

Gold(I)-Catalyzed Intermolecular
Hydroalkoxylation of Allenes: A DFT studyRobert S. Paton^{*,†} and Feliu Maseras^{*,‡}

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ABSTRACT



The mechanistic and regiochemical aspects in the Au(I)-catalyzed intermolecular hydroalkoxylation of allenes have been studied computationally. The most favorable pathway is nucleophilic attack of an Au(I)-coordinated allene, which occurs irreversibly. An Au(I)-catalyzed mechanism is proposed that allows the facile interconversion of regioisomeric allylic ether products. The regioisomers are connected via a stabilized diether intermediate with a C–Au σ -bond, which successfully explains the observed regioselectivity for the thermodynamic product.

Homogeneous gold complexes provide a rich source of novel catalytic transformations of interest to the organic community.¹ The use of N-heterocyclic carbenes (NHCs) as ligands has been found to give the necessary electronic and

steric stabilization to the cationic Au-catalyst.² Various groups have demonstrated the utility of Au(I) catalysis in the intramolecular hydroalkoxylation of γ - and δ -hydroxy allenes to produce alkyl allylic ethers.³ Recently the use of [NHC]Au(I) compounds has been found to efficiently catalyze the intermolecular hydroalkoxylation of allenes with alcohols at room temperature (Scheme 1).⁴ The related

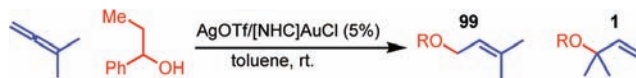
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Scheme 1. [NHC]Au(I)-Catalyzed Hydroalkoxylation of Allenes



intermolecular hydroamination of allenes using N-unsubstituted carbamates is also catalyzed by [NHC]Au(I).⁵

Here we report the results of computational studies into the Au(I) catalyzed intermolecular hydroalkoxylation reac-

tion.⁶ DFT investigations of gold catalysis at similar levels of theory have been shown to perform well, providing invaluable insight into aspects of mechanism and selectivity.⁷ We studied the hydroalkoxylation of 1,1-dimethylallene by MeOH, in the presence of the [NHC]Au catalyst shown in Figure 1. Of particular interest were the catalytic mechanism

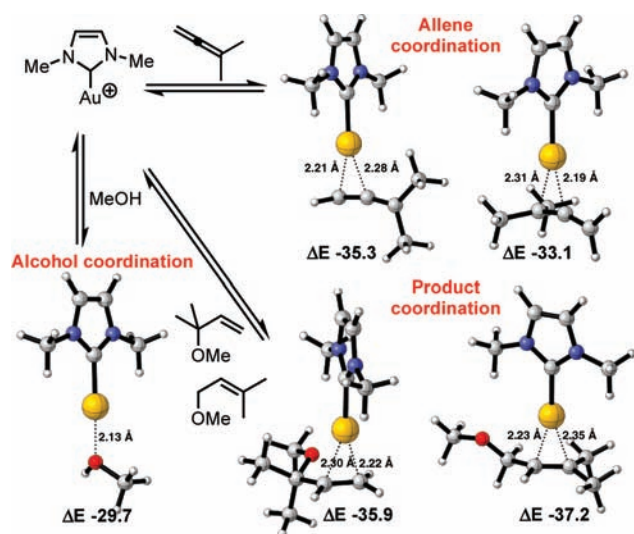


Figure 1. Catalyst coordination to reactants and products. Solution phase energies in kcal mol⁻¹.

and the regiochemical outcome of the alcohol addition. We also performed QM/MM calculations⁸ for selected cases (see Supporting Information) using a much larger catalyst in which the NHC ligand possesses 2,5-*i*PrPhenyl substituents rather than Me groups, which was the optimal catalyst in experiment. Reassuringly, mechanistic and regioisomeric conclusions from both sets of calculations were consistent, and here we discuss the results obtained at the full DFT level.

First we investigated coordination of the Au-catalyst to reactants (allene and alcohol) and product (allylic ether) species (Figure 1). Coordination of the π -acidic Au to both C=C bonds of the allene was considered, in addition to coordination to the alcohol oxygen, since mechanistic and computational studies support the formation of hydroxygold

species in water.⁹ All coordination energies are quite high, above 30 kcal mol⁻¹, but this is unlikely to block the catalyst because there are other species in solution that can also coordinate to gold and displace the organic substrates. Au(I)-complexes formed with the allene are 3–6 kcal mol⁻¹ more stable than with the alcohol, consistent with allene activation via cationic gold coordination. We were interested to find that complexation to either of the isomeric allylic ether products is more favorable than to the allene. This suggested the possibility of Au-catalyzed transformations involving the allylic ether products should also be considered.

We next considered the uncatalyzed addition of MeOH to the allene. In the absence of catalysis by Au, (or a Brønsted acid/base), allene hydroalkoxylation could occur via a cyclic transition structure (TS), in which nucleophilic attack by the alcohol occurs as another alcohol molecule acts as a proton shuttle (Figure 2). The computed potential energy barrier of

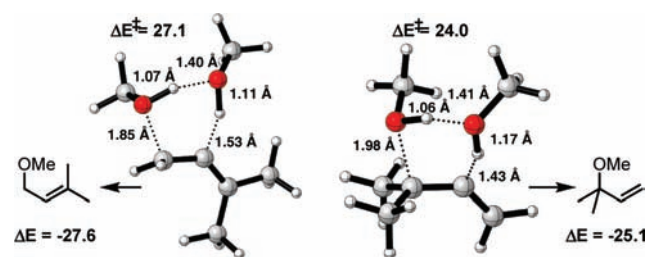


Figure 2. Uncatalyzed (background) reaction. Solution phase energies in kcal mol⁻¹ relative to the separated reagents.

24.0 kcal mol⁻¹ is quite high, and things get worse when entropic corrections are introduced, resulting in the calculated activation free energy of 40.5 kcal mol⁻¹. This strongly suggests that the background reaction will not readily occur at room temperature. For Au-catalysis, we calculated a variety of possible pathways. These included the possibility of nucleophilic activation, namely the *syn*-addition of a methoxygold species to a C=C bond (forming a Au σ -alkenyl intermediate) and a concerted pathway analogous that shown for the uncatalyzed reaction (Figure 2), in which the shuttling proton is replaced by cationic Au. Structures and energetics for these alternative pathways are collected in the Supporting Information. The lowest activation barriers were observed for nucleophilic attack of an Au-coordinated allene, favored comfortably over the other pathways by 12.8 kcal mol⁻¹. There are four possible pathways for attack of the alcohol to the Au-coordinated allene. The alcohol is able to attack the allene from the same side as the coordinated catalyst (termed inner-sphere mechanism) or from the opposite side (outer-sphere mechanism).

While Teles¹⁰ has proposed an inner-sphere mechanism for the addition of water/alcohols to alkynes, the outer-sphere

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(6) DFT optimizations were performed with PBE0 density functional and the 6-31G(d,p) basis set, using Stuttgart-Dresden relativistic effective core potentials for Au. Single point energies were evaluated in solvent using a PCM description of the experimentally used solvent, toluene, using UFF atomic radii. These were implemented with the Gaussian03 package: Frisch, M. J.; et al. Gaussian 03, revision D.01; Gaussian, Inc.: Pittsburgh, PA, 2005. Energies presented correspond to potential energies with zero point and solvent corrections, unless otherwise stated. Tests presented in the Supporting Information prove that the main results of this work are unchanged by the use of another functional (B3LYP), a larger basis set, or the introduction of entropic effects.

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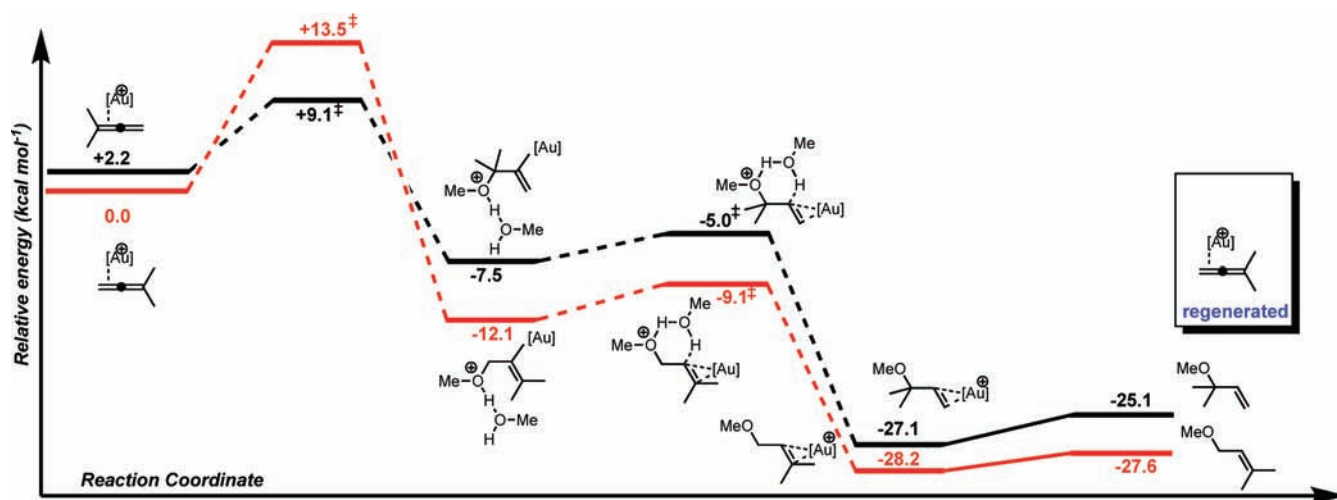


Figure 3. [NHC]Au(I)-catalyzed hydroalkoxylation reaction coordinate for both regioisomeric pathways. Solution phase energies in kcal mol⁻¹ relative to the separated reagents.

mechanism has received support in the addition of oxygen and nitrogen nucleophiles to alkenes.¹¹ Moreover, the attack can take place at either allene terminus. Figure 3 presents the energy profile for the favored path for each regioisomer. It is clear that the rate-limiting step is the initial attack of the alcohol on the allene. This initial addition step leads to the formation of a Au σ -alkenyl intermediate more stable than the starting materials. TSs were located for the protonation of these intermediates, and this process is calculated to occur with retention of the alkene geometry. The formal Au–C σ -bond is lost, although these TS lead to allylic ether products in which the Au is now coordinated to the π -bond. Overall, allene hydroalkoxylation is calculated to occur irreversibly, as the products lie over 28 kcal mol⁻¹ below the starting materials, creating a large barrier to the reverse reaction.

Of the four transition states corresponding to alcohol attack on the Au-coordinated allene, presented in Figure 4, the outer-sphere mechanism at the more substituted allene end is most favorable. This is consistent with a Markovnikov-type addition, while the outer-sphere TS minimizes unfavorable steric interactions as the two methyl groups are oriented out of the plane of the allyl system. The same energetic preferences were seen in calculations using a much bulkier NHC ligand. The Au(I)-activated pathway possessed a much lower activation barrier than the background reaction (9.1 vs 24.0 kcal mol⁻¹), since the TS is stabilized by a developing C–Au σ -bond. The profile presented in Figure 3 predicts attack of the alkoxy group on the methylated end of the allene, and the analysis of the structures' relative energies in Figure 4 corroborates this result. Unfortunately, this is at odds with the experimental data. Experimentally, the major product is the internal alkene regioisomer corresponding end.

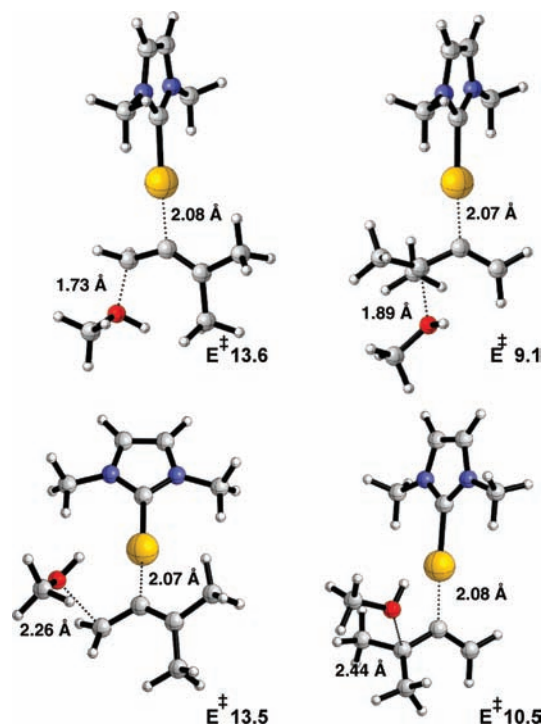


Figure 4. Inner- and outer-sphere TSs for nucleophilic attack of the allene. Solution phase energies in kcal mol⁻¹.

This isomer is computed to be thermodynamically more stable, but its formation is kinetically less favorable. Because allene hydroalkoxylation was calculated to be irreversible (i.e., under kinetic control), this prompted us to consider possible pathways for product regioisomerization. The catalyst coordinates more strongly to the allylic ethers than to the allene, so possible Au-catalyzed transformations of the hydroalkoxylation products were considered. We calcu-

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lated that the addition of another molecule of alcohol to an allylic ether can occur readily (Figure 5).

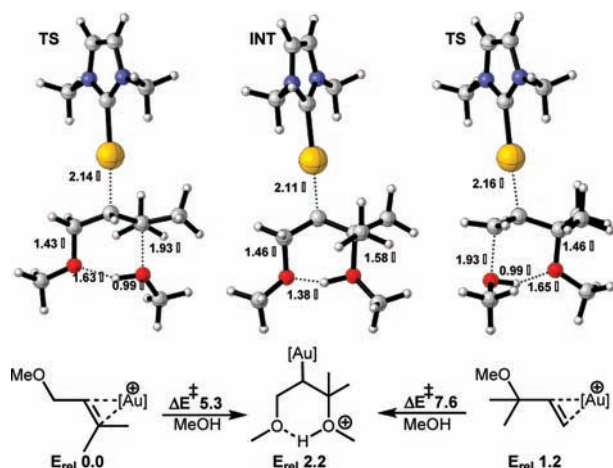


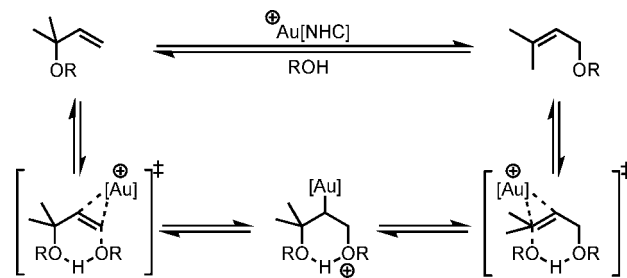
Figure 5. Au(I)-catalyzed interconversion of regioisomeric allylic ethers. Solution phase energies in kcal mol⁻¹.

The Au(I)-catalyzed addition of MeOH to either regioisomeric allylic ether occurs with a small energetic barrier (5.3 and 7.6 kcal mol⁻¹), forming a protonated diether intermediate stabilized by a hydrogen bond. This is chair-shaped with the Au(I) in a pseudo equatorial position. It has been recently reported that [NHC]Au(I) catalysts can catalyze the rearrangement of allylic acetates, at 80 °C.¹² DFT calculations showed that this allylic acetate rearrangement proceeds via the formation of a cyclic acetoxonium intermediate with a free energy barrier of 14.3 kcal mol⁻¹,¹³ in a process electronically similar to a metal catalyzed Cope rearrangement.¹⁴ The gas phase free energy barriers here are 16.0 and 14.1 kcal mol⁻¹, although bimolecular steps in solution are probably overestimated by around 5 kcal mol⁻¹ this way.¹⁵ These computed barriers for product interconversion are smaller than for the initial nucleophilic attack of the allene. Nucleophilic attack of the C=C bond is aided by the allylic oxygen coordinating to the alcohol proton, which also acts to stabilize the diether intermediate. In contrast, we were unable to optimize any intermediates resulting from the attack of an alkene without a neighboring alcohol group. The proposed mechanism is also consistent with the regioselective Au(I)-catalyzed hydroalkoxylation of alkoxyallenes,¹⁶ where the allylic acetal is calculated to be energetically more stable and is the observed major product.¹⁷ Allene hydroamination gives contrasting regioselectivity: this divergence could

arise as the isomerization pathway is much less favorable than for hydroalkoxylation so products cannot interconvert.¹⁸

The proposed pathway of [NHC]Au(I)-catalyzed allylic ether isomerization is illustrated in Scheme 2. Au(I)-coordination

Scheme 2. Proposed Mechanism for Allylic Ether Isomerisation



activates the C=C bond to nucleophilic attack from ROH, which is aided by hydrogen-bonding to the allylic oxygen. Attack of either regioisomeric allylic ethers forms a chair-shaped cyclic intermediate that allows the interconversion of the products, finally yielding the more stable regioisomer. The two regioisomeric products are thus in equilibrium, and as a result only the most stable one, corresponding to alkoxylation in the terminal position is observed.

DFT calculations have been used to study the mechanistic and regiochemical aspects of the Au(I)-catalyzed intermolecular hydroalkoxylation of allenes. The most favorable catalytic pathway is the nucleophilic attack of a Au(I)-coordinated allene, which occurs irreversibly. The predicted kinetic product is at odds with the experiment, however, a further Au(I)-catalyzed interconversion of the regioisomeric allylic ether products can occur. This rearrangement is predicted to be more facile than the initial allene hydroalkoxylation, and resembles the recently discovered Au(I)-catalyzed rearrangement of allylic acetates. We are therefore able to rationalize the experimentally observed regioselectivity for the thermodynamic product. Studies into the stereochemical aspects of hydroalkoxylation are underway and will be reported in due course.

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Supporting Information Available: Cartesian coordinates for all optimized structures with SCF energies, free energies and solvation energies; imaginary frequencies of all TSs. Structures and energetics for alternative Au(I)-catalytic pathways and QM/MM results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) The calculated solution phase (dichloromethane) DE between the allylic acetal and vinyl ether is 1.8 kcal mol⁻¹. See Supporting Information.

(18) The intermediate formed from a second nucleophilic addition is 14.5 kcal mol⁻¹ higher in energy than the allylamine formed in the reaction of 1,1-dimethylallene with acetylamine.