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Mechanistic Insights about the Ligand-Enabled Oxy-arylation/vinylation of Alkenes via Au(I)/Au(III) Catalysis

Mathilde Rigoulet,[a] Karinne Miqueu,[b] and Didier Bourissou*[a]

Abstract: The mechanism of oxy-arylation/vinylation of alkenes catalyzed by the (MeDalphos)AuCl complex was comprehensively investigated by DFT. (P,N)Au(Ph)²⁺ and (P,N)Au(vinyl)²⁺ are key intermediates accounting for the activation of the alkenols and for their cyclization by outer-sphere nucleophilic attack of oxygen. The 5-exo and 6-endo paths have been computed and compared, reproducing the peculiar regioselectivity difference observed experimentally between 4-penten-1-ol, (E) and (Z)-4-hexen-1-ols. Examining the way the alkenol coordinates to gold (more η² or η¹) can offer, in some cases, a simple way to predict the favored path of cyclization.

Introduction

Over the past 10 years, the repertoire of gold catalysis has been extended to Au(I)/Au(III) catalysis, with three complementary approaches based on external oxidants, photoredox conditions and most recently ligand-enabled oxidative addition.[1] The associated synthetic developments include C–C and C–X (X = N, S, Se ...) cross-couplings, but also the combination of Au(I)/Au(III) cycles with π-activation at gold.[2] This enables to perform a variety of intra as well as intermolecular 1,2-difunctionalization reactions of alkenes, with O, N and C-based nucleophiles (Figure 1a).[3]

It is to note that gold is not a simple copy of the other transition metals in these transformations. It displays complementary behavior, in particular high functional group tolerance.[4] Moreover, the aforementioned oxidative/photoredox/ligand-enabled approaches result in different reaction profiles of gold with respect to the preference for electron-enriched/deprived aryl substrates,[2c,h] as well as exo/endo regioselectivity.[2c,h]

These synthetic developments have stimulated mechanistic studies to better understand the way the reactions proceed and what influence them. From an experimental viewpoint, the stereochemical outcome of the reaction (syn/anti addition across the C–C double bond as most often determined by D-labeling experiments) was used as reporter to distinguish inner- and outer-sphere paths (Figure 1b). All reactions reported to date apparently follow the outer-sphere path, whatever the conditions (external oxidants, light-mediated or ligand-enabled).[2a,c,h]

Two computational studies have also been reported recently.[6–8] In 2016, Yu and co-workers studied the oxy-arylation of alkenes under dual gold photoredox conditions, showing that Au(III)-aryl complexes are first generated by dual gold photoredox conditions, showing that Au(III)-aryl complexes are first generated by
radical addition to gold and single electron transfer, followed by coordination of the alkene, cyclization and reductive elimination.[5] Earlier this year, Zhang and co-workers investigated the ligand-enabled 1,2-diarylation of alkenes, considering both the coupling of aryl alkenes with aryl iodides and that of iodoaryl alkenes with indoles.[8] The reactions were found to involve π-activation not migratory insertion, and the exo/Markovnikov regioselectivities observed experimentally were nicely reproduced theoretically.

Here we report a complementary Density Functional Theory (DFT) study we have carried out on the intramolecular oxy-arylation/vinylation of alkenes (Figure 1c). We have shown these reactions to be efficiently catalyzed by the (MeDalphos)AuCl complex (thanks to ligand-enabled oxidative addition). The outer-sphere path was supported experimentally by the observed trans selectivity of the alkene difunctionalization. Moreover, an unprecedented switch of regioselectivity, 5-exo vs. 6-endo cyclization, was noticed between Z- and E-substituted internal alkenols. Special attention was thus given to the influence of the substitution pattern of the alkene: terminal, Z/E-internal. The geometry and electronic structures of the key π-alkene Au(III) complex, prior to cyclization by outer-sphere nucleophilic attack, turned to be decisive.

Results and Discussion

The outer-sphere catalytic cycle proposed to account for the oxy-arylation/vinylation of alkenes catalyzed by (MeDalphos)AuCl is displayed in Scheme 1. It starts by oxidative addition of the aryl/vinyl iodide substrate triggered by the hemilabile (P,N) ligand. Following iodide abstraction by the silver salt, the alkenol coordinates to gold and the pendant hydroxyl group attacks the C–C double bond (anti to gold). Finally, reductive elimination induces C(sp²)–C(sp³) coupling and releases the product. The oxidative addition step has already been comprehensively studied experimentally and computationally.[5a,5b] The outer-sphere mechanism was supported experimentally over the alternative inner-sphere pathway (involving migratory insertion) by the selective formation of anti addition products from internal alkenols (as well as D-labeled N-tosyl pent-4-enyl amines),[8] and computationally by Zhang and co-workers in their recent study of 1,2-diarylation reactions.[8] In this work, we focused on the activation, cyclization and arylation/vinylation of the alkenols at gold. To this end, we studied computationally the structure and reactivity of the key (P,N)Au(Ph)³⁺/(P,N)Au(vinyl)²⁺ complexes 2/2v, considering terminal as well as internal alkenols and giving special attention to the regioselectivity (5-exo vs. 6-endo cyclization).

The main objective of this computational study was to gain further mechanistic insight on such gold-catalyzed transformations. In particular, it was our aims (i) to identify the key intermediates and analyze their structure/reactivity, and (ii) to compute and compare the different cyclization modes to shed light into the regioselectivity (5-exo vs. 6-endo) and better understand the influence of the alkenol substitution pattern (terminal, Z/E internal).

The calculations were carried out on the real systems, without simplification of the (P,N) ligand, at the SMD(CH₂Cl₂)-B3PW91-D3(BJ)/SDD + f(Au), 6-31+G** (other atoms)/B3PW91/SDD + f(Au), 6-31G**(other atoms) level of theory. Solvent and dispersion effects were taken into account, but not the counter-anion.[10]

To begin with, we investigated the oxy-phenylation reaction and studied the (P,N)Au(Ph)³⁺ complex, the key reactive species towards alkenols. Two minima were located on the potential energy surface (PES). In both cases, the 3-coordinate gold center adopts T-shape geometry with the phenyl group in internal (trans) or phosphorus (Z) (Figure 2). The (P,N) ligand is highly dissymmetric electronically: the phosphine is a stronger σ-donor ligand than the amine and exerts a stronger trans influence. Consistently, complex 2 with the phenyl group trans to nitrogen was found to be much more stable than 2’. Considering the very large energy gap between the two isomers (29.6 kcal/mol), only 2 was then considered.

Scheme 1. Simplified catalytic cycle proposed to account for the 1,2-oxy-arylation/vinylation of alkenols catalyzed by the (P,N)AuCl complex (with 4-penten-1-ol as model substrate, only showing the 5-exo cyclization product obtained experimentally).

Figure 2. Cis and trans forms of the (P,N)Au(Ph)³⁺ complex. Relative Gibbs free energies in parentheses, in kcal/mol.
Oxy-arylation of 4-penten-1-ol (terminal alkenol)

The reaction of the (P,N)Au(Ph)_2 complex 2 with 4-penten-1-ol was explored first, as benchmark oxy-arylation reaction proceeding exclusively by 5-exo cyclization to give a 2-benzyltetrahydrofuran (Scheme 2). [26]

The alkenol can bind to gold via either the C–C double bond or the oxygen atom. Energy minima for the two coordination modes were localized on the potential energy surface (Scheme 3, Figure S2). [12] In the π-complex 3, the C–C double bond is oriented about perpendicular to the gold coordination plane of (C=C)Au=O (−105.5°) in order to minimize steric repulsions. The Au–N distance is short, 2.267 Å (vs. 2.194 Å in 2), indicating strong N→Au interaction (it is found as a donor-acceptor interaction by NBO analysis and the respective delocalization energy ΔE(2) = 51.6 kcal/mol). The formation of the π-complex 3 is exergonic by 4.5 kcal/mol. The corresponding O-adduct 3° lies significantly higher in free energy, in line with the hard, oxophilic character of Au(I). However, the formation of 3° is probably an unproductive path. Indeed, from 3°, no transition state (TS) could be located for the insertion of the alkene into the Au–O bond. If the alkenol coordinates via the oxygen atom, it is likely 3° then converts into the π-complex (3) from which the oxy-arylation reaction proceeds readily.

The energy profiles for the 5-exo and 6-endo oxophenylation of 4-penten-1-ol were both computed. They are depicted in Figure 3. From the π-complex 3, nucleophilic addition of the pendant alcohol can occur either on the C1 atom (internal alkenol) or on the C2 atom (terminal CH2). [14] The respective transition states (TS1 LOAD and TS1 ON1) then evolve into the O-protonated intermediates A1 LOAD and A2 LOAD (Figure 3). The activation barrier for the 5-exo cyclization is very low (TS1 ON1 ΔG° = 2.7 kcal/mol), it is significantly smaller than that of the 6-endo cyclization (TS1 LOAD, ΔG° = 8.6 kcal/mol), in line with the full 5-exo regioselectivity observed experimentally. Of note, the formation of the C–O bond is slightly more advanced in TS1 LOAD (1.878 Å vs. 1.639 Å for A2 LOAD) than that of the C3–O bond in TS1 LOAD (2.043 Å vs. 1.568 Å for A2 LOAD).

The cyclized intermediates 4 LOAD then readily react with KPO4 to give the monocatonic complexes 5O along with K[Ph]HPO4. [15] This deprotonation step is highly exergonic (ΔG° < −40 kcal/mol), making the formation of 5O irreversible. Reductive elimination finally induces C(sp2)–C(sp2) coupling and affords the oxy-phenylation products as π-adducts of the (P,N)Au⁺ fragment. This step is also highly exergonic, by 24.7 kcal/mol from 5O and 26.9 kcal/mol from 5O. The activation barriers for the formation of 2-benzyltetrahydrofuran and 3-phenyltetrahydropryan are very similar, 17.9 and 17.0 kcal/mol, respectively. These values fall in the same range than those computed for related C(sp2)–C(sp2) couplings at gold(III) [16] and are consistent with a reaction proceeding within hours at room temperature (this step is likely rate-determining).

Of note, deprotonation of the cyclized intermediates 4 LOAD by KPO4 facilitates the C(sp2)–C(sp2) coupling step, the activation barriers for the reductive elimination of 4 LOAD were found to be 6.9–7.9 kcal/mol larger than for the deprotonated intermediates 5O (Figure S3). [12,17]

The mechanism of C(sp2)–C(sp2) coupling at gold(III) deserves some comments. It involves concerted cleavage of the Au–Ph/Au–alkyl bonds and formation of the Ph–alkyl bond. The corresponding 3-center transition state TS2,2,19 is depicted in Figure 3. The Au–N distance noticeably increases (2.279 Å in 4 LOAD, which somewhat reduces the coordination number at gold and thereby facilitates the reductive elimination, in line with that previously reported with simple phosphine ligands. [18]

Thus, the energy profiles computed for the reaction of 4-penten-1-ol with the (P,N)Au(Ph)_2 complex 2 are consistent with the facile and selective formation of 2-benzyltetrahydrofuran. Cyclization of the π-complex 3 by outer-sphere nucleophilic attack of the oxygen atom is the regio-discriminating step. Deprotonation by KPO4 is assumed to occur after this cyclization, while the rate-determining step is most likely the final reductive elimination leading to C(sp2)–C(sp2) coupling.

Oxy-arylation of (Z) and (E) 4-hexen-1-ols (internal alkenols)

The reaction of the (P,N)Au(Ph)_2 complex 2 with internal alkenols was then investigated. The E and Z isomers of 4-hexen-1-ol were considered with the aim to analyze the different outcomes we unexpectedly observed with these substrates experimentally. Indeed, if both (E) and (Z)-4-hexen-1-ol underwent the gold-catalyzed oxy-arylation reaction to give a single product resulting from trans-addition across the C=C bond, a complete switch of regioselectivity was observed. [28,19] The Z substrate selectively underwent 5-exo cyclization to produce a tetrahydrofuran derivative, whereas the E substrate reacted exclusively via a 6-endo process to give a pyran ring (Scheme 4).

First, we explored the oxy-phenylation of (Z)-4-hexen-1-ol, where only the 5-exo product was obtained, as for 4-penten-1-ol. The energy profile is depicted in Figure 4 with the π-complex...
3 as common gateway for the attack of the O atom to the two carbon atoms of the C=C double bond, C_i and C_Me. As for the internal alkenol, π-coordination of (Z)-4-hexen-1-ol to gold is slightly exergonic (by 5.3 kcal/mol in this case). The largest impact of the additional methyl group is found in the 5-exo cyclization (TS1_OHS). Its activation barrier increases by 4.3 kcal/mol at ΔG° = 7.0 kcal/mol (vs. 2.7 kcal/mol for 4-penten-1-ol). This increase is tentatively attributed to steric factors as it is this carbon atom (C_Me) that receives the bulky (P,N)Au(Ph) fragment. Comparatively, the activation barrier for the 6-endo cyclization (TS1_OHS) is only marginally affected at ΔG° = 9.0 kcal/mol (vs. 8.6 kcal/mol for 4-penten-1-ol). In the end, the transition state 

Figure 3. Energy profiles (ΔG in kcal/mol) for the 5-exo (black)/6-endo (blue) oxy-phenylation of 4-penten-1-ol by the (P,N)Au(Ph)²⁺ gold complex 2.

Calculations performed at the SMD(CH₂Cl₂)-B3PW91-D3(BJ)/SDD+f(Au), 6-31G** (other atoms) level of theory in the presence of K₂PO₄, K₃HPO₄ and K⁺ are included in all steps to ensure correct energy balance. Structures of the TSs with main distances in Å.

Scheme 4. Switch of regioselectivity observed upon catalytic oxy-arylation of (Z/E)-4-hexen-1-ols.²⁵⁺
TS1_{OH5Z} remains lower in energy than TS1_{OH6Z}, in agreement with the 5-endo regioselectivity, but the difference between the 5-endo and 6-endo paths is only 2.0 kcal/mol (instead of 5.9 kcal/mol for 4-penten-1-ol).

Once again, the two cyclized intermediates 4_{OH5Z} and 4_{OH6Z} are readily deprotonated by K_3PO_4, making the cyclization process overall strongly exergonic and thus irreversible (the transformation of the \( \pi \)-complex 3 into the monocationic complexes 5_{O5Z} and 5_{O6Z} is thermodynamically downhill in energy by \( >30 \) kcal/mol). The reductive elimination step is minimally affected by the methyl substituent. From 5_{O5Z} and 5_{O6Z}, C(sp^2)-C(sp^3) coupling involves activation barriers of 15.2–16.3 kcal/mol (see Figure S5 for the calculations from the protonated intermediates)\(^2\) and it is strongly exergonic, by 29.2–30.5 kcal/mol.

The reaction with the (E)-4-hexen-1-ol was also considered. Here, significant differences were noticed compared to (Z)-4-hexen-1-ol and 4-penten-1-ol, in particular in the cyclization step (Figure 5). The most favorable paths for the nucleophilic attack of the oxygen atom to C_i and C_{Me} derive from distinct \( \pi \)-complexes 3_E and 3'_{E}, which differ in the way the C=\( \pi \) bond coordinates to gold. 3_E is connected to the 6-endo cyclization transition state TS1_{OH6E} and 3'_{E} to the 5-exo one, TS1'_{OH5E}. 3'_{E} is slightly higher in energy than 3_E (by 2.1 kcal/mol), and TS1_{OH6E} lies 0.9 kcal/mol below TS1'_{OH5E} in this case, in line with the 6-endo selectivity observed experimentally. Of note, the activation barrier for the 6-endo cyclization of (E)-4-hexen-1-ol (5.5 kcal/mol) is significantly lower than those found for 4-penten-1-ol and (Z)-4-hexen-1-ol (8.6 and 9.0 kcal/mol, respectively), and consistently, the transition state TS1_{OH6E} is earlier (the distance of the forming C···O bond is 2.335 Å, vs. 2.012–2.043 Å for the terminal and Z-alkenols, respectively). The reductive elimination (C(sp^2)-C(sp^3) coupling) remains the rate-determining step, with an activation barrier \( \Delta G^\ddagger \approx 6 \) of \(~18\) kcal/mol for both the tetrahydropyran and tetrahydrofuran products, corroborating the weak impact of the substitution of the double bond of the alkenol by Me on this step.

Thus, the energy profiles computed for the reaction of the (P,N)Au(Ph)_2^+ complex 2 with 4-penten-1-ol, (Z)-4-hexen-1-ol and (E)-4-hexen-1-ol nicely parallel the experimental results. The \( \pi \)-complexes deriving from the coordination of the C=\( \pi \) bond to gold(III) are key intermediates. From there, outer-sphere nucleophilic attack of the oxygen atom is governing the regioselectivity. Considering the different paths and locating the corresponding transition states, 5-exo cyclization was found to be indeed favored for the terminal and Z-alkenols, while the E-alkenol undergoes preferentially 6-endo cyclization.

Figure 4. Energy profiles (\( \Delta G \) in kcal/mol) for the 5-exo (black)/6-endo (blue) oxy-phenylation of (Z)-4-hexen-1-ol by the (P,N)Au(Ph)_2^+ gold complex 2 computed at the SMD(CH_2Cl_2)-B3PW91-D3(BJ)/SDD + f(Au), 6-31 + G**(other atoms))/B3PW91/SDD + f(Au), 6-31G**(other atoms) level of theory in the presence of K_3PO_4, (K_2HPO_4 and K^+ are included in all steps to ensure correct energy balance).
Previous computational studies have shown that π-complexes play a key role in nucleophilic additions to π-CC bonds promoted by transition metals. It was pointed out early on that the preferred site of nucleophilic attack may be related to the coordination mode of the π-CC bonds (η^2 to η^1 slippage), potentially enabling to predict regioselectivity (Figure 6).[21]

For example, G. Ujaque, A Lledos and I. Fernández recently studied the origin of anti-Markovnikov regioselectivity in the hydroamination of alkenes catalyzed by Rh(I) and Au(I) complexes.[21c,d] In both cases, the structure of the reactive π-complex was found to control regioselectivity. The relative contribution of the terminal and internal C atoms in the LUMO was found to be critical, not their atomic charges. Zhang et al. also emphasized the role of π-complexes in the 1,2-diarylation of alkenes catalyzed by the (P,N)Au complex, but here, regioselectivity was proposed to result rather from charge control and electrostatic interactions.[8]

Structure of the gold(III) π-complexes

Given these precedents, the structure of the π-complexes involved in the cyclization of 4-penten-1-ol, (Z)-4-hexen-1-ol and (E)-4-hexen-1-ol promoted by the (P,N)Au(Ph)^2+ gold(III) complex 2 were analyzed in-depth and compared. Their optimized geometries are displayed in Figure 7.[22] In the π-complex 3, the AuC distance (2.261 Å) is much shorter than the AuC distance (2.781 Å, Δ(AuC) 0.73 Å) indicating strong slippage of the C=C double bond towards η^1-type coordination. The (Z) internal alkenol also binds to complex 2 in a highly dissymmetric manner although the difference between the AuC distances is not as large in 3'Z (AuC^Z 2.417 Å, AuC, 2.781 Å, Δ(AuC) 0.36 Å). Remarkably, the two π-complexes deriving from (Z)-4-hexen-1-ol are close in energy (ΔG = 2.1 kcal/mol) but adopt quite different coordination modes. In 3'Z, the C=C double bond is dissymmetrically coordinated to gold. The AuC^Z distance (2.332 Å) is significantly shorter than the AuC,

Figure 5. Energy profiles (ΔG in kcal/mol) for the 5-exo (black)/6-endo (blue) oxy-phenylation of (E)-4-hexen-1-ol by the (P,N)Au(Ph)^2+ gold complex 2 computed at the SMD(CH_2Cl_2)-B3PW91-D3(BJ)/SDD + f(Au), 6-31+G**(other atoms)/B3PW91/SDD + f(Au), 6-31G**(other atoms) level of theory in the presence of K_2PO_4, K_2HPO_4 and K^+ are included in all steps to ensure correct energy balance.

Figure 6. Schematic representation of nucleophilic additions to alkenes promoted by transition metals and the influence η^2/η^1 coordination may have on regioselectivity.
distance (2.872 Å), the difference between the two (Δ(Au–C) 0.54 Å) being at halfway of those found in 3 and 3Z. In stark contrast, the π-complex 3E adopts a quasi symmetric η1⁺-type structure, with AuC and AuC distances of 2.564 and 2.525 Å, respectively (Δ(AuC) 0.039 Å). The η1 / η1' slippage of the C=C bond at gold from complexes 3, 3'E and 3Z to 3E is also apparent from the Wiberg Bond Indexes (WBI) for the C=C and Au–C bonds (Figure 7).

The electronic structure of the π-complexes was also thoroughly analyzed. The relevant orbital for the outer-sphere nucleophilic attack of the oxygen atom to the π-activated C=C bond is the LUMO. It is mainly associated with the interaction of the πC–C of the alkenol with the σ*Au of the gold fragment (Figures 8, S8 and S9).[12] The contributions of the two carbon atoms of the C=C double bond (on which the cyclization may occur) were assessed by an orbital composition analysis (their relative weight is expressed in %). Accordingly, the LUMO was found to be strongly polarized towards the internal carbon atom C with involved in 5-exo cyclization for the π complexes 3 and 3Z deriving from 4-penten-1-ol (85.5 % C) and (2Z)-4-hexen-1-ol (81.0 % C) respectively, as well as for the π-complex 3'E deriving from (E)-4-hexen-1-ol (83.5 % C) respectively. In contrast, the two carbon atoms contribute about equally to the LUMO of complex 3E involved in 6-endo cyclization, and the contribution of C in this case, in line with the observed 6-endo cyclization.

Overall, these results nicely parallel our experimental observations and suggest that the regioselectivity outcome of the alkenol cyclization is to some extent encoded into the π-complexes. It is noteworthy that in this case, orbital and charge effects apparently fail in line to drive the nucleophilic attack of O towards 5-exo or 6-endo cyclization (Figure 9). The origin of the switch of regioselectivity observed for the E-internal alkenol is likely the symmetric η1'-type coordination of the C=C double bond at gold in 3E, resulting in a larger coefficient on C in the LUMO, and a higher atomic charge at C than at C. If calculations are to be used to predict the preferred cyclization mode, it may be possible to simply refer to the π-complex when it adopts a single well-defined coordination.
Figure 9. Schematic representation of the 5-exo/6-endocyclization of alkenols at gold according to the coordination mode and electronic structure of the respective π-complex (C, C, and CMe refer to the terminal, internal, and Me-substituted carbon atoms of the C–C double bond, respectively).

Oxy-vinylation of terminal and Z/E-internal alkenols

Besides aryl iodides, the (MeDalphos)AuCl complex was shown to readily activate vinyl iodides and to efficiently catalyze the oxy-vinylation of alkenols. This transformation was also investigated by DFT with the aim to further assess the impact of the alkenol coordination on regioselectivity. Experimentally, 4-penten-1-ol and (Z)-4-hexen-1-ol undergo 5-exo cyclization, while we obtained a mixture of 5-exo and 6-endo cyclizations to adequately compare the two paths and analyze the regioselectivity.

The oxy-vinylation of (Z)-4-hexen-1-ol was then considered (Figure 12). The corresponding vinyl π-complex 3v was found to be significantly lower than for the addition to the internal carbon atom C2 (8.3 vs. 2.1 kcal/mol), but it remains smaller than that required for the 6-exo cyclization (by 2.1 kcal/mol). As for the corresponding oxy-phenylation reaction, the structure of 3v may be anticipated to favor 5-exo over 6-endo cyclization, in line with experimental observations. This assumption was confirmed by computing the reaction profile for the oxy-vinylation (Figure 11). Most relevant are the transition states for the nucleophilic attack of oxygen from the π-complex 3v. The activation barrier for the addition to the internal carbon atom C2 (TS1vOH) of the π-complex 3v was found to be significantly lower than for the addition to the terminal carbon atom C1 (TS1vOH) (Δ(ΔG°) = 5.4 kcal/mol). 5-Exo cyclization via TS1vOH is thus clearly favored over 6-endo cyclization, and subsequent deprotonation with K2PO4 drives the reaction forward.

The oxy-vinylation of (Z)-4-hexen-1-ol is very important in...
the π-complex, namely 3v₂ and 3'v₂ (Figure 12). They adopt quite different structures. In 3v₂, the C=C double bond slips towards η¹ coordination with AuC₆Me and AuC distances of 2.375 and 2.707 Å, respectively (Δ(AuC) = 0.34 Å). It is polarized as indicated by the relative contributions of C₆Me and C in the LUMO (80.3% and 19.7%, respectively), and the atomic charges (q = −0.04 at C₆Me, −0.38 at C, Δq = 0.34 e). In contrast, 3v₂ adopts a more symmetric η²-type structure, with AuC₆Me and AuC distances of 2.445 and 2.615 Å, respectively (Δ(AuC) = 0.17 Å). Here, the contribution of C₆Me in the LUMO is predominant (C₆Me: 69.3%, C: 30.7%) and the charge is higher at C₆Me than C (Δq = 0.19 e). The two π-complexes are quasi isoenergetic (ΔG = 0.5 kcal/mol). To compare the 5-exo and 6-endo routes for cyclization, it is thus needed to locate the corresponding transition states (see Figure 12, right). As expected from the structure of the respective π-complexes, 3v₂ readily connects with the 5-exo product (via TS₁v₂O₅E), while the 6-endo product is easily obtained from 3v₂ (via TS₁v₂O₆E). The corresponding transition states are low in energy (activation barriers of 4.3 and 5.4 kcal/mol, respectively) and actually very close (ΔG = 0.6 kcal/mol), in agreement with the competitive occurrence of 5-exo and 6-endo cyclization observed experimentally.

Overall, the DFT study of the oxy-vinylation nicely parallels the experimental results and corroborates the conclusions reached for the oxy-phenylation. The regioselectivity of the reactions is dictated by the cyclization step and here, the π-complex clearly plays a major role. When one coordination mode (η¹ or η²) is unambiguously favored, it is possible to refer to the geometry and/or electronic structure of the π-complex to explain and predict the regioselectivity. In this study, this is the case for 4-penten-1-ol and (Z)-4-hexen-1-ol which distinctly form dissymmetric polarized π-complexes and exclusively undergo 5-exo cyclization. However, when several π-complexes with η¹ and η²-like structures are close in energy, as for (E)-4-hexen-1-ol, it is necessary to perform a comprehensive mechanistic study and locate the transition states for the most
favorable paths of 5-exo/6-endo cyclizations in order to describe accurately the reaction and come to reliable conclusions.

Conclusion

This comprehensive DFT study provides mechanistic insights into the intramolecular oxy-arylation/vinylation of alkenols catalyzed by the (MeDalphos)AuCl complex and unravels the factors dictating its regioselectivity. The way alkenols coordinate to the (P,N)Au(Ph)\textsuperscript{2+} and (P,N)Au(vinyl)\textsuperscript{2+} complexes (\(\eta^1\) or \(\eta^2\)) plays a major role. With terminal and Z-internal alkenols, the \(\pi\)-complexes adopt \(\eta^1\)-like structures. The occurrence of 6-endo cyclization with E-internal alkenols likely finds its origin in competitive \(\eta^1\)-type coordination of the C=C double bond at gold. Here, orbital and charge effects fall in line to drive the nucleophilic attack of the pendant oxygen atom towards 5-exo or 6-endo cyclization. In the most favorable cases, referring to the \(\pi\)-complexes may be enough to predict the preferred path of cyclization (5-exo vs. 6-endo).

Such theoretical studies shed light into the structure and reactivity of key intermediates within ligand-enabled Au(I)/Au(III) catalytic cycles. This work also advances our understanding on the factors controlling the addition of nucleophiles to \(\pi\)-substrates at transition metals, an elementary step involved in many catalytic transformations.

Computational Details

All optimizations were performed using the Gaussian 16 package\textsuperscript{[24]} and the B3PW91 hybrid functional\textsuperscript{[25]} on the real systems, without taking into account the counter-ion. All stationary points involved were fully optimized in gas phase. The gold atom was described with the relativistic electron core potential SDD and associated basis set, augmented by a set of f-orbital polarization functions.\textsuperscript{[26]} The 6-31G** basis set was employed for all other atoms. Frequency calculations were undertaken to confirm the nature of the stationary points, yielding one imaginary frequency for transition states (TS), corresponding to the expected process, and all of them positive for minima. The connectivity of the transition states and their adjacent minima was confirmed by intrinsic reaction coordinate (IRC) calculations.\textsuperscript{[27]}

For better accuracy of the Gibbs free energies, the energy profiles were computed at the SMD(CH\textsubscript{2}Cl\textsubscript{2})-B3PW91-D3(BJ)/SDD + f(Au), 6-31 + G**(other atoms)/B3PW91/SDD + f(Au), 6-31G** (other atoms) level of theory in the presence of K\textsubscript{3}PO\textsubscript{4}, K\textsubscript{2}HPO\textsubscript{4} and K\textsuperscript+ are included in all steps to ensure correct energy balance.

Figure 12. Energy profiles (\(\Delta G\) in kcal/mol) for the 5-exo (black)/6-endo (blue) oxy-vinylation of (Z)-4-hexen-1-ol (left) and (E)-4-hexen-1-ol (right) by the (P,N)Au(vinyl)\textsuperscript{2+} gold complex 2v computed at the SMD(CH\textsubscript{2}Cl\textsubscript{2})-B3PW91-D3(BJ)/SDD + f(Au), 6-31 + G**(other atoms)/B3PW91/SDD + f(Au), 6-31G** (other atoms) level of theory in the presence of K\textsubscript{3}PO\textsubscript{4}, K\textsubscript{2}HPO\textsubscript{4} and K\textsuperscript+ are included in all steps to ensure correct energy balance.
bond and the Wiberg bond indexes of the Au–C and C–C bonds. Second Order Perturbation Theory analyses were also performed to assess the strength of N—Au interactions in some cases (stabilizing interaction $\Delta E(2)$ in kcal/mol).

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Conflict of Interest
The authors declare no conflict of interest.

Data Availability Statement
The data that support the findings of this study are available in the supplementary material of this article.

Keywords: complex density · functional theory · gold · mechanism · regioselectivity

[7] We have previously showed that the weakly coordinating SbF$_6$ anion does not play a key role.\cite{6} Displacement of SbF$_6$ by iodobenzene from (P,N)Au–S bonds proceeds with a very low activation barrier, affording the i-adduct. Then, oxidative addition to gold occurs easily with an accessible activation barrier but higher than that of SbF$_6$, \cite{12} which displays a discrete ion pair structure.
[8] Z’ was localized on the PES by imposing some constraint, namely a quasi linear PAuP alignment \cite{17}.
[12] The mechanistic alternative in which deprotonation occurs before the cyclization transition state was located from TS$_{1}$exo (3v) and C$_{1}$, C$_{2}$ via a TS$_{1}$endo (3v) and C$_{1}$, C$_{2}$ forms.\cite{18} The activation barriers of 34.2 kcal/mol, the cyclization of 4-pent-1-enolate with the OH group, while C$_{1}$, C$_{2}$ via a TS$_{1}$endo (3v) and C$_{1}$, C$_{2}$ forms.
[14] The mechanistic alternative in which deprotonation occurs before the cyclization step was also considered but it is not competitive. With an activation barrier of 34.2 kcal/mol, the cyclization of 4-pent-1-enolate-$\pi$ coordinated to the (P,N)Au(Ph)$^{+}$ complex 2 is indeed much more demanding energetically than that of 4-pent-1-enolate (Figure $\text{S}_{4}$).\cite{19}

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**DFT calculations** provide valuable insights into the mechanism of the oxy-arylation/vinylation of alkenes catalyzed by gold. The way alkenols coordinate to (MeDalphos)Au(R')²⁺ (R' = phenyl, vinyl) was found to significantly depend on their substitution pattern (terminal, Z/E internal) and to play a major role in the 5-exo/6-endo regioselectivity.

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**Mechanistic Insights about the Ligand-Enabled Oxy-arylation/vinylation of Alkenes via Au(I)/Au(III) Catalysis**

Dr. M. Rigoulet, Dr. K. Miqueu*, Dr. D. Bourissou*

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