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Hydroalkylation of Alkynyl Ethers via a Gold(I)-Catalyzed 1,5-Hydride Shift/Cyclization Sequence

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Abstract: A series of alkynyl ethers react with an electrophilic gold(I) catalyst to produce a range of structurally complex spiro or fused dihydrofurans and dihydropyrans via a 1,5-hydride shift/cyclization sequence. This hydroalkylation process, which is performed under practical experimental conditions, can be applied to terminal as well as ester-substituted alkynes. It allows the efficient conversion of secondary or tertiary sp^3 C–H bonds into new C–C bonds by the nucleophilic addition of a vinylgold species onto an oxonium intermediate. The stereoselectivity of the cycloisomerization process toward the formation of a new five- or six-membered cycle appears to be dependent on steric factors and the alkyne substitution pattern.

Introduction

Au and Pt catalysts[1] have recently shown their efficiency in a series of transformations involving the transfer of a nucleophilic group onto an alkyne followed by ring closure on the resulting stabilized carbocationic intermediate (eq 1).[2] These cycloisomerizations generally involve the use of nucleophilic oxygen- or sulfur-containing functionalities as migrating groups. Surprisingly, only little work has been done regarding the application of this gen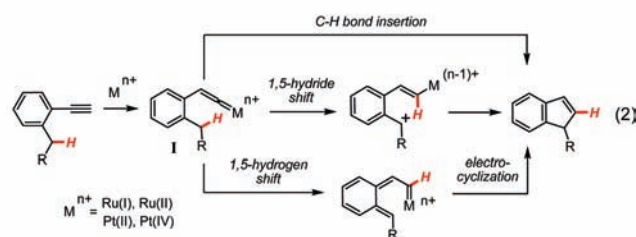eral concept to the more challenging C–H bond functionalization[3] via a direct transfer of a hydride onto a gold- or platinum-activated alkyne.[4–6]
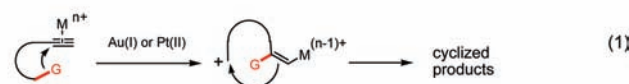


A few examples of metal-catalyzed intramolecular hydroalkylation of alkynes, which generally concern the synthesis of indenes from 2-substituted ethynylbenzenes, have however been previously reported in the literature (eq 2).[7] These formal platinum- or ruthenium-catalyzed 5-*endo* cycloisomerizations were however proposed to proceed via the initial in situ formation of a metal vinylidene species **I**. Indenes could then be formed either by an insertion of the metal-vinylidene into the benzylic C–H bond[7c] or by a sequence of a hydride transfer from the benzylic position to this latter species followed by ring closure[7a] or by a hydrogen shift/electrocyclisation sequence.[7b]

(1) For recent selected reviews on Au and Pt catalysis, see: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (b) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (c) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (d) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (e) Li, Z.; Brower, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (g) Gorin, D. J.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (h) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (j) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (k) Jiménez-Nùnez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (l) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(2) For selected examples, see: An, S. E.; Jeong, J.; Baskar, B.; Lee, J.; Seo, J.; Rhee, Y. H. *Chem. Eur. J.* **2009**, *15*, 11837. (a) Zou, Y.; Garayalde, D.; Wang, Q.; Nevado, C.; Goeke, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10110. (b) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062. (c) Wang, S.; Zhang, L. *J. Am. Chem. Soc.* **2006**, *128*, 14274. (d) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishis, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423. (e) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328.

(3) For a selection of recent reviews on C–H bond functionalization, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (b) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (c) Godula, K.; Sames, D. *Science* **2006**. (d) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422–6425–312, 67–72. (e) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683.

(4) For a recent example of a direct 1,*n*-hydride shift from a benzylic position to a platinum-activated alkyne, see: (a) Yang, S.; Li, Z.; Jian, X.; He, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 3999. For a transformation of alkynyl ethers into dihydropyrans, initiated by a hydride transfer onto a rhodium activated alkyne, see: (b) Shikanay, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. A gold-catalyzed hydride transfer to alkyne/fragmentation sequence leading to allenes has been reported recently; see: (c) Lo, V. K.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2008**, *10*, 517.

(5) A series of transformations involving a hydride transfer to a gold- or platinum-carbene followed by cyclization onto the resulting carbocation have been reported; see for instance: (a) Cui, Li; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (b) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (c) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6152.

■ *hydride* transfer / cyclization sequence on alkynyl ethers (this study)
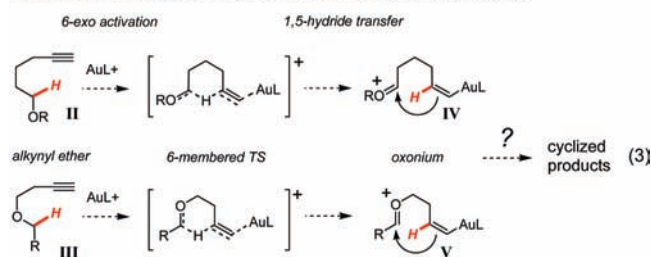
In this context and in relation with our interest in gold catalysis,[8] we conceived that a 6-*exo* activation of alkynyl ethers of type **II** or **III** by a gold(I) complex might induce a 1,5-hydride shift from a position α to the oxygen onto the alkyne (eq 3). This transfer could proceed through a six-membered transition state to furnish cyclized products after trapping of the oxonium **IV** or **V** by the vinylgold species.[9,10] A similar approach using PtI$_4$ or K$_2$PtCl$_4$ as the catalyst in acetonitrile at 120 °C for the conversion of terminal alkynes of type **II** and **III** was very recently reported by Sames and collaborators.[11] While the mechanism of the reaction could not be undoubtedly established (via Pt-vinylidene formation or via alkyne actrivation), the described Pt-catalyzed transformation selectively furnished in this case 5-*exo* alkenylation products in moderate to good yields (33−86%) (eqs 4 and 5).
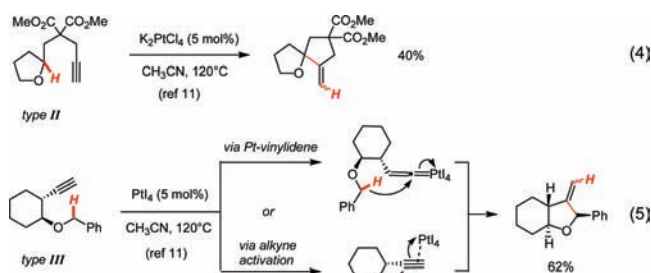
We report herein the results of our investigations in this area which allowed us to develop an efficient and practical procedure to convert a large variety of alkynyl ethers into structurally complex products via a gold(I)-catalyzed 1,5-hydride shift/cyclization sequence.

Results and discussion

Optimization of the Catalytic System. The easily accessible terminal alkyne **1a** was initially chosen as a model substrate to determine some appropriate reaction conditions for this transformation. The principal results of this optimization study are

compiled in Table 1.[12,13] We first focused our attention onto the use of PtCl$_2$, which proved to be an efficient catalyst in previously reported transformations involving hydride shifts.[4a,7a,c] However, no reaction was observed in the present case when reacting **1a** with 4 mol % of PtCl$_2$ in toluene at 100 °C for 7 h (Table 1, entry 1). The use of AuBr$_3$ alone or in combination with a silver salt in refluxing 1,2-dichloroethane did not give better results (Table 1, entries 2 and 3), and only traces of ketone **6a**, resulting from the hydration of the alkyne by residual water present in the solvent, were observed.[14] A series of air-stable gold(I) complexes were next examined as potential catalysts. Triphenylphosphine-based catalyst [Ph$_3$PAuNCCH3SbF$_6$][15] (**C1**) was not very stable under the reaction conditions (refluxing chloroform for 1 h), but traces of a cyclized product, namely, cyclohexene **3a**, could however be observed (Table 1, entry 4). The same observations were made in the case of the more electrophilic phosphite-based catalyst **C2**[15] (Table 1, entry 5). The use of biphenylphospine-based catalysts had a remarkable effect on the efficiency of the transformation (Table 1, entries 6−11). Reaction of **1a** with [JohnPhosAuNCCH$_3$SbF$_6$] (**C3**)[15] in refluxing chloroform led to the complete consumption of the substrate and the formation of three different cyclized products, **3a**, **4a**, and **5a**, of which cyclohexene **3a** was the major component (45%) (Table 1, entry 6). The yield of **3a** could be slightly improved to 57% when complex **C4**[15] possessing the bulkier *tert*-butylXPhos ligand was used as the catalyst (Table 1, entry 7). Changing the nature of the weakly coordinating counteranion from SbF$_6^-$ to NTf$_2^{-16}$ had a negative effect on the rate of the reaction and the product distribution since the yield of **3a** diminished, whereas the quantity of the hydration product **6a** increased (Table. 1, compare entries 7 and 8). The activity of complex **2** possessing the XPhos ligand was comparable to that of **C4**. If the product distribution was

(6) For C−H bond fonctionalization by a hydride transfer/cyclization sequence leading to the intramolecular formation of a new C−C bond, see: (a) McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972. (b) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (c) Pastine, S. J.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (d) Noguchi, M.; Yamada, H.; Sunagawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3327. (e) Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199. (f) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1987**, *109*, 3136 No substrate possessing an alkyne functionality as the hydride acceptor was involved in these reports.

(7) (a) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471. (b) Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289. (c) Bajracharya, G. B.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6204. See also: (d) Barluenga, J.; Fañanás-Mastral, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594.

(8) For recent contributions, see: (a) Odabachian, Y.; Le Goff, X.-F.; Gagosz, F. *Chem.−Eur. J.* **2009**, *15*, 8966. (b) Odabachian, Y.; Gagosz, F. *Adv. Synth. Catal.* **2009**, *351*, 379. (c) Böhringer, S.; Gagosz, F. *Adv. Synth. Catal.* **2008**, *350*, 2617. (d) Istrate, F.; Buzas, A.; Dias Jurberg, I.; Odabachian, Y.; Gagosz, F. *Org. Lett.* **2008**, *10*, 925. (e) Istrate, F.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (f) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141.

(9) The cyclization of type III alkynyl ethers with Rh$_2$(tfa)$_4$ has been reported recently; see ref 4b. The reaction was however restricted to the use of alkynyl sufones as substrates.

(10) For Lewis acid mediated cycloisomerization of substrates of type **II** and **III** possessing an α,β-unsaturated carbonyl moiety as the hydride acceptor instead of an alkyne, see ref 6a−c.

(11) See: Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525. Interestingly, the authors reported that a variety of gold catalysts led to poor yields of the desired cycloisomerization products under their experimental conditions. Furthermore, the Pt-catalyzed transformation selectively furnished 5-*exo* alkenylation products of type **5** and **8**, thus highlighting the difference in reactivity between platinum and gold catalysts. No example of formation of cyclohexene product of type **3** or formal [3 + 2] adduct of type **4** or the use of ester-substituted alkynes was reported.

(12) See Supporting Information for more details concerning the optimization of the catalytic system.

(13) Control experiments showed that HNTf$_2$ and AgNTf$_2$ were not suitable catalysts for this transformation.
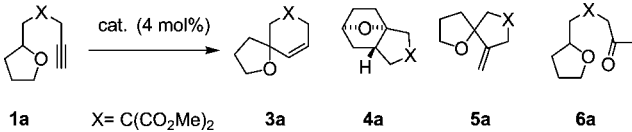
(14) For a selection of reports on gold-catalyzed hydration of alkynes, see: (a) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448. (b) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. (c) Casado, R.; Contel, M.; Laguna, M.; Romero, P.; Sanz, S. *J. Am. Chem. Soc.* **2003**, *125*, 11925. (d) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563.

(15) For the synthesis of gold complexes C1, C2, C3, C4, and 2, see: Amijs, C. H. M.; López-Carrillo; Raducan, V. M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.

(16) For the synthesis of gold complexe C5, see: Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

Table 1. Optimization of the Catalytic System with Model Substrate **1a**[a]

				%[b]			
entry	catalyst	conditions	time	**3a**	**4a**	**5a**	**6a**
1	PtCl$_2$	toluene	100 °C	7 h				
2	AuBr$_3$	1,2-DCE[c]	80 °C	1 h				<3
3	[AuBr$_3$(4 mol %) AgNTf$_2$ (12 mol %)]	1,2-DCE[c]	80 °C	1 h				<3
4[d]	**C1**	CDCl$_3$	60 °C	1 h	<3			
5[d]	**C2**	CH$_2$Cl$_2$	40 °C	13 h	<3			
6	**C3**	CDCl$_3$	60 °C	26 h	45	14	9	32
7	**C4**	CDCl$_3$	60 °C	13 h	57	9	5	29
8	**C5**	CDCl$_3$	60 °C	72 h	41	6	5	48
9	**2**	CDCl$_3$	60 °C	7 h	59	9	5	27
10	**2**	toluene	100 °C	2 h	59	8	4	29
11	**2**	**CH$_3$NO$_2$**	**100 °C**	**10 h**	**75 (74)[e]**	**15**	**4**	**6**

[a] Reaction conditions: 0.1 mmol of **1a** in 0.5 mL of solvent with 4 mol % of catalyst. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] 1,2-DCE: 1,2-dichloroethane. [d] Catalyst degradation was observed. [e] Isolated yield.
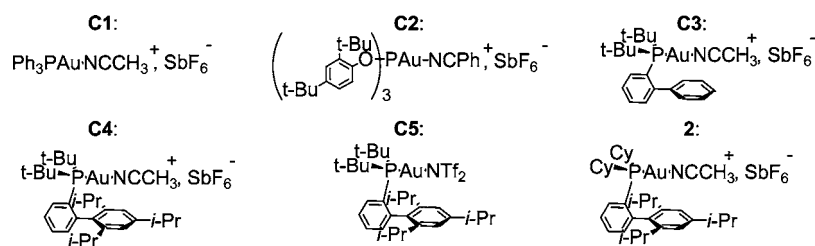
identical, the mixture was however obtained in a shorter reaction time (Table 1, compare entries 7 and 9). A final screening of various solvents showed that the reaction could be even more rapid when the reaction was performed in dry toluene at 100 °C with complex **2** as the catalyst (Table 1, entry 10).[17] Interestingly, the use of nitromethane[18] had the opposite effect on the kinetics but significantly improved the selectivity of the transformation (Table 1, entry 11). Under these conditions, the formation of ketone **6a** was minimized and cyclohexene **3a** could be isolated in 74% yield. Nitromethane appeared to be the solvent of choice for this transformation, enhancing catalyst stability and limiting the highly competitive and undesired hydration of the alkyne by traces of water. In light of these results, the use of complex **2** in refluxing nitromethane was chosen as the optimal catalytic system to study the scope of this new transformation. It is noteworthy that these experimental conditions are particularly practical since neither flame-dried glassware, an inert atmosphere, nor a carefully dried solvent[19] are required to produce cyclohexene **3a** in high yield.[20]

Reactivity of C(2)-Linked THFs and Dioxolane Derivatives. The transformation of substrate **1a** into cyclohexene **3a** is synthetically remarkable: the activation of the terminal alkyne by the

electrophilic gold catalyst **2** allows the redox transformation of an sp^3 C–H bond into a quaternary center with formation of a new C–C bond. Notably, the ring-closure step was rather selective, and less than 5% of isomeric five-membered cycle **5a** could be observed. We were however surprised by the unexpected formation of tricyclic compound **4a** that results from a formal [3 + 2] addition of the alkyne moiety onto the THF ring. Unfortunately, no gold catalyst favoring the formation of **4** could be found despite intensive investigation.[20]

A series of other C(2)-linked tetrahydrofurans **1b**–**h** were reacted under the optimized reaction conditions in order to delineate the scope of the transformation and acquire information regarding the influence of the substitution pattern of the substrate on the product distribution. The results of this study are presented in Table 2. The replacement of the esters in the linker by two diacetoxymethyl groups did not significantly affect the course of the reaction in terms of efficiency and selectivity (Table 2, entry 1). In this case, a 3.7:1 mixture of cyclohexene **3b** and the [3 + 2] adduct **4b** was isolated in 70% yield. Substrates **1c**–**f** bearing an additional substituent at position C(5) of the tetrahydrofuran ring reacted as well to furnish mixtures of **3c**–**f** and **4c**–**f** in yields ranging from 74% to 82% (Table 2, entries 2–5). Even if these transformations afforded cyclohexene products of type **3** as the major compounds, the presence of this substituent tended to slightly improve the formation of the [3 + 2] adducts of type **4**. The **3:4** ratios observed in those cases were indeed generally lower than those obtained in the reactions of substrates **1a** and **1b**. Substitution at the alkyne was also examined. The reactions of the more electrodeficient alkynes bearing a terminal ester group were highly selective. For instance, substrates **1g** and **1h** led exclusively to the formation of cyclohexenes **3g** and **3h**, which

(17) The hydration product **6a** became the major product (>80%) when toluene was not distilled prior to use.
(18) For examples of gold-catalyzed reactions using nitromethane as the solvent, see: (a) Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464. (b) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056. (c) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002.
(19) By comparison with hydride transfer reactions catalyzed by platinum or ruthenium; see refs 4a, b, 7.
(20) See Supporting Information for more details.

Table 2. Substrate Scope: C(2)-Linked THFs and Dioxolanes

entry	substrate	trans:cis [a]	products	isolated yield	3:4 [a]
1 [b]	1b	—	3b 4b	70%	3.7:1
2	1c	2:1	3c (1.4:1)[c] 4c	82% [d]	5.1:1
3	1d	2:1	3d (1.5:1)[c] 4d	76% [d]	2.3:1
4	1e	2.5:1	3e (1.3:1)[c] 4e	82% [d]	1.5:1
5	1f	1.6:1	3f (1.7:1)[c] 4f	74% [d]	2.1:1
6	1g	—	3g	91%	—
7	1h	4.5:1	3h (4.5:1)[c]	78%	—
8 [e]	1i	—	3i	73% [f]	—
9	1j	—	3j	65%	—

[a] Determined by ^{1}H NMR spectroscopy. [b] X = C(CH_2OAc)_2. [c] dr determined by ^{1}H NMR spectroscopy. [d] Global yield (3 + 4). [e] In nitropropane at 130 °C. [f] Isolated as the deprotected dioxolane form.

were isolated in, respectively, 91% and 78% yields (Table 2, entries 6 and 7). These results contrast with those reported by the groups of Urabe[4b] and Sames.[6c] The former noticed that ester-substituted alkynes were not suitable substrates in a related rhodium-catalyzed transformation,[21] and the latter showed that α,β-unsaturated esters analogous to **1g** could not be cyclized via a Lewis acid catalyzed reaction.[22]

The transformation could also be applied to dioxolane derivatives possessing either a terminal or an ester-substituted alkyne as illustrated by the conversion of substrates **1i** and **1j** into **3i** and **3j** (Table 2, entries 8 and 9). This extension of the procedure is synthetically attractive since cyclohexenone derivatives, in which the keto functionality is protected as a dioxolane, can be obtained. It should be noticed that the reaction of **1i**
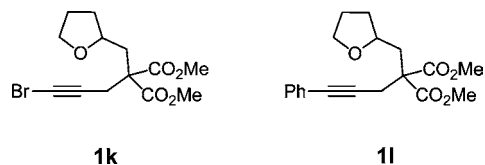
Figure 1. Unreactive substrates.

was conducted in nitropropane at 130 °C to ensure the full conversion of the substrate.[23,24] Even if the transformation could be applied to a range of tetrahydrofuran derivatives, limits in reactivity were observed with bromoalkyne **1k** and internal alkyne **1l**, which did not to afford cyclized products whatever the conditions used (Figure 1).[25]

Reactivity of C(3)-Linked THF Derivatives. We next turned our attention to the reactivity of C(3)-linked tetrahydrofuran derivative, since those had proved to be suitable substrates in the Lewis acid catalyzed reaction of α,β-unsaturated carbonyl compounds developed by Sames and co-workers.[6c] As seen from the results compiled in Table 3, a series of C(2)-linked tetrahydrofurans **7a**−**e** could be reacted under the same optimized reaction conditions, to achieve the efficient functionalization of secondary C−H bonds.

The reaction of terminal alkyne **7a** afforded a mixture of *exo*-methylene cyclopentane **8a** and cyclohexene **9a** in excellent yield (95%) (Table 3, entry 1). Interestingly, a high selectivity toward the formation a new five-membered cycle was obtained. This result contrasts with that obtained in the case of the isomeric C(2)-linked tetrahydrofuran **1a**, which selectively afforded cyclohexene **3a** (compare Table 1, entry 11 and Table 3, entry 1). The selectivity of the transformation was improved when compounds **7b** and **7c** possessing an additional alkyl group at the C(5) position of the tetrahydrofuran ring were used as the substrates (Table 3, entries 2 and 3). *exo*-Methylene cyclopentane **8b** and **8c**, which were isolated in, respectively, 93% and 88% yield, were indeed the sole cycloisomerized products of the reactions in these cases. At the opposite, a decrease in selectivity was observed with ester-substituted alkyne **7d** and a 1:1 mixture of five- and six-membered cycles was produced. Unlike substrate **1k**, bromoalkyne **7e** proved to be a suitable substrate for this transformation, affording *exo*-bromomethylene cyclopentane **8e** in 75% yield as a mixture of *cis* and *trans* isomers. Similarly to C(2)-linked tetrahydrofuran derivatives **1k,l** (Figure 1), internal alkynes **7f** and **7g** were unreactive under these conditions (Figure 2).

Reactivity of Alkynyl Benzyl Ethers. We next attempted the same cycloisomerization on alkynyl benzyl ether substrates in which the oxygen atom is part of the tether.[4b] The results obtained for terminal alkynes **10a**−**c** were highly disappointing since the reaction was sluggish and no cycloisomerized products of types **11** or **12** could be obtained (eq 6).

10a R^1=(CH$_2$)$_2$Ph, R^2=H
10b R^1=iPr, R^2=H
10c R^1-R^2=(CH$_2$)$_4$
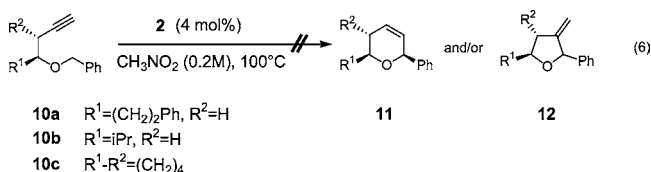
However, the transformation proved to be efficient in the case of the same substrates possessing an additional ester group at the terminus of the alkyne. 2,6-*cis*-Disubstituted dihydropyrans **11d**−**f** were thus produced in moderate to good yields (65−88%) and high selectivity (up to 25:1) (Table 4).[26]

Deuterium Labeling Experiments and Mechanistic Proposals. 1. Cycloisomerization of Terminal Alkynes. To obtain more insight into the mechanism of these cycloisomerizations, a series of deuterium labeling experiments were conducted. We first focused our attention on terminal alkynes, such as **1a**, which afforded cyclohexene **3a** as the major product. Deuterium-labeled substrates **12** and **16** were thus prepared and reacted under the experimental conditions previously used (Scheme 1).

In the reaction of **12**, the deuterium atom at position α to the oxygen was cleanly transferred to the vinylic position C(3) of cyclohexene **13**, thus supporting a mechanism involving a hydride transfer. In addition, the cycloisomerization of deuterated alkyne **16** afforded selectively cyclohexene **17** in which the deuterium atom was exclusively incorporated at position C(2). Notably, part of the deuterium content was lost during the process as the result of a probable deuterium/hydrogen exchange with traces of waters prior to cycloisomerization.[27] These results strongly suggest a cycloisomerization mechanism involving a direct 1,5-hydride shift onto a gold-activated alkyne. The sequence shown in Scheme 2 is therefore proposed as the most likely mechanism for the conversion of terminal alkynes such as **1a** into cyclohexene **3a**. The electrophilic gold(I) activation of the alkyne in **1a** could induce a 1,5-hydride shift that would lead to the formation of an oxonium ion **20**. Interaction of this cationic species with the pendant nucleophilic vinylgold moiety might generate a new cyclopropenium intermediate **21**. Carbocation **23**, which would finally collapse into cyclohexene **3a** after elimination of the gold(I) catalyst, might directly be formed from **21** or more probably in a stepwise fashion by a 1,2-alkyl shift operating on an intermediate gold-carbene **22**. The probable involvement of **22** in this process is supported by the formation of byproduct **4a** and **5a** (see Table 1) and by a presumably more favorable formation of the new C−C bond at the more nucleophilic β-carbon of the vinylgold moiety.[28]

A mechanism involving a sequence of a 1,5-hydride shift onto an intermediate gold-vinylidene complex **24**, followed by a nucleophilic trapping of the intermediate oxonium **25** by the vinyl gold species, could not be envisaged (Scheme 3).[29] This mechanism would indeed not account for the deuterium

(21) Only alkynyl sufones could be used as substrates for this transformation; see ref 9.

(22) The reported transformation could only be performed with more electron-withdrawing keto functionality (aldehyde or ketone); see ref 6c.

(23) The conversion in nitromethane was 20% after 6 h.

(24) The dioxolane functionality in **3i** proved to be rather labile. While the ¹H NMR spectroscopy NMR of the crude reaction mixture attested to the presence of **3i**, this latter could not be isolated by flash chromatography as its dioxolane-protected form.

(25) Substrates **1k** ad **1l** were recovered unchanged whatever reactions conditions were used (in refluxing nitromethane or nitropropane).

(26) These results are similar, in terms of reactivity and selectivity, to those reported by Urabe and co-workers for the Rh-catalyzed cycloisomerization of alkynyl benzyl ethers.[4b] Ester substrates such like **10d**−**f** were however described as inert under their conditions.

(27) This deuterium/hydrogen exchange, which might proceed via the formation of an intermediate gold-acetylide, is frequently observed in gold-catalyzed transformations. See, for example, ref 8a. See also: Cheong, P. H.-Y.; Morganelli, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 4517.

(28) See Scheme 6 for a discussion concerning the selectivity observed for the reaction of **1a**.

(29) For examples of transformations involving the formation of gold-vinylidene intermediate, see: (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (b) Maname, V.; Hannen, P.; Fürstner, A. *Chem.−Eur. J.* **2004**, *10*, 4556. (c) Fürstner, A.; Maname, V. *J. Org. Chem.* **2002**, *67*, 6264.

Table 3. Substrate Scope: C(3)-Linked THF

Reaction: R^1-substituted THF with alkyne tether ($X = C(CO_2Me)_2$) **7a–e** → **2** (4 mol%), CH$_3$NO$_2$ (0.2M), 100 °C → **8** + **9**

entry	substrate	*trans:cis*[a]	products		isolated yield	8:9[a]
1	7a	—	8a	9a	95%	6:1
2	7b	1:3	8b (1:3)[b]		93%	—
3	7c	1:3	8c (1:3)[b]		88%	—
4	7d	—	8d	9d	81%	1:1
5[c]	7e	—	8e (4.3:1)[b]		75%	—

[a] Determined by ^{1}H NMR spectroscopy. [b] dr determined by ^{1}H NMR spectroscopy. [c] The conversion of **7e** was 85%.
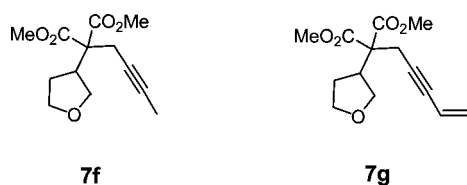
7f

7g

Figure 2. Unreactive substrates.

incorporation patterns observed for the reaction of D-labeled substrates **12** and **16**.

The formation of the [3 + 2] adduct **4a** and cycloisomerized compound **5a** as byproduct in the reaction of substrate **1a** could be explained by two divergent reaction pathways starting from the same intermediate **22** (Scheme 4).

Gold-carbene **22** could suffer a 1,2-hydride shift leading to the formation a tertiary carbocation **27**. Regeneration of the catalyst would subsequently afford *exo*-methylene cyclopentane **5a**. The proposed sequence accounts for the results obtained for the transformations of deuterated substrates **12** and **16** (see Scheme 1). For each of the byproducts **14** and **18**, the deuterium atom was indeed found to be exclusively incorporated at a single vinylic position.[30] This stereoselective transformation might be due to a 1,2-hydride shift operating exclusively via conformer **26**, as the presence of the sterically demanding tetrahydrofuran moiety should disfavor the formation of the other possible conformer **28**. Intermediate **22** might alternatively suffer a 1,5-hydride shift that would lead to the formation of a new intermediate oxonium ion **30** through a transition state of type **29**.[5] A subsequent trapping of this oxonium by the resulting alkylgold moiety would furnish the [3 + 2] adduct **4a**. This reaction pathway also accounts for the deuteration pattern obtained for the reaction of deuterated substrates **12** and **16** (see Scheme 1). The greater amount of [3 + 2] adduct generally obtained with substrates possessing a substituent at position C(5) of the THF ring (**1c–f**, Table 2, entries 2–5) might be due to the enhanced stability of the intermediate tertiary oxonium, which would render the 1,5-hydride shift more competitive. An alternative direct insertion of the gold-carbene into the C–H bond of the tetrahydrofuran moiety might also be envisaged to explain the formation of **4a**.[31]

We next focused our attention on the case of terminal alkynes such as **7a**. The reaction of deuterium-labeled substrate **31** selectively afforded compound **32** in which the deuterium atom

**Table 4.** Formation of Dihydropyrans

entry	substrate	products	isolated yield	cis:trans[a]
1	**10d**	**11d**	65%	16:1
2	**10e**	**11e**	74%	>25:1
3	**10f**	**11f**	88%	>25:1

[a] Determined by ^{1}H NMR spectroscopy.

Scheme 1. Cycloisomerization of Deuterium-Labeled Substrates **12** and **16**
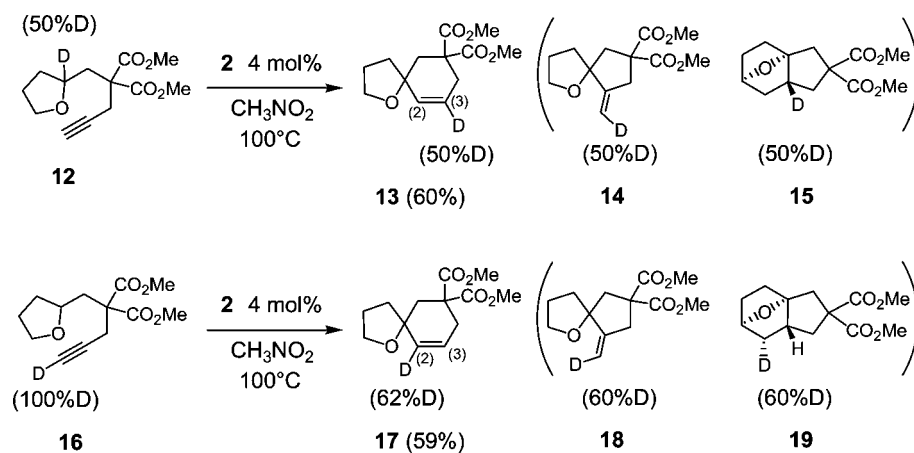
**Scheme 2.** Mechanistic Proposal for Conversion of **1a** into **3a**
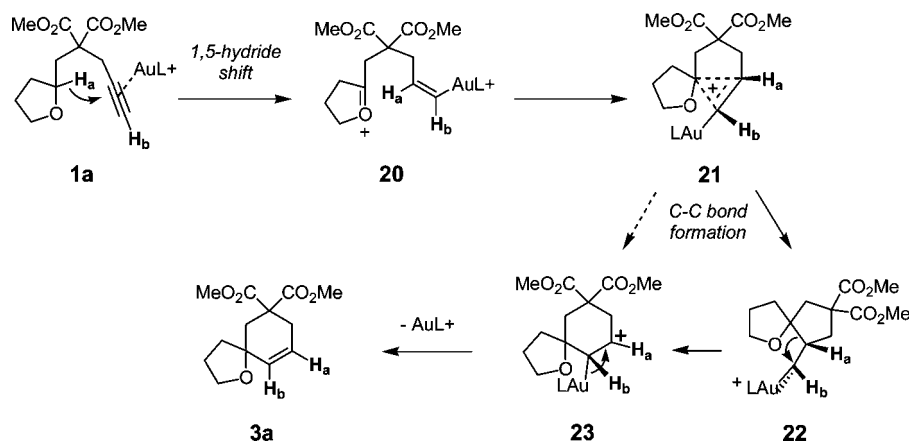
was exclusively incorporated at a single vinylic position (Scheme 5). The byproduct **33** also showed a unique deuterium pattern.[27]

These results are similar to those obtained for the reaction of deuterated alkyne **16** (see Scheme 1). One may therefore assume that the cycloisomerization of terminal alkynes of type **7a** also
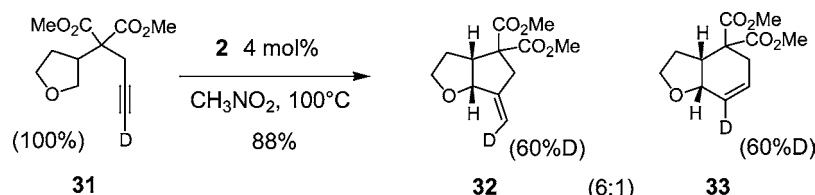
Scheme 3
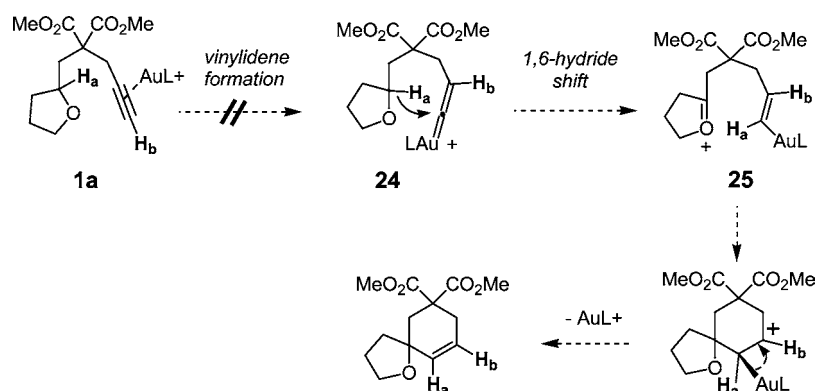
Scheme 4. Mechanistic Proposal for the Formation of Byproducts **4a** and **5a**
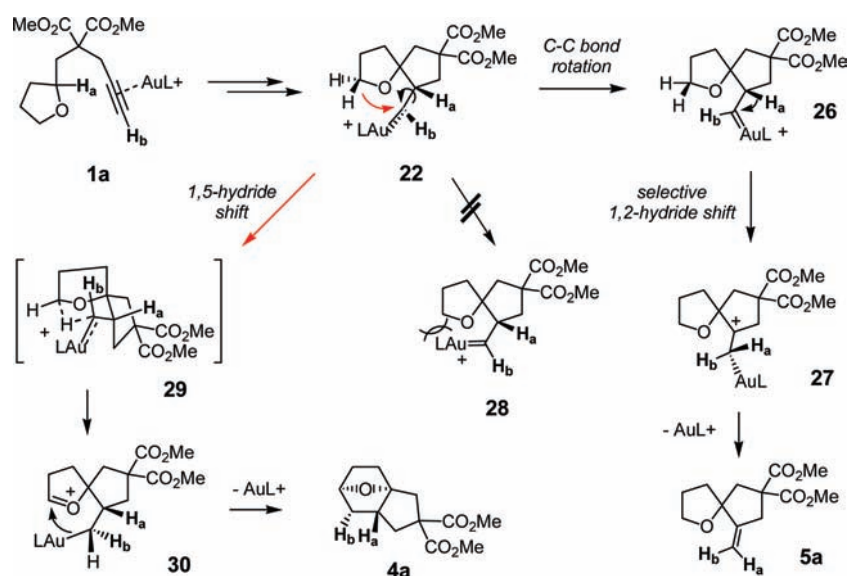
Scheme 5. Cycloisomerization of Deuterium-Labeled Substrates **31**

involves an initial 1,5-hydride shift onto a gold-activated alkyne. The reaction pathways leading to compounds **8a** and **9a** should then be similar to those presented in Schemes 2 and 4.

While terminal alkynes such as **1a** exhibited a preference for the formation of cyclohexene compounds of type **3a**, the reverse behavior was observed in the case of terminal alkynes such as **7a**, which mainly led to the formation of *exo*-methylene cyclopentane compounds of type **8a**. This reverse selectivity might be explained by considering the relative stability of intermediates **35** and **36** that would lead to, respectively, **8a** and **9a** (Scheme 6). For the cycloisomerization of substrate **1a**, the steric constrains in spiro intermediate **22** should favor its rearrangement into cation **23** and then the formation of cyclohexene **3a** as the major compound. These constraints should be weaker for the fused bicyclic intermediate **35**, thus allowing a rapid 1,2-hydride shift leading to **8a** rather than a 1,2-alkyl shift leading to **36**.

2. Cycloisomerization of Substituted Alkynes. Even though transformation was attempted with a series of substituted alkynes of type **1**, **6**, or **10**, only those possessing an ester group as the substituent furnished cyclized products (with the exception of bromoalkyne **6e**). The unreactivity of substituted alkynes **1k,l** and **7f,g** might be attributed to the presence of possible steric interactions between the substituent at the terminus of the alkyne
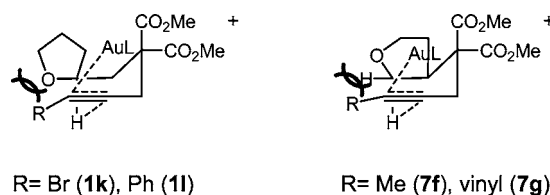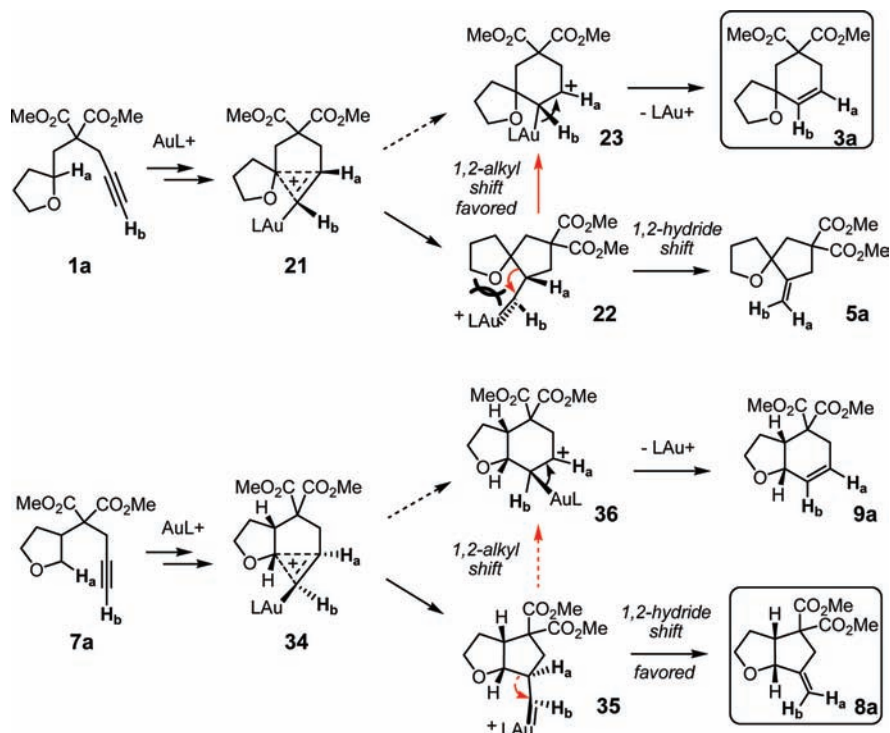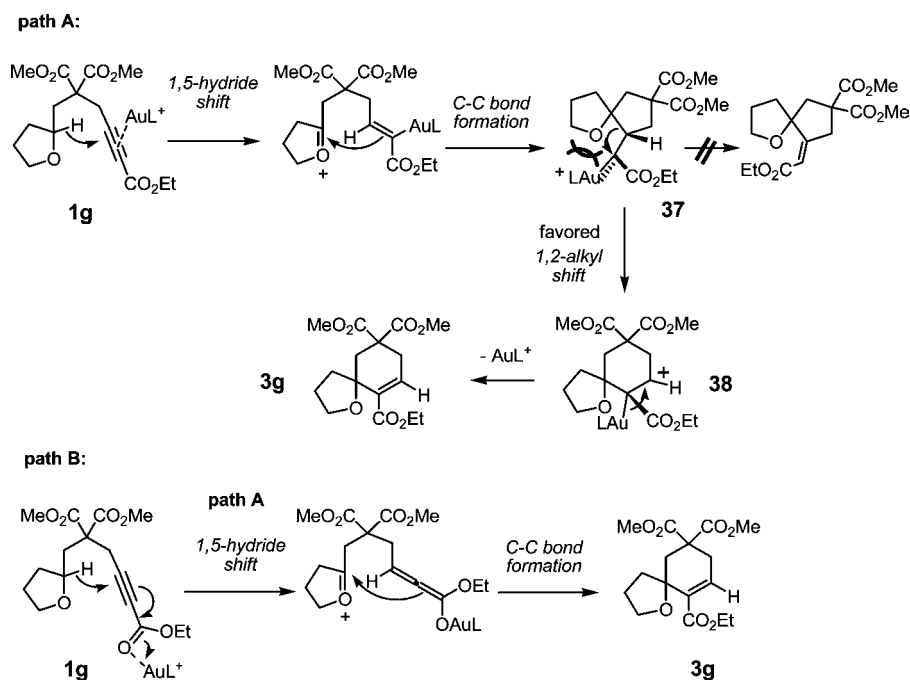

R= Br (**1k**), Ph (**1l**)   R= Me (**7f**), vinyl (**7g**)

Figure 3. Steric interactions during the hydride transfer step for substituted alkynes **1k,l** and **7f,g**.

**Scheme 6.** Source of Selectivity for the Cycloisomerization of **1a** and **7a**

Scheme 7. Possible Reaction Pathways for the Cycloisomerization of Ester-Substituted Alkynes

path A:

path B:

and the THF ring during the 1,5-hydride shift process (Figure 3). Electronic effects might also be invoked, as the hydride transfer should probably be less favorable in the case of more electron-rich alkynes.

Although the same steric interactions could be invoked in the case of ester-substituted alkynes **1g**, **1h**, **1k**, **7d**, and **10a−c**, the electron deficiency of the alkyne moiety might compensate for this negative effect and allow the hydride transfer. Two mechanisms could be proposed for the cycloisomerization of these substrates, depending on the nature of their activation (Scheme 7).

A mechanism similar to those presented for the transformation of terminal alkynes (see Scheme 2) and initiated by a 1,5-hydride shift onto a gold-activated alkyne could account for the structure of the products (Scheme 7, path A). Alternatively, an initial coordination of the cationic gold(I) complex to the keto functionality of the ester could induce an hydride transfer that would subsequently lead to the formation of the cycloisomerized products after a nucleophilic addition of the gold allenoate moiety onto the oxonium intermediate (Scheme 7, path B). This latter mechanism is however less probable as cationic gold(I) complexes are known to preferentially activate alkyne rather

Scheme 8. Mechanistic Proposal for the Formation of Dihydrofurans **11a**−**c**
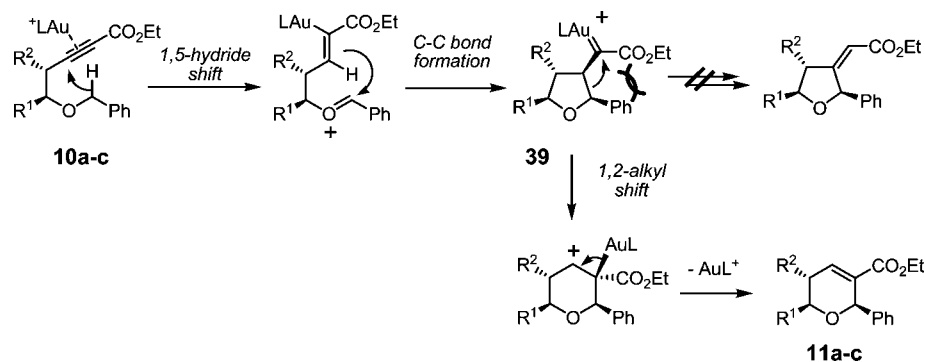
than keto functionalities.[32] Moreover, it would hardly account for the formation of isomeric compound **8d** obtained during the transformation of substrate **7d** (see Table 3, entry 4).

Although the reaction of terminal alkynes of type **1** generally led to mixture of products, the reactions of ester-substituted alkynes **1g**−**i** were stereospecific toward the formation of a new six-membered cycle. This might be explained by an even more favorable intermediate of type **38** (by comparison with the terminal alkyne case cycloisomerization; see Scheme 6) as the presence of the additional ester group would destabilize the intermediate gold-carbene **37** (see Scheme 7, path A). The same argument and steric constrains may be invoked to explain the selective formation of dihydrofurans **11a**−**c** via intermediate **39** (Scheme 8).

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(30) Minor byproducts **14** and **18** were not isolated, but their deuterium patterns could be determined by ^{1}H NMR spectroscopy of the crude reaction mixture. See Supporting Information for more details.

(31) For selected recent examples of formal C-H insertions of gold carbenes, see: (a) Escribano-Cuesta, A.; López-Carrillo, V.; Janssen, D.; Echavarren, A. M. *Chem.—Eur. J.* **2009**, *15*, 5646. (b) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809. (c) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993.

(32) Au(I) catalysts have been proposed to coordinate preferentially to multiple carbon−carbon rather than to keto functionalities. This preference is reversed for Au(III) catalysts. See for instance: (a) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817. (b) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (c) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500.

Conclusion

In summary, we have shown that a series of readily available alkynyl ethers could react with an electrophilic gold(I) catalyst to produce a range of structurally complex spiro or fused dihydrofurans and dihydropyrans. This hydroalkylation process, which could be applied to terminal as well as ester-substituted alkynes, allows the efficient conversion of secondary or tertiary sp^3 C−H bonds into new C−C bonds under practical conditions. A series of deuterium labeling experiments have brought some support to a general reaction mechanism involving an initial 1,5-hydride shift onto a gold(I)-activated alkyne followed by the nucleophilic addition of the vinylgold species onto the resulting intermediate oxonium. The stereoselectivity of the cycloisomerization process toward the formation of a new five- or six-membered cycle appears to be dependent on steric factors and alkynes substitution. This study opens opportunities for the development of new gold-catalyzed cycloisomerizations, as it was shown that a hydride species could be used as a valuable partner for the general concept of gold-catalyzed nucleophilic group transfer/cyclization sequence.

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

JA9100134