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Gold(I)-Catalyzed Ring Expansion of Cyclopropanols and Cyclobutanols

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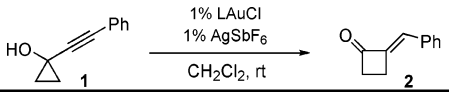
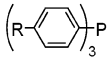
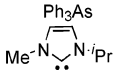
Transition metal-promoted ring expansion reactions of 1-vinylcycloalkanols provide a powerful method for construction of a variety of cyclic ketones.[1] Similarly, 2-alkylidenecycloalkanones are potentially available from the corresponding rearrangement of 1-alkynylcycloalkanols; however, only a few examples of transition metal-catalyzed expansion of 1-alkynylcyclobutanols to alkylidenecyclopentanones have been reported.[2,3] A number of transformations involving the addition of heteroatom[4] nucleophiles or π-bonds[5] to gold(I)-activated alkynes have recently been described. We hypothesized that related cationic gold(I) complexes might be capable of catalyzing ring expansion[6] reactions by promoting migration of nucleophilic σ-bonds to alkynes.

On the basis of this hypothesis, treatment of alkynylcyclopropanol **1** with 1 mol % $(PPh_3)AuSbF_6$ produced desired alkylidenecyclobutanone **2** in 95% yield as a single olefin isomer (Table 1).[7] The yield and rate of the rearrangement was improved by employing electron-deficient arylphosphines as ligands. For example, when the cationic gold complexes derived from tris(4-trifluoromethylphenyl)phosphinegold(I) chloride (**3**) were utilized as the catalyst, cyclobutanone **2** was produced in 99% yield after only 25 min. Conversely, the reaction was significantly less efficient when complexes bearing electron-rich ligands were employed as catalysts.

With these results in hand, we examined the scope of the tris-(4-trifluoromethylphenyl)phosphine gold(I)-catalyzed ring expansion (Table 2). A range of alkyl-substituted alkynes afforded good to excellent yields of the expected cyclobutanone products (entries 1 and 2). Aryl substituents were uniformly well tolerated with electron-withdrawing, electron-donating, and halide-substituted aryl alkynyl cyclopropanols expanding with excellent yields (entries 3−6). Notably, iodoalkynyl cyclopropanol **20** smoothly underwent expansion catalyzed by 1 mol % **3**, providing vinyl iodide **21** in 88% yield (entry 10). Trimethylsilyl and *tert*-butyldimethylsilyl ethers also undergo gold(I)-catalyzed ring expansion in excellent yields in the presence of 2 equiv of methanol (entries 7−9). The alkyne need not be substituted, as demonstrated by gold(I)-catalyzed conversion of alkyne **18** into 2-methylenecyclobutanone **19** (entry 9). Furthermore, cationic gold(I) complex **3** promotes the selective migration of the more substituted carbon of 2-substituted cyclopropanols **22** and **24** to afford substituted cyclobutanones **23** and **25** (entries 11 and 12).

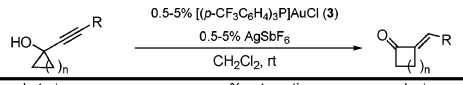
Table 1. Ligand Effects on Au(I)-Catalyzed Ring Expansion

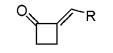
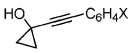
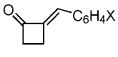
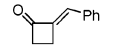
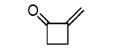
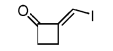
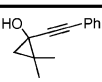
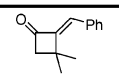
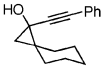
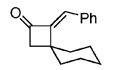
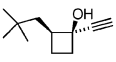
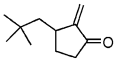
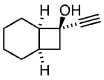
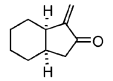
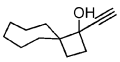
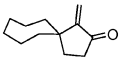
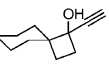
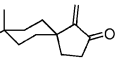


entry	ligand (L)		time	yield[b]
1		R = H	115 min.[a]	95%[c]
2		R = MeO	160 min.[a]	90%
3		R = Cl	85 min.[a]	97%
4		R = CF_3	25 min.[a]	99%
5	t-Bu_3P		24h	54%[d]
6	Ph_3As		24h	16%
7			24h	63%

[a] Time to 99% conversion of **1** by ^{1}H NMR. [b] Determined by ^{1}H NMR vs internal standard (mesitylene). [c] 5% cyclopentenone. [d] 13% cyclopentenone.

Table 2. Scope of Au(I)-Catalyzed Ring Expansion[a]



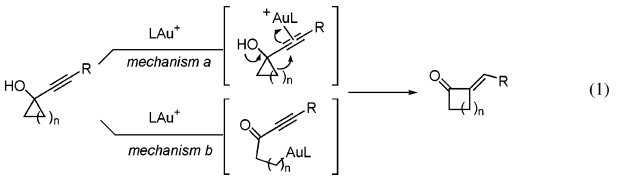
entry	substrate		% cat.	time	product	yield
1		R = ^{n}Hex (**4**)	1.0	12h		(**5**) 81%
2		R = ^{t}Bu (**6**)	0.5	6h		(**7**) 98%
3		X = *p*-Cl (**8**)	0.5	12h		(**9**) 94%
4		X = *p*-CF_3 (**10**)	0.5	12h		(**11**) 94%
5		X = *p*-CN (**12**)	0.5	12h		(**13**) 98%
6		X = *p*-OMe (**14**)	0.5	12h		(**15**) 97%
7[b]		R = TMS (**16**)	1.0	40min.		(**2**) 95%
8[b]		R = TBS (**17**)	1.0	4.5h		(**2**) 97%
9[b]		(**18**)	1.0	50min.		(**19**) 90%[c]
10		(**20**)	1.0	8h		(**21**) 88%
11		(**22**)	1.0	12h		(**23**) 61%
12		(**24**)	5.0	48h		(**25**) 74%[d]
13		(**26**)	1.0	10h		(**27**) 73%
14		(**28**)	2.0	24h		(**29**) 66%
15		(**30**)	2.0	20h		(**31**) 72%
16		(**32**)	2.0	16h		(**33**) 82%

[a] Reaction conditions: 0.5−5.0% **3** in CH_2Cl_2, rt. [b] MeOH (2 equiv) added. [c] Determined by ^{1}H NMR vs internal standard (mesitylene). [d] 4:1 mixture of cyclobutanone/cyclopentenone.

Alkynylcyclobutanols were also found to be viable substrates for gold(I)-catalyzed ring expansion.[8] Reaction of cyclobutanol **26**, prepared in two steps from cyclobutanone **7**, provided 2-methylenecyclopentanone **27** in 73% yield (entry 13). Furthermore, bicyclic cyclopentanone **29** and spiro ring systems **31** and **33** were likewise obtained with selective migration of the more substituted carbon of the cyclobutanol.

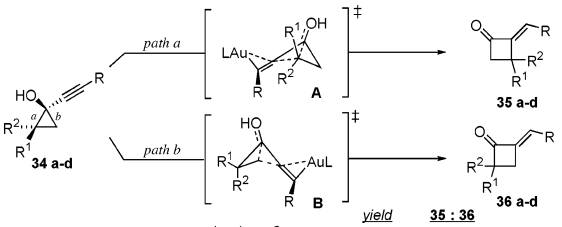
We envisioned two possible mechanisms for this rearrangement (eq 1). In mechanism *a*, coordination of cationic gold(I) to the alkyne moiety induces a 1,2-alkyl shift. Mechanism *b* involves gold(I) activation of the cycloalkanol[6,9] to give alkyl gold(I) complex that subsequently undergoes insertion into the alkyne.[10] The (*E*)-

10.1021/ja052831g CCC: $30.25



(1)

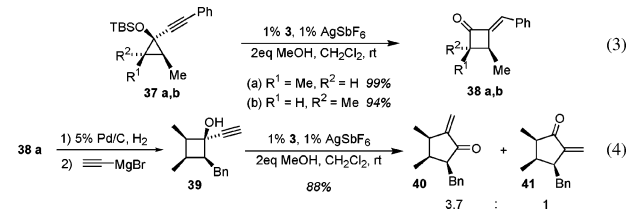
olefin geometry of the resulting alkylidene cycloalkanes[11] and the selective migration of more substituted cycloalkanol carbons is most consistent with mechanistic hypothesis *a*. Gold(I)-catalyzed rearrangement of substituted cyclopropanols **34a**−**d** further supports mechanism *a* and provides insight into the stereoelectronic demands of ring expansion (eq 2). Consistent with the expected migratory aptitude, gold(I)-catalyzed rearrangement of **34a** afforded only **35a**. Increasing the size of the alkynyl substituent to phenyl in **34b** produced a decrease in the selectivity presumably as a result of an increase in $A^{1,3}$ strain between the R^1 and R groups in proposed transition state **A**. This interaction is more pronounced between R^2 and R as demonstrated in the ring expansion of **34c**, which selectively furnished cyclobutanol **36c** derived from migration of the less substituted carbon.[12] In accord with this hypothesis, reaction of terminal alkyne **34d** favors migration of the more substituted carbon as a result of a decrease in $A^{1,3}$ strain between R^2 and R in transition state **A**.



(2)

	yield	35 : 36
(a) R = H, R^1 = ^{i}Pr, R^2 = H	80%	only **35**
(b) R = Ph, R^1 = ^{i}Pr, R^2 = H	82%	4.6:1
(c) R = Ph, R^1 = H, R^2 = ^{i}Pr	91%	only **36**
(d) R = H, R^1 = H, R^2 = Bn	88%	1.7:1

Additionally, gold(I)-catalyzed ring expansion is stereospecific with respect to the migrating carbon (eq 3). *cis*-Dimethylcyclopropane **37a** quantitatively afforded *cis*-cyclobutanone **38a**, while *trans*-dimethylcyclopropane **37b** gave only *trans*-cyclobutanone **38b** in 94% yield. Benzylidenecyclobutanone **38a** was then converted into cyclobutanol **39** in two steps. Gold(I)-catalyzed ring expansion of **39** also proceeded stereoselectively to afford a 3.7:1 mixture of cyclopentanones **40** and **41** in 88% yield (eq 4).



(3)

(4)

In conclusion, we have developed a gold(I)-catalyzed ring expansion of 1-alkynylcyclobutanols and cyclopropanols to alkylidenecycloalkanones. The reaction stereoselectively provides a single olefin isomer and is stereospecific with regard to substituents on the ring. Thus, a sequence involving two gold(I)-catalyzed ring expansion reactions allows for the stereoselective preparation of a highly substituted cyclopentanone.[13] A mechanism involving migration of a carbon−carbon σ-bond onto a gold(I)-activated alkyne accounts for the observed stereoselectivity and migratory aptitude in substituted cycloalkanols. Efforts aimed at further exploiting gold(I)-catalyzed rearrangements of strained ring systems are ongoing in our laboratories.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (c) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563.

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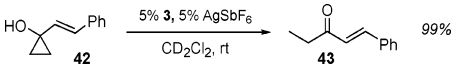
(6) For reviews of Ag(I)-catalyzed rearrangement of strained σ-bonds, see: (a) Paquette, L. A. *Acc. Chem. Res.* **1971**, *4*, 281. (b) Bishop, K. C., III. *Chem. Rev.* **1976**, *76*, 461. For Au-catalyzed rearrangement of small ring hydrocarbons, see: (c) Meyer, L. U.; de Meijere, A. *Tetrahedron Lett.* **1976**, 497.

(7) Yield of **2** after treatment of **1** for 24 h with other catalysts: $(CH_3CN)_4Pd(BF_4)_2$ 0%, $Pd(O_2CCF_3)_2$ 8% ((*Z*)-**2**), $PtCl_2$ 0%, $PtCl_4/AgSbF_6$ 9%, $AgSbF_6$ 3%, $AuCl_3/AgOTf$ 4%, HBr 0%. See also: Wasserman, R. E.; Cochoy, R. E.; Baird, M. S. *J. Am. Chem. Soc.* **1969**, *91*, 2376.

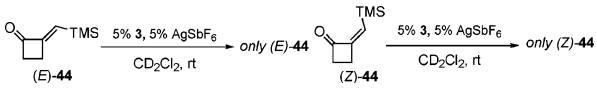
(8) Under identical reaction conditions, Au(I)-catalyzed reaction of nonterminal alkynylcyclobutanols produced complex mixtures.

(9) For stoichiometric formation of triphenylphosphinegold(I)-homoenolates from cyclopropanols, see: Murakami, M.; Inouve, M.; Suginome, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3649. In accord with this report, we found that **3** catalyzed the rearrangement of vinylcyclopropanol **42** to ketone **43**.



(10) A related mechanism has been proposed for formation of methylidene cyclopentanones by Pd(II)-catalyzed rearrangement of a vinylcyclobutanols. See: Nishimura, T.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 2645.

(11) Consistent with the kinetic formation of (*E*)-alkenes, olefin geometry in cyclobutanone **44** is not isomerized under the reaction conditions.



(12) For an example of reversal of migratory aptitude in ring expansion due to inductive effects, see: Trost, B. M.; Ornstein, P. L. *J. Org. Chem.* **1985**, *48*, 1133.

(13) For recent approaches to highly substituted cyclopentanones from vinyl cyclopropanes, see: (a) Navseschuk, C. G.; Rovis, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3264. (b) Davies, H. M. L.; Xiang, B.; Kong, N.; Stafford, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 7461.

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