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**Gold(I)-Catalyzed Reaction of 1-(1-Alkynyl)-cyclopropyl Ketones with Nucleophiles: A Modular Entry to Highly Substituted Furans\*\****Junliang Zhang and Hans-Günther Schmalz\**

Highly substituted furans are found as key structural elements in many bioactive natural products and important pharmaceuticals. They also represent versatile building blocks for the synthesis of more elaborate heterocyclic compounds.<sup>[1,2]</sup> The search for efficient general routes to substituted furans is an important, continuing goal of organic synthesis. Several studies have focused on metal-catalyzed methods for furan synthesis (Scheme 1). These include the cyclization of allenyl ketones,<sup>[3]</sup> 3-alkyn-1-ones,<sup>[4]</sup> or 2-(1-alkynyl)-2-alken-1-ones<sup>[5]</sup> through nucleophilic attack of the carbonyl oxygen atom to a transition-metal-coordinated C–C double or triple bond (Mode A, Scheme 1). Alternatively, alkylidene cyclopropyl ketones<sup>[6]</sup> or cyclopropenyl ketones<sup>[7]</sup> are prone to metal-catalyzed cycloisomerization to afford furans through (regio-selective) cleavage of the three-membered ring and subsequent cyclization (Mode B, Scheme 1).

As cyclopropanes are readily accessible and reactive because of their ring strain,<sup>[8,9]</sup> we designed 1-(1-alkynyl)-cyclopropyl ketones **1** (Scheme 2) that contain both an alkyne and a cyclopropane unit as starting materials for cyclization reactions catalyzed by transition metals. Although both modes A and B (to form 2,3-dihydrofurans<sup>[10]</sup>) are potentially possible pathways for metal-mediated reactions involving **1**, we envisioned that furan formation through attack of the carbonyl oxygen atom on the alkyne (Mode A) seemed to be particularly feasible.

Herein, we present a mild and efficient method for the synthesis of multiply substituted furans starting from compounds of type **1**. In particular, we show that the atom-economical gold(I)-catalyzed cascade process allows access to condensed ring systems (for example, furo[*b*]cycloheptenes) under ring expansion.

First, we examined the reaction of (racemic) ketone **2a** using different metal catalysts (5 mol %) with MeOH (2 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (Table 1). Remarkably, the ring-expanded bicyclic cycloheptafuran **3aa** was formed regiose-

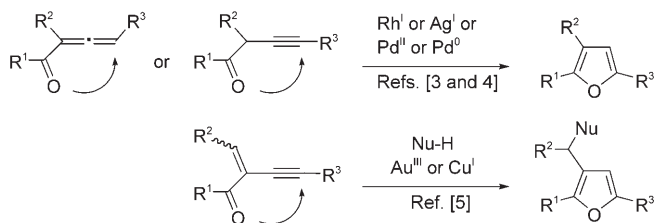
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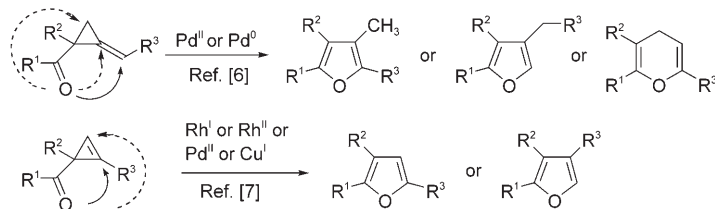


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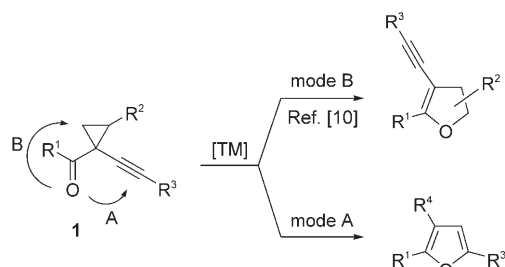
Mode A: participation of an alkyne or allene



Mode B: opening of a 3-membered ring



**Scheme 1.** Transition-metal-catalyzed synthesis of furans. Nu = nucleophile.



**Scheme 2.** Two possible modes of reaction for the cyclization of **1**. [TM] = transition metal reagent.

**Table 1:** Effect of catalyst on the reaction of **2a** to give **3aa**.

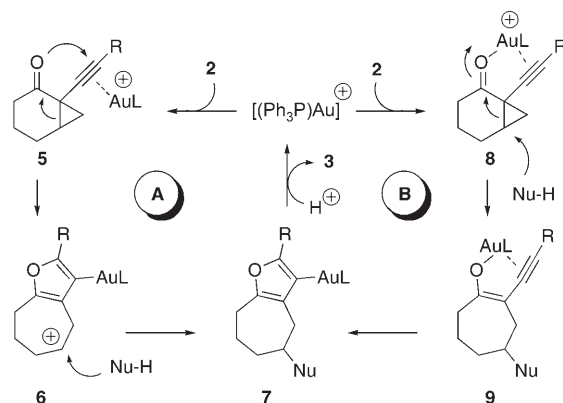
Entry	Catalyst	(Amount)	Time	Yield [%]
1	none	–	24 h	0
2	Cu(OTf) <sub>2</sub>	(5 mol %)	16 h	74
3	In(OTf) <sub>3</sub>	(5 mol %)	22 h	41
4	Ga(OTf) <sub>3</sub>	(5 mol %)	16 h	55
5	Sc(OTf) <sub>3</sub>	(5 mol %)	18 h	63
6	Yb(OTf) <sub>3</sub>	(5 mol %)	24 h	70
7	AuCl	(5 mol %)	1 h	66
8	AuCl <sub>3</sub>	(5 mol %)	1 h	68
9	AgOTf	(5 mol %)	1 h	85
10	(PPh <sub>3</sub> )AuOTf	(5 mol %)	< 5 min	90
11	(PPh <sub>3</sub> )AuOTf	(1 mol %)	< 10 min	91

Tf = triflate = trifluoromethanesulfonyl.

lectively in all cases as the only major product. Lewis acids such as Cu(OTf)<sub>2</sub>, In(OTf)<sub>3</sub>, Ga(OTf)<sub>3</sub>, Sc(OTf)<sub>3</sub>, and Yb(OTf)<sub>3</sub> were active, but only modest yields were obtained after long reaction times. Faster reactions were observed

using AuCl, AuCl<sub>3</sub>, and AgOTf as the catalyst;<sup>[11]</sup> AgOTf afforded the product in a respectable 85 % yield after 1 h. Significantly, we found that (Ph<sub>3</sub>P)AuOTf<sup>[12]</sup> is a particularly efficient catalyst for this reaction. With only 1 mol % of this catalyst, the cascade ring expansion/furan formation was complete after less than ten minutes at room temperature to afford pure **3aa** in 91 % yield (Table 1, entry 11). No trace of the isomeric product (**4aa**) could be detected.

Two plausible mechanisms can be envisioned for this novel Au<sup>I</sup>-catalyzed transformation (Scheme 3).<sup>[11]</sup> In cycle **A** (Scheme 3), a cationic Au<sup>I</sup> species first coordinates to the triple bond to generate an intermediate **5**. Nucleophilic attack of the carbonyl oxygen atom on the activated triple bond with concomitant (regioselective) cleavage of the cyclopropane would generate a carbocation **6**, which can be trapped by a nucleophile (MeOH). Protonolysis of the resulting organogold intermediate **7** gives product **3** and regen-



**Scheme 3.** Possible mechanisms of the Au-catalyzed transformation. L = ligand.

erates the Au<sup>I</sup> catalyst. Alternatively (cycle **B**, Scheme 3), a chelate complex **8** could form as a primary intermediate, which could be attacked by the nucleophile (MeOH) in a regioselective homo-Michael-type addition to generate an Au-enolate **9**, which then undergoes cycloisomerization to afford intermediate **7**.

To probe the scope of the reaction, we performed a series of experiments with different ketones of type **2** and also varied the nucleophile (Table 2). While (Ph<sub>3</sub>P)AuOTf was used as it was found to be the most effective catalyst, some reactions were also studied using AgOTf for comparative purposes.

A variety of O nucleophiles, such as alcohols (including *tert*-butanol),<sup>[13]</sup> phenols, or acetic acid, react smoothly to afford the desired products (Table 2). An N-nucleophilic 2-pyrrolidone could also be employed to give the corresponding N-alkylated product (Table 2, entry 10); however, the reaction was slower than those performed using alcohols as the nucleophiles. When indole was used as the nucleophile, the C3 alkylation product was formed selectively in good yield (Table 2, entry 7). The reaction tolerates a wide range of R

**Table 2:** Au<sup>I</sup>-catalyzed ring expansion/cyclization reactions of substrates **2** with different nucleophiles.<sup>[a]</sup>

Entry	Ketone	R	Nu-H	Prod.	Yield [%] <sup>[b]</sup>
1	<b>2a</b>	Ph	MeOH	<b>3aa</b>	91 (85)
2	<b>2a</b>	Ph	<i>i</i> PrOH	<b>3ab</b>	90 (85)
3	<b>2a</b>	Ph	<i>t</i> BuOH	<b>3ac</b>	85 (77)
4	<b>2a</b>	Ph	Ph-C≡C-CH <sub>2</sub> OH	<b>3ad</b>	77 (88)
5	<b>2a</b>	Ph	<i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> -OH	<b>3ae</b>	84
6	<b>2a</b>	Ph	AcOH	<b>3af</b>	84 (61)
7	<b>2a</b>	Ph	indole	<b>3ag</b>	73 (31)
8	<b>2b</b>	1-cyclohexenyl	MeOH	<b>3ba</b>	80
9	<b>2c</b>	cyclopropyl	MeOH	<b>3ca</b>	82
10	<b>2c</b>	cyclopropyl	2-pyrrolidone	<b>3ch</b>	68 (59)
11	<b>2d</b>	<i>n</i> -butyl	MeOH	<b>3da</b>	86
12	<b>2e</b>	H	MeOH	<b>3ea</b>	76
13	<b>2f</b>	TMS	MeOH	<b>3ea</b>	35

[a] Unless otherwise specified, reactions were carried out as follows: a solution of (racemic) ketone **2** (0.5 mmol), (Ph<sub>3</sub>P)AuOTf (1 mol %), and nucleophile (2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2.8 mL) was stirred at RT for 15 min. [b] Yields of isolated products; yield given in parenthesis refer to reactions performed with AgOTf (5 mol %, 1 h). [c] Indole (1.5 equiv). [d] 6 h. TMS = trimethylsilyl.

groups on the alkyne in substrate **2**.<sup>[13]</sup> Besides phenyl, alkyl, and alkenyl substituents, even a cyclopropyl unit is tolerated (Table 2, entries 9 and 10). This result demonstrates the remarkable chemoselectivity of the reaction.

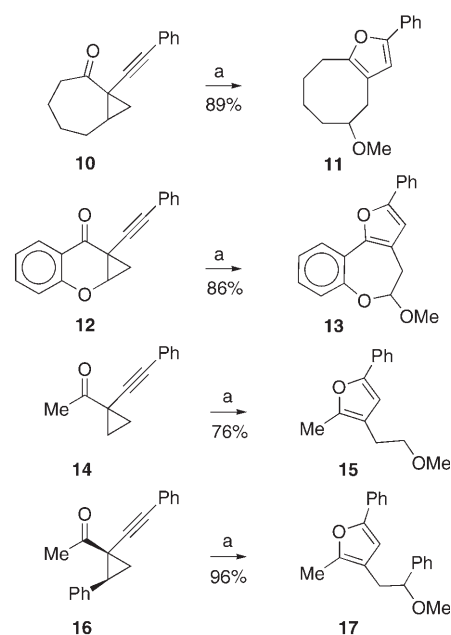
The generality of the method was also investigated using the cycloheptane derivative **10**, the 2,3-methanochromanone derivative **12**, and the monocyclic 1-(1-alkynyl)cyclopropyl ketones **14** and **16**, all of which afforded the expected products (**11**, **13**, **15**, and **17**) in good yields (Scheme 4). In the case of **16**, nucleophilic addition occurs at the more substituted position of the cyclopropane ring.

Remarkably, no reaction took place when **16** was subjected to the standard reaction conditions (1 mol % of (Ph<sub>3</sub>P)AuOTf, CH<sub>2</sub>Cl<sub>2</sub>, RT) in the absence of a nucleophile. Furthermore, no reaction was observed when Et<sub>3</sub>SiH was used as a potential hydride source in place of a nucleophile. These facts contradict a mechanism involving a carbocation intermediate; however, further studies are necessary to obtain deeper mechanistic insights.

In conclusion, a gold-catalyzed cascade reaction was developed which provides efficient access to highly substituted furans under mild conditions. The substrates can be readily prepared from the corresponding enones through cyclopropanation.<sup>[14]</sup> Further studies concerning both the mechanism and possible synthetic applications of the methodology are currently being carried out.

## Experimental Section

A solution of cyclopropyl ketone **2a** (105 mg, 0.5 mmol) and methanol (32 mg, 1.0 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> was added to a solution of Ph<sub>3</sub>AuOTf (generated by mixing equal equivalents of (Ph<sub>3</sub>P)AuCl

**Scheme 4.** The generality of the reaction. Conditions: a) (Ph<sub>3</sub>P)AuOTf (1 mol %), MeOH (2.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, RT.

and AgOTf, with AgCl filtered off) in CH<sub>2</sub>Cl<sub>2</sub> (0.00625 M, 0.8 mL, 0.005 mmol). The mixture was stirred for 15 min at room temperature. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (cyclohexane/ethyl acetate 10:1) to afford 110 mg of **3aa** (91 %) as a light yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.63–7.59 (m, 2H), 7.40–7.32 (m, 2H), 7.25–7.18 (m, 1H), 6.48 (s, 1H), 3.41 (s, 3H), 3.35 (tt, *J* = 9.3, 2.7 Hz, 1H), 2.96–2.82 (m, 2H), 2.81–2.70 (m, 1H), 2.61 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.30–2.16 (m, 1H), 2.08–1.96 (m, 1H), 1.82–1.54 ppm (m, 2H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>): δ = 153.12, 150.23, 131.06, 128.52, 126.58, 123.17, 116.67, 108.90, 79.69, 56.18, 35.76, 31.17, 28.34, 22.77 ppm; IR (neat): ν = 2926, 2850, 1600, 1580, 1551, 1485, 1444, 1091, 757 cm<sup>-1</sup>; MS (70 eV): *m/z* (%): 242 (100) [*M*<sup>+</sup>]; HRMS calcd for C<sub>16</sub>H<sub>18</sub>O<sub>2</sub> [*M*<sup>+</sup>]: 242.1307, found: 242.131. For preparative procedures and spectroscopic data for all new compounds, see the Supporting Information.

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- [1] For reviews, see: a) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. T. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955; b) B. A. Keay, *Chem. Soc. Rev.* **1999**, *28*, 209; c) X. L. Hou, Z. Yang, H. N. C. Wong in *Progress in Heterocyclic Chemistry, Vol. 14* (Eds.: G. W. Gribble, T. L. Gilchrist), Pergamon, Oxford, **2002**, p. 139.
- [2] a) R. J. Sundberg in *Comprehensive Heterocyclic Chemistry, Vol. 5* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, New York, **1984**, p. 313; b) H. Heaney in *Natural Products Chemistry* (Ed.: K. Nakanishi), Kodansha, Tokyo, **1974**, p. 297; c) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795; d) M. Shipman, *Contemp. Org. Synth.* **1995**, *2*, 1.
- [3] a) J. A. Marshall, E. D. Robinson, *J. Org. Chem.* **1990**, *55*, 3450; b) J. A. Marshall, G. S. Bartley, *J. Org. Chem.* **1994**, *59*, 7169;

- c) J. A. Marshall, E. M. Wallace, *J. Org. Chem.* **1995**, *60*, 796; d) A. S. K. Hashmi, *Angew. Chem.* **1995**, *107*, 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; e) A. S. K. Hashmi, T. L. Ruppert, T. Knofel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; f) A. S. K. Hashmi, L. Schwarz, J. H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285; g) S. Ma, L. Li, *Org. Lett.* **2002**, *4*, 941; h) S. Ma, Z. Yu, *Angew. Chem.* **2002**, *114*, 1853; *Angew. Chem. Int. Ed.* **2002**, *41*, 1775; i) S. Ma, J. Zhang, L. Lu, *Chem. Eur. J.* **2003**, *9*, 2447; j) M. H. Suhre, M. Reif, S. F. Kirsch, *Org. Lett.* **2005**, *7*, 3925.
- [4] a) Y. Fukuda, H. Shiragami, K. Utimoto, H. Nozaki, *J. Org. Chem.* **1991**, *56*, 5816; b) A. V. Kel'in, V. Gevorgyan, *J. Org. Chem.* **2002**, *67*, 95; c) A. W. Sromek, A. V. Kel'in, V. Gevorgyan, *Angew. Chem.* **2004**, *116*, 2330; *Angew. Chem. Int. Ed.* **2004**, *43*, 2280.
- [5] a) T. Yao, X. Zhang, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 11164; b) N. T. Patil, H. Wu, Y. Yamamoto, *J. Org. Chem.* **2005**, *70*, 4531.
- [6] a) S. Ma, J. Zhang, *Angew. Chem.* **2003**, *115*, 193; *Angew. Chem. Int. Ed.* **2003**, *42*, 184; b) S. Ma, L. Lu, J. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 9645.
- [7] a) A. Padwa, J. M. Kassir, S. L. Xu, *J. Org. Chem.* **1991**, *56*, 6971; b) S. Ma, J. Zhang, *J. Am. Chem. Soc.* **2003**, *125*, 12386.
- [8] For selected recent examples, see: a) I. S. Young, M. A. Kerr, *Angew. Chem.* **2003**, *115*, 3131; *Angew. Chem. Int. Ed.* **2003**, *42*, 3023; b) M. Yu, B. L. Pagenkopf, *J. Am. Chem. Soc.* **2003**, *125*, 8122; c) M. Lautens, W. Han, J. H.-C. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 4028; d) C. Meyers, E. M. Carreira, *Angew. Chem.* **2003**, *115*, 718; *Angew. Chem. Int. Ed.* **2003**, *42*, 694; e) F. Bertozzi, B. V. Gandersen, M. Gustafsson, R. Olsson, *Org. Lett.* **2003**, *5*, 1551; f) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 5099; g) I. S. Young, M. A. Kerr, *Org. Lett.* **2004**, *6*, 139.
- [9] For a review, see: H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151.
- [10] a) U. M. Dzhemilev, R. I. Khusnutdinov, N. A. Shchadneva, G. A. Tolstikov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1990**, 1598; *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1990**, *39*, 1447; b) S. Husbands, W. Fraser, C. J. Suckling, H. C. S. Wood, *Tetrahedron* **1995**, *51*, 865.
- [11] For recent reviews on gold-catalyzed reactions, see: a) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206; *Angew. Chem. Int. Ed.* **2006**, *45*, 200; b) A. Hoffmann-Röder, N. Krause, *Org. Biomol. Chem.* **2005**, *3*, 387; c) A. S. K. Hashmi, *Angew. Chem.* **2005**, *117*, 7150; *Angew. Chem. Int. Ed.* **2005**, *44*, 6990; d) A. S. K. Hashmi, *Gold Bull.* **2004**, *37*, 51; e) A. Arcadi, S. D. Giuseppe, *Curr. Org. Chem.* **2004**, *8*, 795; f) A. S. K. Hashmi, *Gold Bull.* **2003**, *36*, 3; g) G. Dyker, *Angew. Chem.* **2000**, *112*, 4407; *Angew. Chem. Int. Ed.* **2000**, *39*, 4237; for selected recent examples, see: h) J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2006**, *118*, 3054; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091; i) N. Morita, N. Krause, *Angew. Chem.* **2006**, *118*, 1930; *Angew. Chem. Int. Ed.* **2006**, *45*, 1897; j) C. Brouwer, C. He, *Angew. Chem.* **2006**, *118*, 1776; *Angew. Chem. Int. Ed.* **2006**, *45*, 1744; k) X. Han, R. A. Widenhoefer, *Angew. Chem.* **2006**, *118*, 1779; *Angew. Chem. Int. Ed.* **2006**, *45*, 1747; l) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105; m) E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt, V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112; n) J. Zhang, C.-G. Yang, C. He, *J. Am. Chem. Soc.* **2006**, *128*, 1798; o) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442; p) D. J. Gorin, N. R. Davis, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 11260; q) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962; r) X. Yao, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 6884.
- [12] Phosphane-stabilized Au<sup>I</sup> salts with weakly coordinating anions have successfully been used also in other laboratories; see, for example, Ref. [3j], Ref. [11], as well as: a) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804; b) X.-Y. Liu, C.-H. Li, C.-M. Che, *Org. Lett.* **2006**, *8*, 2707.
- [13] It should be noted that *t*BuOH could not be used as the nucleophile<sup>[5a]</sup> and the R group on the alkyne could not be alkyl<sup>[5b]</sup> in a similar transformation, thus indicating that the highly strained cyclopropane in our system may provide the driving force for the reaction.
- [14] J. Cossy, N. Furet, S. Bouzbouz, *Tetrahedron* **1995**, *51*, 11751.