J|A|C|S
ARTICLES
Published on Web 12/13/2007

Gold(I)-Catalyzed Intramolecular [4+2] Cycloadditions of Arylalkynes or 1,3-Enynes with Alkenes: Scope and Mechanism

Cristina Nieto-Oberhuber,[†,‡] Patricia Pérez-Galán,[†] Elena Herrero-Gómez,[†] Thorsten Lauterbach,[†] Cristina Rodríguez,[†] Salomé López,[†] Christophe Bour,[†] Antonio Rosellón,[†] Diego J. Cárdenas,[‡] and Antonio M. Echavarren*[,†,‡]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain and Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

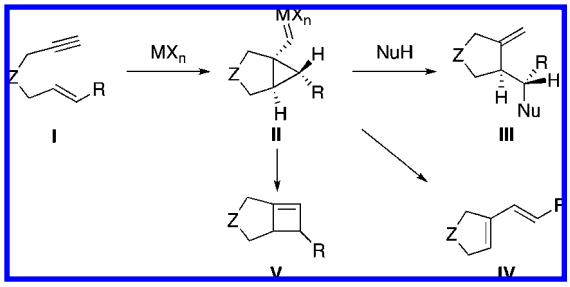
Received August 8, 2007; E-mail: aechavarren@iciq.es

Abstract: The cyclizations of enynes substituted at the alkyne gives products of formal [4+2] cyclization with Au(I) catalysts. 1,8-Dien-3-ynes cyclize by a 5-*exo-dig* pathway to form hydrindanes. 1,6-Enynes with an aryl ring at the alkyne give 2,3,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalenes by a 5-*exo-dig* cyclization followed by a Friedel−Crafts-type ring expansion. A 6-*endo-dig* cyclization is also observed in some cases as a minor process, although in a few cases, this is the major cyclization pathway. In addition to cationic gold complexes bearing bulky biphenyl phosphines, a gold complex with tris(2,6-di-*tert*-butylphenyl)phosphite is exceptionally reactive as a catalyst for this reaction. This cyclization can also be carried out very efficiently with heating under microwave irradiation. DFT calculations support a stepwise mechanism for the cycloaddition by the initial formation of an *anti*-cyclopropyl gold(I)-carbene, followed by its opening to form a carbocation stabilized by a π interaction with the aryl ring, which undergoes a Friedel−Crafts-type reaction.

Introduction

Enynes **I** react via the *5-exo-dig* pathway with electrophilic transition metal complexes or halides MX_n acting as catalysts to give a variety of cycloisomerization and addition derivatives via cyclopropyl metal carbenes **II** intermediates (Scheme 1).[1,2] Thus, reaction with nucleophiles R′OH (alcohols or water)[1,2] or electron-rich aromatic systems[3,4] gives products of type **III**, whereas in the absence of nucleophiles, dienes **IV** or, less commonly, cyclobutenes **V** can be obtained.[1,5,6] In addition to the nucleophilic attack at intermediates **II** to give products **III**, certain carbon nucleophiles also react at the carbene carbon[4] in a process that is similar to the intermolecular cyclopropanation

Scheme 1



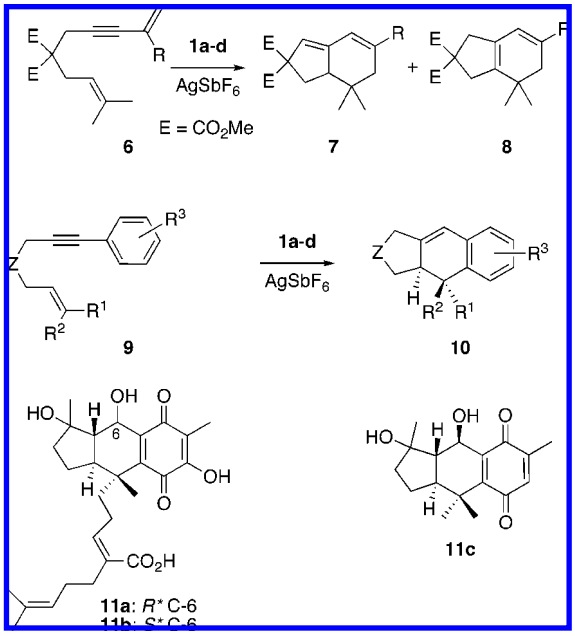
with alkenes catalyzed by gold(I).[7] Similar pathways take place in the gold(I)-cyclization of 1,5-[8] and 1,7-enynes.[9]

For some of these transformations, cationic complexes generated by chloride abstraction from [AuCl(PPh_3)] have proven to be very reactive catalysts.[10] However, enynes bearing

[†] Institute of Chemical Research of Catalonia (ICIQ).
[‡] Universidad Autónoma de Madrid.

(1) Reviews: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431−436. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. (d) Zhang, L.; Sunm, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271−2296. (e) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2−42. (h) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211.
(2) (a) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511−10520. (b) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2003**, *9*, 2627−2635. (c) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M. N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706−713. (d) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293−1300.
(3) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427−7430.
(4) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698−700.
(5) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638. (b) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647−3650. (c) Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050. (d) Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901−903. (e) Fürstner, A.; Szillat, H. F.; Gabor, B.; Mynott, R. *J. Am. Chem. Soc.* **1998**, *120*, 8305−8314. (f) Trost, G. A. Doherty, *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (g) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785−6786. (h) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863−11869. (i) Oi, S.; Tsukamoto, I.; Miyano, S.; Inoue, Y. *Organometallics* **2001**, *20*, 3704−3709. (j) Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433−4436. (k) Chatani, N.; Inoue, H.; Kotsuma, T.; Murai, S. *J. Am. Chem. Soc.* **2002**, *124*, 10294−10295. (l) Oh, C. H.; Bang, S. Y.; Rhim, C. Y. *Bull. Korean Chem. Soc.* **2003**, *24*, 887−888. (m) Peppers, B. P.; Diver, S. T. *J. Am. Chem. Soc.* **2004**, *126*, 9524−9525. (n) Miyanohana, Y.; Inoue, H.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 8541−8543. (o) Bajracharya, G. B.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 892−897.

Scheme 2



substituted alkynes, in particular those with an aryl group, are quite reluctant to undergo cycloisomerization and alkoxycyclization reactions.[2d,10a] We decided to prepare new gold(I) complexes bearing bulky, biphenyl-based phosphines **1a**−**d**, which have been shown by Buchwald et al. to be excellent ligands for Pd-catalyzed reactions.[11] Indeed, upon being mixed with Ag(I) salts, complexes **1a**−**d** lead to very active catalysts.[12] More convenient are cationic complexes **2a**−**b** and **3**,[6b] which are stable crystalline solids that can be handled under ordinary conditions, yet are very reactive as catalysts in a variety of transformations.[13,14,15] The structures of **1a**−**d**, **2a**−**b**, and **3** have been confirmed by X-ray crystallography.[16] Gold complexes with N-heterocyclic ligands have also been prepared.[12,17] These complexes bearing these highly donating ligands are of moderate

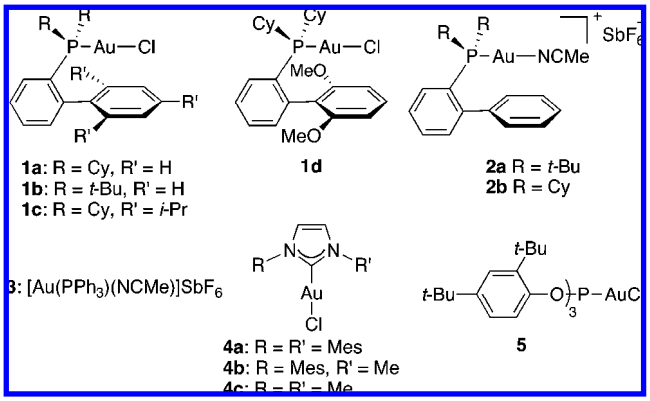


Figure 1.

electrophilicity and react with 1,6-enynes to form intermediates **II** that are less prone to undergo skeletal rearrangement, which allows their intermolecular trapping by alkenes to form cyclopropanes.[7] Recently, we have prepared new gold(I) complex **5** bearing tris(2,6-di-*tert*-butylphenyl)phosphite as a bulky ligand, whose cationic derivative formed in situ by chloride abstraction with $AgSbF_6$ is the most electrophilic Au(I) catalyst that we have tested thus far in reactions with substituted enynes (Figure 1).[7]

Cationic complexes formed in situ from **1a**−**d** catalyze the formal [4+2] cycloaddition of substituted dienynes **6** and arylenynes **9** under mild conditions (Scheme 2).[12] In contrast, the thermal intramolecular [4+2] cycloaddition of dienynes of type **6** has been described to proceed at temperatures as high as 600 °C,[18] although milder conditions (heating at 110−250 °C) are required for the intramolecular reaction of conjugated enynes with ynamines.[19] Reaction of substrates **9** to give **10** is of particular interest as pycnantuquinones A (**11a**) and B (**11b**)[20] have the carbon skeleton of tricyclic compounds **10**. These quinones have been isolated from an African tree and display antihyperglycemic activity in mice.[20] Recently, pycnantuquinone C (**11c**), a new member of this family, has been isolated from an alga.[21] Products somewhat related to **10** have been obtained by Grigg et al. by palladium-catalyzed intermolecular [2+2+2] cycloaddition reaction of enynes with aryl or vinyl halides[22] and by Ohno et al. by intramolecular Pd-catalyzed tandem cyclization of bromoenynes.[23] A different type of cyclization, in which the phenyl group participates in the process, has been observed in the gold-catalyzed cycloisomerization of allenynes.[24]

Here, we describe the scope and limitations of the gold-catalyzed [4+2] cycloaddition reaction. For this reaction, we have found that in addition to **1a**−**d** and **2a**−**b**, precatalyst **5** is exceptionally reactive. This cyclization is also substantially

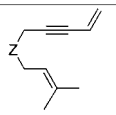
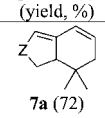
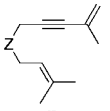
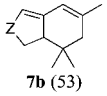
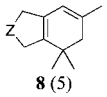
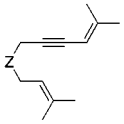
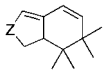
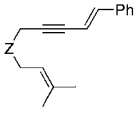
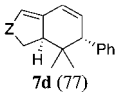
(6) (a) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146−6148. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 5916−5923. (c) Ferrer, C.; Raducan, M.; Nevado, C.; Claverie, C. K.; Echavarren, A. M. *Tetrahedron* **2007**, *63*, 6306−6316. (d) Cabello, N.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D.; Echavarren, A. M. *Eur. J. Org. Chem.* **2007**, 4217−4223.
(7) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029−6032.
(8) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141−1144.
(9) Cabello, N.; Rodríguez, C.; Echavarren, A. M. *Synlett* **2007**, 1753−1758.
(10) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. (b) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1677−1693.
(11) (a) Kaye, S.; Fox, J. M.; Hicks, F. A.; Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789−794. (b) Walker, S. D.; Border, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (c) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978−13980. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696. (e) Barder, T. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 5096−5101.
(12) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178−6179.
(13) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *11*, 1694−1702.
(14) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5451−5455.
(15) (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105−1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358−1373.
(16) Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455−5459.
(17) de Fremont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411−2418.
(18) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218−4219.
(19) (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776−5777. (b) See also: Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514−5515.
(20) Fort, D. M. *et al. J. Org. Chem.* **2000**, *65*, 6534−6539.
(21) Laird, D. W.; Poole, R.; Wikström, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671−674.
(22) Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157−160.
(23) (a) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 5103−5106. (b) Related cyclization of allenenes with aryl halides: Ohno, H.; Miyaura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2647−2650.

accelerated by heating the reactions in CH_2Cl_2 under microwave irradiation. We also report a DFT theoretical study on the mechanism of the reaction of arylenynes **9** that indicates that the [4+2] cycloaddition is a stepwise process, which occurs by opening of the initial cyclopropyl gold(I) carbenes to form a carbocation that undergoes a Friedel−Crafts-type reaction.

Experimental Results

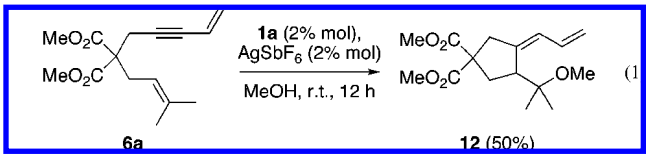
Cycloaddition of Dienynes. 1,8-Dien-3-yne **6a** reacts by a 5-*exo*-*dig* pathway[25] to give hydrindane **7a** with **1a**/$AgSbF_6$ as the catalyst (Table 1, entry 1). Similarly, **6b** gives **7b** along with regioisomeric diene **8** as a minor compound (Table 1, entry 2). The same ratio of **7b** and **8** (∼5:1) was obtained by using other Au(I) catalysts. Dienynes **6c** and **6d** also provided hydrindanes **7c** and **7d**, respectively (Table 1, entries 3−9). Diene **7d** was obtained as a single diastereoisomer, whose configuration was determined by NOESY. Hydrindanes **7c** and **7d** were obtained in short times and in good yields with **2a** under microwave heating (Table 1, entries 4, 7, and 9; see below) or with **5**/$AgSbF_6$ at room temperature (Table 1, entries 5 and 8).

Table 1. Au(I)-Catalyzed Cyclization of 1,8-Dien-3-ynes **7a**-**d** [Z = $C(CO_2Me)_2$][a]

entry	substrate	catalyst	time (min)	product(s) (yield, %)
1	 **6a**	**1a** / $AgSbF_6$	60	 **7a** (72)
2	 **6b**	**1a** / $AgSbF_6$	60	 **7b** (53) +  **8** (5)
3	 **6c**	**2a**	120	 **7c** (52)
4[b]	**6c**	**2a**	10	**7c** (72)
5	**6c**	**5** / $AgSbF_6$	30	**7c** (70)
6	 **6d**	**2a**	120	 **7d** (77)
7[b]	**6d**	**2a**	12	**7d** (90)
8	**6d**	**5** / $AgSbF_6$	15	**7d** (71)
9[b]	**6d**	**5** / $AgSbF_6$	10	**7d** (75)

[a] Reactions carried out at room temperature in CH_2Cl_2 with 2 mol % catalyst. [b] Reaction under microwave heating in CH_2Cl_2 at 80 °C with 2 mol % catalyst.

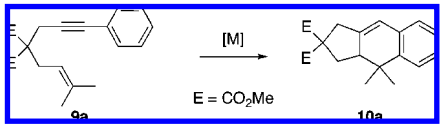
When the reaction of dienyne **6a** was carried out in MeOH as solvent with catalyst **1a**/$AgSbF_6$, compound **12** (eq 1) was obtained as a result of a 5-*exo*-*dig* methoxycyclization[2,6b] via an intermediate of type **II** (Scheme 1).



(1)

Cycloaddition of Arylenynes. We examined in detail the reaction of arylenyne **9a** with different Au(I) catalysts (2 mol %) as well as with $PtCl_2$ (Table 2). Although the cycloaddition proceeded well with [AuCl(PPh_3)]/$AgSbF_6$, it was considerably faster with catalysts generated from complex **1a** or with **2a** (Table 2, entries 1−3). Among the assayed solvents, the best results were obtained in CH_2Cl_2 (Table 2, entry 3). Slower reactions were obtained in other solvents, whereas in acetonitrile, the reaction did not proceed (Table 2, entries 4−9). The cationic catalyst generated from complex **5** provided **10a** in quantitative yield (Table 2, entry 10), whereas $PtCl_2$ was inefficient under these conditions (Table 2, entry 11). The reaction can also be carried under microwave heating (Table 2, entries 1−16).[26] The best results were obtained in CH_2Cl_2 or 1,2-dichoroethane, in which the cyclization of **9a** could be carried out cleanly in only 1 min at 50 °C with **2a** (Table 2, entries 12 and 13) or in 30 s with **5** and $AgSbF_6$ (Table 2, entry 16). Gas chromatography and ^1H NMR analysis show exceptionally clean reaction mixtures in these cycloadditions.

Table 2. Cyclization of Arylenyne **9a**



entry	[M] (mol %)	solvent	conditions[a]	time	yield (%)
1	[AuCl(PPh_3)]/$AgSbF_6$ (2)	CH_2Cl_2	A	12 h	83
2	**1a** /$AgSbF_6$ (2)	CH_2Cl_2	A	2 h	85
3	**2a** (2)	CH_2Cl_2	A	2 h	83
4	**2a** (2)	acetone	A	6 h	81
5	**2a** (2)	toluene	A	20 h	27
6	**2a** (2)	DMF	A	20 h	25
7	**2a** (2)	$MeNO_2$	A	5 h	77
8	**2a** (2)	Et_2O	A	20 h	78
9	**2a** (2)	MeCN	A	20 h	< 2
10	**5**/$AgSbF_6$ (2)	CH_2Cl_2	A	2 h	99
11	$PtCl_2$ (5)	CH_2Cl_2	A	24 h	< 2
12	**2a** (2)	CH_2Cl_2	B	1 min	93[b]
13	**2a** (2)	DCE	B	1 min	92[b]
14	**2a** (2)	acetone	B	1 min	74[b]
15	**2a** (2)	toluene	B	1 min	16[b]
16	**5**/$AgSbF_6$ (2)	CH_2Cl_2	B	0.5 min	95[b]

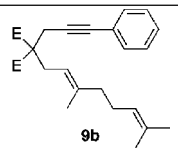
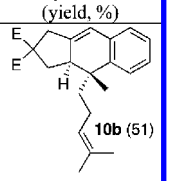
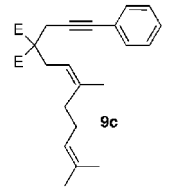
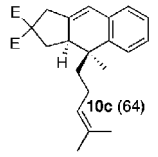
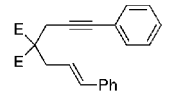
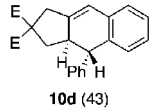
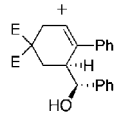
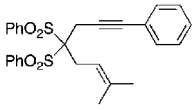
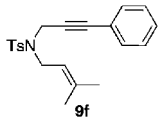
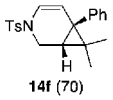
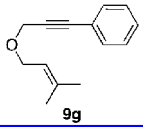
[a] A = room temperature. B = microwave heating, 50 °C. [b] Yield determined by GC.

Substituted arylenynes **9b**−**d** reacted with catalysts **1a**−**d** to give 2,3,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalenes **10b**−**d** stereospecifically (Table 3). Thus, *E*/*Z* diastereomers **9b** and **9c** provided tricyclic compounds **10b** and **10c**, respectively (Table 3, entries 1−6), as a result of retention of the alkene configuration. Retention of configuration was also observed in the cyclization of *trans*-cinammyl derivative **9d** (Table 3, entries 7−10). In the cycloadditions of **9b** and **9d**, substantial rate accelerations were observed using complex **5** as the precatalyst (Table 3, entries 5 and 11). In the presence of water, enyne **9b** also provided alcohol **13** (Table 3, entry 9), the product of an *endo*-hydroxycyclization.[2b] This cyclization was more efficiently carried out under microwave heating (Table 3, entry 10). In

(24) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596−7599.
(25) For the involvement of intermediates of type **VI**: (a) Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1085−1087. (b) Trost, B. M.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **1994**, *116*, 2183−2184.
(26) See the Supporting Information for additional data.

contrast to the efficient cyclization of **9d**, phenylenyne **9e** failed to cyclize with Au(I) catalysts (Table 3, entry 12). Tosylamide **9f** also failed to afford a [4+2] cycloaddition product and led instead to azabicyclo[4.1.0]hept-4-ene **14f** with catalyst **2a** (Table 3, entry 13), the product of an *endo*-cyclization.[10b] Ether **9g** also failed to give a [4+2] cycloaddition product (Table 3, entry 14). The lack of reactivity of **9e**−**g** can be attributed to the electron-withdrawing effect of the groups at the tether, which presumably disfavor formation of the initial Au(I)-alkyne complex.

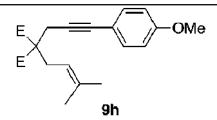
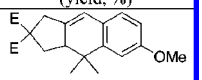
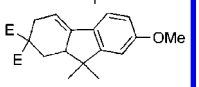
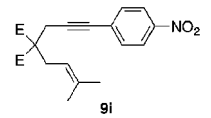
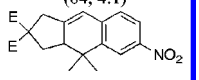
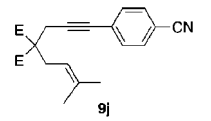
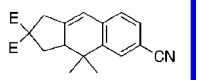
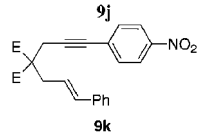
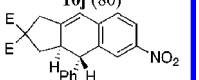
Table 3. Au(I)-Catalyzed Cyclization of Arylenynes **9b-d** (E = CO_2Me)[a]

entry	enyne	[Au(I)]	time	product (yield, %)
1	 **9b**	**1a** / $AgSbF_6$	36 h	 **10b** (51)
2	**9b**	**1b** / $AgSbF_6$	20 h	**10b** (45)
3	**9b**	**1d** / $AgSbF_6$	18 h	**10b** (76)
4	**9b**	**2a**	18 h	**10b** (78)
5	**9b**	**5** / $AgSbF_6$	30 min	**10b** (60)
6	 **9c**	**1d** / $AgSbF_6$	48 h	 **10c** (64)
7	 **9d**	**1a** / $AgSbF_6$	12 h	 **10d** (43)
8	**9d**	**1d** / $AgSbF_6$	12 h	**10d** (67)
9[b]	**9d**	**2a**	40 h	**10d** (38) +  **13d** (40)
10[c]	**9d**	**2a**	20 min	**10d** (85)
11	**9d**	**5** / $AgSbF_6$	30 min	**10d** (90)
12	 **9e**	**2a**	40 h	-
13	 **9f**	**2a**	12 h	 **14f** (70)
14	 **9g**	**2a**	40 h	-

[a] Reaction run with 2 mol % catalyst in CH_2Cl_2 at room temperature. [b] Reaction in acetone at room temperature with 5% mol catalyst. [c] Reaction under microwave heating at 80 °C with 2 mol % catalyst in CH_2Cl_2.

The cycloaddition tolerates a variety of para substituents at the aryl ring. Thus, substrates **9h**−**i** with methoxy, nitro, and cyano groups reacted efficiently to give products **10h**−**i** (Table 4). Interestingly, in the case of **9h**, in addition to **10h**, cycloadduct **15h** was also obtained as a minor product (Table 4, entries 1−3). Product **15h** is the result of an initial 6-*endo*-*dig* cyclization.[27] Although the cyclization of **9h** was accelerated by microwave heating, the **10h**/**15h** ratio was identical to that obtained at room temperature (Table 4, entry 3). As before, faster reactions at room temperature were observed using **5** as the precatalyst (Table 4, entries 6, 8, and 11). Tricyclic compound **10k** was obtained as single stereoisomer. The structure of cycloadduct **10i** has been confirmed by X-ray crystallography.[28]

Table 4. Au(I)-Catalyzed Cyclization of Arylenynes **9h-k** (E = CO_2Me)[a]

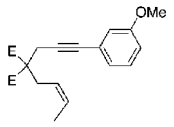
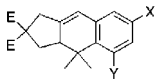
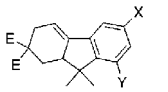
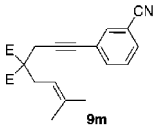
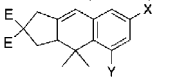
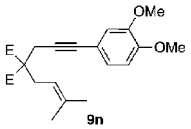
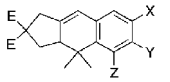
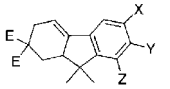
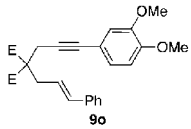
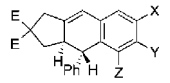
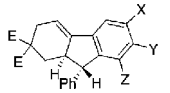
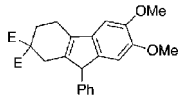
entry	enyne	[Au(I)]	time	product(s) (yield, %)
1	 **9h**	**1d** / $AgSbF_6$	3 h	 **10h** (77) +  **15h** (19) (96, 4:1)
2	**9h**	**2a**	3 h	**10h** + **15h** (75, 4:1)
3[b]	**9h**	**2a**	12 min	**10h** + **15h** (84, 4:1)
4	 **9i**	**2a**	3 h	 **10i** (74)
5[b]	**9i**	**2a**	10 min	**10i** (81)
6	**9i**	**5** / $AgSbF_6$	20 min	**10i** (65)
7	 **9j**	**2a**	96 h	 **10j** (68)
8	**9j**	**5** / $AgSbF_6$	3 h	**10j** (80)
9	 **9k**	**2a**	54 h	 **10k** (58)
10[b]	**9k**	**2a**	50 min	**10k** (75)
11	**9k**	**5** / $AgSbF_6$	2 h	**10k** (96)

[a] Reactions run with 2 mol % catalyst in CH_2Cl_2 at room temperature. [b] Reaction under microwave heating at 80 °C with 2 mol % catalyst in CH_2Cl_2.

Substrates with meta substituents **9l-o** gave, as expected, mixtures of regioisomeric cycloadducts (Table 5). Thus, in the case of **9l**, four products were obtained with **2a** or **5**/$AgSbF_6$ with catalysts at room temperature (Table 5, entries 1 and 3). However, under microwave heating with catalyst **2a**, substrate **9l** afforded only compounds **10l** and **10′l** (Table 5, entry 2). Nitrile derivative **9m** reacted more sluggishly than **9l** to give a 1:1 mixture of regioisomers **10m**/**10′m** in 52% yield using **2a** (5 mol %) as catalyst (Table 5, entry 4). In the reaction of **9n** carried out for 3 h, 2,3,9,9a-tetrahydro-1*H*-fluorenes **15n** and **15′n** were also formed in low yields (Table 5, entry 7). These compounds could not be obtained pure. The result with substrate **9o** is noteworthy as, although the reaction with **2a** at room temperature led to a mixture of four products, reaction under microwave heating with **2a** or with **5**/$AgSbF_6$ at room-temperature gave **15′′o** as single regioisomer in excellent yield

(Table 5, entries 8−10). Product **15″o** is the result of an initial endo-dig cyclization followed by the isomerization of the alkene to the internal position.

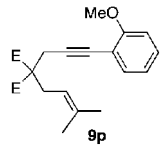
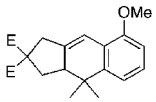
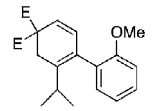
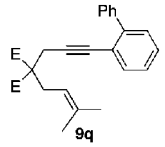
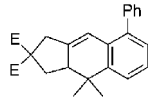
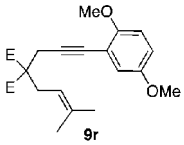
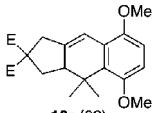
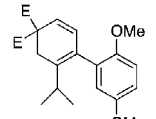
Table 5. Au(I)-Catalyzed Cyclization of Arylenynes **9l-o** (E = CO_2Me)[a]

entry	enyne	[Au(I)]	time	product(s) (yield, %)
1	 **9l**	**2a**	1 h	 **10l**: X = OMe, Y = H (54) **10'l** : X = H, Y = OMe (35) +  **15l**: X = OMe, Y = H (6) **15'l** : X = H, Y = OMe (5)
2[b]	**9l**	**2a**	20 min	**10l** + **10'l** (92, 2:1)
3	**9l**	**5** / $AgSbF_6$	30 min	**10l** + **15l** (59, 16:1) **10'l** + **15'l** (37, 11:1)
4[c]	 **9m**	**2a**	54 h	 **10m**: X = CN, Y = H (26) **10'm**: X = H, Y = CN (26)
5	 **9n**	**1a** / $AgSbF_6$	3 h	 **10n**: X = Y = OMe, Z = H **10'n** : X = H, Y = Z = OMe **10n** + **10'n** (53, > 10:1)
6[b]	**9n**	**2a**	30 min	**10n** + **10'n** (92, 2:1)
7	**9n**	**2a**	3 h	**10n** + **10'n** (70, 6:1) +  **15n**: X = Y = OMe, Z = H (8) **15'n** : X = H, Y = Z = OMe (2)
8[d]	 **9o**	**2a**	15 h	 **10o**: X = Y = OMe, Z = H (40) **10'o** : X = H, Y = Z = OMe (51) +  **15o**: X = Y = OMe, Z = H (5) **15'o** : X = H, Y = Z = OMe (2)
9[b]	**9o**	**2a**	20 min	 **15″o** (93)
10	**9o**	**5** / $AgSbF_6$	8 h	**15″o** (96)

[a] Reaction run using 2 mol % catalyst in CH_2Cl_2 at room temperature. [b] Reaction under microwave heating at 80 °C with 2 mol % catalyst in CH_2Cl_2. [c] Reaction run using 5 mol % catalyst. [d] Reaction in the presence of 4 Å molecular sieves.

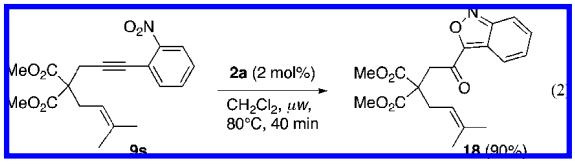
Alternatively, aryl enynes **9p**−**r** with ortho substituents gave products **10p**−**r**, respectively (Table 6). The structure of cycloadduct **10q** was confirmed by X-ray crystallography. In the reactions of **9p** and **9r**, cyclohexadienes **16p** and **16r** were also obtained as minor compounds (Table 6, entries 1−4, and 6). These cyclohexadienes arise by a 6-endo cyclization followed by cyclopropane opening followed by 1,2-H migration (see below).

Table 6. Au(I)-Catalyzed Cyclization of Arylenynes **9p-r** (E = CO_2Me)[a]

entry	enyne	[Au(I)]	time	product(s) (yield, %)
1	 **9p**	**1d** / $AgSbF_6$	1 h	 **10p** (83) +  **16p** (16)
2	**9p**	**2a**	3 h	**10p** +**16p** (99, 2.5:1)
3[b]	**9p**	**2a**	18 min	**10p** +**16p** (87, 2:1)
4	**9p**	**5**/$AgSbF_6$	1 h	**10p** +**16p** (99, 5:1)
5	 **9q**	**2a**	20 h	 **10q** (80)
6	 **9r**	**2a**	3 h	 **10r** (62) +  **16r** (28)

[a] Reactions run with 2 mol % catalyst in CH_2Cl_2 at room temperature. [b] Reaction under microwave heating at 80 °C with 2 mol % catalyst in CH_2Cl_2.

Reaction of enyne **9s** bearing an ortho-nitro group gave exclusively benzo[*c*]isoxazole (anthranil) derivative **18** in 90% yield, instead of the expected cycloadduct as a result of a preferred attack of the nitro group at the alkyne (eq 2). Related anthranils have been obtained by Asao and Yamamoto in the cyclization of *o*-(alkynyl)nitrobenzenes catalyzed by $AuBr_3$.[29]

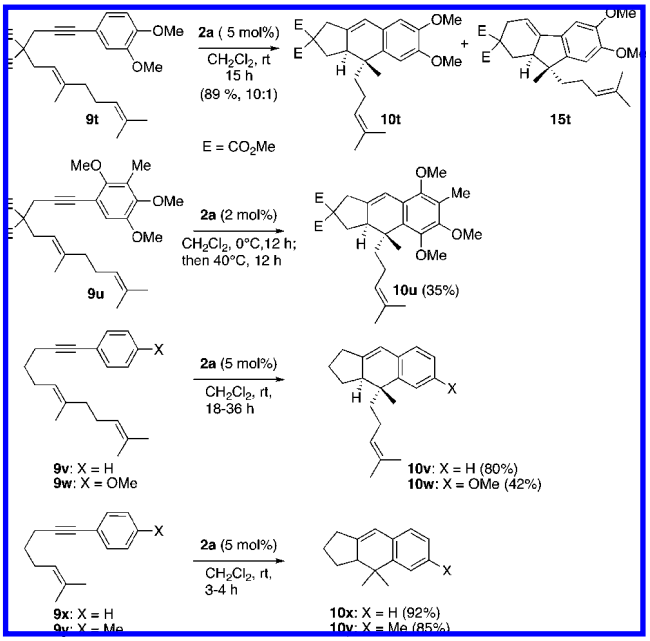


As models for the synthesis of the pycnanthuquinones **11a**−**c**, we assayed the cycloadditions of arylenynes **9t**−**y** (Scheme 3). The reaction of **9t** with catalyst **2a** (5 mol %) gave a 10:1

(27) Interestingly, this was the major pathway in the Pt(II)-catalyzed cycloaddition of arylalkynes with enesulfonamides or enamides: Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367−370.

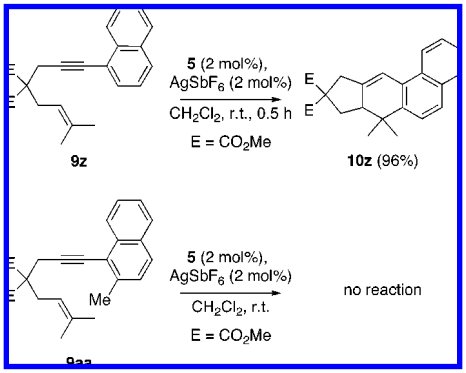
mixture of **10t** and tetrahydro-1*H*-fluorene **15t**, which could not be obtained pure. The presence of excess silver salt led to poor results. Thus, a less clean reaction was observed with **2a** and $AgSbF_6$ (3 mol % each), which led to ~ 3:1 ratio of **10t** and **15t** and the formation of several uncharacterized byproducts. The reaction of **9u** proceeded with many Au(I) catalyst, although the isolated yields were low. After much experimentation, a 35% yield of **10u** was achieved using catalyst **2a**. Substrates **9v**−**y** also react with catalyst **2a** to give tricyclic compounds **10v**−**y**. It is interesting to note that these cyclizations proceed smoothly with substrates that do not benefit from the effect of gem-substitution (Thorpe−Ingold effect) from substituents at the tether.

Scheme 3

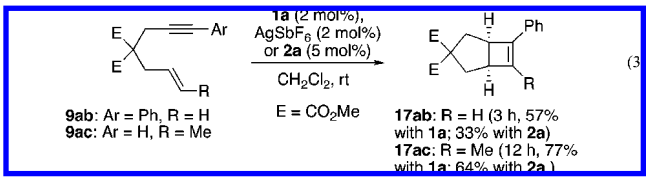


Tetracyclic compound **10z** was obtained in excellent yield with **5**/$AgSbF_6$ in 30 min from 1-naphthyl derivative **9z** (Scheme 4). The same yield was realized using **2a** as catalyst, but the reaction required 12 h at room temperature. No cycloadduct could be obtained from substrate **9aa**, in which the reactive position of the naphthalene (C-2) has been blocked with a methyl group.

Scheme 4



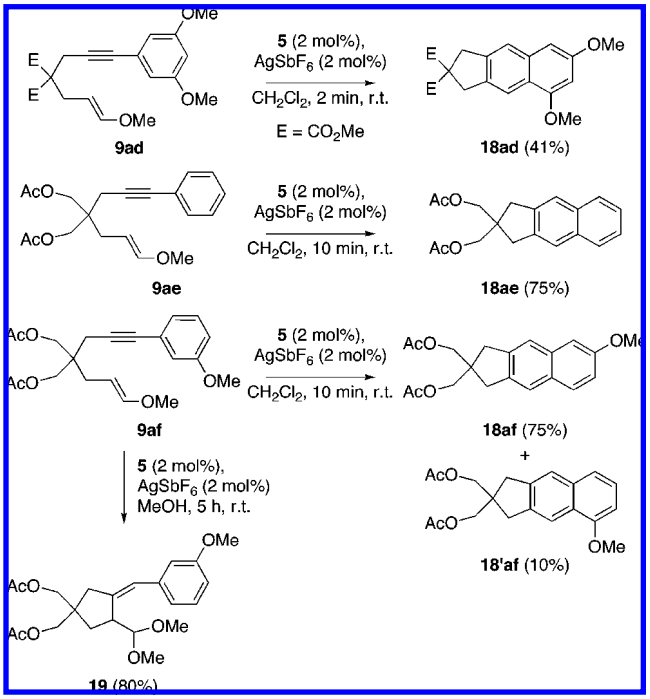
Enynes **9ab** and **9ac** gave cyclobutenes **17ab** and **17ac** under these conditions, which suggests that the [4+2] cycloaddition only proceeds with substrates bearing alkenes substituted at the terminal position with groups capable of stabilizing the developing positive charge (eq 3). Using precatalyst **5** substrates **9ab** and **9ac** led to complex mixtures or variables, probably due to the relatively high reactivity of the resulting cyclobutenes in the presence of Au(I) and/or Ag(I). Cyclobutenes related to **17** had been obtained by Trost et al. using palladacyclopentadienes as catalysts[5a,b] and, more recently, by Fürstner et al. by using Pt(II) as catalyst under a CO atmosphere.[30]



(3)

We also examined the cycloaddition of arylalkynes with enolethers (Scheme 5). Substrates **9ad**−**af** reacted with the gold(I) catalyst generated from **5** to give cyclopenta[*b*]naphthalenes **18ad**−**af** in remarkably fast reactions (2−10 min). The resulting products result from a [4+2] cycloaddition followed by elimination of MeOH. Alternatively, when the reaction of **9af** was performed in MeOH, dimethyl acetal **19** was obtained in 80% yield, as a result of trapping of the initial intermediate of the cycloaddition process (see below).[2b]

Scheme 5

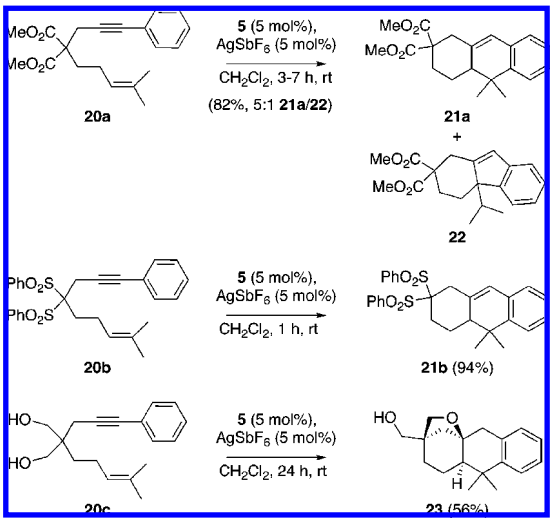


The cyclization of 1,7-enynes **20a**−**c** was also examined (Scheme 6). In contrast to the behavior of 1,7-enynes unsubstituted at the alkyne, which suffer single cleavage skeletal rearrangement,[9] these substrates led to [4+2] cycloadditions. Thus, cyclization of **20a** afforded the expected tricycle **21a** along with fluorene derivative **22** as a minor product. Reaction of **20b** proceed uneventfully to provide **21b**, whereas diol **20c** gave **23**, in which one of the primary alcohols has been added to the

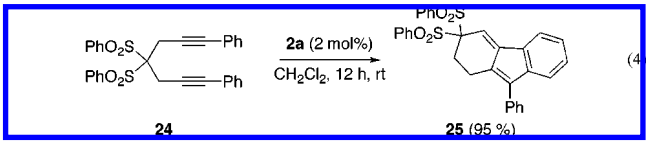
(28) See Supporting Information.
(29) Asao, N.; Sato, K.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 5675−5677.

alkene in a subsequent reaction catalyzed by Au(I) or H^+. The relative configuration of **23** was assigned on the basis of NOESY experiments in $CDCl_3$ and benzene-d_6.

Scheme 6



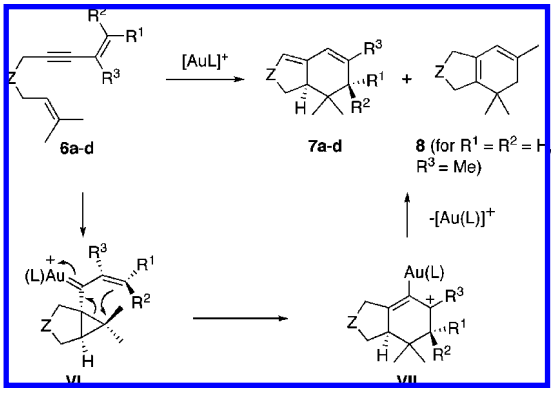
Finally, we also tried the cyclization of diaryldiyne **24** with catalyst **2a** (eq 4). The reaction proceeded in 12 h at room temperature to give adduct **25** in 95% yield, the product of an endo cyclization process. No reaction was observed with similar diynes that were arylated only at one of the alkynes. As part of a broader study on this cyclization carried out by the group of Liu,[31,32] compound **25** was also obtained in the reaction of **24** with $[AuCl(PPh_3)]/AgSbF_6$ (room temperature, 12 h, 81%).



Mechanistic Discussion. The cyclization of dienynes **6** presumably proceeds through intermediates such as **VI**, which undergo ring expansion in a process that is reminiscent of the Nazarov cyclization to form allyl cation **VII** (Scheme 7). This is followed by loss of a proton followed by proto-demetalation to give dienes **7a**−**d** and **8**. Regioselective proton loss occurs under kinetic control, as products **7a**−**b** (see Table 1) are 2.5−3.5 kcal·mol^{-1} less stable than dienes like **8** (PM3 calculations). Formation of intermediate **VI** in the cyclization is supported by the isolation of adduct of *exo-di*g methoxycyclization **12** form **6a** (eq 1). The stereochemistry shown in the cyclization of **VI** to **VII** is consistent with the isolation of **7d** as a single isomer in the cyclization of **6d** (Table 1).

In order to understand the different behavior observed in the cycloadditions of arylalkynes with alkenes depending on the substitution at the alkene, we performed DFT calculations on model gold(I)-complexes **VIIIa**−**b**. Results shown in Schemes

Scheme 7



8−11 take into account the solvent effect for CH_2Cl_2 by means of polarized continuum model.[33]

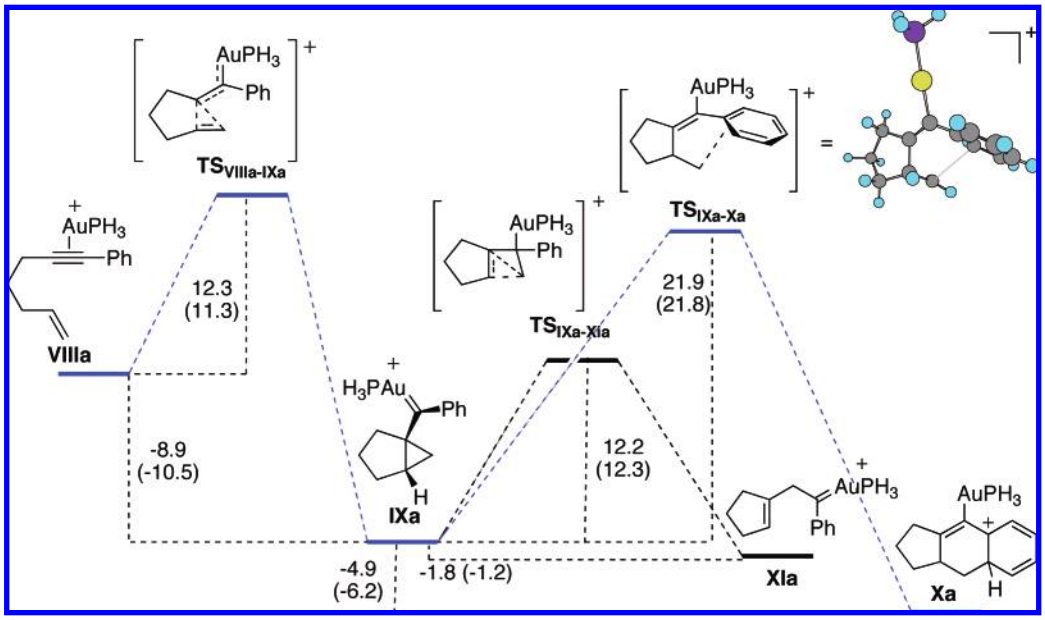
Gold(I)-complex of hept-6-en-1-ynylbenzene (**VIIIa**) react through $\mathbf{TS_{VIIIa-IXa}}$ to give anti-cyclopropylgold(I) carbene **IXa** (Scheme 8) in an exothermic transformation ($\Delta G = -10.5$ kcal·mol^{-1}). The second step of the cycloaddition proceeded by opening of the cyclopropane to give Wheland intermediate **Xa** via transition state $\mathbf{TS_{IXa-Xa}}$, in which the incipient primary carbocation is stabilized in a π-interaction with the aryl ring. Although moderately exothermic ($\Delta G = -6.2$ kcal·mol^{-1}), the activation energy ($\Delta G^{\ddagger} = 21.8$ kcal·mol^{-1}) is higher than that required for the skeletal rearrangement pathway to give **XIa** ($\Delta G^{\ddagger} = 12.3$ kcal·mol^{-1}), which is the intermediate in the double cleavage rearrangement of complex **VIIIa**.[6] This activation energy is similar ($\Delta G^{\ddagger} = 14.2$ kcal·mol^{-1}) than that required in the same step of the double cleavage rearrangement of 1-octen-6-yne,[6a] which shows that methyl and phenyl groups have similar effects on this reaction.

We also examined the evolution of gold(I)-complex **VIIIa** by an endocyclic pathway via intermediate **XIIa** (Scheme 9). In this case, the activation energy to reach $\mathbf{TS_{VIIIa-XIIa}}$ is lower than that for the exocyclic pathway. Although a Friedel−Crafts-type process could also be found from endo cyclopropyl gold(I) carbene **XIIa** to give **XIIIa** via $\mathbf{TS_{XIIa-XIIIa}}$, the activation energy for his process is much higher than that required for the formation of bicyclo[3.2.0]heptyl carbocation **XIVa**. Therefore, for model complex **VIIIa**, the more favorable pathways would be the skeletal rearrangement via **XIa** (Scheme 8) or formation of a bicyclo[3.2.0]hept-6-ene via **XIVa**. This is consistent with the experimental results shown in eq 3 for **9ab**.

For the cyclization of **VIIIb**, *anti*-cyclopropyl gold(I)-carbene **IXb** is formed in an almost thermoneutral process (Scheme 10). This system corresponds to the Au(I) complex of substrate **9x** (Scheme 3). Interestingly, **IXb** opens to form **IX′b**, an aryl-stabilized π-cation complex (Scheme 10b). The transition state connecting intermediates **IXb** and **IX′b** was not located. It is important to stress that intermediates **IXb** and **IX′b** are both stationary points in the reaction coordinate with different bond lengths and angles and not canonical forms, although the difference in energy is small. At the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) level, ΔG was found to be 3.6 kcal·mol^{-1}, whereas at a higher level (B3LYP/ 6-311+G(d,p) (C,H,P) LANL2DZ (Au)) the energies are more similar ($\Delta G = 2.0$ kcal·

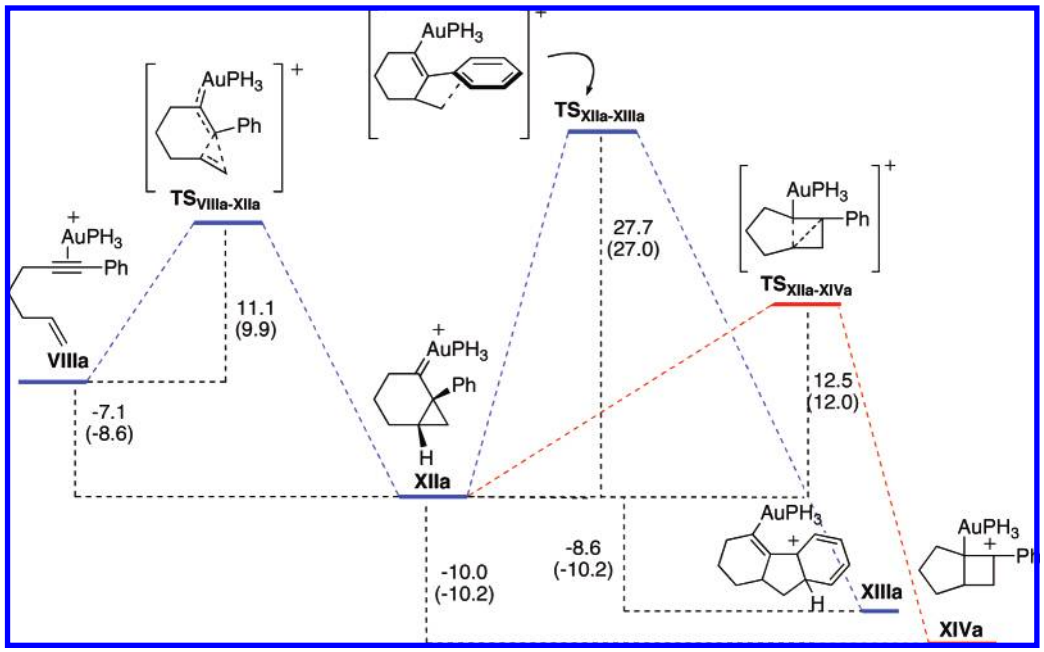
(30) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244−8245.
(31) Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R. S. *J. Am. Chem. Soc.* **2006**, *128*, 11372−11373.
(32) Different structures were assigned by Shibata *et al.* in the gold(I)-catalyzed cyclization of diaryldiynes of type **24**: Shibata, T.; Fujiwara, R.; Takano, D. *Synlett* **2005**, 2062−2066.
(33) Gas phase DFT calculations and additional details are provided as part of the Supporting Information.

Scheme 8. Reaction Pathway and Energies for the Exo-cycloaddition of **VIIIa** to Wheland Intermediate **Xa** or Double Cleavage Skeletal Rearrangement Gold(I) Carbene **XIa**[a]



[a] Calculations at the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) level (+ZPE-corrected electronic energies are given in Kcal·mol^{-1}; ΔG in brackets), including solvent effect for CH_2Cl_2.

Scheme 9. Reaction Pathway and Energies for the Endo-cycloaddition of **VIIIa** to Wheland Intermediate **XIIIa** or Cyclobutene Precursor **XIVa**[a]



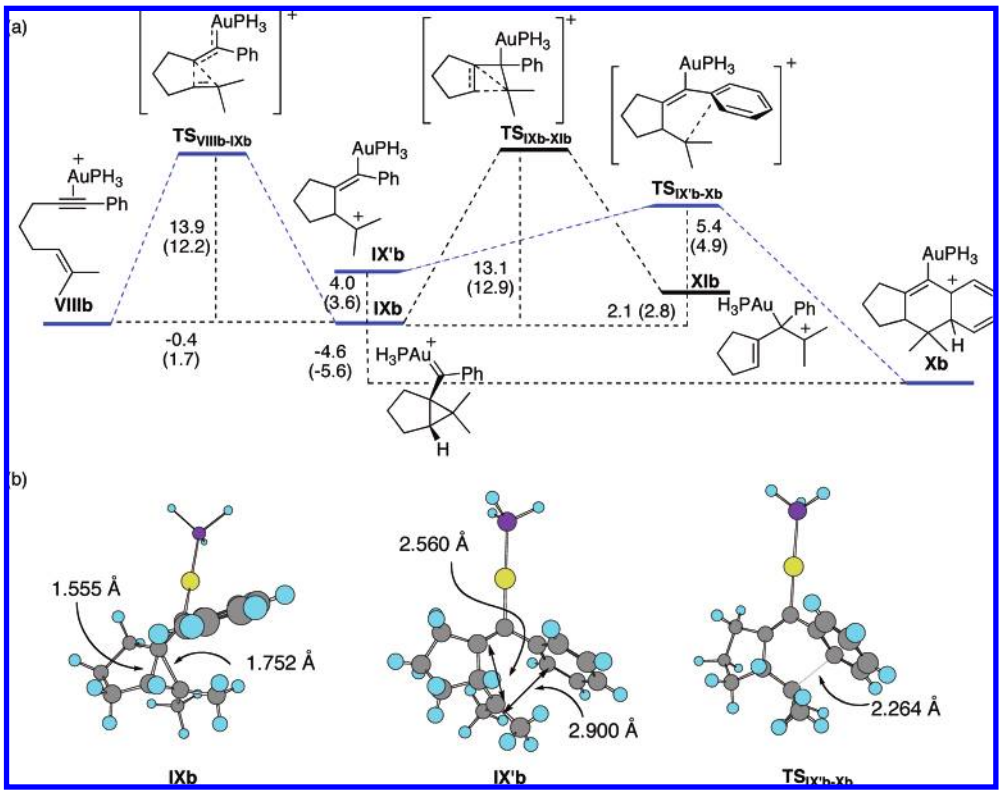
[a] Calculations at the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) level (+ZPE-corrected electronic energies are given in Kcal·mol^{-1}; ΔG in brackets), including solvent effect for CH_2Cl_2.

mol). The second step of the cycloaddition takes place to give Wheland intermediate **Xb** with low activation energy in an exothermic process via $\mathbf{TS_{IX'b-Xb}}$. The stepwise nature of this cycloaddition is further supported by the isolation of **19** in the reaction of **9af** carried out in MeOH (Scheme 5).

The skeletal rearrangement via $\mathbf{TS_{IXb-XIb}}$ and **XIb** requires a relatively high activation energy. Interestingly, in contrast to that found for **XIVb**, DFT calculations show that the skeletal rearrangement for the dimethyl substituted 1,6-enyne would proceed by a single cleavage mechanism.[5,6] The barrier for this single cleavage rearrangement is higher that that calculated for (*E*)-6-octen-1-yne ($\Delta G = 9.1$ Kcal·mol^{-1}),[6a] which is probably due to the stabilizing effect of the phenyl group on the carbene in **IXb**.

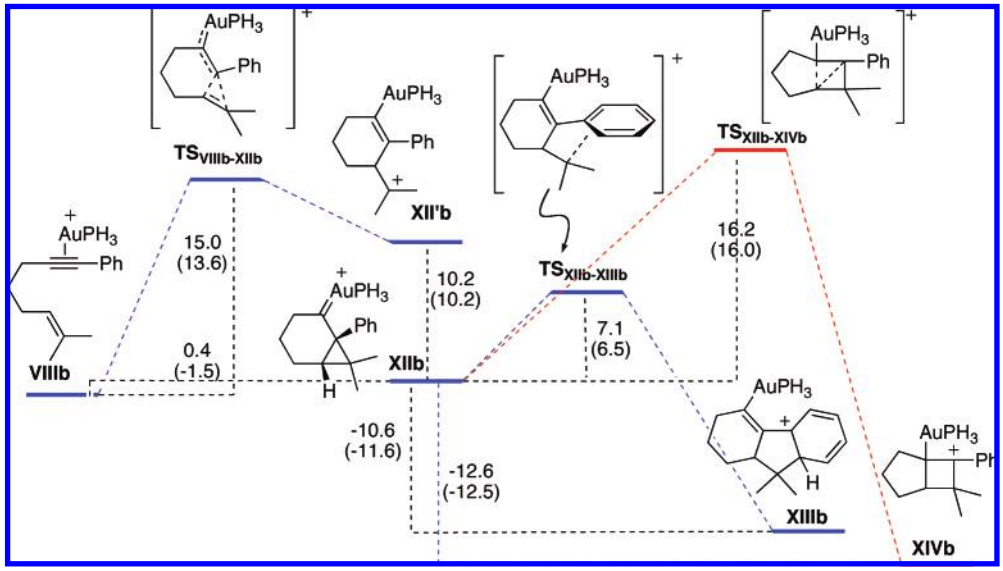
A similar pathway is probably followed in the cyclizations of 1,7-enynes **20a**−**c** shown in Scheme 6. Formation of fluorene derivative **22** as a minor product can be explained by a 1,2-hydrogen shift of a six-membered ring analogue of cation of **IX′b** followed by a Friedel−Crafts cyclization.

Scheme 10. Reaction Pathway and Energies for the Exo-cycloaddition of **VIIIb** to Wheland Intermediate **XIIIb** and Selected Distances for $\mathbf{TS_{IX'b-Xb}}$, **IXb**, and **IX′b**[a]



[a] Calculations at the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) level (+ZPE-corrected electronic energies are given in Kcal·mol^{-1}; ΔG in brackets), including solvent effect for CH_2Cl_2.

Scheme 11. Reaction Pathway and Energies for the Endo-cycloaddition of **VIIIb** to Wheland Intermediate **XIIIb** or Cyclobutene Precursor **XIVb**[a]

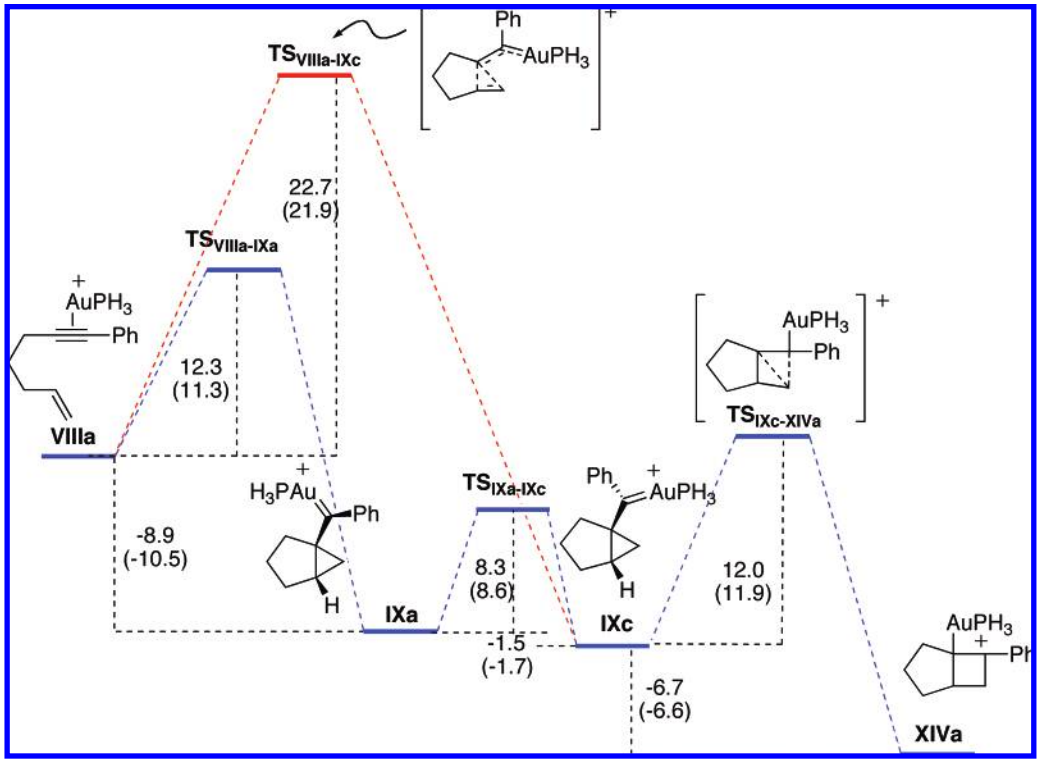


[a] Calculations at the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) level (+ZPE-corrected electronic energies are given in Kcal·mol^{-1}; ΔG in brackets), including solvent effect for CH_2Cl_2.

In the alternative cyclization of **VIIIb** by the endocyclic pathway, we found intermediate **XII′b** preceding formation of cyclopropyl gold(I) carbene **XIIb**, although the transition state connecting these two intermediates could not be found (Scheme 11). Intermediate **XIIb** then evolves by a Friedel−Crafts-type process via $\mathbf{TS_{XIIb-XIIIb}}$ to form **XIIIb**. The alternative formation of bicyclo[3.2.0]heptyl carbocation **XIVb** via $\mathbf{TS_{XIIIb-XIVb}}$ proceeds with a much higher activation energy. Cyclohexadienes **16p** and **16r** (Table 6) are presumably formed by a 1,2-H shift from intermediates **XII′b**.

Although the pathway shown in Scheme 9 for the opening of **XIIa** to form bicyclo[3.2.0]heptyl carbocation **XIVa** provides

Scheme 12. Alternative Reaction Pathway and Energies for the Reaction of **VIIIa** to Cyclobutene Precursor **XIVa** via **IXc**[a]



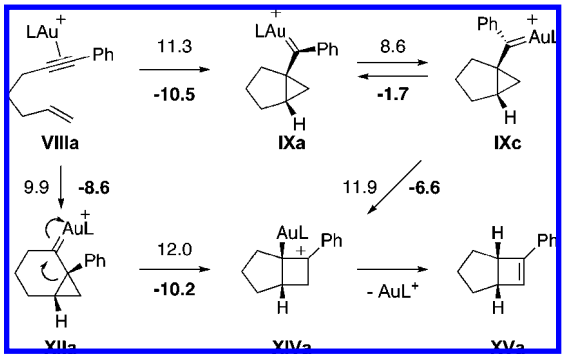
[a] Calculations at the B3LYP/6-31G(d) (C, H, P), LANL2DZ (Au) Level (+ZPE-corrected electronic energies are given in Kcal·mol^{-1}; ΔG in brackets), including solvent effect for CH_2Cl_2.

a reasonable pathway for the formation of cyclobutenes **17ab** and **17ac** (eq 3), we found an alternative pathway after examining the reactivity of *syn*-cyclopropyl gold(I) carbene **IXc** (Scheme 12). The direct formation of this intermediate from **VIIIa** is unlikely, as the activation energy is almost twice as large as that required for the formation of *anti*-cyclopropyl gold(I) carbene **IXa**. However, rotation around the cyclopropane-carbene bond is a facile process in this case ($\Delta G^{\ddagger} = 8.6$ kcal·mol^{-1}), which actually favors formation of *syn*-**IXc**. The same activation energy was found in the gas-phase calculations.[33] This is in sharp contrast with that previously found for the corresponding cyclopropyl gold(I) carbene formed from (*E*)-oct-6-en-1-yne, for which an activation of 24.7 kcal·mol^{-1} (gas phase) was found, favoring the *anti*-cyclopropyl carbene by 4.6 kcal·mol^{-1}.[6a] The low rotational barrier can be attributed to the conjugation of the cyclopropane with the phenyl ring in $\mathbf{TS_{IXa-IXc}}$.[33]

syn-Cyclopropyl carbene **IXc** then opens to form **XIVa** with an activation energy of 11.9 kcal·mol^{-1} (Scheme 12). These results indicate for the formation of **XIVa** from **VIIIa** the anti- to syn-isomerization pathway might compete with the opening of **XIIa** (Scheme 13). Benzylic carbocation **XIVa** presumably undergoes a proton-elimination, followed by the protonolysis of the C−Au bond to form **XVa**.

Overall, according to the DFT calculations, the mechanism of the [4+2] cycloaddition of arylenynes proceeds via **VIIIb**−**Xb**, followed by aromatization to form alkenyl gold intermediate **XVI**, which undergoes proto-demetalation to form **XVII** (Scheme 14). For systems related to model **VIIIb** (i.e., substrate **9x** coordinated to $Au(PH_3)^+$), the rate determining step is the attack of the alkene to the alkyne coordinated to Au(I) and not

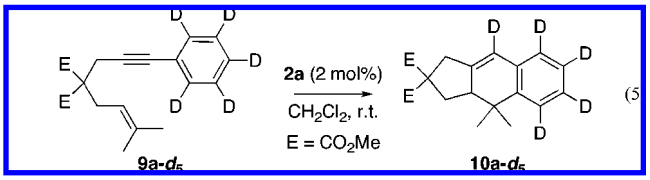
Scheme 13. Two Pathways for the Formation of 6-Phenylbicyclo[3.2.0]hept-6-ene **(XVa)** from **VIIIa**[a]



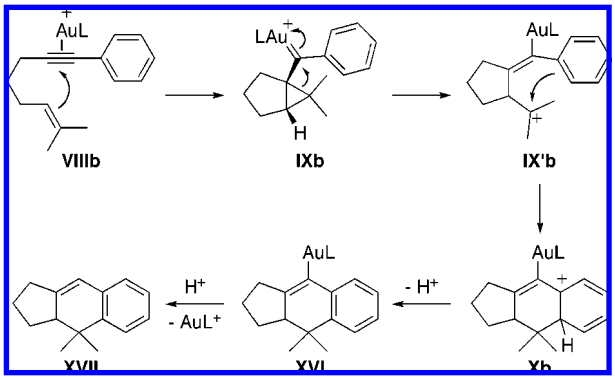
[a] Energies correspond to $\Delta G^{\ddagger}$ and ΔG (boldface) in Kcal·mol-1.

the electrophilic aromatic substitution, which explains the relative insensitivity to the presence of electron-withdrawing substituents at the para position (see Table 4).

In order to further confirm this mechanism we performed the reaction of $\mathbf{9a-d_5}$ with catalyst **2a** in CH_2Cl_2. As expected, the deuterium that is lost from the aryl ends up at the positioninitially activated by gold (see **Xb** in Scheme 10) leading to $\mathbf{10a-d_5}$ (66% deuterium content at the alkene) (eq 5).



Scheme 14. Mechanism for the [4+2] Cycloaddition of Arylenynes.



We also monitored by ^{1}H NMR the cyclization of enyne **9a** catalyzed by complex **2a** between 282 and 305.5 K. The reaction followed pseudo-first-order kinetics, with $\Delta G^{\ddagger} = 22.4 \pm 0.5$ kcal·mol^{-1}, $\Delta H^{\ddagger} = 12.6 \pm 0.1$ kcal·mol^{-1}, $\Delta S^{\ddagger} = -33.1 \pm 0.5$ cal·K^{-1}·mol^{-1}. The activation enthalpy is higher than that determined in the skeletal rearrangement for an enyne without the phenyl substituent at the alkyne,[10a] which is consistent with the lower reactivity of 1,6-enynes substituted with an aryl at the alkyne in metal-catalyzed reactions.[2d]

Conclusions

We have found novel reactivity of alkenyl- and aryl-substituted 1,6-enynes by using highly alkynophilic Au(I) complexes with biphenyl phosphines or a bulky phosphite as ligands. While thermal intramolecular [4+2] cycloadditions (dehydro-Diels−Alder reactions) of enynes with alkenes only take place at high temperatures, these transformations proceed with cationic Au(I) catalysts under mild conditions to provide bi- or tricyclic ring systems. In particular, the cationic Au(I) complex generated from complex **5** is the most active catalyst assayed for this type of cyclizations and allows to obtain complex systems at room temperature in short reactions times.

The intramolecular [4+2] cycloadditions of arylalkynes with alkenes proceeds stepwise by the initial formation of a *anti*-cyclopropyl gold(I)-carbene, followed by its opening to form a carbocation stabilized by a π interaction with the aryl ring and a Friedel−Crafts-type reaction. Aryl substituents stabilize intermediate gold carbenes, which results in higher barriers for their skeletal rearrangement and lower ones for their anti to syn isomerization. This cycloaddition tolerates a variety of functional groups at the aryl, including electron-releasing (OMe) and electron-withdrawing (CN, NO_2) substituents at ortho, meta, and para positions. The reaction can also be extended to 1,7-enynes and also proceeds satisfactorily in the absence gem-dialkyl effect at the tether between the allyl and propargyl chains. Progress toward the synthesis of the pycnanthuquinones by using this cycloaddition is underway.

Acknowledgment. This work was supported by the MEC (Projects CTQ2004-02869, CTQ2007-60745/BQU, Consolider Ingenio 2010, Grant CSD2006-0003, predoctoral fellowships to C.N.-O., P.P.-G., E.H.-G., Juan de la Cierva postdoctoral contract to T.L., postdoctoral fellowship to C.B., and Torres Quevedo postdoctoral contracts to S. L. and A. R.), Farmiva (postdoctoral fellowship to C. R.), the AGAUR (2005 SGR 00993), and the ICIQ Foundation. We thank Dr. J. Benet-Buchholz and E. Escudero-Adán (X-ray diffraction unit, ICIQ) for the structures of **5**, **10i**, and **10q** and Eloísa Jiménez-Núñez for obtaining crystals of **5** suitable for X-ray diffraction.

Supporting Information Available: Additional data on reactions under microwave irradiation, characterization data, X-ray diffraction data, additional computational data, Cartesian coordinates, and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA075794X