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Mechanism of the [(NHC)Au^I]-Catalyzed Rearrangement of Allylic Acetates. A DFT Study

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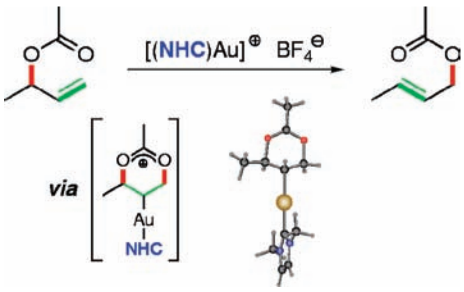
ABSTRACT



The DFT study of the mechanism of the rearrangement of $H_2C{=}CHC(CH_3)OCOCH_3$ to $(CH_3)(H)C{=}CHCH_2OCOCH_3$ catalyzed by $[(NHC)Au]^+$ (NHC = N-heterocyclic carbene) shows that a low energy path exists, with a barrier of 14.2 kcal·mol^{-1}, going through a six-membered ring acetoxonium intermediate and where gold coordinates one of the carbon atoms in the alkene system. The qualitative features of the mechanism are not affected by the introduction of other NHC ligands, counterions, or solvation effects.

The use of gold complexes as carbophilic π-acids in homogeneous catalysis is currently the subject of intense research.[1] As a subset of substrates, propargylic esters, which undergo intramolecular 1,2- or 1,3-ester migration, have attracted increasing attention.[2] Recently, their *allylic* counterparts have also appeared as an interesting class of compounds in the context of gold catalysis.[3] The allylic rearrangement provides an efficient and atom-economical access to primary oxo derivatives. We notably reported the [3,3] sigmatropic rearrangement of allylic esters catalyzed by [(NHC)Au^I] compounds.[3b,4] The mechanism we proposed for this transformation involves an alkene π-activation/oxo-cyclization sequence (Figure 1), following the lines of a cyclization-induced rearrangement as defined by Overman.[5,6] Nevertheless, other hypotheses could be envisaged, such as oxygen activation, ionization of the acetate, and the formation of an allyl cation.[7]

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(1) For recent general reviews, see: (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (d) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (e) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (f) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917.

(2) For reviews, see: (a) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (b) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350.

(3) (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985. (b) Marion, N.; Gealageas, R.; Nolan, S. P. *Org. Lett.* **2007**, *9*, 2653. Erratum: *Org. Lett.* **2008**, *10*, 1037]. (c) Porcel, S.; López-Carrillo, V.; García-Yebra, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1883.

(4) For a review focused on NHC−Au complexes in catalysis, see: Marion, N.; Nolan, S. P. *Chem. Soc. Rev.* **2008**, *37*, 1776.

(5) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.

(6) Siebert, R.; Tantillo, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 8686.

10.1021/ol802430m CCC: $40.75

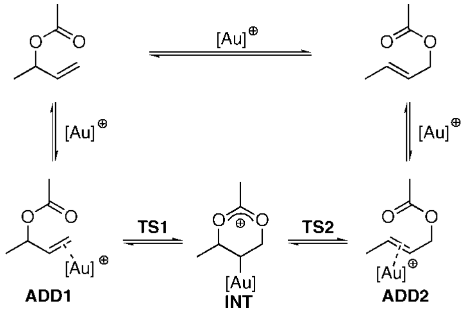

Figure 1. General scheme of the Au-catalyzed allylic rearrangement reaction.

In order to clarify these mechanistic aspects, we set out to conduct a computational study[8] using the systems presented in Figure 2.[9] Additionally, we envisioned, with this study, to gain important insights into the observed dependence of the reaction as a function of the nature of the NHC substituents.[10]

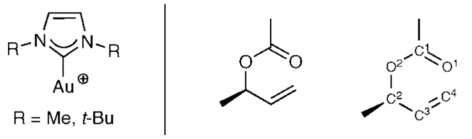

Figure 2. Structures of the catalyst (left) and of the reactant along with atoms numbering (right).

First, we investigated the uncatalyzed rearrangement reaction. The process takes place in one step with a transition state **uncatTS1** displaying a 6-membered ring in a boat conformation (Figure 3) with a relatively high barrier of 31.7 kcal•mol^{-1}. The transition state corresponds, as expected, to the simultaneous breaking of the C^2−O^2 bond and formation of the C^4−O^1 bond. The C^2−O^2 and C^4−O^1 distances are almost identical at 2.082 and 2.092 Å, respectively. These distances are quite long and suggest that the transition state can be viewed as an anionic acetate fragment (Mulliken charge −0.48 au; NBO charge, −0.51 au) interacting with a positive carbocation (+0.48 au; +0.51 au). The geometry is relatively similar to those previously computed for intramolecular nucleophilic substitution by the groups of Zipse[11] and Birney,[12] who showed the reaction to be pseudopericyclic.[13]

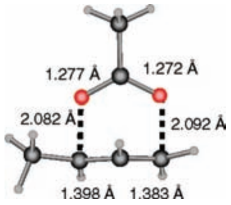

Figure 3. Computed transition state **uncatTS1** for the uncatalyzed reaction.

We then analyzed the reaction with the simplest NHC catalyst, where R is methyl (Figure 2). The reaction corresponds to the general scheme we previously proposed as illustrated in Figure 1. The gold moiety coordinates to the π-electrons of the alkene producing a first adduct **ADD1**, 29.0 kcal.mol^{-1} below the energy of the individual reactants. This is a large stabilization energy but reasonable for the gas phase estimate of coordination of an olefin to a cationic gold center.[8e] We will use this point as origin for relative energies (see Table 1). Then the intramolecular nucleophilic attack of the carbonyl on the alkene takes place, leading to **TS1**, 14.2 kcal•mol^{-1} above **ADD1**. **TS1** leads to intermediate **INT**, which is a 6-membered stabilized 1,3-acetoxonium, 9.9 kcal•mol^{-1} above **ADD1**. **INT** evolves through **TS2** to a second adduct **ADD2**, where the gold catalyst is coordinated to the rearranged product. The relative energies of **TS2** and **ADD2** are 10.7 and −1.0 kcal•mol^{-1}, respectively. **INT** is in a quite shallow well, in agreement with related mechanisms.[6]

Table 1. Relative Gibbs Free Energies (kcal•mol^{-1}) of the Key Structures for the Different Models Considered

	R = CH$_3$ gas	R = t-Bu gas	R = CH$_3$ solvent	R = CH$_3$ + BF$_4^-$ gas
ADD1	0.0	0.0	0.0	0.0
TS1	14.2	15.5	17.3	14.3
INT	9.9	10.6	14.4	11.2
TS2	10.7	11.3	14.9	12.8
ADD2	−1.0	−2.7	−0.3	−0.6

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(7) The formation of a π-allyl cation from an allyl acetate has been evoked by Echavarren in the gold-catalyzed allyl−allyl coupling reaction, see ref 3c.

(8) For computational studies on *propargylic* acetates in Au catalysis, see: (a) Correa, A.; Marion, N.; Fensterbank, L.; Malacria, M.; Nolan, S. P.; Cavallo, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 718. (b) Soriano, E.; Marco-Contelles, J. *Chem.—Eur. J.* **2008**, *14*, 6771. (c) Shi, F.-Q.; Li, X.; Xia, Y.; Zhang, L.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 15503. (d) Lemière, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207. (e) Marion, N.; Carlqvist, P.; Gealageas, R.; de Frémont, P.; Maseras, F.; Nolan, S. P. *Chem.—Eur. J.* **2007**, *13*, 6437. (f) Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434.

(9) All calculations were carried out at the DFT level with the B3LYP functional as implemented within the Gaussian03 package. Gold was described by the SDD combination of relativistic effective core potentials and valence functions, and the 6-31+G(d,p) basis set was applied for the rest of the atoms. Solvation effects (dichloroethane) were evaluated in selected cases through PCM calculations (with UFF atomic radii) on the gas-phase optimized geometries. Quoted energies are Gibbs free energies at 298K, 1 atm (with gas-phase entropic corrections computed using harmonic oscillator approximation) unless otherwise noted. No open-shell states were considered, following previous work on a palladium-catalyzed Cope reaction.[6]

(10) For recent reviews on NHCs, see: (a) de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2008**, *37*, 1776. (b) Hahn, F. E.; Jahnke, M. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 3122.

(11) Zipse, H. *J. Am. Chem. Soc.* **1997**, *119*, 1087.

(12) Birney, D. M.; Xu, X.; Ham, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 189.

(13) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossio, F. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 557.

The structures for complexes **TS1** and **INT** are shown in Figure 4. The O^1-C^4 and C^2-O^2 distances of 1.575 and 1.534 Å are much shorter than in the midpoint of the uncatalyzed process **uncatTS1**. Gold coordination to the central carbon C^3 stabilizes the negative charge of this moiety of the molecule, and greatly facilitates the process. It is worth noting that gold occupies an equatorial position in the cyclohexane-like 6-membered ring formed in these structures. It is also possible to compute another structure with gold coordination in the axial position at the same carbon C^3, but the energy is much higher. The corresponding transition state **axTS1** has a relative energy of 26.7 kcal·mol^{-1} above **ADD1**. This large preference is likely associated to a combination of steric crowding in the axial position and the desire for the C−O and C−Au bonds to be aligned.

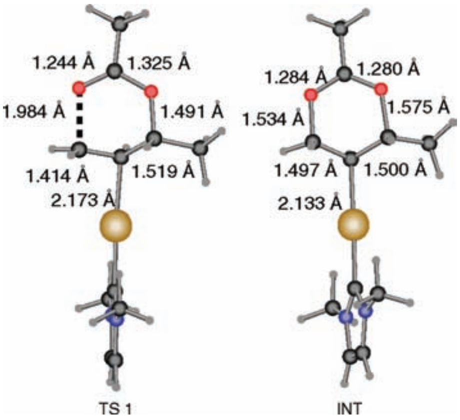

Figure 4. Computed structures of **TS1** and **INT**.

We considered next the possibility that the catalyst coordinates to one of the oxygen centers. In fact, one of the possible adducts was more stable than **ADD1**, but the corresponding transition states **O1TS** and **O2TS** had relative energies of 25.1 and 22.9 kcal·mol^{-1}, above **ADD1**, and are thus unable to compete with **TS1**. These results, taken together with the short O^1-C^4 and C^2-O^2 bond distances in **INT**, seem to exclude the possibility of an ionized acetate in this transformation. All mentioned structures are in the Supporting Information.

We also analyzed on this model system the *E*/*Z* selectivity of the process. Experimental data indicate that the *E* isomer is preferred but that the *Z* isomer also exists as minor product in some cases. The profile presented above leads to the *E* isomer. If one wants to go to the *Z* isomer, the initial conformer has to be different and is labeled as **ZADD1**. The structure of **ZADD1** and the corresponding transition state **ZTS1** are presented in Figure 5.

These differ from the previously discussed structures in the arrangement around the C^2-C^3 bond. **ZADD1** and **ZTS1** have relative energies of 2.7 and 16.4 kcal·mol^{-1} above **ADD1**. The critical comparison here is between **ZTS1** and **TS1**, which had a relative energy of 14.2 kcal·mol^{-1}. The difference of 2.2 kcal·mol^{-1} is fully compatible with the experimental observation of a preference for the *E* product, with some presence of the *Z* isomer.

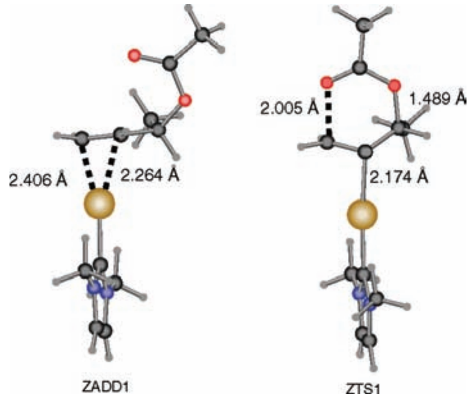

Figure 5. Computed structures of **ZADD1** and **ZTS1**.

We shifted then our attention to more elaborate models of the experimental system. The resulting computed energies are summarized in Table 1. First, we considered the reaction with a different catalyst, bearing bulky *t*-Bu groups on the NHC (Figure 2). The effect of this change on the computed mechanism is negligible; the energy profile is almost the same as with a NHC with R = Me (Table 1). For example, the first energy barrier is 15.5 kcal·mol^{-1} with R = *t*-Bu compared to 14.2 kcal·mol^{-1} with R = Me. This result is in fact consistent with the structure in Figure 4 where it can be seen that, even with methyl substituents, the NHC plane is orthogonal to the plane of the 1,3-acetoxonium moiety in order to minimize steric congestion. Without surprise, the bulkier *t*-Bu groups go thus to the same region with no steric hindrance, hence affecting only slightly the overall energetics of the reaction. We therefore believe that the lower conversions to rearranged product observed with less hindered NHC ligands on gold are more likely explained by the lower stability with respect to decomposition of the corresponding catalytically active [(NHC)Au]X cationic adducts.[14]

Table 1 presents results highlighting the role of two other parameters on the energy profile: solvation and counterions. The reaction is performed in a weakly polar solvent such as dichloromethane or 1,2-dichloroethane. Solvation was found to play a minor role in the energy profile, with an increase of only 3.1 kcal·mol^{-1} in the barrier from **ADD1** to **TS1**. The solvent favors charge separation, but no strong changes occur due to this effect throughout the reaction. The relative energy of the adduct with respect to the separate reactants is significantly reduced (from 29.0 to 7.2 kcal·mol^{-1}), which is the reason why we chose **ADD1** as origin of energies, but this has no effect on the reaction mechanism.

The gold catalyst is introduced in the reaction media in the form of a chloride salt that then reacts with silver tetrafluoroborate. The positive charge of the catalyst and the

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(14) For a study on several [(NHC)AuL]X cationic complexes, see: de Frémont, P.; Marion, N.; Nolan, S. P. *J. Organomet. Chem.* DOI: 10.1016/j.jorganchem.2008.10.047.

low polarity of the solvent means that the reacting system is likely associated to a tetrafluoroborate anion after the precipitation of silver chloride. Counteranions have been found to critically affect organometallic processes in selected cases.[15] The anion interacts with the cationic systems by making hydrogen bonds with the organic substrate. This interaction can be illustrated by structure **BF4INT** (Figure 6). Considering this effect, the energy profile remains practically unchanged (Table 1). The barrier is almost identical with (14.3 kcal•mol^{-1} in **BF4TS1**) or without the anion (14.2 kcal•mol^{-1} in **TS1**). It seems that the anion is always able to find an appropriate position in the environment of the cationic system and results in similar electrostatic interactions. The energetics involved in Table 1 show a reaction feasible under the experimental conditions for this process, oil bath reflux for 12 h or microwave heating at 80 °C for 12 min.

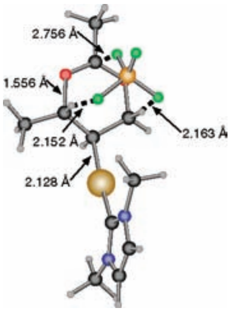

Figure 6. Computed structure of **BF4INT**.

In summary, we have computationally investigated the pathways leading to the gold-catalyzed sigmatropic rearrangement of allylic esters. Several pathways, which are produced by different initial coordination modes, were found to be possible, but only one exhibited catalytic activity when compared to the uncatalyzed process. In this mechanism, the catalyst binds the organic substrate through the olefinic bonds, and the reaction proceeds through a 6-membered ring acetoxonium intermediate. Overall, it can be stated that the catalytic effect of gold in this reaction lies in its high ability to stabilize developing charge in the transition states along the rearrangement path.

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Supporting Information Available: Cartesian coordinates for all computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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