Cycloaddition

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Direct Observation of a Cationic Gold(I)–Bicyclo[3.2.0]hept-1(7)-ene Complex Generated in the Cycloisomerization of a 7-Phenyl-1,6-enyne**

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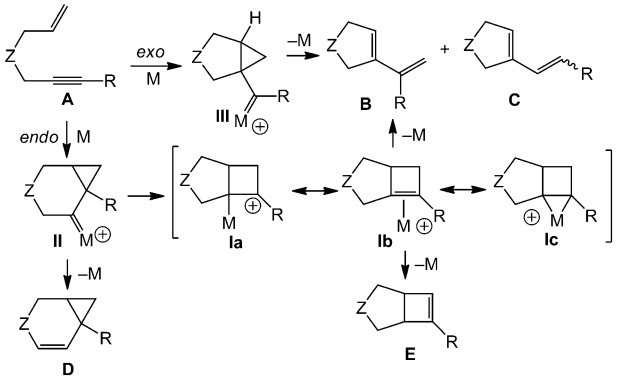
The cycloisomerization of enynes catalyzed by electrophilic noble-metal complexes,[1] in particular Au and Pt,[2] has attracted considerable attention owing to the formation of skeletal rearrangement products, including vinylcyclopentenes (**B** and **C**), bicyclo[4.1.0]heptenes (**D**), and bicyclo-[3.2.0]hept-6-enes (**E**) from 1,6-enynes (**A**; Scheme 1).[3,4]

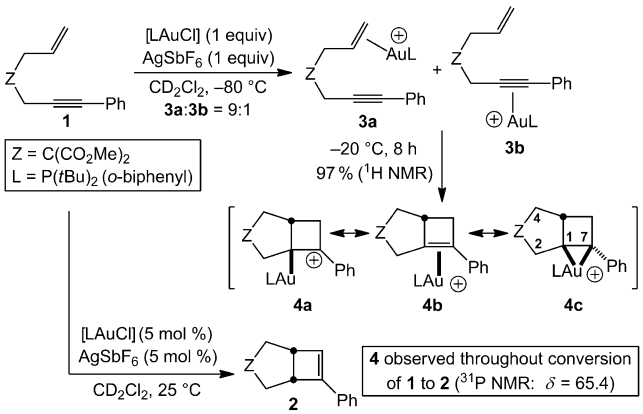


Scheme 1. Ligand- and substrate-dependent pathways for enyne cycloaddition catalyzed by electrophilic noble-metal complexes.

Fürstner first posited that these outcomes were consistent with the intermediacy of metal-stabilized nonclassical cyclopropylmethyl-, cyclobutyl-, and homoallylic carbocations/carbenes accessed through attack of the C=C moiety on a metal-complexed C≡C bond (Scheme 1),[5] and mechanistic thought in this area has evolved largely within this conceptual framework. The involvement of nonclassical carbocations/carbenes is supported by a wealth of indirect experimental evidence, including trapping experiments, isotopic labeling studies, and stereochemical analyses, and through numerous computational studies.[1,2] Absent, however, is direct experimental evidence regarding the structure and reactivity of these cationic complexes, as no organometallic intermediate has been observed spectroscopically in any of these transformations.[6–10]

Platinum(II),[11] gold(I),[12,13] and rhodium(II)[14] complexes catalyze the cycloisomerization of 7-aryl-1,6-enynes (**A**, R = Ar) to form vinylcyclopentenes **C** and/or bicyclo-[3.2.0]hept-6-enes **E** (Scheme 1). Directly implicated in these and related[15,16] transformations is the strained bicyclo-[3.2.0]hept-1(7)-ene species **I**, presumably generated through 6-*endo*-cyclization followed by 1,2-alkyl migration from cyclopropyl carbene **II** and consumed either by ring opening to form **B** and/or 1,3-hydrogen migration to form **E** (Scheme 1).[11–14] Possible contributors to **I** include the metalated cyclobutyl carbenium ion **Ia**, the π-alkene complex **Ib**, and the metallacyclopropane complex **Ic**. In this context, it appeared likely that contribution of the latter forms would engender stability to **I** not realized in the corresponding cyclopropyl carbene intermediates **II** or **III**, such that **I** might represent a local minimum on the reaction coordinate. Indeed, here we report the selective generation, spectroscopic characterization, and reactivity analysis of a gold–bicyclo-[3.2.0]hept-1(7)-ene complex formed in the gold-catalyzed cycloisomerization of a 7-phenyl-1,6-enyne.

Toward detection of a reactive bicyclo[3.2.0]hept-1(7)-ene complex, we investigated the gold(I)-catalyzed conversion of the 7-phenyl-1,6-enyne **1** into the 6-phenylbicyclo[3.2.0]hept-6-ene **2** reported by Echavarren (Scheme 2).[12] In an initial experiment, a 1:1:1 mixture of **1**, [LAuCl] (L = P(*t*Bu)$_2$(*o*-biphenyl)), and $AgSbF_6$ in CD_2Cl_2 was mixed thoroughly at −78 °C. ^{31}P and ^{1}H NMR analysis at −80 °C showed formation of an approximately 9:1 mixture of π-alkene and π-alkyne



Scheme 2. Gold-mediated conversion of **1** into **4**.

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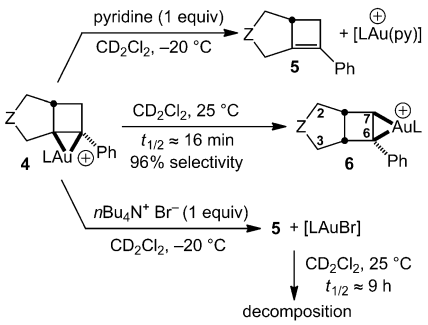
complexes **3a** and **3b** that together constituted around 90% of the reaction mixture (Scheme 2).[17–19] When this solution was warmed at −20 °C for 8 h, **3a** and **3b** were consumed to form the gold–7-phenylbicyclo[3.2.0]hept-1(7)-ene complex **4** in 97% yield (^{1}H NMR spectroscopy).[17] Complex **4** was likewise the only phosphine-containing species observed by ^{31}P NMR spectroscopy ($\delta = 65.4$) during the catalytic conversion of **1** into **2** (Scheme 2).

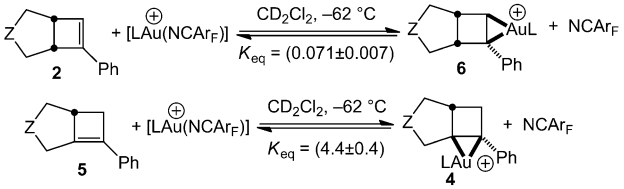
Complex **4** was thermally unstable and was characterized in solution at or below −20 °C by NMR spectroscopy and by comparison with free 7-phenylbicyclo[3.2.0]hept-1(7)-ene **5** (see below).[20] Coordination of gold to the C1–C7 bond of the bicyclo[3.2.0]heptene ligand was established by the large upfield shift ($\Delta\delta = -20$) of the C1 carbon atom of **4** relative to **5** and by the presence of phosphorous coupling to both the C1 ($\delta = 126.9$; $J_{CP} = 13.8$ Hz) and C7 carbon atom ($\delta = 141.2$; $J_{CP} = 7.5$ Hz) of the bicycloheptene ligand of **4** in the ^{13}C NMR spectrum. ^{1}H–^{1}H NOESY analysis established binding of the $[LAu]^+$ fragment to the convex face of the bicycloheptene ligand. Regarding the electronic structure of **4**, the C7 ($\delta = 141.2$) and C7-phenyl resonances ($\delta = 131.8$, 129.1, 127.2) of **4** were shifted downfield only slightly relative to those of free **5** ($\delta = 137.59$ (C7), 128.6, 127.7, 125.0 (Ph)) in the ^{13}C NMR spectrum;[21] this observation points to modest accumulation of positive charge at the C7 carbon atom of **4** and hence nominal contribution of the cyclobutyl cation structure **4a**. Rather, the $^1J_{C1C7}$ coupling constant of **4** ($^1J_{C1C7} =$ 33 Hz) was diminished significantly relative to that of **5** ($^1J_{C1C7} = 61$ Hz),[21] consistent with sp^3 hybridization of the C1 and C7 carbon atoms of the bicycloheptene ligand of **4**. This observation points to significant $d \rightarrow \pi^*$ back-bonding and the predominant contribution of the metallacyclopropane structure **4c** (Scheme 2).[22] The metallacyclopropane character of **4** stands in sharp contrast to the predominant σ-bonding character of extant gold–π-alkene complexes,[18] a discrepancy attributed to the strain associated with free **5**.[23]

Treatment of **4** with pyridine or nBu$_4$N$^+$ Br$^-$ (1 equiv) at −20 °C led to quantitative formation of free **5** and $[LAu(py)]^+$ SbF$_6^-$ or [LAuBr], respectively (Scheme 3); warming the latter solution at 25 °C led to the slow ($t_{1/2} \approx 9$ h) decomposition of **5** without detectable formation of **2** or vinylcyclopentene. Conversely, warming a solution of **4** at 25 °C led to rapid ($t_{1/2} \approx 16$ min) 1,3-hydrogen migration to form the thermally sensitive gold–6-phenylbicyclo[3.2.0]hept-6-ene complex **6** in 82% yield at 85% conversion (96% selectivity) without detectable formation of vinylcyclopentene (Scheme 3).[24]



Scheme 3. Isomerization and ligand displacement reactions of **4**.

As was the case with **4**, the $^1J_{C6C7}$ coupling constant of **6** ($^1J_{C6C7} = 35$ Hz) was diminished significantly relative to that of free **2** ($^1J_{C6C7} = 63$ Hz).[25] The strain of **2**, although attenuated relative to **5**,[23] is apparently sufficient to significantly bias the gold–alkene bond of **6** toward the metallacyclopropane structure. However, the lower strain of **2** relative to **5** was evidenced by the about 60-fold lower binding affinity of **2** to the $[LAu]^+$ fragment relative to that of **5**, determined by displacement of the weak σ-donor ligand NCAr$_F$ (NCAr$_F$ = NC-3,5-C$_6$H$_3$(CF$_3$)$_2$) from $[LAu(NCAr_F)]^+$ SbF$_6^-$ (Scheme 4).[26] The higher binding affinity of **5** relative to **2** is significant, considering that the binding affinity of the trisubstituted alkene 2-methyl-2-butene to $[LAu]^+$ is approximately 350 times greater than is that of the tetrasubstituted alkene 2,3-dimethyl-2-butene.[18]



Scheme 4. Equilibrium binding affinities of **2** and **5** to $[LAu]^+$ relative to NCAr$_F$ (NCAr$_F$ = NC-3,5-C$_6$H$_3$(CF$_3$)$_2$).

In summary, the stoichiometric reaction of 1,6-enyne **1** with [LAuCl]/AgSbF$_6$ at −20 °C led to selective (97%) formation of the gold–bicyclo[3.2.0]hept-1(7)-ene complex **4**, which is the only phosphine-containing species observed in the gold-catalyzed conversion of **1** into **2**. Complex **4** undergoes rapid 1,3-hydrogen migration at room temperature ($t_{1/2} \approx 16$ min) to form the gold–bicyclo[3.2.0]hept-1(7)-ene complex **6** with more than 90% selectivity. ^{13}C NMR analysis of both **4** and **6** established the dominant metallacyclopropane character of these complexes, which differs markedly from the predominant σ-donating character of known cationic, two-coordinate gold–π-alkene complexes.[18]

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[1] a) V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem.* **2008**, *120*, 4338–4386; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268–4315; b) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382; c) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215–236; d) A. Marinetti, H. Jullien, A. Voituriez, *Chem. Soc. Rev.* **2012**, *41*, 4884–4908; e) I. D. G. Watson, F. D. Toste, *Chem. Sci.* **2012**, *3*, 2899–2919.

[2] a) P. Y. Toullec, V. Michelet, *Top. Curr. Chem.* **2011**, *302*, 31–80; b) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478–3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410–3449; c) C. Nieto-Oberhuber, S. Lopez, E. Jiménez-Núñez, A. M. Echavarren,

Chem. Eur. J. **2006**, *12*, 5916 – 5923; d) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326 – 3350; e) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271 – 2296.

[3] Enyne cycloisomerization with skeletal rearrangement is also catalyzed by electrophilic post-transition metals.[4] However, enyne cycloisomerizations catalyzed by Pd^{II}–, Rh^{I}–hydride, and stable Ru^{II}–carbene complexes occur through mechanistically distinct pathways.[1]

[4] a) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294 – 10295; b) Y. Miyanohana, N. Chatani, *Org. Lett.* **2006**, *8*, 2155 – 2158.

[5] A. Fürstner, H. Szillat, B. Gabor, R. Mynott, *J. Am. Chem. Soc.* **1998**, *120*, 8305 – 8314.

[6] For reviews of intermediates generated in gold-catalyzed reactions, see: a) A. S. K. Hashmi, *Angew. Chem.* **2010**, *122*, 5360 – 5369; *Angew. Chem. Int. Ed.* **2010**, *49*, 5232 – 5241; b) H. Schmidbaur, A. Schier, *Organometallics* **2010**, *29*, 2 – 23.

[7] Organometallic intermediates have been detected in Ti^{II}–[8] and Ru^{II}–carbene-catalyzed enyne cycloisomerization.[9]

[8] S. J. Sturla, N. M. Kablaoui, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 1976 – 1977.

[9] a) T. R. Hoye, S. M. Donaldson, T. J. Vos, *Org. Lett.* **1999**, *1*, 277 – 280; b) M. P. Schramm, D. S. Reddy, S. A. Kozmin, *Angew. Chem.* **2001**, *113*, 4404 – 4407; *Angew. Chem. Int. Ed.* **2001**, *40*, 4274 – 4277.

[10] Echavarren has observed the inactive gold – π-alkene complex from stoichiometric reaction of 5,5-bis(methoxycarbonyl)-1,7-enyne with $[LAu(NCMe)]^+ SbF_6^-$. M. García-Mota, N. Cabello, F. Maseras, A. M. Echavarren, J. Pérez-Ramírez, N. Lopez, *ChemPhysChem* **2008**, *9*, 1624 – 1629.

[11] a) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244 – 8245; b) T. Matsuda, S. Kadowaki, T. Goya, M. Murakami, *Synlett* **2006**, 575 – 578.

[12] a) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178 – 6179; b) C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2008**, *130*, 269 – 279.

[13] A. Escribano-Cuesta, P. Perez-Galan, E. Herrero-Gomez, M. Sekine, A. A. C. Braga, F. Maseras, A. M. Echavarren, *Org. Biomol. Chem.* **2012**, *10*, 6105 – 6111.

[14] K. Ota, S. I. Lee, J.-M. Tang, M. Takachi, H. Nakai, T. Morimoto, H. Sakurai, K. Kataoka, N. Chatani, *J. Am. Chem. Soc.* **2009**, *131*, 15203 – 15211.

[15] a) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509 – 1511; b) S. Couty, C. Meyer, J. Cossy, *Angew. Chem.* **2006**, *118*, 6878 – 6882; *Angew. Chem. Int. Ed.* **2006**, *45*, 6726 – 6730; c) J. Blum, H. Beer-Kraft, Y. Badrieh, *J. Org. Chem.* **1995**, *60*, 5567 – 5569; d) S. I. Lee, S. M. Kim, M. R. Choi, S. Y. Kim, Y. K. Chung, W.-S. Han, S. O. Kang, *J. Org. Chem.* **2006**, *71*, 9366 – 9372.

[16] Stable bicyclo[*n*.2.0]alkenes ($n \geq 4$) possessing a bridgehead C=C bond have been isolated from the cycloisomerization of 1,*m*-enynes ($m \geq 7$): Y. Odabachiana, F. Gagosz, *Adv. Synth. Catal.* **2009**, *351*, 379 – 386, and references therein.

[17] The major species (^{31}P NMR: $\delta = 62.2$) was assigned as the π-alkene complex **3a** on the basis of the large upfield shift of the terminal-vinyl proton resonance of **3a** ($\Delta\delta \approx 1$) relative to **1** in the ^1H NMR spectrum at −80 °C.[18] The minor species was assigned as the π-alkyne complex **3b**, owing to the presence of carbon–phosphorous coupling in the ^{31}P NMR spectrum of the ^{13}C-labeled isotopomer **3b**-5,6,7-$^{13}C_3$ ($\delta = 62.6$, dd, $J = 4.9$, 27.5 Hz) generated from the ^{13}C-labeled enyne **1**-5,6,7-$^{13}C_3$. Significant broadening of both the ^{31}P and ^1H NMR resonances of **3a** and **3b** at −20 °C, presumably as a result of facile π-ligand exchange, precluded accurate determination of the **3a**/**3b** ratio as a function of conversion. Preferential formation of **3a** relative to **3b** is in accord with the relative binding affinities of a terminal alkene and an internal aryl alkyne to gold.[18,19]

[18] a) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2009**, *131*, 6350 – 6351; b) T. J. Brown, M. G. Dickens, R. A. Widenhoefer, *Chem. Commun.* **2009**, 6451 – 6453.

[19] T. J. Brown, R. A. Widenhoefer, *J. Organomet. Chem.* **2011**, *696*, 1216 – 1220.

[20] ^1H NMR for **4** (−20 °C, 500 MHz, aliphatic resonances only): $\delta =$ 3.74 (s, 3H), 3.28 (s, 3H), 3.24 (d, $J = 14.9$ Hz, 1H), 3.12 (d, $J =$ 14.9 Hz, 1H), 3.07 (dtd, $J = 1.5$, 4.3,15 Hz, 1H), 2.84 (ddd, $J =$ 4.0, 5.2, 9.4 Hz, 1H), 2.77 (dd, $J = 3.2$, 14.9 Hz, 1H), 2.51 (dd, $J =$ 9, 14.2 Hz, 1H), 2.22 (dd, $J = 5.8$, 14.2 Hz, 1H), 1.35 (d, $J =$ 16.2 Hz, 9H), 1.24 ppm (d, $J = 16.2$ Hz, 9H).

[21] The phenyl ^{13}C resonances of **4** and **5** were identified by comparison to the corresponding C_6D_5 isotopomers [D_5]-**4** and [D_5]-**5**, respectively. The $^1J_{C1C7}$ coupling constants of **4** and **5** were determined by analysis of the ^{13}C-labeled isotopomers **4**-1,2,7-$^{13}C_3$ and **5**-1,2,7-$^{13}C_3$, respectively.

[22] For discussions of $^1J_{CC}$ coupling constants and the electronic structure of transition metal–alkene complexes, see: a) B. R. Bender, J. R. Norton, M. M. Miller, O. P. Anderson, A. K. Rappé, *Organometallics* **1992**, *11*, 3427 – 3434; b) R. Benn, A. Rufiñska, *J. Organomet. Chem.* **1982**, *238*, C27 – C30; c) J. W. Fitch, E. B. Ripplinger, B. A. Shoulders, S. D. Sorey, *J. Organomet. Chem.* **1988**, *352*, C25 – C28; d) L. Krivdin, G. Kalabin, *Prog. Nucl. Magn. Reson. Spectrosc.* **1989**, *21*, 293 – 448.

[23] a) W. F. Maier, P. v. R. Schleyer, *J. Am. Chem. Soc.* **1981**, *103*, 1891 – 1900; b) G. Oba, G. Moreira, G. Manuel, M. Koenig, *J. Organomet. Chem.* **2002**, *643*, 324 – 330; c) J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311 – 365.

[24] The ^1H NMR resonances corresponding to **6** became obscured at more than 85% conversion.

[25] Determined by analysis of the ^{13}C-labeled isotopomers **6**-6-$^{13}C_1$ and **2**-6-$^{13}C_1$. ^1H NMR for **6** (−20 °C, 500 MHz, aliphatic resonances only): $\delta = 4.66$ (d, $J = 4.8$ Hz, 1H), 3.99 (dd, $J = 2.9$, 7.9 Hz, 1H), 3.67 (s, 3H), 3.21 (ddd, $J = 1.4$, 3.0, 7.6 Hz, 1H), 3.15 (s, 3H), 2.69 (d, $J = 14.0$ Hz, 1H), 2.55 (d, $J = 14.4$ Hz, 1H), 2.29 (dd, $J = 8.2$, 14.4 Hz, 1H), 2.08 (dd, $J = 7.8$, 14.0 Hz, 1H), 1.30 (d, $J = 16.6$ Hz, 9H), 0.86 ppm (d, $J = 16.6$ Hz, 9H).

[26] Enhanced π-backbonding and increased bond strength with increasing alkene strain has been calculated for platinum – alkene complexes: J. Uddin, S. Dapprich, G. Frenking, B. F. Yates, *Organometallics* **1999**, *18*, 457 – 465.

