Organic & Biomolecular Chemistry

PERSPECTIVE

Transition metal-catalysed intermolecular reaction of allenes with oxygen nucleophiles: a perspective

María Paz Muñoz*

Transition metal catalysed hydroalkoxylation of allenes has received much attention in recent years, and both the intra- and intermolecular versions have been reported. Gold(I) complexes are among the most active catalysts for these processes. This critical perspective article will cover the progress in this field, analysing the intermolecular metal-catalysed reaction of allenes using palladium, iridium, rhodium, ruthenium, gold and platinum, in the presence of alcohols, water or carboxylic acids, and the mechanistic implications of these processes depending on the metal used.

Introduction

Allenes are rather unique structures that contain two π-orbitals perpendicular to each other. Although the structure of allenes was predicted a long time ago,[1] they were considered as chemical curiosities due to the difficulty to distinguish them from the corresponding alkynes. The development of IR and Raman spectroscopy made possible the characterisation of these compounds and the development of their chemistry. Over 150 natural products contain allenes or cumulenic structures, some of them showing pharmacological activity (steroids, prostaglandins, amino acids, nucleosides, *etc.*). Their industrial potential has also been shown, and numerous patents cover the use of allenes as dyes, drugs, antioxidants, (co)polymers suitable for paints, fibres, elastomers, printable films and heat- or corrosion-resistant materials.[2]

The synthetic utility of allenes is extensive, and chemo-, regio-, stereo- and positional-selective transformations have been developed during the past 20 years,[3] with the reaction of allenes with nucleophiles being one of the most studied. Among these transformations, the transition metal-catalysed hydroalkoxylation reaction of allenes is an atom economic process, which results in the formal addition of oxygen-based nucleophiles to one of the carbon–carbon double bonds of the allenic system.

The intramolecular hydroalkoxylation reaction of allenes has been extensively studied,[4] and different modes of cyclisation can be observed upon careful selection of the tether connecting the allenes with the oxygen nucleophile, the length of the chain or the metal used. The most common products in these reactions are 5 and 6 membered rings (furan or pyran type products), but in the case of β-lactam systems, even 7-membered rings can be obtained. In the case of dihydrofurans, enantioselective versions have been reported with Au(I) catalysts and chiral ligands. Some general examples are shown in Scheme 1.[5]

However, there are fewer examples of the intermolecular hydroalkoxylation reaction, which will be the focus of this perspective article. This reaction has received much attention over the past few years mainly due to the development of new and more efficient gold complexes that are able to catalyse this reaction under mild conditions. Although the gold-catalysed version has given the best results for the formation of allyl ethers, the use of other metals has enabled the discovery/development of different reactivities. The most interesting feature of the intermolecular reaction is that each metal allows the formation of different products, from allyl or vinyl ethers to acetals, giving this reaction great potential, and opening the possibilities of new structures obtained by the use of other transition metals.

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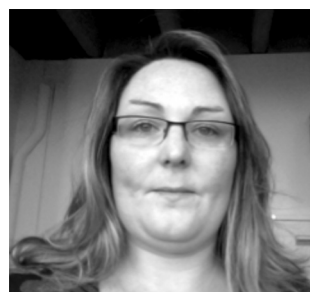
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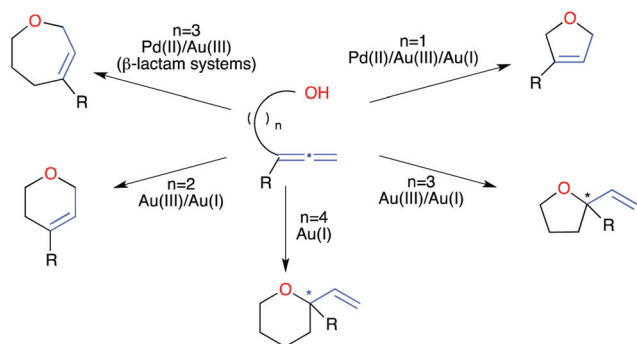
Scheme 1 General examples of intramolecular transition metal-catalysed hydroalkoxylation of allenes.[5]

The hydroalkoxylation reaction also differs mechanistically from the much more explored reaction of allenes with nitrogen nucleophiles,[6] and has also been extended to carbon-based nucleophiles, with the gold-catalysed hydroarylation of allenes with electron-rich aromatic rings and indoles,[7] the palladium-catalysed addition of carbon nucleophiles[8] and oxindoles to allenes,[9] and more recently the platinum catalysed-version to give bis(indolyl)alkanes.[10]

This perspective article will cover the metal-catalysed intermolecular reaction of allenes with oxygen nucleophiles, like alcohols, water and carboxylic acids, in which one or more molecules of the nucleophile are added to the allenic system, with no by-products being formed. The reaction with different metals will be analysed, from the first palladium-catalysed examples to the new mechanism proposed for the gold-catalysed process, and the new reactivities encountered when other metals are used. The peculiarities of each case will be examined taking into account the advantages and disadvantages of each method, and paying particular attention to the mechanism involved in the reaction with each transition metal.

Palladium-catalysed hydroalkoxylation and hydrocarboxylation of allenes[11]

Although the hydroalkoxylation reaction has been much explored in the past 10–15 years, this reaction is not new. The first report on the palladium-catalysed reaction of dimerization of allenes in the presence of carboxylic acids, as oxygen-based nucleophiles, was reported in 1967 by Shier.[12] In this reaction a C–C bond is formed between the two internal carbon atoms of two allenes and acetate is added to one or the two molecules of allene. Allyl acetate was also observed in the reaction, from the attack of acetate to one molecule of the allene (Scheme 2).
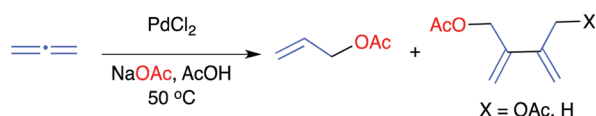
Scheme 2 First Pd-catalysed reaction of allenes with oxygen-nucleophiles.

The palladium-catalysed dimerization of allene gas in the presence of water or alcohols to give allylic alcohols or ethers
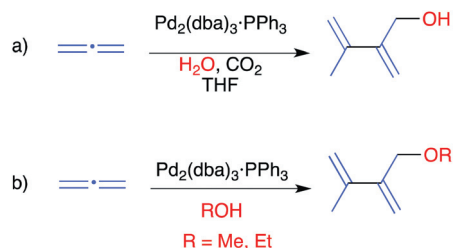

**Scheme 3** Pd-Catalysed dimerisation of allenes in the presence of water or alcohols.

was reported in 1984 by Inoue.[13] They found that the reaction with water had to be carried out in the presence of CO_2 atmosphere (Scheme 3, a), but the reaction with alcohols occurred in the absence of CO_2 (Scheme 3, b).

More than 10 years later, Rutjes applied the hyrdoalkoxylation of 1-methoxy-1,2-propadiene in the reaction with an alcohol to form an allylic acetal, as a mixture of two isomers, a precursor to functionalised dihydropyrans and tetrahydrooxepines (Scheme 4).[14,15]

The proposed mechanism for this process involves oxypalladation of the methoxyallene after coordination of the palladium to the more electron-rich oxygen-substituted double bond, followed by protonolysis of the resulting vinyl–palladium intermediate. This concept was also applied in the synthesis of highly functionalised chiral oxepines from monosacharaides (Scheme 5).[16]
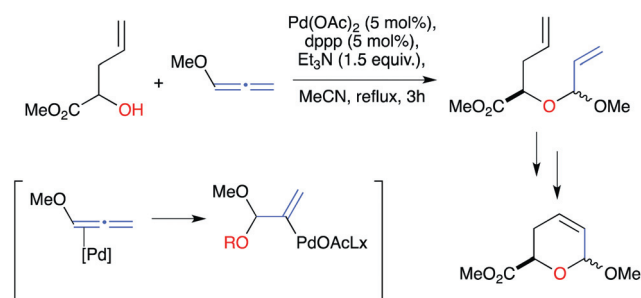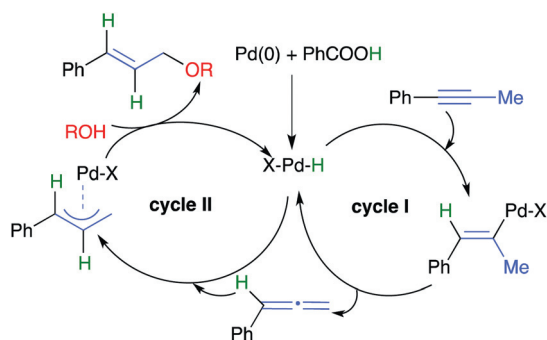

Scheme 4 Application of the Pd-catalysed hydroalkoxylation of allenes to the synthesis of tetrahydrooxepine precursors.
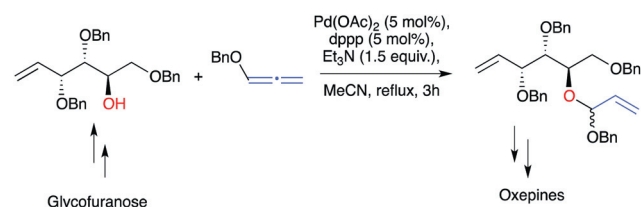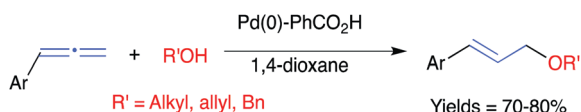

Scheme 5 Application of the Pd-catalysed hydroalkoxylation of allenes to the synthesis of monosacharides.

It is also worth mentioning the reaction reported by Yamamoto et al. of the palladium–benzoic acid catalysed hydroalkoxylation of internal alkynes to obtain allyl ethers (Scheme 6).[17] This reaction is proposed to occur via hydropalladation of the alkyne with the active catalysts, a palladium-hydride formed from the Pd(0)

Scheme 6 Mechanism of the Pd-catalysed hydroalkoxylation of alkynes via allenes.†[1]
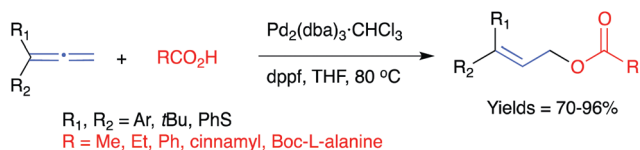

Scheme 7 Pd-Catalysed hydroalkoxylation of aryl allenes.

and the benzoic acid in the first step of the reaction, and subsequent β-hydrogen elimination (cycle I, Scheme 6), to form an allene intermediate that is trapped by the palladium-hydride to give a π-allylpalladium that reacts with the alcohol to form the product and regenerate the Pd–H species (Cycle II, Scheme 6).

This concept was further developed by the same group, and a smooth Pd(0)-PhCOOH catalysed addition of alcohols to aryl allenes was reported a few years later (Scheme 7).[18] Again, they proposed that the role of the carboxylic acid was the formation of hydridopalladium species, active catalysts in this reaction (see catalytic cycle II in Scheme 6).

π-allylpalladium species have also been proposed in the hydrocarboxylation of allenes to form allyl esters, by taking advantage of the formation of palladium-hydride species between the Pd(0) catalysts and the acid employed in the reaction, in this case in a stoichiometric manner (Scheme 8).[19]

**Scheme 8** Pd-Catalysed hydrocarboxylation of allenes.

The reaction works well only with aromatic mono allenes with electron-donating and electron withdrawing groups at the *para*-position, and with 1,1-disubstituted aromatic allenes, and hydrocarboxylation occurs at the less substituted allenic carbon to give the linear allylic esters. However, when allenes with aliphatic substituents containing hydrogens in the α position were used, 1,3-butadiene type products were obtained due to β-hydride elimination from the π-allylpalladium intermediate (Scheme 9).

Again, this reaction works by employing alkynes as starting materials. They are transformed *in situ* into the allene derivatives, and then react with the stoichiometric carboxylic acid in the same manner as the reaction with alcohol described in Scheme 6.[18]
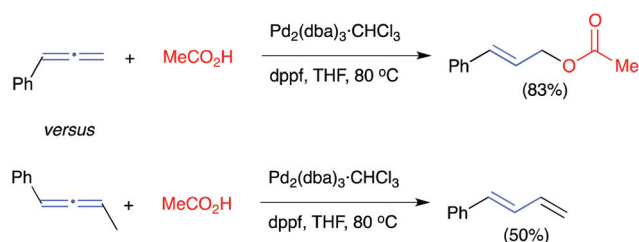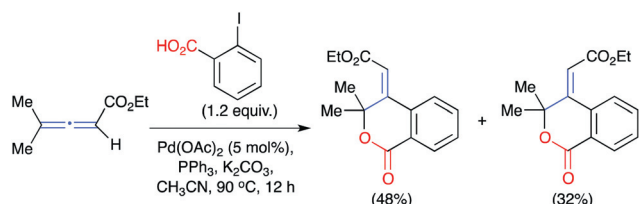

Scheme 9 Scope of Pd-catalysed hydrocarboxylation of allenes.

π-Allylpalladium species are also involved in the synthesis of allyl acetates from allenes in the presence of aryl iodides, as reported by Savic *et al.* (Scheme 10).[20] Under optimised conditions, allenes reacted with aryl iodides in the presence of AcONa to afford the corresponding allyl acetates in moderate yields, as mixtures of regioisomers and stereoisomers, by attack of the aryl–palladium species formed by oxidative addition of the aryl iodide to the central carbon of the allene, with subsequent attack of acetate onto the terminal carbons of the π-allyl-palladium intermediate.[21]
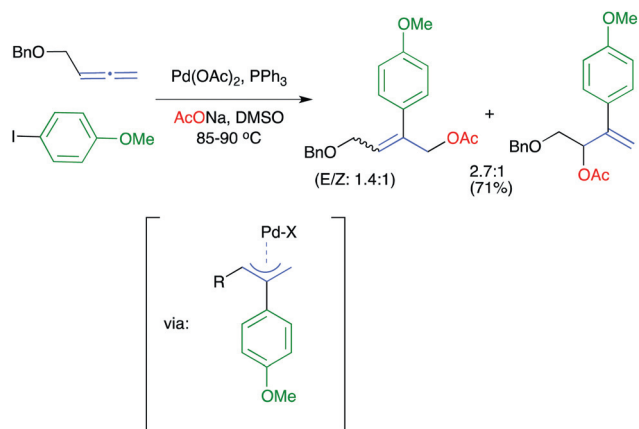
Scheme 10 Pd-Catalysed synthesis of allyl acetates from allenes.

When the oxygen nucleophile is a phenol, benzoic acid or benzyl alcohol, containing an iodide substituent in the *ortho*-position, the palladium-catalysed reaction with allenes gives regioselectively functionalised benzofurans, isocumarins, and benzopyrans depending on the substituent on the allene, as described by Swamy *et al.* in 2009. A representative example is shown in Scheme 11.[22]

**Scheme 11** Pd-Catalysed synthesis of isocoumarines from allenes.

Iridium-catalysed hydrocarboxylation of allenes

Metal-hydrides and π-allyl-metal intermediates have also been found in the reaction of 1,1-dimethylallene and carboxylic acids

in the presence of iridium catalysts. However, in this case, a reversed regioselectivity was observed with the organic acid being attached to the more substituted carbon of the allenic system (Scheme 12).[23,24]
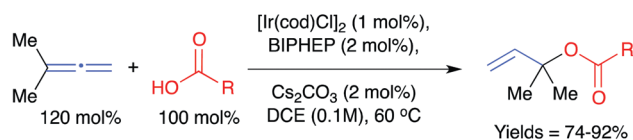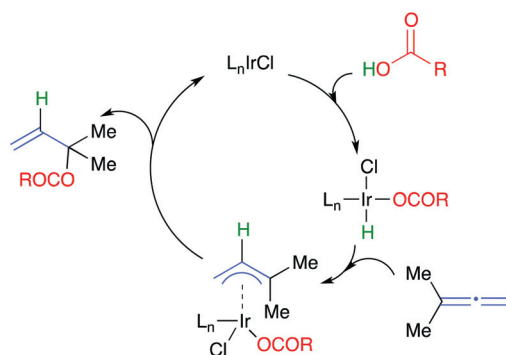

Scheme 12 Reverse Ir-catalysed hydrocarboxylation of allenes.

The reaction was tested with commercially available 1,1-dimethylallene (but also worked with other 1,1-substituted allenes), and worked well with aromatic, heteroaromatic, and α,β-unsaturated acids, as well as α-hydroxyacids and aminoacids, without protection of the other functionalities present, giving in all cases a by-product-free reverse prenylation of the carboxylic acids.

A preliminary mechanistic study, and deuterium labelling experiments with deuterated benzoic acid, showed the reaction might proceed, as in the case of the palladium-catalysts, by formation of an iridium-hydride from protonation of the metal with the carboxylic acid, and hydrometallation to form the allyl–iridium intermediate. C–O reductive elimination from the more substituted carbon forms the product and regenerates the catalyst. When deuteriobenzoic acid (O–^{2}H) was used, deuterium incorporation into the central carbon of the allenic system was observed, which is consistent with this mechanism (Scheme 13). Reaction of the reverse prenyl esters in the same conditions in the presence of other acids did not give exchange in the carboxylate, which suggested that the reaction is not reversible.


Scheme 13 Mechanism of the Ir-catalysed prenylation of carboxylic acids.†
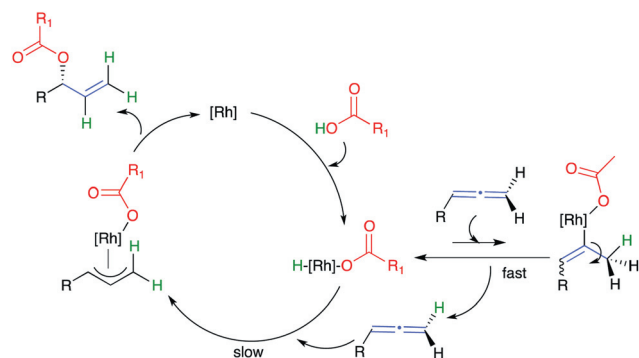
Rhodium-catalysed hydrocarboxylation and hydroalkoxylation of allenes

Very recently the enantioselective rhodium-catalysed hydrocarboxylation of allenes to give branched allylic ester has been reported by Breit *et al.*[25] The reaction works in a similar way to

† The hydrogens coloured in green in mechanistic schemes indicate the deuterium position when deuterated alcohols or carboxylic acids were employed in the reactions.
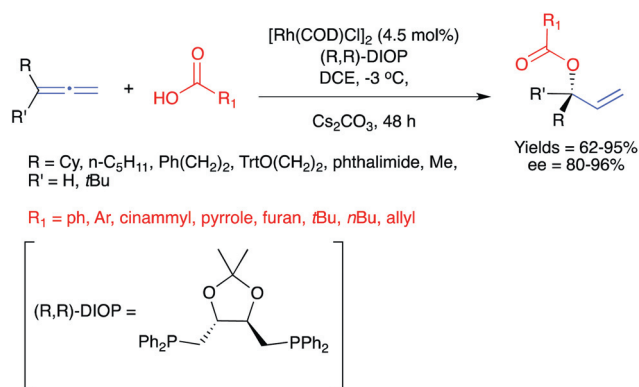
Scheme 14 Enantioselective Rh-catalysed coupling of allenes with carboxylic acids.

Scheme 15 Proposed mechanism for the Rh-catalysed hydrocarboxylation of terminal allenes.†

the palladium- and iridium-catalysed versions mentioned before, and the carboxylic acid is attached to the most substituted carbon of the allenic system as in the iridium-catalysed version, although in the case of rhodium it seems to be more general and have a better scope (Scheme 14).

(R,R)-DIOP was the best ligand for high enantioselectivities, and the reaction could be carried out under very mild conditions (−3 °C, in 1,2-dichloroethane, 48 h) when a catalytic amount of Cs_2CO_3 was used as additive. The reaction works well for electron-rich and electron-poor derivatives of benzoic acid, as well as cinnamic acid and aliphatic (linear and branched) carboxylic acids, although elevated temperatures are needed in the last case. As for the scope of the allenes, the reaction works for monosubstituted allenes with different functionalities, even with unprotected alcohols. When 1,1-unsymmetrically disubstituted allenes were tested, the corresponding tertiary alcohol was obtained with high yield and excellent enantioselectivity.

Deuteration experiments were carried out with deuterated benzoic acid, and deuterium incorporation was observed in the terminal carbon of the allene. This could be rationalised by formation of a rhodium-hydride, by reaction of the rhodium catalysts with the carboxylic acid as the active species in the reaction, followed by a fast hydrometallation of the less substituted double bond of the allene to give a σ-vinyl–rhodium that after β-hydride elimination will give the allene with deuterium incorporation. This allene can then undergo slower hydrometallation on the more substituted double bond to give the π-allyl–rhodium complex that after reductive elimination with external

attack of the carboxylate will give the branched product (Scheme 15).

In contrast, there is only one example of the rhodium-catalysed intermolecular hydroalkoxylation of allenes.[26] The reaction works with diphenylphosphinyl allenes[27] and different substituted phenols. By using rhodium and a chiral ligand ((R)-DTBM-segphos), high enantioselectivities are observed (depending on the bulkiness of R in the allene), in the first asymmetric hydroalkoxylation of allenes reported to date (Scheme 16).

The reaction also involves π-allyl–rhodium intermediates, and the observation that it works only with phenols underlines their role in the mechanism. NMR studies of the process using the complex [Rh(OH)((R)-BINAP)]$_2$ have shown that the hydroxorhodium complex (observable by ^{31}P NMR) is transformed into the π-phenoxorhodium complex (also observable by ^{31}P NMR), before formation of the π-allyl rhodium by reaction with the allene. The phenoxy is then transferred, in this case to the central carbon of the allene. This regioselectivity is complementary to that observed with palladium and iridium, where the oxygen-nucleophile was attached to the terminal carbons of the allenic system (Scheme 17). An explanation for the enantioselectivity observed is that protonolysis of the π-allyl–rhodium intermediate takes place from the side opposite to the rhodium.
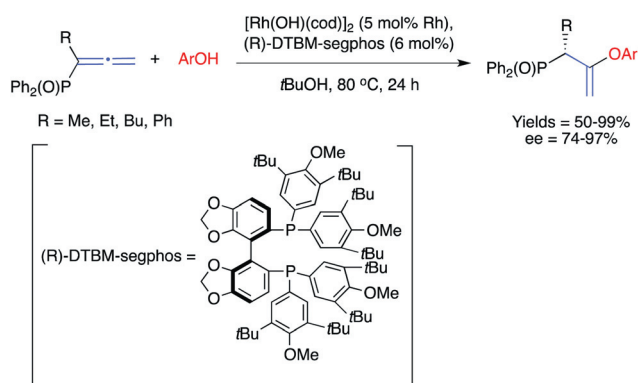
Scheme 16 Rh-Catalysed asymmetric hydroalkoxylation of diphenylphosphinoallenes.
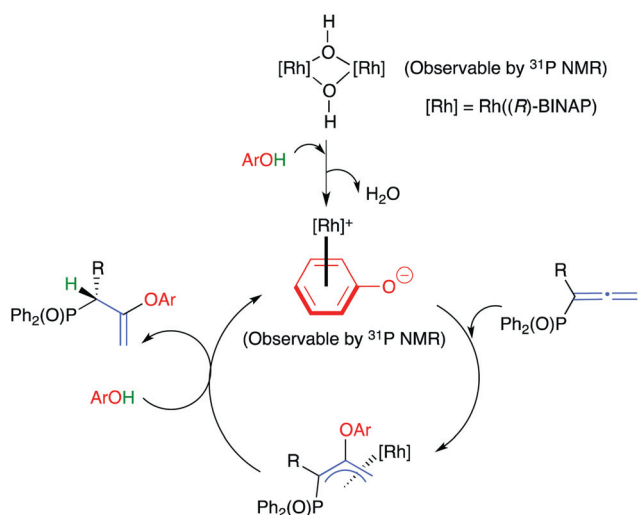

**Scheme 17** NMR-Observable intermediates in the catalytic cycle.†

Ruthenium-catalysed hydration of allenes

There is only one example of ruthenium-catalysed intermolecular reaction of allenes with water and, along with formation of methyl ketones, dimerization of the allene also occurs.[28] However, in contrast to the palladium-catalysed reactions reported by Shier and Inoue, the water attacks the central carbon of the allenic system and then dimerization occurs. The best reaction conditions found were when Ru$_3$(CO)$_{12}$ was used as catalyst with CF$_3$CO$_2$H as additive in a mixture of iPrOH:H$_2$O under CO atmosphere. The dimeric γ,δ-unsaturated ketone was always the major product (Scheme 18). The reaction gave moderate yields with mono alkyl allenes, but the yield significantly dropped when cyclohexylallene was used as the substrate.

Mechanistic studies showed that the dimerization product was not produced from the reaction of the methylketone formed with another molecule of allene, but from the reaction of two molecules of the allene with one molecule of water. Deuteration studies using D$_2$O showed deuterium incorporation in the olefinic position of the dimer and the α-positions on the methyl ketones. These results led to a proposed mechanism involving ruthenium-hydrides formed from protonation of the Ru(0) complex. However, no π-allyl–ruthenium intermediates were proposed in contrast to the palladium or iridium reactions. η^2-Coordination of this ruthenium-hydride to the allene and attack of one molecule of water to the central carbon forms an enol complex that can tautomerise to the ketone. Reductive elimination gives the methyl ketone, and reaction with a second molecule of allene builds the dimeric γ,δ-unsaturated ketone (Scheme 19).
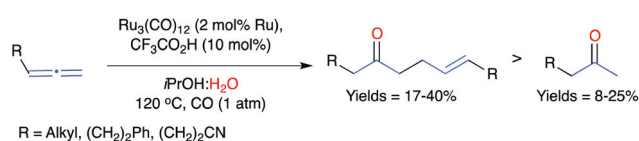

Scheme 18 Ru-Catalysed hydrative dimerisation of allenes.
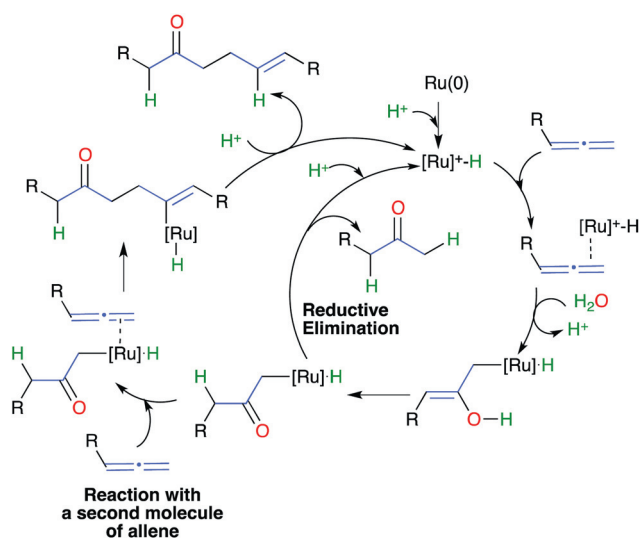
Scheme 19 Proposed mechanism for the hydrative dimerisation of allenes catalysed by Ru(0)/acid.†

Gold-catalysed hydration and hydroalkoxylation of allenes

The first report of a reaction between allene gas and methanol in the presence of a gold catalyst dates from 1998 when Teles and co-workers reported cationic gold(I)-complexes as highly efficient catalysis for the addition of alcohols to alkynes.[29] The product obtained was the acetal 2,2-dimethoxypropane, probably formed by isomerisation of the allene gas to the propyne and then gold-catalysed reaction with two molecules of methanol in a normal alkyne hydroalkoxylation process (Scheme 20).
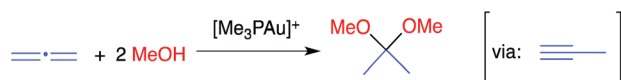
**Scheme 20**   Au-Catalysed reaction of allene gas with methanol.

However, it was ten years later before Widenhoefer reported the first gold(I)-catalysed regio- and stereoselective intermolecular hydroalkoxylation of allenes with alcohols to form (E)-alkyl allylic ethers.[30] The reaction was sensitive to the nature of the ligand and the counterion, and it was found that the gold(I) NHC complex (1,3-bis(2,6-diidopropylphenyl)imidazole-2-ylidine) AuCl in combination with AgOTf in toluene gave the best results (Scheme 21).
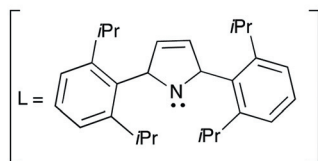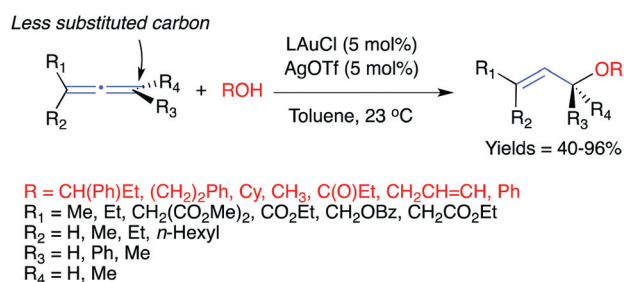
Scheme 21   First Au-catalysed intermolecular hydroalkoxylation of allenes reported by Widenhoefer.

The reaction works for mono-, 1,1- and 1,3-disubstituted, trisubstituted and tetrasubstituted allenes and with a range of primary and secondary alcohols and phenol. The hydrocarboxylation of 1-methyl-3-phenyl-allene was achieved using propionic acid as the oxygen-based nucleophile.

In all cases the alcohol was delivered to the less hindered carbon of the allenic system. Experiments using MeOD led to formation of the product with exclusive incorporation of deuterium in the central carbon of the allene, suggesting the involvement of gold–vinyl intermediates. Besides, when the reaction was carried out with an enantiomerically enriched allene, partial racemization was observed (dependent on the alcohol concentration). This partial racemization was explained via equilibrium between the η^2-gold coordination to the allene and a gold–σ-allyl cation, with the gold attached to the central carbon of the allene (Scheme 22). Attack of the alcohol at the less substituted
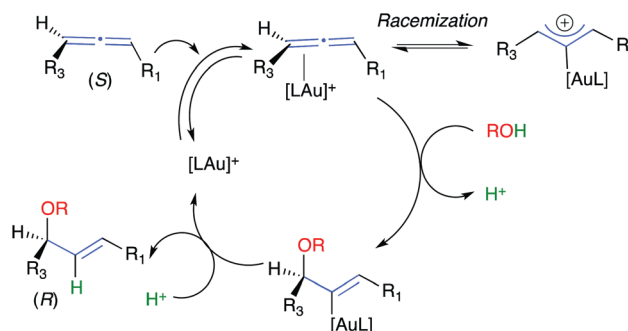

Scheme 22   Mechanism proposed by Widenhoefer.†

carbon via the outer-sphere of the η^2-gold complex to form a vinyl–gold intermediate will be followed by protonation with retention of configuration, which gives the (E)-alkyl allyl ether.

The gold(I)-catalysed hydration of allenes was also reported by Widenhoefer et al.,[31] using a similar system. In this case, the toluene had to be replaced by a solvent miscible with water, like dioxane, for best results. Under these conditions, hydration of mono-, 1,1-, 1,3-substituted, and trisubstituted allenes was achieved in moderate yields. In most cases only the product of the attack of water to the less hindered terminal carbon was obtained. However, when the substitution in the 1,3-positions was similar, mixtures of both regioisomers were obtained (Scheme 23).
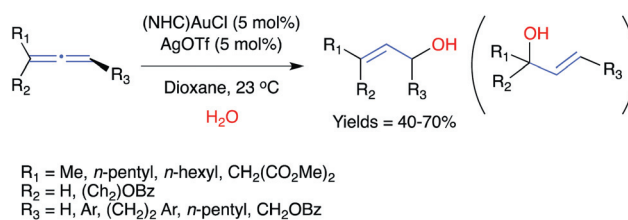
Scheme 23   Au-Catalysed hydration of allenes.

At the same time, Yamamoto et al. also reported the gold-catalysed intermolecular hydroalkoxylation of allenes in comparison with the hydroamination reaction and showed it to proceed through a completely different mechanism.[32,33] The reaction of different mono-, 1,1-, and 1,3-substituted allenes with various alcohols (phenol gave a complex mixture) was reported in the presence of cationic gold(I)-catalyst ([Ph3PAu]+), to occur with mono addition at the terminal carbon of the allenic system, and without any chirality transfer, resulting in the formation of allylic ethers, and suggesting that the alcohol is transferred after racemization of the allene. This result is in accordance with the results obtained by Widenhoefer (Scheme 24).
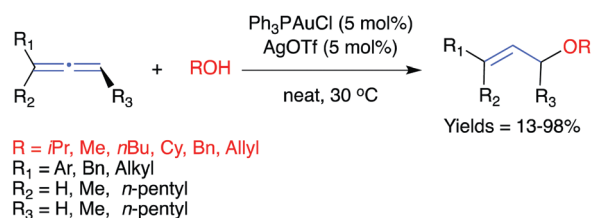
Scheme 24   Au-Catalysed intermolecular hydroalkoxylation of allenes reported by Yamamoto.
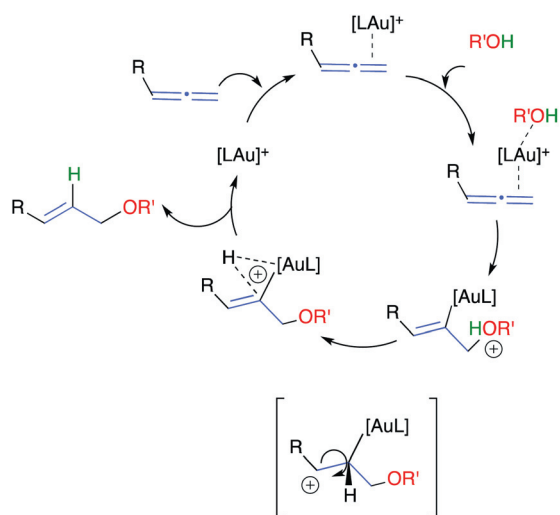
Scheme 25 Mechanism proposed by Yamamoto.†

Scheme 27 Au-Catalysed hydroalkoxylation of alkoxyallenes to give acetals.

Scheme 28 Proposed mechanism for the formation of acetals.

Experiments with MeOD, also showed deuterium incorporation in the central carbon of the allene. The proposed mechanistic cycle is very similar to the one proposed by Wide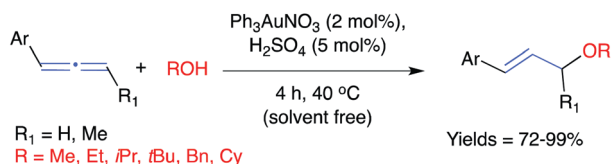nhoefer, where the coordination of the allene to the gold and addition of the alcohol generates the vinyl–gold intermediate. However, in contrast to the mechanism previously proposed, Yamamoto *et al.* describe the addition of the alcohol through the inner-sphere of the gold-complex. Protonolysis then occurs to produce the allyl ether and regenerate the catalysts. Formation of the *E*-allylic ethers is explained by the free rotation in the intermediate before the protonolysis (in brackets, Scheme 25).
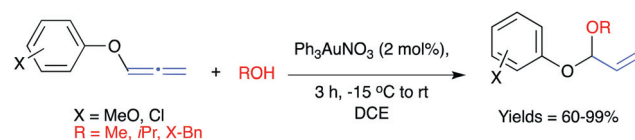
In this paper the involvement of gold allyl cations, π-allyl gold and η^1-allyl gold species is discussed. However, the experimental evidence seems to be against them, and the classical vinyl–gold intermediate is preferred to explain the observed outcome of the reaction.

In 2009 Zhang and co-workers also reported the regio- and stereoselective hydroalkoxylation of aryl allenes in the presence of catalytic amounts of Ph$_3$PAuNO$_3$ and H$_2$SO$_4$, under solvent free conditions.[34] The reaction works well with primary, secondary and tertiary alcohols, with addition always occurring to the less substituted carbon of the allenic system. Mono aryl allenes with electron donating and electron withdrawing groups give the corresponding *E*-allyl ethers in good yields, and an example of the reaction of 1,3-disubstituted allene is also reported (Scheme 26).
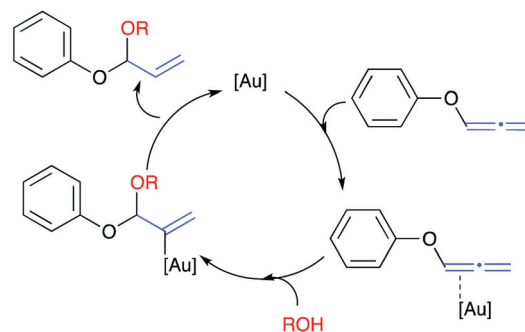
allene to drive the alcohol to full conversion. Although the yield of the acetals depends on their stability during purification, the addition of small amounts of Et$_3$N helped the authors to obtain good yields (Scheme 27).

The reaction works for alkoxyallenes with aromatic groups, and secondary and benzyl alcohols with electron donating and electron withdrawing groups. The proposed mechanism is similar to the ones mentioned before, but in this case the gold cation coordinates the double bond with the more substituted electron-rich oxygen to form the η^2-gold complex. Then addition of the alcohol to the chelated double bond forms the vinyl–gold complex, which after protonolysis gives the corresponding allylic acetal (Scheme 28).

As mentioned before, this was the only compound observed in the iridium-catalysed hydrocarboxylation of 1,1-dimethyl allenes (see Scheme 12), and the results are in accordance with the oxo-palladation of 1-methoxy-1,2-propadiene (see Scheme 4). However, this is not the first example where, in a gold catalysed reaction, the oxygen-based nucleophile attacks to the more substituted carbon of the allenic system. In 2008, Horino *et al.* described the gold-catalysed intermolecular reaction of *N*-tosyl-4-vinylidene-2-oxazolidinones with alcohols to give the product of the addition to the proximal allenic double bond, which seems to be activated by both the cationic gold complex (formed by the combination of (PPh$_3$)AuCl and AgSbF$_6$) and the strongly electron withdrawing tosyl group (Scheme 29).[36]

Scheme 26 Au-Catalysed hydroalkoxylation of allenes reported by Zhang.

The Ph$_3$PAuNO$_3$ catalyst was also used by the same group for the hydroalkoxylation of alkoxyallenes to give allylic acetals.[35] The reaction works at −15 °C in DCE with a slight excess of the
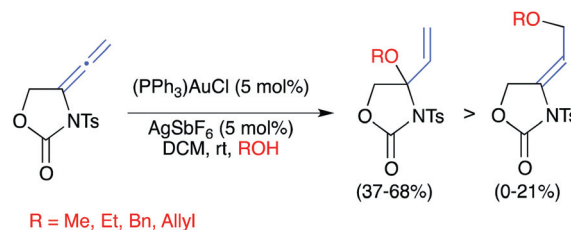
Scheme 29 Au-Catalysed reaction of N-tosyl-4-vinylidene-2-oxazolidinones with alcohols.

The use of an excess of alcohol (5 equivalents) was essential to improve the regioselectivity towards the addition to the more substituted carbon of the allenic system. The reaction works for primary alcohols, and allyl alcohols with alkyl and aryl substituents in β- and γ-positions. The use of sterically bulky secondary alcohols decreased the yield of the most substituted regioisomer, favouring the attack to the terminal carbon of the allene, and tri-substituted alcohols, such as *tert*-butanol, gave no reaction. The regioselectivity was also affected by the electronegativity and steric bulk of the substituent on the nitrogen: changing the tosyl group for a benzoyl completely reversed the regiochemistry of addition, and with a benzyl group no reaction was observed.

The authors suggested a catalytic cycle involving coordination of the gold complex to the central carbon of the allene to give after attack of the alcohol, a vinyl gold intermediate, which is supported by deuteration studies in the presence of methanol-d. Here deuterium was incorporated in the central carbon of the allenic system after protonolysis (Scheme 30).
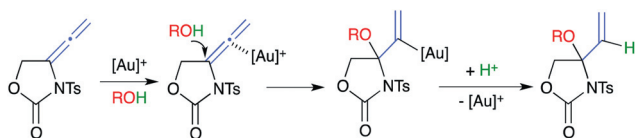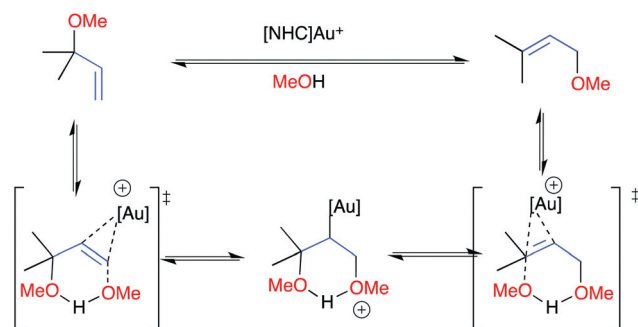

Scheme 30 Proposed mechanism for the reverse hydroalkoxylation.†

More recently, Maseras *et al.* have reported a DFT study that showed an alternative mechanism for the gold(I)-catalysed hydroalkoxylation of mono allenes, where the attack of the nucleophile occurs primarily to the more substituted carbon of the allene, and then a gold-catalysed isomerisation of the kinetic product gives the less substituted, thermodynamically more stable allyl ether observed in most of the cases.[37] The calculations were done with the [NHC]AuCl, used by Widenhoefer, 1,1-dimethyl allene and methanol as model substrates and the regiochemical outcome of the reaction was first studied. Coordination of the catalysts to both double bonds was considered as well as formation of alkoxygold species, although the last one was showing to be higher in energy so allene activation *via* cationic gold coordination was favoured. The background reaction in the absence of catalysts was ruled out due to a higher activation energy of 40.5 kcal mol^{-1}, which suggests that the reaction does not occur at room temperature. Different pathways were calculated for the addition of methanol to the activated allene, including syn-addition of a methoxygold species to the double bond, a concerted pathway *via* a cyclic transition structure involving a second molecule of methanol, and attack of the alcohol to the coordinated allene to one or the other double bond, from the same side as the catalysts (inner-sphere), as proposed by Yamamoto, or from the opposite side (outer-sphere), as proposed by Widenhoefer.

Calculations showed clearly that the rate-limiting step was the initial attack of the alcohol on the allene to form the gold σ-alkenyl complex, itself more stable than the starting material. Of all the possibilities, attack of the alcohol onto the more substituted terminal carbon from the outer-sphere of the gold-coordinated allene was more favourable, consistent with a Markovnikov-type addition, where the two methyl groups are oriented out of the plane of the allyl system in the transition
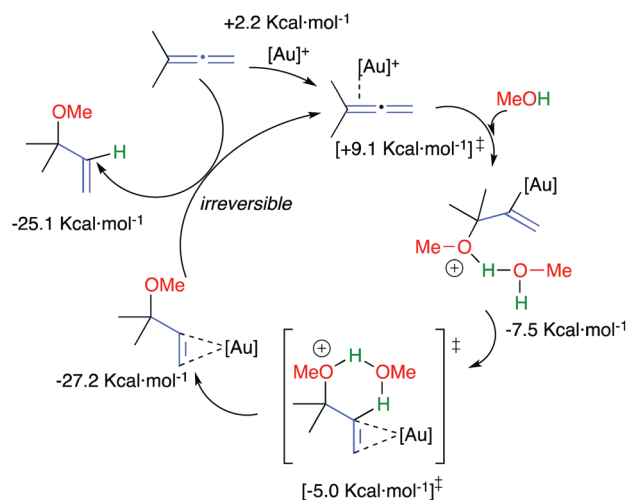
Scheme 31 DFT-Calculations for the Au-catalysed intermolecular hydroalkoxylation of allenes.†


Scheme 32 Proposed mechanism for the allyl ethers interconversion.

state. Protonation of this intermediate with retention of the alkene geometry gives the product of the attack of the methanol to the more substituted end of the allyl system in an irreversible reaction (Scheme 31).

Although the more thermodynamically stable product from the attack of the alcohol to the less substituted terminus of the allene is the one observed experimentally, calculations showed that this is kinetically less favourable. Therefore a gold-catalysed regioisomerisation between the two possible allyl ethers was studied. It was found that attack of the alcohol on either terminal carbon of the allene was aided by hydrogen-bonding to form a chair-shaped cyclic intermediate that allows interconversion of the products, yielding the more stable one. Therefore it is was concluded that the two products are in equilibrium, and only the most stable one is observed, explaining all the experimental results including the example of the reaction of alkoxyallenes where the allylic acetal is calculated to be energetically more stable and it is observed as the major product (Scheme 32).

These DFT calculations suggested that the concentration of the alcohol might be important for the formation of one or the other regioisomer, which is in agreement with the results obtained by Horino *et al.* This concept has been proven more recently by Lee *et al.* in a study where the gold(I)-catalysed iso-merisation of the *tert*-allylic ethers to primary allylic ethers was retarded by excess of alcohol (Scheme 33).[38]
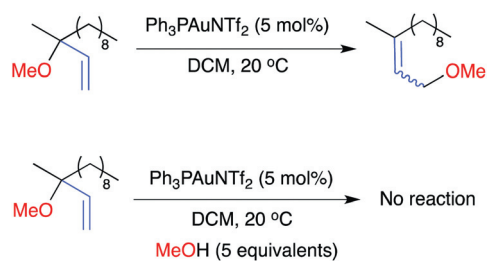
Scheme 33 Au-Catalysed reaction of *tert*-allyl ether in the presence and absence of excess alcohol.

It was found that carrying out the reaction with the [NHC]Au⁺ complex used by Widenhoefer, in the presence of 10 equivalents of the alcohol, and using DMF as solvent, gave the regioisomers of the attack of the alcohol to the more substituted carbon of the allene in regioselectivities of 99 : 1 in most of the cases. These reaction conditions were complementary to the ones used before (Scheme 34).
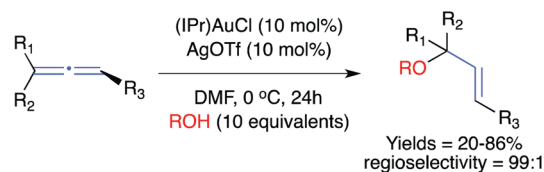
Scheme 34 Au-Catalysed reverse hydroalkoxylation of allenes.

Despite all the studies on the intermolecular reaction of allenes with alcohols in the presence of gold complexes, and the understanding of the factors that influence the regiochemistry of the addition, the enantioselectivity of the reaction remains an unsolved challenge. Racemization of the allene occurs in all the cases studied, so new catalytic systems are needed to avoid this pathway.

Platinum-catalysed hydroalkoxylation of allenes

There is only one platinum-catalysed example of the reaction of allenes and alcohols, and in this case instead of mono addition and formation of allyl ethers, addition of two molecules of alcohol to the terminal carbon of the allene with complete saturation of the second double bond was observed, to give aliphatic acetals (Scheme 35).[39]
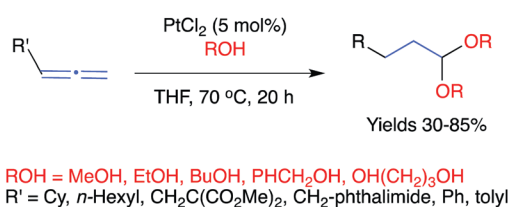
Scheme 35 First Pt-catalysed dihydroalkoxylation of allenes.
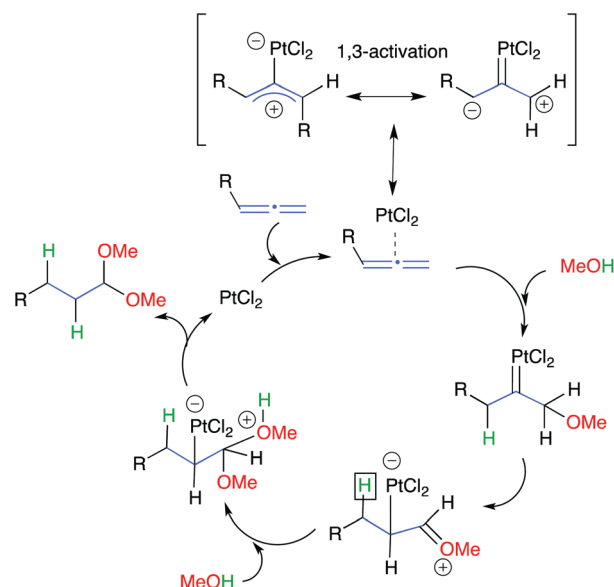
Scheme 36 Proposed mechanism involving Pt-carbene intermediates.†

The reaction works only for mono-substituted allenes with different alcohols. The construction of cyclic acetals or aldehydes was possible if the reaction was carried out in water.

Preliminary mechanistic studies ruled out the involvement of allyl ethers and alkynes as intermediates in this reaction. Deuteration studies showed total incorporation of two deuterium atoms, one on the central carbon and the other one in the internal more substituted carbon of the allene. This suggested a different mechanism involving activation of the allene by the coordination of the platinum to the central carbon, like in a zwitterionic platinum carbene, and 1,3 addition of the alcohol to the allene to form a platinum carbene as the key intermediate (Scheme 36).

Conclusions

This perspective article has shown how the use of different catalytic systems has made the reaction of allenes with oxygen nucleophiles a very versatile reaction in terms of products obtained and mechanistic implications.

In terms of the structural diversity that the metal-catalysed hydroalkoxylation of allenes can afford, the following summary can be made:

- Dimerisation of allenes with attack of one molecule of alcohol or water has been obtained with palladium and ruthenium catalysts, giving the products of the attack to the terminal or central carbon of the allene respectively.

- Allyl ethers or esters can be obtained if gold or iridium catalysts are used, and the attack of the oxygen nucleophile to the most or less substituted carbon of the allenic system will depend on the catalysts and the conditions employed.

- In rhodium-catalysed reactions the alcohol attacks the central carbon of the allene resulting in formation of vinyl ethers. However, the progress is so far limited to the reaction between diphenilphosphino allenes and phenols.

- Acetals can also be obtained either by palladium or gold-catalysed reaction of alkoxyallenes with alcohols (allyl acetals), or by platinum catalysed reaction of mono allenes with attack of

two molecules of alcohol and complete reduction of the second double bond (aliphatic acetals).

As for the mechanistic implications, different metal complexes and intermediates have been proposed, from the metal-hydrides and π-allyl–metal intermediates on the reaction with palladium, iridium or rhodium with carboxylic acids,[40] vinyl–palladium or gold intermediates, to zwitterionic platinum-carbenes.

Despite the huge progress in this context over recent years, important challenges remain. For instance, the only enantioselective examples of hydroalkoxylation of allenes are the rhodium-catalysed reactions with diphenylphosphino allenes and phenols, and the rhodium-catalysed hydrocarboxylation of allenes. However, none of the other metals have been reported to date to give enantioselective transformations.

Although it seems that the factors controlling the attack of the alcohol to the more or less substituted carbon of the allenic system are now well understood in the case of the gold complexes, other challenges to face are the generalisation of the reaction where the alcohol attacks to the central carbon of the allene to give vinyl alcohols, and the understanding of the features in the metal system that will give preferentially one isomer *versus* the others.

Regarding mechanistic studies, although a lot of investigations are being focussed on the gold catalysed systems, and DFT calculations have shown a clear picture in accordance with the experimental results, deeper mechanistic studies are needed to understand the new reactivity obtained with other metals.

Finally, although in this perspective article only reaction of allenes with oxygen nucleophiles has been covered, other nucleophiles can give similar reactivities. As mentioned in the introduction, reaction with nitrogen nucleophiles have already been studied, but reaction with carbon nucleophiles, which have a greater potential to give more complex structures, have only just started to be explored.

Reaction with the metals mentioned in this article or other metals yet to be explored (like iron, nickel, silver) in the presence of different nucleophiles will open new avenues for reactivities not observed so far, and for diverse application in the fields of organic chemistry and biochemistry.

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