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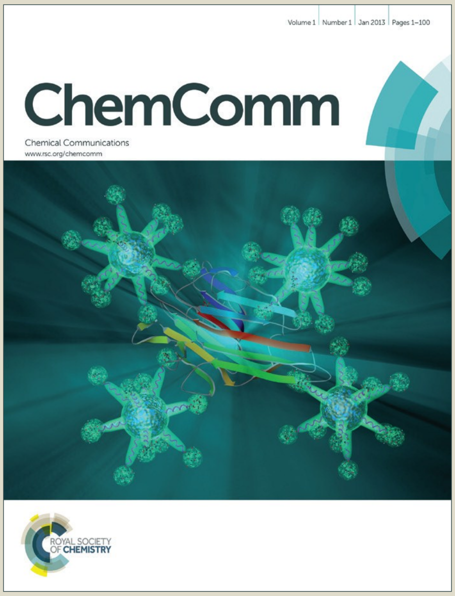

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# Gold-Catalyzed Cyclization of 1,6-Diynyl Dithioacetals via 1,7-Carbene Transfer and Aromatic C-H Functionalization

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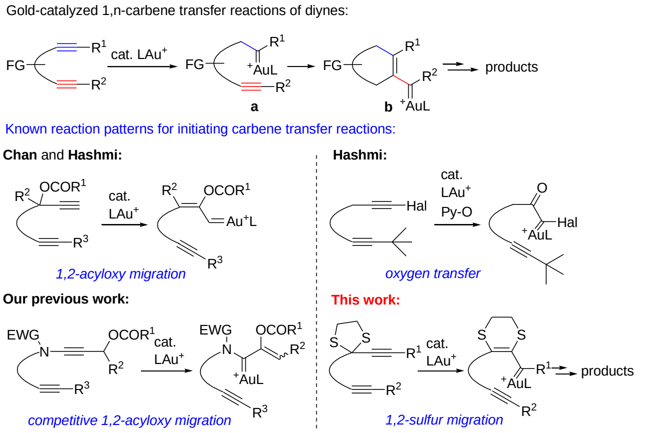
**A gold-catalyzed cyclization of 1,6-diynyl dithioacetals has been developed, which provides an attractive route to diverse-substituted benzo[*a*]fluorene derivatives. The reaction is initiated through 1,2-sulfur migration of propargyl dithioacetal moiety to generate a vinyl gold carbene, which is followed by carbene transfer to the remaining alkyne and aromatic substitution to furnish the fused products in generally good to high yields.**

In recent years, gold-catalyzed reactions involving gold-carbenes have attracted considerable attention since they serve as highly reactive intermediates in the construction of diversely functionalized structures.[1] Particularly, gold-catalyzed carbene transfer reactions of 1,n-diynes have emerged as one of the new and atom-economical methodologies for the synthesis of fused polycyclic architectures.[2-3] These reactions are initiated through the selective activation of one of the alkynes by gold catalyst to trigger an efficient generation of a gold-carbene intermediate **a**, which are followed by carbene transfer across the second alkyne to give a new type of alkenyl gold-carbene **b**, possibly via the formation of a cyclopropene intermediate (Scheme 1). These methods are highly attractive in the development of domino-type reactions since these processes allow the sequential formation of two gold-carbene species, which can mediate multiple C-C bond formations in an efficient way. So far three strategies have been developed to initiate the carbene transfer reactions in this area. Chan[2a,d] and Hashmi[2c,e] et al. demonstrated that a 1,2-acyloxy migration of propargyl esters can be utilized to initiate the formation of gold-carbene. Hashmi et al. found that gold-carbenes generated through oxygen-transfer from *N*-oxides could be transferred to a tethered alkyne, and the reactions were terminated by alkyl migration or sp$^3$ C-H insertion.[2b] We have reported a gold-catalyzed cycloisomerization of 1,6-diynes containing an ynamide propargyl ester moiety via a competitive 1,2-acyloxy migration followed by [3+2] cycloaddition.[2f] However, these reactions usually require special substituted alkynes such as terminal alkynes, halo- or $^t$Bu-substituted alkynes or ynamides. Therefore, the development of a strategy that utilization of an efficient method to induce the gold-carbene formation with high chemo- and regioselectivities and with a wide reaction scope is still highly desired. Recently, we have developed a gold-catalyzed ring-expansion of heterocycle-ynes involving generation of gold-carbene intermediates through 1,2-sulfur migration.[4] Inspired by these results and during our continuous interest in gold-catalyzed reactions of 1,n-diynes,[5] we envisioned that it might be possible to achieve the carbene transfer reactions of 1,n-diynes via 1,2-sulfur migration as the initiating step, which may provide new reaction patterns of the putative gold-carbene species and allow the efficient access to diversely functionalized polycycles. 1,2-Sulfur migration reactions have also been described in gold catalysis by Wang[6] and Toste[7] et al for the synthesis of indenes or vinyl sulfides. Herein, we report our success on gold-catalyzed cycloisomerization of 1,6-diynyl dithioacetals. The resultant gold-carbene undergoes the formal aromatic C-H insertion to furnish the benzo[*a*]fluorene derivatives, which are important classes of compounds that can be applied in medicinal chemistry.[8] It was also noted that there are only limited methods for the synthesis of benzo[*a*]fluorenes.[9]



**Scheme 1.** Gold-catalyzed carbene transfer reactions of diynes

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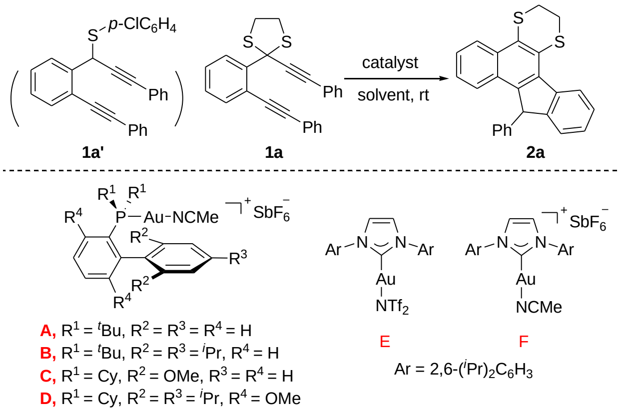
To test our hypothesis, we initially focused on the carbene-transfer reaction of 1,6-diynyl sulfide **1a'** in the presence of 5 mol% Johnphos(MeCN)AuSbF$_6$ (catalyst **A**) in THF (Table 1). However, no reaction occurred even heating the reaction mixture up to 80 °C. To our delight, when 1,6-diynyl dithioacetal **1a** was employed, the polycyclized 11-phenyl-11*H*-benzo[*a*]fluorene **2a** with an expanded thio-containing heterocycle was formed efficiently at room temperature in 84% yield within 1 h (Table 1, entry 1). The results indicated that an efficient 1,2-sulfur migration reaction occurred during the process. Next, the effect of different phosphine ligands on gold catalysts was examined. While both of the $^t$BuXphos and SPhos showed high catalytic activities, the latter enabled the reaction to be completed within a shorter period (1 h) and with an improved product yield (90%, entries 2-3). The use of more crowded Brettphos resulted in the formation of **2a** in a lower yield with a longer reaction time (24 h, 59%, entry 4). PPh$_3$AuSbF$_6$ formed in situ provided **2a** in a moderate yield of 51% after stirring for 21 h (entry 5). The gold-*N*-heterocyclic-carbene (NHC) complexes **E** and **F** were tested, which afforded **2a** in 84% and 56% yields, respectively (entries 6-7). Gold(III) complex of PicAuCl$_2$ (dichloro(2-pyridinecarboxylato)gold) and AuCl$_3$ could also catalyze this transformation to give **2a** in 56% and 77% yields, respectively (entries 8-9). The reaction also proceeded in various solvents such as DCM, DCE, MeCN and toluene, and the yields of **2a** were in the range of 68-85% (entries 10-13). The use of SPhosAuCl or AgSbF$_6$ alone led to a partial decomposition of the substrate with the prolonging of the reaction time, while the desired **2a** was not observed (entries 14-15).

**Table 1**. Optimization of reaction conditions.



| entry | catalyst (mol%) | solvent | time (h) | yield (%)[a] |
|---|---|---|---|---|
| 1 | **A** (2) | THF | 1 | 84 |
| 2 | **B** (2) | THF | 10 | 81 |
| 3 | **C** (2) | THF | 1 | 90 |
| 4 | **D** (2) | THF | 24 | 59 |
| 5 | PPh$_3$AuCl/AgSbF$_6$ (5) | THF | 21 | 51 |
| 6 | **E** (2) | THF | 11 | 84 |
| 7 | **F** (2) | THF | 25 | 56 |
| 8 | PicAuCl$_2$ (2) | THF | 26 | 56 |
| 9 | AuCl$_3$ (5) | THF | 11 | 77 |
| 10 | **C** (2) | DCM | 1 | 85 |
| 11 | **C** (2) | DCE | 1 | 83 |
| 12 | **C** (2) | MeCN | 1 | 79 |
| 13 | **C** (2) | toluene | 1 | 68 |
| 14 | SPhosAuCl (2) | THF | 26 | 0 (87) |
| 15 | AgSbF$_6$ (5) | THF | 21 | 0 (70) |

[a] Isolated yields. The yields of the recovered **1a** are shown in parentheses.

With optimized reaction conditions established (Table 1, entry 3), we then examined the substrate scope of this carbene transfer reaction. The results are shown in Table 2. The effect of aryl substituents on R$^1$ group was first evaluated. Electron-withdrawing groups such as *p*-F and *p*-Cl on the aryl rings tolerated well in the reaction, furnishing **2b** and **2c** in 88% and 77% yields, respectively. Stronger electron-withdrawing groups such as *p*-CO$_2$Me and *p*-CF$_3$ resulted in the formation of **2d** and **2e** in lower yields of 65-71%, possibly due to the reduced nucleophilicity of these aryl rings. Substrates bearing electron-rich aryl substituents such as *p*-Me or 3,4,5-(MeO)$_3$ groups underwent cyclization reactions smoothly to give **2f** and **2g** in 85% and 82% yields, respectively. The reaction of 1-naphthyl-containing substrate **1h** proceeded very slowly in THF. However, the desired dibenzo[*a*,*g*]fluorene **2h** could be isolated in 45% yield within 2 h when switching the solvent to DCE and using 5 mol% gold catalyst. Next, the effect of R$^2$ substituents was examined. For aryl substituents, both of the electron-deficient and electron-rich substituents were compatible, leading to **2i**-**2k** in 79-85% yields. However, when R$^2$ was a propyl group, the desired **2l** was obtained in only 19% yield, along with 25% of **3l** derived from 1,2-C-H insertion of the gold-carbene intermediate. Employing $^t$Bu-substituted substrate **1m** resulted in the formation of indene product **4m** in good yield, while no desired benzo[*a*]fluorine was formed. This may be due to the steric hindrance of the $^t$Bu group, which prevent the carbene transfer to the $^t$Bu-substituted alkyne. In addition, the parent phenyl ring substituted with -Cl functionality (**1n**) was also suitable for this transformation, furnishing **2n** in 73% yield. The structure of benzo[*a*]fluorene products was confirmed by the X-ray crystallographic analyses of **2f**, **2g** and **2h**.[10]

Interestingly, the reaction outcome could be altered when diynes bearing certain electron-rich aryl ring at the terminus of the first alkyne were used as the substrates. For example, a methoxy group located at the *para*-position on aryl ring led to a mixture of benzo[*a*]fluorene **2o** and an unusual isomer **2o'** in which the MeO group located at the C-3 position in 87% combined yield with a ratio of 1.8:1 (eq 1). The ratio of **2o**: **2o'** could be changed to 1:1.4 by switching the gold catalyst to 5 mol% Johnphos(MeCN)AuSbF$_6$. It was noted that these two products could not be separated from each other through column chromatography. A single crystal was prepared from the mixture of **2o** and **2o'**. The X-ray crystallographic analysis indicated a statistically disordered isomer superposition of 80% **2o'** and 20% **2o**. Pure **2o** was obtained through repeated recrystallization and characterized by X-ray crystallographic analysis. In the case of $^t$Bu-substituted substrate **1p**, a 1*H*-cyclobuta[*a*]indene derivative **6** was obtained in 35% yield (eq 2). The appearance of a seven-membered thio-containing heterocycle in **6** indicated that a 1,3-sulfur migration occurred during the process. The formation of **6** can be rationalized

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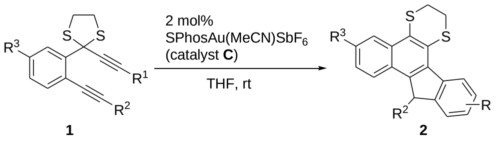
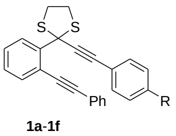
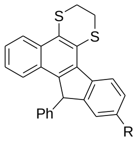
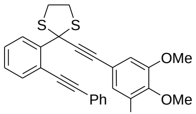
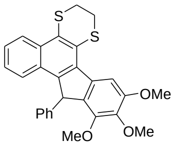
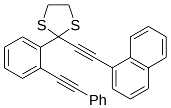
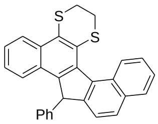
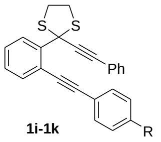
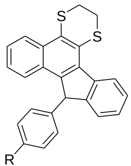
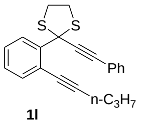
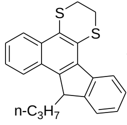
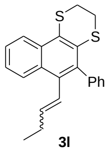
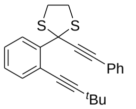
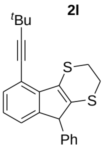
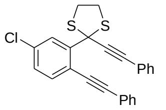
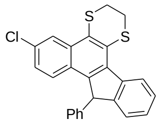
**Table 2**. Gold-catalyzed synthesis of benzo[*a*]fluorene derivatives.

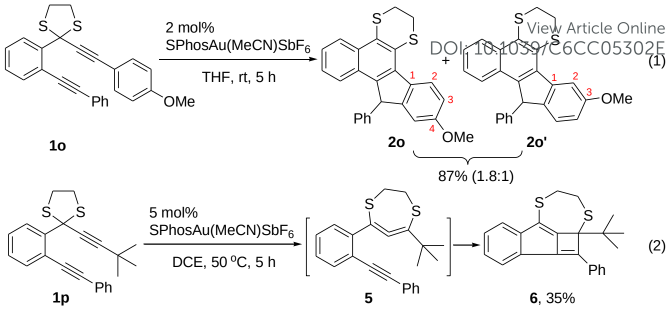


| Substrate | Product | | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
|  **1a-1f** |  | **2a**, R = H | 1 | 90 |
| | | **2b**, R = F | 1.5 | 88 |
| | | **2c**, R = Cl | 1 | 77 |
| | | **2d**, R = $CO_2Me$ | 4 | 65 |
| | | **2e**, R = $CF_3$ | 2 | 71 |
| | | **2f**, R = Me | 1 | 85 |
|  **1g** |  | **2g** | 4 | 82 |
|  **1h** |  | **2h** | 4.5 | 45[b] |
|  **1i-1k** |  | **2i**, R = Cl | 1.5 | 79 |
| | | **2j**, R = $CF_3$ | 3 | 85[b] |
| | | **2k**, R = MeO | 2 | 82 |
|  **1l** |  **2l** +  **3l** | | 13[c] | **2l**: 19<br>**3l**: 25 (*E*/*Z* = 1.8:1) |
|  **1m** |  | **4m** | 2 | 87[b] |
|  **1n** |  | **2n** | 1.5 | 73 |

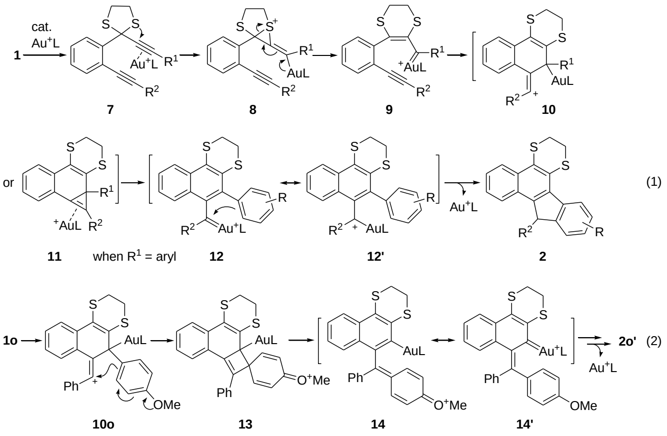
[a] Isolated yields. [b] Reaction was carried out in DCE catalyzed by 5 mol% catalyst **C**. [c] 5 mol% catalyst **C** was used.

through gold-catalyzed 1,3-sulfur migration of propargyl dithioacetals followed by formal [2+2] cycloaddition[11] of cyclic allene intermediate **5**. Wang et al. reported that a 1,3-sulfur migration could proceed from propargyl 1,3-dithianes.[6b] Our results demonstrated that propargyl dithioacetals might also underwent 1,3-sulfur migration to generate a higher strained 7-membered cyclic allene depending on the substitution pattern of the substrates.

We propose the following reaction mechanism for this novel transformation (Scheme 2, eq 1). The reaction is initiated by attack of the sulfur atom to the gold-activated alkyne followed by 1,2-sulfur migration to generate a gold-carbene species **9**. The gold-carbene moiety in **9** undergoes further reaction with



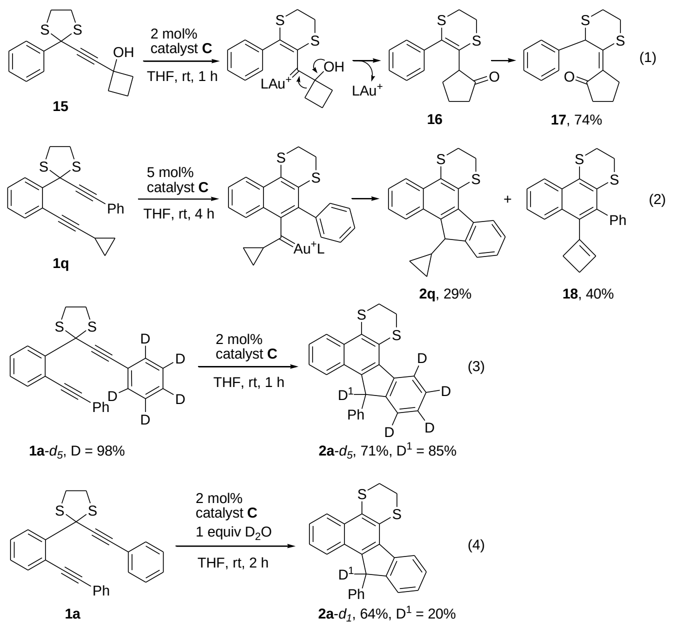
the remaining alkyne to produce a new gold carbene **12** or cation **12′**. The detailed reaction pathway from **9** to **12/12′** is not clear yet, possibly a vinyl cationic species **10** or gold-coordinated cyclopropene intermediate **11** are involved. Subsequent nucleophilic attack of the phenyl ring to gold carbene in **12/12′** leads to the formal C-H insertion product **2**.[12] To account for the formation of **2o′** in the case of *para*-MeO-substituted aryl alkyne **1o**, a possible reaction pathway is shown in Scheme 2, eq 2. Due to the stronger nucleophilicity of the methoxyphenyl group, it may attack the vinyl cation in **10o** to give a spirocyclic intermediate **13**. This is followed by cyclobutene ring-opening to give an intermediate **14** or generation of a gold carbene **14′**. These two structures are possibly in resonance. Subsequent ring-closure from **14** or **14′** and 1,3-H migration affords **2o′**.



**Scheme 2.** Possible reaction mechanism

To verify the intermediacy of the proposed gold-carbenes, we envisioned that the substrates terminated with a cycloalkane could be employed to trigger an efficient ring-expansion reaction of the resulting gold-carbene species. Therefore, the reaction of propargyl dithioacetal **15** bearing a cyclobutanol moiety catalyzed by 5 mol% of catalyst **C** was examined. The ring-enlarged product **17** was indeed formed in 74% yield as a single *E*-isomer (eq 1). It was noted that **17** was derived from the initially generated cyclopentanone **16** via double bond isomerization. Additionally, gold-catalyzed cyclization of **1q** with a cyclopropyl ring[13] afforded the desired benzo[*a*]fluorene **2q** along with a cyclobutene product **18** (eq

2). These results supported our assumption that two gold carbene species were possibly involved in the process. We also prepared the deuterium-labeled diyne **1a**-$d_5$ bearing five deuterium atoms on the aromatic ring in order to probe the mechanism of C-H insertion process. It was found that one of the deuterium moved to the bridged carbon on five-membered ring in product **2a**-$d_5$ (eq 3). In this case, the deuterium incorporation of $D^1$ decreased to 85%. The results indicated that a small amount of water existed in the reaction mixture might also participate the hydrogen transfer process. In fact, addition of 1.0 equiv $D_2O$ to non-deuterated **1a** led to 20% deuterium incorporation at the bridged carbon in **2a**-$d_1$ (eq 4). The exchange of H and D from non-deuterated product **2a** was excluded based on the results of the reaction of **2a** with $D_2O$ under gold-catalyzed conditions.[14] These results implied that the aromatic C-H-insertion process occurred stepwisely in an intermolecular manner through the electrophilic aromatic substitution.[12a-b,15]



**Scheme 3.** Mechanistic studies

In summary, we have developed a gold-catalyzed 1,7-carbene transfer reaction of 1,6-diynyl dithioacetals to benzo[*a*]fluorenes. 1,2-Sulfur migration is utilized to initiate the first gold-carbene formation. Subsequent carbene transfer followed by aromatic substitution furnishes the fused products in generally good to high yields. The postulated gold-carbene intermediates were supported by ring-expansion reactions. Deuterium-labeling experiments indicated that C-H functionalization of aromatic ring occurred stepwisely, possibly via electrophilic aromatic substitution. Further application of this reaction mode to other diyne systems is currently ongoing in our laboratory.

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10 CCDC-1481264 (catalyst **C**), 1485534 (**2f**), 1485536 (**2g**), 1485535 (**2h**), 1481261 (**2o**), 1481263 (**2o** and **2o'**), 1481258 (**6**) and 1481260 (**17**) contain the supplementary crystallographic data for this paper.
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14 See supporting information.
15 An intermolecular kinetic isotope effect (KIE) of $k_H/k_D$ = 1.1 was observed using **1a** and **1a**-$d_5$ as the substrates, implying that the C-H bond cleavage at the phenyl ring is likely not involved in the rate-determining step. See supporting information for detail.