



Conference paper

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Unravelling mechanistic insights in the platinum-catalysed dihydroalkoxylation of allenes

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Abstract: The mechanism of the platinum-catalysed dihydroalkoxylation of allenes to give acetals has been studied experimentally and by computational methods. Our findings further explain divergent reactivity encountered for platinum- and gold-vinyl intermediates after the first nucleophilic attack onto the coordinated allene, as well as provide new details on the catalytic cycle with platinum, uncovering enol ethers as resting states of the catalytic cycle, a $S_E O_x$ process *via* Pt(IV)–H as the final protodemetalation step after the second nucleophilic attack when neutral platinum complexes are used, and a fast acid promoted addition of methanol to enol ethers when cationic platinum complexes are employed.

Keywords: allenes; catalysis; gold; hydroalkoxylation; ICPOC-24; mechanism; platinum.

Introduction

In recent years a lot of attention has been paid to gold-catalysis [1–13] and numerous mechanistic studies have been carried out to understand the remarkable reactivity and selectivity of gold complexes [14–18]. In general, platinum exhibits similar reactivity to gold, however there are increasing examples where under similar conditions, these two metals give different products, implying that different mechanisms are operating with both catalytic systems [19–25]. Understanding the differences between the two metals and the pathways they can be involved in is crucial for the development of more efficient reactions and novel methods.

Transition metal catalysed reaction of allenes [26–34] with nucleophiles is one of the most representative examples where the choice of metal has profound implications in the outcome and selectivity, including enantioselectivity, of the reaction [35–42]. For example, the intermolecular reaction of allenes with palladium or gold catalysts in the presence of oxygen nucleophiles gives allyl ethers with the regioselectivity of the addition controlled by the substitution on the allene and the reaction conditions (Scheme 1a and b) [43–52]. However, reported examples of the reaction in the presence of rhodium give preferentially vinyl ethers by attack of the nucleophile to the central carbon of the allene (Scheme 1c) [53]. The metal-catalysed intermolecular addition of other nucleophiles (e.g. amines [54–61], azides [62, 63], electron-rich aromatic groups [64–70] and azoles [71–74]) to allenes has been widely reported. In general, allyl derivatives are obtained as the main products of the reaction when gold complexes are used.

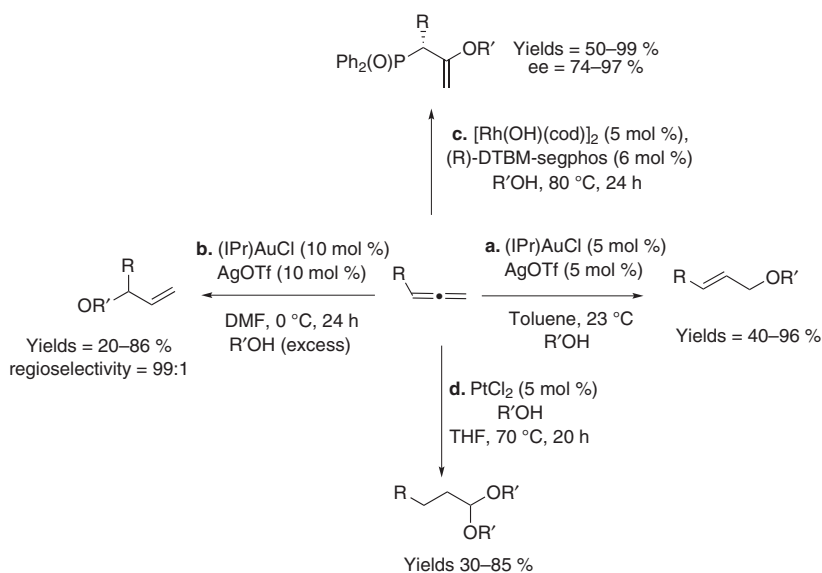
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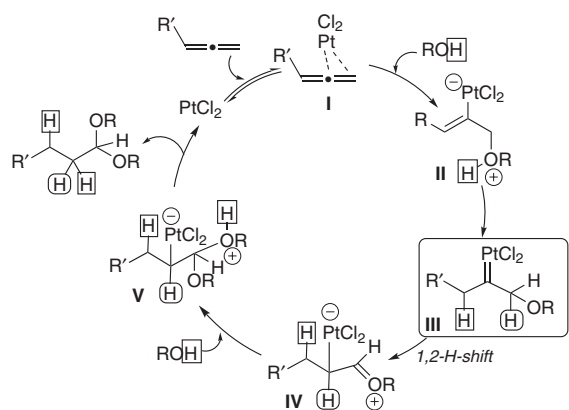
Scheme 1: Divergent reactivity on the nucleophilic addition of alcohols to allenes catalysed by different metals. (a and b) Au-catalysed addition of alcohols to allenes to form allyl ethers. (c) Rh-catalysed addition of alcohols to allenes to form vinyl ethers. (d) Pt-catalysed double addition of alcohols to allenes to form acetals.

In this area, we have reported the platinum-catalysed dihydroalkoxylation of allenes [75] which give acetals by double addition of alcohol nucleophiles to the terminal double bond of the allene, and complete saturation of the second double bond (Scheme 1d). This reaction constitutes a remarkable example of different reactivity of platinum and gold complexes under similar conditions. The platinum-catalysed process leads to acetals with complete chemoselectivity, and formation of allylic alcohols, the typical outcome in the reactions of allenes with alcohols in the presence of gold catalysts, is never observed.

Our previous studies on the mode of coordination in pyridine-platinum-allene complexes [76, 77] showed that although η^2 -coordination of the platinum to the allene was observed in the ground state in solution [78–82], slipped structures with the platinum shifted towards the central carbon of the allene, resembling η^1 -coordination mode, were revealed in solid state [83, 84]. Interestingly, reported X-ray structures of gold-allene complexes show the gold always shifts toward the terminal carbon of the allene [85, 86]. The fluxional behaviour of our platinum complexes in solution studied by SSTD NMR [76], revealed that the helical and rotational movement of the platinum around the allene occur intramolecularly and are closely related to each other, confirming η^1 -staggered structures as possible intermediates. We also found a divergent behaviour of platinum-allene complexes when compared to gold regarding ligand exchange that occurs mainly *via* a ligand-independent dissociative mechanism, where coordinating solvents might be involved in the stabilisation of the intermediates.

The slipped structures resembling η^1 -coordination of the platinum complex to the central carbon of the allene found in our studies (I, Scheme 2), would initially support the formation of a platinum carbene (III, Scheme 2), as a new key intermediate proposed in the catalytic cycle for the formation of acetals from allenes catalysed by platinum. This metallic carbene intermediate has not been proposed in similar gold-catalysed processes in which vinyl-gold intermediates (analogous to II, Scheme 2) give allyl alcohols as final products *via* protonolysis of the C–Au bond.

These studies already highlight several points of discrepancy in the reactivity of platinum and gold systems in the presence of allenes. However, although there have been increasing numbers of reported experimental examples of this divergent reactivity, these differences have not been fully studied from a mechanistic point of view. Here we report experimental and computational evidence to explain that divergence, as well as new details on the catalytic cycle with Pt, uncovering enol ethers as intermediate resting states, a $S_E O_x$ process *via* Pt(IV)–H as the final protodemetalation step when neutral platinum complexes are used, and a fast acid promoted addition of methanol to enol ethers when cationic platinum complexes are employed.



Scheme 2: Initial mechanistic proposal for the platinum-catalysed addition of alcohols to allenes to give acetals [75].

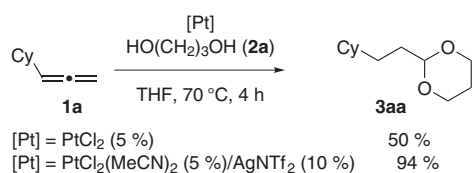
Results and discussion

In our original work, PtCl_2 was used as catalysts for the reaction with allenes and alcohols with reaction times up to 20 h. In order to find a faster system for kinetic analysis, we tested a cationic platinum complex generated *in situ* from $\text{PtCl}_2(\text{MeCN})_2$ and AgNTf_2 . The cationic catalyst gave stable cyclic acetal **3aa** in 94 % isolated yield after only 4 h when using cyclohexyl allene **1a** as model substrate in the presence of propanediol **2a** (Scheme 3).

However, although faster, the kinetic behaviour of the cationic catalyst was more complicated, showing induction periods in most cases and what seemed to be a negative order in diol. Although kinetic analysis has to be done with caution due to the induction periods observed, we carried out the analysis of the reaction in the presence of methanol (**2b**) as nucleophile using the cationic platinum catalyst to give acetal **3ab** (see SI for full details) [87]. In this case pseudo-zero order in allene was observed, suggesting a fast equilibrium shifted towards the coordination of the platinum to the allene. The reaction also showed negative order in methanol (−1.22), which could suggest an off-cycle equilibrium involving the alcohol to generate inactive species in the catalytic cycle.

It has been proposed before that platinum complexes react with alcohols to form alkoxide complexes (Pt-OR) [88–92]. In our system, cationic platinum species could react with methanol to form $[\text{Pt-OCH}_3]$ complexes, inactive catalyst in the dihydroalkoxylation reaction. In this process up to 2 equivalents of HNTf_2 (10 mol %) would be also generated. In order to test this hypothesis and shift the equilibrium towards the active cationic platinum complexes the reaction was performed under standard conditions in the presence of HNTf_2 (100 mol %). We observed faster reaction for acetal formation with disappearance of the induction period previously observed and positive order (0.84) in methanol, which indeed supports the off-cycle equilibrium between cationic platinum complexes and platinum-alkoxides and suggests that the presence of HNTf_2 accelerates the reaction (Fig. 1) (See SI for details).

The kinetic analysis of the reactions with PtCl_2 and methanol revealed a positive first order in methanol, which suggest that the off-cycle equilibrium, although possible, is not so predominant in the reaction with the neutral catalyst (See SI for details).



Scheme 3: Reaction comparing neutral and cationic platinum complexes.

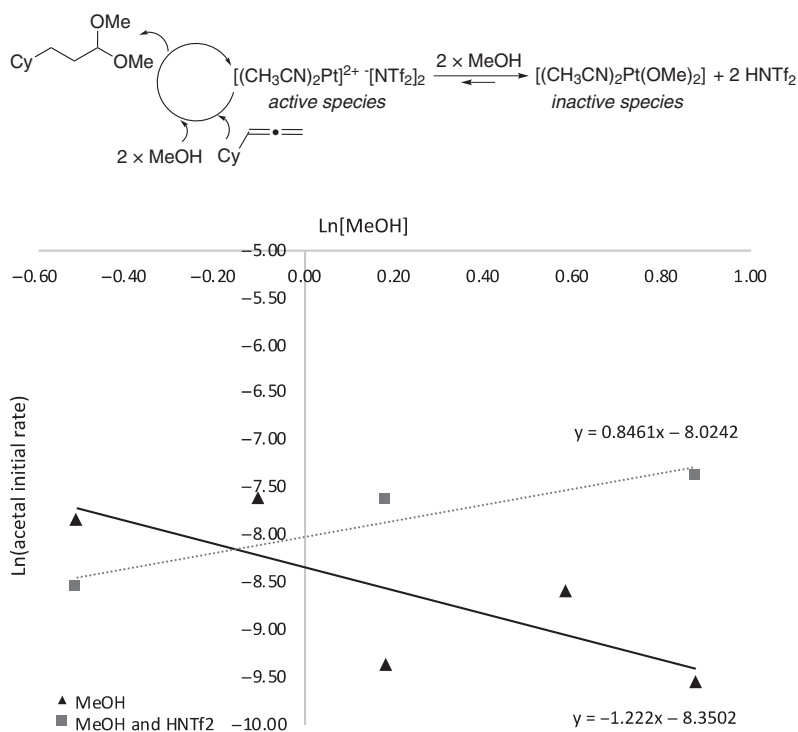
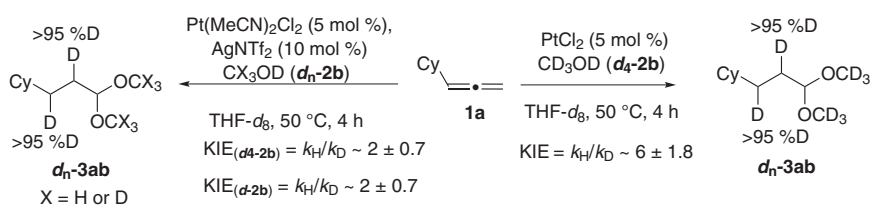


Fig. 1: Order in methanol in the absence (triangles) and presence (squares) of acid to confirm off-cycle pre-equilibrium involving [Pt–OCH₃].

The main point of diversion in the catalytic cycle when comparing platinum and gold systems is the vinyl-metal intermediate formed after first nucleophilic attack into the coordinated allene-metal complex (**II**, Scheme 2). Deuteration experiments using cyclohexyllallene **1a** in the presence of PtCl₂ or PtCl₂(MeCN)₂/AgNTf₂ and CH₃OD (**d-2b**) and CD₃OD (**d₄-2b**) showed in all cases deuterium incorporation from the alcohol into the central and internal carbon of the allene to give *d*-acetal **d_n-3ab**. This would be consistent with protonation of the internal carbon in a vinyl-platinum intermediate, as the favoured process in platinum intermediates, instead of the most commonly observed protonolysis of the Csp²–Au bond.

The KIE observed comparing the reactions with CH₃OH and CD₃OD for cyclohexyllallene **1a** were high with the neutral complex (KIE ~ 6) and moderate with the cationic system (KIE ~ 2), which suggests involvement of protonation events from the methanol in the rate limiting step at some point in the catalytic cycle with both catalysts (Scheme 4) (See SI for details).

The first protonation event could take place after the first nucleophilic attack and formation of the vinyl-platinum intermediate. Comparing computationally the vinyl-platinum and -gold models (Fig. 2) and their protonation by MeOH in similar conditions, suggested that protonation of the internal carbon of the vinyl-platinum does not seem to be the rate limiting step, which indicates that the alcohol might be involved later in the process in a higher energy step.



Scheme 4: Deuteration experiments and KIE when using *d_n*-methanol.

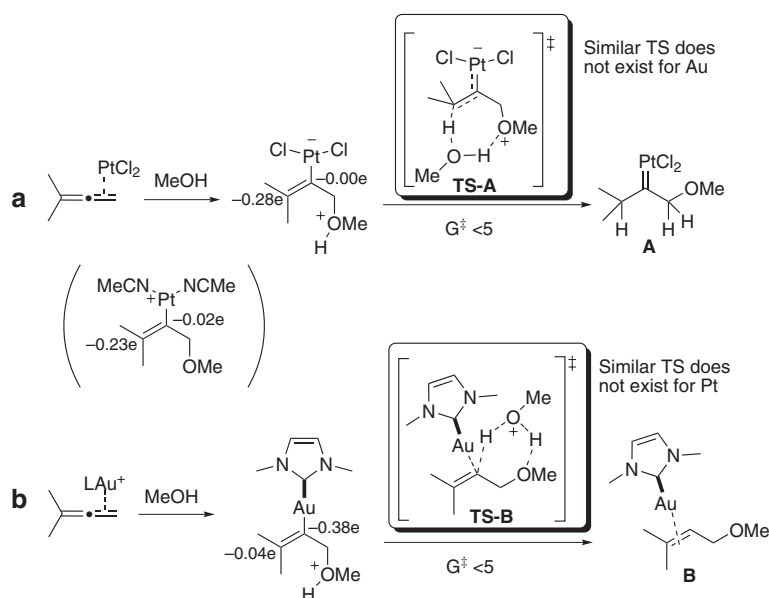


Fig. 2: Theoretical comparison of the vinyl metal complexes for Pt and Au and their protonation. Structures and $\Delta G^\ddagger/G$ energies (kcal mol⁻¹) computed at the M06/6-311+G(d,p) (SDD) level of theory, including solvent effects (IEFPCM, solvent = THF). (a) Formation and protonation of vinyl-Pt complex. (b) Formation and protonation of vinyl-Au complex.

The calculations were run in an implicit solvent model (IEFPCM, solvent = THF), including also one or two explicit molecules of methanol to simulate the microenvironment at the key points of the transition states during the reaction. We did not consider the inclusion of more molecules of methanol because of the conformational ambiguity that they would introduce. Calculations showed that the presence of the metal increases the basicity of the double bond and both carbon atoms are possible subjects of protonation. However, the computed NPA charges show opposite trends in both cases, since α carbon is more negative when bound to gold (-0.38 e) than to platinum (ca. 0.0 e), whilst β carbon is more negative bound to platinum (ca. -0.25 e) than to gold (-0.04 e) (Fig. 2) [93, 94]. Regarding the final adducts, a carbene species (**A**) is formed by protonation of the β carbon. This carbene is stable in the case of platinum but kinetically unstable in the presence of gold, and in fact, during computation, the gold carbene analogue to **A** is attacked by methanol to form an Au-C-OMe fragment, breaking the carbene. As a consequence, it was not surprising that transition state **TS-A** was only located for platinum but not for gold, whilst **TS-B** was located for gold, and not for platinum. Interestingly, the two located protonation processes occur almost barrierless ($\Delta G^\ddagger = < 5$ kcal/mol). Thus, the reactivity of platinum and gold in the vinyl structures is absolutely opposite and complementary.

The coordination and nucleophilic attack steps were also calculated using PtCl₂, propanediol (**2a**) and methyl-allene (**1b**) as the model system (Fig. 3) (See SI for details). The η^2 -coordination of Pt to the external double bond of allene forms **I**, which is the most stable isomer of the (allene)-PtCl₂ species. The nucleophilic attack of propanediol to **I** seems to be relatively facile leading to **II** [95], which evolves by virtually barrierless protonation of the most internal carbon atom of the allene, generating **III** (Fig. 3). We observed that the indirect proton transfer through the second oxygen atom of the diol, which is acting as a proton shuttle [96], is much easier than the direct transfer from the internal OH through a 5-membered cyclic structure [97, 98]. If methanol instead of propanediol is the proton source, two molecules of methanol are necessary, one attached to the terminal carbon, while the other one is acting as a shuttle facilitating the proton transfer. Whatever the proton source, a platinum carbene **III** is formed in this step, which proceeds through a 1,2 H-shift, forming a zwitterionic species **IV**.

This 1,2-H shift step was experimentally confirmed in the reaction with readily synthesised *d*₂-benzyl allene (**1c**), with deuterium in the terminal position of the allene. In the presence of cationic platinum complex with the non-deuterated diol (**2a**), we observed 1,2-D shift with high deuterium incorporation in the central carbon of the allene to give *d*-acetal **d**₂-**3ca** with a KIE ~ 1 (Scheme 5a) (See SI for details). The KIE

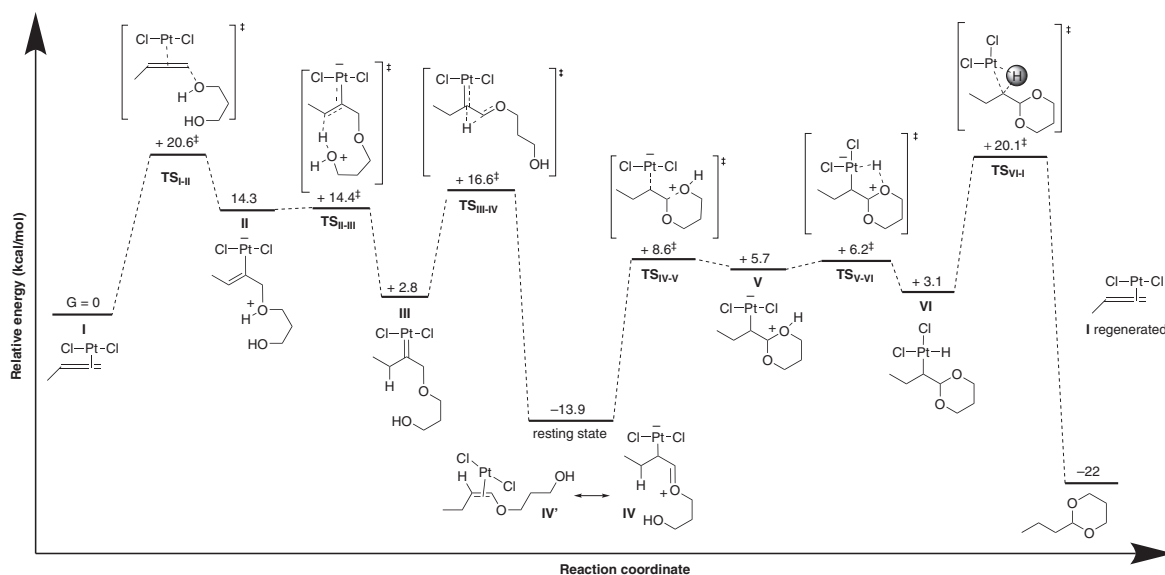
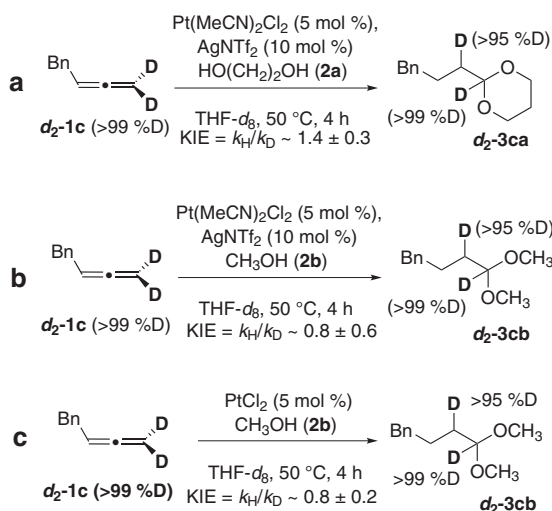


Fig. 3: Energy profile of the reaction catalysed by PtCl_2 with methylallene (**1b**) and 1,2-propanediol (**2a**) as model substrates, computed at the M06/6-311+G(d,p) (SDD) level of theory, including solvent effects (IEFPCM, solvent = THF). Relative energies in kcal mol^{-1} .



Scheme 5: Experiments with d_2 -allene and KIEs. (a) Reaction with diol **2a** and cationic Pt catalyst. (b) Reaction with MeOH and cationic Pt catalyst. (c) Reaction with MeOH and neutral Pt catalyst.

to form d_2 -**3cb** when methanol (**2b**) was used (Scheme 5b) and in the presence of methanol and the neutral platinum catalyst (Scheme 5c) was also ~ 1 suggesting that the 1,2-H shift is not the rate limiting step with either catalytic system.

Our preliminary investigations experimentally ruled out allyl ethers and alkynes as intermediates in the platinum-catalysed dihydroalkoxylation of allenes [75]. Interestingly, when analysing the kinetic profiles of the reaction of benzyl allene **1c** with PtCl_2 , we observed a *Z*-enol ether analogue formed mainly, with traces of the *E*-isomer. These enol ethers were then consumed during the reaction time. The formation of enol ether intermediates was not detected when the cationic platinum catalyst was used. This suggests that enol ether are plausible intermediates in the catalytic cycle at least when neutral platinum complexes are used. Indeed, the zwitterionic species **IV** (Fig. 3) can be better described as its resonance structure, the vinyl ether **IV'** [99–102], which according to its calculated energy, is the resting state of the mechanism with PtCl_2 as catalyst.

To test this hypothesis, we synthesised the enol ether **4** (*E/Z*, 1:0.5) that would be formed in the reaction with benzyl allene **1c** and reacted it in the presence of cationic and neutral platinum catalysts and also in the presence of acid to give the acetal **3cb** (Scheme 6) (See SI for details).

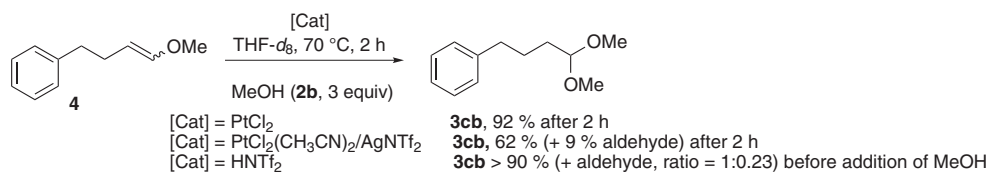
In these experiments, a ¹H NMR spectrum was taken before addition of MeOH. In the reaction with PtCl₂ only enol ether **4** was observed, and clean full conversion to acetal **3cb** was seen after 2 h of addition of MeOH. However, in the reaction with the cationic system half of the enol ether was already transformed into the acetal even before addition of extra methanol. This was even more pronounced in the presence of HNTf₂ that gave fast conversion to the acetal after sonication in the absence of extra methanol. The reaction with cationic platinum complex and in the presence of HNTf₂ gave also formation of the corresponding aldehyde from hydrolysis of the acetal in the acidic media [103].

These results imply that after the attack of the first methanol to the allene, there could be two possible pathways for the transformation of the enol ethers into the acetal final products: acid-mediated or platinum-catalysed. In the reaction with cationic platinum, there could be traces of acid in the media due to the off-cycle preequilibrium of the platinum with the methanol helping in that conversion. This would be also supported by the observed acceleration of the reaction when acid was added (*vide supra*). The reaction from enol ether is faster in the presence of acid and with the cationic complex, which could explain why enol ethers are not observed in the latter case. In the reaction with PtCl₂, the platinum catalysed process would occur. Interestingly, when the reaction of the enol ether and PtCl₂ was sonicated, we observed a great increase in initial rate and better conversion, which suggest that coordination of the PtCl₂ to the double bond of the enol ether is needed for the second addition of methanol to happen. Addition of the second methanol to the enol ether would form an alkyl platinum intermediate (**V**, Fig. 3) that after protodemetalation would give the acetal final product and regenerate the catalytically active platinum species.

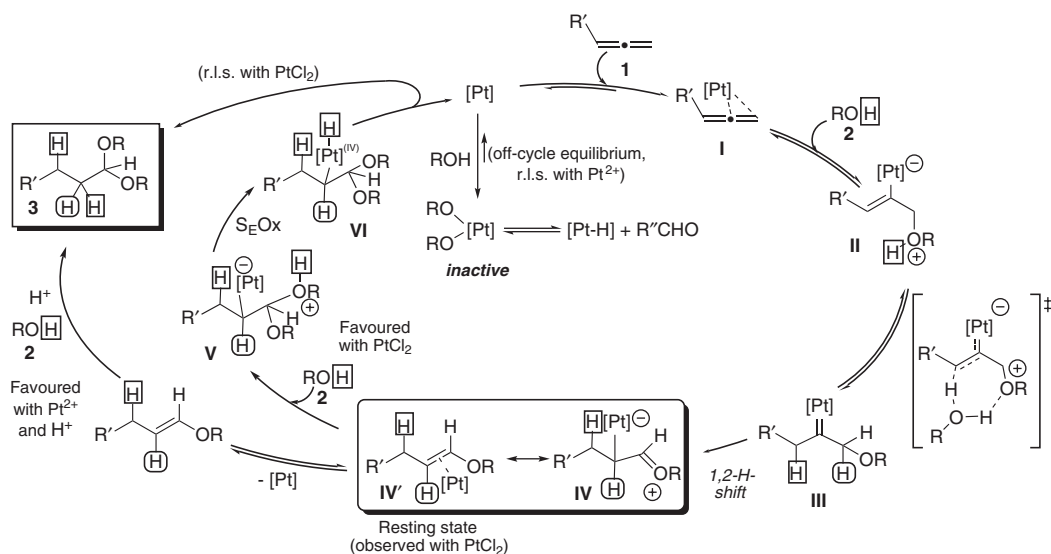
Protodemetalation of alkyl-platinum complexes can occur *via* two mechanisms: direct S_E2 or S_EOx *via* Pt(IV)–H intermediates [104–107]. The possible involvement of Pt–H in the catalytic cycle was investigated by adding TEMPO as a Pt–H trap [108] and Et₃SiH to form [Pt(IV)–H] complexes *in situ* [109]. Reactions of cyclohexyl allene **1a** with diol **2a** in the presence of 1 equivalent of TEMPO with PtCl₂ and Pt²⁺ were completely inhibited [110–112]. Traces of enol ethers were observed only in the reaction with PtCl₂. The reaction from the enol ether **4** was also inhibited in the present of TEMPO, reinforcing them as intermediates, resting states in the reaction, in particular when PtCl₂ is used.

In contrast, the reactions in the presence of 1 equivalent of silane showed faster kinetics with both catalysts, supporting the hypothesis that Pt–H are indeed involved in the final steps of the catalytic cycle (see SI for details).

As mentioned previously, the off-cycle equilibrium between the cationic platinum and alcohols can give mono or di-alkoxide complexes, inactive species in the catalytic cycle. These platinum-alkoxides can also be in equilibrium with platinum mono or di-hydrides formed *via* β-H elimination [88]. However, in the reactions using CD₃OH and either catalysts, we did not observe any deuterium incorporation in the acetal product, therefore ruling out that Pt–H species formed from Pt–OCH₃ are involved in the proton transfer in this process. Instead, DFT calculations revealed a proton transfer from oxygen to platinum to form a Pt–H bond (TS_{v,VI}, Fig. 3) and reductive elimination in a three membered transition state (TS_{v,I}, Fig. 3). The transition state of the final protodemetalation step (cleavage of a Csp³–Pt) bond presents the highest activation energy of all (ΔG[‡] ~ 34 kcal mol⁻¹ from the enol ether resting state) and can be considered the rate limiting step, at least for the neutral PtCl₂ catalyst. This data is in accordance with the KIE observed in the reaction with MeOD and explains the involvement of Pt–H in the process and the effect of TEMPO and silane in the reaction.



Scheme 6: Reactions with enol ether as starting material.



Scheme 7: Revised mechanistic proposal accounting for all experimental data and DFT calculations.

The behaviour and mechanism of the system in the presence of the cationic species $\text{Pt}^{+2}(\text{MeCN})_2$ seems to be more difficult to rationalize. When compared, the electronic features of neutral PtCl_2 or cationic $\text{Pt}^{+2}(\text{MeCN})_2$ are quite different, affecting the barrier heights of the different transition states (see SI for details). For example, as could be expected, a more positive Pt centre favours the nucleophilic attack of the alcohol in $\text{TS}_{\text{I,II}}$ (Fig. 3) and disfavours at the same time the protonation of the vinyl-platinum species in $\text{TS}_{\text{II,III}}$, which can become the rate limiting step in certain conditions with Pt dication. In any case, the largest differences appear at the end of the catalytic cycle, after intermediate **V**, where cationic Pt is not able to abstract the H, as was the case in $\text{TS}_{\text{V,VI}}$. We were not able to locate the corresponding structure or any similar one. Instead, a very fast acid catalysed process could occur from the enol ether to form the acetal without the involvement of the cationic platinum in the final steps of the reaction as suggested by the experimental evidence (Scheme 7).

Conclusions

In conclusion, we present here experimental and computational evidence to further explain divergent reactivity that platinum and gold present in the reaction of alcohol nucleophiles and allenes to give acetals or allyl ethers, respectively. Computational comparison of key vinyl-metal intermediates revealed that platinum and gold species are opposite and complementary, explaining the formation of allyl ethers from gold intermediates by protonation of the C–Au bond and formation of platinum carbenes by protonation of the internal carbon. This platinum carbene is able to evolve to platinum coordinated enol ethers, true intermediates (observed experimentally) and resting states in the catalytic cycle. From the resting state, two possible pathways can take place depending on the nature of the catalyst employed. With neutral platinum complexes, protodemetalation *via* $\text{Pt(IV)}\text{-H}$ in a $\text{S}_{\text{E}}\text{Ox}$ type mechanism seems to be favoured with reductive elimination as the rate limiting step for the reaction. With cationic platinum complexes, the enol ether reacts with more alcohol in an acid promoted process, in which the acid can come from an off-cycle equilibrium between the platinum complex and alcohols.

Understanding the hidden details of the mechanism operating in the platinum-catalysed dihydroxylation of allenes has allowed the rational development of more synthetically useful processes, such as the platinum-catalysed bisindolylolation of allenes [70], where double addition on indoles to the terminal or less substituted carbon of the allene gives 3,3'-bisindolylmethane derivatives (BIMs), and more recently the

intra-intermolecular version of this reaction to give tetrahydropyrido[1,2a]indoles [69], a new type of 2,3'-BIMs, attractive structures for the pharmaceutical industry. In the latter case, the reaction of allylindoles initially gives cyclic allyl indoles that isomerise *via* platinum carbenes into vinyl indoles, main products of the reaction in cases where the external nucleophilic attack is less favoured, supporting these intermediates (analogous to the enol ethers reported here) as the resting states of the reaction.

Understanding the differences between gold and platinum in the reactivity with allenes and nucleophiles has been crucial for the more recent development a novel Pt–Au bimetallic catalyst system in the reaction with heteroaromatic allenes [72]. In these reactions, gold is responsible for a very fast first carbocyclisation reaction, in which cyclic vinyl-gold intermediates are involved to give cyclic allyl derivatives. These allyl intermediates are able to engage in a second catalytic cycle catalysed by Pt–Au bimetallic species in the homogeneous and heterogeneous phases to generate the cyclic vinyl derivatives analogous to the enol ether described here *via* a Pt–Au bimetallic carbene intermediate. Second nucleophilic attack then occurs at the terminal carbon of the allene or at the more reactive bimetallic carbene carbon, depending on the nature of the nucleophile, giving a novel family of multi heteroaromatic structures through tandem cyclisation/C–X coupling reaction. This novel approach has opened new avenues for research in our group and others, highlighting again the importance of mechanistic investigations for the advance of organic synthetic methods.

Associated content: Supporting Information.

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