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Unveiling the Reactivity of Propargylic Hydroperoxides under Gold Catalysis

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Abstract: Controlled gold-catalyzed reactions of primary and secondary propargylic hydroperoxides with a variety of nucleophiles including alcohols, phenols, 2-hydroxynaphthalene-1,4-dione, and indoles allow the direct and efficient synthesis of β-functionalized ketones. Besides, the utility of some of the resulting products for the selective preparation of fused polycycles has been demonstrated. In addition, density functional theory (DFT) calculations and ^{18}O-labeling experiments were performed to obtain an insight into various aspects of the controlled reactivity of propargylic hydroperoxides with external nucleophiles under gold catalysis.

INTRODUCTION

The last decade has witnessed dramatic growth in the number of reactions catalyzed by gold complexes because of their powerful soft Lewis acidic nature.[1] In particular, activation of alkynes toward attacks by oxygen nucleophiles such as carbonyls, carboxylic acids, and alcohols, is an important C–O bond-forming reaction.[2] Although many efforts have been made in these fields and

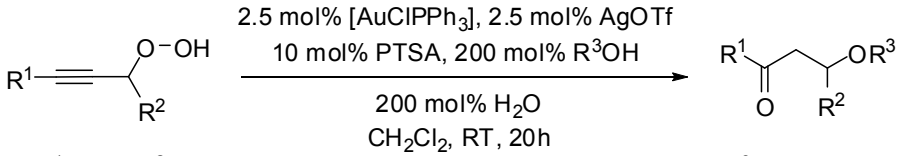
despite that alkylhydroperoxides are important reactants in several processes,[3] metal-catalyzed reactions of alkynes bearing a hydroperoxide moiety have remained unexplored. It should be mentioned that recently, even the formation of hydroperoxides by a one-pot sequence of gold-catalyzed isomerization/autoxidation has been described, these peroxides survived the presence of the gold catalysts.[4] Encouraged by our recent results in catalytic processes,[5] we decide to analyze the possibility of performing metal-catalyzed reactions to unravel the reactivity of propargylic hydroperoxides. Moreover, the mechanism of the reactions has additionally been investigated by a theoretical study.

RESULTS AND DISCUSSION

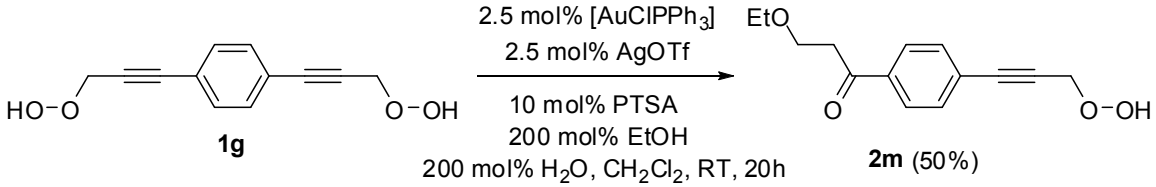
Propargylic hydroperoxides **1a–h** required for our study were easily prepared from the corresponding propargylic bromides in one-pot procedure (see Supporting Information for details). To explore the reactivity of alkynes **1** towards metal catalysis we selected hydroperoxide **1a** as a model substrate. $PdCl_2$, $AuCl_3$, AuCl, and $PtCl_2$, either failed to catalyze the reaction or gave a complex reaction mixture. Gratifyingly, after considerable experimentation, it was found that using a catalyst system consisting of [Au(OTf)PPh_3] (2.5 mol%), generated in situ from Au$ClPPh_3$ and AgOTf,[6] and *p*-toluenesulfonic acid (PTSA) (10 mol%) in the presence of ethanol (200 mol%) in dichloromethane, the reaction proceeded cleanly and afforded β-alkoxy ketone **2a** in 46% yield (Scheme 1). On the basis of the structure of **2a**, we believed that ambient H_2O in the reaction system was involved in this Au(I)-catalyzed reaction. The addition of 2.0 equivalent of H_2O raised the yield of **2a** up to 66% (Scheme 1). In order to show the beneficial use of water, we performed the gold-catalyzed reaction of hydroperoxide **1a** with ethanol under otherwise identical conditions but working under anhydrous conditions and replacing PTSA·H_2O by methanesulfonic acid. The dramatic decrease of yield in the formation of β-alkoxy ketone **2a**, did clearly establish the essential role of water for this transformation. Change on the nature of the counterion has little effect in the reaction, because alternate counterions ($AgSbF_6$, $AgBF_4$) showed a minimal effect to improve the yield of the product. Using [AuClIPr] or $Ph_3PAuNTf_2$ as the gold catalysts did not improve the

reaction outcome. The comparative studies of β-alkoxy ketone formation without addition of PTSA demonstrated that the presence of the Brønsted acid gives higher yields, acting the acid additive as a beneficial collaborator.[7] Optimization of solvent revealed that chlorinated solvents were superior to acetonitrile or aromatic solvents. No advantage accrues from changing the dichloromethane for ethanol as solvent. Under the optimized reaction conditions, we investigated the generality of the gold-catalyzed transformation of differently substituted propargylic hydroperoxides **1b–g**. As shown in Scheme 1, the above process in a one-pot operation from readily available alkynyl hydroperoxides and alcohols (methanol, ethanol, ethylene glycol) serves as a general approach to β-alkoxy ketones **2b–l**.[8] Interestingly, secondary alkynyl hydroperoxide **1f** also undergoes this interesting transformation to give in an efficient manner β-alkoxy ketones **2k** and **2l**. The selective transformation of diols bearing similar hydroxyl groups is one of the significant challenges in organic synthesis.[9] Interestingly, the mildness of the method allows the control of both the mono and the double reaction of bis(hydroperoxide) **1g** (Scheme 1).

Scheme 1. Controlled gold-catalyzed reaction of propargylic hydroperoxides with alcohols.

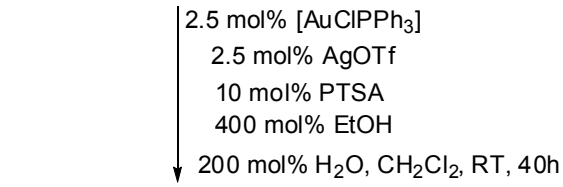


1a R^1 = Ph, R^2 = H — **2a** R^3 = Et (66%)
1a R^1 = Ph, R^2 = H — **2b** R^3 = Me (59%)
1b R^1 = 4-BrC_6H_4, R^2 = H — **2c** R^3 = Et (73%)
1b R^1 = 4-BrC_6H_4, R^2 = H — **2d** R^3 = Me (75%)
1c R^1 = 4-$MeOC_6H_4$, R^2 = H — **2e** R^3 = Et (67%)
1c R^1 = 4-$MeOC_6H_4$, R^2 = H — **2f** R^3 = Me (80%)
1c R^1 = 4-$MeOC_6H_4$, R^2 = H — **2g** R^3 = $(CH_2)_2OH$ (72%)
1d R^1 = 2-Thiophenyl, R^2 = H — **2h** R^3 = Et (62%)
1d R^1 = 2-Thiophenyl, R^2 = H — **2i** R^3 = Me (72%)
1e R^1 = CH_2OBn, R^2 = H — **2j** R^3 = Et (57%)
1f R^1 = Ph, R^2 = Me — **2k** R^3 = Et (70%)
1f R^1 = Ph, R^2 = Me — **2l** R^3 = Me (75%)



1g

2m (50%)

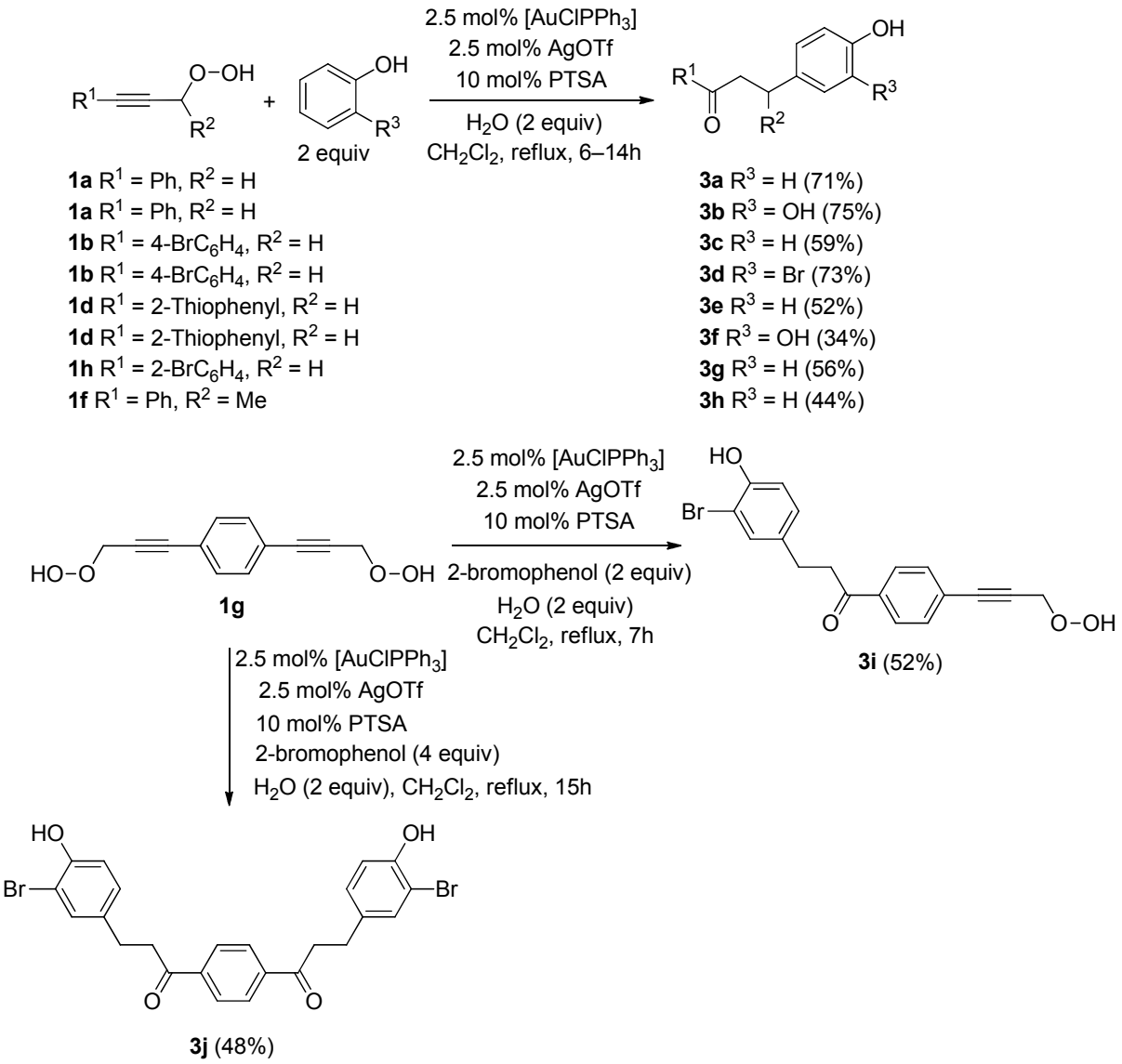


2n (47%)

When we investigated the reactivity of propargylic hydroperoxides **1** with phenols at room temperature the starting materials were recovered. Only after heating at reflux temperature, the gold-catalyzed reactions evolved. Surprisingly, the use of substituted phenols including catechol did not result in the formation of the corresponding phenoxy ketones; arylketones **3a–h** were obtained instead as the result of a hydroarylation reaction (Scheme 2).[10] 1,4-Type Friedel-Crafts reactions of phenols remain underdeveloped owing to problems rooted in reaction selectivities (chemo- and regio-) and reactivities.[11] Fortunately, compounds **3** were exclusively isolated as the

para-substituted phenol regioisomers. Besides, the gold(I)-catalyzed selective monoarylation of bis(hydroperoxide) **1g** as well as the double hydroarylation reaction were successfully developed (Scheme 2).

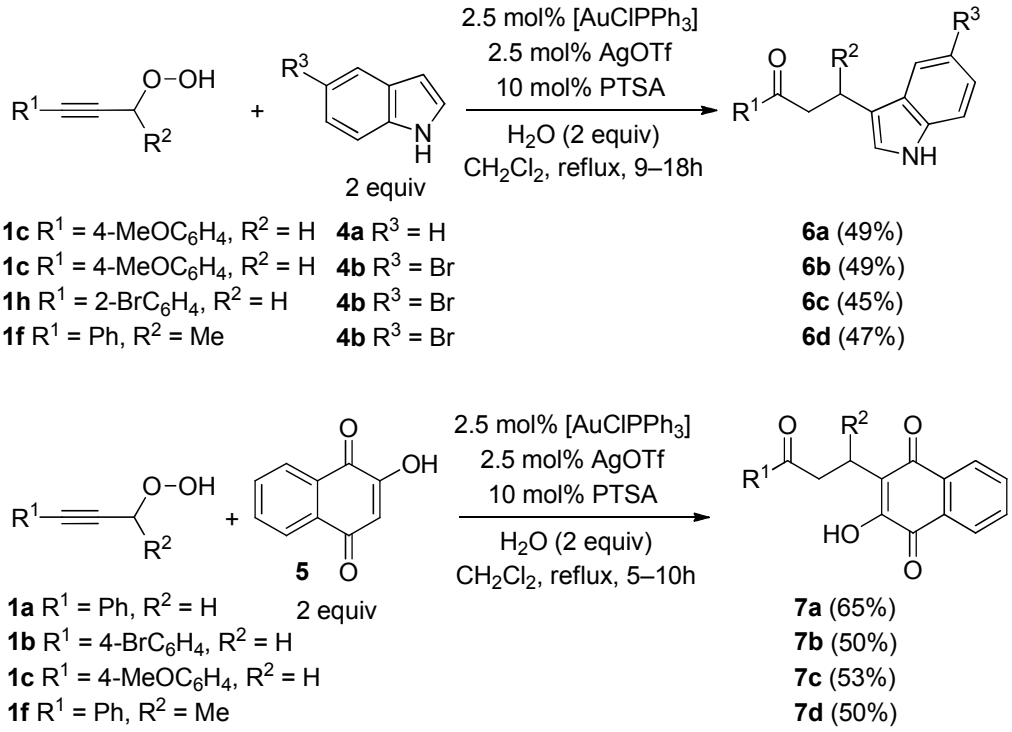
Scheme 2. Controlled gold-catalyzed reaction of propargylic hydroperoxides with phenols.



To investigate the scope of external carbon nucleophiles, we focused on two different nuclei, **4** and **5**, which are envisioned to deliver quinone and indole[12] derivatives bearing a skeleton of potential biological interest. It turned out that indole and 5-bromo-1*H*-indole are suitable external nucleophiles for the reaction with primary and secondary propargylic hydroperoxides **1**. Worthy of note, despite that C–C bond formation through C–H functionalization of quinones

remains a challenge due to their unique electronic properties and their ability to coordinate with metals,[13] our conditions were also effective for the direct C–coupling of hydroperoxides **1** with the electron-deficient cyclic olefin 2-hydroxynaphthalene-1,4-dione. Both types of substrates either indole or naphthoquinone provided in a totally selective fashion the desired 3-(1*H*-indol-3-yl)-1-arylpropan-1-ones **6a–d** and 2-hydroxy-3-(3-oxo-3-arylpropyl)naphthalene-1,4-diones **7a–d** in synthetically useful yields (Scheme 3).

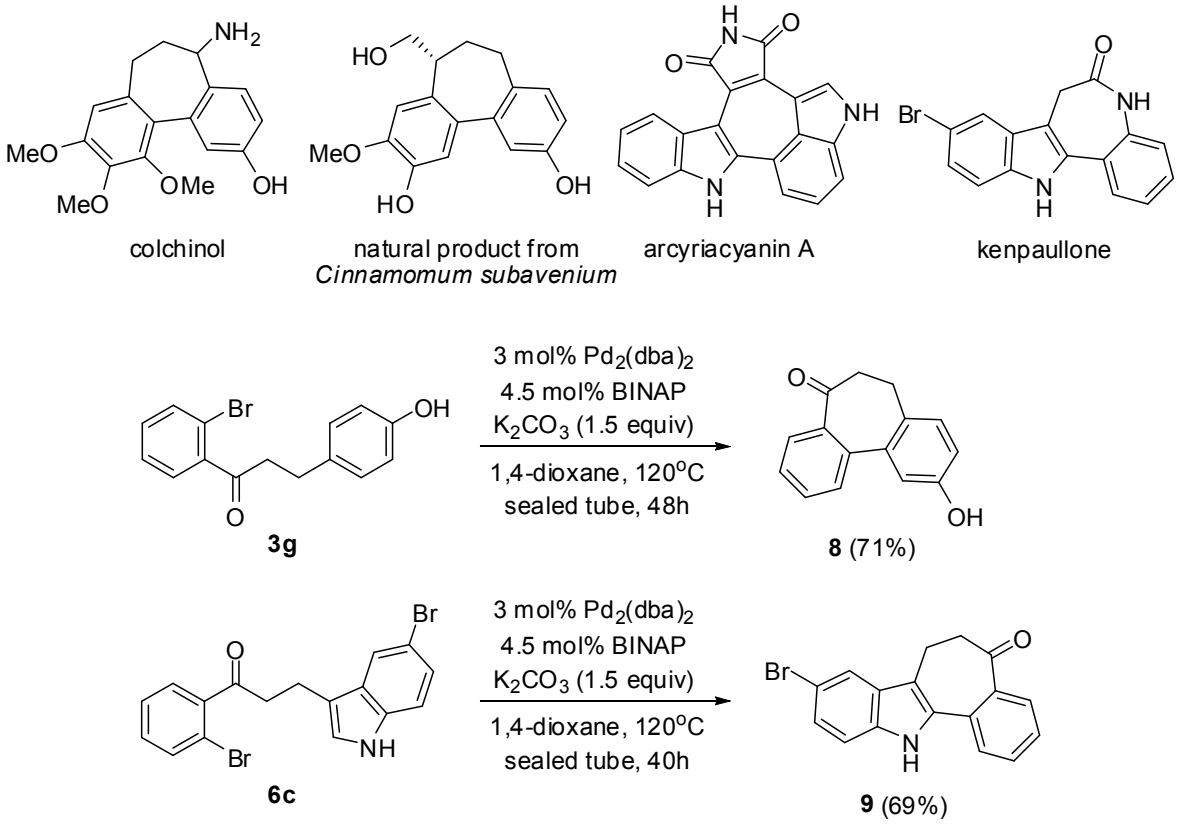
Scheme 3. Controlled gold-catalyzed reaction of propargylic hydroperoxides with indole and quinone derivatives.



To capitalize on the above findings for the preparation of different products, a route for a polycyclic core which appears in several products of biological interest was envisioned. Indole-fused seven-membered benzocycles are essential components of alkaloids such as ambiguine, caulersin, silicone, oxophenylarcyriaflavin, paullones, and arcyriacyanin A, which show a wide array of biological properties.[14] On the other hand, bis(benzo)-fused seven-membered carbocycles can be found in cytotoxic colchinols and allocolchicinoids.[15] Thus, the concise methods for the construction of these polycyclic skeletons are highly attractive. To achieve the desired conversion

to the natural product frameworks from our products, we performed the direct synthesis of tricycle **8** and tetracycle **9** from β-functionalized ketones **3g** and **6c**, respectively (Scheme 4). Upon treatments of **3g** and **6c** under palladium-catalyzed conditions, the corresponding polycyclic compounds **8** and **9** were obtained in fair yields (Scheme 4).

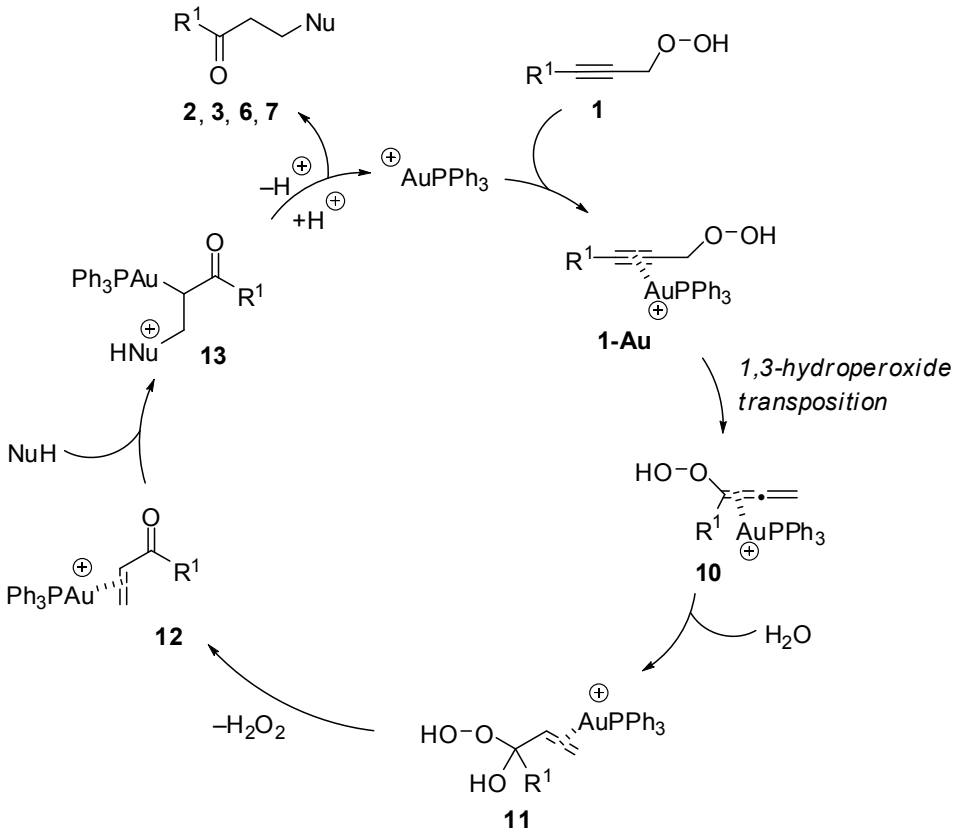
Scheme 4. Palladium-catalyzed cyclization of β-aryl ketones.



The reaction of propargylhydroperoxides to yield β-funtionalized ketones may be catalyzed by the Au(I) salt. The catalytic reaction is likely divided into five parts.[16] Firstly, coordination of the carbon–carbon triple bond of propargylic hydroperoxides **1** to the Au(I) salt gives gold-π-alkynyl complex **1-Au**. Species **1-Au** evolves through a 1,3-hydroperoxide transposition to intermediate **10**. Regioselective nucleophilic addition of water to the disubstituted allene double bond in gold-allenyl complex **10** to give intermediate **11**, followed by loss of hydrogen peroxide provides the α,β-unsaturated ketonic gold complex **12**. Next, 1,4-addition of the corresponding external nucleophile to the species **12**,[17] would form the gold intermediate **13**. Demetalation linked

to proton transfer provides final products **2**, **3**, **6**, or **7** and regenerates the gold catalyst, closing the catalytic cycle (Scheme 5).

Scheme 5. Mechanistic explanation for the gold-catalyzed controlled preparation of β-functionalized ketones.

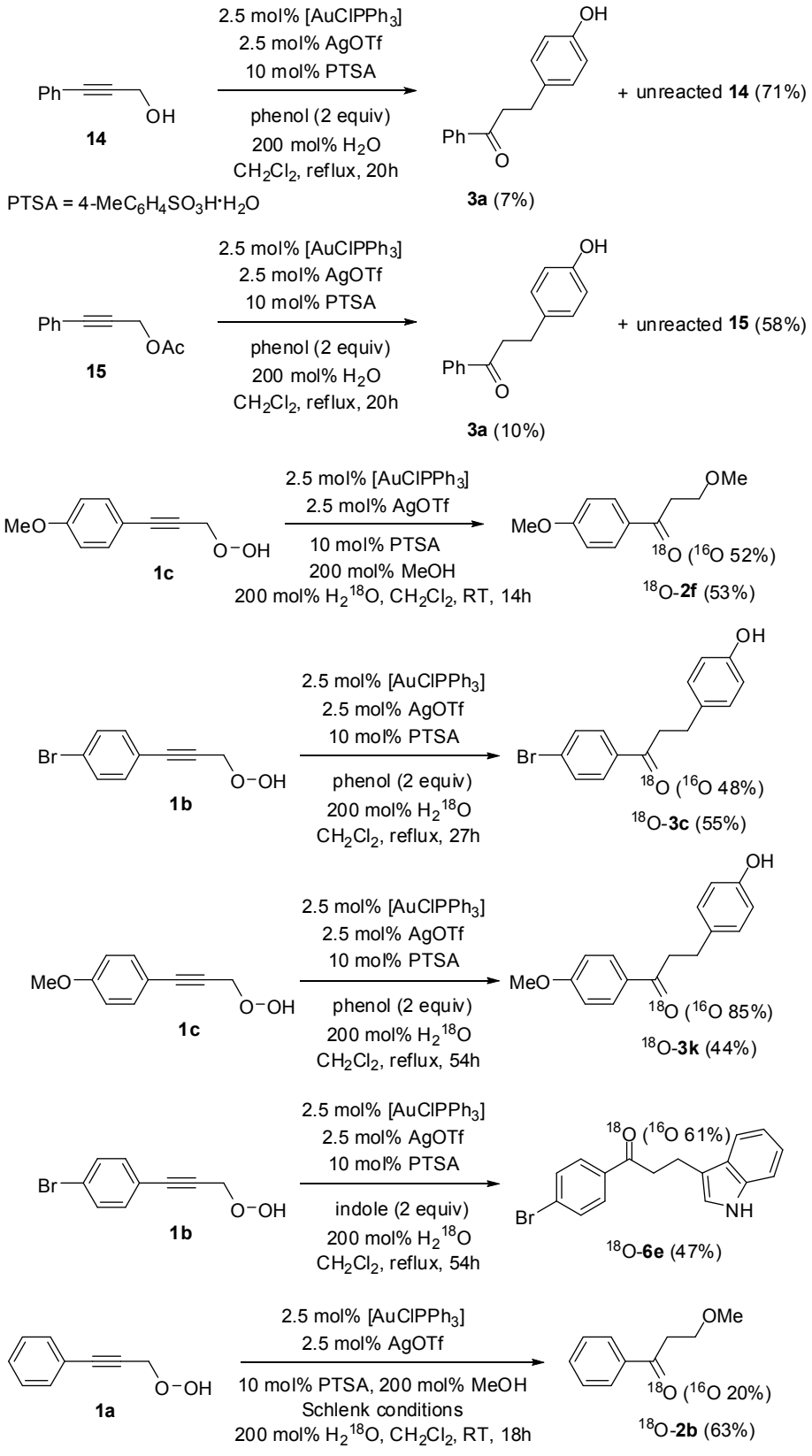


To shed light on the active participation of the propargylic hydroperoxide moiety in the transformation, some control and ^{18}O-labeling experiments were carried out. Insight into the direct participation of the hydroperoxide group in the gold-catalyzed process was obtained by running control experiments with a propargylic alcohol and its acetate.[18] Thus, both the reaction of 3-phenylprop-2-yn-1-ol **14** as well as the reaction of its acetate **15** with phenol were run under the optimum reaction conditions (Scheme 6). Notably, the β-functionalized ketone formation event was cut down because compound **3a** was formed from **14** and **15** in only 7% and 10% yields, respectively, under otherwise identical conditions. NMR and mass spectrometric analyses of the product of reaction of propargylic hydroperoxide **1a** with ethanol in presence of $H_2{}^{18}O$ with isotope abundance of 97% (Scheme 6), showed that the β-functionalized ketone was ^{18}O-labelled (48%),

revealing that the carbonylic oxygen was not coming from the hydroperoxide moiety. When $H_2{}^{18}O$ was added to the gold-catalyzed reaction between propargylic hydroperoxide **1b** and phenol, product ^{18}O-**3c** with 52% ^{18}O content was formed in 55% yield, further indicating that external H_2O is involved in this reaction (Scheme 6). A similar trend was observed for compounds ^{18}O-**3k** and ^{18}O-**6e**, but the efficiency of the labeling process was lower (Scheme 6). ^{18}O-Labelled isomers in Scheme 6 contain, as much, a 50% of ^{18}O-isotope abundance which may be not consistent with a solely water assisted mechanism; meaning that a competitive pathway implying hydroperoxide ^{16}O during the formation of intermediates **12** is involved. However, taking into account the almost absence of product **2a** by performing the experiment under anhydrous conditions, we are confident that the carbonylic oxygen in products **2**, **3**, **6**, and **7** was not coming from the hydroperoxide moiety. The explanation for the partial (<50%) ^{18}O-labelling in ketones **3** and **6** using $H_2{}^{18}O$, may arise from the presence of ambient $H_2{}^{16}O$ in the open air reaction system. Thus, when we performed the gold-catalyzed reaction of hydroperoxide **1a** with methanol under Schlenk conditions but using PTSA·H_2O in presence of $H_2{}^{18}O$ (97% of ^{18}O), product ^{18}O-**2b** with 80% ^{18}O content was formed (Scheme 6, bottom equation).

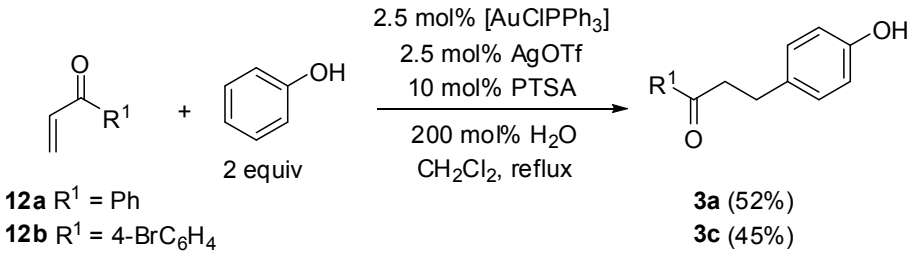
Here the use of isotopic labels has been used with mechanistic purposes to confirm and indeed quantify the transfer of molecular components between species. Besides, the preparation of ^{18}O-labeled compounds may be of pharmaceutical interest because the use of labeled compounds becomes increasingly interesting for the development of new drugs;[19] for example, labeled derivatives are necessary for metabolite studies as well as for production of novel radiotracers intended for complex imaging studies in humans. Obviously, our gold-catalyzed reaction is suited for the synthesis of ^{18}O-labeled β-functionalized ketones.

Scheme 6. Control and ^{18}O-labeling experiments.



We also decided to isolate the intermediate α,β-unsaturated ketones and to submit these carbonyl compounds to the reaction conditions to demonstrate their intermediacy in this novel reaction. Decomplexed α,β-unsaturated ketones **12a**, **12b**, and **12e** were isolated when the reactions of their corresponding hydroperoxides **1a**, **1b**, and **1e** were quenched after 3 h with hydrochloric acid (1 M). These observations were informative but insufficient. Consequently, the decomplexed unsaturated ketones **12a** and **12b** were allowed to react with phenol under gold-catalyzed conditions. The reactions did form 3-(4-hydroxyphenyl)-propan-1-ones **3a** and **3c** in reasonable yields (Scheme 7); thus accounting for the intermediacy of unsaturated ketones **12**.

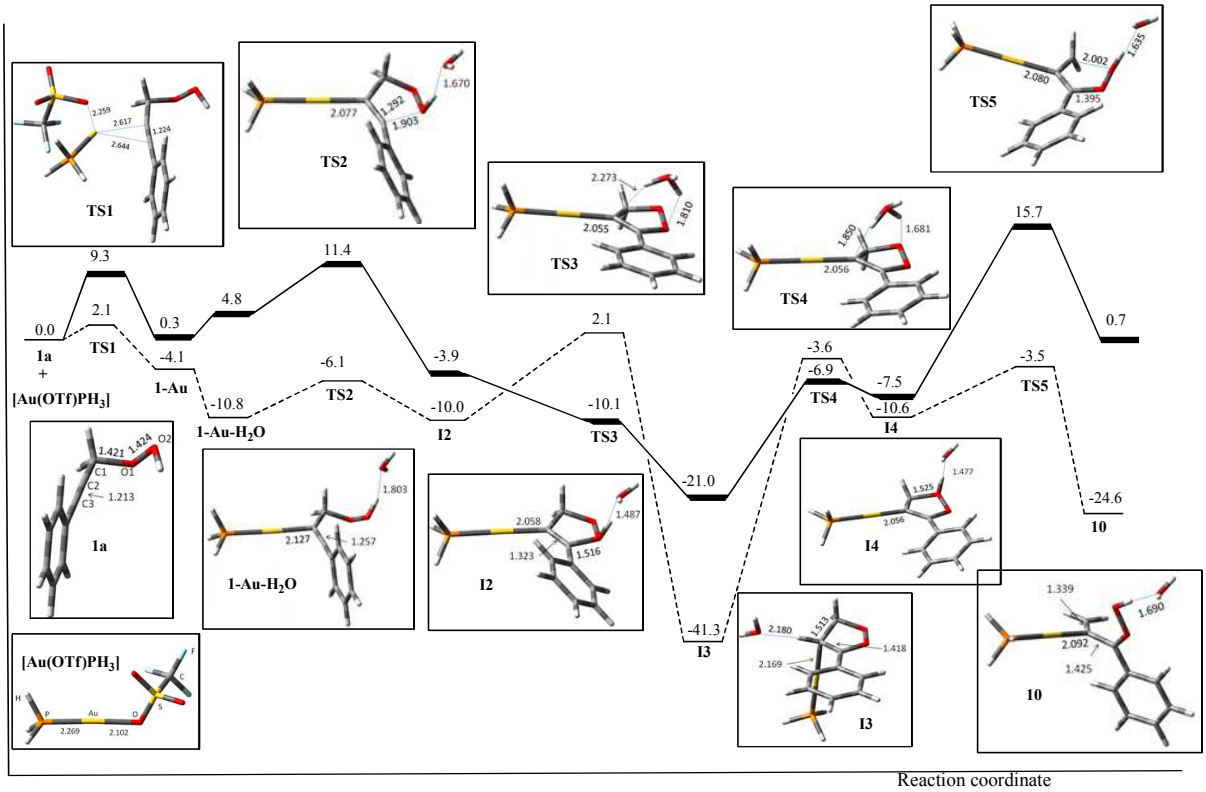
Scheme 7. Gold-catalyzed reaction of intermediate α,β-unsaturated ketones with phenol.



Theoretical calculations on the gold(I)-catalyzed controlled preparation of **2b** from **1a** in Scheme 1, support the mechanistic proposal shown in Scheme 5. The computational study indicates that the starting hydroperoxide transforms into the corresponding ketone through five consecutive stages, whose electronic energy in the gas phase and Gibbs energy in CH_2Cl_2 solution profiles are collected in Figures 1 and 2. Unless otherwise stated we shall discuss in the text relative Gibbs energies in solution. The first stage corresponds to the separation of the $Au(PH_3)^+$ moiety from the triflate anion and the bonding of this cation to the C2 atom of the propargylic hydroperoxide (see Figures 1 and 1S),[20] with a Gibbs energy barrier of 9.3 kcal/mol. Isolated reactants and intermediate **1-Au** could easily reach the chemical equilibrium but, actually, it is shifted to product side due to the further evolution of **1-Au**. Experiments show that the replacement of AgOTf by $AgSF_6$ or $AgBF_4$ hardly affects the product yield. Besides, we have checked that triflate anion does not directly participate in any of the remaining reaction steps, so we eliminated it from our reactant systems (see Computational Details).[21]

The second reaction stage involves the 1,3-transposition of the hydroperoxide group. It takes place with the direct assistance of a water molecule from the reaction medium (see Figures 1 and 2S). The work of Hashmi *et al* on the hydration of alkynes catalyzed by gold(I) already pointed out the relevant role played by several environmental water molecules to reduce the involved barriers.[22] Intermediate **1-Au** undergoes a four step transformation: an intramolecular cyclization (**TS2 → I2)**, a 1,3-H transfer from O2 to C2 (**TS3 → I3**), a new 1,3-H transfer from C2 to O1 (**TS4 → I4**), and, eventually, the opening of the cycle (**TS5 → 10**). The most stable structure along this piece of the reaction mechanism is the endoperoxide **I3**, which lies 21.0 kcal/mol below reactants energy. At the end of the 1,2-dioxole ring opening, the allene **10** is formed, being the rate-limiting step for the OOH transposition the endoperoxide ring opening.

Figure 1. Electronic energy in the gas phase (dashed line) and Gibbs energy in CH_2Cl_2 solution (continuous line) profiles obtained for the first and second stages of the gold-catalyzed reaction of the alkynic hydroperoxide 1a at the M06/6-31++G(d,p) (LANL2DZ + f for Au) theory level. All the energies are referred to the reactants: alkynic hydroperoxide (1a) + [Au(OTf)PH_3].



In the third reaction stage, a water molecule is added to the C2–C3 double bond of allene **10**. Knowing the relevant role played by environmental water[22] we included a chain of three water molecules, one extreme donating an OH group to C3 and the other a H atom to C2; both moieties are added on perpendicular faces. The relative Gibbs energy barrier for the OH donation is significantly larger (**TS6**, 13.1 kcal/mol above reactants) than that for the H donation (**TS7**, 0.3 kcal/mol under reactants), which ends up in the stable intermediate **11**, able to rotate around the single C2–C3 bond.

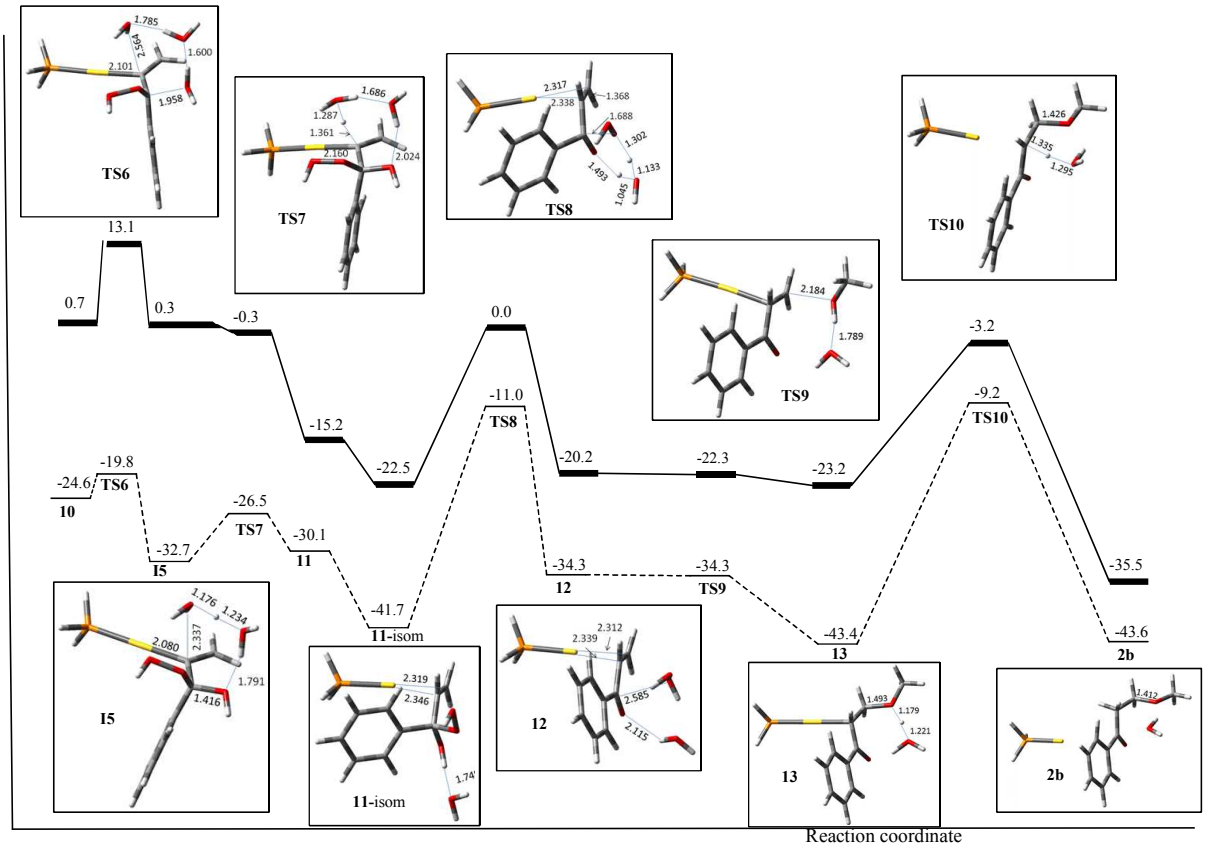
The fourth reaction stage is the concerted elimination of H_2O_2 from C3 in **11**, thus yielding the α,β-unsaturated carbonyl intermediate **12**. A water molecule acts as a bifunctional catalyst, extracting the H atom from the OH group at C3 and donating one of its H atoms to the leaving OOH fragment.[24] Molecular description of the third and fourth reaction stages corroborates isotopic labeling experiments.

The isomerization of propargylic alcohols to α,β-unsaturated carbonyl compounds is known as Meyer–Schuster rearrangement, and it has been widely used recently to perform organic synthesis with atom economy.[25] Several reaction mechanisms have been proposed depending on the catalyst used, which vary from acid catalysts to transition metals such as Ru, Re, Au and Ag, including oxo-metal catalysts.[25] The mechanism here outlined from isolated reactants **1** to intermediates **12** resembles a Meyer–Schuster rearrangement, but notably, the presence and geometry characteristics of the OOH functional group allow a new mechanism to happen, which cannot apply to porpargylic alcohols.

Finally, the fifth reaction stage corresponds to the addition of an alcohol molecule to the C1–C2 bond of intermediate **12**, where we considered methanol as a model alcohol. Similarly to water, the addition of methanol happens in two steps; one for the bonding of the RO moiety (**TS9 →13),** with practically no energy barrier relative to the preceding intermediate, and the last one for the addition of the H atom (**TS10 → 2b**).

Figure 2. Electronic energy in the gas phase (dashed line) and Gibbs energy in CH_2Cl_2 solution (continuous line) profiles obtained for the third, fourth, and fifth stages of the gold-catalyzed

reaction of the alkynic hydroperoxide 1a at the M06/6-31++G(d,p) (LANL2DZ + f for Au) theory level. All the energies are referred to the reactants: alkynic hydroperoxide (1a) + [Au(OTf)PH_3].



Conclusions

In conclusion, selective gold-catalyzed reactions of primary and secondary propargylic hydroperoxides with alcohols or carbon nucleophiles allow the direct and efficient synthesis of β-functionalized ketones. The scope of these protocols has been investigated and the utility of the resulting products for the selective preparation of fused polycycles has been demonstrated. In addition, density functional theory (DFT) calculations and ^{18}O-labeling experiments were performed to obtain an insight into various aspects of the controlled reactivity of propargylic hydroperoxides with external nucleophiles under gold catalysis. At present time, the application of this methodology into the selective preparation of different types of heterocyclic compounds is ongoing in our group.

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

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