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Gold-Catalyzed [4C+3C] Intramolecular Cycloaddition of Allenedienes: Synthetic Potential and Mechanistic Implications

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Dedicated to Professor Josep Font on the occasion of his 70th birthday

Transition-metal-catalyzed cycloadditions are among the most powerful methods for rapidly assembling polycyclic products from simple acyclic precursors.[1] We recently reported a Pt-catalyzed [4C+3C] cycloaddition between dienes and tethered allenes, a transformation that provides a short and stereoselective route to synthetically useful bicyclo[5.3.0]decane skeletons. The reaction proceeds with 10 mol% of $PtCl_2$, but typically requires heating at elevated temperatures (110 °C) for efficient conversions.[2]

The well known ability of gold salts to promote reactions of allenes via electrophilic activation pathways,[3] suggested that gold complexes might also catalyze the aforementioned annulations. However, preliminary assays with substrates containing terminally monosubstituted allenes led to disappointing results.[2] We therefore decided to carry out a computational study to establish a reliable mechanism and gain insights into potential differences in the performance of platinum and gold catalysts.

Herein we present the results of such a study that support the originally hypothesized mechanism with $PtCl_2$ and, importantly, provided impetus for further investigation of a gold-catalyzed process. This research led to the discovery that the cationic gold complex generated in situ from [(IPr)AuCl][4] and $AgSbF_6$ promotes a particularly efficient reaction, which can be now carried out at *room temperature*. The mildness of the new conditions allowed the intramolecular [4C+3C] cycloaddition of allenes with several dienes, and even with furans, dienes that gave very poor results under the $PtCl_2$-promoted conditions.[2]

As previously stated, the mechanistic assumption underlying the Pt-catalyzed [4C+3C] cycloadditions consists of an initial allene activation to generate a metal–allyl cation intermediate, which could participate in a [4π+2π] cycloaddition with the diene to provide the cycloheptene skeleton.[2] A subsequent 1,2-hydride shift on the resulting carbene should yield the final adduct and regenerate the catalyst. This outcome and other alternatives were explored by means of DFT calculations,[5] using the dimethylallene **1a'** as model substrate, and $PtCl_2$, AuCl, or $AuCl_3$ as catalysts. The results with $PtCl_2$ are consistent with the originally proposed mechanism (Figure 1). The initial step (selected as energy reference) involves coordination of the allene to the metal center. This species (**2**) evolves easily to the metal–allyl cation intermediate **3** (energy barrier of 8.0 kcal mol^{-1}). The cycloaddition step conveys a low barrier (1.1 kcal mol^{-1}) and gives rise to the expected carbene **4**, the most stable intermediate within the overall catalytic cycle. The transition state for the cycloaddition (**ts2**) is consistent with a *synchronous and concerted* process, involving an *exo-like* (extended) approach of the allyl–metal cation to the diene.[6,7] Efforts to identify alternative stepwise pathways for the cycloaddition were unsuccessful. The last step, consisting of a 1,2-H-shift with simultaneous coordination of the newly formed C=C double bond to the metal, features the highest relative energy barrier of the profile (25.6 kcal mol^{-1}, **ts3**), and might thus be rate-determining.

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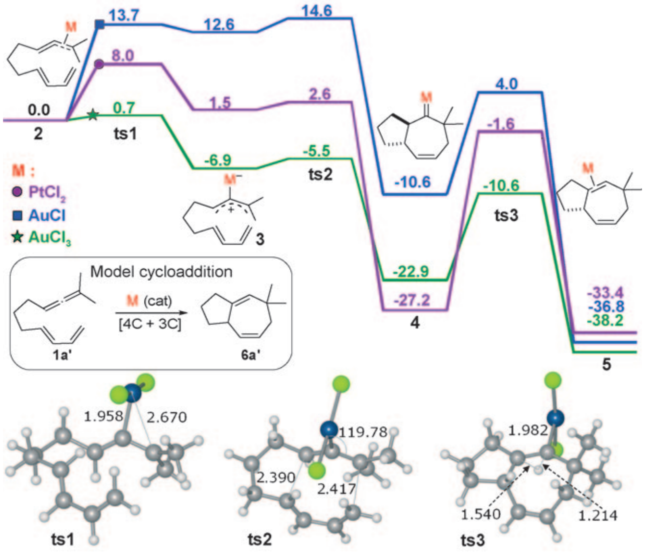
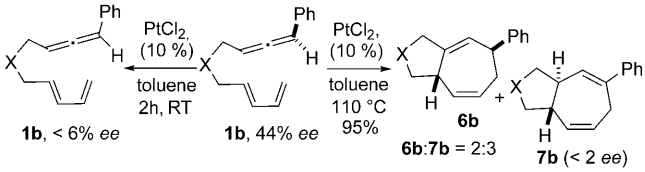


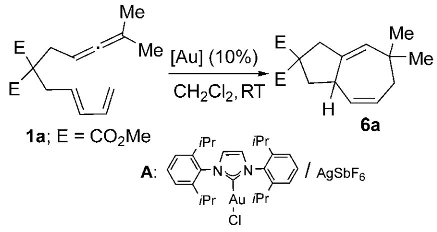
Figure 1. DFT energy profiles (electronic energies) for the cycloaddition of **1a'**, and structures of the transition states (**ts1–3**) found with $PtCl_2$.

In consonance with this mechanism, treatment of enantioenriched substrate **1b** (44% *ee*, Scheme 1),[8] with 10 mol% of $PtCl_2$ at 110°C provided the major cycloadduct **7b** in racemic form. When the same reaction was carried out for 2 h at room temperature (temperature at which the cycloaddition does not occur), **1b** was recovered after 2 h, as a racemate (*ee* <6%). The loss of chiral information is consistent with a fast and reversible metal–allyl cation formation.



Scheme 1. Stereochemical mechanistic probe.

As can be deduced from the diagrams in Figure 1, the reaction profile for the process promoted by AuCl or $AuCl_3$ is qualitatively similar to that obtained for $PtCl_2$, but significantly less demanding in terms of electronic energy barriers. Consequently, dimethylallenyl precursors analogous to **1a'** might experience the cycloaddition under mild conditions upon treatment with such gold salts. Indeed, when allenediene **1a** was treated with 10 mol% of $AuCl_3$ or AuCl, the desired [4C+3C] cycloadduct **6a** was obtained in good yield (Scheme 2). Remarkably, screening of other Au catalysts revealed that this cycloaddition was particularly rapid and efficient with the Au^I complex $[[(IPr)AuCl]/AgSbF_6]$ (**A**),[4] which features a σ-donating *N*-heterocyclic carbene (IPr) ligand. Accordingly, NMR monitoring of the cycloaddition of **1a** using 10 mol% of several catalysts revealed that while complex **A** promoted the formation of 90% of the cycloadduct **6a** after just 40 min at 0°C, most of the starting allenediene (**1a**) remained intact after several hours of treatment with 10 mol% of $PtCl_2$ or AuCl at that temperature.[7]



[Au]	Yield[a]	Time [h]
$AuCl_3$	81	2
AuCl	79	2
A	91	0.5
A	90[b]	0.7

[a] Isolated yield of **6a**.
[b] Conversion at 0°C.

Scheme 2. Gold-catalyzed [4C+3C] cycloaddition of allenediene **1a**.

In agreement with this higher activity, the calculated DFT-energy profile for a model $(NHC)Au^+$ catalyst (Figure 2) showed a particularly favorable energetic scenario, exhibiting a significantly lower energy barrier for the 1,2-H shift step (8.6 kcal mol^{-1}). Curiously, this step appears to require a small conformational change on the seven-membered ring prior to the H-shift (from **4** to **4'**).[7] The energy values and optimized geometries for the most relevant transition-state structures are depicted in Figure 2.

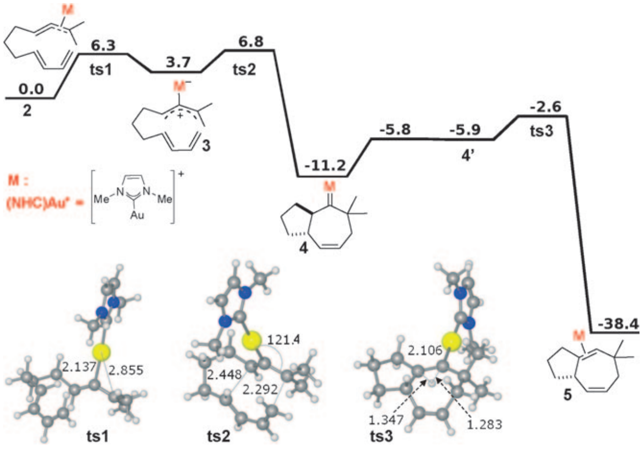
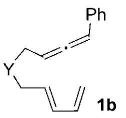
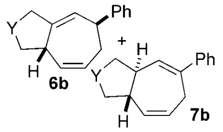
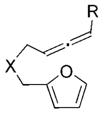
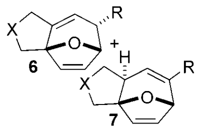
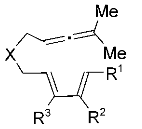
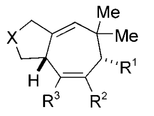
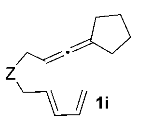
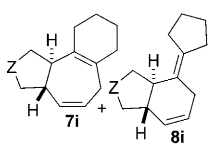


Figure 2. DFT energy profile for the cycloaddition of **1a'** with $NHCAu^+$, and structures of the relevant transition states (**ts1–3**).

The excellent reactivity profile of complex **A** led us to test its performance with other allenedienes. The results are summarized in Table 1. Importantly, in contrast to the reaction with $PtCl_2$, which required heating for efficient conversions, the cycloaddition of the phenyl-substituted allene **1b** took place smoothly, at room temperature, to give the cycloadducts **6b** and **7b** in 85% yield after 3 h (Table 1, entry 1). Use of other gold complexes such as AuCl, $AuCl_3$, or $[PPh_3AuCl]/AgSbF_6$, led to less than 40% of conversion, even after 24 h at room temperature.

Gratifyingly, complex **A** also catalyzes the cycloaddition of furan–allene derivatives **1c–e** (Table 1, entries 2–5), substrates that performed very poorly under standard Pt-catalyzed conditions as well as with other gold catalysts. Indeed,

Table 1. Au ([(IPr)AuCl]/$AgSbF_6$)-catalyzed [4C+3C] cycloaddition of **1**.[a]

Entry	Allenediene, **1**		Cycloadducts (**6**, **7**)	**6**:**7** (ratio)[b]	Yield (time)[c]
1	**1b**			**6b**:**7b** (1:2)	85 (3)
2	**1c**, R = Me			**6c**:**7c** (1:3)	82 (1)
3	**1d**, R = Ph			**7d**	50 (12)
4	**1e**, R = *t*Bu			**7e**	57 (20)
5	**1e**			**7e**	85 (3)[d]
6	**1f**, R^1 = Me[e]			**6f**	93 (2)
7	**1g**, R^2 = Me[e]			**6g**	84 (2)
8	**1h**, R^3 = Me[e]			**6h**	77 (2)
9	**1i**			**7i**:**8i** (3:1)	66 (3)
10[f]	**1i**			**7i**	74 (2)
11[g]	**1i**			**7i**	70 (2)

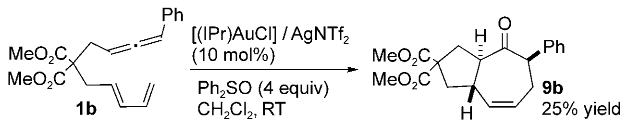
[a] Conditions: [(IPr)AuCl] (10%) and $AgSbF_6$ (10%) in CH_2Cl_2 (0.15 M) at room temperature (20–25 °C) unless otherwise noted. X = $C(CO_2Et)_2$, Y = $C(CO_2Me)_2$, and Z = NTs. [b] Determined by NMR spectroscopy. [c] Yield of isolated product (%) after the reaction time (hours). [d] Reaction at 85 °C in 1,2-dichloroethane. [e] Unspecified substituents are H. [f] Carried out with AuCl (10 mol%) at room temperature. [g] Carried out with $AuCl_3$ (10 mol%) at room temperature.

whereas AuCl, $AuCl_3$, [Ph_3PAuCl]/$AgSbF_6$, chloro[(1,1′-biphenyl-2-yl)di-*tert*-butylphosphine]gold(I)/$AgSbF_6$ or (dichloropyridine-2-carboxylato)gold(III),[9] led to low conversions and/or formation of several unidentified side products, the reaction of **1c** with **A** (10 mol%) provided the cycloadducts **6c** and **7c** in 82% combined isolated yield, in less than 1 h at *room temperature* (Table 1, entry 2).

The reaction also proceeds with furan derivatives **1d** and **1e**, providing the expected cycloadducts with complete selectivity (Table 1, entries 3–5). As expected, sterically hindered substrate **1e** (Table 1, entry 5, R = *t*Bu) resulted in a slower reaction, but full conversion could be achieved after 3 h at 85 °C, providing the cycloadduct **7e** with complete selectivity and excellent yield. The above-mentioned results (Table 1, entries 1–5) clearly indicate that the use of complex **A** is critical for the success in cycloadditions involving terminally monosubstituted allenes such as **1b**–**e**. Noteworthy, the well known synthetic potential of oxabridged systems similar to those present in products **7c**–**e**, bodes well for the potential applicability of the method in the preparation of target-relevant bicarbocyclic systems.[10]

As can be seen in Table 1, the presence of substituents at the diene unit was well tolerated (**1f**–**h**, Table 1, entries 6–8), and the corresponding [4C+3C] cycloadducts were obtained in good yields (77–93%), and with complete stereocontrol. Surprisingly, the reaction of cyclopentylallene derivative **1i** in the presence of catalyst **A**, in addition to providing the expected tricycle **7i** that results from a 1,2 alkyl shift in the intermediate carbene species, led also to a minor cycloadduct identified as the bicycle **8i** (Table 1, entry 9). This product must arise from a competitive Au-catalyzed [4C+2C] annulation process, as the reaction doesn′t proceed under thermal activation.[11] In this particular case we found that the [4C+3C] cycloadduct **7i** can be more efficiently obtained by using either AuCl (74% yield, 2 h) or $AuCl_3$ (70% yield, 2 h) (Table 1, entries 10 and 11).[12]

Finally, as an additional experimental mechanistic proof, precursor **1b** was treated with [(IPr)AuCl]/$AgNTf_2$ (10 mol%) in the presence of diphenyl sulfoxide (4 equiv), conditions previously used for oxidative trapping of gold carbenes.[13] In addition to observing the formation of traces of **6b** and **7b** and recovering unreacted **1b**, we could isolate the ketone **9b** (25% yield, Scheme 3). This result is consistent with the participation of carbene species of type **4** in the catalytic cycle, and confirms the potential of the method to directly obtain stereochemically rich oxygenated bycyclic products.



Scheme 3. Oxygen atom transfer from the sulfoxide to the carbene gold(I) species.

In summary, we have discovered that the Au complex generated in situ from [(IPr)AuCl] and $AgSbF_6$ catalyzes the [4C+3C] intramolecular cycloaddition of a variety of allenedienes at *room temperature*. The new conditions represent a significant step forward in terms of the scope and versatility with respect to the previous $PtCl_2$-catalyzed process, and opens the door for the development of asymmetric versions. According to DFT calculations, the cycloaddition must involve the formation of a metal–allyl cation intermediate and its subsequent concerted cycloaddition with a 1,3-diene. These studies point to a 1,2-hydride shift on the generated carbene intermediate as the rate-limiting step of the process. The mechanistic insights derived from the described theoretical and experimental studies, in addition to providing a detailed account of the transformation, might help to explain and design other gold-mediated processes.

Experimental Section

General procedure for performing the [4C + 3C] cycloaddition with complex A (exemplified for the cycloaddition of 1c): A solution of compound **1c** (50 mg, 0.16 mmol) in CH_2Cl_2 (0.4 mL) was added to a suspension of [(IPr)AuCl] (10.1 mg, 0.016 mmol) and $AgSbF_6$ (5.6 mg, 0.016 mmol) in CH_2Cl_2 (0.4 mL) in a dried Schlenk tube under argon. The mixture was stirred at room temperature for 1 h and then filtered through a short pad of florisil by eluting with Et_2O. The filtrate was concentrated and purified by flash chromatography (1–4% Et_2O/hexanes) to afford a mixture of cycloadducts **6c** and **7c** (41 mg; 82%, **6c**:**7c**=1:3).[7]

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Keywords: allenes · carbocycles · cycloaddition · density functional calculations · gold · homogeneous catalysis

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[2] B. Trillo, F. López, M. Gulías, L. Castedo, J. L. Mascareñas, *Angew. Chem.* **2008**, *120*, 965–968; *Angew. Chem. Int. Ed.* **2008**, *47*, 951–954.

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[5] Calculations were performed with Gaussian 03 using the B3LYP functional. Metal centers were described by the lanl2dz pseudopotential and their associated basis set, and the main-group elements by the 6-31Gd basis set. See Supporting Information for details.

[6] This type of *exo*-like (extended) transition state also explains the observed stereseoselectivity (see reference [2]).

[7] See the Supporting Information for details.

[8] Enantioenriched **1b** was prepared following the procedure described in: M. Ogasawara, H. Ikeda, T. Nagano, T. Hayashi, *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090.

[9] For leading references on other uses of these gold complexes, see: a) C. Nieto-Oberhuber, S. López, A. M. Echavarren, *J. Am. Chem. Soc.* **2005**, *127*, 6178–6179, and references therein; b) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem.* **2004**, *116*, 6707–6709; *Angew. Chem. Int. Ed.* **2004**, *43*, 6545–6547; See also references [3a–f].

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[11] Further details on this new [4C+2C] Au-catalyzed cycloaddition, as well as the possibility for promoting it in a chemoselective manner are being experimentally and theoretically investigated and will be reported in due course. CCDC-711014 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] The fact that the cycloaddition of terminally disubstituted allene **1i** proceeds efficiently with AuCl and $AuCl_3$ is in agreement with the results obtained with **1a** (see Scheme 2).

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