J|A|C|S COMMUNICATIONS

Published on Web 02/10/2009

Au(I)-Catalyzed Cycloisomerizations Terminated by sp^3 C−H Bond Insertion

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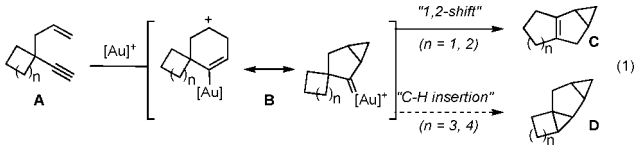
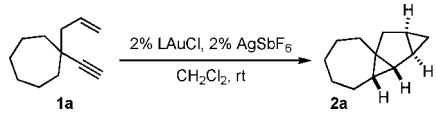
Cationic gold(I) complexes have emerged as powerful π acids capable of promoting a diverse range of enyne cycloisomerization reactions.[1] In these reactions, the gold catalyst not only serves to activate the alkyne toward nucleophilic addition[2] but also plays a role in stabilizing the cationic intermediates produced in the cyclization event.[3] In many of these cases, the stabilization arises from interactions of the gold catalyst with the directly bonded carbocation.[4] Thus, transformations in which these intermediates display reactivity that is reminiscent of electrophilic metal-stabilized carbenes have been developed.[5,6] However, in contrast to other electrophilic metal−carbenoid species, insertion of the gold-stabilized cationic intermediates into sp^3 C−H bonds is rare.[7,8] We envisioned that access to such a transformation might provide insight into the importance of the gold complex not only in the stabilization of the cationic intermediates but also in the subsequent reactivity of these species.[9]

With the aim of examining the potential of cationic gold(I)−carbenoid intermediates to participate in this class of reactions, we revisited the gold-catalyzed cycloisomerization of 1,5-enynes **A**.[10] While we had previously observed that gold-catalyzed cycloisomerizations of cyclobutane- and cyclopentane-derived enynes (**A**, $n = 1, 2$) were terminated by a ring expansion to afford **C**,[10b] we postulated that larger, more flexible rings might allow for an intramolecular C−H insertion via gold−carbenoid intermediate **B** (eq 1).



(1)

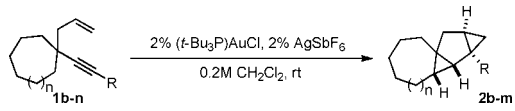
In order to explore this hypothesis, 1,5-enyne **1a** possessing a cycloheptyl skeleton at the C4 position was allowed to react under our standard conditions for cycloisomerization of 1,5-enynes [2% $(Ph_3P)AuCl/AgSbF_6$] (eq 2). We were pleased to find that the reaction proceeded smoothly to provide tetracyclic compound **2a** in 75% yield after 1 h. On the basis of the observation that electron-donating ligands are preferred for reactions involving trapping of the gold(I)−carbenoid intermediates, we examined *N*,*N*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) and [tri(*tert*-butyl)phosphine]gold(I) chloride as catalysts. Gratifyingly, both of these complexes showed improved reactivity (10−15 min) in the cycloisomerization reaction and produced **2a** in better yield. Notably, in all cases, neither the competing deprotonation from gold−carbenoid intermediate **B** to afford spiro[5.6]dodeca-1,4-diene nor the 1,2-alkyl shift to provide ring-expansion product **C** were observed.

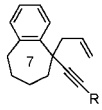


(2)

Under these optimized reaction conditions, a number of cycloheptyl- or cyclooctyl-substituted 1,5-enynes **1** undergo the gold(I)-catalyzed cycloisomerization/C−H insertion reaction (Table 1). For example, in addition to terminal alkynes, substrates containing alkyl and aryl alkynes participate in the gold(I)-catalyzed reaction to afford the desired products in excellent yield (entries 2−4). Furthermore, the C−H insertion reaction occurs independently of the electronic nature of the substituent at the acetylenic position (entries 5−9). Moreover, gold(I)-catalyzed cycloisomerization of **1k** and **1l** afforded bis(cyclopropanes) **2k** and **2l** in excellent yield without competing functionalization of the aromatic C−H bonds (entries 10 and 11). The structure of **2l** was unambiguously confirmed by X-ray diffraction analysis (Figure 1).

Table 1. Gold(I)-Catalyzed Cycloisomerization of 1,5-Enynes



entry		N	R	time (min)	yield (%)[a]
1	**1b**	2	H	15	**2b** 86
2	**1c**	2	Me	15	**2c** 80
3	**1d**	1	Ph	60	**2d** 80
4	**1e**	2	Ph	60	**2e** 82
5	**1f**	1	*p*-MeO-C_6H_4	30	**2f** 83
6	**1g**	2	*p*-MeO-C_6H_4	30	**2g** 80
7	**1h**	1	*p*-EtO_2C-C_6H_4	30	**2h** 85
8	**1i**	2	*p*- EtO_2C-C_6H_4	30	**2i** 81
9	**1j**	1	*p*-O_2N-C_6H_4	30	**2j** 76
10	**1k**		Me	15	**2k** 78
11	**1l**		Ph	30	**2l** 81
12	**1m**		CO_2Et	90	**2m** 60[b]
13	**1n**		CHO	90	**2m** 51[b]

[a] Isolated yield. [b] Isolated yield after reduction to the corresponding alcohol using LAH.

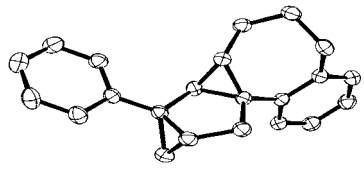


Figure 1. ORTEP of **2l** (CCDC 703508). Hydrogens have been omitted for clarity.

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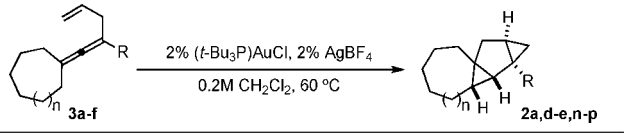
Table 2. Gold(I)-Catalyzed Cycloisomerization of 1,4-Enallenes



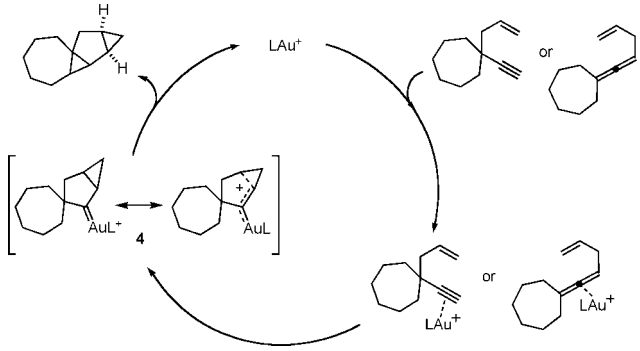
entry		*n*	R	time (h)	yield (%)[a]
1	**3a**	1	H	2	**2a** 73
2	**3b**	1	Bn	2	**2n** 83
3	**3c**	2	Bn	2	**2o** 62
4	**3d**	1	Ph	2	**2d** 88
5	**3e**	2	Ph	2	**2e** 85
6	**3f**	2	*p*-CF_3−C_6H_4	2	**2p** 63

[a] Isolated yield.

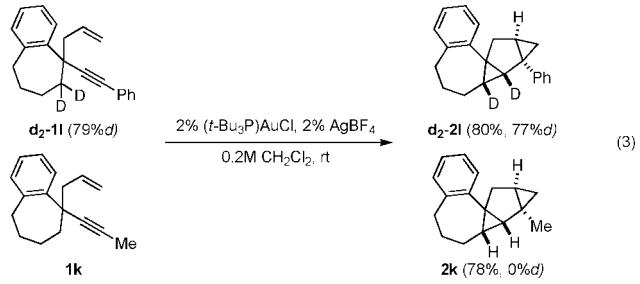
We considered that intermediate **B** might also be accessed through a gold(I)-catalyzed cyclization of a 1,4-enallene.[11] While the desired reaction did not occur at room temperature, we were pleased to find that 1,4-enallenes were converted into the anticipated cyclopropane adducts at slightly elevated temperatures (Table 2).

A proposed mechanism for these transformations is outlined in Scheme 1. Complexation of the cationic gold(I) complex to the alkyne or allene moiety induces an intramolecular addition of the alkene, leading to gold(I)-stabilized cationic intermediate **4**. This intermediate then undergoes a formal sp^3 C−H insertion to generate the tetracyclic adduct.

Scheme 1. Mechanistic Proposal for Au(I)-Catalyzed Cycloisomerization

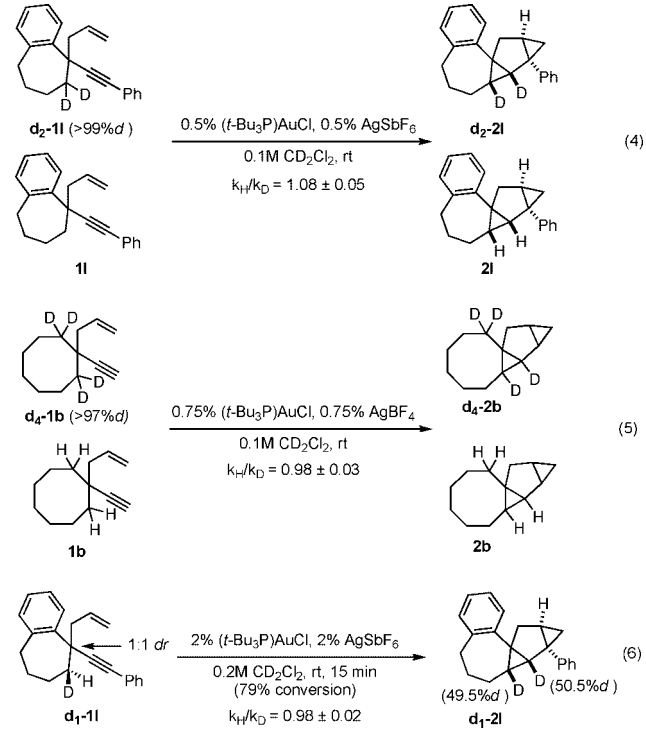


To gain insight into the mechanism of the sp^3 C−H functionalization, a double-labeling crossover experiment was carried out. Gold(I)-catalyzed cycloisomerization of a 1:1 mixture of **d_2-1l** and **1k** afforded **d_2-2l** and **2k** with complete deuterium incorporation exclusively in **d_2-2l** (eq 3). This experiment strongly suggests an *intramolecular* transfer of the sp^3 C−H bond to gold(I)-stabilized cationic intermediate **4**.



(3)

The fact that no H/D scrambling occurred during the cycloisomerization (eq 3) allowed us to directly measure a kinetic isotope effect by monitoring the reaction of a 1:1 mixture of deuterium- and hydrogen-labeled compounds. Thus, a small normal intermolecular kinetic isotope effect (k_H/k_D) of 1.08 was measured for the gold-catalyzed cycloisomerization of **1l** (eq 4). In order to interpret this result, we considered two possibilities: (1) the coordination/cyclization steps in the proposed mechanism (Scheme 1) are reversible, and therefore, the isotope effect is due (at least partially) to the C−H functionalization event; (2) one of the first two steps is irreversible, and therefore, the small measured isotope effect is derived from the coordination/cyclization step. Moreover, the fact that changing the fragment containing the C−H bond from a seven-membered ring in **1l** to an eight-membered ring in **1b** (eq 5)[12] had only a minor impact on the observed kinetic isotope effect led us to conjecture that these values are largely due to the coordination and/or cyclization steps. The observation that essentially no kinetic isotope effect was measured in the gold-catalyzed cycloisomerization of diastereomers of **d_1-1l** (eq 6) is consistent with this possibility.

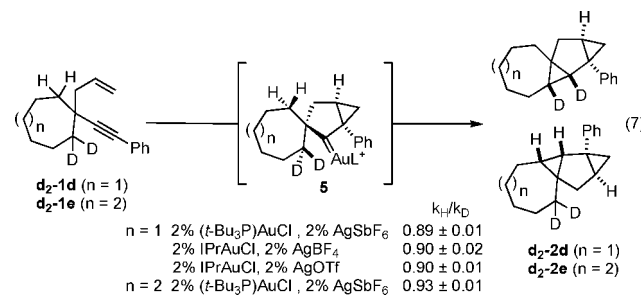


(4)

(5)

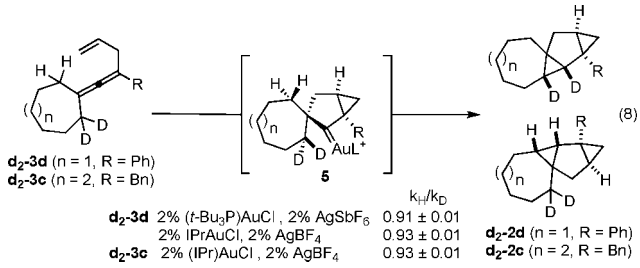
(6)

In order to probe this hypothesis, we examined the gold-catalyzed cyclization of **d_2-1d**. In this case, the coordination/cyclization of **d_2-1d** produces cationic intermediate **5**, which can insert into either a C−H or C−D bond; this allows for direct measurement of the isotope effect of the C−H insertion step, irrespective of the reversibility of the first steps (eq 7). Since this step involves cleavage of a C−H bond, we were surprised to find that an inverse kinetic isotope effect was measured for the [tri(*tert*-butyl)phosphine]gold(I)-catalyzed cycloisomerization of **d_2-1l**. Moreover, similar values were obtained using cationic (IPr)gold(I) as the catalyst, independent of the counterion.



(7)

To further verify this observation, the gold-catalyzed cycloisomerization of allene **d_2-3d** was examined. Since the identical gold−carbenoid **5** is postulated as an intermediate in the cycloisomerization of **d_2-3d**, a similar kinetic isotope effect would be anticipated. Indeed, inverse isotope effects were also measured for the (phosphine)gold(I)- and (*N*-heterocyclic carbene)gold(I)-catalyzed rearrangements of allenes **d_2-3d** and **d_2-3c** (eq 8).



Intramolecular C−H insertion reactions of metal−carbenoid complexes typically exhibit primary kinetic isotope effects k_H/k_D of 1.1−3.1.[13] Since inverse primary kinetic isotope effects (k_H/k_D = 0.93−0.89) were measured for the C−H insertion of the gold(I)-stabilized cationic intermediate, a mechanism analogous to those proposed for metal−carbenoid insertion[14] into C−H bonds does not adequately account for the measured isotope effects. Significant normal kinetic isotope effects are also generally observed for the C−H bond undergoing hydride transfer to a carbocation.[15] Thus, our measured inverse kinetic isotope effects for the C−H insertion suggest that a mechanism involving a simple hydride to a carbocation-like intermediate is unlikely; the experimental inverse isotope effects require that the transition state for hydride transfer have larger force constants for the C−H bond than for cationic intermediate **5**.[16] Alternatively, and by analogy to other metal-catalyzed C−H activation reactions,[17] formation of a σ complex between the hydrogen atom and cationic gold(I) preceding the hydrogen transfer event may account for the observed inverse isotope effect.

In conclusion, we have developed a gold(I)-catalyzed sequential cycloisomerization/sp^3 C−H bond functionalization of 1,5-enynes and 1,4-enallenes that provides tetracyclododecane and tetracyclotridecane derivatives, respectively. These transformations represent rare examples of sp^3 C−H bond insertion by a cationic gold(I)−carbenoid intermediate. It is difficult to draw conclusions about the nature of the bonding and stabilization of the cationic intermediate by the gold catalyst from these experiments; however, the studies presented herein further support the hypothesis that the transition metal plays an integral role in the subsequent transformations of these cationic intermediates. Further studies of the mechanism and scope of the reactivity of cationic gold(I)−carbenoid intermediates as well as application of this present strategy are ongoing and will be reported in due course.

Acknowledgment. F.D.T. thanks NIHGMS (RO1 GM073932), Merck Research Laboratories, Bristol-Myers Squibb, and Novartis for funding. Y.H. gratefully acknowledges a Grant-in-Aid for Young Scientists (B) (19750071) for partial support. We thank Prof. R. G. Bergman (UC Berkeley) for helpful suggestions and discussions.

Supporting Information Available: Typical experimental procedures, spectral data for all of the new compounds, and a CIF file for **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA808780R