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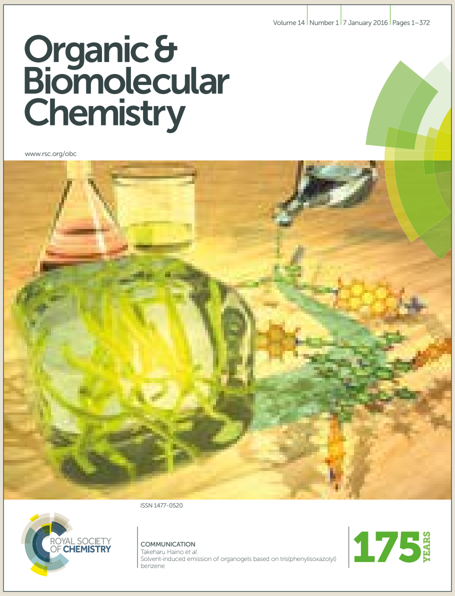

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Nucleophile Dependent Formation of 6- and 7-Membered *N*-Heterocycles by Platinum-Catalysed Cyclisation of 1,5-Bisallenes

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An unprecedented Pt-catalysed cyclisation of *N*-tethered 1,5-bisallenes in the presence of oxygen nucleophiles is reported, where formation of 6- or 7-membered rings is driven by the choice of nucleophile and the mechanism dictated by the nucleophile and the electronic properties of the bisallene. The reaction in the presence of alcohols gives preferentially vinyltetrahydropyridines with an extra alkoxy group and Pt-H as the active species in the catalytic cycle, while formation of di- and tetrahydroazepines with an extra hydroxyl group is favoured when water is used as nucleophile, *via* nucleophilic attack/carbocyclization as the favoured pathway. The products obtained are frequently found in the core of natural products with important biological activities, so understanding this complex mechanistic behaviour and exploiting this new methodology will have a big impact in organic synthesis and organometallic chemistry.

Allene chemistry in the presence of transition metal complexes is nowadays a very important topic that underpins many challenges and advances in organic synthesis.[1] Although a lot of attention has been paid in recent years to reactions involving allenes, progress using non-conjugated bisallenes has been much slower due to issues controlling the selectivity of the processes and the high reactivity of these systems.[2] In this area, 1,5-bisallenes have shown to be excellent building blocks for transition metal-catalysed cyclisations and cycloadditions, offering versatile reactivity (tail-to-tail, head-to-head or tail-to-head) for the constructions of carbo- and heterocycles of different sizes depending on the metal employed and the reaction conditions.[3] For example, 5-membered rings seem to be favored under palladium catalysis,[4] while 7-membered rings have been obtained from 1,5-bisallenes by thermal or Rh(I)-catalysed cyclisation.[4a, 5] Interestingly, formation of 6-membered rings in these systems has been observed in Rh(I)-catalysed cyclisation with external bis-,[6] or mono-allenes.[5b] An unusual example of twisted head-to-head [2+2] cycloaddition has also been reported using gold(I) complexes, limited to *N*-tethered 1,5-bisallenes.[7]

Following our investigations into metal-catalysed reactions of allenes with nucleophiles,[8] we were interested in the platinum-catalysed cyclisation of 1,5-bisallenes in the presence of oxygen nucleophiles (Scheme 1).

The only example reported to date of incorporation of an external nucleophile is the Pd(0)-catalysed cyclisation of 1,5-bisallenes with primary amines and organic halides to give 10-membered azacycles.[9,10] On the other hand, the use of platinum in the reaction with 1,5-bisallenes is scarce. The only reported example is the reductive cyclisation of 1,5-bisallenes catalysed by a Pt-phosphine complex in the presence of $SnCl_2$ and H_2 to give 5-membered rings.[11]

Our initial screening using $PtCl_2$ in MeOH with model 1,5-bisallene **1a** gave bis-acetal **2a** by double dihydroalkoxylation of each allene,[8c] as well as triene **3aa**,[12] and traces of two cycles **4aa**[13] and **5aa** (Scheme 1).[14] The use of a cationic Pt-complex under the same conditions avoided formation of acetal **2a**. Interestingly, the outcome of the reaction was very sensitive to reaction conditions, catalyst[15] and nucleophile.[16] Mixtures of triene **3aa** and vinyl-tetrahydropyridine **4aa** with an extra methoxy group in the final skeleton were preferentially obtained in the reaction when alcohols were used as nucleophile, with the best results obtained with a mixture of THF:ROH (10:1) at 70ºC for 1.5 h (R = Me, Et, Pr, Scheme 1).

More interestingly, when H_2O was used as nucleophile under similar conditions, we found a switch in the regioselectivity to form di- and tetrahydro-*1H*-azepines with an extra hydroxyl group as the only cycles (**5ad** and **6ad**, Scheme 1). Further optimization revealed that with the same cationic platinum complex at 70ºC, a 1:3 ratio of THF:H_2O was crucial to selectively form cycloheptadienes, without traces of the triene.

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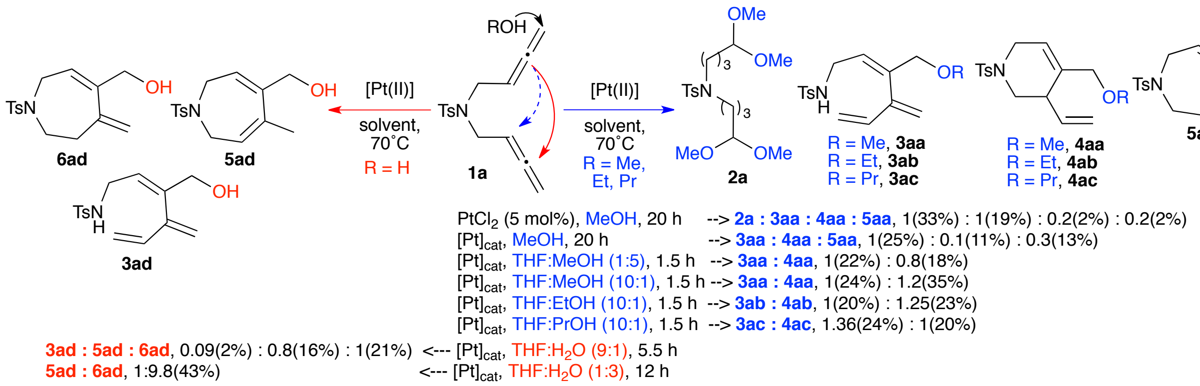
Products were not completely stable to purification by column chromatography, partly explaining the low isolated yields obtained. Additionally, we observed decomposition of the triene and the bisallenes with cationic platinum complexes in slow reactions and when no nucleophile was present, which is in agreement with results previously reported.[10e] Reaction with only $AgSbF_6$ (10 mol%) led to recover unreacted starting material.



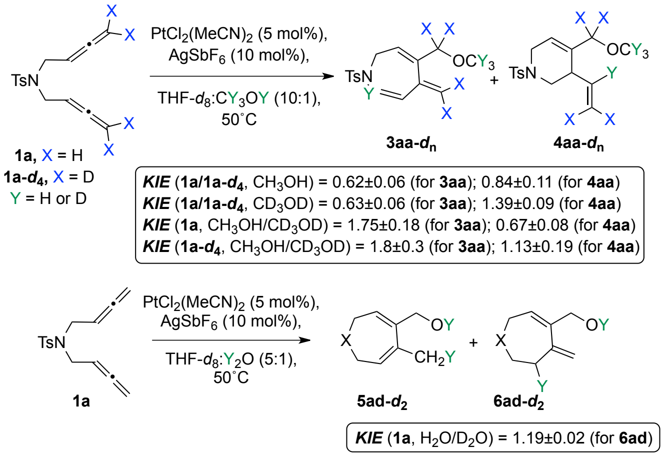
Scheme 1. Nucleophile dependent Pt-catalysed alkoxy- or hydroxycyclisation of 1,5-bisallenes. $[Pt]_{cat}$ = $PtCl_2(MeCN)_2$ (5 mol%)/$AgSbF_6$ (10 mol%). Isolated yields (%).

Since the understanding of the mechanism could help to find ways of improving the yields and selectivity of the reaction and in order to understand this unexpected divergent reactivity encountered depending on the nucleophile, we performed a mechanistic investigation of both reactions (see SI).

The kinetic experiments were carried out measuring ^1H NMR spectra at different reaction times in THF-d_8:CD_3OD or THF-d_8:CH_3OH 10:1 and THF-d_8:D_2O or THF-d_8:H_2O 5:1 at 50ºC (temperature limited by the boiling point of THF-d_8). An induction period was observed in all cases, which unexpectedly was longer when protonated nucleophiles (CH_3OH and H_2O) were used. The kinetic analysis and the order of the different components was measured using the initial rates method and/or the graphical method after the induction period,[17] using bisallene **1a** as model substrate.

The order in CD_3OD was found to be 1 for the formation of both products, triene **3aa** and cycle **4aa.** In the reaction with methanol as nucleophile, the order in platinum calculated using the initial rates was 1 for cycle **4aa**, but could not be determined for the formation of triene **3aa**. The graphical method (with and without the induction period) did not give better results, suggesting changes in the catalytic species in unknown ways or a fast catalysts deactivation process. The decay in concentration of the bisallene followed pseudo-zero order kinetics, suggesting an "off cycle" rate-limiting step. Besides, when the reaction was performed with the **1a-*d*₄** analogue (in CH_3OH and CD_3OD), the consumption of the bisallene was faster, with a secondary KIE ~ 0.5, suggesting a change in hybridization from sp^2 to sp^3 in at least one of the terminal carbon of the bisallene in the turnover-limiting step.

The kinetic measurements using water were performed using mixtures of THF-d_8:D_2O 5:1 at 50ºC, which led to the formation of a small amount of triene **3ad**. Data obtained for the formation of triene **3ad** and cycle **5ad** in the reaction with D_2O could not be analyzed in all cases, due to the low concentration of these products. In the reaction with water, the order in platinum was 0.5 for the formation of cycle **6ad**, which suggests that dimeric species of platinum complexes could be involved.[18] In contrast to the reaction in methanol, the bisallene displayed first order kinetics decay in the reaction with water and no KIE, suggesting different mechanisms are operating with both nucleophiles.



Scheme 2. Labelling experiments and KIEs with deuterated analogues.

The reaction using deuterated nucleophiles and deuterated bisallene **1a-*d*₄** (TsN-) under optimized conditions showed high incorporation of deuterium in the products at the positions shown in Scheme 2 (see SI). KIEs were calculated for all the processes using the initial rates method after the induction period, using **1a** and deuterated bisallene **1a-*d*₄**, in the presence of CH_3OH or CD_3OD and H_2O or D_2O (Scheme 2).

The KIE was measured in THF:water, 10:1 mixtures at 50 °C. No clear KIE (~1) was observed when D_2O was used in the formation of cycle **6ad** after the induction period. Similarly, no clear KIE (~1) was observed in the formation of cycle **4aa** in the reaction with CH_3OH or CD_3OD with the protonated or deuterated bisallenes. Interestingly, primary KIE ~ 1.8 was observed in the formation of triene **3aa** when CD_3OD was used, and inverse secondary KIE ~ 0.63 was observed in the

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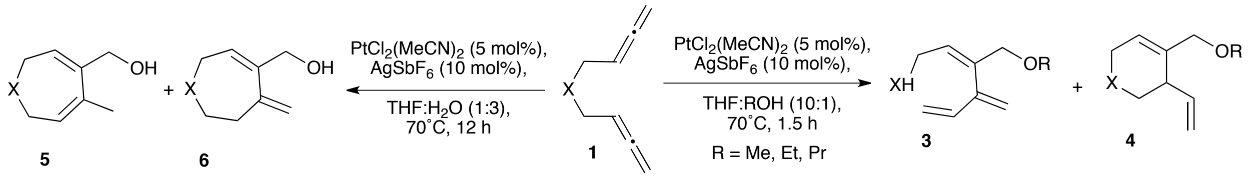
formation of deuterated triene when **1a-d_4** was used as starting material, suggesting a change in hybridisation from sp^2 to sp^3 in the turnover-limiting step of the formation of the triene (Scheme 2).[19]

In order to gain more insight into the possible intermediates and evaluate how the electronic properties of the sulfonamide group, intrinsically a strong electron-withdrawing group, affected the reaction outcome, we carried out the reactions of 1,5-bisallenes with different *para*-substituents in the phenylsulfonyl group in methanol and water under the optimized conditions. Mixtures of trienes **3** and vinylcyclohexenes **4** were obtained in methanol in similar ratios when ED-substituents are present in the sulfonamide, while the ratio of **3** increases with EW-substituents and cycloheptadienes **5** are also obtained. In water, tetrahydro-*1H*-azepines **6** were the major products in all cases (Scheme 3).

To our surprise the Hammett plots obtained for all products using both nucleophiles showed a change of the sign of the slope, with a concave shape for all the compounds in both reactions. This suggests that different mechanisms are operating depending on the electronic properties of the tethers in bisallenes **1** with both nucleophiles, which is remarkable giving the inherent electron-withdrawing nature of the sulfonamide group (Figure 1 and 2).[20]



X = Ts, R = Me, **5ad** + **6ad**, 1:9.8, (43%)	**1a**, X = TsN	X = Ts, R = Me, **3aa** (24%) + **4aa** (35%)
X = PhSO$_2$N, R = Me, **5bd** + **6bd**, 1:7.8 (52%)	**1b**, X = PhSO$_2$N	X = PhSO$_2$N, R = Me, **3ba** (21%) + **4ba** (28%)
X = *p*MeO-PhSO$_2$N, R = Me, **5cd** + **6cd**, 1:10 (42%)	**1c**, X = *p*MeO-PhSO$_2$N	X = *p*MeO-PhSO$_2$N, R = Me, **3ca** (33%) + **4ca** (31%)
X = *p*Cl-PhSO$_2$N, R = Me, **5dd** + **6dd**, 1:7.6 (46%)	**1d**, X = *p*Cl-PhSO$_2$N	X = *p*Cl-PhSO$_2$N, R = Me, **3da** (43%) + **4da** (19%)
X = *p*CF$_3$-PhSO$_2$N, R = Me, **5ed** + **6ed**, 1:8.5 (52%)	**1e**, X = *p*CF$_3$-PhSO$_2$N	X = *p*CF$_3$-PhSO$_2$N, R = Me, **3ea** (36%) + **4ea** (7%) + **5ea** (6%)
X = *p*NO$_2$-PhSO$_2$N, R = Me, **5fd** + **6fd**, 1:5.9 (35%)*	**1f**, X = *p*NO$_2$-PhSO$_2$N	X = *p*NO$_2$-PhSO$_2$N, R = Me, **3fa** (34%) + **4fa** (5%) + **5fa** (6%)

Scheme 3. Pt-catalysed divergent alkoxy- and hydroxycyclisation of *para*-phenylsulfonyl tethered 1,5-bisallenes. * 5-membered ring **18f** obtained in 3% (see SI).

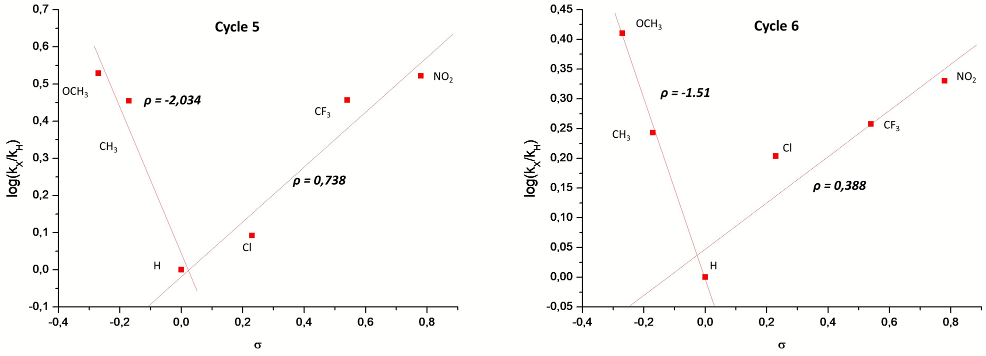


Figure 1. Hammett plots of the hydroxycyclisation products, cycles **5** and **6**, in THF-d_8:D$_2$O, 5:1 at 50ºC.

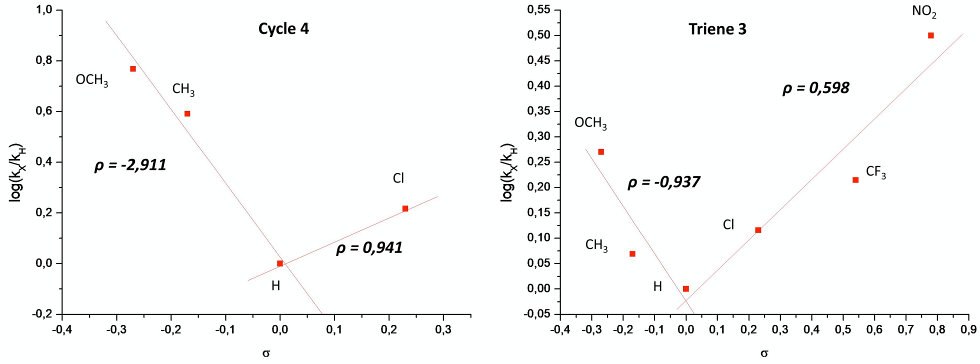


Figure 2. Hammett plots of the alkoxycyclisation products, cycle **4** and triene **3**, inTHF-d_8:CD$_3$OD, 10:1.[21]

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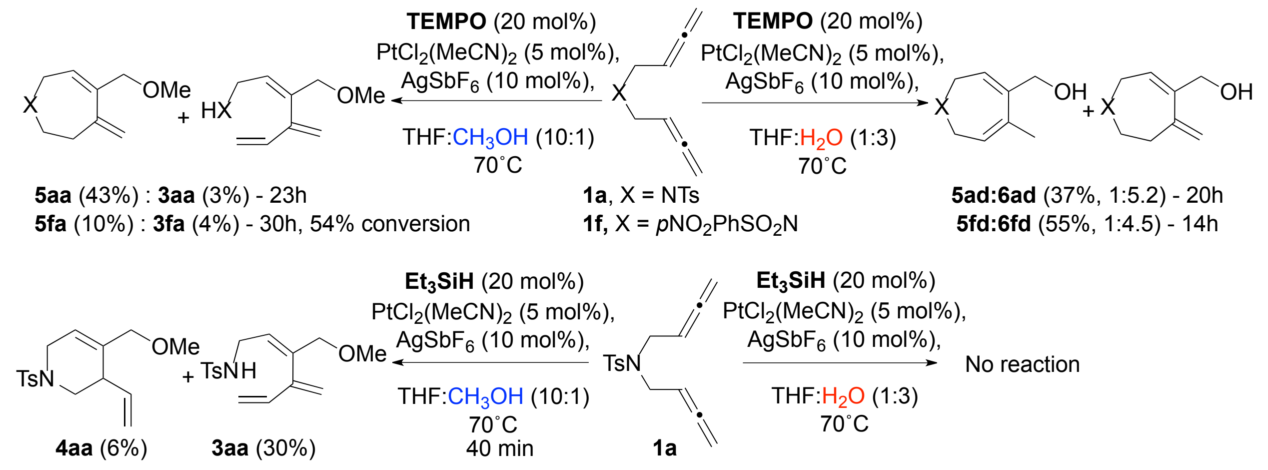
In order to provide alternative mechanisms to explain the concave Hammett plots observed, we explored the involvement of platinum hydrides (Pt-H) in our processes, which have been reported to form when platinum complexes are in the presence of alcohols.[22] We performed the reaction in the presence of TEMPO, which has been reported to inhibit the formation of metal hydrides,[23] and Et$_3$SiH, which has been shown to form Pt(IV)-H by oxidative addition to Pt(II) complexes (Scheme 4).[24]



Scheme 4. Reactions in the presence of TEMPO and Et$_3$SiH.

The reaction of bisallenes **1a** (Me-) and **1f** (NO$_2$-) with MeOH in the presence of TEMPO led to an increase in reaction time, with formation of trienes **3** and the azepine cycle **5** (not observed before under these conditions), inhibiting the formation of vinylcyclohexenes **4** (Scheme 4). In contrast, reaction of bisallenes **1a** and **1f** with H_2O in the presence of TEMPO led to hydro-1H-azepines **5** and **6** similarly to when no TEMPO was present. Besides, Et$_3$SiH inhibited the reaction with H_2O and led to the fast formation of triene **3aa** and cycle **4aa** with MeOH, although in different yield than the standard reaction (Scheme 5). This suggests that Pt(II)-H could be indeed involved as active catalysts in the formation of vinyl-tetrahydropyridines **4** and trienes **3** in the reaction with MeOH, but formation of cycloheptadienes **5** and **6** with water occurs with no involvement of Pt-H as active catalyst.[25]

In view of these results, we propose different mechanisms depending on the nucleophile and the electronic properties of the tether in bisallenes **1** for the formation of 6- and 7-membered rings and trienes (Scheme 5).

In the reaction with MeOH, formation of Pt(II)-H would explain the induction period observed and the order 1 in MeOH and Pt (“off cycle”, rate-limiting step).[26] Addition of the Pt(II)-H to the internal or external double bonds of one of the allenes would give intermediates **7** and **10**.[27] Formation of cycle **4** when EW-substituents are present in the sulfonamide could be explained by nucleophilic addition to **7** with concomitant formation of platinacycle **8** (ρ = 0.9, slight increase in electron density in a concerted process as the turnover-limiting step), from which reductive elimination would form cycle **4** and Pt(0), that can be protonated by MeOH to regenerate Pt-H.

Alternatively, the reaction of bisallenes with ED-substituents in the sulfonamide would favour carbometalation of **7** (ρ = -2.9, moderate decrease in electron density in the turnover-limiting step forming the Pt(II)-π-allyl cation; KIE ~ 1; methanol not involved), followed by nucleophilic attack to the π-allyl-Pt(II) intermediate **9** to give **4** and Pt(0).

Pt(II)-H can also be involved in the formation of trienes from bisallenes bearing ED-substituent in the sulfonamide. Cyclisation of intermediate **10** with semiconcerted attack of the methanol to give platinacycle **11** (ρ = -0.9, slight decrease in electron density in the Pt(II)-π-allyl with cationic character before nucleophilic attack; primary KIE ~ 1.8 in methanol; inverse secondary KIE, change in hybridization in the terminal carbon from sp^2 to sp^3), followed by fast 1,5-H shift to give **12** and reductive elimination would give trienes **3**. Alternatively, trienes with EW-substituents in the sulfonamide could be formed from **13** *via* nucleophilic attack (ρ = 0.6, slight increase in electron density) and cyclisation of the vinyl-platinum **14** to give intermediates **16** or **17**, which would suffer elimination, aided by the EW properties of the sulfonamide group,[28] without the involvement of Pt(II)-H. This alternative pathway seems to be operative for the formation of azepines **5** in the reaction with methanol in the presence of TEMPO and at high MeOH concentration.

The trapping experiments also showed that Pt-H are not the active catalyst in the formation of azepines in water. The reaction in water would proceed through coordination of the platinum to one[29] or both allenes, **13**, followed by nucleophilic attack and carbocyclisation *via* a vinyl-Pt(II) intermediate **14** with EW-substituted sulfonamides (ρ = 0.7 for cycle **5** and 0.4 for cycle **6**)[11b,30] or formation of platina(IV)cycle **15** (ED-substituents, ρ = -1.5 for cycle **5** and -2.0 for cycle **6**),[5b,31] followed by nucleophilic attack to form **16** or **17**. We did not observe isomerisation of cycles **5** and **6** once formed or deuterium scrambling in any of the allylic position when the reaction was carried out in deuterated water. This

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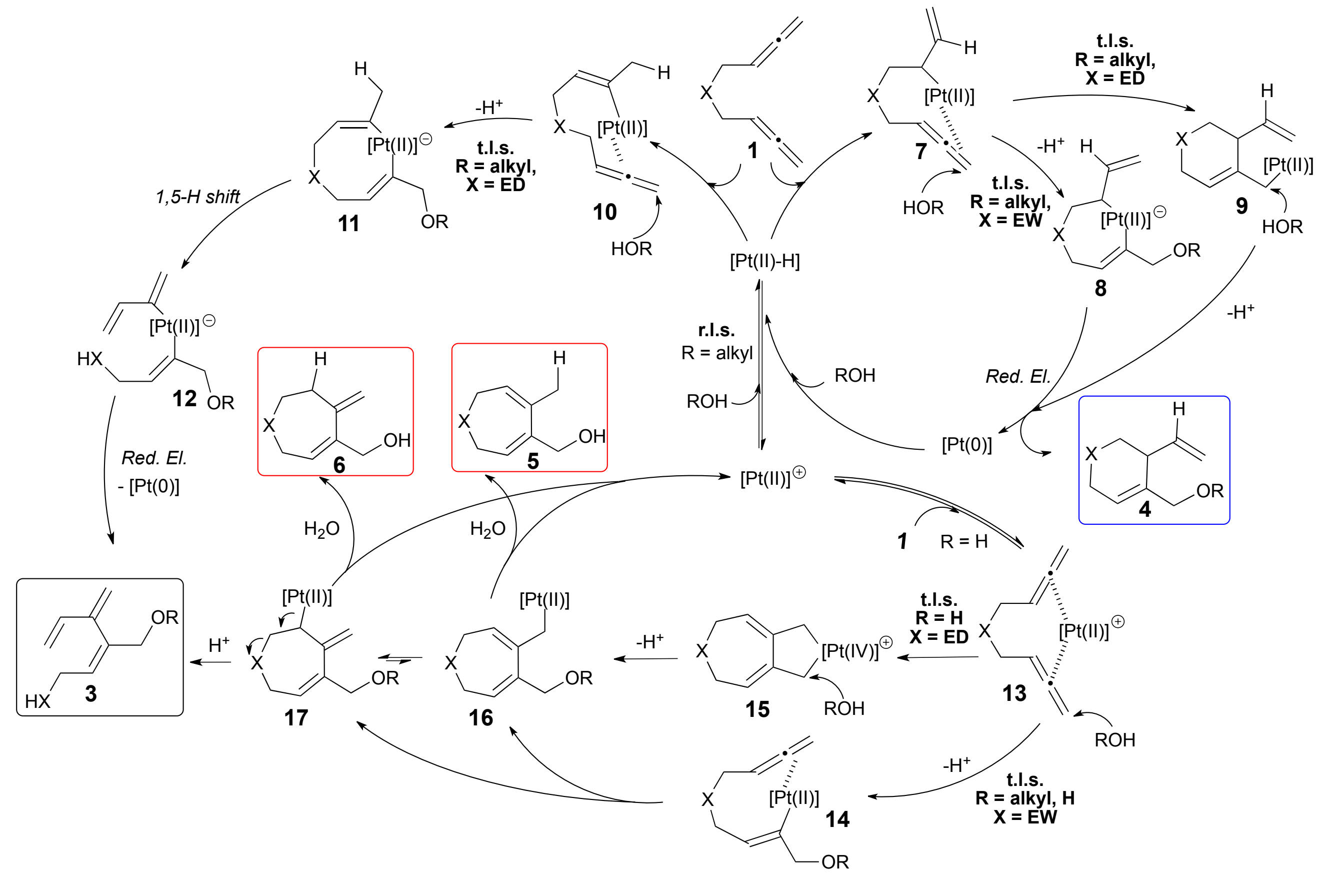
suggests that equilibrium between the Pt(II)-π-allyl intermediates **16** and **17** could be responsible for the favoured generation of cycle **6**. The analysis of Hammett constants *vs* log(ratio **6**:**5**) was linear with a slight negative slope (ρ = -0.17),[32] which indicates that the equilibrium could be slightly favoured toward intermediate **17** with ED-substituted sulfonamides and toward **16** with EW-substituted ones. Besides, intramolecular protodemetallation of intermediate **16** is possible to form cycle **5**, whereas in the case of cycle **6**, this proton transfer in intermediate **17** is more difficult and has to be assisted by an external molecule of H_2O. This is supported by the increase in cycle **6** formation as the amount of H_2O in the media increases in a linear correlation for the TsN-derivative (see SI).

In conclusion, unprecedented platinum-catalysed hydroxy- and alkoxycyclisations of bisallenes to give 6- or 7-membered rings with extra functionalities have been discovered. These new reactions are important additions to the growing pallet of bisallene chemistry and highlight the importance of the less explored platinum catalysis in this area. Although simple at first sight, a deeper mechanistic investigation revealed a complex scenario with several pathways involved depending on nucleophile and electronic properties of the bisallene. Understanding these mechanisms with help to improve efficiency and extend this methodology to more complex systems with interest for synthetic chemists and pharmaceutical industry.[33,34]



Scheme 5. Proposed divergent mechanistic pathways. Active species $[Pt(II)]^+$ and [Pt(II)-H] are presented for simplicity. r.l.s. = rate limiting step. t.l.s. = turnover-limiting step.

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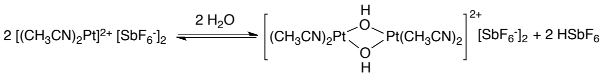

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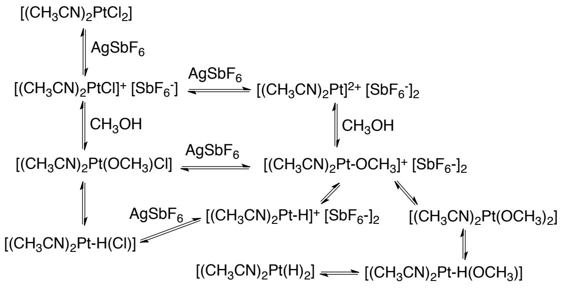
26 Complex equilibrium between cationic platinum(II) complexes, platinum(II)-alkoxides, platinum(II)-hydrides and di-hydrides might be involved. Formation of $[Pt(II)-(H)_2]$ species will be more difficult with deuterated methanol, explaining the shorter induction period.



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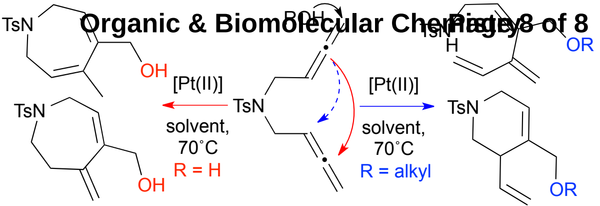

Divergencies unravelled in new Pt-catalysed alkoxy- and hydroxycyclisation of *N*-tether 1,5-bisallenes to give vinyl-tetrahydropyridines with alcohols and hydro-*1H*-azepines with water.