Gold Catalysis

DOI: 10.1002/anie.200802517

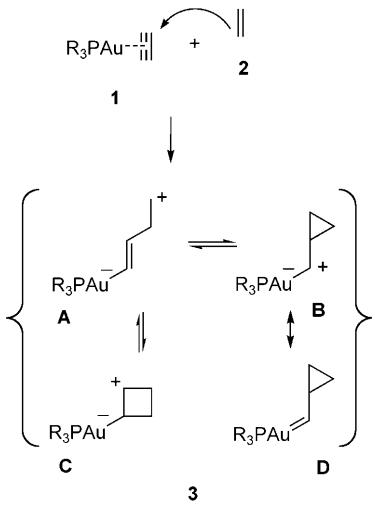
"High Noon" in Gold Catalysis: Carbene versus Carbocation Intermediates

*A. Stephen K. Hashmi**

carbenes · carbocations · gold · homogeneous catalysis · reactive intermediates

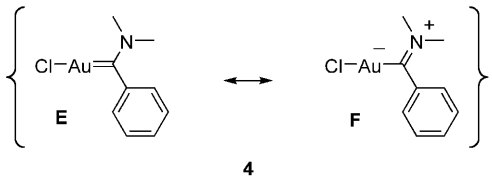
In the past eight years, homogeneous catalysis of organic reactions by gold complexes has developed into a unique and highly useful tool for organic synthesis.[1] The preparative advantages of these reactions are quite clear,[2] but the mechanistic aspects often are not. While labeling studies,[3] the identification of side products,[4] spectroscopy/spectrometry in situ,[3c,5] trapping of intermediates,[5b,6] and quantum chemical investigation[4a,7] have led to a good understanding of several reaction pathways, the electronic structure of a crucial intermediate of many reactions is still a matter of debate. Many gold-catalyzed reactions, in particular the cycloisomerizations of enynes,[8] proceed by the initial electrophilic attack of a gold–alkyne complex **1** on an alkene **2**, leading to the intermediate **3** (Scheme 1).

Fürstner and Morency[9] now suggest that among the different mesomeric/tautomeric formulas **A**–**D**, which represent the true electronic structure of intermediate **3** and are reminiscent of a "nonclassical" carbocation, carbocation **A** is the most important. Thus the widespread[8] popular description of intermediate **3** as carbenoid **D** is misleading.



Scheme 1. Mesomeric/tautomeric forms **A**–**D** of the intermediate **3**.

A crystal structure analysis of the chloridogold "carbene" complex **4**, known since 1982,[10] strongly supports this suggestion. Its bond lengths are typical for Au–C(sp^2) single bonds, and the C–N bond is even shorter than a typical imine double bond! Thus rather than a Fischer-type gold "carbene" complex **E**, the mesomeric iminium cation structure **F** is a realistic description (Scheme 2).



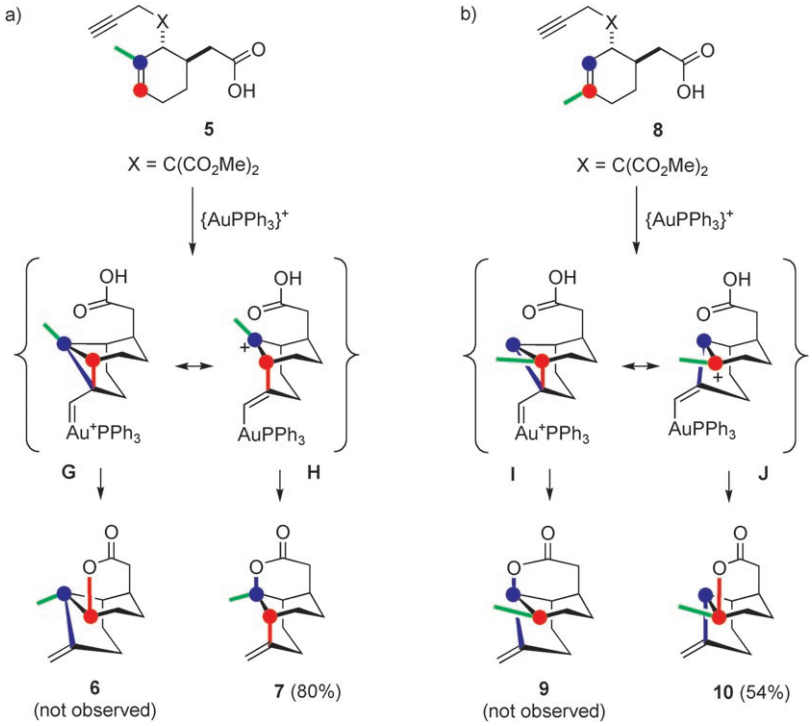
Scheme 2. Mesomeric forms **E** and **F** of a Fischer-type gold "carbene".

Since most catalytic intermediates bear neutral phosphane ligands rather than anionic chlorido ligands, this stable complex **4** cannot be compared directly with intermediates of a catalytic cycle. (For example, $\{R_3PAu\}^+$ is a cationic fragment, while {ClAu} is a neutral fragment). At first glance, one could assume that discussion of the contribution of different mesomeric/tautomeric forms is only semantic in nature and may be relevant for computational or theoretical chemists but not for the synthetic chemist. As Fürstner and Morency mention in a footnote in their paper, typical reactions used as an indication of a gold carbene intermediate, for example the oxygen-transfer reaction from a sulfoxide,[11] can also easily proceed through a carbocation intermediate and thus cannot be used to determine the contribution of the two forms **A** and **C**.

So, if on the one hand the two species undergo the same chemical transformations and on the other hand many reactions are typically associated with carbenoid species—for example, in cyclopropanation reactions[6a,12] or 1,2 H-shifts to deliver alkenes[13]—why not use the carbene form in descriptions of these intermediates? The use of the alternative carbocation form would be mandatory only when experimental results could not be explained with the carbene structure.

[*] Prof. Dr. A. S. K. Hashmi
Organisch-Chemisches Institut
Ruprecht-Karls-Universität Heidelberg
Im Neuenheimer Feld 270, 69120 Heidelberg (Germany)
E-mail: hashmi@hashmi.de
Homepage: http://www.hashmi.de

This is exactly what Fürstner and Morency now report. In a series of experiments associated with enyne cycloisomerizations, they investigated the influence of a simple methyl substituent (in green in Scheme 3a) as in the example of substrate **5**. Electronically, the substituent would stabilize carbocation structure **H** and thus ultimately direct a nucleophile to the position at which the methyl group is attached (blue carbon atom in **H**) to deliver **7**. On the other hand, the methyl substituent would make the very same carbon atom less accessible in a nucleophilic attack to the carbenoid species **G** for steric reasons. In fact one could expect an attack of the nucleophile at the less hindered cyclopropyl carbon (red carbon atom in **G**) to deliver **6**. In the experiment the nucleophile attacks at the position of the methyl group and delivers exclusively **7**; this can be explained only by the distinct dominance of the carbocation form **H**.



Scheme 3. The position of the methyl group also determines the position of the nucleophilic attack. Details given in text.

The regioselectivity completely switches when the methyl group (in green in Scheme 3b) is at the opposite end of the C=C bond (as in **8**), which underlines the electronic influence of the methyl group. Again this could hardly be explained by the carbenoid intermediate **I** (which would give rise to **9** upon attack of the nucleophile at the less hindered (blue) carbon atom of **I**), but it can be explained by the carbocation **J** (which would give rise to **10** upon attack at the cationic (red) carbon atom of **J**).

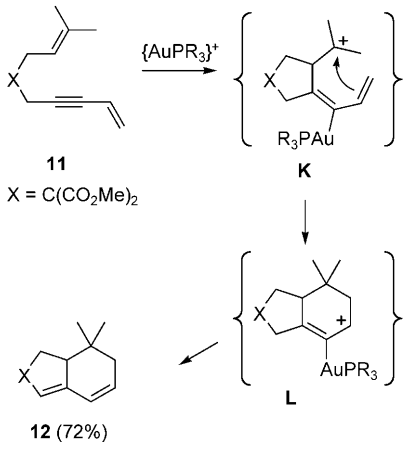
Since the substrates of Fürstner and Morency are hardly extraordinary, the question arises whether this finding has broader implications. Here one has to keep in mind that the methyl substituents are not "innocent": they do stabilize the carbocationic form. Thus in an undisturbed system the situation might be different. The unsubstituted derivative of **5/8** lacking the methyl substituent on the C=C bond delivers a mixture of both products (analogues of **7** and **10**) in a 60:11 ratio; the high regioselectivity is lost.

As a proof of this principle, previous results in the literature can be checked to see whether these can now be explained on this basis. In an analysis of the published experiments,[8] several examples of exactly this type can be found, one being the conversion of **11** to **12**. In the original literature[14] a cyclopropylcarbene intermediate is postulated, but here, too, the more substituted cyclopropyl carbon atom should be less reactive towards the nucleophile, and the alternative carbocationic form **K** readily leading to intermediate **L** would nicely explain the product formed (Scheme 4).

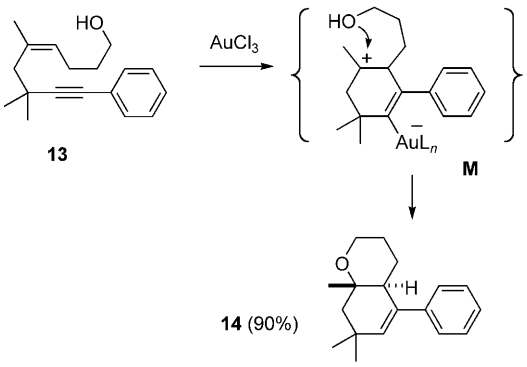
Another perfectly suitable example is the conversion of the 1,5-enyne **13** to **14**.[15] This time a gold(III) precatalyst was used (Scheme 5). Again the vinylic methyl group directs the incoming nucleophilic hydroxy group to the more substituted position, which would be explained conveniently by the carbocationic intermediate **M**.

In fact most of the even less related known cyclizations of enynes can be discussed on a similar basis using a carbocationic form of the intermediate. The future will show whether an example can be found providing unambiguous evidence for a gold carbene intermediate with a clear domination of the carbene form.

Overall, the investigation of Fürstner and Morency clearly shows that for many examples the carbocationic intermediate is the most important one. This significant finding must be considered in the formulation of mechanistic proposals in the future. One can expect that the relative stability of forms **A**–**D** is a function of the substitution pattern, and without cation-stabilizing substitu-



Scheme 4. The formation of **12** from **11** can be explained easily by the carbocationic intermediate **K**.



Scheme 5. The carbocationic intermediate **M** would readily explain the formation of **14** from **13**.

ents it is still unclear which description of the intermediate is most suitable; the results indicate only that without the methyl substituent the conversion is less effective for Fürstner's and Morency's examples, but whether this is related to the carbocation being less readily accessible or the carbene-like intermediate being less reactive cannot yet be decided.

Published online: August 5, 2008

[1] a) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407 – 4409; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237 – 4239; b) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3 – 9; c) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51 – 65; d) N. Krause, A. Hoffmann-Röder, *Org. Biomol. Chem.* **2005**, *3*, 387 – 391; e) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150 – 7154; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990 – 6993; f) A. S. K. Hashmi, G. Hutchings, *Angew. Chem.* **2006**, *118*, 8064 – 8105; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896 – 7936; g) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395 – 403; h) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478 – 3519; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410 – 3449; i) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333 – 346; j) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180 – 3211.

[2] A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev.* **2008**,10.1039/b615629k.

[3] For example: a) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553 – 11554; b) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526 – 4527; c) A. S. K. Hashmi, J. P. Weyrauch, W. Frey, J. W. Bats, *Org. Lett.* **2004**, *6*, 4391 – 4394; d) J. Zhang, C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2006**, *128*, 1798 – 1799; e) I. V. Seregin, V. Gevorgyan, *J. Am. Chem. Soc.* **2006**, *128*, 12050 – 12051.

[4] For example: a) B. Martín-Matute, D. J. Cardenas, A. M. Echavarren, *Angew. Chem.* **2001**, *113*, 4890 – 4893; *Angew. Chem. Int. Ed.* **2001**, *40*, 4754 – 4757; b) A. S. K. Hashmi, M. Blanco, D. Fischer, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387 – 1389.

[5] For example: a) J. Guzman, B. C. Gates, *J. Catal.* **2004**, *226*, 111 – 119; b) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey, J. W. Bats, *Angew. Chem.* **2005**, *117*, 2858 – 2861; *Angew. Chem. Int. Ed.* **2005**, *44*, 2798 – 2801; c) J. Roithová, J. Hrusák, D. Schröder, H. Schwarz, *Inorg. Chim. Acta* **2005**, *358*, 4287 – 4292.

[6] For example: a) K. Miki, K. Ohe, S. Uemura, *Tetrahedron Lett.* **2003**, *44*, 2019 – 2022; b) S. López, E. Herrero-Gómez, P. Pérez-Galán, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 6175 – 6178; *Angew. Chem. Int. Ed.* **2006**, *45*, 6029 – 6032; c) A. S. K. Hashmi, E. Kurpejovic, M. Wölfle, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2007**, *349*, 1743 – 1750.

[7] For example: a) J. H. Teles, S. Brode, M. Chabanas, *Angew. Chem.* **1998**, *110*, 1475 – 1478; *Angew. Chem. Int. Ed.* **1998**, *37*, 1415 – 1418; b) B. Straub, *Chem. Commun.* **2004**, 1726 – 1728; c) O. N. Faza, C. S. López, R. Álvarez, A. R. de Lera, *J. Am. Chem. Soc.* **2006**, *128*, 2434 – 2437.

[8] a) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380 – 2386; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328 – 2334; b) L. Zhang, J. Sun, S. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271 – 2296; c) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206 – 209; *Angew. Chem. Int. Ed.* **2006**, *45*, 200 – 203.

[9] A. Fürstner, L. Morency, *Angew. Chem.* **2008**, *120*, 5108 – 5111; *Angew. Chem. Int. Ed.* **2008**, *47*, 5030 – 5033.

[10] U. Schubert, K. Ackermann, R. Aumann, *Cryst. Struct. Comm.* **1982**, *11*, 591 – 594.

[11] C. A. Witham, P. Mauleón, N. D. Shapiro, B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 5838 – 5839.

[12] C. Nieto-Oberhuber, M. P. Munoz, E. Bunuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456 – 2460; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402 – 2406.

[13] A. S. K. Hashmi, M. Wölfle, F. Ata, M. Hamzic, R. Salathé, W. Frey, *Adv. Synth. Catal.* **2006**, *348*, 2501 – 2508.

[14] C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178 – 6179.

[15] The difference between gold(I) and gold(III) precatalysts is another point of debate; there is evidence for reduction of gold(III) in situ: A. S. K. Hashmi, M. C. Blanco, D. Fischer, J. W. Bats, *Eur. J. Org. Chem.* **2006**, 1387 – 1389. For the phenol synthesis (a special subtype of the enyne cycloisomerization) it has been proven that the activity of heterogeneous catalysts is not based on gold(0): S. Carrettin, M. C. Blanco, A. Corma, A. S. K. Hashmi, *Adv. Synth. Catal.* **2006**, *348*, 1283 – 1288.

