Au^I-catalyzed cycloisomerization of 1,5-enynes bearing a propargylic acetate: formation of unexpected bicyclo[3.1.0]hexene†

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The use of *N*-heterocyclic carbene (NHC) as a ligand in the gold(I)-catalyzed cycloisomerization of enyne results in the assembly of a new carbocyclic product.

Recent reports have employed gold(I) and gold(III) complexes as homogeneous catalysts capable of facilitating several organic transformations.[1] For instance, gold catalysts in both oxidation states perform enyne cycloisomerization,[2] one of the most efficient means of converting acyclic precursors into complex polycyclic structures.[3] The reactivity of gold complexes toward enynes leads notably to the formation of bicyclic [*n*.1.0] derivatives[4] that are of great synthetic interest, since the cyclopropane ring is a widely encountered motif in natural products.[5]

As we recently reported the syntheses of several air- and moisture-stable (NHC)AuCl complexes[6] (NHC = *N*-heterocyclic carbene) (Fig. 1), we were interested in testing these in such cycloisomerization reactions. We focused our attention on the specific dienyne **1**, which bears an acetate at the propargylic position, since we previously reported its reactivity in the presence of $PtCl_2$ (Scheme 1).[7,8] Substrate **1** formally contains 1,6 and 1,5 enynes that lead, after 1,2 migration of the acetate, to **2** and **3**, respectively. With $PtCl_2$, the bicyclo[4.1.0]heptene **2** is formed preferentially, while the bicyclo[3.1.0] compound **3** is only a minor product. Fürstner *et al.* showed that this transformation with simple enynes was catalyzed equally well by Pt^{II} or Au^I.[9] Since ligand effects have been studied only scarcely in this chemistry, it was of interest to examine whether Au^I would provide a similar selectivity to Pt^{II} in this specific system, and furthermore if ligands such as NHCs could support such a transformation. To the best of our knowledge, the influence of only a limited set of tertiary phosphine and NHC ligands has been studied in this reaction to date.[2e,10]

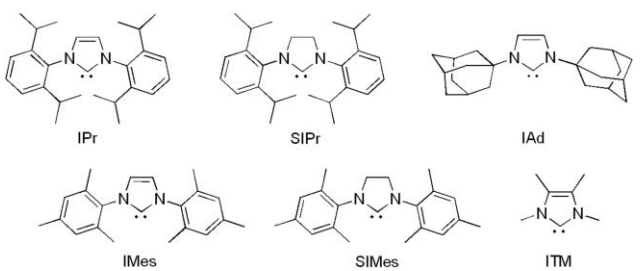

Fig. 1 Structures of NHC ligands.

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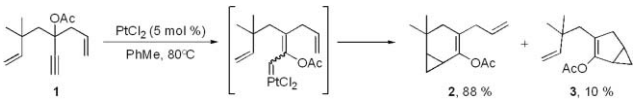
† Electronic Supplementary Information (ESI) available: Experimental procedures and compound characterization. See DOI: 10.1039/b602839j



Scheme 1 $PtCl_2$-catalyzed cycloisomerization of **1**.

We subjected dienyne **1** to an equimolar mixture of IPrAuCl and $AgBF_4$ (2 mol%) in CH_2Cl_2 at rt. After 5 minutes, no starting material remained; isolation and purification yielded **2** and **3** in moderate yields, and a novel compound **4** as the major product. The ^1H NMR data suggested **4** was a cycloisomerized product displaying three propanoid and one extra vinylic protons. ^1H–^1H and ^1H–^{13}C HSQC (heteronuclear single quantum correlation) NMR experiments did not permit the unequivocal assignment of the structure of the new product. To determine unambiguously the atom connectivity in **4**, we prepared **1′**, the *para*-nitrobenzoate analogue of **1**, and subjected it to cycloisomerization conditions.[11] Suitable crystals of the purified product were grown and the structure was elucidated by X-ray diffraction (Fig. 2). Surprisingly, in **4′** the cyclopropane ring has migrated to the former propargylic position, making **4** a formal vinylcyclopropane rearrangement of **3**.

To examine the influence of the NHC ligand, we carried out reactions with various (NHC)AuCl complexes in conjunction with $AgBF_4$ (Table 1). The widely studied IMes (*N,N′*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) and SIMes (*N,N′*-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene) ligands[12] presented similar reactivities (Table 1, entries 1 and 2), affording, in good overall yields, the three bicyclic compounds in comparable ratios; **4** remaining the major product. Slightly more encumbered than IMes, IPr (*N,N′*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) showed a comparable reactivity (Table 1, entry 3), while its saturated counterpart SIPr yielded **2** and **4** in equal proportion (Table 1, entry 4). When the extremely sterically demanding[13] IAd (*N,N′*-1,3-bis(adamantyl)imidazol-2-ylidene) was used, the cyclohexene compound became major and both cyclopentene derivatives were obtained in smaller amounts (Table 1, entry 5). At this point, it seemed that the formation of **4** was disfavored for ligand steric reasons. We then examined the sterically unencumbering ITM

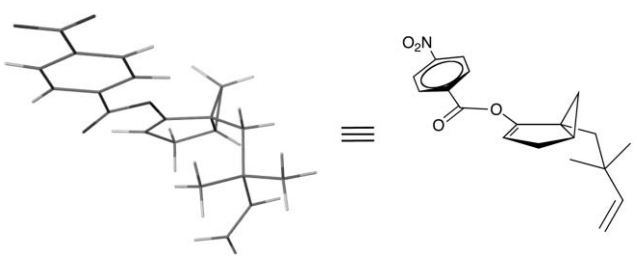
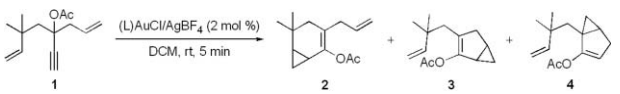


Fig. 2 Stick representation of **4′**.

Table 1 Effect of NHC ligands on the cycloisomerization of **1**[a]



Entry	L	**2**	**3**	**4**
1	IMes	26%	12%	40%
2	SIMes	23%	9%	40%
3	IPr	30%	12%	42%
4	SIPr	41%	13%	36%
5	IAd	54%	6%	35%
6	ITM	52%	8%	12%
7	PPh_3	50%	2%	12%

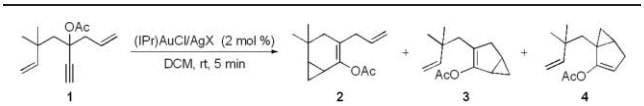
[a] NMR yields, averaged from two runs.

(1,3,4,5-tetramethylimidazol-2-ylidene), which favored even more the formation of **2** (Table 1, entry 6). Interestingly, it appears that the formation of the unprecedented [3.1.0] derivatives requires very specific steric and electronic properties from the ancillary ligand at the gold center. Finally, the commercially available $(PPh_3)AuCl$ showed similar selectivity as (ITM)AuCl (Table 1, entry 7).

Next, we examined the effect of salt additives (Table 2), and found the **2** : **3** : **4** ratio to be significantly influenced by the counterion. Formation of **4** was not observed using silver triflate, while no reaction occurred with silver acetate[14] (Table 2, entries 4 and 5). A different trend was observed with fluorinated anions, which increased the ratio **2** : **4** from small (boron) to large (antimony) perfluoro anions (Table 2, entries 1–3). Thus, it appears that the formation of the bicyclo[4.1.0] derivative is favored with more weakly bound counterions.

When coordinating acetonitrile was used as solvent *in lieu* of CH_2Cl_2, the reaction time increased to 1 hour. Furthermore, two control reactions were performed separately with IPrAuCl and $AgBF_4$. The former was inactive toward dienyne **1**. The latter afforded the allene corresponding to a [3,3]-transposition of the propargyl acetate.[15] These experiments support the notion of a cationic gold complex as an active catalytic species. To obtain such a complex, we reacted IPrAuCl with $AgPF_6$ in acetonitrile. Despite reports accounting for the high instability of cationic gold(I) complexes,[16] we were able to isolate $[(IPr)Au(NCMe)]^+PF_6^-$, whose structure was confirmed by X-ray diffraction studies (Fig. 3).‡ Interestingly, this complex decomposes rapidly when dried under vacuum but is stable in an acetonitrile solution for several days.[17] Next, we performed the cycloisomerization of dienyne **1** with this novel cationic species. Without the need for silver additives, which are usually very hygroscopic and light-sensitive, we obtained similar results as when an equimolar mixture of IPrAuCl and $AgPF_6$ (Scheme 2). This result supports the

Table 2 Effect of silver salt additive on the cycloisomerization of **1**[a]



Entry	AgX	**2**	**3**	**4**
1	$AgBF_4$	30%	12%	42%
2	$AgPF_6$	32%	19%	39%
3	$AgSbF_6$	40%	18%	27%
4	AgOTf	63%	13%	—
5	AgOAc	Starting material recovered		

[a] NMR yields, averaged from two runs.

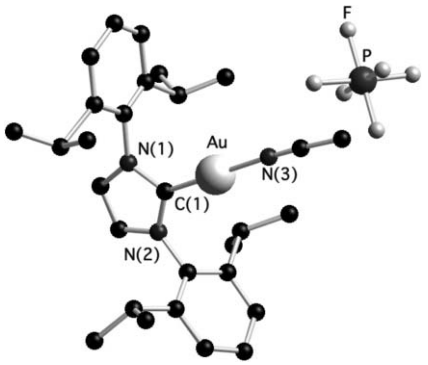
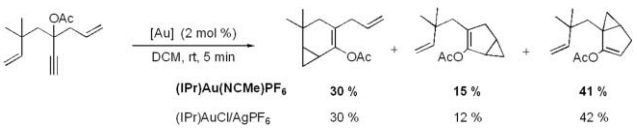


Fig. 3 Ball-and-stick representation of $[(IPr)Au(NCMe)]PF_6$.

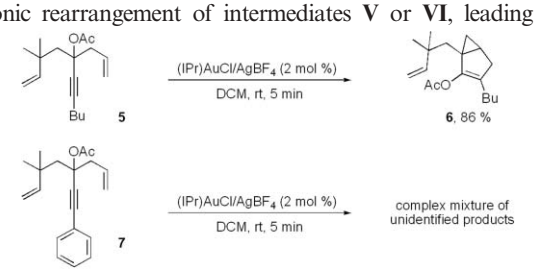


Scheme 2 Cycloisomerization of **1** catalyzed by $[(IPr)Au(NCMe)]^+PF_6^-$.

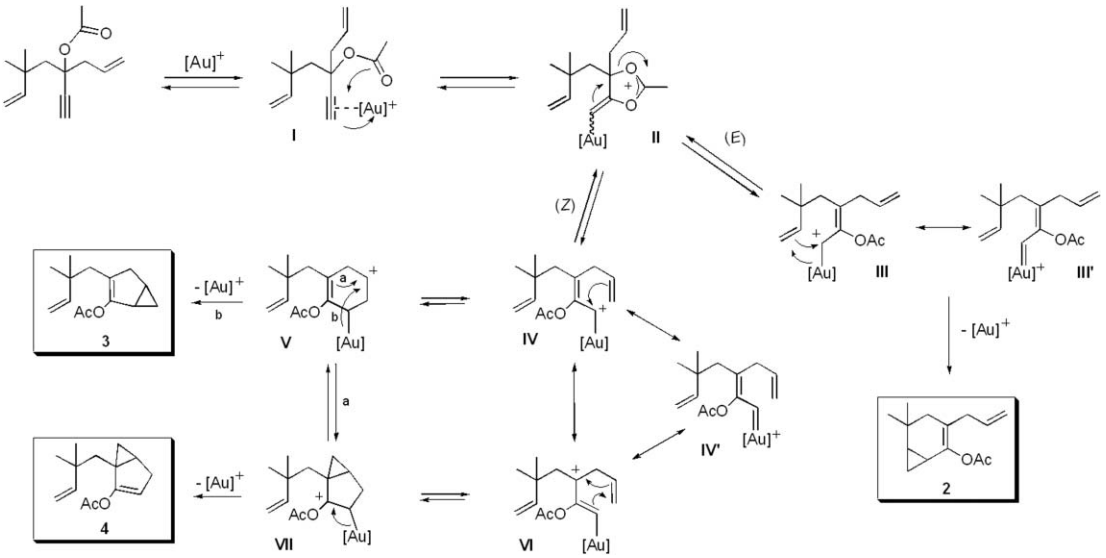
cationic nature of the catalytically-active species. Furthermore, $[(IPr)Au(NCMe)]PF_6$ allowed us to decrease the catalyst loading to 1 mol% without increasing the reaction time and to 0.1 mol% if the mixture was stirred for 1 hour.

Finally, to further test the scope of the reaction, we synthesized two different 1,5-enynes (**5** and **7**) and subjected them to cycloisomerization (Scheme 3). Amazingly, simple modifications of the acetylenic substitution pattern appear crucial in controlling the outcome of the reaction. While **1** yielded a mixture of three products and **7** a mixture of unidentified products, **5** produced exclusively **6**, a bicyclo[3.1.0]hexene of type **4**. The reasons for such a selectivity are still unclear, but it is noteworthy that even in the NMR spectrum of the crude product, no trace of other cycloisomerized compounds was observed.

These results, and particularly the formation of the unprecedented product **4**, led us to explore some mechanistic aspects of this transformation. We first considered the possibility of a vinylcyclopropane rearrangement of **3** into **4**. A thermal rearrangement is easily ruled out since the reaction occurs at rt. The reaction of **3** under cyclization conditions resulted in the recovery of the starting material at rt and its degradation upon heating, excluding a hypothetical Au-catalyzed rearrangement. In order to explain the formation of the three bicyclic cyclopropyl compounds, we propose a cationic pathway (Scheme 4). The route leading to **III** and **IV** (that can be viewed as gold-methylidenes **III′** and **IV′**) is similar to the one we proposed for the $PtCl_2$-catalyzed cycloisomerization.[7,18] From **IV**, a 6-*endo* cyclization process, followed by collapse of the carbon–gold bond, would provide **3**. Cationic rearrangement of intermediates **V** or **VI**, leading to a



Scheme 3 Au-catalyzed cycloisomerization of 1,5-enynes.



Scheme 4 Proposed mechanism for the cycloisomerization of **1**.

bicyclo[3.1.0]hexane cation **VII**, which could be further stabilized *via* an oxonium, would produce unprecedented **4**.

In summary, we have reported the formation of an unprecedented bicyclo[3.1.0]hexene in the cycloisomerization of 1,5-enynes, catalyzed by (NHC)Au complexes. Moreover, we have shown that the nature of the ligand on gold and the counterion have a significant effect on the outcome of the reaction. Studies aimed at improving the selectivity and understanding the mechanistic aspects of this reaction are ongoing.§

Notes and references

‡ *Crystal data.* ($C_{19}H_{21}NO_4$), M = 327.37, triclinic, space group P-1, a = 7.194(1), b = 8.756(2), c = 13.875(3) Å, α = 82.241(4), β = 81.536(4), γ = 80.279(4)°, V = 846.6(3) Å^3, T = 273(2) K, Z = 2, μ = 0.090 mm^{-1}, 1018 reflections measured using a Bruker SMART 1 K CCD diffractometer, 301 unique (R_{int} = 0.0587), wR_2 = 0.1612, R_1 = 0.0668 for all data. CCDC 267108. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602839j

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