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Gold-Catalyzed Tandem C–C and C–O Bond Formation: A Highly Diastereoselective Formation of Cyclohex-4-ene-1,2-diol Derivatives

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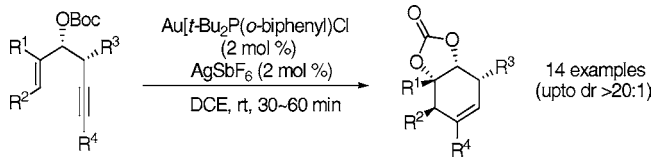
ABSTRACT



We have reported an efficient gold(I)-catalyzed tandem cyclization of *tert*-butyl carbonate derivatives of hex-1-en-5-yn-3-ol where nucleophilic participation of the *O*-Boc group appears to intercept a carbocationic (or cyclopropyl carbene) Au intermediate. This novel protocol leads to densely functionalized cyclohexene-3,4-diol derivatives where 1,2- or 1,2,3-stereocenters are controlled in a highly diastereoselective fashion.

Tandem reactions in which multiple bonds are formed in a chemo-, regio-, and stereoselective fashion are highly valued because of the need to synthesize increasingly complex natural targets or pharmaceutical agents. Recently, gold catalysis has provided a highly potent means of triggering addition reactions on alkyne[1] and proved effective in a number of consecutive C−X (heteroatom) and C−C bond-forming processes.[2] In this context, cyclizations of 1,5-enynes forming multiple stereocenters and functionalities in a single operation would present a valuable opportunity.[3] Earlier examples of the gold-catalyzed cycloisomerization of 1,5- or 1,6-enyne led to [*n*,1,0]bicycloalkene ($n = 3, 4$), where the catalytic cycle is terminated by 1,2-H-shift from Au-carbenoid.[4] A synthetically more appealing approach would be trapping the cationic intermediate by appropriate nucleophile, such as alcohol or amine,[2a,5a−c] and σ-bond via Wagner−Meerwein 1,2-shift.[5d]

O-Boc carbonate is another promising nucleophile for a possible trapping cationic intermediate because it could generate 1,2- or 1,3-diols in a protected form. A formal

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(1) For recent reviews on gold catalysis, see: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (b) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 2.

(2) For stereoselective tandem C−C and C−X bond formations, see: (a) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091. (b) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (c) Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132. (d) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804. (e) Gupta, A. K.; Rhim, C. Y.; Oh, C. H.; Mane, R. S.; Han, S. H. *Green Chem.* **2006**, *8*, 25.

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(4) (a) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. For applications of such process in natural product synthesis, see: (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (c) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2904.

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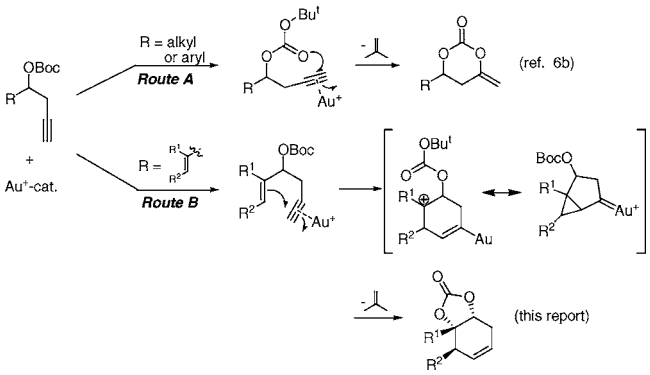
addition of acetate or carbonate on alkene, as compared to that on alkyne,[6] has the inherent advantage of generating stereogenic center(s) and therefore have been utilized in a number of noncatalyzed versions.[7] However, Au-catalyzed functionalizations of isolated alkene have been far less precedented than those of alkyne and typically occur under harsh conditions.[8] On the other hand, alkene functionalization of 1,5-enyne could occur under very mild conditions by virtue of alkyne activation by gold complex.

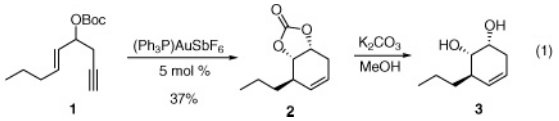
In the course of our study on the cyclization of *O*-Boc carbonates derived from homopropargylic alcohols (route A, Scheme 1),[6b] we found that chemoselectity changes from

Scheme 1. Switch of Chemoselectivity: *O*- vs *C*-Nucleophile



O-Boc (*O*-nucleophile) to alkene (*C*-nucleophile) when an alkenyl tether is positioned at the appropriate position (route B).[9] Herein, we report the realization of this concept, terminating in the synthesis of densely functionalized cyclohex-4-ene-1,2-diol derivatives, which constitute useful intermediates of substantial synthetic interest. A notable feature of this novel cyclization is that three contiguous stereocenters, including a quaternary carbon, are controlled in a highly diastereoselective fashion.

Initially, we tested **1** with $(PPh_3)AuSbF_6$ in DCE for the cyclic carbonate formation (Scheme 1, route A). In a complex mixture, we could obtain **2** in 37% yield after 3 h at rt, whose constitution was confirmed by ^1H, ^{13}C, COSY, and DEPT-NMR experiments for the hydrolyzed diol **3** (eq 1).

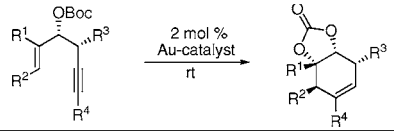


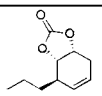
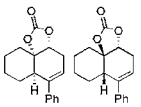
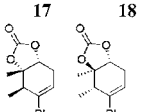
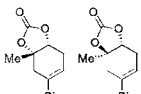
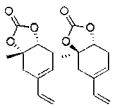
As indicated in Scheme 1, the intermediacy of alkenyl group in the cyclization could be significantly enhanced by the presence of a carbocation stabilizing group at R^1. We

(6) (a) Kang, J. E.; Lee, E. S.; Park, S. I.; Shin, S. *Tetrahedron Lett.* **2005**, *46*, 7431. (b) Kang, J. E.; Shin, S. *Synlett* **2006**, 717. (c) Buzas, A.; Gagosz, F. *Org. Lett.* **2006**, *8*, 515. (d) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274.

(7) (a) Duan, J. J. −W.; Smith, A. B. *J. Org. Chem.* **1993**, *58*, 3703. (b) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chm. Soc.* **2005**, *127*, 4586.

Table 1. Gold-Catalyzed Cyclization of 1,5-Enyne into Cyclohex-4-ene-1,2-diol Derivative



entry	substrate	condition[a] method	product	yield[b] (dr)[c]
1	R^1=R^3=R^4= H, R^2= *n*-Pr (**1**)	80 min, **B**	 **2**	46% (>20:1)
2	R^1 = Me, R^2, R^3, R^4 = H (**4**)	60 min, **A**	 **5**	57%
3		20 min, **B**		78% (7.8:1)
4	R^1 = Ph, R^2, R^3, R^4 = H (**6**)	30 min, **B**	 **7**	84% (>20:1)
5	R^1, R^2 = Me, R^3, R^4 = H (**8**)	30 min, **B**	 **9**	63% (16:1)
6	R^1, R^2, R^3 = Me, R^4 = H(**10**)	30 min, **B**	 **11**	87% (8:1)
7	R^1, R^2 = $(CH_2)_4$, R^3, R^4 = H(**12**)	30 min, **B**	 **13**	79% (14:1)
8	R^1, R^2 = $(CH_2)_3$, R^3, R^4 = H (**14**)	30 min, **B**	 **15**	79% (13:1)
9	R^1, R^2 = $(CH_2)_3$, R^3 = H, R^4 = Ph (**16**)	60 min, **A**	 **17** **18**	46% (**17**)[e] 9% (**18**)
10		60 min, **B**		71% (**17**)[e] 6% (**18**)
11	R^1, R^2 = Me, R^3 = H, R^4 = Ph (**19**)	60 min, **B**	 **20** **21**	73% (**20**)[e] 7% (**21**)
12	R^1 = Me, R^2, R^3 = H, R^4 = Ph (**22**)	60 min, **B**	 **23** **24**	61% (**23**)[e] 21% (**24**)
13	R^1 = Me, R^2, R^3 = H, R^4 = vinyl(**25**)	60 min, **B**	 **26** **27**	57% (**26**)[e] 19% (**27**)

[a] All reactions were conducted at rt in DCE. Method A: $Au(PPh_3)SbF_6$ (5 mol %) in DCE (0.2 M). Method B: Au[(*t*-Bu_2P(*o*-biphenyl)] SbF_6 (2 mol %). [b] Isolated yield of the major diastereomer after chromatographic purification. [c] Diastereomeric ratio (in parentheses) was determined on the basis of the isolated yield after flash column chromatography. [d] For structural identifications, see ref 10 and the Supportiing Information. [e] Less than 5% of exo-isomers were isolated.

were pleased to find that placing Me at R^1 (**4**) improved the yield, producing **5** (57%) using $Au(PPh_3)SbF_6$ (5 mol %) (Table 1, entry 2). A careful optimization in terms of counteranion, ligand, and solvent identified Au[*t*-Bu_2P(*o*-biphenyl)]SbF_6 as optimal catalyst[10] which produced 46% of **2** and 78% of **5** (along with its 1,2-diastereomer, 10%) at

rt and 2 mol % of catalyst loading (entries 1 and 3).[11] The presence of a phenyl group at R^1 led to 84% of bicyclocarbonate **7**, with no other detectable diastereomer (dr >20:1, entry 4). Incorporation of alkyl at R^2 and/or R^3 was well accommodated, producing **9** and **11** in good yields, although in the latter case, a slightly reduced diastereoselectivity was observed (entries 5 and 6).[11] Cyclic substrates were viable and delivered tricyclic carbonate **13** and **15** smoothly (entries 7 and 8). Substrate having an internal alkyne (**16**, **19**, **22**, and **25**) also underwent smooth cyclizations, although in this case, a small amount of exo-isomers as well as diastereomers were obtained (entries 9−13). Interestingly, the diastereomeric ratio increased when an electron-rich and bulky ligand was used (entries 9 and 10) and also when a substituent was present at R^2 (entries 11 and 12).[12] For **17**, single-crystal X-ray crystallography allowed an unambiguous assignment of the relative stereochemistry (Figure 1).

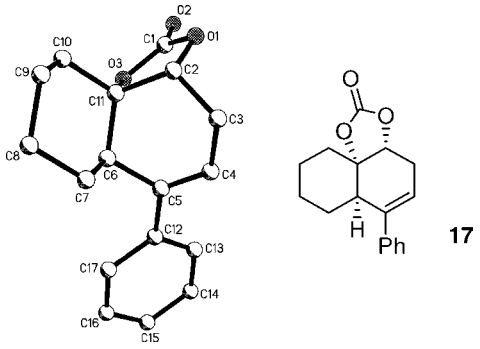
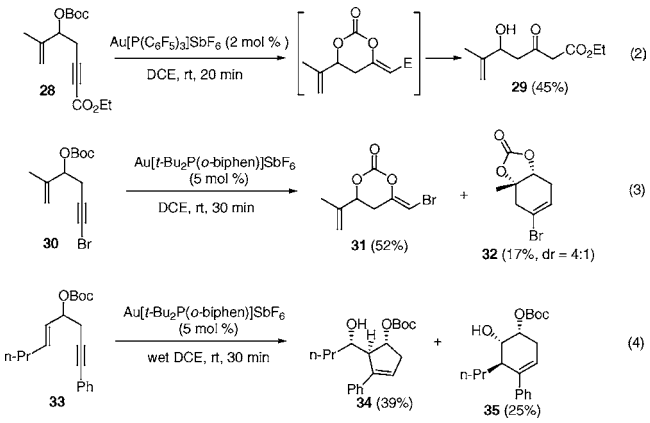


Figure 1. Relative stereochemistry in **17** by X-ray crystallography

To further probe the effect of acetylene substituents, we prepared substrates **28**, **30**, and **33** (Scheme 2). As expected, the ester group in **28** puts unfavorable electronic bias toward the desired cyclization and induces attack of *O*-Boc on alkyne, and hydrolyzed product **29** was isolated in 45% yield.

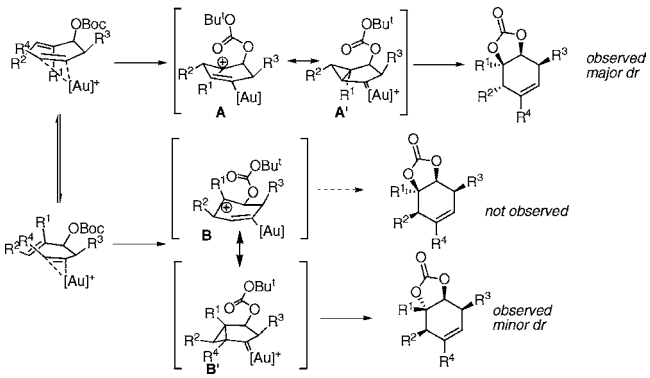
Scheme 2. Further Substrate Scope



Bromo-substituted **30** also favored addition on alkyne to produce **31** (52%) along with desired **32** (17%). In the case of **33**, devoid of R^1 substituent, an alternative 1,3-functionalization occurred to deliver **34** as a major product (39%) as well as **35** (25%, single isomer).

A consistently high level of stereochemical control can be rationalized on the basis of the *6-endo-dig* transition state as depicted in Scheme 3. Cyclization through the attack of

Scheme 3. Proposed Stereochemical Course of the Cyclization



O-Boc group on the carbocationic **A** seems disfavored for stereoelectronic reasons, and the attack on cyclopropyl gold complex **A′** (or **B′** for minor isomer) seems most consistent with our observations. Together with the importance of cation-stabilizing ability at R^1 in the current cyclization, we believe that the actual intermediate species is a resonance hybrid of **A** and **A′** (or **B** and **B′**).[13] Alternatively, a concerted pathway is also consistent with the observed diastereoselectivity.

The evolution of **33** under the current gold catalysis reveals another evidence of involvement of non-classical, carbene stabilized Au-intermediate as shown in Scheme 4. In this case, carbene-stabilized cationic intermediate **C** can have two

(8) For a review, see: (a) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. See also: (b) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (c) Yang, C. -G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966. For reviews on hydroaminations, see: (d) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

(9) For examples of alkene or arene participating as *C*-nucleophile in gold catalysis, see: Neito-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. and ref 2(b).

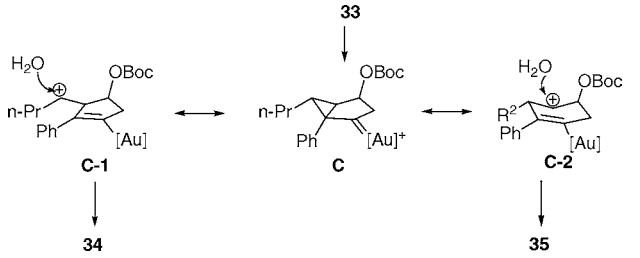
(10) Brønsted acid ($HNTf_2$) resulted largely in a deprotection of the Boc group. $AgSbF_6$ does not lead to any desired product. AuCl, $AuCl_3$, and $PtCl_2$ with or without ligand led to a much reduced yield of the desired product. See the Supporting Information (Table S1) for details. For Au[*t*-Bu_2P(*o*-biphenyl)]SbF_6 complex, see: Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5455.

(11) The structural identification of isomers was deduced from X-ray (**17**), DEPT (6-endo- vs 5-exo-isomers for R^4 = H), and selective 1D-NOE (relative stereochemistry) and COSY experiments. See the Supporting Information for details.

(12) Dewar−Chatt−Duncanson model of alkyne−metal (d^{10}) complex indicates a significant in-plane bending of alkyne substituent, which results in a steric interaction between R^2 and R^4 substituent. (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939.

(13) For in-depth discussions on the duality of the cyclopropyl gold−carbene and the carbocationic gold complex, see ref 1d.

Scheme 4. Evolution of **33**



mesomeric extremes, i.e., **C-1** and **C-2**, both corresponding to secondary carbocation in classical terms. The stereoselective formation of **34** and **35** presumably evolves from **C-1** and **C-2**, respectively, which form resonance hybdrids with **C**. Notably, a lack of cation-stabilizing ability in **33** slows down the attack of the internal *O*-Boc nucleophile.

In summary, we report herein a novel Au(I)-catalyzed assembly of densely functionalized cyclohexene derivatives in a highly stereoselective tandem reaction. It is noteworthy that the nucleophilic participation of the *O*-Boc group in the gold-catalyzed cyclization has been expanded to include a formal nucleophilic attack on an alkene. Subsequent studies directed at target-oriented synthesis are currently underway in this laboratory.

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Supporting Information Available: Representative experimental procedure for the cyclization, ^{1}H and ^{13}C NMR spectra of all substrates, full characterizations of all products, and X-ray crystallographic data of **17** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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