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Published on Web 10/13/2006

A Gold-Catalyzed Unique Cycloisomerization of 1,5-Enynes: Efficient Formation of 1-Carboxycyclohexa-1,4-dienes and Carboxyarenes

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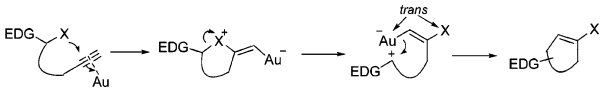
Received August 27, 2006; E-mail: lzhang@chem.unr.edu

Transition metal-catalyzed enyne cycloisomerization is one of the most important strategies for forming functionalized cyclic structures.[1] Lately, Au catalysis[2] has elicited new excitement in this active research area, and novel modes of enyne cycloisomerization have been revealed. Among a range of applicable enyne substrates, 1,5-enynes are one of the most studied and have been efficiently converted into cyclic products such as bicyclo[3.1.0]-hexenes,[3] cyclohexadienes,[4] methylenecyclopentenes,[5] and heterobicycloalkenes.[6] These reactions are often proposed to proceed with initial formation of a cyclopropyl gold carbenoid.[7]

Recently we showed that the alkenylgold intermediates generated in situ from propargylic esters were significantly nucleophilic and participated efficiently in intramolecular C−C bond formation reactions.[8] We reason this C−C bond formation reaction can be generally applied to other alkyne substrates as well, and a unique cycloisomerization strategy is envisioned. As shown in Scheme 1,

Scheme 1. General Design of Au-Catalyzed Cycloisomerization

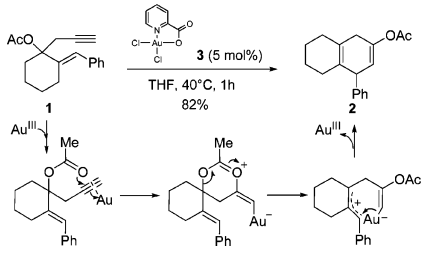


Au activation of the C−C triple bond can result in a migration of the nucleophilic X group, providing the carbon cation generated is sufficiently stabilized. Subsequent nucleophilic attack[9] by the alkenylgold will then lead to cyclized products.

Our effort in implementing this novel strategy[10] led to the development of an efficient synthesis of 1-carboxycyclohexa-1,4-dienes and carboxyarenes from 5,1-enyn-4-yl carboxylates. Significantly, this novel Au-catalyzed cycloisomerization of 1,5-enynes does not likely undergo the often-invoked initial formation of cyclopropyl gold carbenoid. Herein we disclose the results of this study.

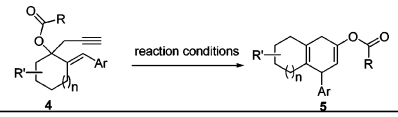
On the outset, we chose 1,5-enyne **1** as the substrate, with acetoxy as the migrating group (Scheme 2), with two considerations in

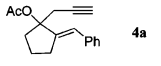
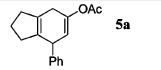
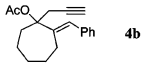
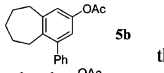
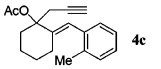
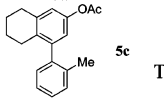
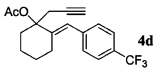
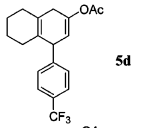
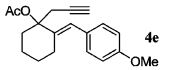
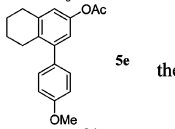
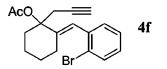
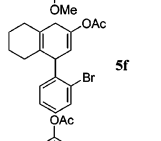
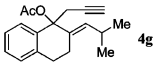
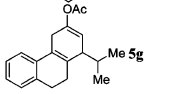
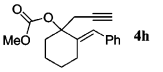
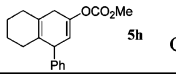
Scheme 2. Initial Au^{III}-Catalyzed Reaction of 1,5-Enyne Acetate **1**



mind: (1) the phenyl group can provide further stabilization to the carbon cation, permitting an efficient migration of the acetoxy group, and (2) the cyclohexane ring can provide conformation control to the allylic cation. Gratifyingly, this reaction did proceed in high efficiency under carefully optimized reaction conditions [i.e., 5 mol % of dichloro(pyridine-2-carboxylato)gold (**3**),[11] THF, 40 °C, 1 h], and 1-acetoxycyclohexa-1,4-diene **2**[12] was isolated in 82% yield. Other solvents, such as CH_3CN, toluene, and $ClCH_2$-CH_2Cl, were suitable as well but with diminished efficiency. The likely mechanism of this reaction is proposed in accordance with the general strategy (Scheme 2).

Table 1. Au^{III}-Catalyzed Cycloisomerization of 1,5-Enynes



Entry	Enyne **4**[a]	Cyclohexadiene **5**	Reaction conditions	Yld.
1	 **4a**	 **5a**	5 mol % **3** CH_2Cl_2, rt, 5 h	78%
2[b]	 **4b**	 **5b**	5 mol % **3** CH_3CN, 40°C, 2 h then, DDQ, rt, 40 min	71%
3[b]	 **4c**	 **5c**	10 mol % **3** CH_3CN, 60°C, 1 h Then, DDQ, rt, 40 min	72%
4	 **4d**	 **5d**	5 mol % **3** 5 mol % $KAuCl_4$ CaO (2 eq) CH_3CN, 60°C, 3h	74%
5[b]	 **4e**	 **5e**	5 mol % **3** THF, rt, 2h then, DDQ, rt, 40 min	70%
6	 **4f**	 **5f**	5 mol % **3** 5 mol % $KAuCl_4$ CaO (2 eq) CH_3CN, 60°C, 5h	64%
7	 **4g**	 **5g**	5 mol % **3** THF, 40°C, 15min	86%
8	 **4h**	 **5h**	5 mol % **3** CH_3CN, 60°C, 30min	65%

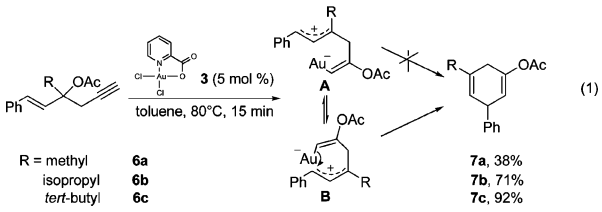
[a] Enynes **4** were conveniently prepared by reacting enones with propargylaluminate followed by acetylation or methylcarbonation. [b] Due to the difficulty of purification, the cyclohexadiene product was dehydrogenated using DDQ to afford the corresponding biaryl acetate.

The initial scope study of this reaction with substrates derived from arylidene-substituted cyclic ketones is shown in Table 1.[13] Enynes **4** with different ring sizes were generally tolerated, as both five- and seven-membered substrates reacted smoothly, yielding cyclohexa-1,4-diene **5a** and aromatized product **5b**[14] in good yields (entries 1 and 2). Besides phenyl group, various other aryl groups, including electron-rich (entry 5), electron-poor (entry 4), and sterically demanding ones (entries 3 and 6), were compatible with this reaction, and generally good yields of the corresponding cyclohexadienes were isolated (entries 4 and 6). In the cases of *p*-methoxyphenyl and *o*-tolyl groups (entries 3 and 5), the reaction

10.1021/ja066220f CCC: $33.50

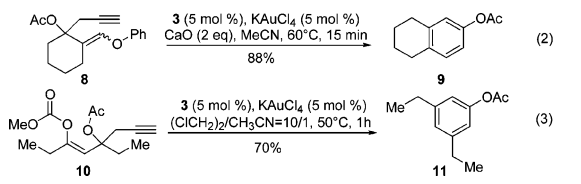
mixtures were subsequently treated with DDQ to yield biaryls **5c** and **5e** for ease of purification. Interestingly, the aryl group, important for the stabilization of the intermediate allylic cation, can be placed on the other side of the allyl moiety. Hence, enyne **4g** derived from α-tetralone cyclized efficiently, affording functionalized tetrahydrophenathrene **5g** in 86% yield in only 15 min. Besides acetoxy group, methoxycarboxy group can be the migrating entity as well, giving rise to cyclohexadienyl carbonate **5h** in fairly good yield (entry 8). A remarkable observation from Table 1 is the substantial variation of the reaction conditions from entry to entry. While dichloro(pyridine-2-carboxylato)gold (**3**) is the catalyst/precatalyst of choice, the reaction temperature and solvent were optimized, as no single set of conditions worked well for all the substrates. Noteworthy are the conditions used for the difficult substrates **4d** and **4f**. The slow reaction of these substrates always led to catalyst decomposition and incomplete reaction, and increasing the catalyst loading did not noticeably improve the conversion. However, the catalyst system appeared to be substantially stabilized by the addition of $KAuCl_4$.[15] The addition of CaO[16] further improved the reaction yields.

To expand the scope of this remarkable reaction, we examined substrates derived from linear aryl-substituted enones (eq 1). While



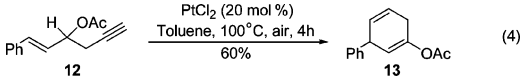
enyne **6a** was converted into cyclohexadiene **7a** in only 38% yield with 48% **6a** remaining due to catalyst decomposition, replacing its methyl group with a bulky isopropyl group (i.e., enyne **6b**) resulted in faster reaction and 71% yield. Further increasing the steric size by using a ^{t}Bu group (i.e., enyne **6c**) substantially enhanced the desired reactivity, and **7c** was isolated in excellent yield. This reactivity trend of enynes **6** can be rationalized with conformational analysis of the proposed allylic cation intermediates **A** and **B**: bulky R groups prefer conformer **B** in order to minimize steric interactions, leading to facile 6-*endo* cyclization, while R = Me likely leads to a predominance of conformer **A**, resulting in slow reaction and unsatisfactory conversion. This rationale is also in accordance with the observation that the enyne derived from *trans*-cinnamaldehyde (i.e., compound **12**, R = H) did not yield the cyclohexadiene product under the same reaction conditions.

The existence of an aryl group in the substrates, however, is not a necessity. We envisioned that the role of the aryl group to stabilize the allylic cation can be readily fulfilled by other electron-donating groups. For example, treatment of enyne **8** with a phenoxy substituent at the C−C double bond led to efficient formation of aromatized acetate **9**,[17] with the expected facile elimination of phenol (eq 2). Moreover, linear enyne **10**, with methoxycarboxy



as the stabilizing group, also underwent similar tandem cycloisomerization and aromatization, affording aryl acetate **11** in good yield upon ready elimination of methanol and CO_2 (eq 3). This approach provides an efficient formation of phenolic acetates with much flexibility in aromatic substitution pattern.

Further expanding the scope of this chemistry to substrates derived from enals was unsuccessful with Au catalysts. However, $PtCl_2$ provided an encouraging alternative. As shown in eq 4, enyne



12, derived from *trans*-cinnamaldehyde, was converted into cyclohexadiene **13** in 60% yield. Notably, 20 mol % of $PtCl_2$ was needed, and the reaction was run under air, as nitrogen protection led to significant retardation and inferior yield. The role of oxygen in this reaction is to be further studied.[18]

In summary, we have developed a unique Au-catalyzed 1,5-enyne cycloisomerizatioin involving carboxy group migration and Au-mediated C−C single bond formation. 1-Carboxycyclohexa-1,4-dienes and carboxyarenes can be prepared with good efficiency and with flexible substitution patterns. Further study in applying the novel Au-catalyzed migratory cycloisomerization strategy to other substrates is underway.

Acknowledgment. This work is supported by the University of Nevada, Reno and ACS PRF (no. 43905-G1).

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected reviews, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067−2096. (b) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16. (c) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215−236.
(2) For general reviews of gold catalysis, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3−9. (c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431−436. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990−6993. (e) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795−812. (f) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387−391.
(3) (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859.
(4) (a) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705−9710. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807.
(5) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129−4132.
(6) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963.
(7) For pioneering work in 1,6-enyne cycloisomerization involving cyclopropyl gold carbenoid, see: Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. For an exception in the case of dienynol, see: Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340−9341.
(8) (a) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 8414−8415. (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805.
(9) Alternatively, an electrophilic reaction of the cation with the C−C double bond, followed by facile elimination of Au, is possible. For a similarly proposed mechanism, see: Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473−4475.
(10) After our submission, a study employing a similar strategy appeared, see: Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062−12063.
(11) Au^I complexes, such as $Au(PPh_3)SbF_6$, did not catalyze this reaction.
(12) The structure of **2** was deduced from extensive NMR studies. The cyclohexa-1,4-diene motif is supported by the characteristic long-range coupling between H-3 and H-6 (J = 7.5 Hz).
(13) Substrates with internal C−C triple bonds did not yield desired products.
(14) Due to the partial aromatization upon column purification of the corresponding cyclohexadiene product and for the ease of purification, the reaction mixture was treated with DDQ subsequently to yield arene **5b**.
(15) $KAuCl_4$ itself does not catalyst the reaction. Its role is likely to scavenge the pyridine-2-carboxylate upon the decomposition of catalyst **3**.
(16) CaO was intended to trap the acid generated upon catalyst decomposition.
(17) The structure of **9** was confirmed by independent preparation of it from commercially available 5,6,7,8-tetrahydro-2-naphthol.
(18) $(PhIO)_n$ has been used together with $PtCl_2$ previously, and Pt(IV) was suggested as the likely catalytic species, see: Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468−12469.

JA066220F