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Synthesis of 3-Oxa- and 3-Azabicyclo[4.1.0]heptanes by Gold-Catalyzed Cycloisomerization of Cyclopropenes

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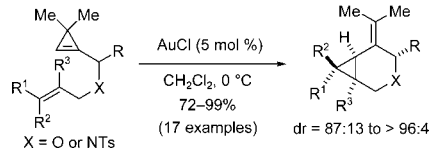
ABSTRACT



Allyl 3,3-dimethylcyclopropenylcarbinyl ethers or sulfonamides undergo gold-catalyzed cycloisomerization leading to 5-isopropylidene-3-oxa- and 3-azabicyclo[4.1.0]heptanes in excellent yields and with high diastereoselectivities. These reactions constitute the first examples of intramolecular cyclopropanation of an alkene by a gold carbene generated by electrophilic ring opening of a cyclopropene in the presence of gold(I) chloride.

Homogeneous gold catalysis has become a particularly active research area due to the exceptional ability of gold complexes to act as carbophilic Lewis acids and hence activate unsaturated compounds, notably alkynes, alkenes, and allenes, toward nucleophilic attack.[1] The formation of compounds containing three-membered rings by gold-catalyzed reactions has elicited considerable interest. Efficient *intermolecular* cyclopropanation of olefins has been reported with gold carbenes generated from diazoesters,[2] from enynes by cycloisomerization,[3−5] or from propargylic esters by 1,2-acyl migration.[6] Gold-catalyzed reactions of enynes that proceed with *intramolecular* cyclopropanation of the olefin are also well-documented.[1,3] In particular, propargylic esters have been widely used as valuable synthetic equivalents of α-diazoketones.[7−9] However, for this latter class of substrates, a gold carbene is not responsible for the cyclopropanation of the olefin which more likely proceeds through nucleophilic attack of the alkene onto

(1) For selected reviews, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (f) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (i) Muzart, J. *Tetrahedron* **2008**, *64*, 5815–5849. (j) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221.

(2) Prieto, A.; Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J.; Pérez-Galán, P.; Delpont, N.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 1790–1793, and references therein.

(3) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.

(4) López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029–6032. See also ref 11.

(5) For one example of intermolecular cyclopropanation of styrene with a gold carbene generated by cycloisomerization of a 2-alkynylaryl oxirane, see: Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059–5062.

(6) (a) Miki, K.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019–2022. (b) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002–18003. (c) Gorin, D. J.; Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 14480–14481.

(7) (a) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546–2547. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (c) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901–2904. (d) Fürstner, A.; Hannen, P. *Chem.—Eur. J.* **2006**, *12*, 3006–3019. (e) Boyer, F.-D.; Le Goff, X.; Hanna, I. *J. Org. Chem.* **2008**, *73*, 5163–5166. (f) Fürstner, A.; Schlecker, A. *Chem.—Eur. J.* **2008**, *14*, 9181–9191. (g) Moreau, X.; Goddard, J.-P.; Bernard, M.; Lemière, G.; López-Romero, J. M.; Mainetti, E.; Marion, N.; Mouriès, V.; Thorimbert, S.; Fensterbank, L.; Malacria, M. *Adv. Synth. Catal.* **2008**, *350*, 43–48. (h) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056–2057.

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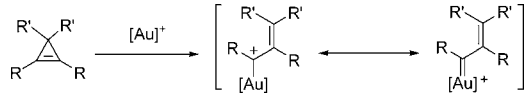
the activated alkyne, followed by stepwise 1,2-acyl migration.[7−9] *Intramolecular* cyclopropanation of olefins has been successfully achieved with cyclopropyl gold carbenes generated from enynes by cycloisomerization[10,11] or with cyclopentenylidene gold complexes produced by Nazarov-type cyclization from vinyl allenes.[12] However, due to their mode of formation, such gold carbenes are unavoidably either attached to or embedded in cyclic structures.

The rearrangement of cyclopropenes in the presence of transition metal complexes is a well-known method for generating metal vinylcarbene complexes.[13] The implication of cyclopropenes in gold-catalyzed reactions is relatively recent, and not surprisingly, the observed reactivity stems from the formation of gold-stabilized allylic carbocations or gold carbenes.[14−16] The actual nature of such species has been a matter of discussion,[16,17] but recent studies reveal that the degree of bonding and the reactivity of such organogold species depend on the substituents and the ancillary ligand (Scheme 1).[15−18]

Scheme 1. Reactivity of Cyclopropenes with Gold Catalysts

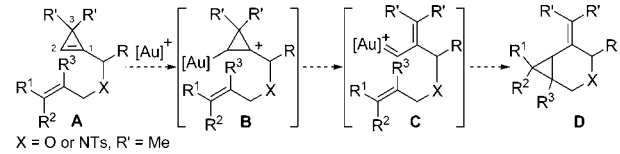


To date, allyl gold carbocations arising from the ring opening of cyclopropenes have been intercepted by nucleophiles as illustrated by the addition of alcohols to 3,3-dialkylcyclopropenes leading to allylic ethers,[14c] the isomerization of 1-aryl-2-vinyl- or 3-aryl-cyclopropenes to indenes,[14a,b] and the formation of regioisomeric mixtures of indenes and furanones from 3-aryl-3-cyclopropene carboxylates.[14c] Additionally, their carbenoid character was highlighted by examples of intermolecular cyclopropanation of styrene or (*Z*)-stilbene using 3,3-disubstituted cyclopropenes as substrates.[14c,d,15] However, no examples of *intramolecular* cyclopropanation of an alkene by an organogold, generated from cyclopropenes, have yet been disclosed.[19]

Herein, we report the first examples of gold-catalyzed cycloisomerizations of cyclopropene derivatives that proceed with intramolecular cyclopropanation of an olefin and lead to 3-oxa- and 3-azabicyclo[4.1.0]heptanes in excellent yields and with high diastereoselectivities.

Allyl cyclopropenylcarbinyl ethers or sulfonamides **A** were considered as substrates to examine whether the allyl gold cations resulting from their ring opening would achieve the cyclopropanation of the remote olefin. Regioselectivity was a first critical issue to consider. We surmised that for cyclopropenes **A** attack of a gold(I) electrophilic species would preferentially generate a secondary cyclopropyl cation **B**. Subsequent ring opening would then produce the gold-stabilized carbocation **C** regioselectively, a precursor of 3-oxa- and 3-azabicyclo[4.1.0]heptanes **D** if the planned transformation could be successfully achieved. However, substitution at C3 became mandatory to handle stable cyclopropene derivatives, and allyl 3,3-dimethylcyclopropenylcarbinyl ethers or sulfonamides **A** (R′ = Me) were thus selected as substrates. Additionally, their synthesis was readily achieved in two steps by addition of 3,3-dimethylcyclopropenyllithium, generated in situ from 1,1,2-tribromo-3,3-dimethylcyclopropane, to various aldehydes or *N*-tosylaldimines, followed by alkylation with allylic bromides (Scheme 2).[20]

Scheme 2. Gold-Catalyzed Cycloisomerization of Cyclopropenes **A**



Initial studies were carried out with cyclopropene **1**, and the catalytic activity of various gold complexes was evaluated (Table 1). Not surprisingly, no reaction took place with $(Ph_3P)AuCl$ (Table 1, entry 1), but we were pleased to see

(8) For theoretical studies, see: (a) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437. (b) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718–721. (c) Soriano, E.; Marco-Contelles, J. *Chem.—Eur. J.* **2008**, *14*, 6771–6779.

(9) Formation of cyclopropanes from enynes connected through an aromatic ring and bearing a propargylic acetate appeared to be promoted by a cinnamyl gold carbene. See ref 7h.

(10) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402–2406. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Jiménez-Núñez, E.; Buñuel, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 1694–1702. (c) Kim, S. M.; Park, J. H.; Choi, S. Y.; Chung, Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 6172–6175.

(11) For examples of olefin cyclopropanation with allyl gold cations generated from enynes bearing a propargyl ether, see: Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6152–6155.

(12) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.

(13) For a review on transition metal chemistry of cyclopropenes, see: Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(14) (a) Zhu, Z.-B.; Shi, M. *Chem.—Eur. J.* **2008**, *14*, 10219–10222. (b) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956–2959. (c) Bauer, J. T.; Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2008**, 6405–6407. (d) Zhou, Y.; Trewyn, B. G.; Angelici, R. J.; Woo, L. K. *J. Am. Chem. Soc.* **2009**, *131*, 11734–11743. (e) After this manuscript was submitted, gold-catalyzed cycloisomerization of enynes with cyclopropenes have been also reported, see: (e) Li, C.; Zeng, Y.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, DOI: 10.1002/anie201002673.

(15) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482–486.

(16) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510–2513.

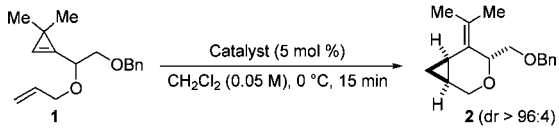
(17) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030–5033.

(18) Salvi, N.; Belpassi, L.; Tarantelli, F. *Chem.—Eur. J.* **2010**, *16*, 7231–7240.

(19) Allylic argento-carbonium ions generated from aryl cyclopropenes can achieve the cyclopropanation of the olefin of an allyl group at C3, see: Padwa, A.; Blacklock, T. J.; Loza, R. *J. Org. Chem.* **1982**, *47*, 3712–3721.

(20) For the preparation of cyclopropenes **A**, see: (a) Simaan, S.; Masarwa, A.; Zohar, E.; Stanger, A.; Bertus, P.; Marek, I. *Chem.—Eur. J.* **2009**, *15*, 8449–8464. (b) Miege, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 248–251.

Table 1. Gold-Catalyzed Cycloisomerization of Cyclopropene **1**



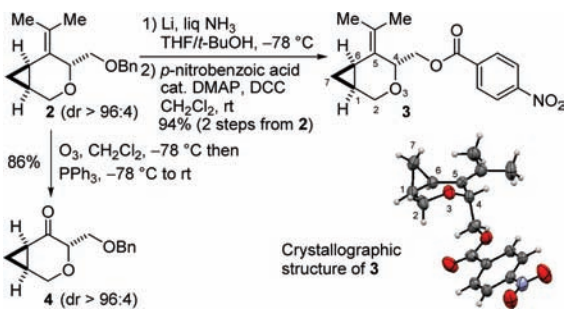
entry	catalyst	yield[a]
1	$(Ph_3P)AuCl$	0%[b]
2	$(Ph_3P)AuOTf$	79%
3	$(Ph_3P)AuSbF_6$	83%
4	$(Ph_3P)AuNTf_2$	93%
5	$AuCl_3$	99%
6	$AuBr_3$	98%
7	AuCl	98%

[a] Isolated yield of **2**. [b] No reaction took place after 12 h at rt.

that cationic complexes generated in situ from $(Ph_3P)AuCl$ and AgOTf or $AgSbF_6$ smoothly catalyzed the desired transformation (CH_2Cl_2, 0 °C, 15 min) to afford the oxabicyclic compound **2** in good yields (Table 1, entries 2 and 3).[21] The air-stable catalyst $(Ph_3P)AuNTf_2$ could be conveniently used (Table 1, entry 4),[22] but it was discovered that simple gold salts such as $AuCl_3$, $AuBr_3$, and AuCl provided the highest yields in compound **2** (Table 1, entries 5−7). The latter were equally effective, but AuCl was preferred since it is less hygroscopic and easier to handle. In all these reactions, the oxabicyclic compound **2** was obtained as a single detectable diastereomer (dr > 96:4).[23]

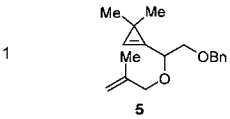
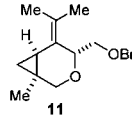
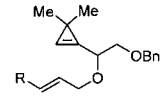
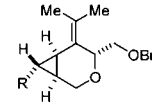
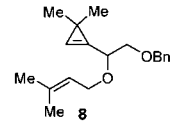
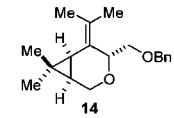
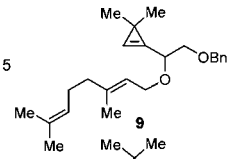
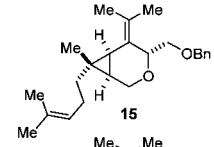
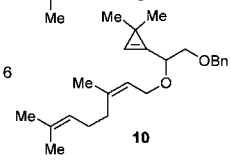
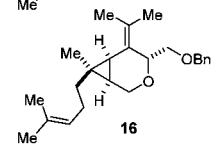
Attempts to determine the relative configuration of **2** by NMR (nOe experiments) were unsuccessful. Therefore, **2** was converted to the crystalline *p*-nitrobenzoate **3** by a two-step sequence involving cleavage of the benzyl ether under reductive conditions followed by esterification of the resulting alcohol with *p*-nitrobenzoic acid (94%, two steps from **2**). The structure of **3** was unambiguously established by single-crystal X-ray diffraction indicating an *anti* relative orientation between the cyclopropane and the benzyloxymethyl group.[24] It was also shown that the use of *gem*-dimethyl-cyclopropenes **A** as substrates did not represent a limitation as the isopropylidene substituent in the cycloisomerization product **2** could be readily cleaved by ozonolysis to provide the 3-oxabicyclo[4.1.0]heptan-5-one (**4**) (86%) without epimerization (Scheme 3).[25]

Scheme 3. Determination of the Relative Configuration of **2** and Access to 3-Oxabicyclo[4.1.0]heptan-5-one (**4**)



The scope of the cycloisomerization was then evaluated with various cyclopropenylcarbinyl ethers **5**−**10** bearing substituents on the allylic ether moiety (Table 2).

Table 2. Scope with Substituted Allylic Ethers

entry	substrate	product[a]	dr	yield
1	 **5**	 **11**	87:13	72%[b]
2	 **6** R = Ph	 **12** R = Ph	> 96:4	93%
3	**7** R = $CH_2OTBDPS$	**13** R = $CH_2OTBDPS$	> 96:4	97%
4	 **8**	 **14**	> 96:4	98%
5	 **9**	 **15**	> 96:4	97%
6	 **10**	 **16**	> 96:4	99%

[a] Reaction conditions: AuCl (5 mol %), CH_2Cl_2 (0.05 M), 0 °C. [b] Isolated yield of the major diastereomer.

Intramolecular cyclopropanation of α,α-disubstituted (Table 2, entry 1) or α,*β*-disubstituted (Table 2, entries 2 and 3) and α,*β*,*β*-trisubstituted olefins (Table 2, entries 4−6) induced by intermediate allyl gold carbenes proceeded equally well, and the corresponding 3-oxabicyclo[4.1.0]heptanes **11**−**16** were isolated in good to excellent yields (72−99%). Except the cycloisomerization of methallyl ether **5** which led to **11** (72%) accompanied by a minor diastereomer (dr = 87:13), all the other oxabicyclic compounds **12**−**16** were generated as single detectable diastereomers.[23] The cycloisomerization of the (*E*)-allylic ethers **6** and **7** took place with retention of the olefin configuration in the final cyclopropanes **12** and **13**.[25] The stereospecificity of the cyclopropanation process was confirmed by the behavior of geranyl ether **9** and neryl ether **10** which led to the

(21) $AgSbF_6$ itself also catalyzed the formation of **2**; however, the reaction was not as clean as with gold salts, and traces of generated byproducts were difficult to separate. Decomposition of **1** was observed in the presence of TfOH. No reaction took place with *p*-TsOH in C_6H_6. See: Al-Dulayymi, J. R.; Baird, M. S. *Tetrahedron* **1990**, *46*, 5703–5714.

(22) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133–4136.

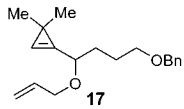
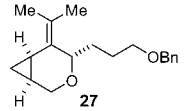
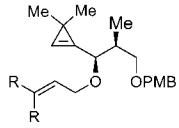
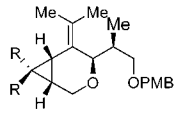
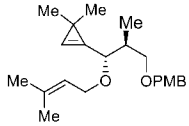
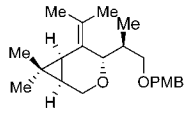
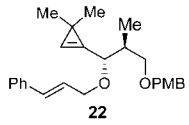
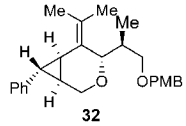
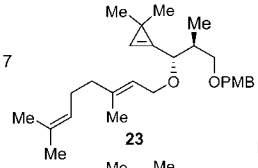
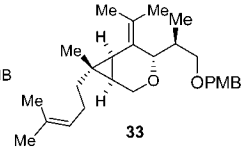
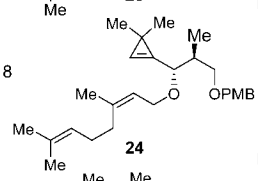
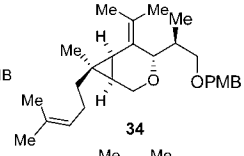
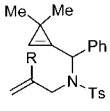
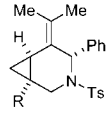
(23) The diastereoselectivity was determined by analysis of the ^1H NMR spectrum of the crude material.

(24) CCDC 773862 (**3**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

epimeric cycloisomerization products **15** (97%) and **16** (99%), respectively (Table 2, entries 5 and 6).[25]

The reactivity of a variety of cyclopropenylcarbinyl ethers or sulfonamides **A** was next investigated (Table 3). As for substrates **1** and **5**−**10** substituted by a benzyloxymethyl group, the diastereoselectivity and the yields of the cycloisomerization were excellent for cyclopropenes **17**−**24** having a benzylic ether at the remote position of an *n*-propyl chain (Table 3, entry 1) or if the chain was branched (Table 3, entries 2−8), whatever the relative configuration of the two stereogenic centers or the substituents on the allylic ether moiety.[23] Preliminary results also indicate that 3-azabicyclo[4.1.0]heptanes are accessible by the cycloisomerization of sulfonamides **25** and **26** which afforded compounds **35** and **36** both in 99% yield (Table 3, entries 9 and 10). As observed previously in the allylic ether series (Table 2, entry 1), the diastereoselectivity was lower for the methallyl-substituted sulfonamide **26** which provided the azabicyclic compound **36** as a 92:8 mixture of diastereomers (Table 3, entry 10).

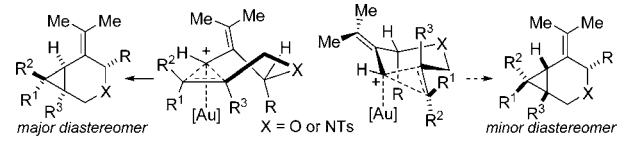
Table 3. Cycloisomerization of Cyclopropenes **A**

entry	substrate	product[a]	dr	yield
1	 **17**	 **27**	> 96:4	93%
2	 **18** R = H	 **28** R = H	> 96:4	87%
3	**19** R = Me	**29** R = Me	> 96:4	92%
4	 **20** R = H	 **30** R = H	> 96:4	93%
5	**21** R = Me	**31** R = Me	> 96:4	90%
6	 **22**	 **32**	> 96:4	84%
7	 **23**	 **33**	> 96:4	98%
8	 **24**	 **34**	> 96:4	97%
9	 **25** R = H	 **35** R = H	> 96:4	99%
10	**26** R = Me	**36** R = Me	92:8	99%

[a] Reaction conditions: AuCl (5 mol %), CH_2Cl_2 (0.05 M), 0 °C.

The *gem*-dimethyl group, which was crucial for substrate stability, presumably has a marked influence not only on the regioselectivity but also on the diastereoselectivity of the cycloisomerization of cyclopropenes **A**.[26] Since intramolecular cyclopropanation of the alkene induced by the gold-stabilized carbocation/gold carbene should proceed through a six-membered cyclic reactive conformer, the isopropylidene group should force the adjacent R substituent to occupy a pseudoaxial position to minimize allylic 1,3-strain. A chairlike transition state, which would predict the opposite sense of stereoinduction, may be disfavored as the R group, and the gold center would be both in an axial position. However, a twist-boat transition state would nicely account for the observed stereochemical outcome and explain the lower diastereoselectivity observed for methallyl ethers or sulfonamides (R^3 = Me) due to steric interactions between the methyl and both the gold center and the R substituent (Scheme 4).

Scheme 4. Rationalization of the Stereochemical Outcome



In conclusion, we have reported the first examples of gold-catalyzed cycloisomerization of cyclopropenes in which the intermediate gold carbenes promote the intramolecular cyclopropanation of an alkene leading to 3-oxa- and 3-azabicyclo[4.1.0]-heptanes with high diastereoselectivity. These reactions further expand the interest of gold carbenes in cyclopropanation and appear complementary to other gold-catalyzed reactions as a route to bicyclo[*n*.1.0]alkanes.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR data for all compounds and crystallographic data (CIF fomat) for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101741F

(25) The relative configuration of **4** was determined by NMR (nOe). The relative orientation of the cyclopropane substituent (Ph and $CH_2OTBDPS$) with the ring junction hydrogens in compounds **12** and **13** was determined by ^1H NMR (see Supporting Information). The relative configuration of the other bicyclo[4.1.0]heptanes was assigned by analogy with the results for compounds **2**, **12**, and **13**.

(26) For a cyclopropenylcarbinyl ether bearing a methyl at C2 and lacking the *gem*-dimethyl group, the cycloisomerization seems to occur with a lower level of regio- and diastereoselectivity. The behavior of cyclopropenes bearing various substitution patterns is currently under investigation.