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

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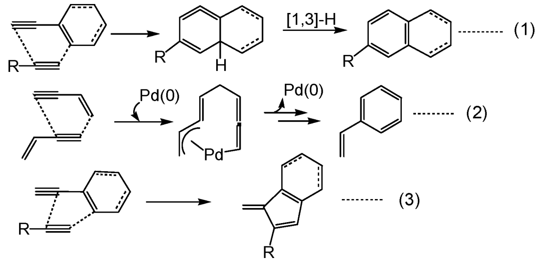
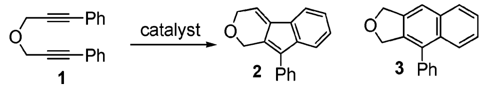
The reactions of enynes (or arenynes) with alkynes were thermally achieved in [4 + 2]-cycloaddition mode, and both theoretic calculation and experimental results support the involvement of a strained cyclic allene as reaction intermediate (eq 1).[1] Such reactions normally require drastic temperatures (>300 °C) for unactivated alkynes (eq 1, R ≠ cyano, ester, aldehyde, and ketone)[1a] unless a metal catalyst is employed.[2] 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).[3] 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,[4] we investigated the cyclization of diyne **1** using $AuPPh_3SbF_6$ and related gold species. Table 1 shows the catalytic results of several active metal complexes. PPh_3AuSbF_6 (2 mol %)[5] is superior to $PtCl_2$ (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.[6] No catalytic activities were observed for $AuClPPh_3$/AgOTf, AuCl, $AuCl_3$, and $AgSbF_6$ (5 mol % each) at 23 °C in toluene or CH_2Cl_2, 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_3AuSbF_6 (2 mol %) in CH_2Cl_2 (23 °C) except substrates **11** and **13** (entries 8 and 10), for which we used $PtCl_2$ and PPh_3AuOTf,[7] respectively. Entries 1−7 show the compatibility of this cycloaddition with diynes **4**−**10** bearing various functional groups, including tosylamide, ester, ketone, phenylsulfonyl, 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.[8] The value of this cyclization is demonstrated by its applicability to construct a strained bicyclic [3.3.0] framework, such as species **24** (64% yield), via $PtCl_2$-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−

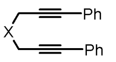
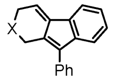
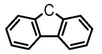
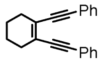
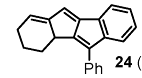
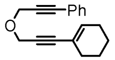
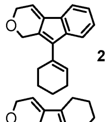
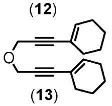
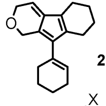
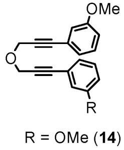
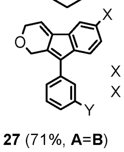
Table 1. Catalytic [3 + 2]-Cycloaddition over Various Catalysts



catalyst[a]	solvent (conditions)	yield
$PtCl_2$	toluene (100 °C, 12 h)	**2** (51%)
$AuClPPh_3/AgSbF_6$	CH_2Cl_2 (23 °C, 0.5 h)	**2** (93%)
$AuClPPh_3$/AgOTf	DCE (50 °C, 6 h)	**2** (18%), **3** (2%)
AuCl	toluene (100 °C, 24 h)	**2** (3%), **3** (14%)
$AuCl_3$	toluene (100 °C, 24 h)	**2** (14%), **3** (15%)
$AgSbF_6$	toluene (100 °C, 24 h)	**2** (6%), **3** (30%)

[a] 5 mol % of $PtCl_2$, $AuClPPh_3$/AgOTf, AuCl, $AuCl_3$, $AgSbF_6$, and 2 mol % of $AuClPPh_3/AgSbF_6$, [diyne] = 0.40 M. [b] Products were separated from a silica column.

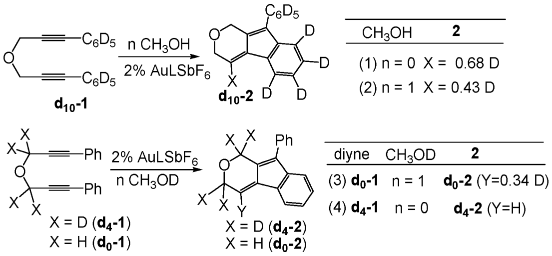
Table 2. Catalytic Intramolecular [3 + 2]-Cycloaddition of Diynes

diynes	products (yields)	catalyst (temp, time)
		
X = NTs (**4**)	**17** (61%)	$[AuL]SbF_6$ (23 ^{0}C, 3 h)
X = $C(CO_2Me)_2$ (**5**)	**18** (90%)	$[AuL]SbF_6$ (23 ^{0}C, 3 h)
X = $C(COMe)(CO_2Et)$ (**6**)	**19** (81%)	$[AuL]SbF_6$ (23 ^{0}C, 3 h)
X = $C(COPh)(CO_2Et)$ (**7**)	**20** (78%)	$[AuL]SbF_6$ (23 ^{0}C, 3 h)
X = $C(SO_2Ph)_2$ (**8**)	**21** (81%)	$[AuL]SbF_6$ (23 ^{0}C, 12 h)
X = CH_2 (**9**)	**22** (72%)	$[AuL]SbF_6$ (23 ^{0}C, 5 h)
X =  (**10**)	**23** (80%)	$[AuL]SbF_6$ (23 ^{0}C, 0.5 h)
 (**11**)	 **24** (64%)	$PtCl_2$ (100 ^{0}C, 5 h)
 (**12**)	 **25** (73%)	$[AuL]SbF_6$ (23 ^{0}C, 3 h)
 (**13**)	 **26** (51%)	[AuL]OTf (100 ^{0}C, 23 h)
	 X = OMe, Y = R (**A**) X = R, Y = OMe (**B**)	
R = OMe (**14**)	**27** (71%, **A**=**B**)	$[AuL]SbF_6$ (23 ^{0}C, 12 h)
R = H (**15**)	**28 A** (37%), **28 B** (37%)	$[AuL]SbF_6$ (23 ^{0}C, 12 h)
R = CH_3 (**16**)	**29 A** (47%), **29 B** (13%)	$[AuL]SbF_6$ (23 ^{0}C, 12 h)

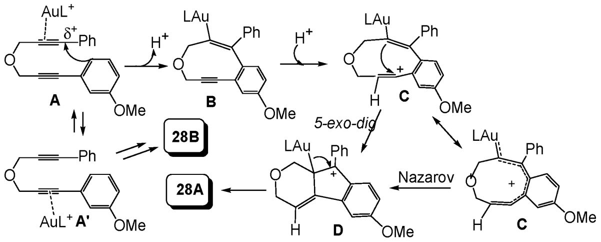
[a] [Diyne] = 0.4 M. [b] Product yields are given after separation from a silica column. [c] L = PPh_3, catalyst loading: 2 mol % of $LAuCl/AgSbF_6$ (CH_2Cl_2), 5 mol % of $PtCl_2$ (toluene) and LAuCl/AgOTf (dioxane).

10.1021/ja0643826 CCC: $33.50

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 PPh_3AuSbF_6 (2%) and PPh_3AuOTf (5%), respectively. Structural elucidation of tetracyclic species **24** relies on ^1H NOE spectra.[8] 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 ^1H NOE effects.[8]

We performed deuterium-labeling experiments to elucidate the cycloaddition mechanism. As shown in Scheme 1, diyne **d_{10}-1** bearing C_6D_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.[9] For undeuterated **d_0-1**, its corresponding product **d_0-2** contained 34% deuterium content at its olefin carbon in the presence of CH_3OD (1.0 equiv, entry 3). No deuterium is scrambled into the alkenyl hydrogen of cycloadduct **d_4-2** if diyne **d_4-1** 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 π-alkyne moiety, to produce vinylgold(I) intermediate **B** with loss of a proton. As 2,6-lutidine acts as a inhibitor,[10] we propose that the electron-rich AuL fragment of species **B** greatly favors protonation at the alkyne functionality to generate vinylcationic 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 Nazazov 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.[11,12]

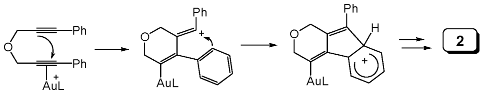
In summary, we report a new efficient intramolecular [3 + 2]-cycloaddition of unactivated arenyne (or enyne)-yne functionalities, catalyzed mainly by the $AuPPh_3SbF_6$ complex (2 mol %) under ambient conditions. The value of this cyclization is reflected by its applicability to a wide range of diyne substrates bearing various functional groups.[13]

Acknowledgment. The authors thank Prof. Wang Sue-Lein for X-ray diffraction study, as well as the National Science Council, Taiwan, for support of this work.

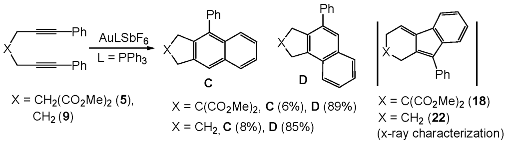
Supporting Information Available: Experimental procedures, X-ray data of [3 + 2]-cycloadduct **18**, spectral data, and NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(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) Dunetz, 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.
(2) For metal-catalyzed [4 + 2]-cycloadditions of enynes with alkynes, see selected reviews and the most recent paper: (a) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Rubina, M.; Conley, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 5828 and references therein.
(3) Danheiser reported a [4 + 2]-cycloaddition of ynones-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.
(5) For recent examples using $AuPPh_3SbF_6$ as π-alkyne activators, see ref 4 and: (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (c) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802. (d) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (e) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (f) Yang, C.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. (g) Munoz, M. P.; Adrio, J.; Carretero, C. J. *Organometallics* **2005**, *24*, 1293. (h) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.
(6) H_2PtCl_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 $AuPPh_3SbF_6$, heating $AuPPh_3OTf$ and diyne **13** in 1,4-dioxane (100 °C, 24 h) did not form a gold mirror in this example.
(8) ^1H 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 PPh_3AuSbF_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 $AuPPh_3SbF_6$ 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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