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Highly Efficient and Tunable Synthesis of Dioxabicyclo[4.2.1] Ketals and Tetrahydropyrans via Gold-Catalyzed Cycloisomerization of 2-Alkynyl-1,5-diols

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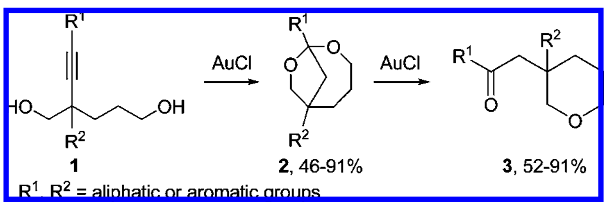
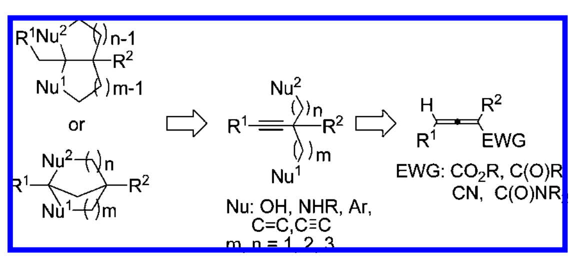
ABSTRACT



A highly efficient gold(I) chloride catalyzed cycloisomerization of 2-alkynyl-1,5-diol (1) to dioxabicyclo[4.2.1] ketal (2) and its further transformation to tetrahydropyran (3) are reported. The diol is readily obtained by the reduction of 2-alkynyl-substituted glutarates, isolated from the Michael addition of allenoates to methyl acrylate. These reactions proceeded smoothly under very mild conditions. A plausible mechanism for the formation of the said tetrahydropyran from the corresponding ketal is proposed.

A contemporary challenge in organic synthesis is the mapping of new chemical spaces through cascade reactions in an atom-economical fashion. This effort requires robust building blocks and powerful transition-metal-catalyzed processes. In this regard, bicyclic ketals or their heterobicyclic counterparts[1] are intriguing structural motifs, not only from the perspective of chemical diversity or biological potential[2] but also because of the stimulating transformations that they could engender. During our investigations on the regioselective functionalization of allenoates[3] we pondered whether these could also open up a manifold of nontrivial transformations, illustrated in Scheme 1. As can be seen from the disconnection strategy, bicyclo-[m+1.n+1.0] or [m+1.n+1.1] compounds could be obtained from transition-metal-catalyzed double cyclization reactions of alkynes bearing two nucleophiles. The latter are easily prepared from the corresponding allenoates using our reported procedure.[3]

Scheme 1. Disconnection of Heterobicyclic Systems Starting from Functionalized Allenes



Given gold's affinity toward alkynes and allenes,[4,5] we envisaged that a gold-catalyzed cycloisomerization of un-

(1) (a) *Exploiting Chemical Diversity for Drug Discovery*; Bartlett, P. A., Entzeroth, M., Eds.; Royal Society of Chemistry: Cambridge, UK, 2006. (b) Kuo, P.-C.; Kuo, T.-H.; Damu, A. G.; Su, C.-R.; Lee, E.-J.; Wu, T.-S.; Shu, R.; Chen, C.-M.; Bastow, K. F.; Chen, T.-H.; Lee, K.-H. *Org. Lett.* **2006**, *8*, 2953.

(2) (a) Smith, A. B., III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675. (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045. (c) Francke, W.; Schroder, W. *Curr. Org. Chem.* **1999**, *3*, 407. (d) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (e) Takano, S.; Yonaga, M.; Mirimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 305. (f) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517.

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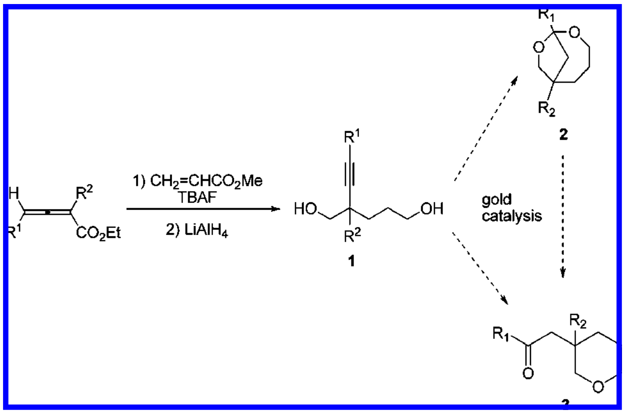
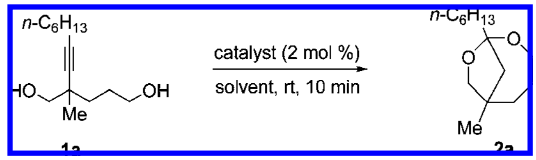
Scheme 2. Synthesis of 2-Alkynyl-1,5-diol **1** and Its Transformations Through a Gold-Catalyzed Cycloisomerization



symmetrical 2-alkynyl-1,5-diols could lead to bicyclo[4.2.1] ketals[6] or functionalized tetrahydropyrans[2a,b] (Scheme 2). The starting diols are readily obtained from the reduction of 2-alkynyl-substituted glutarates isolated from the Michael addition of allenoates to methyl acrylate. Herein, we wish to report that the gold-catalyzed cycloisomerization of 2-alkynyl-1,5-diols to dioxabicyclo[4.2.1] ketals can also be directed toward the synthesis of the corresponding tetrahydropyrans; all of these processes occur in high yields and under mild conditions.

We took a cue from Genet and co-workers' gold-catalyzed cycloisomerization of bishomopropargylic diols to yield strained dioxabicyclic ketals[6a] and screened various gold salts and other metal catalysts using 2-methyl-2-*n*-octynyl-1,5-diol **1a**, which is promptly obtained by LAH reduction of the parent diester.[3b]

Table 1. Optimum Conditions for Cycloisomerization of 2-Alkynyl-1,5-diol **1a** to Dioxabicyclo[4.2.1] Ketal **2a**[a]



entry	catalyst	solvent	yield [%][b]
1	AuCl	CH_2Cl_2	91
2	$AuCl_3$	CH_2Cl_2	88
3	$AuBr_3$	CH_2Cl_2	78
4	$(PPh_3)AuOTf$[c]	CH_2Cl_2	59
5[d]	AgOTf	CH_2Cl_2	76
6[d]	$PtCl_2$	CH_2Cl_2	80
7	AuCl	DCE	88
8	AuCl	$CHCl_3$	90
9	AuCl	Toluene	87
10	AuCl	THF	73
11	AuCl	CH_3CN	45
12	AuCl	MeOH	12

[a] General conditions: 2-alkynyl-1,5-diol **1a** 0.20 mmol, solvent 1.0 mL. [b] Isolated yields. [c] In situ generated from the mixture of $(PPh_3)AuCl$ and AgOTf. [d] Reaction time was prolonged to 24 h.

To our satisfaction, with gold(I) chloride, the reaction proceeded very smoothly—in dichloromethane at room temperature—and was completed in 10 min; the desired dioxabicyclo[4.2.1] ketal **2a** was isolated in 91% yield (Table 1, entry 1). Other metal catalysts as well as solvent effects were investigated. Gold(III) chloride, gold(III) bromide, and triphenylphosphine gold(I) triflate also catalyzed the cycloisomerization efficiently (Table 1, entries 2−4). Silver triflate and platinum(II) chloride could catalyze the reaction too, but in these cases prolonged reaction times (24 h) were needed (Table 1, entries 5 and 6). The reaction with gold(I) chloride proceeded smoothly in 1,2-dichloroethane, chloroform, toluene, and tetrahydrofuran (Table 1, entries 7−10). However, in contrast with Genet's report,[6a] the lowest yield was obtained using methanol as the solvent (Table 1, entry 12), perhaps due to the low stability of the product in the reaction or isolation process.

To examine the scope of this reaction, we investigated other aliphatic and aromatic 2-alkynyl-1,5-diols **1**. The results are outlined in Table 2.

In all cases, the reactions proceeded smoothly under mild conditions, and the desired products were isolated in moder-

(3) (a) Xu, B.; Hammond, G. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 689. (b) Liu, L.-P.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3887. (c) Wang, W.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 3713. (d) Yang, H.; Xu, B.; Hammond, G. B. *Org. Lett.* **2008**, *10*, 5589. (e) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642. (f) Aponte, J. C.; Hammond, G. B.; Xu, B. *J. Org. Chem.* **2009**, *74*, 4623.

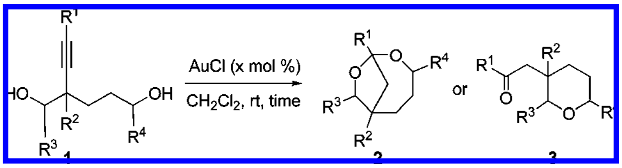
(4) For selected recent reviews on gold catalysis, see:(a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (g) Bongers, N.; Krause, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 2178. (h) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (i) Furstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (j) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (k) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (l) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (m) Nevado, C.; Echavarren, A. M. *Synthesis* **2005**, 167. (n) Widenhoefer, R. A.; Han, X. Q. *Eur. J. Org. Chem.* **2006**, 4555. (o) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (p) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (q) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (r) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (s) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382.

(5) For selected recent articles on Au-catalyzed reactions of carbon−carbon multiple bonds, see:(a) Escribano-Cuesta, A.; Lopez-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem.—Eur. J.* **2009**, *15*, 5646. (b) Li, H.; Widenhoefer, R. A. *Org. Lett.* **2009**, *11*, 2671. (c) Mauleon, P.; Zeldin, R. M.; Gonzalez, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348. (d) Trillo, B.; Lopez, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledos, A.; Mascarenas, J. L. *Chem.—Eur. J.* **2009**, *15*, 3336. (e) Meng, J.; Zhao, Y.-L.; Ren, C.-Q.; Li, Y.; Li, Z.; Liu, Q. *Chem.—Eur. J.* **2009**, *15*, 1830. (f) Li, G.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 3740. (g) Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940. (h) Barluenga, J.; Fernandez-Rodriguez, M. A.; Garcia-Garcia, P.; Aguilar, E. *J. Am. Chem. Soc.* **2008**, *130*, 2764. (i) Zhang, Z.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 283. (j) Tian, G.-Q.; Shi, M. *Org. Lett.* **2007**, *9*, 4917.

(6) (a) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (b) Oh, C. H.; Yi, H. J.; Lee, J. H. *New J. Chem.* **2007**, *31*, 835. (c) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (d) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907. (e) Zhang, Y.; Xue, J.; Xin, Z.; Xie, Z.; Li, Y. *Synlett* **2008**, 940. (f) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121. (g) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191.

1,5-diols, were employed in this interesting transformation, and the tetrahydropyran products **3** were obtained in good yields (Table 2).

Table 2. Gold-Catalyzed Cycloisomerization of 2-Alkynyl-1,5-diols **1** to Dioxabicyclo[4.2.1] Ketals **2** or Tetrahydropyrans **3**[a]



entry	$R^1/R^2/R^3/R^4$	*x* mol %/time	yield [%][b]
1	n-C_6H_{13}/Me/H/H **1a**	6/24 h	**3a**, 91
2	t-Bu/Me/H/H **1b**	2/10 min	**2b**, 52
3	**1b**	6/24 h	**3b**, 52
4	$CypCH_2$/Me/H/H **1c**	2/10 min	**2c**, 87
5	**1c**	6/24 h	**3c**, 83
6	C_6H_5/Me/H/H **1d**	2/10 min	**2d**, 84
7	**1d**	6/24 h	**3d**, 88
8	p-$CH_3OC_6H_4$/Me/H/H **1e**	2/10 min	**2e**, 80
9	**1e**	6/24 h	**3e**, 86
10	p-ClC_6H_4/Me/H/H **1f**	2/10 min	**2f**, 77
11	**1f**	6/24 h	**3f**, 65
12	Me/Me/H/H **1g**	2/10 min	**2g**, 46
13	i-Pr/Me/H/H **1h**	2/10 min	**2h**, 75
14	Bn/Me/H/H **1i**	2/10 min	**2i**, 82
15	n-C_6H_{13}/Et/H/H **1j**	2/10 min	**2j**, 86
16	n-C_6H_{13}/Me/C_6H_5/H **1k**	2/10 min	**2k**[c], 68
17	n-C_6H_{13}/Me/H/Me **1l**	2/10 min	**2l**[d], 79

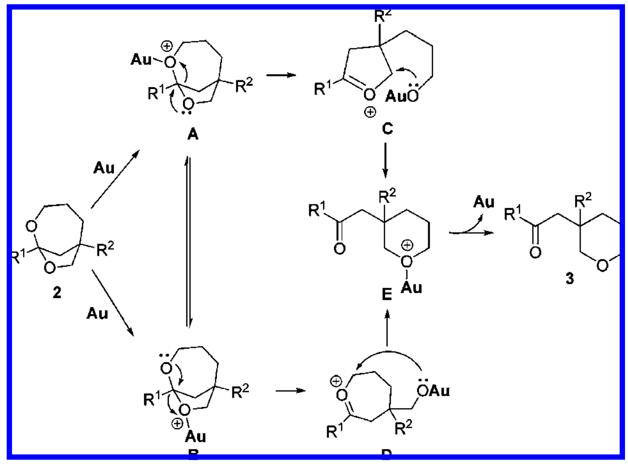
[a] General conditions: 2-alkynyl-1,5-diols **1** 0.20 mmol, AuCl 1.0 mg (2 mol %), CH_2Cl_2 1.0 mL, or 2-alkynyl-1,5-diols **1** 0.20 mmol, AuCl 3.0 mg (6 mol %), CH_2Cl_2 1.0 mL. [b] Isolated yields. [c] Mixture of diastereoisomers in 1.4:1 ratio. [d] Mixture of diastereoisomers in 1:1 ratio.

ate to good yields. The ^{1}H and ^{13}C NMR spectra of the reaction mixture showed that the reaction was completed after 10 min, and the dioxabicyclo[4.2.1] ketal **2** was the only product observed.

During these investigations, we also found that the tetrahydropyran derivative **3a** accompanied the formation of **2a** when the reaction time was prolonged. Initially, we thought that this rearrangement could be induced by acidic conditions,[7] but no tetrahydropyran was observed when various Brønsted acids were employed to catalyze the conversion of **2a** to **3a**. Using trifluoroacetic acid as the catalyst, traces of **3a** were found by TLC when the reaction was conducted at 80 °C in toluene. Oxophilic transition metal catalysts, such as $PdCl_2$, $PdCl_2(CH_3CN)_2$, and $[Rh(cod)Cl]_2$, were tested, but $PdCl_2(CH_3CN)_2$ was the only effective catalyst for the reaction (see Supporting Information). We were pleasantly surprised to discover that tetrahydropyran **3a** could be obtained in excellent yield by simply increasing the gold catalyst loading and prolonging the reaction time. Various substrates, both alphatic and aromatic 2-alkynyl-

(7) Frantisek, L.; Jiri, F.; Petr, T.; Miroslav, V. *Collect. Czech. Chem. Commun.* **1989**, *54*, 3278.

Scheme 3. Plausible Mechanism for the Transformation of Dioxabicyclo[4.2.1] Ketal **2** to Tetrahydropyran **3**



A plausible mechanism for the gold-catalyzed transformation of dioxabicyclo[4.2.1] ketal **2** to tetrahydropyran **3** is outlined in Scheme 3. Gold catalyst activates one of the oxygen atoms to form the intermediate **A** or **B**, which may rearrange to the oxonium intermediate **C** or **D**, respectively. Both of the intermediates would undergo an intramolecular attack to give intermediate **E**, which produces the tetrahydropyran product **3** and regenerates the gold catalyst. We asked ourselves if water could help in the transformation; however, no rate differences were found using wet dichloromethane or dry dichloromethane as the solvent, and the reaction was retarded when 1 equiv of water was added to the reaction mixture: no tetrahydropyran was found.

In summary, we have found a highly efficient gold(I) chloride catalyzed cycloisomerization of 2-alkynyl-1,5-diol to dioxabicyclo[4.2.1] ketal and its transformation to tetrahydropyran under very mild conditions. A plausible mechanism for the formation of tetrahydropyran **3** has been proposed. Other applications derived from this methodology are under consideration.

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Supporting Information Available: The ^{1}H and ^{13}C NMR spectroscopic data, MS, IR, and elemental analysis of the new compounds shown in Tables 1 and 2 and a detailed description of experimental procedures This material is available free of charge via the Internet at http://pubs.acs.org.

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