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Gold(I)-Catalyzed Intermolecular Oxyarylation of Alkynes: Unexpected Regiochemistry in the Alkylation of Arenes

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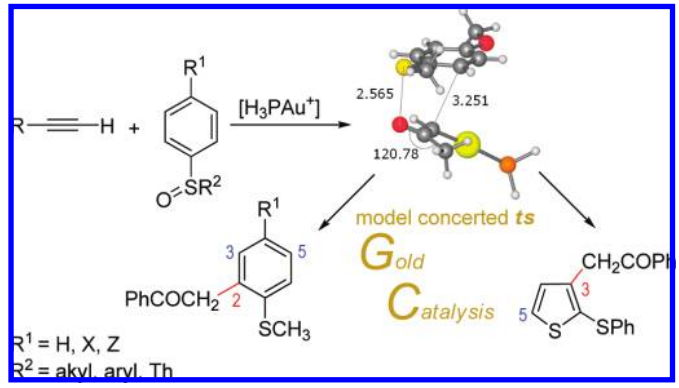
ABSTRACT



The reaction between acetylenes and sulfoxides, studied as a test case for gold-catalyzed intermolecular addition, provides the oxyarylation compounds 3 in good yields. Unpredictably, in all cases a single regioisomer arising from the electrophilic aromatic alkylation at the position adjacent to the sulfur atom is obtained instead of the expected Friedel−Crafts regioisomer. A new concerted mechanism based on DFT calculations is proposed to account for the products in this intermolecular gold(I)-catalyzed reaction.

Despite the fact that the gold-catalyzed *intramolecular* addition of nucleophiles to alkynes has become a mature field,[1] a number of mechanistic questions remain unresolved[2] since the mechanistic information inherent to the *intermolecular* reactions is scarce. Toste's[3a] and Zhang's groups[3b] reported the intramolecular gold-catalyzed addition of sulfoxides to alkynes which occurs through an α-carbonyl gold carbenoid intermediate.[3,4] We have developed the intermolecular addition of an array of sulfoxides **2a**−**e** to alkynes **1a**−**e** to test the regiochemistry of the reaction between the putative α-oxo gold-carbenoid and the nucleophile, an important but unapproachable aspect in the intramolecular reaction. A novel mechanistic proposal based on DFT calculations is presented to rationalize the results of this study.

The intermolecular reaction between acetylenes **1** and sulfoxides **2** catalyzed by 5% Ph_3PAuCl and 7.5% $AgSbF_6$ afforded compounds **3** in good to moderated yields (Table 1). No reaction took place with the internal alkynes PhCCMe and *i*-PrCCMe. Concerning the sulfoxide, the reaction went in a very good yield with the unsubstituted phenyl benzyl sulfoxide **2b** and in a moderate yield with the more electron-deficient sulfoxide **2c**.

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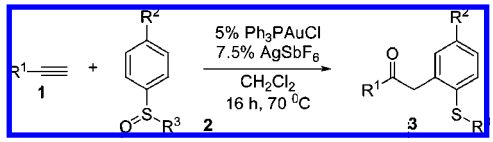
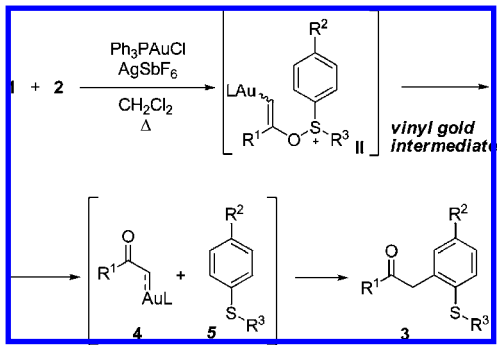
Table 1. Gold(I)-Catalyzed Intermolecular Nucleophilic Addition of Sulfoxides **2** to Alkynes **1**



1		2				
	R^1		R^2	R^3	**3**	yield (%)
1a	C_6H_5	**2a**	OCH_3	CH_3	**3aa**	87
1a	C_6H_5	**2b**	H	$CH_2C_6H_5$	**3ab**	83
1a	C_6H_5	**2c**	Br	CH_3	**3ac**	49
1b	*p*-ClC_6H_4	**2a**	OCH_3	CH_3	**3ba**	71
1c	*n*-C_4H_9	**2a**	OCH_3	CH_3	**3ca**	84
1d	$(CH_3)_3C$	**2a**	OCH_3	CH_3	**3da**	20
1e	CH_3CH_2O	**2a**	OCH_3	CH_3	**3ea**	50

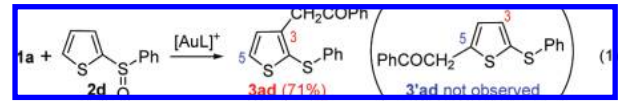
According to the α-carbonyl gold carbenoid mechanism proposed for the intramolecular version of the reaction,[3a] formation of derivatives **3** would take place as shown in Scheme 1. Thus, the initial nucleophilic addition of sulfoxide

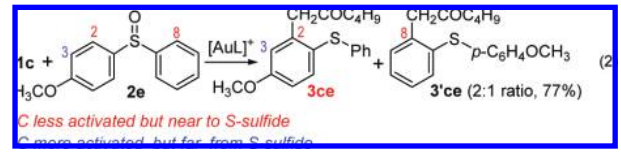
Scheme 1. Observed Single Isomer Formation from Alkenyl Gold Intermediate **II** According to the Mechanism Proposed for the Intramolecular Version of the Reaction



to the gold-activated alkyne would provide the vinyl gold intermediate **II** that would rearrange to give intermediates **4** and **5**. To complete the sequence, reaction between **4** and **5** would yield the α-arylketone via a Friedel−Crafts[5] type reaction. According to this proposal, we should expect the formation of a mixture of regioisomers. However,[6] in all cases of our reaction, only the regioisomer **3** corresponding to the alkylation at the position adjacent to the sulfur was obtained.[7] To verify the consistency of this behavior, asymmetric aryl−heteroaryl and diaryl sulfoxides **2d** and **2e** were tested as nucleophiles. In principle, in the case of sulfoxide **2d** (eq 1) the electrophilic aromatic substitution (EAS) should occur at the more activated C-5 position of thiophene.[8] However, unpredictably, alkylation took place exclusively at the C-3 position (product **3ad**, 71%).

The same trend was observed in the reaction of sulfoxide **2e**. In this case, a 2:1 mixture of the isomers **3ce** and **3′ce** was obtained in a 77% overall yield (eq 2). Once again, the alkylation took place exclusively at the positions adjacent to the thioaryl moiety, regardless of the presence of the directing −OMe group. The violation of the orientation rules of the EAS is a highly remarkable observation,[9] and it led us to consider that in this case additional factors are overriding the expected reactivity pattern.[10] To clarify these factors and to help explain the regiochemistry observed in products **3**, we carried out a detailed mechanistic study of the transformation.





Theoretical calculations[11] on a model reaction between propyne (**1f**) and sulfoxide **2a** catalyzed by [PH_3Au^+] were performed. The optimized geometries of the species involved in the catalytic cycle and the energy profile are shown in Figures 1 and 2 (for computational details, see Supporting

(1) For selected rewiews on gold catalysis, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (d) Krause, N.; Hoffmann-Röder, A. *Org. Biomol. Chem.* **2005**, *3*, 387. (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (f) Hashmi, A. S. K.; Hutchings, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (g) Zhang, L.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (h) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (i) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (j) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (k) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (l) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (m) Crone, B.; Kirsch, S. F. *Chem.−Eur. J.* **2008**, *14*, 3514. (n) Widenhoefer, R. A. *Chem.−Eur. J.* **2008**, *14*, 5382. (o) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (p) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (q) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (r) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (s) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766.

(2) (a) Fürstner, A.; Morency, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5030. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (c) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510, and refs cited therein.

(3) (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (b) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. For further intramolecular gold-catalyzed oxidation of alkynes: (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (d) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225. (e) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394.

(4) For analogous α-oxo gold carbenoids prepared from α-diazoesters, see: (a) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379.

(5) (a) Olah, G. *Friedel-Crafts and Related Reactions*; Wiley and sons: New York, 1964; Vols. 1 and *2*. (b) In the intramolecular reaction, the EAS pathway is supported by inverse secondary KIE consistent with literature examples for Friedel−Crafts alkylations.

(6) (a) Miles, J. A.; Beeny, M. T.; Ratts, K. W. *J. Org. Chem.* **1975**, *40*, 343. (b) Raw, B. C.; Ghosh, K.; Jana, V. *J. Org. Chem.* **1996**, *61*, 9546. For σ_p values of an ethoxy group (0.25) and thioethoxy (0.04), see: Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119.

(7) The substitution pattern observed seems to be fully independent of the nature of the substituent at the *para* position in the aromatic ring on putative intermediate **5** (see products **3aa**, **3ab**, and **3ac**).

(8) Clementi, S.; Marino, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, *2*, 71.

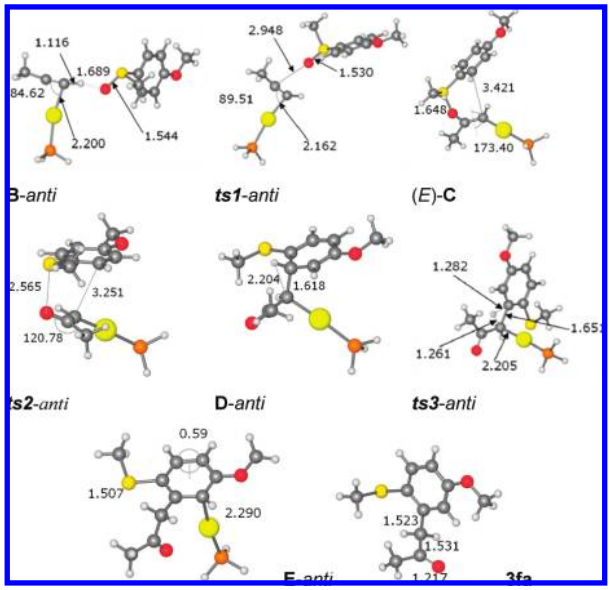


Figure 1. Optimized geometries of the species involved in the catalytic cycle for the *anti* addition.

Information). The reaction seems to proceed through an alkenyl gold intermediate **C** (Figure 3).

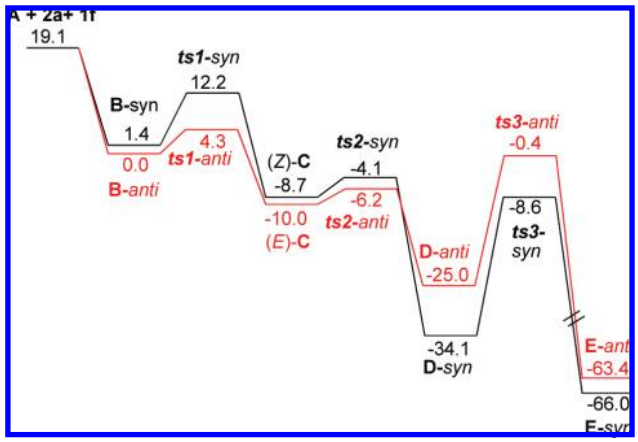


Figure 2. Energy reaction profile for a model reaction between propyne (**1f** and sulfoxide **2a** catalyzed by $[PH_3Au^+]$.

Remarkably, our efforts to identify the formation of α-oxo gold carbenoid **4** plus sulfide **5** (see Scheme 1) were unsuccessful; all attempts evolved to the intermediate **C** or gave rise to unreasonable structures. The analysis of the

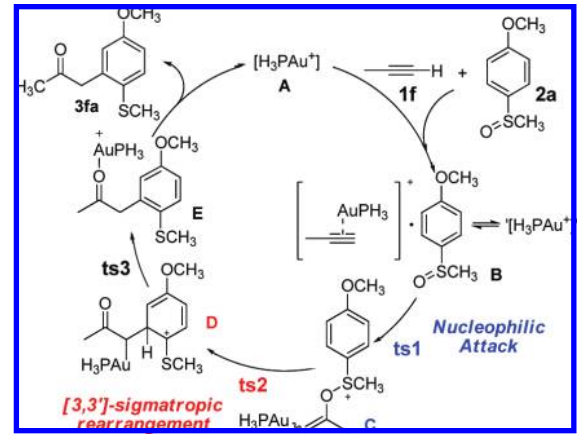


Figure 3. Proposed catalytic cycle based on DFT calculations for the modeled reaction.

potential energy surface showed an alternative pathway where the alkenyl gold intermediate evolves in two steps to the final product **3fa**. The reaction starts with the interaction of the metal catalyst $[PH_3Au^+]$, the sulfoxide **2a**, and the alkyne **1f** giving complexes **B** (**B**-*anti* and **B**-*syn*)[12] selected as our energy reference.

Subsequently, two alternative *anti* or *syn* reaction pathways were identified for the gold-promoted nucleophilic addition of **2a** to **1f**. The energy barriers associated with this step, giving rise to the isomeric alkenyl gold intermediates (*E*)-**C** and (*Z*)-**C**, are 4.3 and 10.8 kcal/mol for *ts***1**-*anti* and *ts***1**-*syn*, respectively, favoring the *anti* pathway by 6.5 kcal/mol. Then, **C** evolves to a new intermediate **D** via [3,3′]-sigmatropic rearrangement involving a six-membered cyclic transition state, *ts***2**, where the S−O α-bond is being broken concomitantly with the formation of a new C3−C3′ α-bond.[13] Similar relative energy barriers of 3.8 and 4.6 kcal/mol were found in this step starting from (*E*)-**C** or (*Z*)-**C**, respectively. The set of calculated C−Au bond lengths in the intermediate **C** and *ts***2** are, respectively, 2.048 and 2.017 Å for the (*E*)- versus 2.041 and 2.020 Å for the (*Z*)-

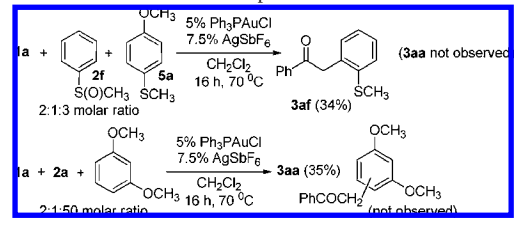
(9) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593.

(10) Since sometimes the metal can be replaced by a proton: (Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211)we heated a mixture of **1a** with sulfoxide **2a** and 5% of tungstic acid, obtaining a 32% yield of **3aa**.

(11) Calculations were performed with Gaussian03 using B3LYP functional. Energy values were obtained by single-point calculations using the 6-311++G(d,p) basis set for C, O, H, and S atoms and the SDD pseudopotential for Au. Solvent effects were included by means of a continuum method.

(12) The ^{31}P-NMR spectrum (CD_2Cl_2, 120 MHz, rt) of a 1:1.5:1:1 mixture of Ph_3PAuCl, $AgSbF_6$, **1a**, and **2a** reveals an equilibrium containing an small amount of free "$((Ph_3)_nPAu^+)$" (sharp singlet at δ 44.5 ppm) (see: Harrison, T. J.; Kozak, J. A.; Corbella-Pan, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525.) and gold complexes **B** containing **1a** and **2a** (broad singlet at δ 35.9 ppm). In the ^{1}H NMR spectrum, signals of free **1a** or **2a** are not observed. The δ 2.6 ppm ^{1}H NMR signal (CD_2Cl_2, 300 MHz, rt) of the S-Me group of **2a** is shifted to δ 3.0 ppm in a 1:1.5:1 mixture of Ph_3PAuCl, $AgSbF_6$, and **2a**. The S-Me δ value remains unaltered when 1 equiv of **1a** is added to the former mixture proving that **2a** remains complexed in the presence of **1a.**

(13) In a trapping experiment, all the attempts failed giving no incorporation of the external nucleophile.



stereoisomer falling in any case within the range of a Au−C single bond.[2a] Next, a 1,2-H shift amounts to the protodemetalation of gold and rearomatization of the π-system giving a new intermediate **E** in which any stereochemical information is lost. This latter step, irrelevant for the selection of the reaction path, occurs with energy barriers of 24.6 (*ts***3**-*anti*) and 25.5 (*ts***3**-*syn*) kcal/mol. Metal releasing of **3fa** from intermediate **E** closes the calculated catalytic cycle. The overall catalytic cycle is depicted in Figure 3.

In conclusion, we report herein an intermolecular gold-catalyzed addition of sulfoxides to alkynes which constitutes an easy approach to functionalize selectively the *ortho* position of an aryl sulfide giving a range of aryl ketones in very good yields. Theoretical calculations performed to explain the experimental findings have shown that this transformation represents a novel case of gold-catalyzed reaction proceeding through a concerted mechanism. The present work also highlights that the intermolecular oxyarylation of alkynes reveals mechanistic details associated to the regioselectivity which remained unnoticed in the study of the intramolecular version.

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Supporting Information Available: Experimental procedures, compound characterization data, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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