Gold Catalysis

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Gold–Gold Cooperation in the Addition of Methanol to Alkynes**

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Gold catalysis is one of the hot topics in current organic synthesis. The "gold-rush" started with the discovery that seemingly inert gold can efficiently catalyze the addition of nucleophiles, such as water or methanol, to alkynes.[1,2] Nowadays is gold efficiently used for the construction of complex structures through reaction cascades based on π activations of multiply unsaturated molecules.[3–11] The key steps are often based on couplings between a C–C triple bond and a C–C double bond. Couplings between two C–C triple bonds are usually initiated by the addition of an alcohol to one of the triple bonds.[12–14]

The generally accepted reaction mechanism for the gold(I)-mediated addition of either water or methanol to an alkyne involves coordination of cationic gold to the C–C triple bond, which promotes the addition of the nucleophile.[15–18] The addition is completed by the migration of a proton bound to the oxygen atom of the incoming nucleophile to the second carbon atom of the multiple bond. The proton migration is assisted by solvent molecules.[15]

Herein, we report an investigation of the gold(I)-mediated addition of methanol to an alkyne by means of electrospray ionization mass spectrometry (ESI-MS),[19] NMR experiments, and theoretical calculations. Furthermore, the key reaction intermediate is characterized by IR multiphoton dissociation (IRMPD) spectroscopy. The reaction was investigated for 1-phenylpropyne, Ph–C≡C–Me, with [AuCl(PMe$_3$)] as the catalyst.[20]

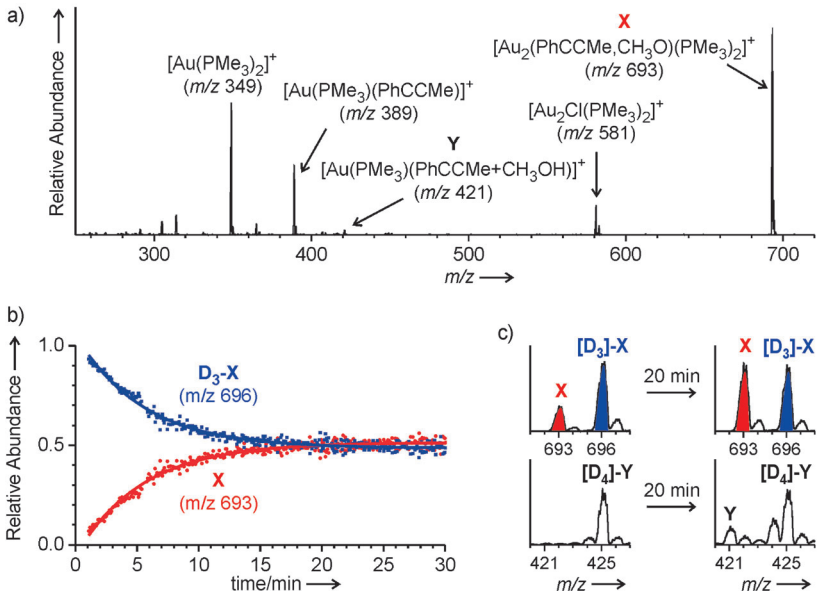

Figure 1. a) ESI-MS source spectrum of a MeOH solution of 1-phenylpropyne with catalyst (2.5 mol% [AuCl(PMe$_3$)]/3 mol% AgSbF$_6$). b) Time dependence of the relative abundances of [D$_3$]-**X** and **X** upon adding CH$_3$OH to a solution of 1-phenylpropyne in CD$_3$OD and the catalyst (CH$_3$OH/CD$_3$OD 1:1 (v/v)) after 1 hour reaction time. The solid lines correspond to fitted exponential functions (see also the Supporting Information, Figure S5). The sections of the MS spectra (c) show the averaged spectra in the beginning (1–5 min) and in the end (26–30 min) of the experiment.

Electrospray ionization of a methanolic solution of 1-phenylpropyne and [AuCl(PMe$_3$)] leads to the [Au(PMe$_3$)$_2$]$^+$ cation and its cluster bound by the chlorine counterion, [Au$_2$Cl(PMe$_3$)$_2$]$^+$ (Figure 1a; for an assignment of minor peaks, see the Supporting Information). Furthermore, two complexes containing the alkyne can be detected: [Au(PhCCMe)(PMe$_3$)]$^+$ and a complex **X** with *m*/*z* 693. Collision-induced dissociation experiments with mass-selected **X** (Supporting Information, Figure S1) as well as analogous experiments in [D$_4$]methanol (Supporting Information, Figure S4) show that **X** contains 1-phenylpropyne, two gold atoms with two trimethylphosphine groups, and a methoxy group. If this ion were a simple cluster of two [Au(PhCCMe)(PMe$_3$)]$^+$ cations bound by a methanolate counterion, a cluster bound by chloride would also be expected, which is however not present in the spectrum. Therefore, the complex **X** may correspond to a possible intermediate. In minor abundance, a complex between the (trimethylphosphino)gold cation and the product of the addition of methanol to 1-phenylpropyne is detected, which is denoted as **Y** (*m*/*z* 421; addition of methanol to 1-phenylpropyne can lead to (*E*)/(*Z*)-2-methoxy-1-phenylpropene or (*E*)/(*Z*)-1-methoxy-1-phenyl-

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propene). **X** is formally related to **Y** by replacement of H by $AuPMe_3$. Thus, we can consider two possible pathways for the formation of **X**: 1) addition of $[Au(OMe)(PMe_3)]$ instead of methanol to the initially formed mononuclear gold complex $[Au(PhCCMe)(PMe_3)]^+$, or 2) addition of methanol followed by deprotonation and subsequent complexation with $Au(PMe_3)^+$ (Supporting Information, Scheme S1).

To check whether **X** represents a possible intermediate in the condensed phase or is formed during the electrospray process, the reaction mixture in CD_3OD was kept for one hour, then diluted to a double volume by CH_3OH and immediately monitored by ESI-MS. The spectra recorded right after the mixing the solvents show dominant abundance of the $[D_3]$-**X** complex (*m*/*z* 696), whereas after about 20 min, the statistically expected 1:1 ratio of the unlabeled **X** and the labeled $[D_3]$-**X** complex is established (Figure 1 b,c). First, this result demonstrates that **X** represents a species formed in the solution and thus it is not a gas-phase artifact. Second, the experiment allows us to determine the half-life of **X** as about 3.7 minutes at 25 °C in the reaction solution (Supporting Information, Figure S5). The same experiment also confirms that species **Y** corresponds to a (trimethylphosphino)gold complex with the product of the methanol addition, because only the $[D_4]$-labeled complex is observed in the beginning. At longer reaction times, we also observe the product of the complexes of the products owing to addition of CH_3OH, CH_3OD, and CD_3OH (*m*/*z* 421, 422, and 424 respectively), but the statistical ratio is still not achieved after 20 min (cf. Figure 1 c). This finding implies that **X** is formed substantially faster than **Y**. Thus, **X** is not a secondary product formed from **Y** by deprotonation and subsequent complexation with $[Au(PMe_3)]^+$. On contrary, **Y** can be formed from **X** by hydrolysis, and this step is a subject to a substantial kinetic isotope effect, as shown by the ratio of signals at *m*/*z* 421 and 422 (exchange of $[Au(PMe_3)]^+$ by H^+ and D^+, respectively).

The structure of intermediate **X** was characterized by IRMPD spectroscopy. This method provides IR spectra for mass-selected ions in the gas phase,[21,22] which are usually assigned based on comparison with the theoretical spectra. Out of many considered isomers of **X**, the most stable structures correspond to complexes with the methoxy group attached to the carbon atom of the C–C double bond in that the second carbon atom of this double bond carries both (trimethylphosphino)gold units.[23] The more stable intermediate is formed by the addition of the methoxy group to the C2 carbon; however, the theoretical IR spectrum of the product of the C1 addition agrees better with the experimental spectrum (Figure 2); most likely, a mixture of both intermediates is sampled by IRMPD. By comparison of the experimental and theoretical spectra, the band at 1490 cm^{-1} can be assigned to a stretching mode of the C–C double bond formed upon addition of gold methanolate to 1-phenylpropyne. The bands at 1275 cm^{-1} and 1125 cm^{-1} agree well with the stretching vibrations of the C–O bonds between the oxygen atom and the carbon atoms of the vinyl and the methyl groups, respectively. The band at 955 cm^{-1} corresponds to the deformation vibration of the phosphine ligands. Clearly, the spectrum of a simple adduct (Figure 2 d) does not explain the experimental spectrum as the characteristic

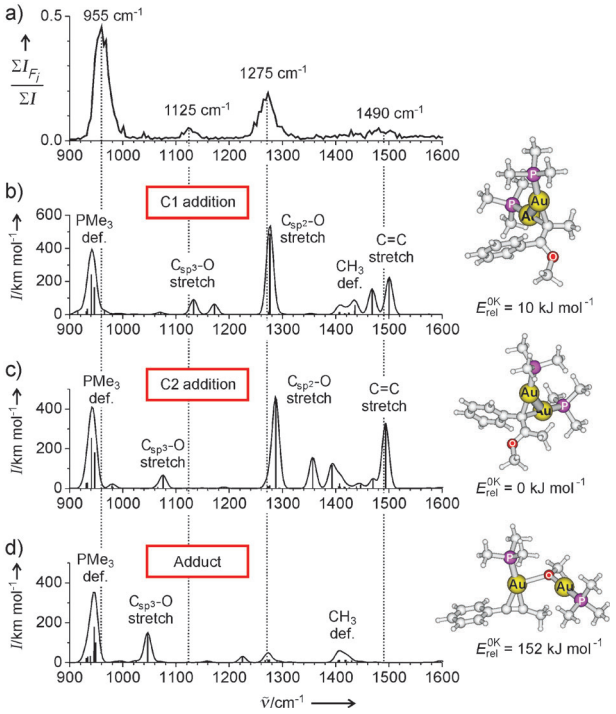

Figure 2. a) IRMPD spectrum of X (*m*/*z* 693) and theoretical IR spectra of possible reaction intermediates (b–d).

modes of the addition product are missing (for more examples, see the Supporting Information, Figure S6).

The reaction was further investigated using NMR spectroscopy (Figure 3). For the C2 addition, we mainly observe the addition of two molecules of methanol (2,2-dimethoxy-1-phenylpropane along with small amounts of 1-phenyl-2-propanone formed by hydrolysis of the ketal with traces of water), which suggests that the second addition is much faster than the first addition of methanol. On the other hand, for the C1 addition, we see clearly products of both the single and the double addition of methanol. This observation can be attributed to the different steric demands of the intermediates and also provides an explanation as to why the intermediate for the less-stable product is preferentially sampled with the IRMPD experiments. Kinetic modeling of the NMR data (Figure 3) predicts that the second addition of the methanol molecule to the C2 carbon atom proceeds about 100 times faster than the first addition, whereas the second step is only six times faster than the first for the C1 addition.

Inspired by these experiments, we have investigated the reaction mechanism for the first addition of methanol using density functional theory.[24] The classically considered reaction pathway, in which the $[Au(PhCCMe)(PMe_3)]^+$ ion is proposed to react with methanol, proceeds with high energy barriers, and the initial methanol addition is endothermic by more than 50 kJ mol^{-1} (Supporting Information, Figure S10, Table S1). However, it has been shown by Lein et al. for the $AuCl_3$-mediated addition of water to alkynes that the reaction is assisted by another molecule of water, which accepts a proton from the incoming H_2O molecule and thereby stabilizes the initial addition product.[15] In the reaction investigated herein (Figure 4 a), such a scenario leads from

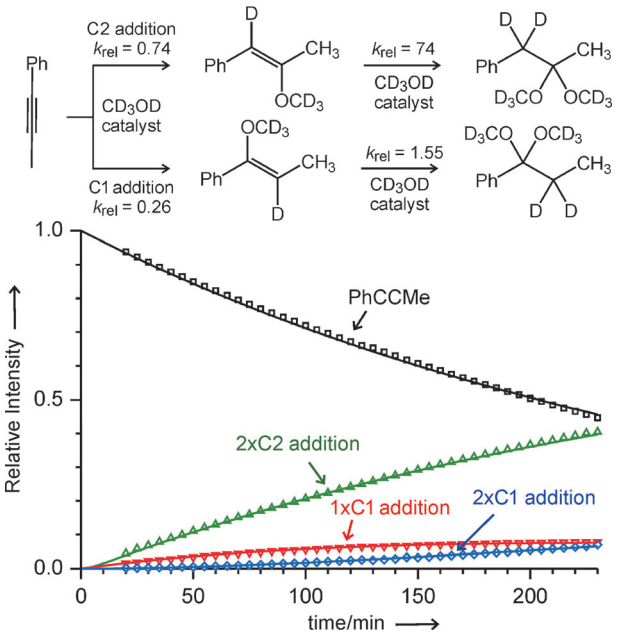

Figure 3. Relative ratios of 1-phenylpropyne and the products of C1 and C2 additions as a function of the reaction time as monitored by NMR spectroscopy. The yield of 1-phenyl-1-methoxypropene is shown in red. Products of the addition of two molecules of methanol (sum of the corresponding ketals and ketones formed upon hydrolysis with a residual moisture) are shown in blue for the C1 addition and in green for the C2 addition. The solid lines correspond to the results of the kinetic modeling according to the equations displayed on top.

the initial structure **1** to transition structures TS**1/2** or TS**1/4** stabilized by hydrogen bonding. Nevertheless, formation of the respective primary products of C2 addition (**2**) and C1 addition (**4**) remains endothermic (23 and 32 kJ mol^{-1}, respectively). The subsequent hydrogen atom migration mediated by the second molecule of methanol is a subject to a higher energy barrier than the initial methanol addition, but it can be expected that involvement of additional solvent molecules lowers this barrier.

The reaction pathway involving two gold atoms starts with adduct **6**, in which the $[Au(PhCCMe)(PMe_3)]^+$ ion is bound to $[Au(MeO)(PMe_3)]$ by the oxygen atom (Figure 4b). The favored reaction pathway corresponds to an *anti*-periplanar addition of $[Au(MeO)(PMe_3)]$ to the triple bond coordinated to the gold cation. The coupling reaction at C2 (TS**6/7**) proceeds with an energy barrier of 27 kJ mol^{-1} and at C1 (TS**6/9**) with an energy barrier of 23 kJ mol^{-1}. The addition is highly exothermic, and it is expected that the (trimethylphosphino)gold cation, which is loosely bound in the less stable isomers **7** and **9**, will easily migrate from the oxygen atom to the carbon to yield the more stable complexes **8** and **10** (formed directly by *syn*-periplanar addition). These product complexes correspond to the intermediates observed with the ESI-MS experiments. The addition to the C1 carbon proceeds with a lower energy barrier, but it leads to a thermodynamically disfavored product, similar to the mechanism involving just one gold cation. We note in passing that possible routes to the formation of **1**, **6**, and $[Au(MeO)(PMe_3)]$ are discussed in the Supporting Information.

The theoretical results thus show that the mechanism involving two (trimethylphosphino)gold cations proceeds with smaller energy barriers and the formations of the intermediates are highly exothermic. The results are consistent with all experimental observations and also with the fact that we observe this intermediate readily and in large abundance. On the other hand, if the mechanistic scenario involving catalysis with just one gold cation should account for the experimental observations, then the endothermic intermediates **2** and **4** would have to be deprotonated and the formation of the complex with another (trimethylphosphino)gold cation would have to be faster than the reprotonation step to form **3** and **5**, respectively.[25–28] This would require that the second gold cation is already involved in the process of the deprotonation, and from the mechanistical point of view it would lead again to the conclusion that two gold cations are involved in the addition of methanol to a triple C–C bond. An alternative route via neutral $[Ph–C(AuPMe_3)=C(CH_3)(OMe)]$ as an intermediate[29,30] appears less likely, because we do not observe such a protonated species by ESI-MS (that is, protonation by H^+ and D^+ should immediately lead to a 1:1 ratio of $[D_3]$-**Y** and $[D_4]$-**Y** in the experiment shown in Figure 1c).

The results presented herein demonstrate that the addition of methanol to a triple C–C bond proceeds with a dual activation mechanism in that the triple bond is activated by the coordination with the gold catalyst and methanol is added in the form of gold methanolate. The dual activation mechanism results in direct formation of *gem*-diaurated intermediates. A similar scenario was recently suggested for cycloisomerization reactions of polyunsaturated hydrocarbons catalyzed by gold(I) complexes.[31–35] Thus, widening of this concept to the additions of O-nucleophiles can have a substantial effect on the mechanistic understanding of the gold-catalyzed reactions. Furthermore, as the addition of alcohol represents an initial step of many cascade reactions involving alkynes, the understanding of the mechanistic aspects may guide in designing new synthetic methods.[36]

Experimental Section

The reaction mixture was prepared by mixing a supernatant solution of $AgSbF_6$ and $[AuCl(PMe_3)]$ in methanol (either CH_3OH or CD_3OD) with 1-phenylpropyne so that a 0.24 M solution of 1-phenylpropyne with 2.5 mol% of the (trimethylphosphino)gold catalyst was prepared (for details, see the Supporting Information). For the mass spectrometry experiments, the reaction mixture was diluted 10-fold.

Mass spectrometry experiments were performed with a TSQ 7000 mass spectrometer[37,38] with a quadrupole–octopole–quadrupole configuration. The ions were generated by electrospray ionization (ESI) from the reaction mixtures described above at soft ionization conditions, and the mass spectra were recorded by scanning the first quadrupole. The IR multiphoton dissociation spectrum of the mass-selected ions (generated as above) with *m*/*z* 693 was recorded with a Bruker Esquire 3000 ion trap mounted to a free electron laser (FEL) at CLIO (Center Laser Infrarouge d'Orsay, Orsay, France).[39] The FEL was operated in the 43 MeV electron-energy range. Each point in the spectrum is an average of 20 measurements. The ions were mass-selected and stored in an ion trap. The fragmentation was induced by four laser macropulses admitted to the ion trap. The

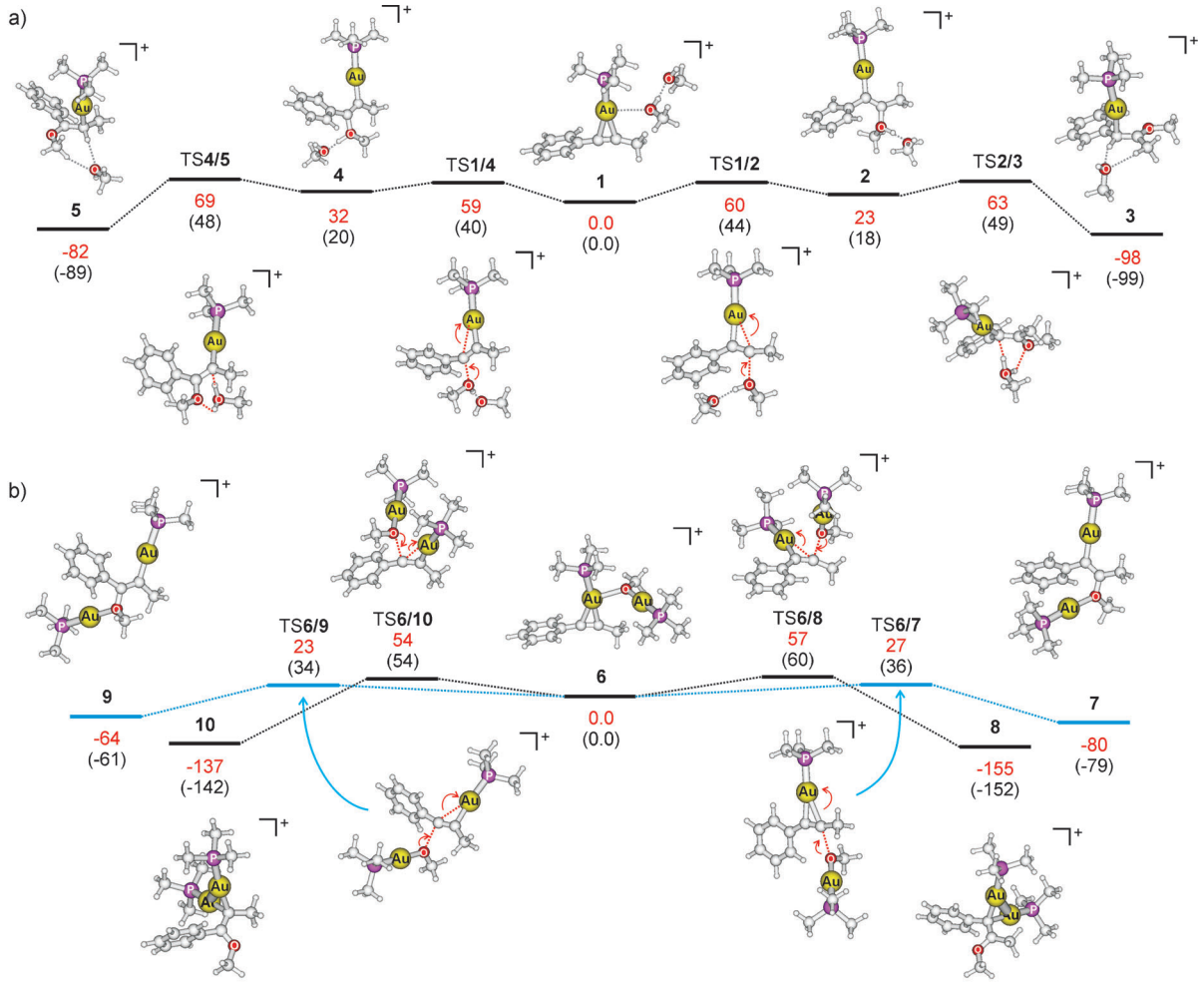

Figure 4. Potential energy surfaces (mPW1PW91/cc-pVDZ:LANL2DZ(Au)) for the $[AuPMe_3]^+$ catalyzed reaction of 1-phenylpropyne with a) methanol assisted by another molecule of methanol and b) with $[Au(OMe)(PMe_3)]$. The relative energies are given in kJ mol^{-1} at 298 K in methanol (red numbers) and at 0 K in the gas phase (black numbers in brackets).

reported IRMPD spectrum is not corrected for the power of the free-electron laser, which slightly changes in dependence of the wavenumbers (Supporting Information, Figure S7).

The NMR experiments were recorded using Bruker AVANCE III (600 MHz) and the δ scale was referenced to a solvent residual peak at $\delta = 3.31$ ppm. The solutions of the catalyst and the reactant were mixed and immediately introduced to the NMR instrument. The instrument was tuned for 20 min and then acquisition was started. The representative spectrum together with the assignments of peaks is shown in the Supporting Information, Figure S8.

Calculations were performed using the density functional theory method mPW1PW91[40,41] as implemented in the Gaussian 09 package.[42] As a basis set, the combination of the cc-pVDZ basis set for C, H, O and P and the LanL2DZ basis set for Au was used. The IR spectra were calculated using a larger basis set (cc-pVTZ for C, H, O, and P and LanL2DZ for Au). All of the reported structures represent genuine minima or transition states on the respective potential-energy surfaces, as confirmed by analysis of the corresponding Hessian matrices. All minima and transition states were further reoptimized using the polarized continuum model for modeling the effect of solvent[43] and frequency calculations were again performed to control the identity of the stationary points as well as to obtain thermochemical corrections for energies at 0 K and Gibbs energies at 298 K. The scaling factor for the calculated IR spectra is 0.96.[44] All optimized structures and their energies are listed in the Supporting Information, Table S1.

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