J|A|C|S
COMMUNICATIONS

Published on Web 06/09/2006

A Highly Efficient Preparative Method of α-Ylidene-β-Diketones via Au^{III}-Catalyzed Acyl Migration of Propargylic Esters

Shaozhong Wang and Liming Zhang*

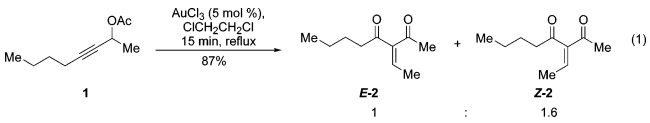
Department of Chemistry/216, University of Nevada, Reno, 1664 North Virginia Street, Reno, Nevada 89557

Received April 21, 2006; E-mail: lzhang@chem.unr.edu

Au salts are powerful soft Lewis acids and readily activate alkynes and allenes toward attacks by a variety of nucleophiles.[1] While these reactions typically result in the formation of Au−C bond-containing intermediates, the nucleophilicity of these organoaurates[2] has rarely been exploited[3] except simple protonation or elimination. Reactions of these Au−C bonds, especially those leading to the formation of C−C bonds, could result in sequential functionalization of alkynes/allenes in a cascade process, substantially enriching Au chemistry.

α-Alkylidene- or benzylidene-β-diketones are versatile synthetic intermediates and, in general, can be prepared through the Knoevenagel condensation of aldehydes/ketones and β-diketones.[4] However, this condensation is often plagued by the formation of Michael adducts and by the isomerization to β,γ-unsaturated products. Furthermore, the double bond geometry of the adduct is mainly governed by steric effects, leading to a mixture of double bond isomers.[5]

Herein, we report our investigation into the nucleophilicity of Au−C bonds following Au activation of alkynes/allenes. A highly efficient and general synthetic method of α-alkylidene or benzylidene-β-diketones is developed, featuring a novel intramolecular acyl migration to nucleophilic Au^{III}−C(sp^2) bonds.



On the outset, we treated oct-3-yn-2-yl acetate (**1**) with $AuCl_3$ (5 mol %) in refluxing $ClCH_2CH_2Cl$. Surprisingly, a clean conversion to an isomeric mixture of 3-ethylidene-2,4-octadiones (**2**) was observed (eq 1). These geometric isomers of **2** were readily separated by flash column chromatography, and their structures were assigned based on spectroscopic studies, including 1D NOESY. This efficient transformation of a simple substrate, such as **1**, into synthetically versatile alkylidene diketones is remarkable and prompted us to optimize the reaction conditions and study its scope.

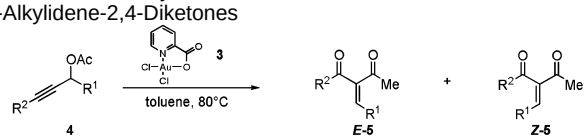
We first examined the influence of solvents on the reaction. Interestingly, this reaction showed remarkable insensitivity to solvent polarity with 5 mol % of $AuCl_3$ as compound **2** was formed in excellent yields both in nonpolar toluene (entry 1, Table 1) and in polar nitromethane (entry 2), while the *E*/*Z* ratio remained largely unchanged. Further experiments proved that toluene was the best solvent, and a quantitative conversion of **1** to **2** was observed with 1 mol % of $AuCl_3$ (entry 3). Attempts to improve the stereoselectivity of this reaction was initially unsuccessful with complex $PyAuCl_3$ (entry 4); however, complex dichloro(pyridine-2-carboxylato)gold(III) (**3**)[6] appeared to be an excellent catalyst/precatalyst[7] as the stereoselectivities were improved significantly (entries 5 and 6). Although the reaction in the presence of complex **3** took substantially longer time to complete than in the cases of $AuCl_3$, its ease of handling and the improved stereoselectivity led us to choose conditions in entries 5 and 6 for studying the reaction scope.

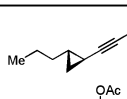
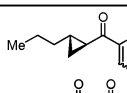
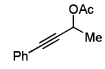
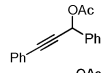
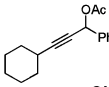
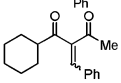
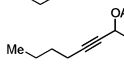
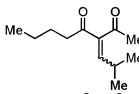
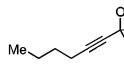
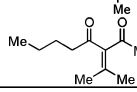
Table 1. Optimizing Reaction Conditions for Au-Catalyzed Formation of **2** from Propargylic Acetate **1**

entry	catalyst	conditions	time (h)	yield of **2** (%)[a]	*E*:*Z*
1	5 mol % of $AuCl_3$	toluene, 80 °C	0.25	>99	1:1.6
2	5 mol % of $AuCl_3$	$MeNO_2$, 80 °C	0.25	94	1:2
3	1 mol % of $AuCl_3$	toluene, 80 °C	0.25	>99	1:1.6
4	5 mol % of $PyAuCl_3$	toluene, 80 °C	12	84	1:2
5	**5 mol % of $LAuCl_2$**[b]	**toluene, 80 °C**	**1.5**	**>99**[c]	**7:1**
6	**1 mol % of $LAuCl_2$**[b]	**toluene, 80 °C**	**3.5**	**>99**[c]	**4:1**
7	5 mol % of $L'AuNTf_2$[d]	$ClCH_2CH_2Cl$, 80 °C	8	26	1:2
8	5 mol % of $PtCl_2$	$ClCH_2CH_2Cl$, 80 °C	12	*e*	
9	5 mol % of $HNTf_2$	$ClCH_2CH_2Cl$, 80 °C	6	*e*	

[a] Estimated by ^{1}H NMR using diethyl phthalate as internal standard. [b] L = pyridine-2-carboxylato. [c] Isolated yield. [d] L′ = 2-(dicyclohexylphosphino)biphenyl. [e] Mostly starting material.

Table 2. Au-Catalyzed Efficient Formation of 3-Alkylidene-2,4-Diketones



entry	propargylic acetate **4**	**3** (mol %)	time (h)	3-alkylidene-2,4-diketone (**5**)	yield (%)[a]	*E* : *Z*[b]
1	 **4a**	5	1	 **5a**	93	2 : 1
2	 **4b**	5	1	 **5b**	91	1.6 : 1
3	 **4c**	5	1	 **5c**	90	2 : 1
4	 **4d**	5	1	 **5d**	97	9 : 1
5	 **4e**	10	3	 **5e**	95	5 : 1
6	 **4f**	5	1	 **5f**	94	-

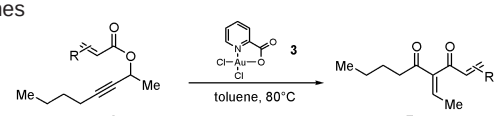
[a] Isolated yield. [b] Estimated by ^{1}H NMR.

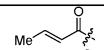
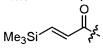
Other catalysts, such as cationic Au(I) complexes (e.g., entry 7), $PtCl_2$ (entry 8), and $HNTf_2$ (entry 9), proved to be largely ineffective.

With the optimal reaction conditions (catalyst **3**, toluene, 80 °C), the scope of this reaction was promptly studied. Table 2 shows the results with various propargylic acetates (**4**). What is immediately apparent is the high efficiency of this reaction as the isolated yields of all the entries are ≥90%. Various substituents at the propargyl alkyne terminus, such as cyclopropyl (entry 1), phenyl (entry 2), and sterically demanding cyclohexyl (entry 4), were all tolerated, and the reactions were completed in an hour with 5 mol % of catalyst **3**. Phenyl substituents at both ends of the propargyl moiety were allowed, and benzylidene derivative **5c** was formed efficiently (entry 3). An isopropyl group α to the propargylic position led to

10.1021/ja062777j CCC: $33.50

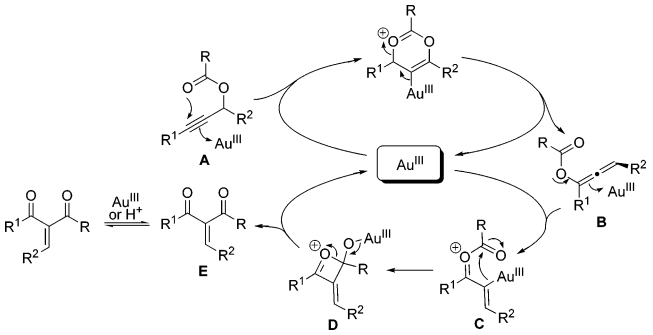
Table 3. Au-Catalyzed Highly Stereoselective Formation of Dienyl Diketones



entry	acyl group in **6**		catalyst **3** (%)	time (h)	yield of **7** (%)[a]	$Z:E$[b]
1		**6a**	5	2	95	50 : 1
2		**6b**	5	1	92	9 : 1
3		**6c**	1	0.5	93	50 : 1
4		**6d**	5	2.5	93	14 : 1
5		**6e**	1	0.4	97	12 : 1

[a] Isolated yield. [b] Estimated by ^{1}H NMR.

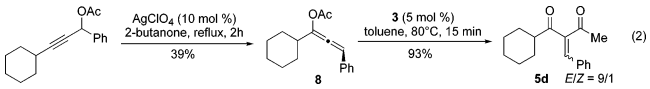
Scheme 1. Proposed Reaction Mechanism



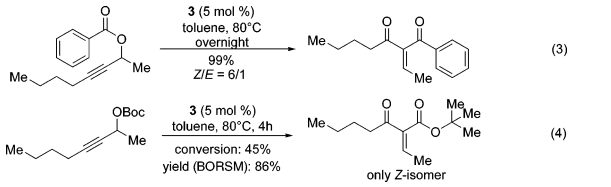
slower reaction, and 10 mol % of catalyst **3** was required to complete the reaction in order to offset its decomposition (entry 5). Although mixtures of *E*/*Z* isomers of **5a**−**e** were obtained, the *E* isomers were always the predominant products. Pronounced selectivities were observed in entries 4 and 5. Remarkably, acetate **4f** derived from a tertiary propargylic alcohol worked equally well, leading to tetrasubstituted alkene **5f** in 94% yield (entry 6).

This general synthetic method of α-ylidene-β-diketones can be applied to highly stereoselective synthesis of versatile dienyl diketones. As shown in Table 3, acryloyl groups with various substituents, including alkyl, phenyl, and silyl groups, were allowed, and dienyl β-diketones (**7**) were obtained in close to quantitative yields. Moreover, these reactions exhibited remarkably high to excellent *Z* selectivity. Interestingly, the erosion of *Z*/*E* selectivity was observed with elongated reaction times, accompanied by appreciable decomposition of catalyst **3**. For example, a 1.4:1 mixture of *Z* and *E* isomers of **7e** was isolated after heating **6e** with 1 mol % of **3** for 40 min.

The proposed mechanism of this reaction is shown in Scheme 1. Hence, propargylic ester **A** undergoes an initial Au-catalyzed 3,3-rearrangement to form carboxyallene **B**, which can be further activated by the same Au^{III} catalyst in situ.[3b,8] The resulting intermediate **C**[9,10] has been shown to react efficiently with nucleophiles at the oxocarbenium moiety;[3b] however, in the absence of suitable nucleophiles, an acyl group migration ensues as the nucleophilic Au^{III}−C(sp^2) attacks the acyl carbonyl group intramolecularly, generating a tetrahedral intermediate (**D**). The collapse of **D** results in α-ylidene-β-diketone **E** with concomitant regeneration of the Au catalyst. The formation of the double bond isomer of **E** is most likely due to isomerization catalyzed by either Au^{III} or H$^+$ formed due to the decomposition of **3**.[4b,11] An alternative route for the acyl migration via intermolecular reaction between a gold allenolate and an acylium is not supported by a cross reaction of esters **4d** and **6b**. No cross product was observed by ^{1}H NMR, GC−MS, and ES-MS. Although the allene intermediate **B** has never been observed during the reaction, the treatment of carboxyallene **8** indeed yielded **5d** with excellent yield and an *E*/*Z* ratio identical to that in entry 4, Table 1 (eq 2).



The scope of this reaction can be further expanded to include benzoates (e.g., eq 3) and carbonates (e.g., eq 4). Particularly noteworthy is that the Boc group survived the reaction conditions and the *tert*-butyl ester was isolated in excellent yield based on recovered starting material, testifying to the mild nature of this transformation.



In conclusion, a highly efficient synthesis of α-alkylidene or benzylidene-β-diketones from readily available propargylic esters is developed. The proposed key transformation is a novel intramolecular acyl migration to nucleophilic Au^{III}−C(sp^2) bonds. Noteworthy features of this method are the excellent yields and the stereoselectivity. High to excellent stereoselectivities were observed in the cases of dienyl β-diketones.

Acknowledgment. This research was supported by the University of Nevada, Reno. We thank Myoung-Geun Song for preparing some of the starting materials.

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 recent reviews, 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.

(2) The nucleophilicity of organoaurates generated via Au activation of C−H bonds has been reported. For terminal alkynes, see: (a) Wei, L.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584−9585. For arenes, see: (b) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (c) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 5964−5965. (d) Shi, Z.; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596−13597.

(3) There are only two exceptions we are aware of: (a) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515−518 (only one example). (b) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804−16805.

(4) For reviews, see: (a) Jones, G. *Org. React.* **1967**, *15*, 204−599. (b) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, p 341.

(5) One exception we are aware of: Tanikaga, R.; Konya, N.; Hamamura, K.; Kaji, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3211−3216.

(6) For its preparation, see: Dar, A.; Moss, K.; Cottrill, S. M.; Parish, R. V.; McAuliffe, C. A.; Pritchard, R. G.; Beagley, B.; Sandbank, J. *J. Chem. Soc., Dalton Trans.* **1992**, 1907−1913.

(7) For a previous study of its role as precatalyst, see: Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6545−6547.

(8) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442−1443.

(9) Alternatively, intermediate **C** can be formed directly from **A** without the intermediacy of carboxyallene **B**.

(10) The selective formation of **C** with R^2 *cis* to Au^{III} has been implied in our previous work (see ref 3b) as well as in our unpublished results.

(11) Inokuchi, T.; Kawafuchi, H. *J. Org. Chem.* **2006**, *71*, 947−953.

JA062777J