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Synthesis of Fused Carbocycles via a Selective 6-*Endo* Dig Gold(I)-Catalyzed Carbocyclization

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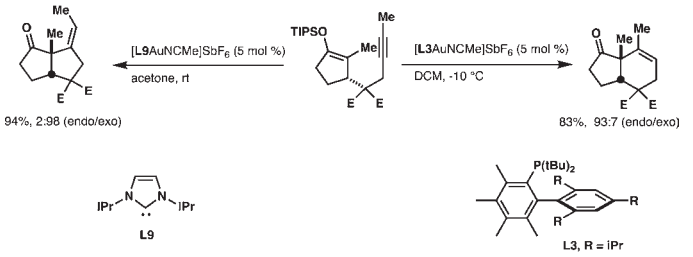
ABSTRACT



A gold-catalyzed synthesis of fused carbocycles via a regioselective 6-*endo* dig process is reported. The selectivity can be modulated by the steric and electronic properties of gold(I) complexes. The ligands can influence the pathway selectivity for the first bond formation rather than through a common intermediate generated after an initial bond formation. This gold(I)-catalyzed transformation provides access to synthetically useful carbocyclic motifs that are found in numerous diterpenoid natural products.

The development of methods that efficiently generate bicyclo[4.3.0]nonanes and bicyclo[4.4.0]decanes possessing quaternary centers at the ring junction constitute a significant challenge in organic synthesis. These structural motifs are embedded in several medicinally important molecules such as diterpenes and steroids. To assemble these scaffolds, one can envisage cyclizations of cyclic enol ethers with alkynes promoted by transition metal catalysts.[1] The high affinity of Au(I/III) salts to alkynes and allenes in the presence of many other functional groups combined with its ability to stabilize cationic charge provides tremendous opportunities for the discovery of novel and useful reactions.[2] Although Au(I)-catalyzed 5-*exo*, 5-*endo*, and 6-*exo* dig cyclizations have been extensively studied by Toste and others,[3] the Au(I)-catalyzed 6-*endo dig* process (**1**→**2**) to generate fused carbocycles has proven to be more challenging (Scheme 1).[1f,4] In fact, Lee reported that phosphino Au(I)-catalyzed reactions of cyclic enol ethers **1** (n = 0, 1) with homopropargylic alkynes exclusively gave the 5-*exo* dig product **3** regardless of the substituents R_1 on the triple bond.[3e]

Recently, it has been shown that divergent reactivity and stereoselectivity in gold-catalyzed reactions can be achieved by variation of the ancillary ligands.[5,6] From this perspective, we envisaged the possibility that both 5-*exo*

† To whom X-ray inquiries should be addressed.

(1) For selected examples, see: (a) Drouin, J.; Boaventura, M. A.; Conia, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1726. (b) Drouin, J.; Boaventura, M. A. *Tetrahedron Lett.* **1987**, *28*, 3923. (c) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773. (d) Iwasawa, N.; Maeyama, H.; Kusama, K. *Org. Lett.* **2001**, *3*, 3871. (e) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463. (f) Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764.

(2) For recent reviews, see: (a) Toste, F. D.; Gorin, D. J. *Nature* **2007**, *446*, 395. (b) Jiménez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (c) Fürtsner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (g) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (h) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (i) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, *5*, 675.

(3) (a) Dankwardt, J. K. *Tetrahedron Lett.* **2001**, *42*, 5809. (b) Suhre, M. H.; Reif, M. S.; Kirsch, F. *Org. Lett.* **2005**, *7*, 3925. (c) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (d) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (e) Lee, K.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2092. (f) Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch, S. F. *Org. Lett.* **2008**, *10*, 1025.

(4) (a) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585. (b) Minnihan, E. C.; Colletti, S. L.; Toste, F. D.; Shen, H. C. *J. Org. Chem.* **2007**, *72*, 6287.

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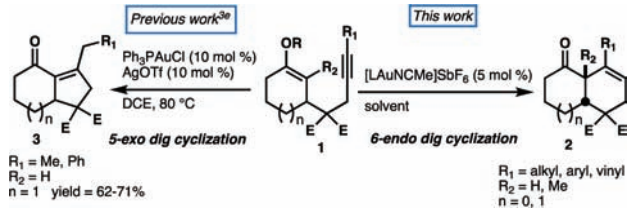
Scheme 1. Gold-Catalyzed Cyclization of Silylenol Ether **1**

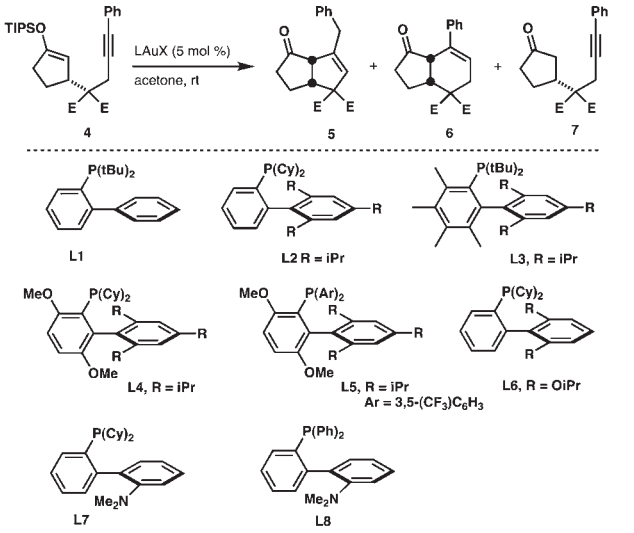


dig and 6-*endo* dig products could be obtained selectively from the same starting material by modulating the steric and electronic properties of the gold(I) catalyst. Herein, we report a gold-catalyzed synthesis of fused carbocycles via a regioselective 6-*endo* dig process.[7]

We started our investigation by examining the cyclization using various phosphino gold(I) salts (Table 1). Treatment of **4** with $Ph_3PAuSbF_6$ in DCM gave the hydrolysis product **7** as the major product (entry 1). Although the replacement of the counterion SbF_6 by BF_4 considerably reduced the hydrolysis product formation (entry 2), no significant increases of the *6-endo* dig product **6** ratio were noticed using either Et_3PAuCl or $(4\text{-}CF_3C_6H_4P)_3$-AuCl (entries 3 and 4) in DCM. Conversely, the cyclization using [**L1**AuNCMe]SbF_6 (2 mol %) in acetone gave **5** and **6** in a ratio of 64:36 in 86% yield (entry 5).[8] On the basis of these results, we hypothesized that an increase of steric interactions between R_1 and the Au(I) complex by having bulkier ligands on the metal could disfavor the 5-*exo* dig cyclization (**1**→**3**). The replacement of JohnPhos (**L1**) by XPhos (**L2**)[8] and Me_4XPhos (**L3**) resulted in an inversion of selectivity favoring the 6-*endo* dig product **6** (entries 6 and 7). Interestingly, the use of other Buchwald ligands such as **L4**, **L5**, and **L7** did not improve the *endo* selectivity or the yield (entries 8, 9, and 11).[9] The cyclization using RuPhos (**L6**)[10] and DavePhos (**L8**) favored the 5-*exo* dig product **5** in a ratio of 71:29 and 62:38 respectively (entries 10 and 12).

Having found that Au(I)-catalyzed carbocyclization using XPhos (**L2**) and Me_4XPhos (**L3**) favors the *6-endo* dig cyclization process, we evaluated the scope of the reaction using various internal alkynes (Table 2). Cyclization of cyclic tetrasubstituted enol ethers **8a**–**c** gave the bicyclic products **9a**–**c** possessing an angular methyl in a ratio of 6-*endo*/5-*exo* ranging from 71:29 to 97:3 in 83–91% yields (entries 1–3). Six-membered ring trisubstituted enol ether **8d** gave the 6-*endo* dig product **9d** in a ratio of 77:23 in 54% yield whereas the conversion

Table 1. Screening Conditions



entry	LAuX	ratio[a] (**5**/**6**/**7**)	yield (%)[b]
1	$Ph_3PAuSbF_6$	22:3:75[c]	87
2	Ph_3PAuBF_4	43:15:58[c]	92
3	$Et_3PAuSbF_6$	66:9:25[c]	93
4	$(4\text{-}CF_3C_6H_4)_3PAuBF_4$	50:15:35[c]	93
5	[**L1**AuNCMe]SbF_6	64:36:0	87
6	[**L2**AuNCMe]SbF_6	37:63:0	89
7	[**L3**AuNCMe]SbF_6	29:71:0	82
8	[**L4**AuNCMe]SbF_6	38:62:0	86
9	[**L5**AuNCMe]SbF_6	54:46:0	72
10	[**L6**AuNCMe]SbF_6	71:29:0	78
11	[**L7**AuNCMe]SbF_6	58:42:0	84
12	[**L8**AuNCMe]SbF_6	62:38:0	90

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yields. [c] Reactions run in DCM.

of phenyl acetylene **8e** exclusively afforded the 6-*endo* dig cyclized compound **9e** in 60% yield (entries 4 and 5). Similarly, conversion of electronic rich alkynes **8f** and **8g** provided the desired bicycle[4.4.0]decenones **9f** and **9g** in 72% and 78% yields respectively, as the sole isomer (entries 6 and 7). However, erosion of the *endo* regioselectivity was observed with electron-deficient alkynes such as **8h**–**j** (entries 8–10). To apply this method in the context of diterpene synthesis, it would be practical for the Au(I)-cyclization to be tolerant toward vinyl groups. To this end, Au(I)-catalyzed cyclization of enynes was examined (entries 11–15). Enynes **8k** and **8l** were converted to the desired dienes **9k** and **9l** as the sole isomer (>95:5) in 60 and 48% yields respectively (entries 11 and 12). Cyclization of enynes **8m** and **8o** gave the corresponding 6-*endo* dig products **9m** and **9o** as the major isomers in good overall yields (entries 13 and 14). Carbocyclization of **8p** using [**L3**AuNCMe]SbF_6 afforded diene **9p** in 84% yield (*endo*/*exo* = 87:13) (entry 15). These results are strikingly different from those previously reported (cf. Scheme 1), in particular, entries 4 and 5.

At first glance, one can hypothesize that steric interactions between the biaryl phosphine ligand and the substrate are at the origin of the difference in selectivities. Indeed, the

(5) (a) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348. (b) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A.; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482.

(6) Alcarazo, M.; Stork, T.; Anoop, A.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 2542.

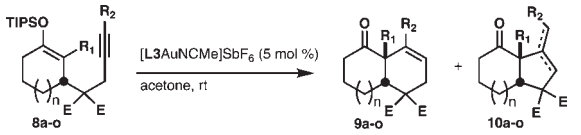
(7) For synthesis of bridgehead ketone via *6-endo dig* cyclization, see: Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *10*, 4236.

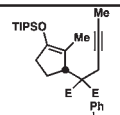
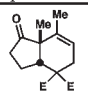
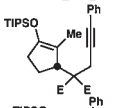
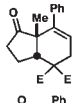
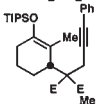
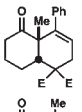
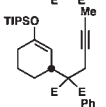
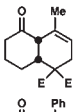
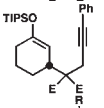
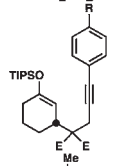
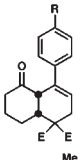
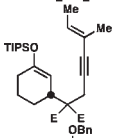
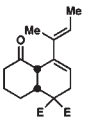
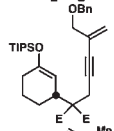
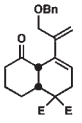
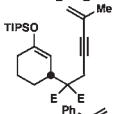
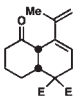
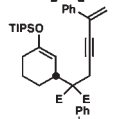
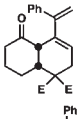
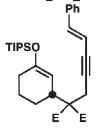
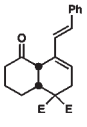
(8) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

(9) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

(10) Gao, H.; Wu, X.; Zhang, J. *Chem. Commun.* **2010**, *46*, 8764.

Table 2. Intramolecular Cyclization of Cyclic Enol Ether with Internal Alkynes



run	substrate		product		yield (**9**/**10**)[b]
1		**8a**		**9a**	83% (93:7)[c]
2		**8b**		**9b**	86% (87:13)
3		**8c**		**9c**	91% (71:29)
4		**8d**		**9d**	54% (77:23)[c]
5		**8e**		**9e**	90% (90:10)[d]
6		**8f** R=MeO		**9f**	72% (>95:5)
7		**8g** R=Me		**9g**	78% (>95:5)
8		**8h**R=COMe		**9h**	75% (71:29)
9		**8i** R = CF_3		**9i**	45% (61:39)
10		**8j** R = NO_2		**9j**	65% (42:58)
11		**8k**		**9k**	60% (>95:5)
12		**8l**		**9l**	48% (>95:5)[d]
13		**8m**		**9m**	86% (82:18)[d]
14		**8n**		**9n**	71% (85:15)[d]
15		**8o**		**9o**	84% (87:13)[e]

[a] Determined by 1H NMR of the crude reaction mixture. [b] Combined isolated yields. [c] Reaction run in DCM at −10 °C. [d] 5 mol % [**L2**AuNCMe]SbF_6 was used. [e] Reaction performed in MeOH.

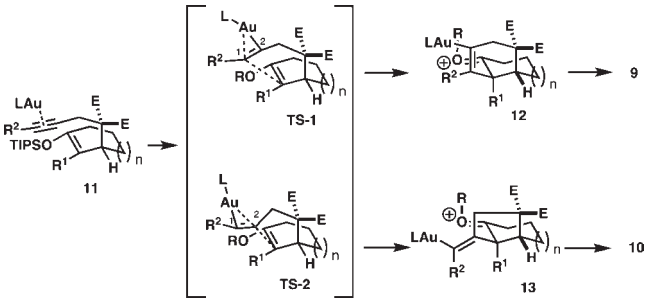
increase of the ligand size favors the formation of the 6-*endo* dig product. However, the electronic factors could not be ignored. Crystallographic data of **L3**AuCl revealed that ∠P−Au−Cl = 169° (Figure 1).[11] On this basis,

(11) See Supporting Information for details.

Figure 1. Crystallographic data of **L3**AuCl.

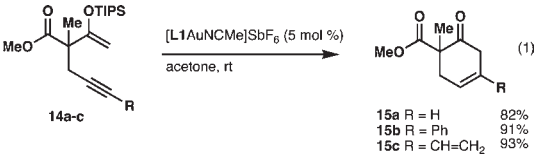
one might assume that bulkiness of the Buchwald ligand could deform the P−Au−C angle at the transition state which would result in a reduction of the Au-dπ→C-pπ overlap (Scheme 2).[12] As a consequence, this would imply a cationic type mechanism where a partial positive charge at C1 is formed at the transition state.

Scheme 2. Proposed Mechanism



On the basis that a neighboring electron-rich substituent R_2 can stabilize the partial charge, one can rationalize that the relative energy of **TS-1** leading to **12** should be lower than that of **TS-2** thus favoring the formation of *endo* dig product **9**. By contrast, electron-withdrawing groups should disfavor **TS-1** and an erosion of the regioselectivity should be observed. The ratio observed for the Au(I)-catalyzed cyclizations of electron-rich and -poor aryl alkynes **8f**−**j** are in agreement with the proposed mechanism (Table 2, entries 6−10).

The cyclization of terminal or internal alkynes on a linear template **14a**−**c** provided the desired 6-*endo* dig cyclized products **15a**−**c** in very good to excellent yields as the sole regioisomer (eq 1).[4b] The reaction conditions prove to be mild as no conjugated enones resulting from a double bond migration were observed.



In another experiment, we investigated the effect of σ-donating ligands on the reaction regioselectivity. To

our surprise, cyclization of enol ether **4** using [IPrAuNCMe]-SbF_6 (**L9**)[13] gave only the 5-*exo* dig ketone **5** in 91% yield as the sole isomer (Scheme 3).[14] Similarly, carbocyclization of tetrasubstituted enol ethers **8a** and **8c** predominantly afforded the 5-*exo* dig products **10a** and **10c** in ratios of 92:8 (94%) and 86:14 (86%) respectively. Aryl alkynes **8h**, **8i** and enyne **8p** were converted to the corresponding 5-*exo* products **10h**, **10i** and **10o** in good yields. These results are in sharp contrast with those depicted in Tables 1 and 2 where the cyclization of the same enol ethers using Me_4X-Phos (**L3**) provided the 6-*endo* dig products. This reveals that divergent regioselectivities can be obtained by modulating the bulkiness and electronic properties of the ancillary ligand. In the case of the cyclization with [IPrAuNCMe]SbF_6 (**L9**), it seems that the electronic density and steric environment of the alkyne are less contributing to the regioselectivity of the reaction. One could attribute this to the ligand size and the σ-donation properties of **L9**.

In summary, we have demonstrated that the gold(I)-catalyzed 6-*endo* dig pathway is accessible and not limited to substrates possessing steric or electronic biases. The ancillary ligand can affect the pathway selectivity for the first bond formation rather than through a common intermediate generated after an initial bond formation. Furthermore, this type of reaction provides an access to synthetically useful motifs that are found in numerous natural products. DFT calculations to gain further insight into the observed selectivity as well as the design and application of new catalysts to the synthesis of diterpenes are currently underway, and the results will be reported in due course.

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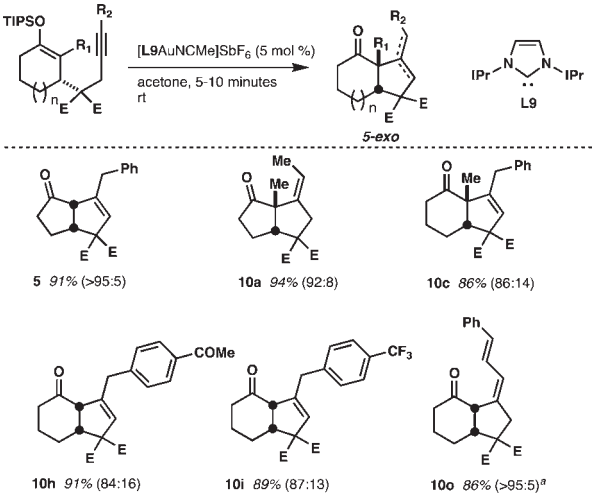
Scheme 3. *5-Exo* Dig Cyclization of Cyclic Enol Ethers[a]



[a] Reaction performed in MeOH.

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Supporting Information Available. Full characterization, experimental details and ^1H and ^{13}C NMR spectra for all new compounds, and crystallographic data (CIF) for **5**, **6**, and **L3**AuCl can be found in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.