Reaction Mechanisms

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# Divergent Mechanisms for the Skeletal Rearrangement and [2+2] Cycloaddition of Enynes Catalyzed by Gold**

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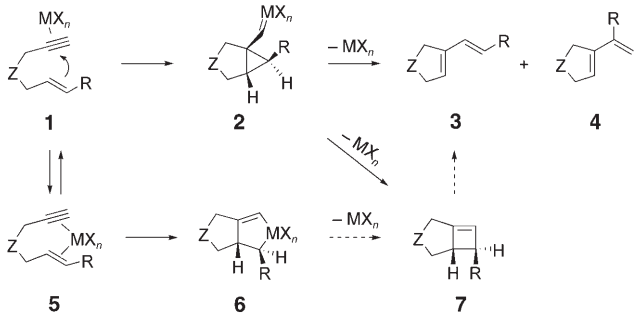
Transition-metal-catalyzed reactions of 1,6-enynes proceed via two general pathways (Scheme 1).[1,2] If the metal coordinates selectively to the alkyne **1**, cyclopropyl–metal




***Scheme 1.***

carbenes **2** are initially formed, which can react with alcohols or water to give products of alkoxy- or hydroxycyclization,[1,2] whereas in the absence of nucleophiles, skeletal rearrangement forms dienes **3** (*single cleavage*) and/or **4** (*double cleavage*).[1,3] Alternatively, coordination of $MX_n$ to the alkyne and the alkene (as in **5**) is followed by oxidative cyclometalation to form **6**, which usually evolves by β-hydrogen elimination to give Alder–ene-type products.[2] Formation of products **3** could also occur by conrotatory ring-opening of cyclobutenes **7**,[4,5] which are formed either from **2** or by reductive elimination of **6**.

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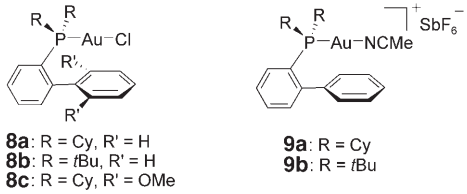
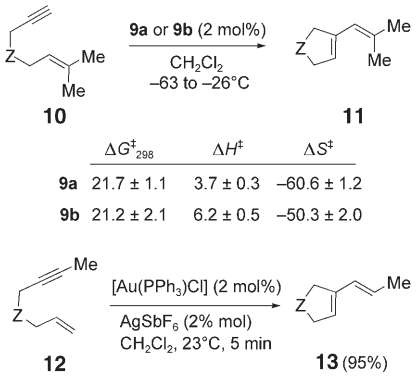
A pathway for the formation of **3** via ring-opening of **7** is favored by most authors.[4,6] However, the formation of dienes **4** requires a different mechanistic rationalization. An earlier mechanistic proposal by Oi et al.[3] suggested a direct pathway for the skeletal rearrangement via intermediates of type **2**. Herein we report experimental and theoretical results that shed new light into this complex mechanistic issue. In particular, this work strongly suggests that cyclobutenes **7** are not necessary intermediates in the skeletal rearrangement of enynes.

Alder–ene-type products have not been observed in $Au^I$-catalyzed reactions, which is consistent with the selective coordination of cationic $[Au(L)]^+$ complexes to the alkyne.[2c,7,8] In the presence of catalysts formed from **8a–c** and $AgSbF_6$,[7b] or new cationic complexes **9a**,**b**, enyne **10**




undergoes a *single cleavage rearrangement* to form **11** quantitatively at a temperature as low as −63 °C (Scheme 2). On the other hand, enyne **12** undergoes a



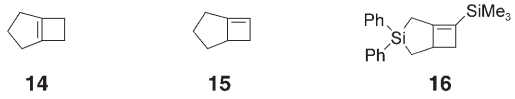

***Scheme 2.*** $Z = C(CO_2Me)_2$. $\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in kcal mol$^{-1}$; $\Delta S^{\ddagger}$ in cal K$^{-1}$ mol$^{-1}$.

*double cleavage* rearrangement with $[Au(PPh_3)]SbF_6$ to give exclusively **13**.[3,9] These are the skeletal rearrangements occurring at the lowest temperatures. Reaction of enyne **10** with catalyst **9a** (−63 to −26 °C) or **9b** (−43 to −28 °C) was monitored by $^1$H NMR spectroscopy in $CD_2Cl_2$. Under these conditions, smooth and quantitative formation of diene **11** was observed without the build up of any intermediate. The rearrangement is pseudo-first order in **10**, which allowed us to determine the thermodynamic parameters shown in Scheme 2.

The large and negative activation entropies suggest that an associative ligand substitution[10] (diene **11** by incoming enyne **10**) is the rate-determining step of the process. These results establish a very low activation energy ($E_a$) for the

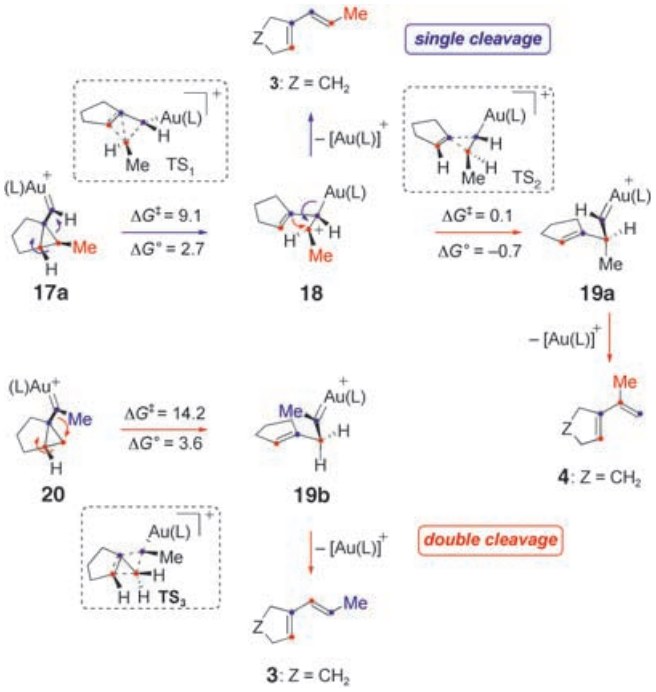
hypothetical conrotatory ring-opening of a cyclobutene of type **7**, which therefore should be a fast process at temperatures as low as −63 °C. This is not consistent with the ring-opening of bicycle **14** and its 6,7-dimethyl derivatives,[11] for which activation energies of 29.0–32.7 kcal mol$^{-1}$ and low entropies of activation (1.4–2.2 cal K$^{-1}$ mol$^{-1}$) have been determined. DFT calculations predict an $E_a$ of 25.6 kcal mol$^{-1}$ for the conrotatory ring-opening of bicyclo[3.2.0]hept-5-ene (**15**) to 1-vinyl-1-cyclopentene ($\Delta G_{298\,K} = -22.5$ kcal mol$^{-1}$).




**14** **15** **16**

It is important to note that **15** has a lower olefin strain (OS = 16.7 kcal mol$^{-1}$) than **14** (OS = 20.5 kcal mol$^{-1}$), which is stable up to 118 °C.[12] Additional evidence against the ring-opening of a cyclobutene in the low temperature skeletal rearrangement of **10** is provided by the isolation of bicycle **16** as a stable compound.[13]

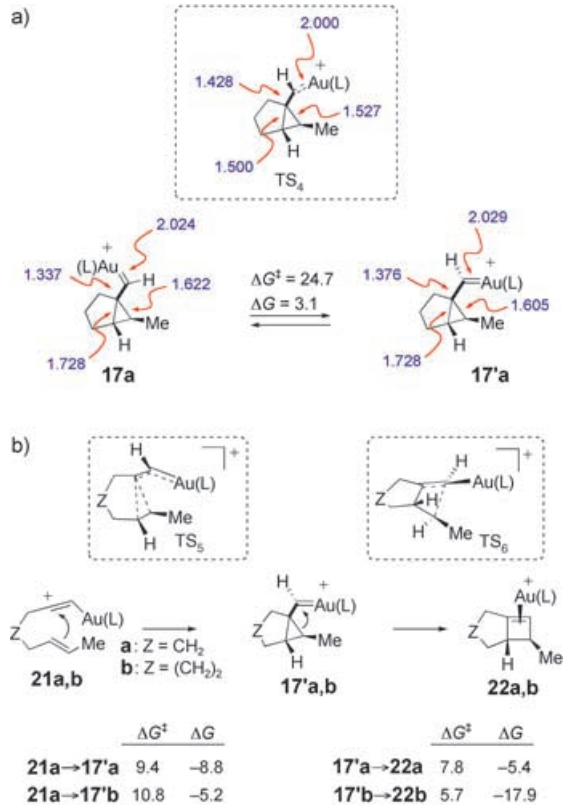
DFT calculations[14] support pathways for the skeletal rearrangement that do not involve the intermediacy of cyclobutenes **7**. Thus, complex **17a** evolves via **TS$_1$** to form cation **18**, which could furnish dienes **3** by elimination of [Au(L)]$^+$ (Scheme 3). Alternatively, a 1,2-shift gives gold




***Scheme 3.*** L = PH$_3$. $\Delta G$ at 298 K (energies in kcal mol$^{-1}$).

carbene **19a** via **TS$_2$** in an almost flat potential surface. Dienes **4** would result from **19a** by β-hydrogen elimination and demetalation. In the case of **20**, which is the intermediate in a reaction of an enyne of type **12**, a double-cleavage rearrangement was found to give **19b** directly, in agreement with the experimental results. This remarkable process involves a 1,2-shift of a metal carbene with concomitant cleavage of the distal C–C bond of the cyclopropane and formation of a double bond.

No direct pathway for the formation of a cyclobutene from **17a** was found. In contrast, *syn*-**17′a** forms **22a** via **TS$_5$**, although the *anti* to *syn* isomerization from **17a** to **17′a** requires a rather high activation energy (Scheme 4).[14] This




***Scheme 4.*** L = PH$_3$. $\Delta G$ at 298 K (energies in kcal mol$^{-1}$) and selected bond lengths [Å] for **17a**, **17′a**, and **TS$_4$**.

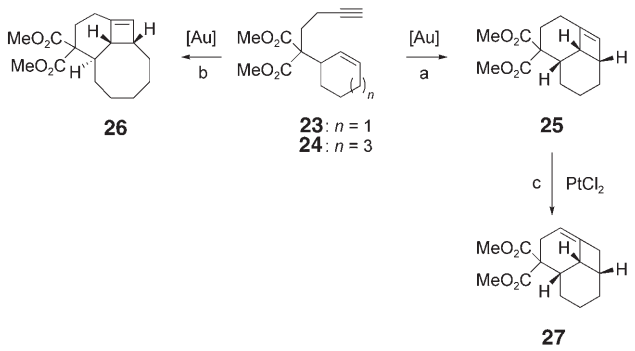
high activation energy of 24.7 kcal mol$^{-1}$ can be attributed to the loss of conjugation between the gold carbene and the cyclopropane, as shown by the significant shortening of the cyclopropane and C=Au bonds and the lengthening of the C–C bond connecting the cyclopropane and the gold carbene in **TS$_4$**. This isomerization process is rather unlikely under the reaction conditions, as the initially formed *anti*-**17a** would undergo a more facile rearrangement via **18** ($\Delta G^{\neq} = 9.1$ kcal mol$^{-1}$, Scheme 3). However, an alternative pathway has been found for a more direct formation of complexes **17′a**,**b** by a *syn*-type attack of the alkene, via **TS$_5$**, to the (alkyne)gold moiety of **21a**,**b** (Scheme 4).

Although the *anti* attack of the alkene is more favorable,[7a] the *syn* attack could compete if substitution at the alkene and/or the alkyne disfavors the skeletal rearrangement. In particular, this should be more favorable for the formation of bicyclo[3.2.0]oct-6-enes from 1,7-enynes, in accordance with the calculations (**17′b**→**22b**, Scheme 4) and experiments.[4] Significantly, cationic gold complexes catalyze the [2+2] cycloaddition of 1,7-enynes. Thus, enynes **23** and **24**

react with complexes $[Au(L)]^+$ at room temperature to give **25** and **26**,[4b,d] respectively (Scheme 5).

Tricycles **25** and **26** do not undergo ring-opening at 120–150 °C to form 1,3-dienes.[15] To study the possible effect of transition metals in the ring-opening of the cyclobutene,[16] **25**




***Scheme 5.*** Reactions of **23** and **24**: a) **9b** (2 mol%), $CH_2Cl_2$, room temp., 14 h (80%); b) **8c** (2 mol%), $AgSbF_6$ (2 mol%), $CH_2Cl_2$, room temp., 45 min (67%); c) $PtCl_2$ (5 mol%), MeCN, 120 °C, 20 h (67%).

was heated in MeCN at 120 °C in the presence of 5 mol% $PtCl_2$ (Scheme 5). Interestingly, under these conditions, $Pt^{II}$,[1,3,4d,f,g] which is a known catalyst for the skeletal rearrangement, does not promote the ring-opening of the cyclobutene but rather promotes isomerization to form the less-strained tricycle **27**.[17]

In summary, calculations on the $Au^I$-catalyzed skeletal rearrangement of enynes support the earlier proposals suggested by Oi et al.[3] and others,[1,4] although Scheme 3 provides a more rigorous and concise mechanistic picture. An alternative pathway has been found for the formation of cyclobutenes via *syn*-cyclopropyl–metal carbenes, formed by a *syn* electrophilic addition of the metal and the alkene to the alkyne. Kinetic experiments indicate that if a conrotatory ring-opening of a cyclobutene intervenes in the skeletal rearrangement, its $E_a$ value would be unreasonably low.

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[1] Reviews: a) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215–236; b) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.* **2002**, *102*, 813–834; c) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317–1382; d) A. M. Echavarren, C. Nevado, *Chem. Soc. Rev.* **2004**, *33*, 431–436.

[2] a) M. Méndez, M. P. Muñoz, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511–10520; b) C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2003**, *9*, 2627–2635; c) M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300.

[3] S. Oi, I. Tsukamoto, S. Miyano, Y. Inoue, *Organometallics* **2001**, *20*, 3704–3709.

[4] a) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1988**, *110*, 1636–1638; b) B. M. Trost, M. K. Trost, *Tetrahedron Lett.* **1991**, *32*, 3647–3650; c) B. M. Trost, M. Yanai, K. Hoogsteed, *J. Am. Chem. Soc.* **1993**, *115*, 5294–5295; d) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869; e) N. Chatani, H. Inoue, T. Kotsuma, S. Murai, *J. Am. Chem. Soc.* **2002**, *124*, 10294–10295; f) F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509–1511; g) G. B. Bajracharya, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 892–897.

[5] For formation of a different type of cyclobutene, see: a) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244–8245; b) see also ref. [7b].

[6] E. Soriano, P. Ballesteros, J. Marco-Contelles, *Organometallics* **2005**, *24*, 3172–3181.

[7] a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456–2460; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406; b) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179.

[8] a) V. Mamane, T. Gress, H. Krause, A. Fürstner, *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655; b) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806–11807; c) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858–10859.

[9] a) N. Chatani, H. Inoue, T. Morimoto, T. Muto, S. Murai, *J. Org. Chem.* **2001**, *66*, 4433–4436; b) C. H. Oh, S. Y. Bang, C. Y. Rhim, *Bull. Korean Chem. Soc.* **2003**, *24*, 887–888.

[10] P. N. Dickson, A. Wehrli, G. Geier, *Inorg. Chem.* **1988**, *27*, 2921–2925.

[11] P. S. Lee, S. Sakai, P. Hörstermann, W. R. Roth, E. A. Kallel, K. N. Houk, *J. Am. Chem. Soc.* **2003**, *125*, 5839–5848.

[12] W. F. Maier, P. von R. Schleyer, *J. Am. Chem. Soc.* **1981**, *103*, 1891–1900.

[13] G. Oba, G. Moreira, G. Manuel, M. Koenig, *J. Organomet. Chem.* **2002**, *643–644*, 324–330.

[14] Calculations at the B3LYP/6-31G(d) (C,H,P), LANL2DZ (Au) level.

[15] The thermal ring-opening of a cyclobutene formed in a reaction of an enyne catalyzed by $PtBr_2$ has been shown to take place at 120 °C in acetonitrile: G. B. Bajracharya, I. Nakamura, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 892–897.

[16] D. J. Tantillo, R. Hoffmann, *J. Am. Chem. Soc.* **2001**, *123*, 9855–9859.

[17] Tricycle **27** is 7.9 kcal mol$^{-1}$ more stable than **25** (PM3 calculation).

  