



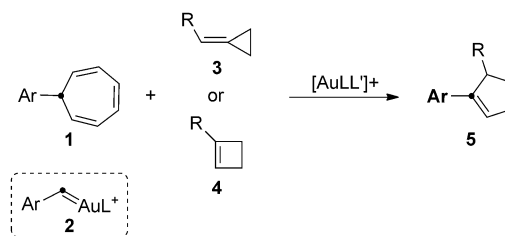
Formal (4+1) Cycloaddition of Methylene-cyclopropanes with 7-Aryl-1,3,5-cycloheptatrienes by Triple Gold(I) Catalysis**

Yahui Wang, Michael E. Muratore, Zhouting Rong, and Antonio M. Echavarren*

Abstract: 7-Aryl-1,3,5-cycloheptatrienes react intermolecularly with methylenecyclopropanes in a triple gold(I)-catalyzed reaction to form cyclopentenes. The same formal (4+1) cycloaddition occurs with cyclobutenes. Other precursors of gold(I) carbenes can also be used as the C₁ component of the cycloaddition.

Carbenes have been widely used as one-carbon synthon in organic synthesis, particularly in the context of cyclopropanation reactions.^[1] However, only a few (4+1) cycloadditions^[2] have been reported mainly with Fischer alkoxy-(alkenyl)carbene complexes^[3] and dialkoxycarbenes.^[2,4] To the best of our knowledge, there is no report on the (4+1) cycloaddition of aryl carbenes with 1,3-dienes, probably because of the known propensity of carbenes to give cyclopropanation products with 1,3-dienes.^[5] We postulated that due to their high strain and unique electronic properties, cyclobutenes^[6] could be used as synthetic equivalents of 1,3-dienes for the development of a formal (4+1) cycloaddition with metal carbenes.

We have recently found that 7-substituted 1,3,5-cycloheptatrienes **1** undergo gold(I)-catalyzed retro-Buchner reaction to form carbenes **2** (Scheme 1).^[7] Herein, we report a novel and potentially general formal (4+1) cycloaddition by reaction of **1** with methylenecyclopropanes **3**^[8] or cyclobutenes **4** to form cyclopentenes **5**. In this transformation, methylenecyclopropanes **3** undergo an isomerization to form cyclobutenes **4** similar to that catalyzed by platinum or palladium.^[9] Therefore, in the reaction between **1** and **3**,



Scheme 1. New strategy for the formal (4+1) cycloaddition.

gold(I) plays a triple catalytic role, isomerizing **3** into **4** and, in parallel, generating gold(I) carbenes **2** from **1**, which cyclopropanate the cyclobutenes. Finally, gold(I) cleaves the internal C–C bond of the resulting bicyclo[2.1.0]pentanes to form the cyclopentenes. This reaction can be viewed as an insertion of one carbon into a double bond, a process that has only been achieved in rare cases with dihalocarbenes.^[10,11]

Methylenecyclopropanes (MCPs) **3** can be readily prepared in one step by the Wittig olefination of carbonyl compounds with commercially available 3-bromo-triphenylphosphonium bromide. We first examined the reaction of phenylmethylenecyclopropane (**3a**) with 7-naphthyl-cyclohepta-1,3,5-triene (**1a**) in the presence of gold(I) complexes (Table 1). Using cationic [(JohnPhos)Au(MeCN)]SbF₆ (**A**) in 1,2-dichloroethane at 120 °C, disubstituted cyclopentene **5a** was isolated in 76 % yield (Table 1, entry 1). Other phosphine or N-heterocyclic carbene gold(I) complexes **B–E** gave lower yields (entries 2–5), whereas complexes **F** and **G** failed to promote this transformation, presumably due to their instability at the temperature required for the retro-Buchner reaction. The reaction also failed with silver(I), copper(II), and platinum(II) catalysts (entries 8–10).

7-Aryl-cyclohepta-1,3,5-trienes containing groups with different electronic and steric effects at the *ortho*, *meta*, or *para* positions reacted with MCPs **3a–h** to yield the (4+1) cycloadducts **5b–m** (Table 2). The (4+1) cycloaddition proceeds satisfactorily with MCP bearing arenes with fluoro-, chloro-, and bromo-substituents. However, the reaction with *o*-bromophenylmethylenecyclopropane (**3f**) led to cycloadduct **5k** in lower yield. The structure of **5k** was confirmed by X-ray diffraction (Figure 1).^[12] To demonstrate the synthetic utility of this method, cyclopentene **5i** was prepared on a 500 mg scale using only 1 mol % gold catalyst **A** in 51 % yield after purification by column chromatography. Alkylmethylenecyclopropanes also reacted to give (4+1) cycloaddition products, although in this case the reactions led to mixtures of regioisomers **5n/n'–5p/p'**.

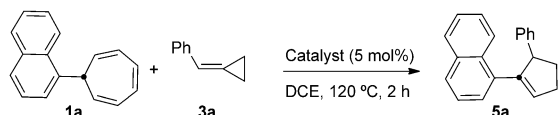
Substrate **3i** reacted intramolecularly using catalyst **E** to form 2,3-dihydro-1*H*-cyclopenta[*l*]phenanthrene (**5q**) by iso-

[*] Y. Wang, Dr. M. E. Muratore, Z. Rong, Prof. A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
Prof. A. M. Echavarren
Departament de Química Analítica i Química Orgànica
Universitat Rovira i Virgili
C/Marcel·li Domingo s/n, 43007 Tarragona (Spain)
E-mail: aechavarren@icicq.es

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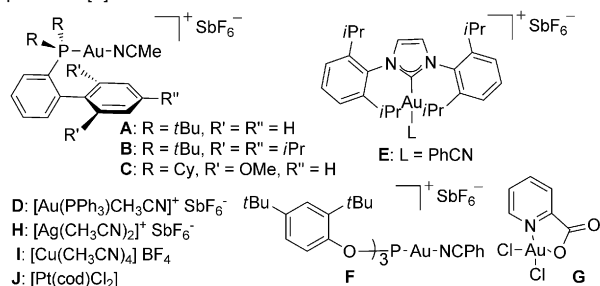
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201404029>.

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Table 1: Gold(I)-catalyzed reaction of 7-(1-naphthyl)-1,3,5-cycloheptatriene (**1a**) with phenylmethylenecyclopropane (**3a**).^[a]


Entry	Catalyst	Yield [%] ^[b]
1	A	81 (76) ^[c]
2	B	25
3	C	28
4	D	< 5
5	E	47
6	F	— ^[d]
7	G	— ^[d]
8	H	— ^[d]
9	I	— ^[d]
10	J	— ^[d]

[a] Reaction at 120 °C (0.2 M in 1,2-dichloroethane), 2 equiv of **3a**, catalyst (5 mol%), 2 h. [b] Yields determined by ¹H NMR spectroscopy using 1,4-diacetylbenzene as internal standard. [c] Yield of isolated product. [d] Not detected.

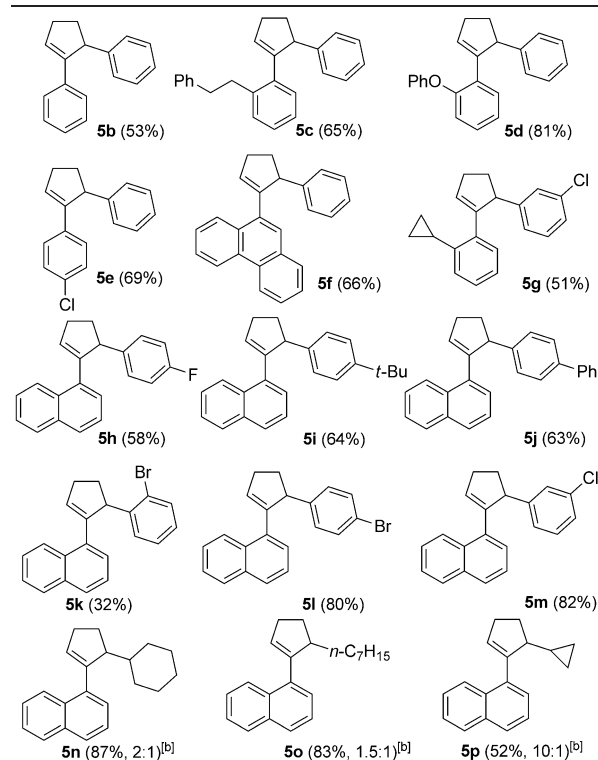
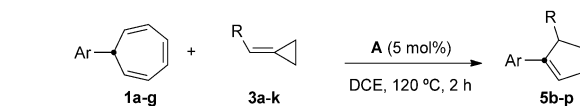


merization of the initially formed adduct **5q** (Scheme 2). In addition, polyarene fragments can be obtained by photochemical cyclization. Thus, compound **5f** can be transformed into a cyclopenta derivative of benzo[*g*]chrysene (**6**) by a one pot photo-induced isomerization/oxidative Mallory cyclization.^[13]

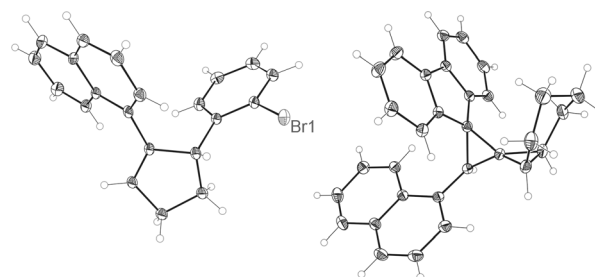
Tetrasubstituted MCP **3m** reacted with **1a** to give only the product of cyclopropanation **7** (Scheme 3 and Figure 1), whose structure was confirmed by X-ray diffraction (Figure 1).^[12] Given that **3m** does not undergo ring-expansion, the isolation of spiro derivative **7** strongly suggests that the cyclopropanation of MCP is not the initial step in the formal (4+1) cycloaddition and that cyclobutenes are likely intermediates in this transformation.

To confirm the hypothesis that cyclobutenes are intermediates in the (4+1) reaction of MCP, we performed the reaction of **1a** with cyclobutene **4a**, which was isolated from the reaction mixture of **1a** and **3g**. Under identical conditions, cycloadduct **5l** was isolated in 77% yield. Trisubstituted cyclobutenes^[14] also took part in the (4+1) cycloaddition reaction to afford cyclopentenones **5r–z** (Table 3).

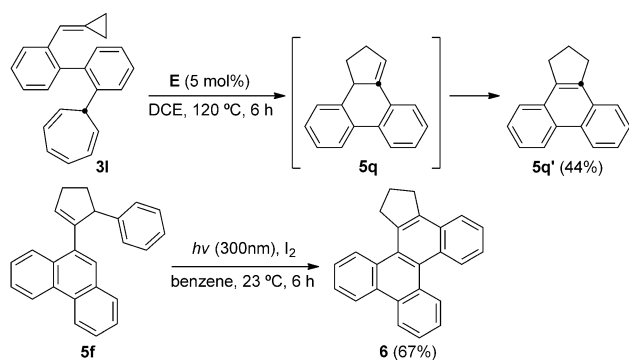
Cyclobutenes also react with intermediate gold(I) carbenes generated by 1,2-acyloxy migration of propargylic acetates^[15] under mild conditions with catalyst **E** to give two separable isomers **5aa–ac** and **5'aa–ac** in good overall yields (Scheme 4). By performing the reaction at room temperature

Table 2: Scope of the formal (4+1) cycloaddition between cycloheptatrienes **1** and methylenecyclopropanes **3**.^[a]


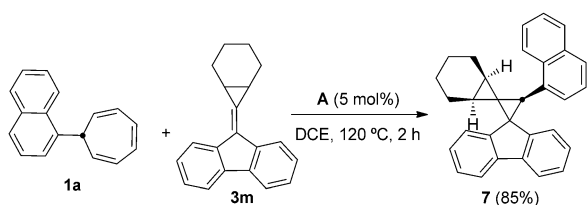
[a] Reaction at 120 °C, 0.2 M in 1,2-dichloroethane, 2 equiv of **3a–k**, catalyst **A** (5 mol%), 2 h. Yields are for isolated products. [b] Reaction time = 3 h. 3-Alkyl-3-arylcyclopent-1-enes **5'n–p** were also obtained as minor regioisomers.


Figure 1. X-ray crystal structures of **5k** and **7**.

at only 60% conversion, bicyclo[2.1.0]pentane **10a**^[16] could be isolated and then transformed cleanly into **5aa** at 40 °C in the presence of gold(I) catalyst. The gold(I) carbene generated from phenyl diazomethane^[17–20] reacted similarly at room temperature with cyclobutene **4c** to form the desired formal (4+1) product **5ad**, along with **10b**.^[21] This bicyclo[2.1.0]pentane was converted quantitatively into cyclopentene **5ad** by warming at 60 °C in the presence of gold complex **A**.

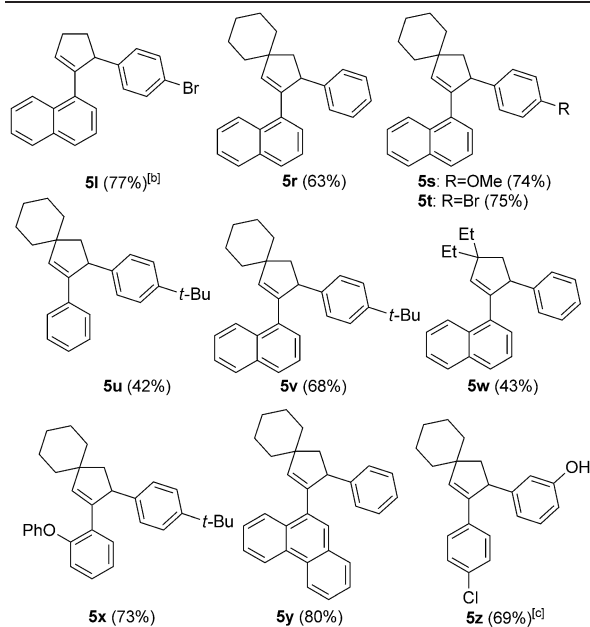
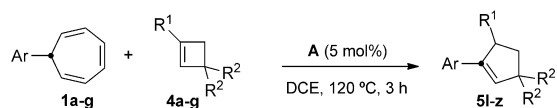


Scheme 2. Intramolecular formal (4+1) cycloaddition and its application to the preparation of a polyparene fragment.

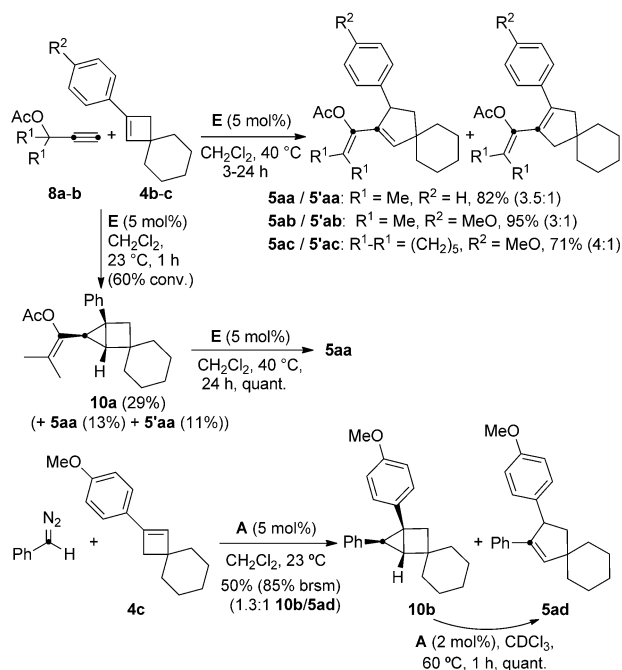


Scheme 3. Probing the mechanism of the formal (4+1) cycloaddition.

Table 3: Scope of the formal (4+1) cycloaddition between cycloheptatrienes **1** and cyclobutenes **4**.^[a]



[a] Reaction at 120 °C, 0.2 M in 1,2-dichloroethane, 2 equiv of **4 a–g**, catalyst **A** (5 mol%), 3 h. Yields are for isolated adducts. [b] Cyclobutene **4 a** was isolated from the reaction mixture of **1 a** and **3 g**. [c] 2 Equiv of 7-(4-chlorophenyl)cyclohepta-1,3,5-triene were used.



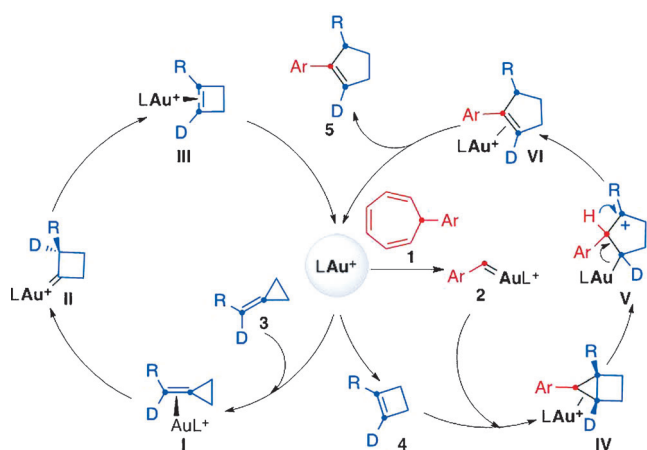
Scheme 4. Formal (4+1) cycloaddition with various gold(I) carbenes.



Scheme 5. Deuterium labeling experiment to probe the mechanism.

To shed additional light on the reaction mechanism, we performed the reaction of cycloheptatriene **1 a** with MCP **[D₁]-3 a** in the presence of catalyst **A** (Scheme 5). In this experiment, **[D₁]-5 a** was obtained with the deuterium label transferred completely to C-3.

According to all experimental data, we propose a mechanism for this formal (4+1) cycloaddition of cycloheptatrienes **1** and MCP in which gold(I) plays a triple role (Scheme 6). In the first catalytic cycle, η^2 -MCP-gold(I) complex **I** undergoes ring expansion to form intermediate **II**, which gives η^2 -cyclobutene-gold(I) complex **III**. Associative ligand exchange with the 7-aryl-1,3,5-cycloheptatriene, followed by retro-Buchner reaction then leads to the highly reactive gold(I) carbene **2**,^[7] which reacts with cyclobutene **4** to form bicyclo[2.1.0]pentane-gold(I) complex **IV**. Cyclopropane opening by gold(I) forms the tertiary carbocation **V**, which leads to complex **VI** by a final 1,2-H shift. The cyclopropanation of **4** by **2**, followed by electrophilic cleavage probably follows a pathway similar to that occurring in the gas phase for the cyclopropanation/retro-cyclopropanation of enol ethers with gold(I) carbenes.^[22] Formation of cyclopentenes from bicyclo[2.1.0]pentanes, the presumed intermediates of these reactions, has been mechanistically examined in a few cases using Rh^I, Zn^{II}, and other catalysts.^[23,24] Formation of regioisomeric 3-alkyl-3-arylcyclopent-1-enes



Scheme 6. Proposed mechanism for the formal (4+1) cycloaddition.

together with **5n-p** in the reaction of alkyl-substituted MCP can be explained by the competitive migration of the aryl group in intermediates **V**.

In summary, we have developed a synthesis of substituted cyclopentenes by a formal (4+1) cycloaddition from methylenecyclopropanes or cyclobutenes with gold(I) carbenes generated under catalytic conditions by retro-Buchner reaction of 1,3,5-cycloheptatrienes or by other methods. Further work on the application of this cycloaddition in synthesis is underway.

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