ORGANIC
LETTERS

2007
Vol. 9, No. 25
5259−5262

Gold-Catalyzed Intramolecular Carbocyclization of Alkynyl Ketones Leading to Highly Substituted Cyclic Enones

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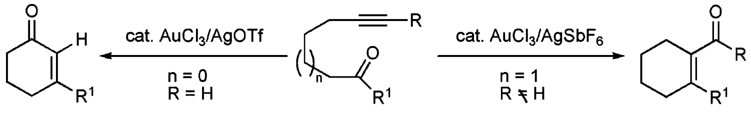
Received October 11, 2007

ABSTRACT



3 **1** **2**

The reaction of the internal alkynyl ketones 1 ($n = 1$) under the combined catalyst, AuCl$_3$ and AgSbF$_6$, gave the enones 2 in good to high yields, whereas that of the terminal alkynyl ketones 1 ($n = 0$) under the combined catalyst, AuCl$_3$ and AgOTf, afforded the cyclic enones 3.

Coinage metal (Au, Ag, Cu) salts act as π-electrophilic Lewis acids and activate alkynes toward nucleophilic attack, allowing the formation of new C−C and C−heteroatom bonds.[1] The intramolecular cyclization of alkynyl−carbonyls and −imines leads to the formation of heterocycles[2] or carbocycles[3] via oxonium or iminium intermediates (eq 1). A different type of cycloisomerization of alkynyl carbonyls using BF$_3$•OEt$_2$ or HCl catalyst was reported by Harding in 1992.[4a] More recently, it was reported that the Lewis acid catalyzed or mediated intra- and intermolecular metathesis of alkyne−*aldehydes* gave the corresponding enones via a formal [2 + 2] cycloaddition and cycloreversion (eq 2).[5] Although similar transformation using alkynyl *ketones* is useful for constructing tetrasubstituted cyclic enones, the Brønsted acid or Lewis acid catalyzed reactions of ketone analogues did not give the desired products in good yields, instead affording a mixture of products.[4a] Furthermore, when

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[1] For recent selected reviews, see: (a) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Pati, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *5*, 121. (d) Pati, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, *5*, 6.

[2] For selected recent coinage-metal-catalyzed synthesis of hetercycles, see: (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (b) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (c) Zhang, J.; Shmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (d) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (e) Harrison, T, J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (f) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (g) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (h) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (i) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. (j) Asao, N.; Yudha, S.; Nogami, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5526.

[3] (a) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650. (b) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921. (c) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399. (d) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (e) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289.

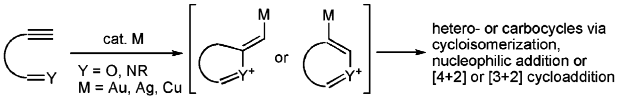
[4] For alkyne ketone metathesis, see: (a) A mixture of cyclopentenyl ketone and cyclohexenone was obtained. Harding, C. E.; King, S. L. *J. Org. Chem.* **1992**, *57*, 883. Also see: (b) Harding, C. E.; Hanack, M. *Tetrahedron Lett.* **1971**, *12*, 1253. (c) Balf, R. J.; Rao, B.; Weiler, L. *Can. J. Chem.* **1971**, *49*, 3135. (d) Hanack, M.; Harding, C. E.; Derocque, J. *Chem. Ber.* **1972**, *105*, 421. (e) Lang, G. L.; Hall, T.-W. *J. Org. Chem.* **1974**, *39*, 3819. (f) Harding, C. E.; Stanford, G. R. *J. Org. Chem.* **1989**, *54*, 3054. (g) Sisko, J.; Balog, A.; Curran, D. P. *J. Org. Chem.* **1992**, *57*, 4341. (h) Grunwell, J. R.; Wempe, M. F.; Mitchell, J. *Tetrahedron Lett.* **1993**, *34*, 7163. (i) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337. (j) Balog, A.; Geib, S. J.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 345. (k) Wempe, M. F.; Grunwell, J. R. *J. Org. Chem.* **1995**, *60*, 2714. (l) Wempe, M. F.; Grunwell, J. R. *Tetrahedron Lett.* **2000**, *41*, 6709. (m) Kurtz, K. C. M.; Hsung, R. P.; Zhang, Y. *Org. Lett.* **2006**, *8*, 231.

[5] For alkyne−aldehyde metathesis, see: (a) stoichiometric use of In(OTf)$_3$, intermolecular reaction: Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 1613. (b) Catalytic use of Yb(OTf)$_3$, intermolecular reaction: Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* **2003**, 552. (c) Catalytic use of AgSbF$_6$, inter- and intramolecular reaction: Rhee, J. U.; Krische, M. *Org. Lett.* **2005**, *7*, 2493.

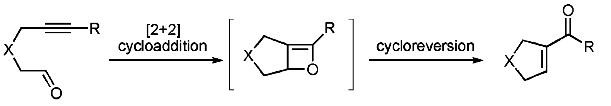
10.1021/ol702455v CCC: $37.00

the cycloisomerization was applied to ketones, we encountered severe limitation on the structure of alkynes[4m] and ketones.[4b−l]

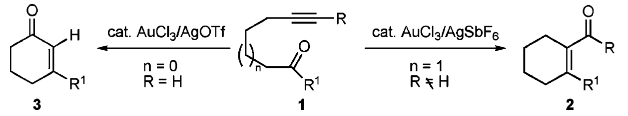
Herein, we report that, by the use of a combined catalyst ($AuCl_3/AgSbF_6$), the transformation of the internal alkynyl ketones **1** into the tetrasubstituted cyclic enones **2** proceeded in good to high yields (eq 3). Furthermore, the terminal alkynyl ketones (R = H) produced the cyclic enones **3** upon treatment with $AuCl_3$/AgOTf (eq 3).



(1)



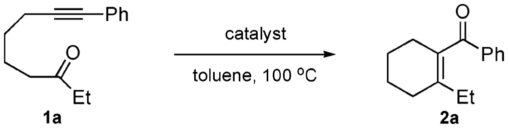
(2)



(3)

Preliminary studies were focused on optimizing the conditions for the formation of the tetrasubstituted α,β-unsaturated enone **2a** from **1a**, using a series of cationic coinage metal catalysts in toluene at 100 °C (Table 1). The use of $AgSbF_6$, AgOTf, $Cu(OTf)_2$, $CuCl_2/AgSbF_6$, AuCl/$AgSbF_6$, or $AuCl_3/AgSbF_6$ afforded good to high yields of **2a** (entries 1, 3, and 5−9). However, the use of the single metal (Ag and Cu) did not give good results for other substrates (**1c**−**m**);[6] the $AuCl_3/AgSbF_6$ combined catalyst exhibited wide applicability. Notably, trace amounts of byproduct, β,γ-unsaturated enone **2a′**, were detected (Scheme 1). It is noteworthy that $AgSbF_6$ catalyst was ineffective in the presence of H_2O (Table 1, entry 4), whereas AgOTf catalyst in the presence of H_2O gave good yield of the corresponding product (entry 2). The reason for this difference is not clear at present. Other coinage metal catalysts, such as AuCl, $AuCl_3$, $AgPF_6$, and $AgBF_4$, were totally ineffective.[7] The Brønsted and Lewis acid catalysts, TfOH and BF_3·OEt_2, were effective (entries 10 and 11), but they did not exhibit the wide applicability observed in the case of $AuCl_3/AgSbF_6$.

Table 1. Optimization of Catalysts for the Intramolecular Carbocyclization of Internal Alkynyl Ketone **1a**

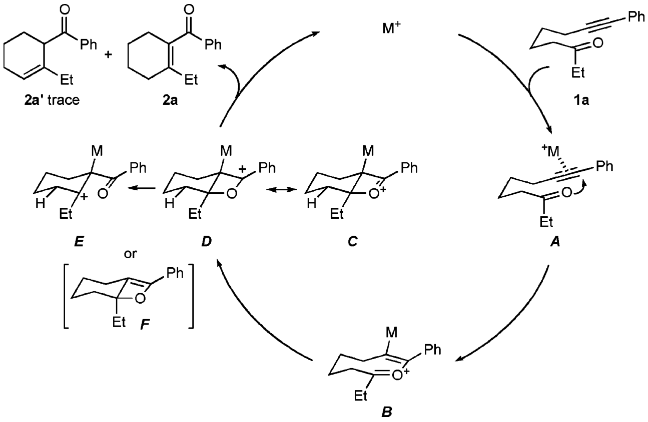


1a **2a**

entry	catalyst (mol %)	time (h)	yield (%)[a]
1	AgOTf (5)	12	73
2	AgOTf (5)/H_2O (1 equiv)	12	71
3	$AgSbF_6$ (5)	1	92 (90)
4	$AgSbF_6$ (5)/H_2O (1 equiv)	12	4[b]
5	$Cu(OTf)_2$ (5)	9	62
6	$CuCl_2/AgSbF_6$ (5/10)	1	65
7	$CuCl_2/AgNTf_2$ (5/10)	24	56
8	AuCl/$AgSbF_6$ (5/5)	1	83
9	$AuCl_3/AgSbF_6$ (2/6)	0.5	89 (87)[c]
10	TfOH (5)	0.5	72
11	BF_3·OEt_2 (5)	24	80

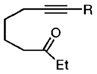
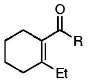
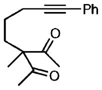
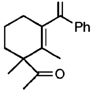
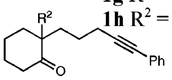
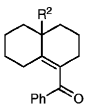
[a] ^{1}H NMR yield of **2a** was determined by using CH_2Br_2 as an internal standard. Isolated yield of **2a** is shown in parentheses. [b] **1a** was recovered in 93% ^{1}H NMR yield. [c] The reaction temperature was 60 °C.

Scheme 1. A Plausible Mechanism for the Gold-Catalyzed Carbocyclization of Internal Alkynyl Ketones



The results of cyclization of the internal alkynyl ketones **1** are summarized in Table 2. Not only the aryl alkynyl ketones bearing electron-donating (**1b**) and electron-withdrawing (**1c** and **1d**) aromatic groups at the alkynyl terminus (entries 2−4) but also the simple alkyl-substituted alkynyl

Table 2. $AuCl_3/AgSbF_6$-Catalyzed Carbocyclization of Internal Alkynyl Ketones[a]

entry	substrates 1		time (h)	products 2		yield (%)[b]
1		**1a** R = C_6H_5	0.5		**2a**	87[c]
2		**1b** R = 4-Me-C_6H_4	1		**2b**	91
3		**1c** R = 4-CO_2Me-C_6H_4	4		**2c**	85
4		**1d** R = 4-CF_3-C_6H_4	24		**2d**	74
5		**1e** R = Pr	1.5		**2e**	54
6		**1f**	7		**2f**	95[d]
7		**1g** R^2 = H	1		**2g**	80
8		**1h** R^2 = CO_2Et	4		**2h**	80[d]

[a] Conditions: $AuCl_3$ (2 mol %), $AgSbF_6$ (6 mol %), **1** (0.5 mmol), toluene (0.2 M), 100 °C. [b] Isolated yields of products **2**. [c] The reaction temperature was 60 °C. [d] $AuCl_3$ (5 mol %) and $AgSbF_6$ (15 mol %) were used.

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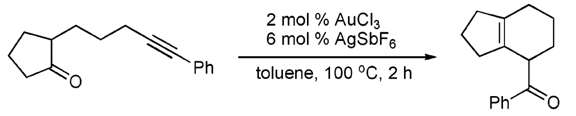
(6) In the presence of the single $AgSbF_6$ catalyst, other substrates (**1c**−**m**) did not give good results even upon increasing the catalyst loading to 15 mol % under the longer reaction times (24 h, the starting materials were recovered in comparable yields.).

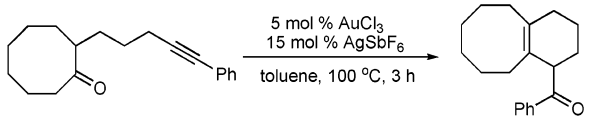
(7) See Supporting Information for additional examples.

ketone **1e** gave the desired α,β-unsaturated enones (entry 5). The reaction of the ketone **1f** with α-substituents proceeded smoothly with use of higher amounts of catalyst, giving the expected enone **2f** in very high yield without forming a β,γ-unsaturated enone byproduct (like type **2a′** in the case of **2a**) (entry 6). The alkynyl cyclohexanones **1g** and **1h** were also suitable substrates for the formation of the bicyclic products **2g** and **2h** (entries 7 and 8). However, the cyclopentanone and cyclooctanone derivatives, **1i** and **1j**, reacted under similar conditions to provide the tetrasubstituted β,γ-unsaturated cyclohexenyl phenones **2i′** and **2j′** in 56 and 30% yield, respectively, without forming α,β-enones (eqs 4 and 5).



(4)

1i **2i'** 55%

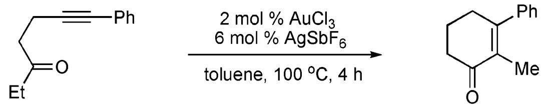


(5)

1j **2j'** 30%

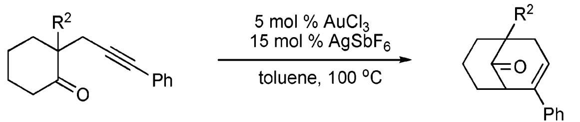
A plausible mechanism is shown in Scheme 1, although it is highly speculative. Coordination of the catalyst M^+ to the alkyne **A** generates the oxetenium intermediates **C**[8] or **D** via the oxonium species **B**. Subsequent ring opening affords the expected ketone **2a**. Perhaps, a small amount of byproduct **2a′** would be formed through **E**; treatment of **2a** under the reaction conditions did not produce **2a′** at all and vice versa. While it cannot be discounted that the alkyne−carbonyl metathesis occurs from the oxete intermediate **F** as reported by Krische[5c] and Hanack,[4b] it seems that intervention of **C**, **D**, and **E** is more reasonable for explaining the formation of the byproduct.

Additionally, the alkynyl ketone **1k** tethered by two methylenes afforded the six-membered α,β-cyclic enone **2k′** instead of forming the four-membered carbocycle (eq 6).[9] The enone **2k′** would be formed through a 6-*endo-dig* cyclization between the enolate of **1k** and the metal activated alkyne. Thus, the reactions of **1l** and **1m** gave the bicyclo[3.3.1]enones **2l′** and **2m′**, respectively (eq 7).



(6)

1k **2k'** 64%

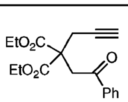
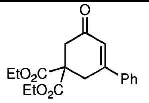
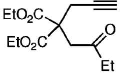
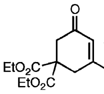
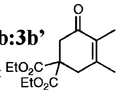
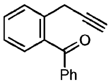
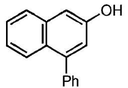
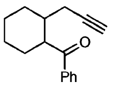
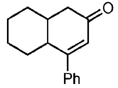


(7)

1l, $R^2 = CO_2Et$
1m, $R^2 = H$

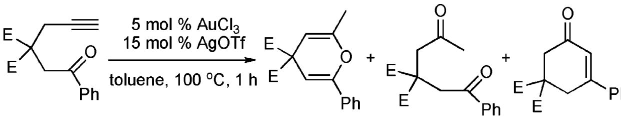
2l' 9 h, 56%
2m' 5 h, 48%

Table 3. $\mathrm{AuCl_3}$/AgOTf-Catalyzed Intramolecular Cyclization of Terminal Alkynyl Ketones[a]

entry	substrates	1	time (h)	products	3	yield (%)[b]
1		**1n**	9		**3a**	80
2		**1o**	10	 	**3b:3b'**	33:45
3		**1p**	10		**3c**	57[c]
4		**1q**	10		**3d**	40[d]

[a] Reaction conditions: 5 mol % of $\mathrm{AuCl_3}$, 15 mol % of AgOTf, **1** (0.5 mmol), toluene (0.2 M), 100 °C. [b] Isolated yields of products **3**. [c] $\mathrm{AuCl_3}$ (10 mol %)/AgOTf (30 mol %) catalysts were used. [d] A 2.2:1 mixture of diastereomers **1q** was used. **3d** was obtained in a 1.7:1 mixture of diastereomers.

Next, we investigated the cyclization of terminal alkynyl ketones (Table 3). In sharp contrast with the internal alkyne ketones, the terminal alkynyl ketone **1n** was converted to the α,β-unsaturated cyclic hexenone **3a** in 80% yield under optimal conditions (entry 1).[7] When the reaction was monitored by TLC, the 4*H*-pyran **4a** was formed after 1 h in 40% yield along with a mixture of diketone **5a** and **3a** in 44% yield (eq 8). The reaction of **4a** under the standard reaction conditions for 2 h afforded a 1:2.6 ratio of **3a** and **5a**, and then the latter was further converted completely to **3a** under the same conditions in 6 h (eq 9). These results clearly indicate that **3a** was formed from diketone **5a**, which was produced from the pyran **4a** through hydrolysis. The exo cyclization of carbonyl oxygen with terminal alkyne followed by isomerization would give **4a**. As expected, when ethyl-substituted ketone **1o** was treated with $\mathrm{AuCl_3}$/AgOTf catalyst, a regioisomeric mixture of **3b** and **3b′** was obtained in 33 and 45% yield, respectively (entry 2). The reaction of *o*-propynylbenzophenone **1p** gave **3c** in a moderate yield, which would be produced through the aromatization of corresponding conjugated cyclic ketone (entry 3). Furthermore, the reaction of a 2.2:1 mixture of diastereoisomers **1q** afforded a 1.7:1 diastereomeric mixture of conjugated bicyclic ketone **3d** in 40% yield (entry 4).



(8)

1n E = CO_2Et **4a** 40% **5a** 44% (**5a**:**3a** = 1.4:1) **3a**

$$\mathbf{4a}\ \xrightarrow[\text{toluene, 100 °C, 2 h}]{\text{5 mol \% AuCl}_3\text{, 15 mol \% AgOTf}}\ \underset{90\%\ (\mathbf{5a}:\mathbf{3a}\,=\,2.6:1)}{\mathbf{5a}\ +\ \mathbf{3a}}\ \xrightarrow[\text{toluene, 100 °C, 6 h}]{\text{5 mol \% AuCl}_3\text{, 15 mol \% AgOTf}}\ \underset{100\%}{\mathbf{3a}} \qquad (9)$$

In conclusion, we have developed an efficient method for constructing highly substituted cyclic enones from alkynyl

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(8) Analogous intermediate **C** was proposed in the $\mathrm{AgSbF_6}$-promoted dehalogenation of α-bromo ketone to form β,γ-unsaturated enone; see: Bégué, J.-P.; Malissaed, M. *Tetrahedron* **1978**, *34*, 2095.

ketones. Further investigation of mechanistic details and application of the present methodology to the synthesis of fused rings are in progress.

Supporting Information Available: Experimental procedures and characterization of relevant compounds (PDF). This material is available free of charge via the Internet at http://pub.acs.org.

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(9) 8-Phenyl-7-octyn-3-one produced a complex mixture of products including 2-ethyl-1-cyclopentenyl(phenyl)methanone (∼10%). The cycloisomerization to five-membered enone was difficult: the reason is not clear at present.