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J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/ja4032727 • Publication Date (Web): 29 Apr 2013

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Gold-Catalyzed Cycloisomerization of 1,6-Diyne Carbonates and Esters to 2,4a-Dihydro-1*H*-fluorenes

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Supporting Information Placeholder

ABSTRACT: A synthetic method to prepare 2,4a-dihydro-1*H*-fluorenes efficiently from gold(I)-catalyzed 1,2-acyloxy migration/cyclopropenation/Nazarov cyclization of 1,6-diyne carbonates and esters is described. The suggested reaction pathway provides rare examples of [2,3]-sigmatropic rearrangement in this class of compounds as well as the involvement of an in situ formed cyclopropene intermediate in gold catalysis. Experimental and ONIOM(QM:QM') (our own *n*-layered integrated molecular orbital and molecular mechanics(quantum mechanics:quantum mechanics')) computational studies based on the proposed Au carbenoid species provide insight into this unique selectivity.

INTRODUCTION

1,n-Diyne cycloisomerizations catalyzed by mono- and trivalent complexes of gold have emerged as one of the most efficient and atom-economical strategies for complex molecule synthesis in a single step.¹⁻³ Included in this rapidly expanding field have been an increasing number of elegant methods to prepare synthetically useful cyclic compounds from 1.*n*-divne carbonates and esters **1** shown in Scheme 1^{3} . The reactions typically involve the allenvl intermediate **II** arising from the propensity of the acyloxy moiety of the gold-activated substrate I to undergo 1,3-migration (Scheme 1, eq 1, path a). The only notable exception to this mode of reactivity is the Au(I)catalyzed concerted 5-endo-dig/7-endo-dig cyclization of syn-1.7-divne benzoates to indeno[1,2-c] azepines via the goldcoordinated adduct **VI** (Scheme 1, eq 2).^{3a} In contrast, the analogous transformations of 1,n-divne esters initiated by a 1,2acyloxy shift, thereby providing access to a potentially wider scope of cycloisomerization products, have so far remained unrealized. With this in mind and as part of studies examining the utility of gold catalysis in organic synthesis,⁴ we became interested in the cycloisomerization chemistry of 1,6-divne carbonates and esters 1 (Scheme 1, eq 1, path b). It was anticipated that such substrates containing a sterically less hindered terminal carbonate or estereal C=C bond might be more prone to 1,2-acyloxy migration and subsequent trapping of the ensuing gold carbenoid adduct III by the remaining alkyne moiety. Cycloreversion of the resulting cyclopropene intermediate IV, the formation of which in gold catalysis is extremely rare, to give the gold carbenoid species V followed by Narazov cyclization would then be expected to provide 2,4a-dihydro-1*H*-fluorene derivatives.⁵⁻⁸ Herein, we report the details of this chemistry that offers an expedient and chemoselective approach to this carbocyclic motif, present in many bioactive natural and synthetic compounds and functional materials,⁹ in good to excellent yields. An ONIOM computational study on the origin of the observed selectivity was also performed employing two different levels of quantum mechanical methods (ONIOM(QM:QM')).¹⁰

Scheme 1. Gold-Catalyzed Reactivities of 1,n-Diyne Carbonates and Esters



RESULTS AND DISCUSSION

We began our investigations by examining the goldcatalyzed cycloisomerizations of 1,6-diyne ester **1a** to establish the reaction conditions (Table 1).¹¹ This initially revealed that treating **1a** with 5 mol % of Au(I) catalyst **A** in dichloromethane at room temperature for 6 h afforded **2a** in 71% yield (entry 1). The structure of the 2,4a-dihydro-1*H*-fluorene product was determined by ¹H NMR spectroscopic measurements and X-ray crystallography (Figure 1).¹² Our studies subsequently showed that when the reaction was repeated with the more sterically crowded gold(I) complex **C** in place of **A** as the catalyst, the product yield increased from 71 to 78% (entry

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3).¹³ In contrast, replacing **A** with the Au(I) phosphine complexes **B** and **D**–**F**, NHC-gold(I) (NHC = N-heterocyclic carbene) complex G, and gold(I) phosphite complex I as the catalyst was found to result in lower product yields of 12-67% (entries 2, 4–6, 9 and 11).¹⁴ In the case of the reactions mediated by Au(I) phoshine complexes E and F, the substrate was also recovered in 70 and 50% yield, respectively (entries 5 and 6). With Au(I) phoshine complex C as the catalyst, a similar outcome was found with 2a obtained in 27% yield on changing the reaction medium from dichloromethane to toluene (entry 13). In contrast, no reaction was detected in control experiments mediated by PPhAuCl, AuCl, NHC-gold(I) complex H or gold(III) complex K, or Au(I) complex C in polar solvents such as acetonitrile and THF (entries 7, 8, 10, 12, 14) and 15). On the basis of the above results, the reaction of 1a in the presence of Au(I) complex C (5 mol %) as catalyst in dichloromethane at room temperature for 6 h provided the optimum conditions.

Table 1. Optimization of the Reaction Conditions^a



^a All reactions were performed at the 0.2 mmol scale with catalyst: **1a** ratio = 1:20 in given solvent at room temperature for 6 h. PNB = *p*-nitrobenzoyl. ^b Isolated yield. ^c Reaction carried out at room temperature for 24 h; values in parentheses denote the yield of recovered starting material. ^d No reaction based on TLC and ¹H NMR analysis of the crude mixture.

The scope of the present procedure was next assessed with a series of 1,6-diyne carbonates and esters, and the results are summarized in Table 2. In general, these experiments showed that with Au(I) complex C as catalyst, the reaction conditions



Figure 1. ORTEP Drawing of 2a with Thermal Ellipsoids at 50% Probability Levels $^{\rm 12}$

proved to be broad and a variety of substituted 2,4a-dihydro-*H*-fluorenes could be furnished in 44–93% yield from the corresponding substrates **1b**–y. Reactions of substrates containing a Bz (**1b**), Ac (**1c**), Cbz (**1d**) or Boc (**1e**) instead of a PNB migrating group were found to be well tolerated under the reaction conditions and furnished **2b–e** in 52–80% yield.





^a All reactions were performed at the 0.2 mmol scale with C:1 ratio = 1:20 in CH₂Cl₂ at room temperature for 2–24 h. Values in parentheses denote isolated product yields. ^b Isolated as an inseparable mixture of diastereomers in a ratio = 1.1:1. ^c Reaction carried out with NHC-gold(I) complex **G** as the catalyst. 1

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Likewise, starting 1.6-divne esters with a pendant arvl (1f-o and 1q-r), thiophene (1p) or cyclohexene (1s) functional group at the alkyne carbon center were found to proceed to give the corresponding tri-, tetra- and pentacyclic adducts in 47-83% yield. The presence of other aryl motifs on the benzoate carbon center of the starting material (1t-v) was found to have little influence on the course of the reaction with 2t-vfurnished in 53-76% yield. The reactions of substrates containing a cyclopropane ring on the benzoate carbon center (1w and 1x) or methyl groups at the C5 position (1y) were observed to be the only exception. In these experiments, while the use of either gold(I) catalysts C or G as the Au(I) catalyst gave similar product yields, the latter was found to form less impurities that were easier to remove by flash column chromatography. More notably, all the above examined cycloisomerizations also demonstrated that the ring-forming process occurs in a highly selective manner with the 1,4-diene isomer of the adduct only being furnished. Added to this, other than a number of unidentifiable decomposition products, no other cyclic adducts that could be formed from an initial 1,3-acyloxy migration step or concerted double cyclization pathway were detected by ¹H NMR analysis of the crude mixtures.

To provide further support as well as to gain a better understanding of the mechanistic premise put forward in Scheme 1, the following control experiments were performed (Scheme 2). In view of recent works showing the likely involvement of Au(I)-activated alkynylgold(I) species in alkyne cycloisomerizations mediated by the metal catalyst,¹⁵ we first examined the reaction of d_1 -1a in dichloromethane with 5 mol % of gold(I) complex C under the conditions described in Scheme 2, eq 1. This gave d_1 -2a in 75% yield and with a D content of 94%, based on ¹H NMR measurements, that led us to rule out the possible involvement of a dual activation pathway in which the alkyne terminus of 1 was activated by two molecules of the Au(I) catalyst. This was further supported by conducting the reaction again for a second time in the presence of an equimolar amount of **11** and obtaining d_1 -**2a** and **21** as the only products in 60 and 65% yield, respectively, based on ¹H NMR analysis of the crude reaction mixture.¹⁶ On the other hand, the Scheme 2. Control Experiments with 1a, d_1 -1a and d_5 -1b Catalyzed by C or G

OPNE PNBO Ph C (5 mol%) (1) CH₂Cl₂, rt, 6 h d**₁-1a** d₁-2a 94% D-content 75% yield, 94% D-content PNBC cyclohexene (50 eq) (2) Ĥ G (5 mol%) 3a 71% yield CH₂Cl₂, rt, 6 h Ph₂SO **PNBO** (5 eq) (3) Ρh 4a 80% yield OB₇ OBz C (5 mol%) (4) CH₂Cl₂, rt, 2 h b d₅-1b 100% D-content d5-2b 75% yield, 80% D-content

posited participation of the gold carbenoid intermediate V shown in Scheme 1, eq 1, is supported by our findings when the reactions of **1a** were repeated with cyclohexene and Ph₂SO catalyzed by NHC-gold(I) complex G under the standard conditions (Scheme 2, eq 2 and 3).^{17,18} In both test reactions, the production of the anticipated trapping products, the cyclopropane and ketone adducts 3a and 4a, was achieved in respective yields of 71 and 80%.¹³ In a final control experiment, the origin of the proton source in the protodeauration process leading to product formation was also shown to likely come from the regeneration of aromaticity or alkene bond in the Nazarov cyclization step.⁷ Under the standard conditions depicted in Scheme 2, eq 4, subjecting d_5 -1b to the gold(I) catalyst C was found to give d_5 -2b in 75% yield and with a D content of 80% at the C9 position of the adduct, as determined by ¹H NMR measurements.

A tentative mechanism for the present gold(I)-catalyzed 2,4a-dihydro-1H-fluorene forming reaction is outlined in Scheme 3. Using 1b as a representative example, this might initially involve activation of the estereal alkyne moiety of the substrate by the Au(I) catalyst to give the gold(I)-coordinated complex Ib. This results in syn 1,2-migration of the carboxvlate functional group to produce gold carbenoid adduct IIIb via 1,3-dioxin-1-ium intermediate VIIb. Trapping of this newly formed organogold species by the remaining C=C bond may then provide the putative cyclopropene adduct IVb.⁶ Further coordination of the π -acidic metal complex to the alkene bond of the bicyclic intermediate might next provide the gold(I)-activated species VIIIb. Subsequent electrophilic ringopening of the cyclopropenyl gold moiety in VIIIb would give the second gold carbenoid adduct Vb and its goldstabilized allylic carbocation isomer Vb'. This is the active species that undergoes Nazarov cyclization,⁷ which upon rearomatization of the ensuing Wheland-type intermediate IXb followed by protodeauration, would regenerate the gold(I) catalyst and deliver 2b.

Scheme 3. Proposed Mechanism for Au(I)-Catalyzed Cycloisomerization of 1,6-Diyne Carbonates and Esters Represented by 1b



To further verify our proposed mechanism shown in Scheme 3, we undertook two-layer ONIOM(QM:QM')¹⁰ computational studies using Gaussian 09.¹⁹ The B3LYP functional was used for both QM layers,²⁰ in combination with three different basis sets, i.e. LANL2MB (B1), [SDD(for Au),6-

31G*(for others)] (B2), and [LANL2TZ(f)(for Au),6-311+G(d,p)(for others)] (B3).²¹⁻²³ Geometry optimizations and frequency calculations were performed at the ONIOM(B3LYP/B2:B3LYP/B1) level, and single-point energy calculations were done on optimized geometries at the ONIOM(B3LYP/B3:B3LYP/B1) level; for the latter, the dichloromethane solvent effect was taken into account with the IEFPCM (integral equation formalism variant of the polarizable continuum model) method.²⁴ UCSF Chimera was used to draw the molecules.²⁵ The ONIOM calculations produced a number of transition states and intermediates on the reaction pathway from **1b** to **2b**. Full geometric and energetic data are summarized in the SI, and key results are presented here (Figure 2). Our calculations show that an intermediate with a sixmembered ring (**Int3**) is easily formed between **IIIb** and **VIIIb** via a transition state for ring closure (**TS3**). A particularly interesting feature of our delineated mechanism is that **Int3** undergoes another ring closure to generate a unique



Figure 2. Reaction energy diagram (in kcal/mol) for the middle stage of the reaction, as obtained at the ONIOM(B3LYP/B3:B3LYP/B1)-PCM//ONIOM(B3LYP/B2:B3LYP/B1) level with zero-point energy corrections.¹⁰ An alternative pathway between **Int3** and **Int5** via **TS4b** is indicated by a dotted line. In the 3-D figures, H, C, O, P, and Au atoms are colored white, grey, red, orange, and gold, respectively. The ball-and-stick representation is used for the high-level QM layer and the stick representation is used for the rest of the system. Schematic drawings of the transition states along with **Int3** and **Int5** are also given below the energy diagram. Relative energy values are given with respect to the energy of isolated **1b** and [AuL(NCCH₃)]⁺ from catalyst **C**.

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cyclopropene adduct Int4 (VIIIb in Scheme 3) via TS4a with an energy barrier of 11.1 kcal/mol. This is followed by a cyclopropene ring-opening process through TS5 that has an energy barrier of 11.3 kcal/mol. As such, this implied that, despite its transient formation, the relative ease in which the cyclopropene intermediate can undergo ring-opening makes it unlikely that the putative cyclic adduct can be trapped experimentally. Our calculations further suggest that there is an alternative pathway from Int3 to Int5 via TS4b that involves gold migration, as shown in Figure 2. As can be seen from the structure of TS4b, this transition state features the geometry of a fourmembered ring that allows efficient 1,3-migration of the gold catalyst. However, TS4b turns out to be slightly higher in energy than TS4a, and thus, this alternative Au migration pathway should be slightly less favorable than that involving cyclopropene formation via TS4a. During the reaction, Nazarov cyclization of Int6 to Int7 has the highest energy barrier (22.1 kcal/mol), suggesting that the prior intermediates (Int5 and Int6 (Vb in Scheme 3)) should be relatively long-lived. For the reaction steps after the formation of Wheland-type intermediate Int7 (IXb in Scheme 3), the benzovl group was found to play a pivotal role in assisting the 1,3-proton migration by accepting and donating the proton appropriately to yield the final product (see Figure S2 in the SI). These calculated results are also consistent with the experimentally observed preferential formation of 3a and 4a and the high D content found at the C9 position of d_5 -2b as reported in Scheme 2, eq 2-4.

CONCLUSIONS

In summary, we have developed a gold(I)-catalyzed strategy for the construction of highly functionalized 2,4a-dihydro-1*H*fluorenes from the respective 1,6-diyne carbonates and esters. Our studies suggest that the tandem process was initiated by a 1,2-acyloxy migration step previously not seen in this class of substrates. It also hints at the possible involvement of an in situ formed cyclopropene intermediate, examples of which have remained conspicuously rare in gold catalysis. Exploration of the scope and synthetic applications of the present reactions are in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried glassware under an argon atmosphere. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received. Compound 1 was prepared following literature procedures.¹¹ Gold complexes A-J were purchased from commercial sources or prepared following literature procedures.¹¹ Solvents were purified following standard literature procedures. Analytical thin layer chromatography (TLC) was performed using pre-coated silica gel plate. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel and gradient solvent system (EtOAc:nhexane as eluent). ¹H and ¹³C NMR spectra were recorded on 300, 400 and 500 MHz spectrometers. 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) or m (multiplet). The number of protons (n) for a given resonance is indicated by nH and coupling constants are reported as a J value in Hz. Infrared spectra were recorded on a FTIR spectrometer. Solid and liquid samples were examined as a thin film between NaCl salt plates. Low resolution mass spectra were determined on a mass spectrometer and reported in units of mass to charge ratio (m/z). High resolution mass spectra (HRMS) were obtained on a LC/HRMS TOF spectrometer using simultaneous electrospray (ESI).

General Procedure for Gold Complex C Catalyzed Cycloisomerization of 1,6-Diyne Carbonates and Esters 1 to 2,4a-Dihydro-1*H*-fluorene Derivatives 2. To a solution of 1,6diyne carbonate or ester 1 (0.2 mmol) in anhydrous CH₂Cl₂ (4 mL) was added gold(I) complex C (10 μ mol). The reaction mixture was stirred at room temperature for 2–24 h until TLC analysis indicated that the reaction was complete. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: *n*hexane:EtOAc:CH₂Cl₂ = 50:1:1) to give the title compound.

General Procedure for Control Reactions of 1a with Cyclohexene and Diphenyl Sulfoxide Catalyzed by Gold Complex G. To a 2 mL CH₂Cl₂ solution containing gold(I) complex G (10 µmol), cyclohexene (10 mmol) or diphenyl sulfoxide (1.0 mmol) was added a solution of 1a (0.2 mmol) in CH₂Cl₂ (3 mL). The reaction mixture was stirred at room temperature for 6 h until TLC analysis indicated that the reaction was complete. The reaction mixture was then concentrated under reduced pressure and purified by flash column chromatography on silica gel (eluent: *n*hexane:EtOAc:CH₂Cl₂ = 50:1:1) to give the product 3a or 4a, respectively.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, crystal structure data (CIF), raw ONIOM data, XYZ coordinates, and complete ref 18. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

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Author Contributions

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ACKNOWLEDGMENT

This work was supported by College of Science Start-Up Grants (to P.W.H.C. and H.H.) from Nanyang Technological University (NTU) and a Science and Engineering Research Council Grant (092 101 0053, to P.W.H.C.) from A*STAR, Singapore. An Undergraduate Research Experience on Campus stipend (to M.J.K.) from NTU is also gratefully acknowledged. We thank Dr. Yong-xin Li of this Division for providing the X-ray crystallographic data reported in this work and the High Performance Computing Centre at NTU for computing resources.

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