Homogeneous Catalysis

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Gold(I)-Catalyzed 5-*endo* Hydroxy- and Alkoxycyclization of 1,5-Enynes: Efficient Access to Functionalized Cyclopentenes**

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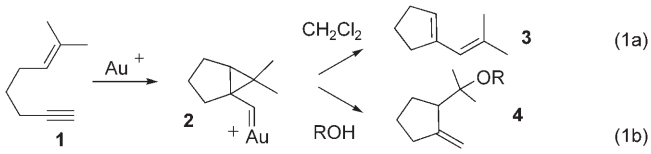
Dedicated to Dr. Gilles Ouvry

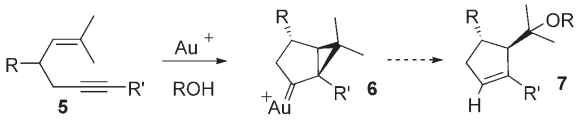
The cyclopentyl unit is found frequently in a wide variety of natural products that exhibit biological activity.[1] As a consequence, the development of practical synthetic routes to form five-membered rings remains of interest. Gold(I) complexes have emerged as efficient and mild catalysts for the activation of alkynes towards addition by a variety of nucleophiles,[2] and their potential has been highlighted by numerous studies related to the conversion of enynes into cycloisomerized products.[3] For example, Echavarren and co-workers reported that 1,6-enynes of type **1** could be transformed into cyclopentadienes of type **3** [Eq. (1a)].[4] The same substrates also underwent a 5-*exo* alkoxycyclization to furnish the *exo*-methylenecyclopentane derivatives of type **4** when an alcohol was used as the solvent [Eq. (1b)].[5]



(1a)

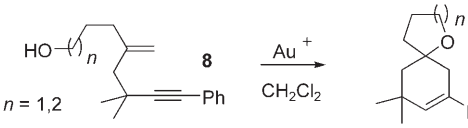
(1b)

By analogy, we surmised that 1,5-enynes, such as **5**, might be valuable precursors of functionalized cyclopentenes (for example, **7**) if a gold-catalyzed 5-*endo* alkoxycyclization was feasible [Eq. (2)].[6]



(2)

In contrast to the results of Zhang and Kozmin,[3f] who found that the intramolecular 6-*endo* alkoxycyclization of enyne **8** led to the exclusive formation of cyclohexene **9** [Eq. (3)],[7] we anticipated that the substitution pattern of the alkene in **5** would favor a 5-*endo* process and that the presence of the R group might lead to the stereoselective

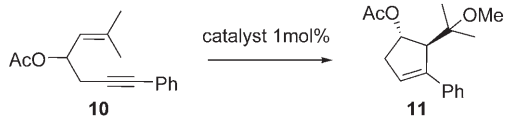


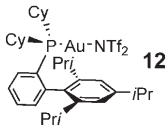
(3)

formation of cyclopentene derivatives **7**. Furthermore, whereas the 5-*exo* alkoxycyclization of 1,6-enynes [Eq. (1b)] is generally limited to terminal alkynes,[8] we believed that our proposed 5-*endo* transformation would be favored with internal alkynes.[6a] This approach would be very useful synthetically, as the cyclopentenes thus produced could serve as valuable precursors for the elaboration of more complex structures.[9]

In a first attempt, the model substrate **10** was treated with $Ph_3PAuNTf_2$[10] (1 mol%) in methanol at room temperature. We observed the stereoselective formation of the desired cyclopentene **11**, which was isolated in 58% yield along with by-products derived from the direct methoxylation of the alkyne (Table 1, entry 1).[11] The use of the bulkier and more

Table 1: Optimization of the catalytic system.[a]



Entry	Catalyst	Solvent	*t*	Yield [%][b]
1	$Ph_3PAuNTf_2$	MeOH	24 h	58
2	$Ad_2nBuPAuNTf_2$	MeOH	24 h	64
3	 **12**	MeOH	40 min	98
4		CH_2Cl_2/MeOH (10:1)	20 min	99

[a] Reactions were carried out at room temperature with a substrate concentration of 0.5 M. [b] Yield of the isolated product. Ad = adamantyl, Tf = trifluoromethanesulfonyl, Cy = cyclohexyl.

electron rich catalyst $Ad_2nBuPAuNTf_2$[10] did not lead to a significant improvement in the yield (Table 1, entry 2). Remarkably, the treatment of **10** with the biphenylphosphine-based catalyst **12**[12] furnished **11** cleanly and rapidly in 98% yield (Table 1, entry 3). Moreover, the use of a 10:1 mixture of CH_2Cl_2 and MeOH as the solvent led to an even faster reaction to form the desired product in very high yield (Table 1, entry 4). In the light of these preliminary results, the

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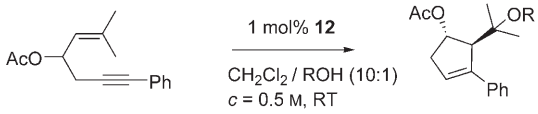
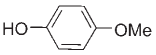
Table 2: Scope of the Au^I-catalyzed alkoxycyclization of enyne **10**.



10 **13a–f**

Entry	ROH	*t*	Product	Yield [%][a]
1		2 h	**13a**	93
2[b]		10 min	**13b**	95
3	*i*PrOH	45 min	**13c**	98
4	cyclohexanol	24 h	**13d**	54
5[c]	H_2O	4.5 h	**13e**	100
6	AcOH	75 min	**13f**	68

[a] Yield of the isolated product. [b] The reaction was carried out with 2 equivalents of *p*-$MeOC_6H_4OH$. [c] The reaction was carried out in a CH_2Cl_2/acetone/H_2O mixture (8:2:1).

experimental conditions described in entry 4 of Table 1 were chosen for the study of this transformation.

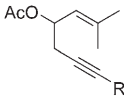
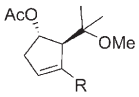
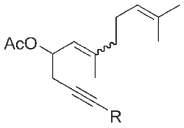
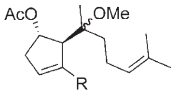
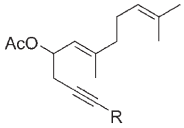
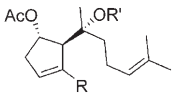
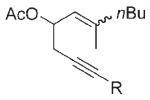
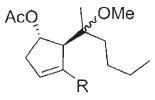
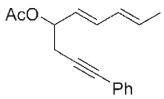
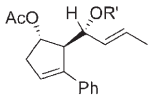
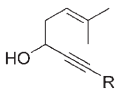
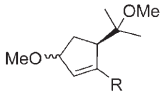
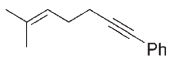
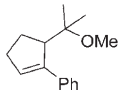
We first focused our attention on the variation of the nucleophile. The reaction proved to be quite general. Enyne **10** reacted with a variety of nucleophiles in the presence of the catalyst **12** (1 mol%) to furnish cyclopentenes **13a–f** in generally high yields (Table 2).

Primary alcohols, secondary alcohols, and phenols were tolerated in the Au^I-catalyzed alkoxycyclization of enyne **10** (Table 2, entries 1–4). Water was also successfully employed as a nucleophile in this transformation: The use of an 8:2:1 CH_2Cl_2/acetone/H_2O ternary mixture gave the best results, with the quantitative formation of the tertiary alcohol **13e** (Table 2, entry 5). Interestingly, acetic acid was also compatible with the catalytic system and underwent reaction with **10** to give the acetoxycyclopentene **13f** (Table 2, entry 6).

The transformation is not limited to aryl-substituted alkynes or trisubstituted alkenes. Vinyl and allyl substituents on the alkyne were also tolerated: The methoxycyclization of enynes **14** and **17** led to the formation of the synthetically valuable 1,3-dienes **25** and **28** in 77 and 78% yield, respectively (Table 3, entries 1 and 4), whereas the reactions of **15** and **18** furnished cyclopentenes **26** and **29** in good yield (Table 3, entries 2 and 5).

The reaction was also efficient when the alkynes were substituted with functionalized aryl groups (Table 3,

Table 3: Scope of the Au^I-catalyzed hydroxy- and methoxycyclization.[a]

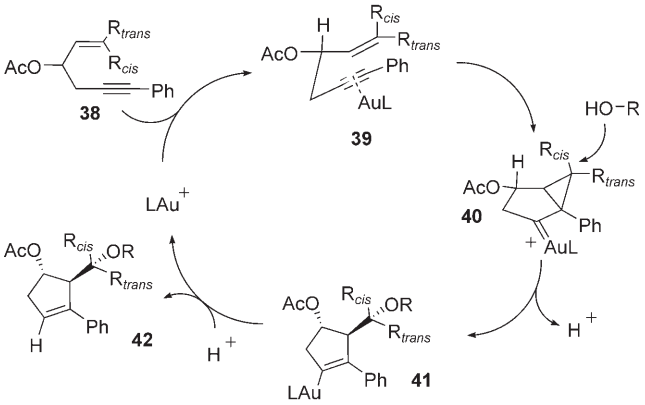
Entry	Substrate	Nucleophile	*t*	Product	Yield [%][b]
1	 **14**: R = vinyl	MeOH	80 min	 **25**	77 (54)[d]
2	**15**: R = methallyl	MeOH	24 h	**26**	87 (75)[d]
3	**16**: R = *p*-$(MeO)C_6H_4$	MeOH	20 min	**27**	93 (95)[d]
4	 **17**: R = vinyl (1:1.5)[c]	MeOH	6 h	 **28**	78 (1:1.5)[e]
5	**18**: R = allyl (1:2)[c]	MeOH	6 h	**29**	64 (1:2)[e]
6	**19**: R = Ph (1:1.5)[c]	MeOH	1 h	**30**	90 (1:1.5)[e]
7	 **19**: R = Ph	MeOH	1 h	 **30**	98 (R′ = Me)
8		H_2O	1 h	**31**	94 (R′ = H)
9	 **20**: R = *p*-BrC_6H_4 (1:2)[c]	MeOH	1 h	 **32**	65 (1:2)[e]
10	 **21**	MeOH	1 h	 **33**	87 (R′ = Me)
11		H_2O	1 h	**34**	82 (R′ = H)
12[f]	 **22**: R = Ph	MeOH	2 h	 **35**	77 (1:1)[e]
13	**23**: R = *p*-$(MeO)C_6H_4$	MeOH	15 min	**36**	87 (2:1)[e]
14	 **24**	MeOH	1 h	 **37**	92

[a] Reaction conditions: 1,5-enyne (0.5 M), **12** (1 mol%), CH_2Cl_2/MeOH (10:1) (or CH_2Cl_2/acetone/H_2O (8:2:1)), room temperature. [b] Yield of the isolated product. [c] *Z*/*E* ratio. [d] Yield when methanol was used as the solvent. [e] Diastereoisomeric ratio. [f] The reaction mixture was heated at reflux.

entries 3 and 9). It proved to be highly stereoselective: The methoxycyclization of a 1:1.5 *E*/*Z* diastereoisomeric mixture of enyne **19** led to the formation of cyclopentene **30** in the same diastereoisomeric ratio (Table 3, entry 6). The diastereomeric ratio also remained unchanged in the product when enynes **17**, **18**, and **20** were used as substrates. The stereospecificity of the reaction was proved through the hydroxy- and methoxycyclizations of the pure *E* isomer of **19**, which furnished the cyclopentenes **30** and **31** as single isomers (Table 3, entries 7 and 8).

Enyne **21** was also converted into derivatives **33** and **34** in good yield without concomitant isomerization of the second alkene functionality (Table 3, entries 10 and 11). Finally, the methoxycyclization was applied to alcohols **22** and **23**, which were converted into cyclopentenes **35** and **36**, respectively, as mixtures of diastereoisomers (Table 3, entries 12 and 13). No competitive formation of the bicyclo[3.1.0]hexanone was observed, thus confirming the rapid nucleophilic attack of methanol.[13] The introduction of an additional methoxy unit in **35** and **36** might result from a nonselective gold-catalyzed substitution of the intermediate acid-sensitive allylic alcohol by methanol.[14]

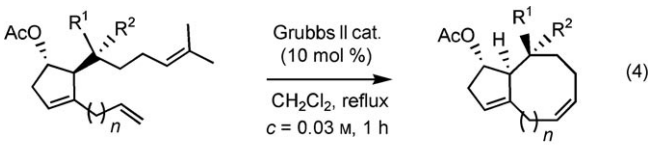
To account for all these observations, a mechanism for the formation of the cyclopentenes is proposed in Scheme 1. Gold(I) activation of the triple bond in enyne **38** promotes the nucleophilic addition of the pendant alkene and leads to the formation of the stabilized gold carbene intermediate **40**. A subsequent stereoselective attack of the oxygenated nucleophile on this intermediate furnishes the vinyl gold species **41**, which is finally protodemetalated to give cyclopentene **42**.[15] The exclusive formation of cyclopentenes could be attributed to the substitution pattern of the alkene moiety in **38**, which ultimately results in the regioselective cleavage of the weakest bond of the cyclopropyl ring in intermediate **40** upon attack by the oxygenated nucleophile.



Scheme 1. Proposed mechanism.

The stereoselectivity observed may be explained by considering the half-chair transition state corresponding to **39**, in which the acetoxy group occupies a pseudoequatorial position. The complete transfer of the stereoinformation from the *cis*- or *trans*-substituted alkene to the final cyclopentene **42** may arise from the configurational stability of the gold carbene **40** in combination with the rapid attack of the nucleophile on this activated species.

To further highlight the synthetic potential of the cyclopentenes obtained in this study, we took advantage of the pendant alkene functionalities present in compounds **28** and **29** to perform a subsequent ring-closing metathesis reaction. Ring-closing metathesis was conducted with the Grubbs II catalyst (10 mol%) in dichloromethane at reflux [Eq. (4)].

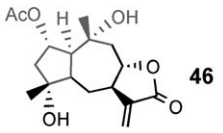


(4)

major **28** (R^1=Me, R^2=OMe, *n*=0) — **43** (R^1=Me, R^2=OMe, *n*=0) 100%

minor **28** (R^1=OMe, R^2=Me, *n*=0) — **44** (R^1=OMe, R^2=Me, *n*=0) 100%

major **29** (R^1=Me, R^2=OMe, *n*=1) — **45** (R^1=Me, R^2=OMe, *n*=1) 100%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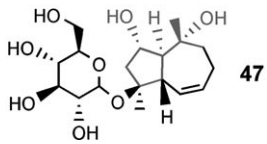
47

We were pleased to observe the rapid consumption of the substrates and the quantitative formation of the corresponding 5,7- and 5,8-fused bicyclic products **43**, **44**, and **45**. Such bicyclic motifs are found in many terpenes, two examples of which are **46** and **47**.[9]

In summary, we have developed an efficient stereoselective gold(I)-catalyzed 5-*endo* hydroxy- and alkoxycyclization of 1,5-enynes which provides concise access to functionalized cyclopentenes. The combination of this cyclization with the powerful ring-closing metathesis reaction furnishes structures that are even more complex. Further studies on this new gold(I)-catalyzed process and its application to the synthesis of natural products are underway.

Experimental Section

General procedure: The catalyst **12** (2.4 mg, 1 mol%) was added to a solution of the 1,5-enyne (0.25 mmol, 1 equiv) in CH_2Cl_2/MeOH (10:1; 0.5 M). The resulting mixture was stirred at room temperature and monitored periodically by TLC. Upon completion of the reaction, the mixture was evaporated to dryness and eluted through a column of silica gel to give the methoxycyclization product.

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[1] See, for example: a) J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2006**, *23*, 26–78;

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[3] For selected examples of the Au^I-mediated cycloisomerization of 1,*n*-enynes, see: 1,3-enynes: a) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442 – 1443; 1,4-enynes: b) X. Shi, D. J. Gorin, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 5802 – 5803; 1,5-enynes: c) M. R. Luzung, J. P. Markham, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 10858 – 10859; d) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978 – 15979; e) F. Gagosz, *Org. Lett.* **2005**, *7*, 4129 – 4132; f) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962—6963; g) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2004**, *126*, 11806 – 11807; h) S. Couty, C. Meyer, J. Cossy, *Angew. Chem.* **2006**, *118*, 6878 – 6882; *Angew. Chem. Int. Ed.* **2006**, *45*, 6726 – 6730; 1,6-enynes: i) C. Nieto-Oberhuber, M. P. Munoz, S. Lopez, E. Jiménez-Nûnez, C. Nevado, E. Herrero-Gomez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677 – 1693.

[4] See Ref. [2c] and [3i]; see also: C. Nieto-Oberhuber, S. Lopez, M. Paz Munoz, D. J. Cardenas, E. Bunuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302 – 6304; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146 – 6148.

[5] See Ref. [3i]; see also: a) M. P. Munoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293 – 1300; b) M. P. Munoz, M. Mendez, C. Nevado, D. J. Cardenas, A. M. Echavarren, *Synthesis* **2003**, 2898 – 2903.

[6] Two 5-*endo* gold(I)-catalyzed processes have been reported previously: a) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2004**, *116*, 5464 – 5466; *Angew. Chem. Int. Ed.* **2004**, *43*, 5350 – 5352; b) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. LaLonde, F. D. Toste, *Angew. Chem.* **2006**, *118*, 6137 – 6140; *Angew. Chem. Int. Ed.* **2006**, *45*, 5991 – 5994.

[7] A single example was reported in which a cyclopentene derivative was formed: see Ref. [3f].

[8] A single example of the methoxycyclization of a 1,6-enyne in which the alkyne is substituted with an aryl group has been reported: see Ref. [3i].

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[14] An alternative gold-catalyzed propargylic substitution could be envisaged; see: M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180 – 14181.

[15] This mechanism is supported by deuterium-labeling experiments (see Supporting Information).

