *63*, 8670. (d) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 2649. (e) Nakamura, I.; Chan, C. S.; Araki, T.; Terada, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2009**, *351*, 1089. (f) Shi, Y.; Roth, K. E.; Ramgren, S. D.; Blum, S. A. *J. Am. Chem. Soc.* **2009**, *131*, 18022. (g) Ueda, M.; Sato, A.; Ikeda, Y.; Miyoshi, T.; Naito, T.; Miyata, O. *Org. Lett.* **2010**, *12*, 2594. (h) Istrate, F. M.; Gagosz, F. *Beilstein J. Org. Chem.* **2011**, *7*, 878. (i) Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; Becker, J. D. B.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133. (j) Hashmi, A. S. K.; Graf, K.; Ackermann, M.; Rominger, F. *ChemCatChem* **2013**, *5*, 1200. (k) Ackermann, M.; Bucher, J.; Rappold, M.; Graf, K.; Rominger, F.; Hashmi, A. S. K. *Chem. Asian J.* **2013**, *8*, 1786. (l) Zhou, T.; Xia, Y. *Organometallics* **2014**, *33*, 4230. (m) Hirner, J. J.; Faizi, D. J.; Blum, S. A. *J. Am. Chem. Soc.* **2014**, *136*, 4740. (n) Kolundndžić, F.; Murali, A.; Pérez-Galán, P.; Bauer, J. O.; Strohmman, C.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8122.
- (13) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem. Int. Ed.* **2015**, *54*, 7862.
- (14) For selected reviews, see: (a) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178. (b) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382. (c) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (d) Yang, W.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2014**, *43*, 2941. (e) Soriano, E.; Fernández, L. *Chem. Soc. Rev.* **2014**, *43*, 3041.
- (15) For cascade cyclizations with gold catalysts reported by our group, see: (a) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326. (b) Naoe, S.; Suzuki, Y.; Hirano, K.; Inaba, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2012**, *77*, 4907. (c) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138. (d) Matsuda, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Eur. J.* **2015**, *21*, 1463. (e) Tokimizu, Y.; Wieteck, M.; Rudolph, M.; Oishi, S.; Fujii, N.; Hashmi, A. S. K.; Ohno, H. *Org. Lett.* **2015**, *17*, 604.
- (16) For a related gold-catalyzed synthesis of furans using allenones, see: Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 2285.
- (17) JohnPhosAuSbF₆·MeCN was not observed in the ¹³P NMR spectra of the reaction mixture after completion of the reaction, presumably because of the instability of this complex at high temperature. However, the presence of JohnPhosAuSbF₆·MeCN or its derivative is important for promotion of the final cyclization, considering the results shown in Table 1 (entry 2 vs 5) and Scheme 4.
- (18) A cross-over experiment in our previous study demonstrated that the rearrangement of the propargyl group proceeds in an intramolecular manner; see ref 13.
- (19) We cannot rule out other mechanisms for the final cyclization step such as an electrocyclization-type concerted pathway promoted by a gold(I) catalyst.