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Gold-Catalyzed Annulation/Fragmentation: Formation of Free Gold Carbenes by Retro-Cyclopropanation

César R. Solorio-Alvarado and Antonio M. Echavarren*,†

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

Received June 1, 2010; E-mail: aechavarren@iciq.es

Abstract: The gold(I)-catalyzed cyclization of 1-(prop-2-yn-1-yl)-2-alkenylbenzenes substituted at the benzylic position with OR groups gives 1,3-disubstituted naphthalenes with concomitant fragmentation of the alkene. One of these annulations proceeds by a retro-cyclopropanation that leads to free gold(I) carbenes.

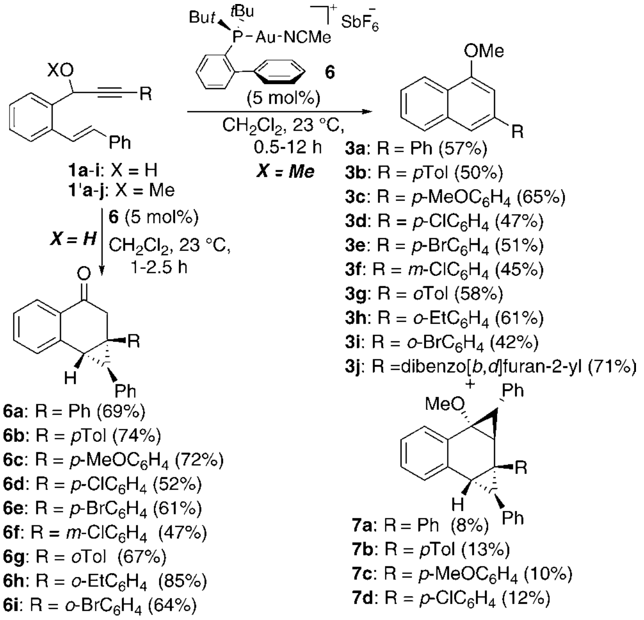
Metal-catalyzed reactions of 1,*n*-enynes lead to a wide variety of cyclic compounds under mild conditions.[1,2] We recently found that 1,*n*-enynes bearing propargyl alcohols, ethers, and silyl ethers react with cationic gold(I) catalysts by a new type of cyclization in which the OR group undergoes a $(1,n-1)$-migration.[3] However, when we tried the gold-catalyzed cyclization of 1,6-enynes **1** and **2**, very different results were obtained (Scheme 1). Substrates **1** with an aryl substituent at the alkene gave naphthalenes **3**[4] by an annulation in which the alkene is cleaved to form simple gold(I) carbenes **5**. This fragmentation proceeds by a gold(I)-promoted retro-cyclopropanation, a process that was recently proposed for the gas-phase cleavage of 1-ethoxy-2-methoxycyclopropane with [AuIMes]$^+$ [IMes =1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene] on the basis of CID experiments and theoretical calculations.[5] Cleavage of cyclopropanes to form metal carbenes was demonstrated with PhWCl$_3$/RAlCl$_2$ (R = Et, Cl).[6] Highly strained bicyclo[1.1.0]butanes also undergo retro-cyclopropanation with Ni(0) or Rh(I) via oxidative addition reactions.[7] Enynes **2** with an enol ether undergo a gold(I)-catalyzed annulation/fragmentation to give naphthalenes **4**.

Scheme 1

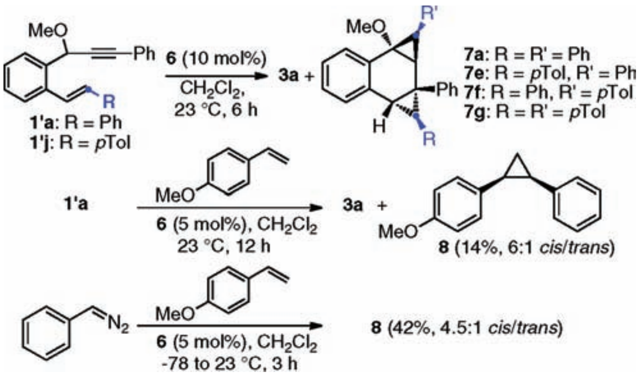
1,6-Enynes **1a**−**i** and **1′a**−**j** bearing OH and OMe substituents at the propargyl position react differently with cationic Au(I) catalysts **6** (Scheme 2).[8] In the former case, products **6a**−**i** of 6-*endo*-dig cycloisomerization were obtained,[9] whereas methyl ethers **1′a**−**i** gave 3-aryl-1-methoxynaphthalenes **3a**−**j** in 45−71% yield. Surprisingly, in addition to the annulation/fragmentation products, we also isolated biscyclopropanes **7a**−**d** with an extra CHPh unit.

These results suggest that gold(I) carbene **5** is formed in the fragmentation process. To confirm the formation of free **5**, we first carried out the reaction of a 1:1 mixture of **1′a** and **1′j** with catalyst **6** (Scheme 3). In this experiment, besides naphthalene **3a** and biscyclopropanes **7a** and **7g**, we also observed formation of **7e** and **7f**, which are the products of crossover cyclopropanation. Furthermore, when the gold(I)-catalyzed annulation of **1′a** was performed in the presence of *p*-methoxystyrene, cyclopropane **8** was obtained (6:1 cis/trans). As a control, the cyclopropanation of *p*-methoxystyrene with phenyldiazomethane and catalyst **6** also led to **8** (4.5:1 cis/trans).[10−12]

Scheme 2



Scheme 3



These results are consistent with a mechanism proceeding by the 6-*endo*-dig gold(I)-promoted cyclization of enynes **1** to form

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† Additional address: Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili, 43007 Tarragona, Spain.

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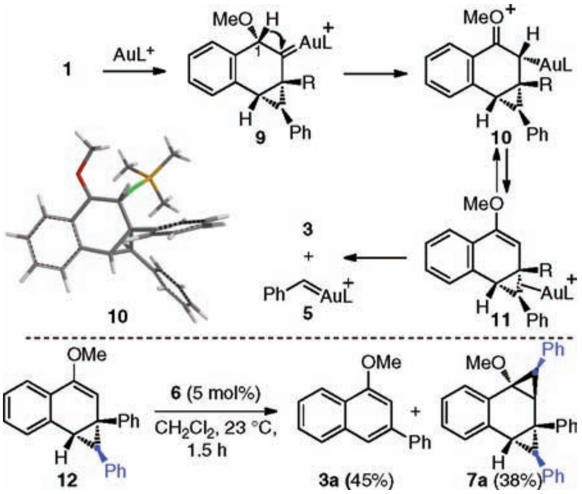
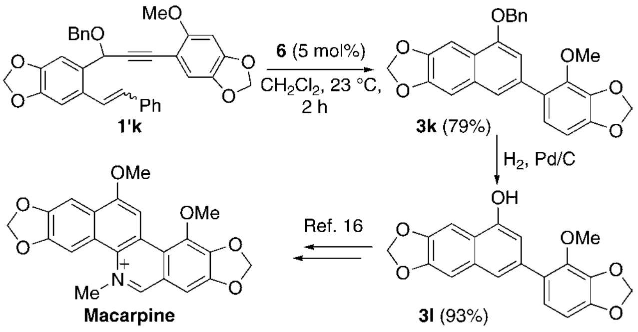
9[1,9] followed by a 1,2-H shift[13] to form alkenylgold(I) complex **10**[14] (Scheme 4). The isomer of **10** with AuL in the convex face would be formed similarly from the C1 epimer of intermediate **9**. Retro-cyclopropanation via **11**, presumably by stepwise cleavage by electrophilic [AuL]$^+$,[5a] would then give naphthalenes **3** and free gold(I) carbene **5**. Experimental support for this proposal was obtained by treatment of enol ether **12** with catalyst **6** (CH_2Cl_2, 23 °C, 1.5 h), which led cleanly to a mixture of 1-methoxy-3-phenylnaphthalene (**3a**) and biscyclopropane **7a**.

Scheme 4



1,3-Disubstituted naphthalenes are a class of compounds not readily available by current methods such as electrophilic substitution/cross-coupling. This annulation allows the preparation of these compounds from enynes **1**, which are readily assembled in a modular form.[15] To illustrate the potential of this method, a formal synthesis of the cytotoxic benzo[*c*]phenanthridine alkaloid macarpine[16,17] was performed (Scheme 5). Thus, gold(I)-catalyzed cyclization of **1′k** gave biaryl **3k** (79% yield), which upon hydrogenolysis provided naphthol **3l**, an intermediate in the total synthesis of macarpine.[16]

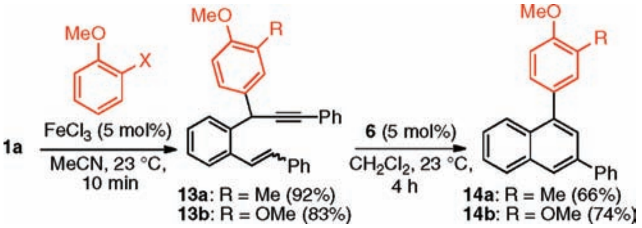
Scheme 5



As shown in Scheme 4, an electron-donating substituent different from OR at the benzylpropargyl position could also be used in the annulation. As it turned out, substrates **13a** and **13b**, which were readily prepared from **1a** and the corresponding arenes in the presence of $FeCl_3$,[18] reacted with catalyst **6** to give **14a** and **14b**, respectively (Scheme 6).

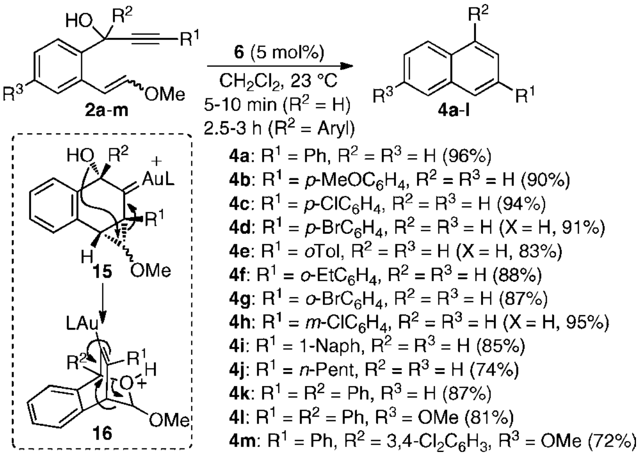
1,6-Enynes **2a**−**m**[8] reacted with catalyst **6** at room temperature to give naphthalenes **4a**−**m** in good to excellent yields (Scheme 7). This is a general annulation that also proceeds with related substrates bearing propargylic OMe groups, although longer reaction

Scheme 6



times were required in these cases.[15] This reaction presumably proceeds by 6-*endo*-dig cyclization to form **15** followed by intramolecular attack of the OR group at the cyclopropane[3] to form **16**. Fragmentation of intermediate **16**,[19] followed by protodeauration,[20] would give naphthalenes **4**.

Scheme 7



4a: R^1 = Ph, R^2 = R^3 = H (96%)
4b: R^1 = *p*-$MeOC_6H_4$, R^2 = R^3 = H (90%)
4c: R^1 = *p*-ClC_6H_4, R^2 = R^3 = H (94%)
4d: R^1 = *p*-BrC_6H_4, R^2 = R^3 = H (X = H, 91%)
4e: R^1 = *o*Tol, R^2 = R^3 = H (X = H, 83%)
4f: R^1 = *o*-EtC_6H_4, R^2 = R^3 = H (88%)
4g: R^1 = *o*-BrC_6H_4, R^2 = R^3 = H (87%)
4h: R^1 = *m*-ClC_6H_4, R^2 = R^3 = H (X = H, 95%)
4i: R^1 = 1-Naph, R^2 = R^3 = H (85%)
4j: R^1 = *n*-Pent, R^2 = R^3 = H (74%)
4k: R^1 = R^2 = Ph, R^3 = H (87%)
4l: R^1 = R^2 = Ph, R^3 = OMe (81%)
4m: R^1 = Ph, R^2 = 3,4-$Cl_2C_6H_3$, R^3 = OMe (72%)

In summary, we have developed new gold(I)-catalyzed annulations of enynes for the synthesis of 1,3-disubstituted naphthalenes that proceed by fragmentation of the alkene. One of these transformations involves the first example of a retro-cyclopropanation promoted by gold(I) in solution.

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Supporting Information Available: Additional data, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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