ORGANIC LETTERS

2007
Vol. 9, No. 23
4917−4920

Gold(I)-Catalyzed Three-Component Additions of 2-(Arylmethylene)cyclopropylcarbinols, Terminal Arynes, and Alcohols: An Efficient Access to 3-Oxabicyclo[3.1.0]hexanes

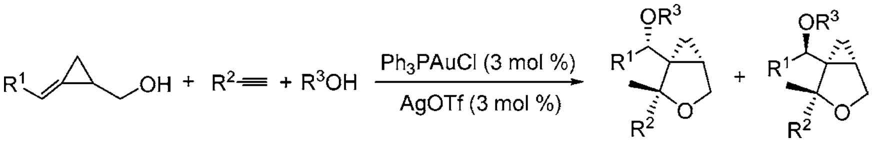
Guo-Qiang Tian and Min Shi*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, China 200032

mshi@mail.sioc.ac.cn

Received September 26, 2007

ABSTRACT



Catalyzed by gold(I), (*E*)- and (*Z*)-2-(arylmethylene)cyclopropylcarbinols, terminal arynes, and alcohols underwent three-component addition reactions to produce 3-oxabicyclo[3.1.0]hexanes in high yields and moderate diastereoselectivities under mild conditions. A plausible mechanism based on an intermolecular tandem hydroalkoxylation/Prins-type reaction pathway has been proposed.

Multicomponent reactions (MCRs) are powerful tools in organic synthesis because these transformations deliver complex molecules straightforwardly in a single operation.[1] During the past few years, gold has emerged as the most efficient catalyst for activation of alkynes, allenes, and alkenes due to its exceptional alkynophilicity.[2] Despite tremendous progress made in this area, efficient three-component additions catalyzed by gold(I) are rare.[3] In this communication, we report efficient gold(I)-catalyzed three-component additions of 2-(arylmethylene)cyclopropylcarbinols,[4] terminal arynes, and alcohols. Last year, Barluenga et al. found a novel tandem 6-exo cycloisomerization/Prins-type cyclization of allyl-substituted 5-hexyn-1-ol derivatives catalyzed by gold and platinum complexes to give eight-membered carbocycles,[5] indicating that enol ether could act as an acceptor for a Prins-type transformation. Recently,

---

[1] (a) Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc.* **2004**, *126*, 13606. (b) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (c) Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 2038. (d) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51. (e) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143. (f) Armstrong, W. R.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123. (g) Kobayashi, S. *Curr. Opin. Chem. Biol*. **2000**, *4*, 338. (h) Zhu, J.-P., Bienayme, H., Eds., *Multicomponent Reaction*; Wiley-VCH: Weinheim, Germany, 2005.

[2] For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3183. (b) Jimémez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (c) Fürster, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (f) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (g) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (h) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (i) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

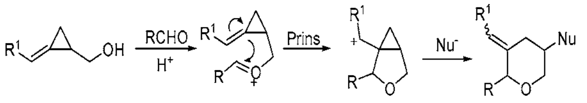
[3] Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

[4] For the preparation of 2-(arylmethylene)cyclopropylcarbinols, see: (a) Turcant, A.; Corre, L. M. *Tetrahedron Lett.* **1976**, *17*, 985. (b) Corre, L. M.; Hercouet, A.; Bessieres, B. *J. Org. Chem.* **1994**, *59*, 5483. For the transformation of 2-(arylmethylene)cyclopropylcarbinols, see: (c) Shao, L.-X.; Li, Y.-X.; Shi, M. *Chem.—Eur. J.* **2007**, *13*, 862. (d) Wang, B.-Y.; Huang, J.-W.; Liu, L.-P.; Shi, M. *Synlett* **2005**, 421. (e) Shi, M.; Tian, G.-Q. *Tetrahedron Lett*. **2006**, *47*, 8059. (f) Shi, M.; Wang, B.-Y. *Synlett* **2006**, 3158.

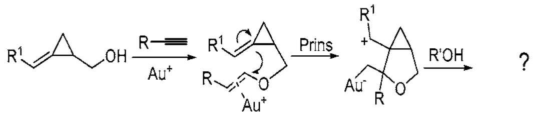
[5] Barluenga, J.; Diéguez, A.; Fernández, A.; Rodaríguez, F.; Fañanás, F. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091.

10.1021/ol702341a CCC: $37.00

we also reported cascade Brønsted acid mediated three-component condensations of 2-(arylmethylene)cyclopropylcarbinols **1** and aldehydes where the Prins reaction mechanism is the key step (eq 1).[6] Thus, we envisaged that, in the presence of gold, a three-component hydroalkoxylation/Prins-type reaction might take place when **1**, an alkyne, and an alcohol were mixed together (eq 2).



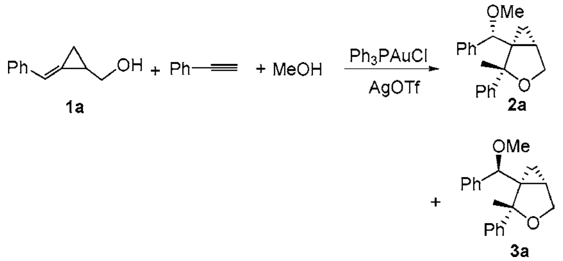
(1)



(2)

Using (*E*)-2-(benzylidenecyclopropyl)methanol **1a**, phenylacetylene, and methanol as substrates, we tested the hypothesis described above. To our delight, we found that the expected three-component adducts **2a** and **3a** were obtained as a pair of diastereoisomers in moderate yields. Following that, we optimized the reaction conditions, and the results are summarized in Table 1. No reaction occurred in methanol at 70 °C (Table 1, entry 1). In addition, complex product mixtures were obtained in 1,2-dichloroethane (DCE) when less than 4 equiv of methanol was added, presumably because substrate **1a** itself could trap the formed cationic intermediate (Table 1, entry 2). Addition of magnesium sulfate or 4 Å molecular sieves suppressed this transformation (Table 1, entries 3 and 4). Using 10 equiv of methanol in DCE at 70 °C, **2a** and **3a** were obtained in 82% total yield (Table 1, entry 5). Decreasing the reaction temperature from 70 to 45 °C, the diastereoselectivities of **2a** and **3a** were improved slightly along with similar yields (Table 1, entries 5−7). A 1.8:1 diastereoselectivity and 87% total yield of **2a** and **3a** were achieved when the reaction was carried out at 35 °C in dichloromethane (DCM) with 6 equiv of methanol (Table 1, entries 8 and 9). Further decreasing the reaction temperature did not improve the total yield of **2a** and **3a** (Table 1, entry 10). Some other solvents were examined under the standard conditions. Toluene, benzene, and tetrahydrofuran (THF) are not suitable solvents for this transformation (Table 1, entries 11−13). In chlorobenzene at 35 °C, the reaction proceeded smoothly to afford **2a** and **3a** in good yield, but with slightly lower diastereoselectivity (Table 1, entry 14). It should be noted that, in the presence of Brønsted acid or Ag(I) salt itself, no reaction occurred under the standard conditions. Therefore, Au(I) is the key catalyst in this multicomponent reaction.

Table 1. Optimization of the Reaction Conditions



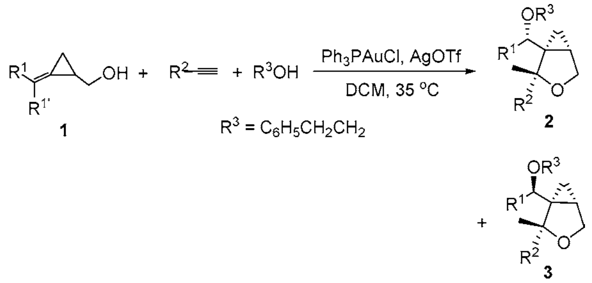
1a, 2a, 3a

entry[a]	MeOH	additive	solvent	temp (°C)	time (h)	yield[b] (%) (**2a/3a**)
1		–	MeOH (1 mL)	70	12	–
2	4 equiv	–	DCE (1 mL)	70	2	complex
3	10 equiv	$MgSO_4$	DCE (1 mL)	70	12	–
4	10 equiv	4Å MS	DCE (1 mL)	70	12	–
5	10 equiv	–	DCE (1 mL)	70	3	82 (1.1:1)
6	10 equiv	–	DCE (0.6 mL)	55	6	77 (1.2:1)
7	10 equiv	–	DCE (0.6 mL)	45	6	80 (1.4:1)
8	6 equiv	–	DCE (0.6 mL)	35	7	89 (1.6:1)
9	***6 equiv***	–	***DCM (0.6 mL)***	***35***	***5***	***87 (1.8:1)***
10	6 equiv	–	DCM (0.6 mL)	rt	10	62 (2.0:1)
11	6 equiv	–	PhMe (0.6 mL)	35	24	complex
12	6 equiv	–	PhH (0.6 mL)	35	24	–
13	6 equiv	–	THF (0.6 mL)	35	24	–
14	6 equiv	–	PhCl (0.6 mL)	35	24	86 (1.6:1)

[a] All reactions were carried out with **1a** (0.3 mmol), phenylacetylene (0.6 mmol), methanol, and catalyst (0.009 mmol) under argon atmosphere. [b] Isolated yields.

With these optimal conditions in hand, we next carried out this three-component addition reaction using a variety of starting materials **1**, terminal arynes, and alcohols as shown in Tables 1 and 2, respectively. 2-Phenylethanol, a sterically more bulky primary alcohol than methanol, reacted with **1a** or **1b** and a variety of substituted phenylacetylenes smoothly to afford **2b**−**f** and **3b**−**f** in excellent yields along with 1.8−2.2:1 diastereoselectivities within 5−24 h (Table 2, entries 1−5). In addition, as can be seen from Table 2,

Table 2. Scope of the Three-Component Addition



1, 2, 3

entry[a]	$R^1/R^{1'}$	R^2	time (h)	yield[b] (%) (**2/3**)
1	C_6H_5/H, **1a**	C_6H_5	7	92 (1.8:1) (**2b/3b**)
2	C_6H_5/H, **1a**	4-MeC_6H_4	5	95 (2.0:1) (**2c/3c**)
3	*p*-ClC_6H_4/H, **1b**	4-MeC_6H_4	5	89 (2.2:1) (**2d/3d**)
4	C_6H_5/H, **1a**	4-BrC_6H_4	24	90 (2.1:1) (**2e/3e**)
5	*p*-ClC_6H_4/H, **1b**	4-BrC_6H_4	24	79 (2.0:1) (**2f/3f**)

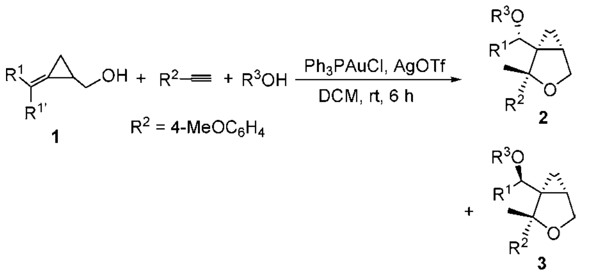
[a] All reactions were carried out with **1** (0.3 mmol), **2** (0.6 mmol), 2-phenylethanol (1.8 mmol), and catalyst (0.009 mmol) under argon atmosphere. [b] Isolated yields.

---

[6] Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 2405.

terminal aryne bearing an electron-donating group is more reactive than phenylacetylene or that bearing an electron-withdrawing group. Therefore, using 4-methoxyphenylacetylene as a substrate, we examined the reactions with a variety of **1** and alcohols under the best conditions. It was found that **1a** reacted with 4-methoxyphenylacetylene and methanol rapidly at room temperature (20 °C), affording **2g** and **3g** in 93% yield within 6 h along with **2g**/**3g** = 2.3:1 (Table 3, entry 1). Under the same conditions, 2-phenylethanol gave **2h** and **3h** in 90% yield and a higher diastereoselectivity (**2h**/**3h** = 2.6:1) (Table 3, entry 2). Whether there was an electron-withdrawing group or an electron-donating group on the aromatic rings of **1**, the three-component addition reactions proceeded smoothly to give the corresponding adducts in good yields and moderate diastereoselectivities (Table 3, entries 3−8). A methoxy group on the aromatic ring of **1** seems to be an exceptional substituent since an inversed diastereoselectivity was observed for **1e** (Table 3, entry 6). Prop-2-en-1-ol and butan-1-ol are also suitable nucleophiles for trapping the formed cationic intermediates (Table 3, entries 9 and 10). Reaction of (*Z*)-2-(benzylidenecyclopropyl)methanol **1g** with 4-methoxyphenylacetylene and 2-phenylethanol furnished the same products as those with **1a**, but in a lower yield (Table 3, entry 11). It should be emphasized here that a cyclopropyl group on the molecular backbone is essential for this reaction since, if using (*E*)-4-phenylbut-3-en-1-ol [(*E*)-Ph−CH═CH−CH_2−CH_2−OH] as a substrate, no reaction occurred under the standard conditions. Product structures of **2a−p** and **3a−p** were determined by ^{1}H and ^{13}C NMR spectroscopic data, HRMS, and microanalysis. Furthermore, the X-ray crystal structure of **2h** was determined (Figure 1), and its CIF data are presented in the Supporting Information.[7]

Table 3. Scope of the Three-Component Addition



entry^a	R^1/R$^{1'}$	R^3	yield^b (%) (**2**/**3**)
1	C_6H_5/H, **1a**	Me	93 (2.3:1) (**2g**/**3g**)
2	C_6H_5/H, **1a**	$C_6H_5CH_2CH_2$	90 (2.6:1) (**2h**/**3h**)
3	*p*-ClC_6H_4/H, **1b**	$C_6H_5CH_2CH_2$	90 (2.7:1) (**2i**/**3i**)
4	*p*-BrC_6H_4/H, **1c**	$C_6H_5CH_2CH_2$	82 (3.0:1) (**2j**/**3j**)
5	*p*-MeC_6H_4/H, **1d**	$C_6H_5CH_2CH_2$	85 (2.7:1) (**2k**/**3k**)
6	*p*-MeOC_6H_4/H, **1e**	$C_6H_5CH_2CH_2$	68 (1:1.3) (**2l**/**3l**)
7	*m*-MeC_6H_4/H, **1f**	$C_6H_5CH_2CH_2$	59 (2.5:1) (**2m**/**3m**)
8	*m*-MeC_6H_4/H, **1f**	Me	69 (2.2:1) (**2n**/**3n**)
9	C_6H_5/H, **1a**	CH_2═$CHCH_2$	92 (2.0:1) (**2o**/**3o**)
10	C_6H_5/H, **1a**	*n*-C_4H_9	86 (2.1:1) (**2p**/**3p**)
11	H/C_6H_5, **1g**	$C_6H_5CH_2CH_2$	62 (2.6:1) (**2h**/**3h**)

[a] All reactions were carried out with **1** (0.3 mmol), 4-ethynylanisole (0.6 mmol), alcohol (1.8 mmol), and catalyst (0.009 mmol) under argon atmosphere. [b] Isolated yields.

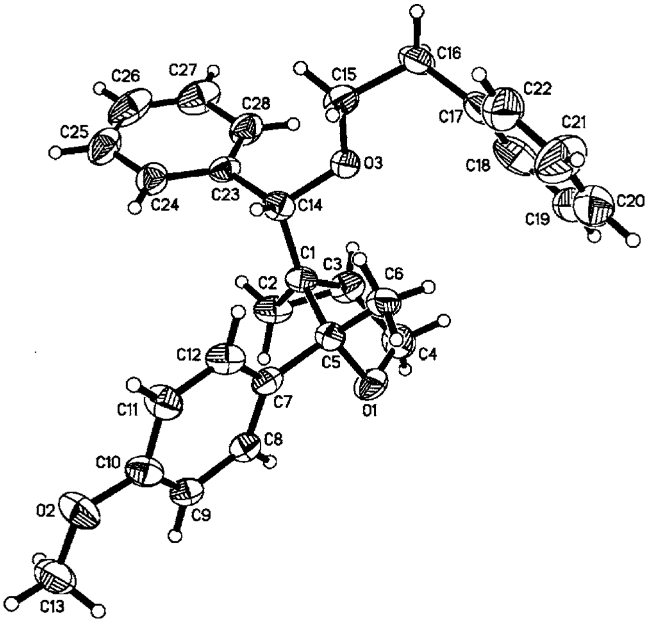
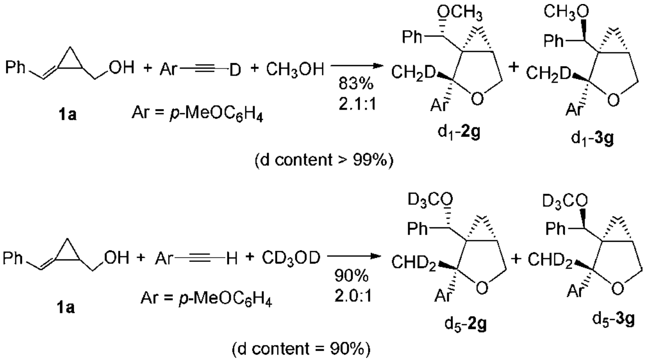


Figure 1. ORTEP drawing of **2h**.

To confirm the mechanism of this addition reaction, we performed deuterium labeling studies with deuterated phenylacetylene and methanol-*d*$_4$. Under the same conditions, reaction of **1a** with deuterated phenylacetylene and methanol afforded **2g**-*d*$_1$ and **3g**-*d*$_1$ in 83% yield. Moreover, reaction of **1a** with phenylacetylene and methanol-*d*$_4$ produced **2g**-*d*$_5$ and **3g**-*d*$_5$ in 90% yields, indicating that two deuterium atoms were incorporated at the terminal alkynyl carbon (Scheme 1).

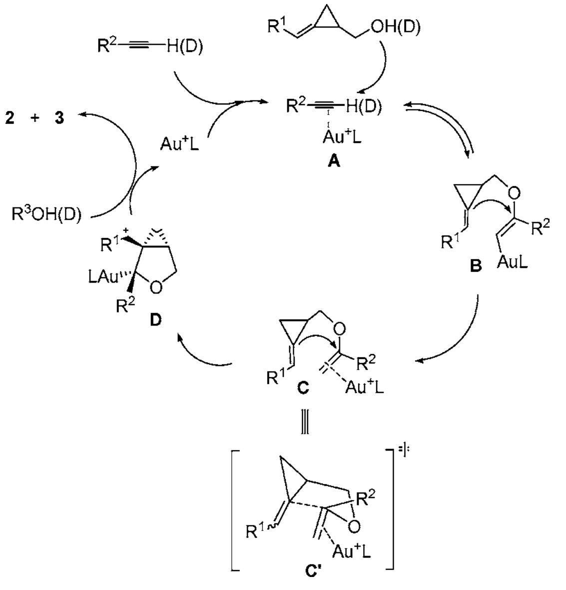
Scheme 1. Deuterium Labeling Experiments



The deuterium labeling experiments support a mechanism that is consistent with our hypothesis described at the beginning of this communication. Activation of aryne by gold(I) forms intermediate **A**, which is attacked by substrate **1** to produce vinylgold species **B**. Species **B** undergoes protodemetalation to furnish intermediate **C**. The intermediate **C** is activated by gold(I) again,[8] and a subsequent intramolecular nucleophilic attack (Prins-type reaction) occurs to afford intermediate **D** stereospecifically. This process may proceed via a chair-like transition state **C′**, which can account for the stereoselectivity. Trapping the organogold cation by an alcohol and the following protodemetalation delivers the three-component adducts and regenerates the gold(I) catalyst (Scheme 2). Along with the clarification of the reaction mechanism, we should point out at the same time that, although the principle of gold-catalyzed hydration of triple bond is well-known in intramolecular addition reaction, intermolecular addition to the triple bond is not an easy task and still remains a real challenge.

In summary, we have developed an efficient three-component addition reaction of 2-(arylmethylene)cyclopropylcarbinols **1**, terminal arynes, and alcohols catalyzed by gold(I). This synthetic protocol furnishes 3-oxabicyclo[3.1.0]hexanes straightforwardly from simple materials under mild conditions, substantially enriching gold chemistry. A plausible mechanism has been proposed that is based on an intermolecular tandem hydroalkoxylation/Prins-type reaction pathway. Clarification of the reaction mechanism and further application of this chemistry are in progress.

Scheme 2. Proposed Mechanism Based on Intermolecular Hydroalkoxylation/Prins-Type Reactions



Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20472096, 203900502, 20672127, and 20732008).

Supporting Information Available: Detailed description of experimental procedures, full characterization of new compounds shown in Tables 1−3, X-ray crystal analysis data of **2h**, and NOESY data of **2a** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702341A

---

(7) The crystal data of **2h** have been deposited in CCDC with number 639926. Empirical formula $C_{28}H_{30}O_3$; formula weight 414.52; crystal color, habit colorless, prismatic; crystal system orthorhombic; lattice type primitive; lattice parameters: $a = 9.932(2)$ Å, $b = 11.444(2)$ Å, $c = 20.640(4)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 2345.9(8)$ Å^3; space group: $P2(1)2(1)2(1)$; $Z = 4$; $D_{\text{calcd}} = 1.174$ g/cm^3; $F_{000} = 888$; diffractometer Rigaku AFC7R; residuals R; $R_w = 0.0501, 0.0808$.

(8) For activation of alkenes by gold, see: (a) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (b) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143. (c) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (e) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966.