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Ligand-Controlled Product Selectivity in Gold-Catalyzed Double Cycloisomerization of 1,11-Dien-3,9-Diyne Benzoates

Weidong Rao,[§] Dewi Susanti,[§] Benjamin James Ayers,[§] and Philip Wai Hong Chan*[,†,‡,§]

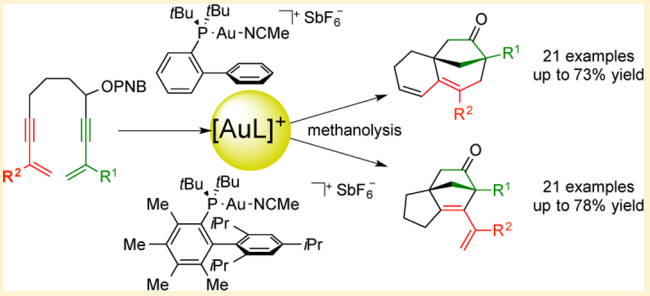
[†]School of Chemistry, Monash University, Clayton, Victoria 3800, Australia

[‡]Department of Chemistry, University of Warwick, Coventry, CV4 7AL, United Kingdom

[§]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A synthetic method to prepare tricyclic bridged heptenones and hexenones from gold(I)-catalyzed double cycloisomerization of 1,11-dien-3,9-diyne benzoates is described. A divergence in product selectivity was achieved by fine-tuning the steric nature of the ligand of the Au(I) catalyst. In the presence of $[MeCNAu(JohnPhos)]^+SbF_6^-$ (JohnPhos = (1,1′-biphenyl-2-yl)-di-*tert*-butylphosphine) as the catalyst, tandem 1,3-acyloxy migration/metallo-Nazarov cyclization/1,6-enyne addition/Cope rearrangement of the substrate was found to selectively occur to afford the bridged heptenone adduct. In contrast, changing the Au(I) catalyst to $[MeCNAu(Me_4tBuXPhos)]^+SbF_6^-$ ($Me_4tBuXPhos$ = di-*tert*-butyl(2′,4′,6′-triisopropyl-3,4,5,6-tetramethyl-[1,1′-biphenyl]-2-yl)phosphine) was observed to result in the 1,11-dien-3,9-diyne benzoate undergoing a more rapid tandem 1,3-acyloxy migration/metallo-Nazarov cyclization/[4 + 2]-cyclization pathway to give the bridged hexenone derivative.



INTRODUCTION

Homogeneous gold catalysis has recently emerged as one of the most powerful synthetic tools for the assembly of highly functionalized, architecturally complex molecules from readily accessible precursors in a single step.[1−12] An illustrative example of this is the rapid increase in the number of elegant routes to synthetically useful cyclic compounds from 1,*n*-diyne and -enyne derivatives.[2−10] From a mechanistic viewpoint, the reactions of these substrates are typically triggered by a gold-mediated 1,2- and 1,3-acyloxy migration step to give the corresponding reactive metallo-carbenoid and -allene species **II** and **III** shown in Scheme 1 for 1,*n*-diyne esters **1**.[1−4] As part of ongoing efforts examining the utility of gold catalysis in organic synthesis,[11] we became interested in the potential reactivity of allenic intermediates **IV** when R′ = R″ = vinyl moiety, the chemistry of which has so far remained unexplored. We anticipated that the vinylic allene motif of the gold-activated species may be prone to a Nazarov cyclization to give the cyclopentadiene **V**.[5,6,12] Subsequent cyclopropanation followed by Cope rearrangement of this in situ formed gold-coordinated adduct and basic methanolysis might be expected to produce the 3,4,7,8-tetrahydro-4a,7-methanobenzo[7]annulen-6(5*H*)-one ring system.[7,8,13,14] However, by fine-tuning the steric nature of the ligand of the Au(I) catalyst, control of chemoselectivity may be possible to reveal a gold(I)-mediated [4 + 2] cycloaddition and basic methanolysis pathway to 1,2,3,6-tetrahydro-3a,6-methanoinden-5(4*H*)-ones.[9,15] Herein, we disclose the details of this chemistry that provides expedient and selective access from 1,11-dien-3,9-diyne benzoates to these two classes of carbocycles, present in many bioactive natural products such as the *ent*-kaurane- and beyerane-type sesquiditerpenes, exemplified by steviol and isosteviol, respectively (Scheme 1).[16] The proposed double cycloisomerizations comprise a regiodivergent pathway that is unprecedented and adds to an increasingly important new facet in gold catalysis concerning ligand-controlled product selectivity.[10]

RESULTS AND DISCUSSION

Our studies commenced by examining the gold(I)-catalyzed cycloisomerization of **1a** to establish the reaction conditions (Table 1).[17] This initially revealed that treatment of the starting ester with 5 mol % of gold(I) phosphine catalyst **A** and 4 Å molecular sieves (MS) in 1,2-dichloroethane at room temperature for 24 h afforded an inseparable >20:1 mixture of **4a** and **5a**, and the cyclopentadiene **6a** in 41% and 45% yields, respectively (entry 1). An increase of 41 to 72% yield of the tricycloadducts was subsequently obtained as the only products when the reaction was conducted for 72 h and the catalyst loading was increased to 10 mol % (entry 2). Changing the catalyst from **A** to the Au(I) complex **B** gave a comparable 68% yield of **4a** and **5a** along with **6a** in 15% yield (entry 3). However, yields of 27% and 50% of the bridged carbocycles

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Scheme 1. Gold-Catalyzed Reactions of 1,*n*-Diyne Esters

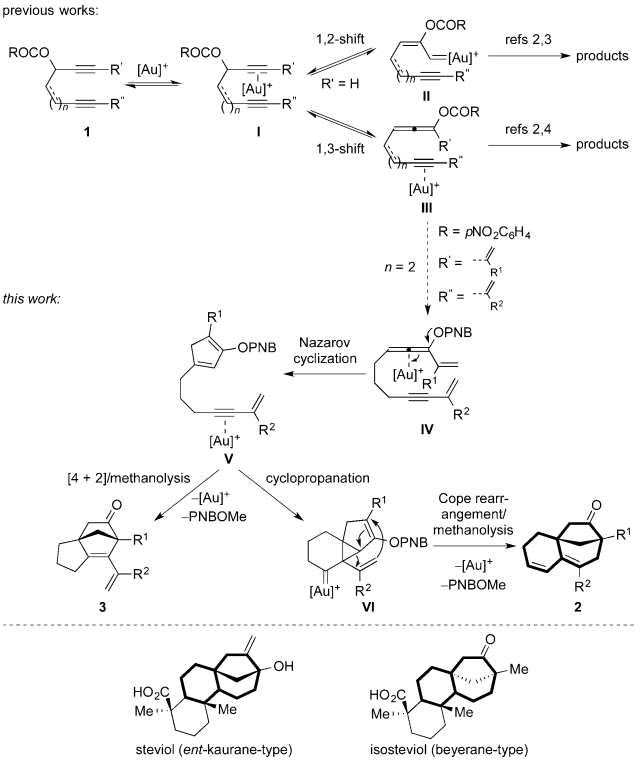
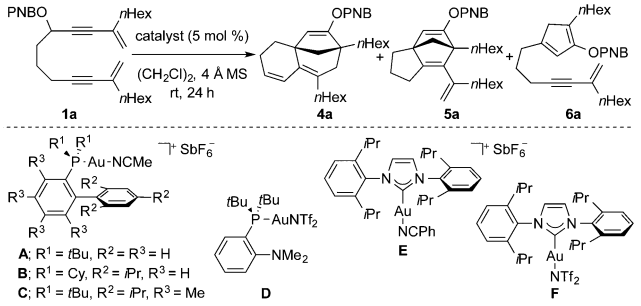


Table 1. Optimization of Reaction Catalyst[a]



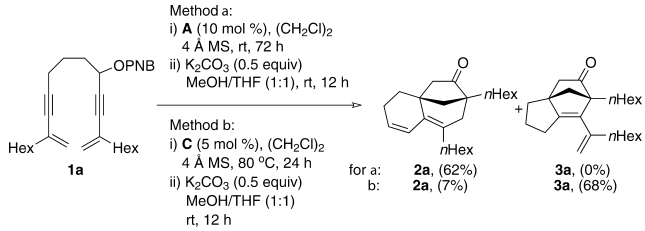
entry	catalyst	4a/5a ratio	yield (%)[b] 4a/5a	yield (%)[b] 6a
1	**A**	>20:1	41	45
2[c]	**A**[d]	**>20:1**	**72**	
3[c]	**B**[d]	>20:1	68	15
4[e]	**C**[d]	<1:7	27	50
5[f]	**C**	**<1:7**	**92**	
6[f]	**A**	>6:1	85	
7[f]	**D**		[g]	
8[e]	**E**[d]	>50:1	60	
9[c]	**F**	>50:1	41	
10	$Ph_3PAuNTf_2$[d]		[h]	

[a]All reactions were performed at the 0.2 mmol scale with 5 mol % catalyst and 4 Å MS (150 mg) in $(CH_2Cl)_2$ at 25 °C for 24 h. [b]Isolated yield. [c]Reaction time = 72 h. [d]Catalyst loading = 10 mol %. [e]Reaction time = 96 h. [f]Reaction temperature = 80 °C. [g]Mixture of unknown products. [h]No reaction based on TLC and ^1H NMR analysis of the crude mixture.

and the cyclopentadiene side-product was furnished with the more sterically crowded Au(I) complex **C** over 96 h (entry 4). Despite the low yield, an interesting change in product selectivity was found, with **4a** and **5a** isolated in a ratio of <1:7. Pleasingly, the yield of the tricarbocycles afforded with Au(I) catalyst **C** could be increased from 27 to 92% in an identical <1:7 ratio and without the formation of **6a** on repeating the reaction at 80 °C for 24 h (entry 5). Likewise, an increase in product yield from 72 to 85% but with a reduction in chemoselectivity was observed with catalyst **A** at 80 °C for 24 h (entry 6). An increase in the selective formation of **4a** over **5a** from >20:1 to >50:1, albeit in lower respective yields of 60 and 41% was achieved under these latter conditions with the NHC-gold(I) (NHC = *N*-heterocyclic carbene) complexes **E** and **F** in place of **A** as the catalyst (entries 8 and 9). In our hands, control experiments with the Au(I) complex **D** and $Ph_3PAuNTf_2$ as the catalyst were the only instances that either resulted in decomposition to an unassignable mixture or no reaction being observed (entries 7 and 10). On the basis of the above results, the procedures described in entries 2 and 5 were deemed to provide the respective optimum reaction conditions to chemoselectively access **4a** and **5a**.

Further studies found that by directly treating the optimum reaction conditions with K_2CO_3 in MeOH/THF (1:1 v/v), the corresponding ketones were afforded, which could be separated by flash column chromatography (Scheme 2). Thus, basic

Scheme 2. Separation of Products by Methanolysis



methanolysis of the crude reaction mixture obtained with the Au(I) catalyst **A** (Method α) gave **2a** in 62% yield. Repeating this for the analogous reaction catalyzed by Au(I) complex **C** (Method β), ketones **2a** and **3a** were furnished in respective yields of 7 and 68%.

With the reaction conditions established, we first sought to evaluate the generality of Method α with the Au(I) complex **A** as the catalyst for a series of 1,11-dien-3,9-diyne benzoates, and the results are summarized in Table 2. Overall, the reaction conditions were found to be broad, with starting esters **1b–e**, **1g–l**, and **1n–v** containing a diverse range of alkyl functionalities at both the R^1 and R^2 positions providing the corresponding tricyclic ketones in 40–73% yield. This included examples containing a cyclohexane (**1d**), ester (**1g,j**), ketone (**1h,i,v**), sulfonamide (**1l,t**) and ether (**1k,r,u**) groups with the structure of **2t** confirmed by X-ray crystallography.[18] The reactions of substrates containing an ethyl 4-nitrobenzoate side-chain (**1f**) at the R^1 position or R^2 = cyclopentyl (**1m**) were observed to be the only exception. In these experiments, while the former gave a lower product yield of 27%, the latter was found to deliver only decomposition products based on TLC and ^1H NMR analysis of the crude mixture.

We next sought to define the scope of the Au(I) complex **C**-catalyzed bridged cyclohexenone-forming cycloisomerization using Method β with the same set of substrates (Table 3). This revealed experiments with **1b,c**, **1e–q** and **1s–v** to proceed well, with the corresponding tricyclic adducts **3b,c**, **3e–q**, and **3s–v** furnished in 47–78% yield. In contrast to our earlier

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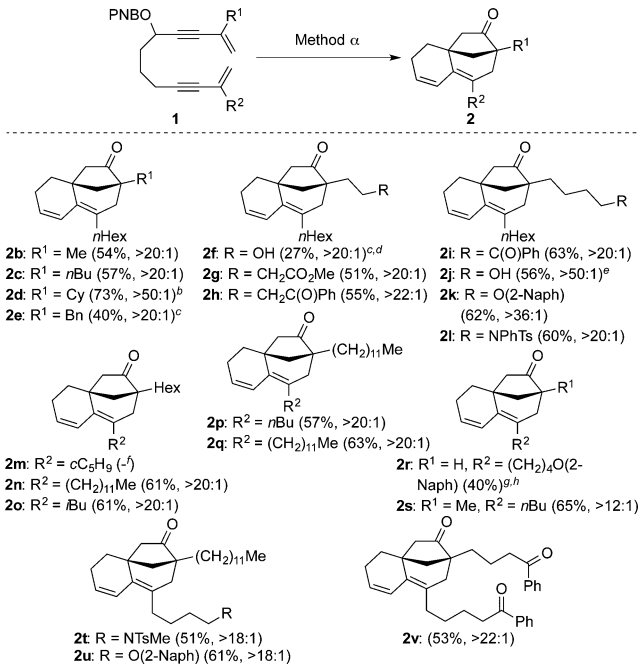
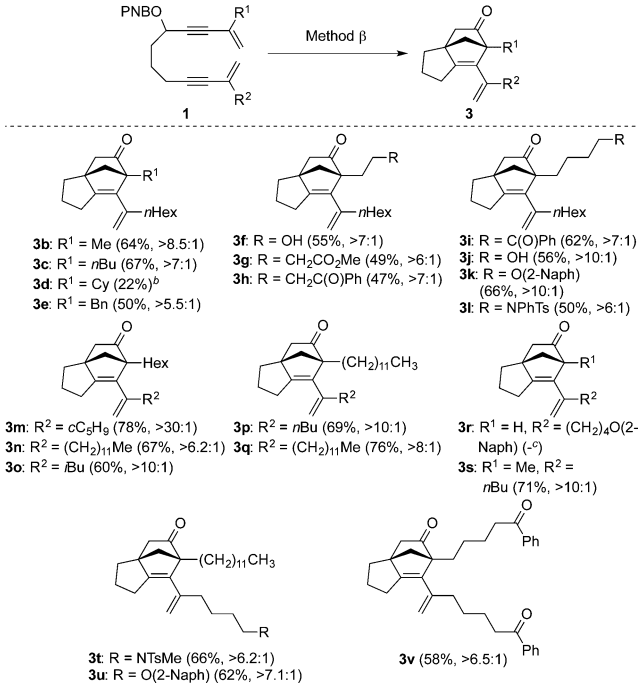
Table 2. Cycloisomerization of 1,11-Dien-3,9-diyne Benzoates 1b-v Catalyzed by A[a]



[a]All reactions were performed following Method α at the 0.2 mmol scale for 1 to 7 d. Values in parentheses denote isolated product yield and ratio of **2**/**3**. [b]Cy = cyclohexyl. [c]Reaction conducted at 40 °C. [d]In **1f**, R^1 = $(CH_2)_2OPNB$. [e]In **1j**, R^1 = $(CH_2)_4OPNB$. [f]Mixture of unknown byproducts. [g]Reaction conducted with 20 mol % of catalyst **A**. [h]Product ratio could not be determined.

Table 3. Cycloisomerization of 1,11-Dien-3,9-diyne Benzoates 1b-v Catalyzed by C[a]

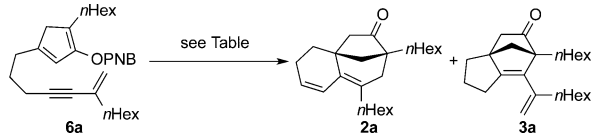


[a]All reactions were performed following Method β at the 0.2 mmol scale for 1 to 3 d. Values in parentheses denote isolated product yields and ratio of **3**/**2**. [b]Product ratio could not be determined. [c]Mixture of unknown byproducts.

findings, the cycloisomerization of **1d** was found to provide the corresponding carbocyclic product **3d** in a lower yield of 22% while **1r** led to a mixture of unknown decomposition products being obtained. However, it was pleasing to find the reaction of **1m** to proceed well in the presence of gold(I) complex **C** under the conditions of Method β to give **3m** in 78% yield.

The mechanistic premise put forward in Scheme 1 predicts that the Au(I)-catalyzed formation of the two carbocyclic products might occur through a pathway involving a common cyclopentadiene intermediate. The isolation of **6a** under certain conditions described in Table 1 supports its participation in the gold(I)-mediated tandem processes. This is further supported by the following control experiments described in Table 4. First

Table 4. Control Experiments with Cyclopentadiene 6a[a]



entry	reaction conditions	2a/3a ratio	yield (%)[a] 2a	3a
1	Method α	>20:1	64	3
2	Method β	<1:7	10	61
3	$(CH_2Cl)_2$, 4 Å MS, 80 °C, 24 h	[b]		

[a]Isolated yield. [b]Recovery of substrate in 93% yield.

is the reaction of the cyclopentadiene adduct with Au(I) catalyst **A** under the optimized conditions of Method α, which delivered the expected tricyclic products **2a** and **3a** in a >20:1 ratio and 64 and 3% yield, respectively (entry 1). Likewise, treatment of the substrate with Au(I) complex **C** under the optimized conditions of Method β afforded **2a** and **3a** in a <1:7 ratio and yields of 10 and 61% (entry 2). The analogous reaction of **6a** with 4 Å MS in 1,2-dichloroethane at 80 °C for 24 h but in the absence of a catalyst led to its recovery in 93% yield (entry 3). This latter test corroborated the role of the gold(I) complex in activating the pendant alkyne moiety in the cyclopentadiene intermediate as well as indicating it to be resistant to thermally driven cyclization processes.

A tentative mechanism for the present gold(I)-catalyzed 1,11-dien-3,9-diyne benzoate cycloisomerization reactions is presented in Scheme 3. This might initially involve selective activation of the acetate alkyne moiety in the substrate by the metal catalyst and 1,3-acyloxy shift of the resulting gold-coordinated intermediate **I** to afford the allene **VII**.[4] Further coordination of the gold(I) complex to the allenic moiety in this newly formed intermediate may then give the organogold species **IV** that is prone to Nazarov cyclization via the cationic 1,4-diene adduct **VIII**.[5,6,13] Subsequent 1,2-hydride migration and deauration of the ensuing gold carbenoid complex **IX** would produce the observed cyclopentadiene **6**. Activation of the remaining pendant alkyne moiety in the monocyclic compound by the Au(I) catalyst would afford the putative metal coordinated 1,3-enyne complex **V**. A divergence in reactivity mode is thought to occur at this point depending on the nature of the phosphine ligand of the gold(I) catalyst.[10] In the presence of Au(I) complex **A**, intramolecular cyclopropanation may lead to the divinylcyclopropane intermediate **VI** via the cationic vinyl gold species **X** (Scheme 3, path *a*).[12] Divinylcyclopropane-cyclohepta-1,4-diene/Cope rearrangement of this second gold carbenoid species would afford the

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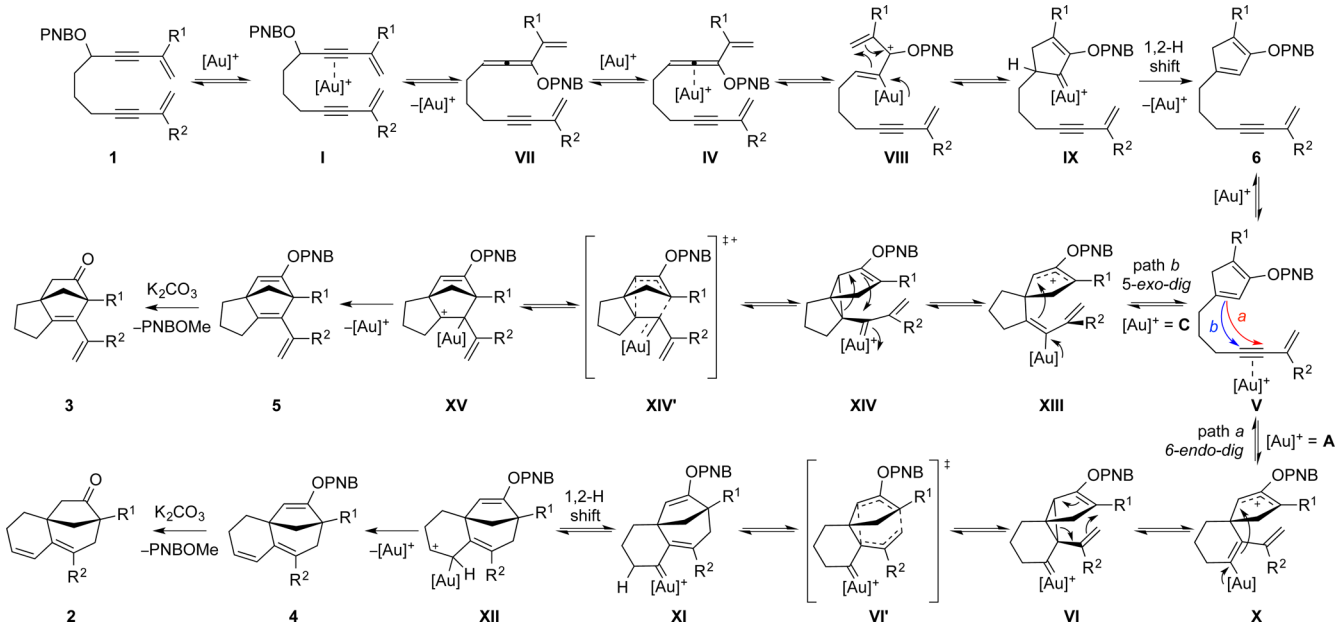
Scheme 3. Proposed Mechanism for the Au(I)-Catalyzed Cycloisomerization of 1,11-Dien-3,9-diyne Benzoates



organogold adduct **XI** via the transition state **VI′**.[7,8,14] Succeeding 1,2-hydride migration would give the cationic alkyl gold species **XII**, which on deauration followed by K_2CO_3-mediated methanolysis would furnish **2** via **4**. Alternatively, the gold-coordinated intermediate **V** formed from reaction of the substrate with the Au(I) complex **C** may undergo a formal stepwise [4 + 2] cycloddition process involving addition of the alkene group to the alkyne moiety (Scheme 3, path *b*).[9,15] Addition of the vinyl gold motif to the carbocation center in the ensuing spiro[4.4]non-1-ene species **XIII** would afford the cyclopropyl gold carbenoid intermediate **XIV**. Ring-opening of the cyclopropane motif with addition of the cyclopentene C═C bond to the carbenoid carbon center in this intermediate would give the alkyl gold complex **XV** via transition state **XIV′**. Deauration of this carbonium species might complete the formal [4 + 2] pathway to deliver **5**, which on K_2CO_3-mediated methanolysis, would provide **3**.

While speculative, the obtained product selectivities could be due to the steric interactions between the phosphine ligands in the Au(I) catalysts **A** and **C** and the substrate. In the case of reactions catalyzed by gold(I) complex **A**, we surmise that the reaction may be under thermodynamic control leading to the gold-coordinated species **V** to undergo 6-*endo-dig* cyclization that results in selective formation of the cycloheptenone product **2** (Scheme 3, path *a*). However, it is postulated that in the case of reactions mediated by gold(I) complex **C**, the increased steric demand exerted by the Me_4*t*BuXPhos ligand might generate unfavorable interactions between it and the terminal alkene motif in vinyl gold intermediate **X**. This could result in the position of equilibrium being pushed toward the spiro[4.4]nonenyl gold species **XIII** and preferential formation of **3** following the 5-*exo-dig* pathway illustrated in Scheme 3, path *b*. Our findings showing a ratio of **4a**/**5a** ≥ 50:1 being achieved in control experiments with **1a** mediated by the NHC-gold(I) complexes **E** and **F**, which are sterically less bulky than both gold(I) phosphine catalysts **A** and **C**, would be consistent with this hypothesis. Likewise, the reactivity found for the Au(I) complex **A**-catalyzed reaction of **1m** would align with unfavorable steric interactions between the 1-cyclopentylvinyl substituent and the vinyl gold moiety that might be anticipated on generating the corresponding spiro[4.5]dec-2-ene species **X**. The contrasting reactivities observed in gold(I) complex **A** and **C**-mediated reactions of **1d** and **1r** would also be in good agreement with the present rationale. In these experiments catalyzed by Au(I) catalyst **C**, the observed reactivities could be due to the significant unfavorable steric interactions between the vinyl motif and the ligand of the metal catalyst and R^1 group in gold carbenoid intermediate **XIV**.

■ CONCLUSIONS

In summary, we have developed a strategy for the assembly of architecturally complex tricyclic bridged heptenones and hexenones by gold(I)-catalyzed cycloisomerization of 1,11-dien-3,9-diynye benzoates. Our studies suggest a novel regiodivergent reaction pathway with chemoselectivity afforded by fine-tuning the steric properties of the biphenylphosphine ligand of the metal catalyst. These double cycloisomerizations represent tandem pathways that have not previously been reported and provide access to biologically relevant scaffolds in a single synthetic step from an acyclic precursor.

■ EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried glassware under argon atmosphere. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. Gold complexes **A**, **D**, and $Ph_3PAuNTf_2$ were purchased from commercial sources and used as received. Substrate **1** and gold complexes **B**, **C**, **E**, and **F** were prepared following literature procedures.[17] Solvents were purified following standard literature procedures. Analytical thin layer chromatography (TLC) was performed using precoated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel and gradient solvent system (*n*hexane/Et_2O or *n*hexane/EtOAc as eluent). ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as s (singlet), br s (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplets), or m (multiplet). The number of protons (*n*) for a given

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resonance is indicated by *n*H and coupling constants are reported as a *J* value in Hertz (Hz). Infrared spectra were recorded on an FTIR spectrometer. Solid and liquid samples were examined as a thin film between NaCl salt plates. High resolution mass spectra (HRMS) were obtained on an LC/HRMS TOF spectrometer using simultaneous electrospray (ESI).

General Procedure for Gold Complex A Catalyzed Cycloisomerization of 1,11-Dien-3,9-Diyne Benzoates 1 to Bridged Cycloheptenones 2. To a solution of 1,11-dien-3,9-diyne benzoate **1** (0.2 mmol) and 4 Å MS (150 mg) in $(CH_2Cl)_2$ (4 mL) was added gold(I) complex **A** (20 μmol). The reaction mixture was stirred at room temperature for 3−7 d until TLC analysis indicated that the reaction was complete. The reaction mixture was filtered through diatomaceous earth, washed with CH_2Cl_2 (10 mL), and the solvent removed under reduced pressure. The crude mixture was dissolved in a solution of THF—MeOH (v/v = 1:1, 6 mL), and K_2CO_3 (13.8 mg, 0.5 equiv) was added. The reaction mixture was stirred at room temperature for 12 h. On completion, saturated ammonium chloride solution (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue purified by flash column chromatography on silica gel (eluent:*n*hexane/Et_2O = 50:1) to afford the title compound.

General Procedure for Gold Complex C Catalyzed Cycloisomerization of 1,11-Dien-3,9-Diyne Benzoates 1 to Bridged Cyclohexenones 3. To a solution of 1,11-dien-3,9-diyne benzoate **1** (0.2 mmol) and 4 Å MS (150 mg) in $(CH_2Cl)_2$ (4 mL) was added gold(I) complex **C** (10 μmol). The reaction mixture was stirred at 80 °C for 24 h until TLC analysis indicated that the reaction was complete. The reaction mixture was cooled to room temperature and filtered through diatomaceous earth, washed with CH_2Cl_2 (10 mL), and the solvent was removed under reduced pressure. The crude mixture was dissolved in a solution of THF—MeOH (v/v = 1:1, 6 mL), and K_2CO_3 (13.8 mg, 0.5 equiv) was added. The reaction mixture was stirred at room temperature for 12 h, and quenched by the addition of saturated ammonium chloride solution (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel (eluent:*n*hexane/Et_2O = 50:1) to afford the title compound.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all starting materials and products, and the CIF file for **2t**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02377.

■ AUTHOR INFORMATION

Corresponding Author

*phil.chan@monash.edu; P.W.H.Chan@warwick.ac.uk

Notes

The authors declare no competing financial interest.

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(17) For the detailed synthesis of **1** and gold(I) complexes **A**–**F**, see the SI.

(18) See Figure S92 in the SI for ORTEP drawing of the crystal structure for **2t**.

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