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The Gold(I)- and Silver(I)-Catalyzed Nicholas Reaction

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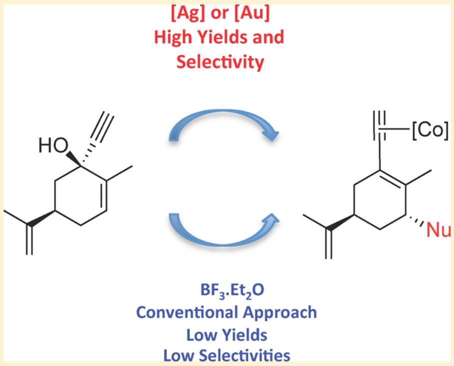
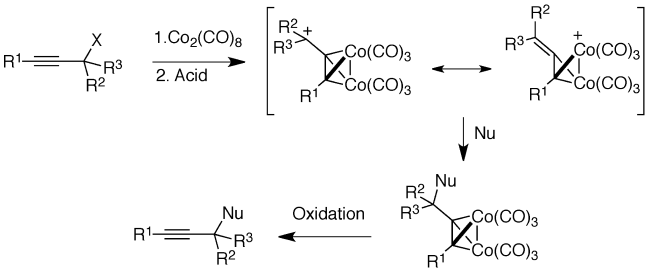
Supporting Information

ABSTRACT: The Au(I) and Ag(I) catalytic Nicholas type reaction has been developed for oxygen and carbon nucleophiles. This process occurs with high reaction yields and selectivity, avoiding the main shortcomings of the acid-promoted standard Nicholas reaction. A catalytic reaction pathway involving trimetallic complex intermediates is proposed.



The trapping of hexacarbonyldicobalt cluster stabilized propargylic cations by nucleophiles (the Nicholas reaction)[1] is a powerful and widely used tool in organic synthesis.[2] The strong stabilization provided by the Co cluster to the carbocation allows the nucleophile to react without the formation of allene byproducts. This carbocation is generated by acid treatment of a preformed propargyl–$Co_2(CO)_6$ complex. The acid used is usually a Lewis acid, but protic acids or clays have been successfully used in the carbocation generation (Scheme 1).[3] Modifications have been introduced to avoid the main shortcomings of the Nicholas reaction, namely the use of acid media and the instability of propargyl–$Co_2(CO)_6$ at temperatures above −40 °C.[4−6]

Scheme 1. The Nicholas Reaction



The ability of gold catalysts to promote S_N-like reactions using benzylic alcohols reported by Asensio and his co-workers[7] led us to investigate the possibility of using gold catalysts to promote the Nicholas reaction. It is known that gold is able to act as a Lewis acid[8] as well as an appealing catalyst in C–C and C–heteroatom bond forming reactions.[9] Succeeding in this endeavor would be of great interest, since the use of acid conditions in the Nicholas reaction would be precluded. This would be important, for example, to produce complex organic architectures using sensitive natural products.[10] Reported herein is the successful attempt to develop a catalytic (gold or silver),[11] room-temperature version of the Nicholas reaction. Yields and selectivities are considerably higher than those obtained under standard (Lewis acid promoted) conditions.

Addition of benzyl alcohol to complex **1** was tested with different gold catalysts, in the presence or in the absence of silver salts, and at two different temperatures, 0 °C and room temperature (Scheme 2). Table 1 compiles the results of the different experiments conducted. Three different products were isolated in variable amounts in these experiments. Compound **2** is the expected Nicholas-type product, since it is known that these reactions occurred with allylic rearrangement.[12] Compound **3** is the elimination product, and compound **4** arises

Scheme 2. Reaction of Compound 1 with Au and Ag Catalysts

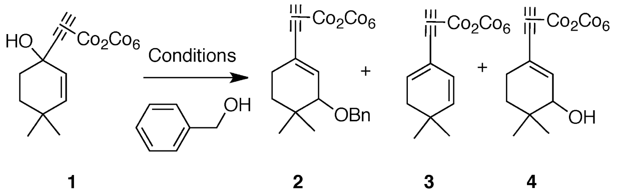


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Table 1. Study of the Reaction of Compound 1 with Different Gold and Silver Catalysts

					yield (%)[c]			
entry	Au cat. (amt (mol %))	cocat. (amt (mol %))	amt of BnOH (equiv)[a]	time (h)[b]	**2**	**3**	**4**	**1**
1	$AuCl_3$ (5)	none	1	48	0	0	0	100
2	$NaAuCl_4{\cdot}2H_2O$ (5)	none	1	48	0	0	0	100
3	Ph_3PAuCl (10)	none	3	48	0	2	20	66
4	Ph_3PAuCl (10)	AgOTf (15)	3	12	49	0	0	0
5	Ph_3PAuCl (10)	$AgSbF_6$ (15)	3	4	57	12	4	0
6	Ph_3PAuCl (5)	NaBArF (7.5)	3	3	55	9	3	0
7	none	$AgSbF_6$ (5)	3	4	77	0	6	0
8	none	$AgSbF_6$ (15)	3	4	68	0	4	0
9	none	$AgSbF_6$ (10)	3	2	68	0	12	0
10	none	AgOTf (15)	3	48	48	0	4	0
11	none	HOTf (15)	3	3	0	100	0	0
12	none	NaBArF	3	48	34	0	0	49

[a] The reactions in entries 3–6 and 9–13 were also carried out with 1 equiv of BnOH. Yields were considerably lower than those reported in the table using 3 equiv of BnOH. [b] The reactions were carried out at room temperature. [c] In isolated product.

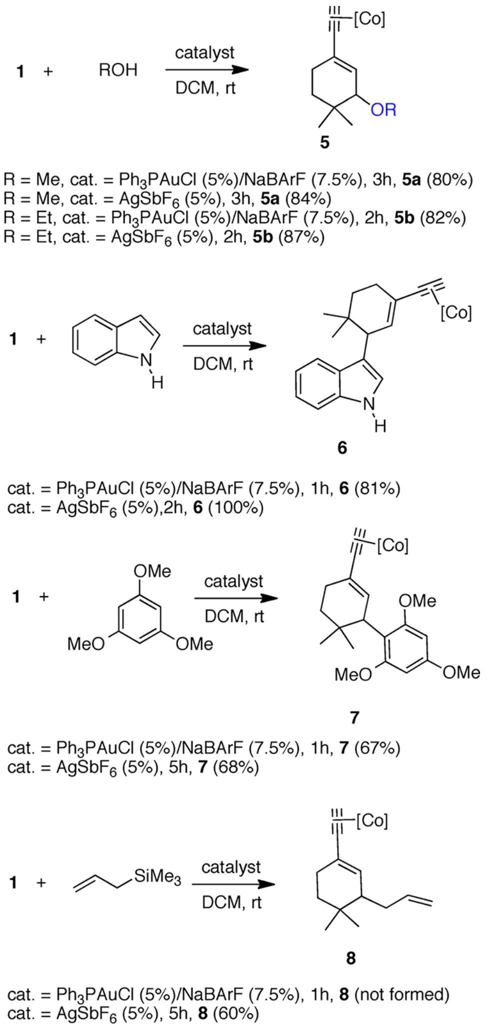
from the addition of water competing with the addition of the benzyl alcohol.[13] As depicted in Table 1, salts of Au(III) (entries 1 and 2) were ineffective in promoting the addition of benzylic alcohol. Complex **1** reacts with neutral Ph_3PAuCl (entry 3), but products derived from the incorporation of benzylic alcohol were not isolated. Instead, elimination product **3** (minor product) and rearranged alcohol **4** were isolated together with unreacted starting material. The use of Ph_3PAuCl in the presence of AgOTf as cocatalyst produces a substantial amount (49% isolated yield) of the desired product **2** (entry 4). Similarly, the mixture $Ph_3PAuCl/AgSbF_6$ (entry 5) affords compound **2** in shorter reaction times (4h vs 12 h) and in higher yields (57% vs 49%). To rule out Ag(I) as the species responsible for these reactions (see below), NaBArF was tested next as cocatalyst for the Au(I) complex (entry 6). Under these conditions, which allowed a decrease in the catalyst load, **2** was formed with times and yields comparable to those of the $AgSbF_6$ experiment.

Even more satisfactory was the reaction of complex **1** with $AgSbF_6$ *in the absence of Au catalysts* (entries 7–10). Now, compound **2** was obtained in 77% isolated yield (entry 7) using $AgSbF_6$ (5% mol). Increasing the load of $AgSbF_6$ does not improve either the yields or the reaction times (entries 8 and 9). The use of AgOTf produced compound **2** in lower yields (entry 10). Product **4**, derived from water incorporation, was obtained in variable amounts in these reactions.[13] To discard the possibility of traces of acid in the catalysts being responsible for the observed reactivity, the reaction was carried out with TfOH under standard conditions (entry 11). Elimination product **3** was obtained as the sole reaction product due to a fast E1 reaction, as expected.[12] This experiment rules out the possibility of traces of TfOH formed in situ from the AgOTf catalysts (in the presence or absence of [Au]) being the active catalysts of the Nicholas reaction. These results could be extrapolated to the hypothetical role of $HSbF_6$ as promoter of the reaction when $AgSbF_6$ salt is used.

Finally, the use of NaBArF in the absence of Au(I) was tested. Compound **2** was isolated in 34% yield after 48 h of reaction at room temperature (entry 12, Table 1), while the analogous reaction in the presence of Au(I) takes place in 3 h under the same conditions, leading to compound **2** isolated in 55% yield.

Having demonstrated the possibility of carrying out a Ag(I)- and Au(I)-catalyzed Nicholas reaction, other nucleophiles were studied next (Scheme 3). Both the mixture Ph_3PAuCl (5%)/NaBArF (7.5%) and $AgSbF_6$ (5%) produced excellent yields of the corresponding adducts **5a,b** with primary alcohols (MeOH and EtOH). Indole and 1,3,5-trimethoxybenzene were also

Scheme 3. Au and Ag Catalytic Nicholas Reaction with diverse O and C Nucleophiles



R = Me, cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 3h, **5a** (80%)
R = Me, cat. = $AgSbF_6$ (5%), 3h, **5a** (84%)
R = Et, cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 2h, **5b** (82%)
R = Et, cat. = $AgSbF_6$ (5%), 2h, **5b** (87%)

cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 1h, **6** (81%)
cat. = $AgSbF_6$ (5%),2h, **6** (100%)

cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 1h, **7** (67%)
cat. = $AgSbF_6$ (5%), 5h, **7** (68%)

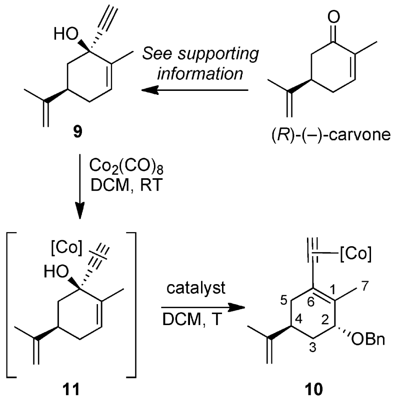
cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 1h, **8** (not formed)
cat. = $AgSbF_6$ (5%), 5h, **8** (60%)

reactive under these reaction conditions, providing good yields of compounds **6** (derived from the attack of the C3 indole carbon atom) and **7**, respectively. Minor amounts of elimination and water addition products (**3** and **4**) were obtained in some cases. The less reactive 1,2,3-trimethoxybenzene and 1,4-dimethoxybenzene were unreactive toward the addition. Elimination and water addition products in variable amounts were the reaction products, together with unreacted starting material. Although Ag(I)-catalyzed reactions were usually faster and cleaner, no significant differences in reactivity between both Au(I) and Ag(I) catalytic systems were found.

However, the differences in reactivity between Au(I) and Ag(I) were exacerbated when allyltrimethylsilane was reacted with substrate **1**. Now, while gold catalyst was inactive, a 60% yield of complex **8** was obtained when $AgSbF_6$ (5%) was the catalyst. While the Co-mediated Hosomi–Sakurai type cyclization is sensitive to the Lewis acid used,[14a] the intramolecular Hosomi–Sakurai reaction in propargylic alcohols has been carried out efficiently both in its Co-mediated version using TMSOTf as promotor and in the absence of Co using Au(I) catalysts.[14b] The dramatic difference in the Au(I) vs Ag(I) reactions observed for complex **8** pointed to a reaction mechanism different from the classical cationic pathway (see below).

To demonstrate that the mechanism of the catalyzed reaction differs from the classical cation formation, the stereochemistry of the catalyzed process in comparison with the standard Nicholas reaction was studied next using the alcohol **9** derived from (*R*)-(−)-carvone (Scheme 4).[15] Whereas benzyl ether **10** was obtained as a 60/40 diastereomeric mixture in the reaction of the preformed propargyl–$Co_2(CO)_6$ complex **11** with $BF_3{\cdot}Et_2O$ at −20 °C for 15 min (standard Nicholas process), a remarkable increase in the diastereoselection was observed in the reaction with $Ph_3PAuCl/NaBArF$ (80/20 mixture) or in the analogous transformation using $AgSbF_6$ (91/9 mixture).[16] The stereochemistry of the major reaction product **10** was spectroscopically determined as the trans diastereoisomer.[17]

Scheme 4. Reactions of Propargylic Alcohol 9 with Different Catalysts



cat. = Ph_3PAuCl (5%)/NaBArF (7.5%), 2h, rt, **10** (81%, 80:20)
cat. = $AgSbF_6$ (5%), 2h, rt, **10** (76%, 91:9)
cat. = $BF_3.Et_2O$, 15', -20ºC, **10** (47%, 60:40)

Results in Scheme 4 clearly demonstrate that the role of the Ag(I) or Au(I) in promoting the reaction is different from the conventional, Lewis acid promoted Nicholas reaction and that the role of these catalysts is not to act as mere cation-forming species. To shed some light on the above processes, aware that considerable additional experimentation and computation would be required before fully understanding the mechanism of this reaction, we first computed the geometry adopted by complex **11** upon coordination of $Co_2(CO)_8$ to the triple bond of compound **9** (DFT calculations were carried out at the PCM(CH_2Cl_2)-M06/def2-SVP//B3LYP/def2-SVP level; see the Supporting Information). Conformer I (Figure 1), where the isopropenyl substituent and the metal fragment are placed in pseudoequatorial and pseudoaxial positions, respectively, is 6.2 kcal/mol more stable than conformer II, having the isopropenyl group in a pseudoaxial position. This suggests that the reaction with the gold(I) catalyst occurs mainly from conformer I.

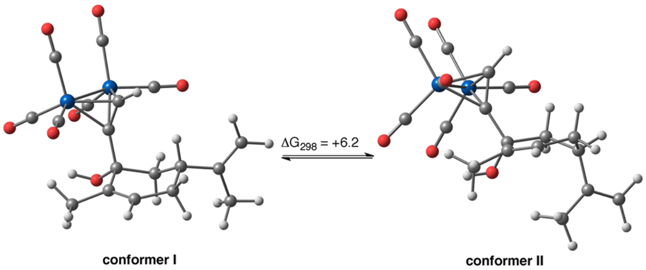


Figure 1. Possible conformations adopted by compound **11**. The relative free energy (ΔG_{298}, computed at 298 K at the PCM(CH_2Cl_2)-M06/def2-SVP//B3LYP/def2-SVP level) is given in kcal/mol.

Thus, the coordination of the gold(I) catalyst to the double bond of the more stable conformer I may lead to two possible trimetallic cationic species: i.e. compound **I-A**, where the gold(I) moiety and the dicobalt fragment are anti, and compound **I-B**, where both metallic moieties are syn (Figure 2a). The species **I-A** lies 2.2 kcal/mol below **I-B**. This is in part due to reduced steric hindrance in this complex and, additionally, to the presence of a stabilizing intramolecular

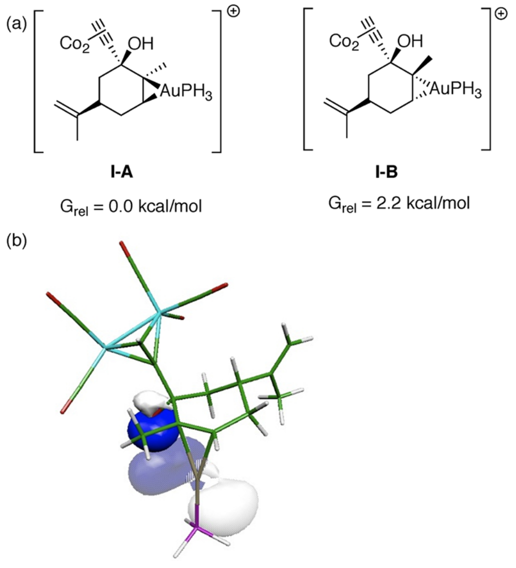
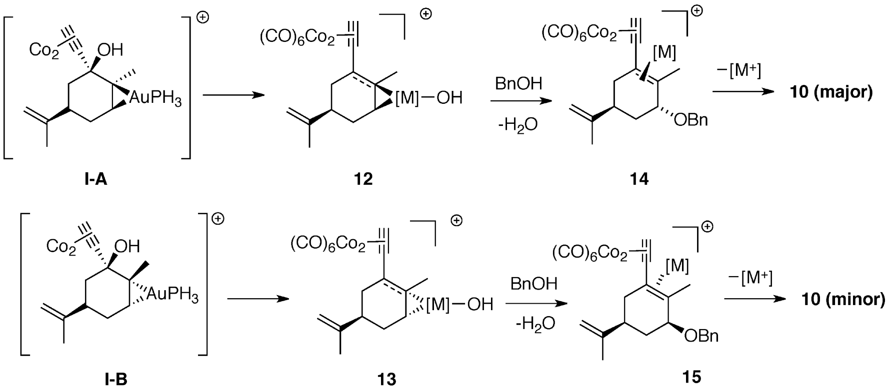


Figure 2. (a) Possible species formed upon coordination of gold(I) to conformer I. (b) NBO orbitals involved in the stabilization of species **I-A**. Relative free energies (ΔG_{298}, computed at 298 K at the PCM(CH_2Cl_2)-M06/def2-SVP//B3LYP/def2-SVP level) are given in kcal/mol.

Scheme 5. Proposed Reaction Pathway for the Catalyzed Au(I) Nicholas' Reaction



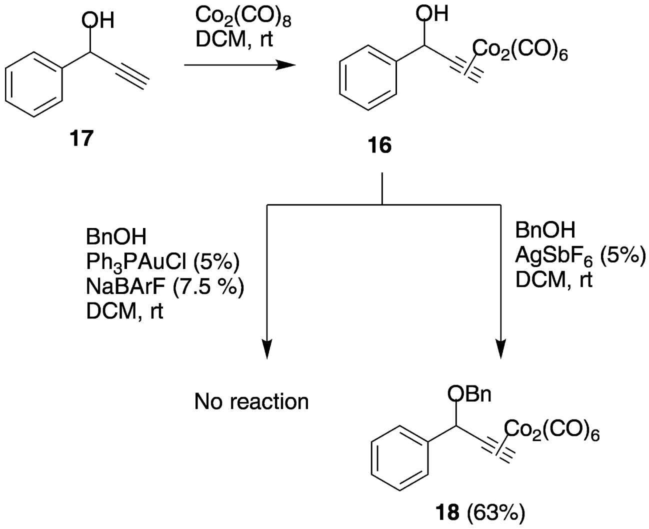
donor−acceptor interaction between the oxygen atom of the alcohol substituent and the gold(I) fragment (Au···O distance of 3.14 Å). Indeed, the second-order perturbation theory (SOPT) of the NBO method locates a two-electron stabilizing delocalization from the lone pair of this oxygen atom to an empty p atomic orbital of the transition metal with a significant associated SOPT energy of $\Delta E(2) = -5.2$ kcal/mol (Figure 2b). Evidently, the stereoselectivity of the reaction would be defined in the coordination step, which is in agreement with the observed experimental results.

From species **I-A** and **I-B** the OH group should migrate to Ag(I) or Au(I), forming new allyl−gold(I) or −silver(I) complexes.[18] Nucleophilic addition to carbon atom C3 would yield the new intermediates **14** and **15**, from which the demetalation occurs, giving the reaction products **10** and regenerating the catalyst. The moderate to strong increase in selectivity observed in the catalytic processes respect to the Lewis acid promoted "classical reaction" is congruent with the participation of polymetallic intermediates such as **12** and **13** (Scheme 5).

Finally, the necessity of the presence of a double bond allylic to the alcohol for the reaction above to occur was addressed. $Co_2(CO)_6$ complex **16**, lacking this structural feature, was prepared from 1-phenyl-2-propyn-1-ol (**17**) and reacted with benzylic alcohol in the presence of Ph_3PAuCl/NaBArF and $AgSbF_6$ (5% loads of catalyst related to the alcohol **16**). Interestingly, the complex **16** was inert toward the Au(I) catalyst, and it was recovered unaltered, while the expected benzyl alcohol adduct **18** was isolated in 63% yield in the presence of Ag(I) catalyst (Scheme 6).[19] Therefore, the catalytic processes developed through this communication do not require an allylic rearrangement to occur.

In summary, an Au(I) and Ag(I) catalytic Nicholas type reaction has been developed. The reaction proceeds smoothly at room temperature in good to excellent yields, minimizing the formation of elimination products. Oxygen and carbon nucleophiles can be used as well. Experimental data obtained from the reactions of chiral carvone derivatives toward Au(I), Ag(I), and $BF_3{\cdot}Et_2O$ pointed to the involvement of trimetallic cationic species in these processes, the coordination of the catalyst to the substrate determining the stereoselectivity. The findings that the Nicholas reaction can be catalyzed by Au(I) and Ag(I) catalysts and that these species participate in the process open the doors to the possibility of effecting asymmetric chiral catalysis. Efforts to fully develop this new methodology are now in progress.

Scheme 6. Ag(I)-Catalyzed Reaction of No-Conjugated Propargylic Alcohols



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving full experimental procedures, spectroscopic data, and ^1H, ^{13}C NMR spectra for all synthesized compounds mentioned in the text as well as additional NMR information for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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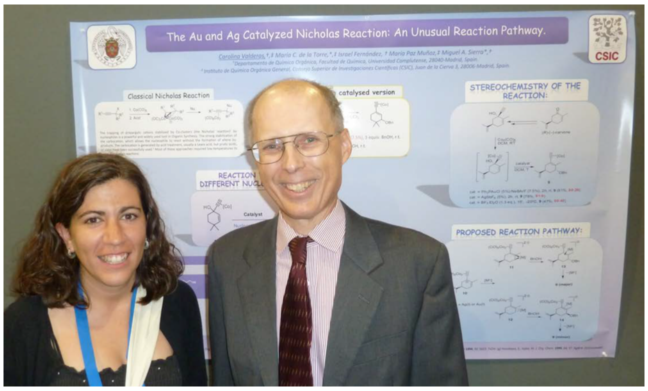
Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biography



This article is based upon a poster presented by Carolina Valderas (pictured here with Dr. John Gladysz) at the first Organometallics Symposium at the ACS meeting in Philadelphia, Pennsylvania on August 21, 2012.[20] Carolina Valderas received her B.S. at Universidad Autónoma de Madrid. During this time, she carried out an undergraduate collaboration at Radboud University of Nijmegen (Netherlands) in the group of Prof. Floris Rutjes. She got her M.S. in Organic Chemistry at Universidad Autónoma de Madrid. In 2010 she began her Ph.D. at Universidad Complutense de Madrid under the supervision of Prof. Miguel A. Sierra and Dr. M. C. de la Torre, the corresponding authors of this paper.

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(9) Among the profusion of reviews devoted to the use of gold catalysts in organic synthesis, see the pertinent reviews in the *Chem. Rev.* thematic issue: *Chem. Rev.* **2008**, *108*.

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(11) The use of stoichiometric amounts of Ag(I) salts to promote the Nicholas reaction from propargyl chlorides has been reported. See the following. (a) $AgBF_4$: Vizniowski, G. S.; Green, J. R.; Breen, T. L.; Dalacu, A. V. *J. Org. Chem.* **1995**, *60*, 7496. (b) $AgSbF_6$: Tumanov, V. V.; Zatonsky, G. V.; Smit, W. A. *Tetrahedron* **2010**, *66*, 2156.

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(13) Alternatively, formation of compound **4** may occur through a metal-assisted HO-intramolecular process analogous to those reported, among others, for gold-/silver-catalyzed reactions of 3-silyloxy-1,4-enynes with alcohols[13a] or Baylis–Hillman acetates into 2-(acetoxymethyl)alk-2-enoates.[13b] See: (a) Haug, T. T.; Harschneck, T.; Duschek, A.; Lee, C.-U.; Binder, J. T.; Menz, H.; Kirsch, S. F. *J. Organomet. Chem.* **2009**, *694*, 510. (b) Liu, Y.; Mao, D.; Qian, J.; Lou, S.; Xu, Z.; Zhang, Y. *Synthesis* **2009**, 1170.

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(15) The stereochemistry at the formed tertiary carbinol center of alkyne **9** was established by comparison of the ^{13}C NMR data of the terpenic domain with those of related derivatives; see: Zhao, L.; Burnell, D. L. *Tetrahedron Lett.* **2006**, *47*, 3291.

(16) It is known that the Nicholas reaction may be reversible under "conventional" Lewis acid conditions. See: (a) Kihara, N.; Kidoba, K. *Org. Lett.* **2009**, *11*, 1313. (b) Asenjo, M.; de la Torre, M. C.; Ramírez-López, P.; Sierra, M. A. To be submitted for publication. Therefore, control experiments to discard the possibility that the diasteroselectivity obtained in reaction **11** with Au(I) or Ag(I) was the result of thermodynamic control were carried out. Thus, 68 mg (0.12 mmol) of a 60/40 mixture of diasteromers of adduct **10** was reacted with 4.2 mg (0.012 mmol, 10%) of $AgSbF_6$ in 2 mL of DCM at room temperature . After 2 h the crude reaction product was analyzed by ^1H NMR. Appreciable decomposition of the starting material was observed together with unreacted **10**. Integration of the signals corresponding to the terminal alkyne hydrogens show that the initial ratio of diasteromers remained unaltered. A second experiment was carried out using 21 mg (0.038 mmol) of a 60/40 mixture of diasteromers of adduct **10** and 0.6 mg (0.0019 mmol, 5%) of $AgSbF_6$ in 1 mL of DCM at room temperature. The reaction mixture was kept at room temperature for 48 h. Compound **10** disappeared, forming a complex reaction mixture lacking any complexed alkyne moiety (^1H NMR). We can conclude safely that, at least under the conditions tested, the intercoversion between diastereomers of compound **10** does not happen.

(17) *Assignment of the absolute configuration of carbon C-2 in compound* **10**. The stereochemistry of the new chiral center C-2 was established on spectroscopic grounds; specifically, it was deduced from the value of the coupling constants of the hydrogens at carbon C-3. First, the signals for both protons were identify by NOE experiments as follows. Irradiation of the broad singlet at 3.85 ppm, attributed to H-2, produced an increase in the signals at 0.87 ppm, assigned to the methyl group C-7, at 4.68 and 4.48 ppm (AB system), assigned to the hydrogens of the methylene group of the benzyloxy substituent at carbon C-2, and at 1.44 and 2.17 ppm. Both signals count for one proton each, and they are attached to the same carbon, which resonates at 35.6 ppm. Therefore, signals at 1.44 and 2.17 ppm must be attributed to methylene at carbon C-3. The signal at 1.44 ppm is a triplet of doublets showing two coupling constants of 13.7 Hz. One of them is due to geminal coupling, while the other one must be due to a trans-diaxial coupling with the hydrogen H-4α axially oriented. Accordingly, since hydrogen H-2 is devoid of a large coupling

constant, it must be β-equatorially oriented and hence the absolute configuration at the new chiral carbon C-2 must be *R*.

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(19) This difference in reactivity between Au(I) and Ag(I) catalysts is appealing, especially taking into account that the Au(I)- and Au(III)-catalyzed propargylic substitution by nucleophiles of uncomplexed alcohols structurally related to **16** is known to produce the corresponding adducts in fair (Au(I)) to good yields (Au(III)). See: (a) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180. (b) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J. M. *Tetrahedron* **2009**, *65*, 1758.

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