Computation-Guided Development of Au-Catalyzed Cycloisomerizations Proceeding via 1,2-Si or 1,2-H Migrations: Regiodivergent Synthesis of Silylfurans

Alexander S. Dudnik,[†] Yuanzhi Xia,[‡,§] Yahong Li,*,[‡,§] and Vladimir Gevorgyan*,[†]

Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60607, Key Laboratory of Organic Synthesis of Jiangsu Province, Department of Chemistry and Chemical Engineering, Suzhou University, Suzhou 215006, China, and Key Laboratory of Salt Lake Resources and Chemistry of Chinese Academy of Sciences, Qinghai Institute of Salt Lakes, Xining 810008, China

Received December 5, 2009; E-mail: liyahong@suda.edu.cn; vlad@uic.edu

Abstract: A novel highly efficient regiodivergent Au-catalyzed cycloisomerization of allenyl and homopropargylic ketones into synthetically valuable 2- and 3-silylfurans has been designed with the aid of DFT calculations. This cascade transformation features 1,2-Si or 1,2-H migrations in a common Au-carbene intermediate. Both experimental and computational results clearly indicate that the 1,2-Si migration is kinetically favored over the 1,2-shifts of H, alkyl, and aryl groups in the β-Si-substituted Au-carbenes. In addition, experimental results on the Au(I)-catalyzed cycloisomerization of homopropargylic ketones demonstrated that counterion and solvent effects could reverse the above migratory preference. The DFT calculations provided a rationale for this 1,2-migration regiodivergency. Thus, in the case of Ph$_3$PAuSbF$_6$, DFT-simulated reaction proceeds through the initial propargyl-allenyl isomerization followed by the cyclization into the Au-carbene intermediate with the exclusive formation of 1,2-Si migration products and solvent effects cannot affect this regioselectivity. However, in the case of a TfO$^-$ counterion, reaction occurs via the initial 5-*endo-dig* cyclization to give a cyclic furyl-Au intermediate. In the case of nonpolar solvents, subsequent ipso-protiodeauration of the latter is kinetically more favorable than the generation of the common Au-carbene intermediate and leads to the formation of formal 1,2-H migration products. In contrast, when polar solvent is employed in this DFT-simulated reaction, β-to-Au protonation of the furyl-Au species to give a Au-carbene intermediate competes with the ipso-protiodeauration. Subsequent dissociation of the triflate ligand in this carbene in polar media due to efficient solvation of charged intermediates facilitates formation of the 1,2-Si shift products. The above results of the DFT calculations were validated by the experimental data. The present study demonstrates that DFT calculations could efficiently support experimental results, providing guidance for rational design of new catalytic transformations.

Introduction

Cycloisomerizations of alkynes and allenes arguably represent the most versatile methodologies for the assembly of heterocycles.[1] Introduction of molecular rearrangements into these processes often provides highly efficient routes toward densely substituted heterocycles. Within this area, Hashmi[2] and later Che[3] reported Au-catalyzed[4] cycloisomerizations of alkynyl and allenyl ketones into furans.[5] These cascades were proposed to proceed via formation of the key putative Au-carbene **1** followed by a formal 1,2-H shift (Scheme 1).[6] Apparently, 1,2-migration of groups other than H, proceeding via intermediate **1**, would allow for an expedient synthesis of diversely functionalized furans with substitution patterns not easily accessible via the


[†] University of Illinois at Chicago.
[‡] Suzhou University.
[§] Qinghai Institute of Salt Lakes, Chinese Academy of Sciences.

(1) For selected reviews on transition-metal-catalyzed transformations of alkynes and allenes, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Kirsch, S. F. *Synthesis* **2008**, 3183. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (d) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (e) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (f) Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514. (g) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265. (h) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (i) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (j) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (k) Abu Sohel, S. M.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269. (l) Majumdar, K. C.; Debnath, P.; Roy, B. *Heterocycles* **2009**, *78*, 2661.
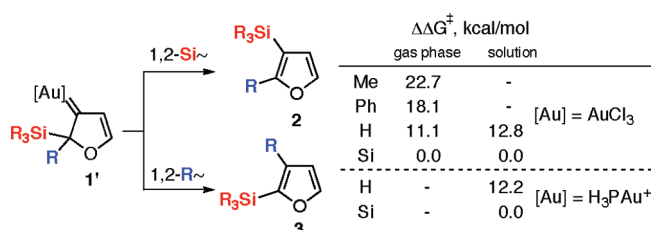
(2) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285.
(3) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325.
(4) For selected recent reviews on Au-chemistry, see: (a) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (f) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *109*, 3326. (g) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (i) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (j) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (k) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075. (l) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.

Scheme 1. 1,2-Group Migrations in the Synthesis of Furans via Au-Carbene Intermediate **1**
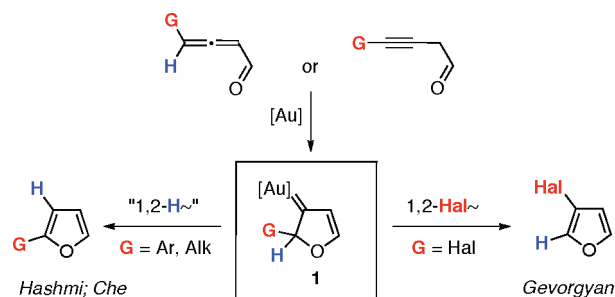
Scheme 2. Regiodivergent 1,2-Si Migrations in the Synthesis of Furans via Au-Carbene Intermediate
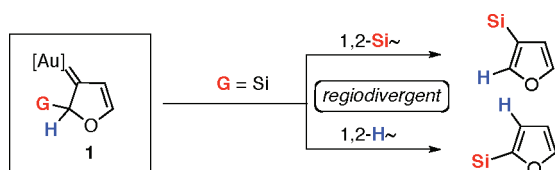
existing methodologies.[7] Along this line, we recently reported the Au-catalyzed regiodivergent synthesis of halofurans involving 1,2-Hal or 1,2-H migration in **1**.[7j] Herein, we wish to report a computation-designed regiodivergent Au-catalyzed cycloisomerization of homopropargyl and allenyl ketones into silylfurans, featuring 1,2-Si or 1,2-H migration in the Au-carbene intermediate **1** (Scheme 2).

Scheme 3. Predicted Activation Energies for the 1,2-Si- versus 1,2-R Migration in the Au-Carbene Intermediate **1'**

| | | $\Delta\Delta G^{\ddagger}$, kcal/mol | |
		gas phase	solution
	Me	22.7	-
	Ph	18.1	-
2	H	11.1	12.8
	Si	0.0	0.0
	H	-	12.2
3	Si	-	0.0

[Au] = AuCl₃ for the upper section, [Au] = H₃PAu⁺ for the lower section.
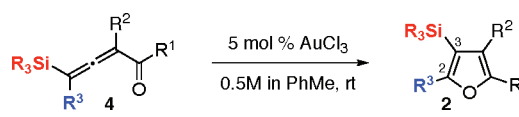
Results and Discussion

Recent DFT study revealed that the Au-catalyzed cycloisomerization of bromoallenyl ketones[7j] proceeds through the Au-carbene **1**, wherein the 1,2-Br migration is kinetically favored over a facile 1,2-H shift.[8] Naturally, we were interested in identifying other migrating groups capable of undergoing a selective 1,2-migration over the 1,2-H shift. Thus, we turned our attention to a silyl group, which is known to undergo a facile 1,2-migration to electron-deficient centers. Despite the well-known 1,2-Si migration to cationic centers,[9,10] little attention was devoted to 1,2-Si shifts to free[11] or metal-stabilized carbenes,[12] especially with a focus on synthetic significance. Also, few studies on migratory aptitudes in these systems have been reported.[11,12]

We envisioned that DFT calculations could shed light on the relative rates of 1,2-migrations of Si, H, and alkyl groups in the Au-carbene **1'** (Scheme 3).[13] Thus, the results of DFT computations[14,15] indicated that the 1,2-Si migration is strongly favored over the 1,2-shifts of methyl, phenyl, and even H in **1'** for both AuCl₃ and H₃PAu⁺ (Scheme 3).[14]

Synthesis of Furans via Au(III)-Catalyzed 1,2-Si Migration in Allenes. It occurred to us that the Au-catalyzed cyclization of silyl allenes **4** could provide a straightforward access to the Au-carbene **1'** via a well-established route (eq 1).[2,6]

(5) For recent reviews on furan synthesis, see: (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850. (b) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076. (c) Patil, N. T.; Yamamoto, Y. *ARKIVOC* **2007**, 121. (d) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955. (e) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2008**, *19*, 176. (f) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87. (g) D'Souza, D. M.; Muller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. For selected recent examples on transition-metal-catalyzed synthesis of furans, see: (h) Zhang, M.; Jiang, H.-F.; Neumann, H.; Beller, M.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1681. (i) Xiao, Y.; Zhang, J. *Adv. Synth. Catal.* **2009**, *351*, 617. (j) Pan, Y.-M.; Zhao, S.-Y.; Ji, W.-H.; Zhan, Z.-P. *J. Comb. Chem.* **2009**, *11*, 103. (k) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814. (l) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (m) Shibata, Y.; Noguchi, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2008**, *10*, 2825. (n) Ji, K.-G.; Shen, Y.-W.; Shu, X.-Z.; Xiao, H.-Q.; Bian, Y.-J.; Liang, Y.-M. *Adv. Synth. Catal.* **2008**, *350*, 1275. (o) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528. (p) Aurrecoechea, J. M.; Durana, A.; Pérez, E. *J. Org. Chem.* **2008**, *73*, 3650. (q) Zhao, L.-B.; Guan, Z.-H.; Han, Y.; Xie, Y.-X.; He, S.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 10276. (r) Shu, X.-Z.; Liu, X.-Y.; Xiao, H.-Q.; Ji, K.-G.; Guo, L.-N.; Qi, C.-Z.; Liang, Y.-M. *Adv. Synth. Catal.* **2007**, *349*, 2493. (s) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905. (t) Arimitsu, S.; Hammond, G. B. *J. Org. Chem.* **2007**, *72*, 8559. (u) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (v) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (w) Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 5342. (x) Blanc, A.; Tenbrink, K.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2009**, *74*, 4360. (y) Yoshida, M.; Al-Amin, M.; Shishido, K. *Synthesis* **2009**, 2454. (z) Egi, M.; Azechi, K.; Akai, S. *Org* **2009**, *11*, 5002. (aa) Liu, F.; Yu, Y.; Zhang, J. *Angew Chem., Int. Ed.* **2009**, *48*, 5505. (ab) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (ac) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (ad) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409. (ae) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (af) Hashmi, A. S. K.; Sinha, P. *Adv Synth. Catal.* **2004**, *346*, 432. (ag) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95.

(6) For Ag-catalyzed synthesis of furans via a formal 1,2-H shift in allenones, see:(a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581.

(7) For selected examples on 1,2-shifts in the synthesis of aromatic heterocycles, see: (a) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98. (b) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (c) Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868. (d) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195. (e) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (f) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (g) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346. (h) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906. (i) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293. (j) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500.

(8) Xia, Y.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. *J. Am. Chem. Soc.* **2008**, *130*, 6940.

(9) For selected examples, see: (a) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. (b) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (c) Becker, D. A.; Danheiser, R. L. *J. Am. Chem. Soc.* **1989**, *111*, 389. (d) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868.

(10) For selected examples of Si-shifts in the synthesis of aromatic heterocycles, see: (a) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081. (b) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050. (c) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407.

(11) (a) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2001**, *66*, 1115. (b) Creary, X.; Wang, Y.-X. *Tetrahedron Lett.* **1989**, *30*, 2493.

Table 1. Au-Catalyzed Cycloisomerization of Allenyl Ketones **4**

| Entry	Substrate	Product	**2**, %[a]
1			**2a**, 90
2			**2b**, 80
3			**2c**, 82
4			**2d**, 87
5			**2e**, 82 (73)[b] [77][c]

[a] Isolated yield of product for reactions performed on 0.5 mmol scale. [b] Isolated yield of **2e** for reaction performed in MeNO$_2$. [c] Isolated yield of **2e** for reaction performed with 1 mol % of catalyst.

The latter intermediate, upon the 1,2-Si shift, should furnish the 3-silylfuran **2**.

(1)
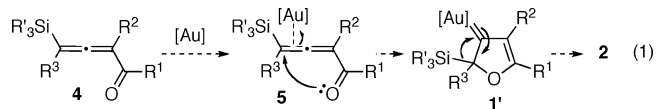
To this end, we have tested the possible cycloisomerization of allenes **4** into 3-silylfurans **2** in the presence of various Au catalysts. Gratifyingly, it was found that α-to-Si alkyl-substituted allenes **4a** and **4b** in the presence of AuCl$_3$ catalyst underwent

a highly selective 1,2-Si migration, affording 3-silylfurans **2a** and **2b** in high yields (Table 1, entries 1−2). Likewise, cycloisomerization of phenyl-substituted allenes **4c,d** proceeded very efficiently to give 3-silylfurans **2c,d** as sole isomers (entries 3−4). To our delight, α-to-Si-unsubstituted allene **4e** cyclized

Scheme 4. Potential Energy Surfaces for the AuCl$_3$-Catalyzed Cycloisomerization of Allenes **4** (R = H)
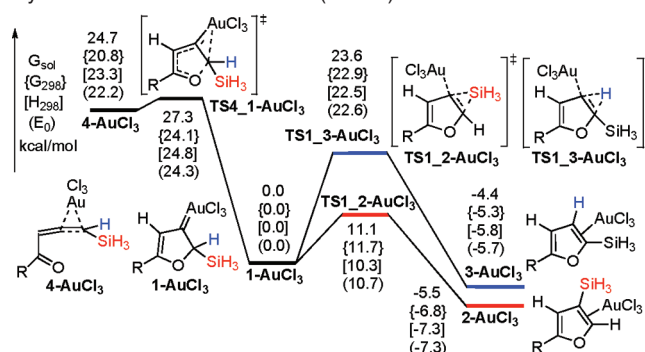
Scheme 5. Generation of Products **2** and **3** from Complexes **2-AuCl$_3$** and **3-AuCl$_3$**
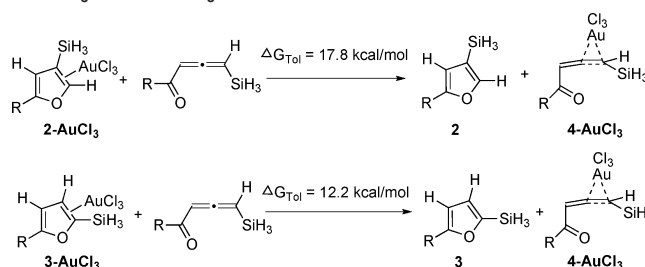
(12) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2002**, *67*, 112.

(13) For selected examples of DFT studies in Au-chemistry, see: (a) Nevado, C.; Echavarren, A. M. *Chem.—Eur. J.* **2005**, *11*, 3155. (b) Comas-Vives, A.; González-Arellano, C.; Corma, A.; Iglisias, M.; Sánchez, F.; Ujaque, G. *J. Am. Chem. Soc.* **2006**, *128*, 4756. (c) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cárdenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (d) Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434. (e) Straub, B. F. *Chem. Commun.* **2004**, 1726. (f) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (g) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (h) Shi, F.-Q.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503. (i) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993. (j) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

(14) B3LYP/6-31G*(LANL2DZ for Au) method was used for all the calculations, and solvation effect was calculated by CPCM model.

(15) See Supporting Information for details.
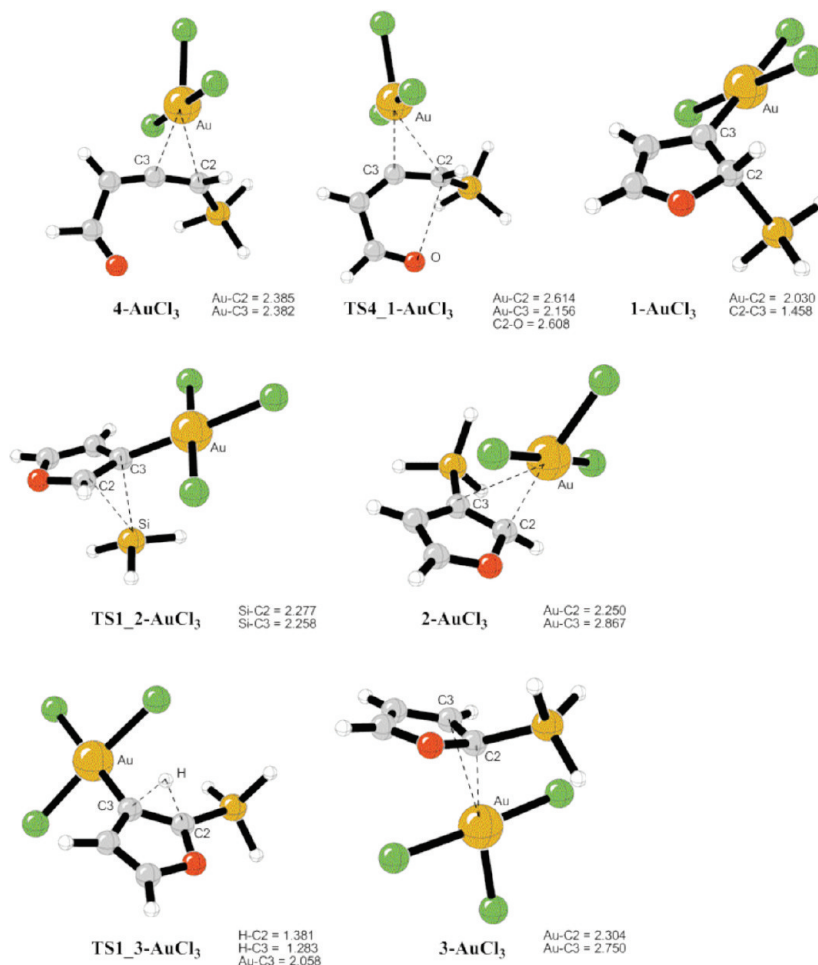
Figure 1. Geometries for the intermediates and transition states given in Scheme 4; selected distances are in angstroms.

in a highly selective manner into a product of the exclusive 1,2-Si over 1,2-H shift **2e** in both toluene or more polar nitromethane solvent (entry 5). Thus, the experimentally observed exclusive Si-migration is in excellent agreement with the computation-predicted higher 1,2-migratory aptitude of Si over H, Alk, and Ar groups. It is worth mentioning that allene **4e** was not stable in the presence of Ph₃PAuOTf complex when performing the reaction in toluene or 1,2-dichloroethane (DCE) solvent. In addition, similarly to AuCl₃, employment of Ph₃PAuSbF₆ catalyst provided exclusive formation of 1,2-Si migration product **2e** in DCE solvent, albeit notable amounts of the desilylated 3-methyl-2-phenylfuran were observed.

The computed energy surface for the Au-catalyzed cycloisomerization of allene **4** (AuCl₃) is provided in Scheme 4.[14] Hence, a highly exergonic (24.7 kcal/mol) cyclization of complex **4-AuCl₃** into the carbene **1-AuCl₃** required an activation energy of 2.6 kcal/mol only. A subsequent kinetically more favorable 1,2-Si migration (**TS1_2-AuCl₃**, activation energy of 11.1 kcal/mol) over the 1,2-H shift (**TS1_3-AuCl₃**, activation energy of 23.6 kcal/mol) led to the product complex **2-AuCl₃**. A requisite ligand exchange reaction proceeded as illustrated in Scheme 5 to complete the catalytic cycle, thus furnishing the final products and regenerating the active allene complex **4-AuCl₃**. The free energy values indicated that the formation of **2** and **3** via the reactions of allene **4** with **2-AuCl₃** and **3-AuCl₃** were both endergonic by 17.8 and 12.2 kcal/mol, respectively (Scheme 5). The optimized structures of key

stationary points along the reaction pathway for the cycloisomerization of allenes **4** are presented in Figure 1.

Counterion Effects on the Au(I)-Catalyzed 1,2-Si Migration in Alkynes. Next, we envisioned that easily accessible homopropargylic ketones **6** could also serve as precursors[7e,j] for the allene **5** toward the common Au-carbene intermediate **1** (eq 2). Alternatively, cyclization of **6** into furyl-Au species **7**,[2,16] followed by its β-protonation at the vinyl-gold moiety,[17] would generate the Au-carbene **1**. Based on the computation results, it was predicted that a subsequent facile 1,2-Si shift in **1** would furnish 3-silylfuran **2**. On the other hand, a counterion-assisted[8,18] 1,2-H shift in **1** or direct α-protonation of the vinyl-Au moiety

(16) (a) Sheng, H.; Lin, S.; Huang, Y. *Synthesis* **1987**, 1022. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (c) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (d) Wang, W.; Xu, B.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 1640.

(17) For examples of the proposed β-electrophilic attack on vinyl-gold, see: (a) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398. (b) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402.

(18) For review on counterion effects in Au-catalysis, see: (a) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. For selected examples, see: (b) Lemière, G.; Gandon, V.; Agenet, N.; Goddard, J.-P.; de Kozak, A.; Aubert, C.; Fensterbank, L.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 7596. (c) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (d) Gorin, D. G.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (e) Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.

in **7** might compete with the 1,2-Si migration, affording the 2-silylfurans **3** (eq 2).

(2)
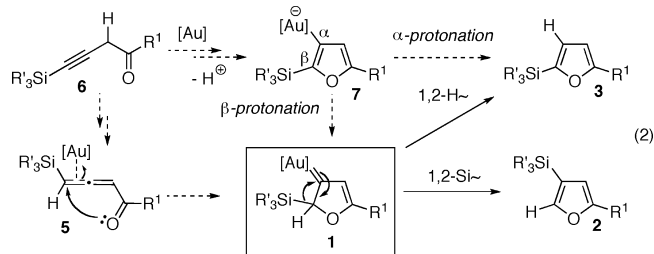
Thus, DFT calculations were performed to evaluate possible counterion effects[8,18] and establish overall reaction pathways for cycloisomerization of homopropargylic ketones **6** in the presence of electrophilic Ph₃PAuOTf and Ph₃PAuSbF₆ catalysts in DCE or toluene solvents, respectively. The potential energy surfaces for the predictions of the effects of TfO⁻ and SbF₆⁻ counterions are depicted in Schemes 6 and 7, respectively. In the case of Ph₃PAuOTf catalyst in DCE solution (Scheme 6), a highly exergonic (21.3 kcal/mol) direct 5-*endo-dig* cyclization of complex **T-C**

proceeded with the simultaneous abstraction of a propargylic H-atom by the TfO⁻ counterion to give the furyl-Au **T-IN1** and HOTf, requiring 10.9 kcal/mol of activation energy. Subsequent endergonic association of HOTf (15.1 kcal/mol) with the α-C-atom of the vinyl-Au moiety in **T-IN1** followed by ipso-protiodeauration of the **T-IN2** intermediate (**T-TS4**, activation energy of 4.9 kcal/mol) provided the product of the formal 1,2-H migration, **T-3**. On the other hand, the kinetically more favorable β-protonation at the vinyl-gold moiety in **T-IN2** (**T-TS2**, activation energy of 4.7 kcal/mol) over the ipso-protiodeauration (**T-TS4**, activation energy of 4.9 kcal/mol) should lead to a competing generation of the Au carbene **T-1**. Subsequent 1,2-Si migration from **T-1** required 10.7 kcal/mol of free energy (**T-TS3**) to give 1,2-Si migration product **T-2**. Alternatively, it was found that a TfO⁻ ligand dissociation reaction could occur efficiently from carbene **T-1** (6.0 kcal/mol) to give the more electrophilic carbene **C-1**, wherein a more kinetically facile 1,2-Si shift (**C-TS1**, activation energy of 10.1 kcal/mol) afforded 3-silylfuran **C-2**. In both carbene intermediates **T-1** and **C-1**, direct 1,2-H migrations were predicted to have higher activation energy barriers than those for direct 1,2-Si shifts

Scheme 6. DFT Predictions for the Ph₃PAuOTf-Catalyzed Reaction ([Au] = AuPH₃, L = OTf, R = H) in 1,2-Dichloroethane Solution[a]
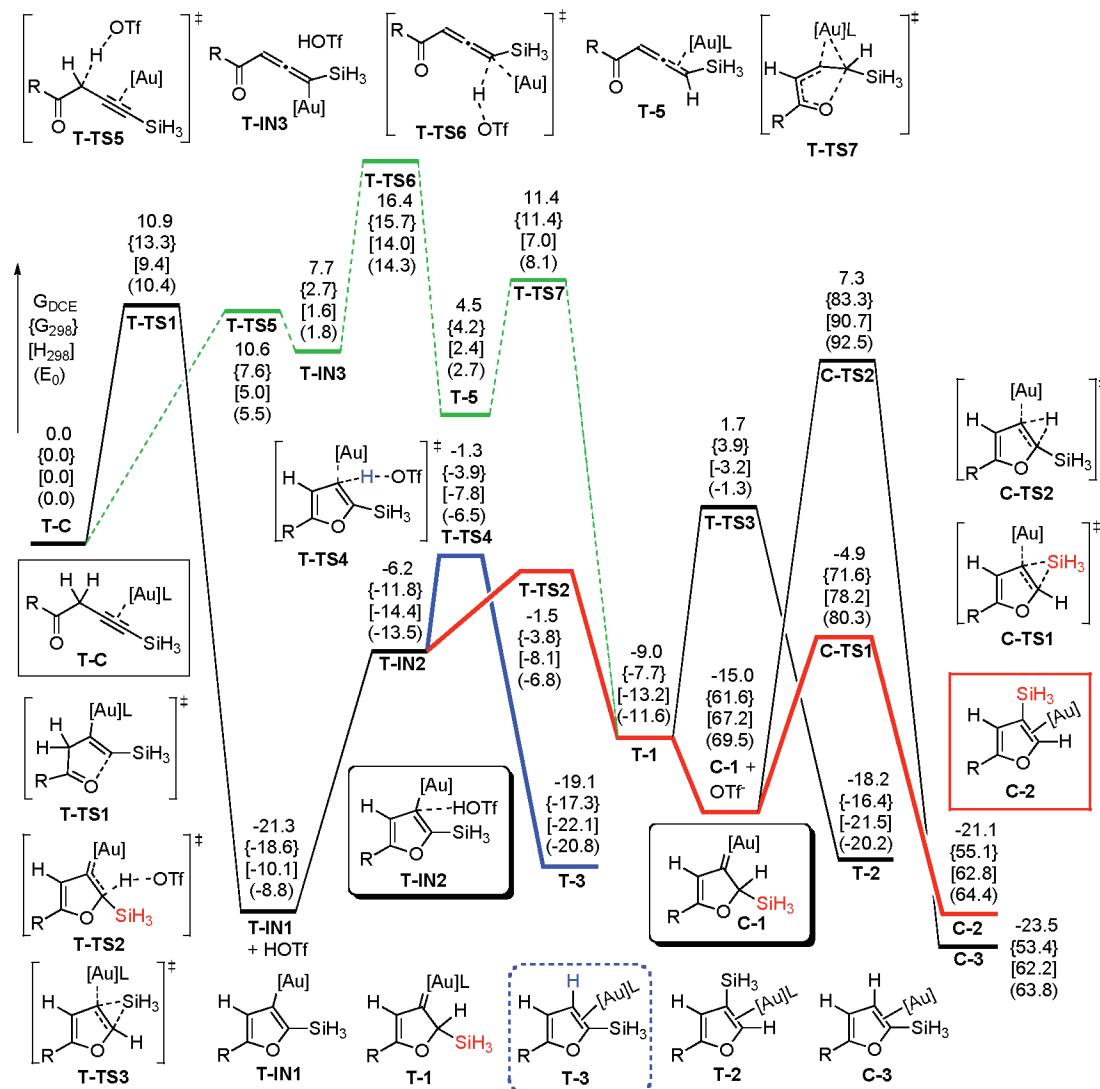
[a] Relative energies (ΔG_{DCE}, ΔG_{298}, ΔH_{298}, ΔE_0) are in kcal/mol.

Scheme 7. DFT Predictions for the Ph$_3$PAuSbF$_6$-Catalyzed Reaction ([Au] = AuPH$_3$, L = SbF$_6$, R = H) in 1,2-Dichloroethane and Toluene Solutions[a]
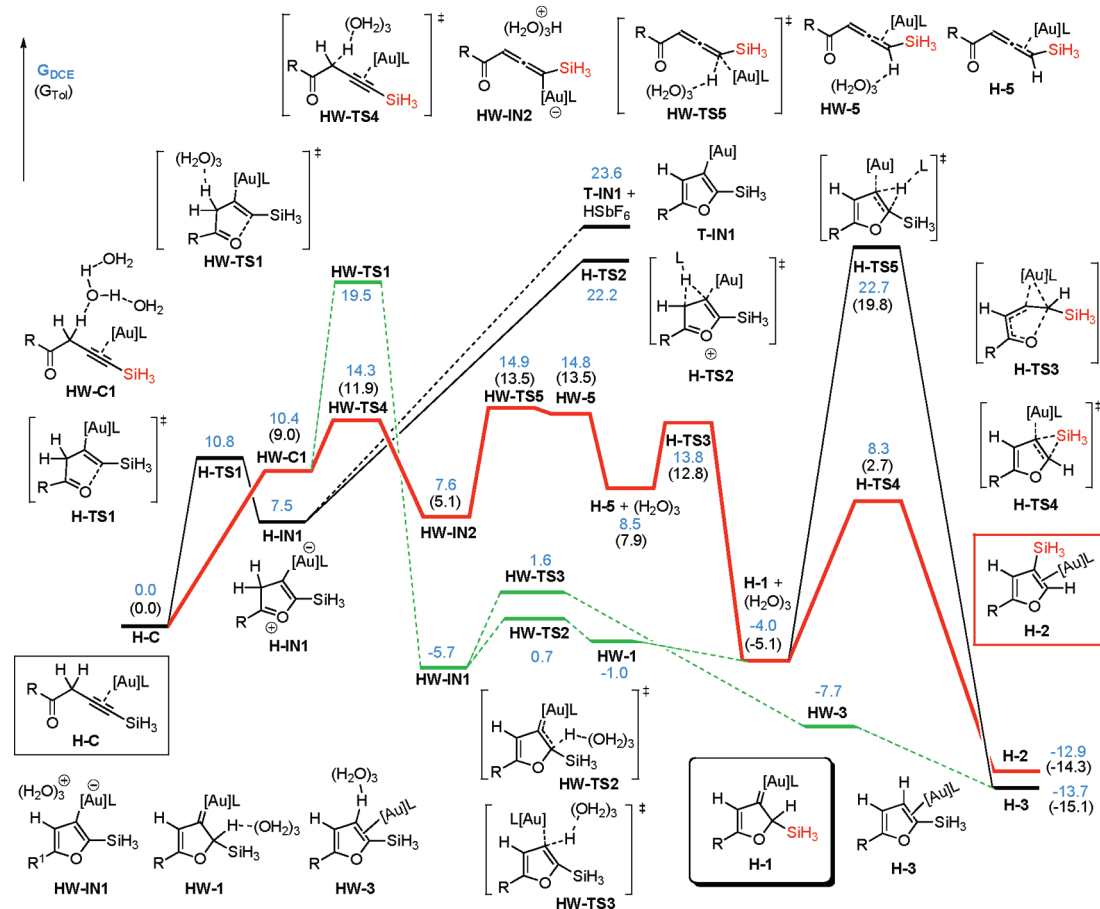
[a] Relative energies (ΔG_{DCE}, ΔG_{Tol}) are in kcal/mol.

(**C-TS2** versus **C-TS1**, activation free energy of 22.3 versus 10.1 kcal/mol, respectively). In addition, an alternative reaction pathway, involving generation of reactive allene-Au complex **T-5** via Ph$_3$PAuOTf-assisted propargyl-allenyl isomerization of **T-C** was found to be higher in energy (**T-TS6**, 16.4 kcal/mol) than the direct cyclization route in DCE. Thus, based on the predicted 0.2 kcal/mol difference between α- (**T-TS4**) and β- (**T-TS2**) protonation paths, competing formation of products **2** and **3** can be expected in the Ph$_3$PAuOTf-catalyzed cycloisomerization of homopropargylic ketone **6**. It should be mentioned that analogous high-energy profiles were later found for the propargyl-allenyl isomerization of **6** into **5** and for the direct 1,2-H shift in Au-carbene intermediates **1** in toluene solvent (*vide infra*). The optimized structures of key stationary points along the reaction pathway for the Ph$_3$PAuOTf-catalyzed cycloisomerization of alkynes **6** are presented in Figure 2.

In the case of Ph$_3$PAuSbF$_6$ catalyst (Scheme 7) in DCE solvent, direct 5-*endo-dig* cyclization of complex **H-C** afforded cyclic zwitter-ionic intermediate **H-IN1** via the **H-TS1** transition state, requiring an activation free energy of 10.8 kcal/mol. However, we were not able to locate the next transition state for the highly endergonic (23.6 kcal/mol) formation of the furyl-Au intermediate **T-IN1** and HSbF$_6$, probably due to the extreme acidity of HSbF$_6$. An alternative pathway, involving a [1,5]-hydride shift via **H-TS2**, was also found to be high in energy (activation free energy of 22.2 kcal/mol). We believe that the extremely high

acidity of HSbF$_6$ and very low nucleophilicity of its conjugate base SbF$_6^-$ complicate DFT simulation of the elementary reaction processes involving a counterion-assisted proton transfer step. This reasoning prompted us to perform DFT calculations of the Ph$_3$PAuSbF$_6$-catalyzed reaction in the presence of a three water molecule cluster (H$_2$O)$_3$, which could model reactivity of a counterion, which is more nucleophilic than the SbF$_6^-$ counterion and much milder than HSbF$_6$ acid in its monoprotonated form. Accordingly, initial coordination of the water cluster to homopropargylic ketone **H-C** provided **HW-C1** endergonically (free energy of 10.4 kcal/mol in DCE).[8,13h] Similarly to the TfO$^-$ counterion, the water cluster could also abstract the propargylic H-atom during a subsequent 5-*endo-dig* cyclization of **HW-C1** (**HW-TS1**, activation free energy of 9.1 kcal/mol) to give the furyl-Au **HW-IN1** and protonated water cluster.[19] However, a lower energy reaction path was found for the complex **HW-C1**. Thus, formation of the activated allene **H-5** from the latter occurred as a stepwise H-abstraction/donation process via transition states **HW-TS4** and **HW-TS5**, respectively. The first step of this process required an activation free energy of only 3.9 kcal/mol in DCE and 2.9 kcal/mol in toluene, respectively, leading to the intermediate **HW-IN2** exergonically. The second quite facile H-donation step to give **HW-5** occurred with an activation energy of 7.3 kcal/mol (DCE) or 8.4 kcal/mol (toluene) and was followed by exergonic decoordination of the water cluster to produce allene-Au complex **H-5**. A facile cyclization of the latter via **H-TS3**
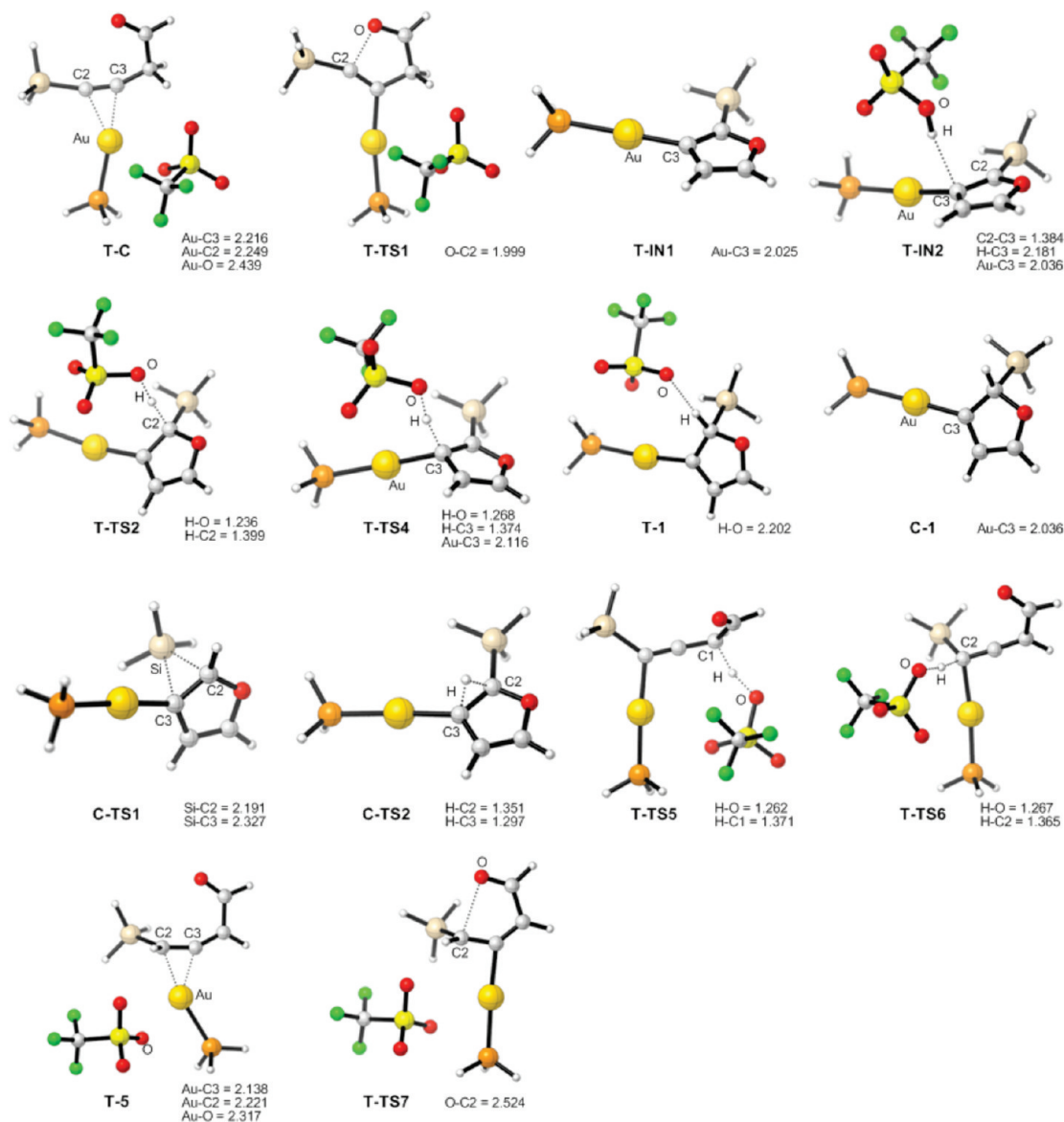
Figure 2. Geometries of the intermediates and transition states for the Ph₃PAuOTf-catalyzed reaction; selected distances are in angstroms.

provided Au-carbene **H-1** with an activation free energy of 5.3 kcal/mol in DCE and 4.9 kcal/mol in toluene. A subsequent 1,2-Si migration in **H-1** via **H-TS4** was strongly favored over the 1,2-H shift (**H-TS5**) in both DCE and toluene solvents, leading to the 1,2-Si migration product complex **H-2**. The optimized structures of key stationary points along the reaction pathway for the Ph₃PAuSbF₆-catalyzed cycloisomerization of alkynes **6** are presented in Figure 3.

To examine the above DFT-based prognosis, we investigated cycloisomerization of the homopropargylic ketones **6** in the presence of various Au catalysts (Table 2). It was found that the experimental results overall are in good agreement with the computational predictions.[14] Thus, the Au-catalyzed cycloisomerization of alkynes **6** in the presence of the non-nucleophilic SbF₆⁻ counterion in DCE gives exclusive formation of 1,2-Si migration products **2f**, **l**, and **k** (entries 1, 7, 11). As suggested by the DFT calculations, switching to Ph₃PAuOTf catalyst in DCE with a more nucleophilic counterion leads to a competing formation of 1,2-Si and 1,2-H migration products **2f** and **3f**, respectively, for the cycloisomerization of **6f** (entry 2). However,

the DFT predictions cannot explain a selective formation of the 1,2-Si migration product **2l** during the cycloisomerization of **6l** (entry 10). In addition, it was found that AuCl₃ could also catalyze cycloisomerization of alkynes **6**; however, the regioselectivity of this reaction toward the 1,2-Si migration product **2f** was poor in a variety of solvents (entries 4−6). Unfortunately, an analogous study on counterion effect in allenyl systems was not possible since allenes **4** were not stable in the presence of Ph₃PAuOTf and even less electrophilic Ph₃PAuOBz complexes.

Solvent Effects on the Au(I)-Catalyzed 1,2-Si Migration in Alkynes. Remarkably, it was found that the solvent effect could dominate over the counterion effect, as evidenced by a reverse regioselectivity observed in the Ph₃PAuOTf-catalyzed cycloisomerization of **6** (Table 2, entries 2 vs 3 and 9 vs 10).[20] Accordingly, when the reaction was conducted

---

(19) Simulation of a base in the Ph₃AuOTf-catalyzed transformation using water cluster demonstrated that the 5-*endo-dig* cyclization path has the lowest energy profile, similarly to that for TfO⁻-counterion base. See Supporting Information for details.

(20) For a single example of a solvent effect in the Au-catalyzed synthesis of pyrroles, see ref 7i.
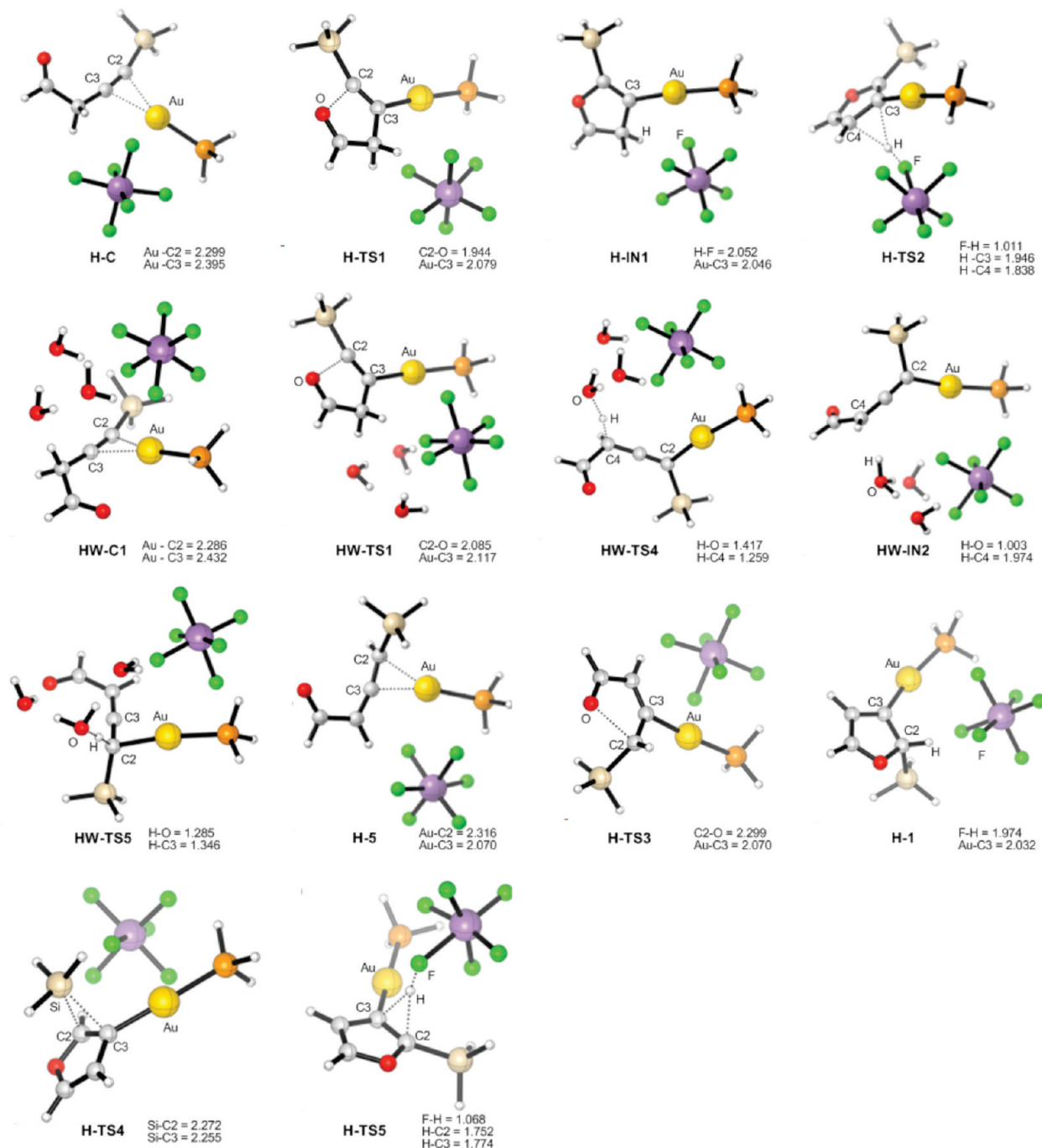
Figure 3. Geometries of the intermediates and transition states for the Ph₃PAuSbF₆-catalyzed reaction; selected distances are in angstroms.

in DCE solution, the preferred formation of 1,2-Si migration products was observed. However, when toluene was employed as a solvent, the 1,2-H migration products were the major ones. To shed light on these quite uncommon results,[20] DFT calculations for evaluation of the solvent effects on the 1,2-H and 1,2-Si migrations were performed. DFT predictions for the Ph₃PAuOTf-catalyzed reaction in DCE solvent were provided in Scheme 6. The results for toluene solvent are outlined in Scheme 8. According to the calculated potential energy surfaces, employment of toluene solvent leads to the intermediate **T-IN2** via 5-*endo-dig* cyclization of **T-C** with a reaction energy profile similar to that for DCE solvent. However, in the case of toluene solvent, there is no difference in activation energy barriers for α- (**T-TS4**) and β- (**T-TS4**)

protonation pathways of furyl-Au complex **T-IN2**. Most importantly, while solvents do not affect the relative barriers of the subsequent 1,2-H and 1,2-Si migrations from Au-carbene intermediates **T-1** or **C-1** much, they alter the stability of the dissociated noninteracting Au-carbene **C-1** and TfO⁻ anion relative to the associated Au-carbene complex **T-1**. For instance, when the reaction is conducted in toluene solution, which has a lower polarity than DCE, the stabilization effects of the solvent on the charged species **C-1** and TfO⁻ are limited (compare relative energies of **C-1** intermediates in Schemes 6 and 8). On the other hand, an alternative direct 1,2-Si migration from carbene **T-1** via **T-TS3** has an activation free energy barrier of 10.7 kcal/mol. Since complex **T-1** does not undergo dissociation of

Scheme 8. Solvation Effect of Toluene on the Ph₃PAuOTf-Catalyzed Reaction (R = H)ᵃ
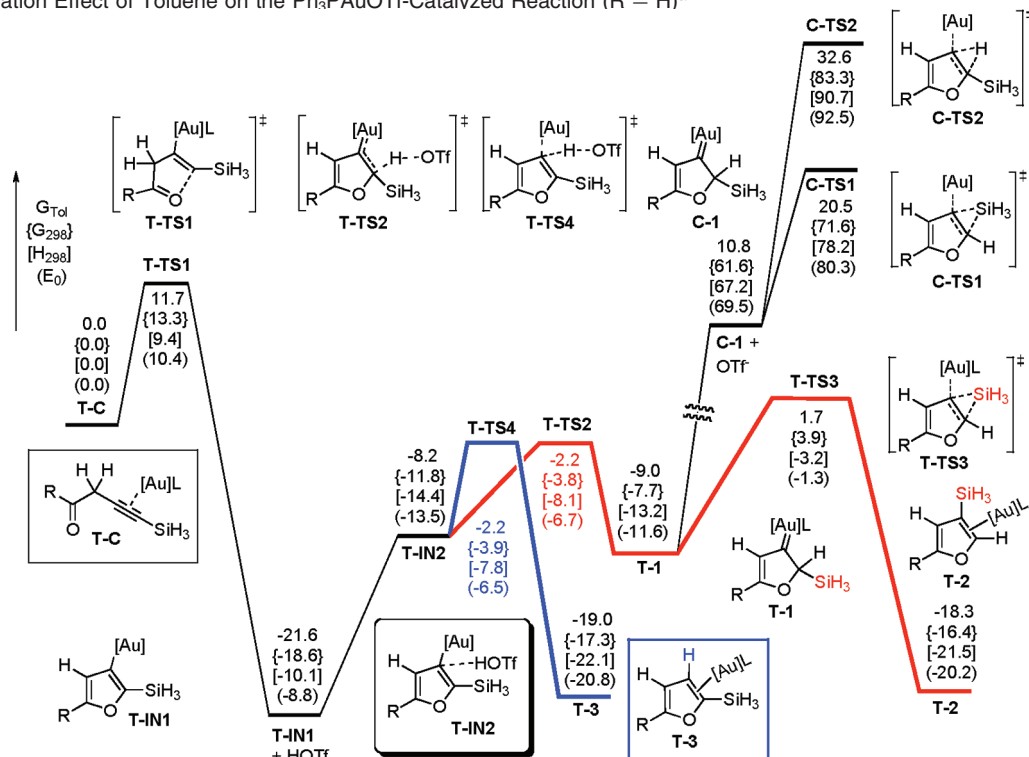
ᵃ Relative free energies in toluene (ΔG_{Tol}) are in kcal/mol.

the TfO⁻ ligand in toluene solution easily, its formation becomes reversible, forcing the reaction to proceed via the α-protonation route **T-IN2** − **T-TS4** − **T3**, which is 3.9 kcal/mol lower in activation free energy than the direct 1,2-Si shift in **T-1**. The DFT calculations suggest that the Ph₃PAuOTf-catalyzed cycloisomerization of **6** in toluene solvent should lead to the 1,2-H migration product **3**, thus supporting the experimentally observed reversed regioselectivity of the reaction (Table 2, entries 2 vs 3 and 9 vs 10). In contrast to the above case, no solvent effect was observed in the DFT-simulated Ph₃PAuSbF₆-catalyzed reactions (Scheme 7). Thus, formation of the allene-Au complex **H-5** and its cyclization into the Au-carbene **H-1** were found to be more efficient than other possible processes in both DCE and toluene solvents. In addition, energies of the direct or base/SbF₆⁻-assisted 1,2-H migrations were much higher than that of the 1,2-Si migration from **H-1**, regardless on the solvent (compare entries 7 and 8 in Table 2). Thus, the experimentally observed migratory preference (Table 2, entries 1, 7, 8, and 11) for the Ph₃PAuSbF₆-catalyzed reactions was in a good agreement with the performed DFT calculations. Finally, it is worth mentioning here that, in contrast to the cycloisomerization of alkynes **6**, employment of solvents more polar than toluene did not affect the AuCl₃-catalyzed cycloisomerization of allenyl ketone **4e** (Table 1, entry 5).

Synthesis of Furans via Au(I)-Catalyzed 1,2-Si Migration in Alkynes. Next, we investigated the scope of the above 1,2-Si migration cascade reaction of alkynes (Table 3). Thus, cycloisomerization of a variety of 4-silyl homopropargylic ketones **6**, possessing aryl (entries 1, 2), primary (entries 7−9), and tertiary (entry 6) alkyl groups, proceeded smoothly affording the C2-unsubstituted 3-silylfurans **2** as sole regioisomers in good to excellent yields (Table 3). It was found that alkynes bearing TMS (entries 1−7), TES (entry 8), and

Table 2. Optimization of the Au-Catalyzed Cycloisomerization of Homopropargyl Ketones **6**

Entry	R¹	Catalyst	Solvent (C, M)	2:3 Ratioᵃ
1	Ph (**6f**)	Ph₃PAuSbF₆	DCE (0.05)	100:0
2		Ph₃PAuOTf	DCE (0.05)	66:34
3		Ph₃PAuOTf	PhMe (0.1)	7:93
4		AuCl₃	PhMe (0.1)	60:40
5		AuCl₃	DCE (0.1)	72:28
6		AuCl₃	MeNO₂ (0.05)	84:16
7	n-C₈H₁₇ (**6l**)	Ph₃PAuSbF₆	DCE (0.05)	100:0
8		Ph₃PAuSbF₆	PhMe (0.05)	100:0
9		Ph₃PAuOTf	PhMe (0.1)	12:88
10		Ph₃PAuOTf	DCE (0.05)	98:2
11	t-Bu (**6k**)	Ph₃PAuSbF₆	DCE (0.05)	100:0
12		Ph₃PAuOTf	PhMe (0.1)	17:83

ᵃ H¹ NMR ratio of products for reactions performed on 0.5 mmol scale.

PhMe₂Si (entry 9) groups could be successfully employed in this transformation. In the case of cycloisomerization of substrates **6** bearing electron-deficient aryl substituents (entries 3−5), the 1,2-H shift competed with the 1,2-Si migration, which resulted in formation of isomeric silylfurans **2** and **3** with good to high degrees of regioselectivity favoring 3-silylfurans **2**. It was also demonstrated that a variety of functional groups such as methoxy (entry 2), bromo (entry 3), cyano (entry 4), and nitro (entry 5) could be tolerated under these reaction conditions.

Conclusion

In summary, we developed a regiodivergent Au-catalyzed cycloisomerization of allenyl and homopropargylic ketones into

Table 3. Au-Catalyzed Cycloisomerization of Homopropargyl Ketones **6**

Entry	Substrate	Product	2, %[a,b]
1			**2f**, 79
2			**2g**, 91
3			**2h**, 91[c]
4			**2i**, 48[d]
5			**2j**, 65[e]
6			**2k**, 71[f]
7			**2l**, 68
8			**2m**, 77
9			**2n**, 67

[a] Isolated yield of product for reactions performed on 0.5 mmol scale. [b] **2f** and **2l** contained 8 and 6% of the corresponding desilylated furan, respectively. [c] 14:1 ratio of **2h:3h**. [d] 10:1 ratio of **2i:3i**. [e] 8:1 ratio of **2j:3j**. [f] GC Yield, **2k** is a volatile compound.

2- and 3-silylfurans featuring 1,2-Si or 1,2-H migrations in a common Au-carbene intermediate. The present methodology constitutes a general and efficient route for the synthesis of 3-silylfurans, important synthons,[21] not easily available via the existing methodologies. Both experimental and computational results indicate that the 1,2-Si migration is kinetically more favored over the 1,2-shifts of H, alkyl, and aryl groups in the β-Si-substituted Au-carbenes. However, according to the experimental data obtained for the cycloisomerization of homopropargylic ketones, counterion and solvent effects may reverse this migratory preference. The DFT calculations provided a

rationale for this 1,2-migration regiodivergency. Accordingly, in the case of Au(I) catalyst possessing non-nucleophilic SbF_6^- counterion, DFT-simulated reaction affords 1,2-Si migration products exclusively via the initial propargyl-allenyl isomerization followed by cyclization into the Au-carbene intermediate regardless of the solvent employed in the reaction. However, in the case of the TfO^- counterion in nonpolar solvents, a pronounced counterion effect is observed. Thus, reaction occurs via the initial 5-*endo-dig* cyclization to give a cyclic furyl-Au intermediate followed by a subsequent ipso-protiodeauration, which is kinetically more favorable than the generation of the common Au-carbene intermediate and leads to the formation of formal 1,2-H migration products. In contrast, when polar

(21) For review on silylfurans, see: Keay, B. A. *Chem. Soc. Rev.* **1999**, *28*, 209.

solvent is employed, β-to-Au protonation of the furyl-Au species, leading to the Au-carbene intermediate, competes with the ipso-protiodeauration. Subsequent dissociation of the triflate ligand in the latter carbene in polar media due to efficient solvation facilitates formation of the 1,2-Si shift products. The above results of DFT calculations were validated by the experimental data. Finally, the present study highlights that DFT calculations could efficiently complement experimental results, providing guidance for design of new transformations and offering a better understanding of this chemistry.

Supporting Information Available: Computational and experimental details as well as full citation of computational methods. This material is available free of charge via the Internet at http://pubs.acs.org.

JA910290C