

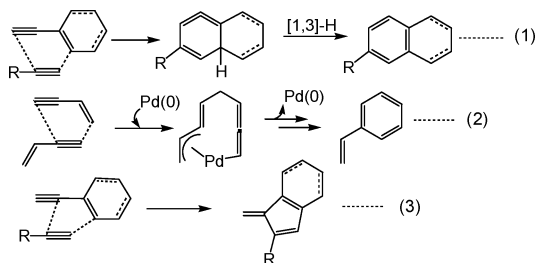
## Gold-Catalyzed Intramolecular [3 + 2]-Cycloaddition of Arenyne-Yne Functionalities

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The reactions of enynes (or arenynes) with alkynes were thermally achieved in [4 + 2]-cycloaddition mode, and both theoretic calculation and experimental results support the involvement of a strained cyclic allene as reaction intermediate (eq 1).<sup>1</sup> Such reactions normally require drastic temperatures (>300 °C) for unactivated alkynes (eq 1, R ≠ cyano, ester, aldehyde, and ketone)<sup>1a</sup> unless a metal catalyst is employed.<sup>2</sup> Yamamoto and Gevorgyan reported the use of Pd(0) catalysts to implement the [4 + 2]-dimerization of enynes at low temperatures ( $T < 100$  °C), and the key step is thought to involve the oxidative dimerization of enynes to form Pd-allyl intermediates (eq 2). To the best of our knowledge, there is no precedent for the efficient [3 + 2]-cycloaddition of enynes (or arenynes) with alkynes in both inter- and intramolecular processes (eq 3).<sup>3</sup> Here, we report realization of an intramolecular [3 + 2]-cycloaddition of unactivated arenyne-yne (or enyne-yne) functionalities with gold catalysts (eq 3), which implement most cycloadditions at ambient conditions.



Stimulated by a report by Echavarren that cationic gold species efficiently catalyzed the [4 + 2]-cycloaddition of arenyne-ene functionalities at 23 °C,<sup>4</sup> we investigated the cyclization of diyne **1** using AuPPh<sub>3</sub>SbF<sub>6</sub> and related gold species. Table 1 shows the catalytic results of several active metal complexes. PPh<sub>3</sub>AuSbF<sub>6</sub> (2 mol %)<sup>5</sup> is superior to PtCl<sub>2</sub> (5 mol %, 100 °C) not only in the production of cyclized species **2** with better yield but also under more mild conditions (23 °C, entry 2). The structure of species **2** is confirmed to have a [3 + 2]-cycloadduct framework.<sup>6</sup> No catalytic activities were observed for AuClPPh<sub>3</sub>/AgOTf, AuCl, AuCl<sub>3</sub>, and AgSbF<sub>6</sub> (5 mol % each) at 23 °C in toluene or CH<sub>2</sub>Cl<sub>2</sub>, but these complexes gave a mixture of species **2** and [4 + 2]-cycloadduct **3** in hot toluene or dichloroethane (DCE) with poor efficiencies (entries 3–6).

We examined further the scope of the [3 + 2]-cycloaddition with alternation of the functionalities and skeletal chain of diyne substrates **4–16**; the results are depicted in Table 2. Most reactions were achieved with PPh<sub>3</sub>AuSbF<sub>6</sub> (2 mol %) in CH<sub>2</sub>Cl<sub>2</sub> (23 °C) except substrates **11** and **13** (entries 8 and 10), for which we used PtCl<sub>2</sub> and PPh<sub>3</sub>AuOTf,<sup>7</sup> respectively. Entries 1–7 show the compatibility of this cycloaddition with diynes **4–10** bearing various functional groups, including tosylamide, ester, ketone, phenylsulfonyle, methylene, and fluorenyl groups; the resulting [4.3.0]-cycloadducts **17–23** were obtained in satisfactory yields (61–90%). The structure of compound **18** has been confirmed by X-ray diffraction study.<sup>8</sup> The value of this cyclization is demonstrated by

**Table 1.** Catalytic [3 + 2]-Cycloaddition over Various Catalysts

catalyst <sup>a</sup>	solvent (conditions)	yield
PtCl <sub>2</sub>	toluene (100 °C, 12 h)	<b>2</b> (51%)
AuCIPPh <sub>3</sub> /AgSbF <sub>6</sub>	CH <sub>2</sub> Cl <sub>2</sub> (23 °C, 0.5 h)	<b>2</b> (93%)
AuCIPPh <sub>3</sub> /AgOTf	DCE (50 °C, 6 h)	<b>2</b> (18%), <b>3</b> (2%)
AuCl	toluene (100 °C, 24 h)	<b>2</b> (3%), <b>3</b> (14%)
AuCl <sub>3</sub>	toluene (100 °C, 24 h)	<b>2</b> (14%), <b>3</b> (15%)
AgSbF <sub>6</sub>	toluene (100 °C, 24 h)	<b>2</b> (6%), <b>3</b> (30%)

<sup>a</sup> 5 mol % of PtCl<sub>2</sub>, AuCIPPh<sub>3</sub>/AgOTf, AuCl, AuCl<sub>3</sub>, AgSbF<sub>6</sub>, and 2 mol % of AuCIPPh<sub>3</sub>/AgSbF<sub>6</sub>, [diyne] = 0.40 M. <sup>b</sup> Products were separated from a silica column.

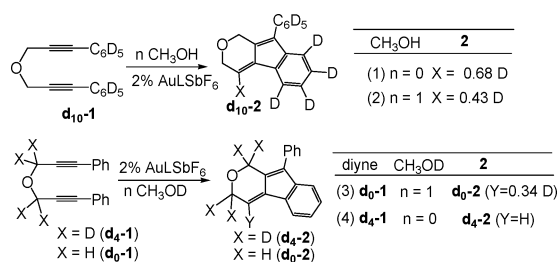
**Table 2.** Catalytic Intramolecular [3 + 2]-Cycloaddition of Diynes

diynes	products (yields)	catalyst (temp, time)
		[AuL]SbF <sub>6</sub> (23 °C, 3 h)
X = NTs ( <b>4</b> )	<b>17</b> (61%)	[AuL]SbF <sub>6</sub> (23 °C, 3 h)
X = C(CO <sub>2</sub> Me) <sub>2</sub> ( <b>5</b> )	<b>18</b> (90%)	[AuL]SbF <sub>6</sub> (23 °C, 3 h)
X = C(OMe)(CO <sub>2</sub> Et) ( <b>6</b> )	<b>19</b> (81%)	[AuL]SbF <sub>6</sub> (23 °C, 3 h)
X = C(COPh)(CO <sub>2</sub> Et) ( <b>7</b> )	<b>20</b> (78%)	[AuL]SbF <sub>6</sub> (23 °C, 3 h)
X = C(SO <sub>2</sub> Ph) <sub>2</sub> ( <b>8</b> )	<b>21</b> (81%)	[AuL]SbF <sub>6</sub> (23 °C, 12 h)
X = CH <sub>2</sub> ( <b>9</b> )	<b>22</b> (72%)	[AuL]SbF <sub>6</sub> (23 °C, 5 h)
X =  ( <b>10</b> )	<b>23</b> (80%)	[AuL]SbF <sub>6</sub> (23 °C, 0.5 h)
		PtCl <sub>2</sub> (100 °C, 5 h)
<b>11</b>	<b>24</b> (64%)	
		[AuL]SbF <sub>6</sub> (23 °C, 3 h)
<b>12</b>	<b>25</b> (73%)	
		[AuL]OTf (100 °C, 23 h)
<b>13</b>	<b>26</b> (51%)	
		[AuL]SbF <sub>6</sub> (23 °C, 12 h)
R = OMe ( <b>14</b> )	<b>27</b> (71%), <b>A=B</b>	
R = H ( <b>15</b> )	<b>28 A</b> (37%), <b>28 B</b> (37%)	[AuL]SbF <sub>6</sub> (23 °C, 12 h)
R = CH <sub>3</sub> ( <b>16</b> )	<b>29 A</b> (47%), <b>29 B</b> (13%)	[AuL]SbF <sub>6</sub> (23 °C, 12 h)

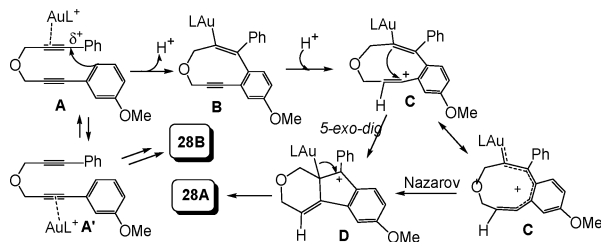
<sup>a</sup> [Diene] = 0.4 M. <sup>b</sup> Product yields are given after separation from a silica column. <sup>c</sup> L = PPh<sub>3</sub>, catalyst loading: 2 mol % of LAuCl/AgSbF<sub>6</sub> (CH<sub>2</sub>Cl<sub>2</sub>), 5 mol % of PtCl<sub>2</sub> (toluene) and LAuCl/AgOTf (dioxane).

its applicability to construct a strained bicyclic [3.3.0] framework, such as species **24** (64% yield), via PtCl<sub>2</sub>-catalyzed cyclization of enediyne **11** in hot toluene (entry 8). This method is further extensible to a [3 + 2]-dimerization of arenyne-enyne and enyne-

Scheme 1



Scheme 2



enyne functionalities as represented by diynes **12** and **13**, which gave bicyclic [4.3.0] products **25** (73%) and **26** (51%) using  $\text{PPh}_3\text{AuSbF}_6$  (2%) and  $\text{PPh}_3\text{AuOTf}$  (5%), respectively. Structural elucidation of tetracyclic species **24** relies on  $^1\text{H}$  NOE spectra.<sup>8</sup> We examined the cyclization regioselectivity of diynes **14**–**16** bearing two different phenyl groups. The two isomeric products **28A**–**28B** and **29A**–**29B** were separable on a silica column. The C(2) carbons of the 3-methoxyphenyl groups of diynes **15** and **16** are thought to be inactive because of steric hindrance. For diyne **15**, the observed product ratio **28A**/**28B** = 1 is indicative of a 2:1 site activity for its 3-methoxyphenyl C(6) carbon versus the phenyl C(2) carbon. The preference for alkenylation at the 3-methoxyphenyl C(6) carbon of diyne **16** is also inferred from the product ratio **29A**/**29B** = 3.6. The structures of compounds **28A**–**29A** were confirmed by  $^1\text{H}$  NOE effects.<sup>8</sup>

We performed deuterium-labeling experiments to elucidate the cycloaddition mechanism. As shown in Scheme 1, diyne **d10-1** bearing  $\text{C}_6\text{D}_5$  produced cycloadduct **2** with 68% deuterium content at its alkenyl carbon. This deuterium content was decreased to 43% when methanol (1.0 equiv) was present.<sup>9</sup> For undeuterated **d0-1**, its corresponding product **d0-2** contained 34% deuterium content at its olefin carbon in the presence of  $\text{CH}_3\text{OD}$  (1.0 equiv, entry 3). No deuterium is scrambled into the alkenyl hydrogen of cycloadduct **d4-2** if diyne **d4-1** was used (entry 4).

Scheme 2 shows our mechanistic speculation to rationalize the preferable [3 + 2]-pathway of this gold-based catalysis. The preference for formation of regioisomer **28A** from diyne **15** suggests that this cyclization is initiated by nucleophilic attack of the 3-methoxyphenyl substituent of intermediate **A** at its Au(I)-containing  $\pi$ -alkyne moiety, to produce vinylgold(I) intermediate **B** with loss of a proton. As 2,6-lutidine acts as an inhibitor,<sup>10</sup> we propose that the electron-rich AuL fragment of species **B** greatly favors protonation at the alkyne functionality to generate vinyl-cationic intermediate **C**, which is subsequently stabilized by the adjacent phenyl group and the vinylgold fragment through a pentadiene cationic delocalization. Such a cationic resonance leads to either a 5-*exo-dig* or Nazarov cyclization of species **C** to give diphenyl carbocation **D**, ultimately leading to formation of major isomer **28A**. This proposed pathway is also supported by the deuterium labeling results depicted in Scheme 2.<sup>11,12</sup>

In summary, we report a new efficient intramolecular [3 + 2]-cycloaddition of unactivated arenyne (or enyne)-yne function-

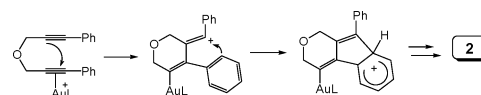
alities, catalyzed mainly by the  $\text{AuPPh}_3\text{SbF}_6$  complex (2 mol %) under ambient conditions. The value of this cyclization is reflected by its applicability to a wide range of diyne substrates bearing various functional groups.<sup>13</sup>

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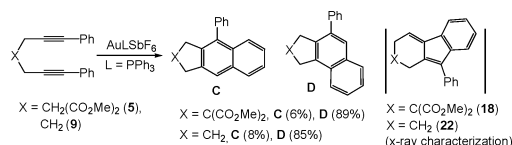
**Supporting Information Available:** Experimental procedures, X-ray data of [3 + 2]-cycloadduct **18**, spectral data, and NMR spectra of key compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (1) For selected examples, see: (a) Burell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 4218. (b) Dunez, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776 and references therein. (c) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917. (d) Rodriguez, D.; Fernanda, M.; Esperon, M.; Navarro-Vázquez, A.; Castedo, L.; Dominguez, D.; Saá, C. *J. Org. Chem.* **2004**, *69*, 3842. (e) González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, *63*, 2854.
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- (3) Danheiser reported a [4 + 2]-cycloaddition of ynone-ynes, which undergoes thermal rearrangement to form a 3-alkenylfuran species. Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.
- (4) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.
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- (6)  $\text{H}_2\text{PtCl}_4$  (5%) and Aliquat 336 were reported to catalyze the transformation of species **1** into [3 + 2]-cycloadduct **2** in 26% yield. See: Badrieh, Y.; Blum, J.; Vollhardt, K. P. C. *J. Mol. Catal.* **1990**, *60*, 323.
- (7) In contrast with  $\text{AuPPh}_3\text{SbF}_6$ , heating  $\text{AuPPh}_3\text{OTf}$  and diyne **13** in 1,4-dioxane (100 °C, 24 h) did not form a gold mirror in this example.
- (8)  $^1\text{H}$  NOE map of key compounds and X-ray data of cycloadduct **18** are provided in Supporting Information.
- (9) In this case, the use of methanol (1.0 equiv) led to formation of byproduct via alkyne hydration, and the desired cyclized **2** was obtained in 51% yield. Water acts an inhibitor for this catalytic reaction.
- (10) In the cyclization of diyne **1**, 2,6-lutidine (5 mol %) completely inhibits this  $\text{PPh}_3\text{AuSbF}_6$ -based catalysis. The inhibition role of 2,6-lutidine is thought to intercept the proton to avoid the formation of intermediate **C**.
- (11) As suggested by one reviewer, the present data also support an alternative reaction mechanism as depicted below.



- (12) A proposed mechanism to rationalize formation of a [4 + 2]-cycloadduct by Au(I) species is provided in Supporting Information; see Scheme S-1.
- (13) Shibata reported formation of skeletally rearranged cycloadducts **D** (85–89%) from diynes **5** and **9** using  $\text{AuPPh}_3\text{SbF}_6$  catalyst (0 °C, 5 h). Following their reported procedures, we still obtained [3 + 2]-cycloadducts **18** and **22** in 85% and 67% yields, respectively, from diynes **5** and **9** in addition to [4 + 2]-cycloadducts **C** (3–5%). The X-ray structure of cycloadduct **18** supports our structural assignment. See: Shibata, T.; Fujiwara, R.; Takano, D. *Synlett.* **2005**, 2062.



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