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Mechanistic aspects of transition metal catalysed 1,6-diene and 1,6-enyne cycloisomerisation reactions

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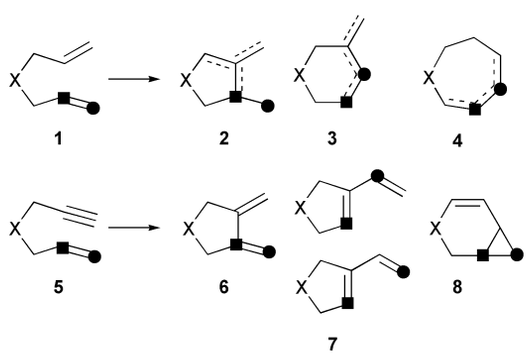
1 Introduction

Within the remit of this review, cycloisomerisation will be restricted to define a reaction in which a section of carbon or carbon–heteroatom chain, which is unsaturated at two positions, is isomerised, with concomitant loss of one or more units of unsaturation, no (formal) loss or gain of any atoms and the generation of one or more ring systems. This review does not aim to be comprehensive and we will only consider 1,6-diene (**1**) and 1,6-enyne (**5**) transition metal *catalysed* cycloisomerisation reactions, Scheme 1, and not metal mediated[1] or oxidative or



Scheme 1

reductive cyclisations. The reader is referred to recent reviews by Trost and Kriche,[2] Trost, Toste and Pinkerton,[3] Trost,[4] Aubert, Buisine and Malacria,[5] and Ojima *et al.*,[6] for a broad coverage of cycloisomerisation reactions and their applications.

The cycloisomerisation of 1,6-dienes (**1**) is the simpler of the two reactions and, amongst other possibilities could give 5-, 6- or 7-membered ring products (**2**–**4**). However, the cyclopentane/ene species (**2**) are most often the primary products and in all cases the original connectivity along what was the seven atom acyclic chain is maintained, see black circles and squares on chains in Scheme 1. In other words, the isomerisation only involves (formal) migrations of hydrogen and associated bond reorganisation and no carbon–carbon bond cleavage. Hepta-1,6-enynes (**5**) often form 5-membered ring cycloisomers. These may be the simple cycloisomers of type (**6**), or, depending on the catalyst system employed, skeletal reorganisation may also be observed such that the original connectivity along the 1,6-heptenyne chain is not maintained in the product and *e.g.* **7** is generated. Furthermore, in recent years a range of new catalysts systems have been discovered that effect 1,6-enyne cycloisomerisation to generate 6- and 7-membered rings and in some cases even bicyclic systems (*e.g.* **8**).

Cycloisomerisations of 1,6-dienes and 1,6-enynes are powerful synthetic processes: fully atom economic,† they produce new rings, common structural motifs in natural products, often with very high control of double bond position and geometry and in a diastereoselective manner. More recently, a few examples have been reported to be rendered highly enantioselective with transition metal catalyst chirality dictating the absolute stereochemistry of the product. These features make transition metal catalysed cycloisomerisations an important topic for further development and, as will become evident in this review, a number of research groups are focusing intensely on this area. For significant advance, there are a number of problems to be solved. These include: improving catalyst efficiency (turnover numbers and rates), increasing selectivity, decreasing substrate specificity and developing more robust catalyst systems. All of these aspects are made complex by the fact that in many cycloisomerisation reactions the transition metal compound added to the reaction in the first place is a *pro*-catalyst, from which a subsequent induction process generates the active species. Consequently, for logical design of ligand architecture, the identification of the active species and the selectivity-determining step(s) is essential and an intimate knowledge of the activation process, or indeed identification of alternative routes to the active species, may facilitate far more efficient cycloisomerisation. In stark contrast, in some processes involving diene or enyne structures, cycloisomerisation may not be desirable, for example in 1,6-diene ring closing metathesis reactions.[7] In these cases inhibiting the undesired generation of cycloisomerisation catalysts is the goal.

In summary, all aspects of cycloisomerisation would benefit from increased mechanistic insight and in the long term this will undoubtedly be the key to increasing catalyst efficiency, inducing or improving regio- chemo- or enantio-selectivities or eliminating cycloisomerisation as a side reaction. As is true with many transition metal catalysed reactions, many cycloisomerisations undergo turnover *via* organometallic intermediates that are present in very low concentrations or are rather transient and thus the reaction mechanisms must often be probed indirectly. Nonetheless, a number of illuminating mechanistic investigations have been performed and the level of understanding of factors which control the selectivity is advancing rapidly. Herein, we review progress to date in this area.

2 Origins and evolution of the reaction class

2.1 1,6-Dienes

The first transition metal catalysed 1,6-diene cycloisomerisation, which was serendipitous, was reported in 1971 by Malone *et al.*[8] A solution of hydrated rhodium trichloride in diallyl ether was heated and this effected cycloisomerisation to give the *exo*-methylene isomer **9** in good yield (≥10^4 turnovers), Scheme 2. A few percent allyl alcohol present in the diallyl ether was essential for reaction and independent reaction of allyl alcohol/methanol with rhodium trichloride gave complex **10** (see inset to Scheme 2) whose structure was established by single crystal X-ray diffraction. Complex **10**, which probably arises *via* an allylrhodation of allyl alcohol, was also effective as a pro-catalyst for the cycloisomerisation reaction.

A few years later the same cycloisomerisation catalysed by cationic Ni-phosphine complexes was studied extensively by Bogdanovic,[9] and Schmitz reported on the Pd-catalysed and the Rh-catalysed cycloisomerisation of *N*,*N*-diallyl acrylamide

† Fully 'atom economic': all atoms in the substrate appear in the product, no reagent is consumed and there is no generation of co-products.

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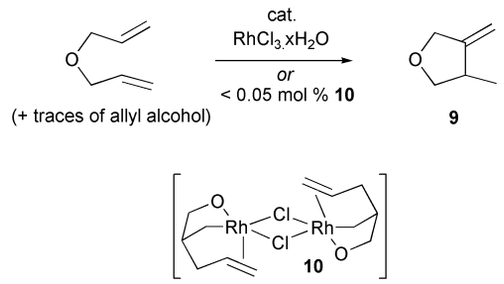
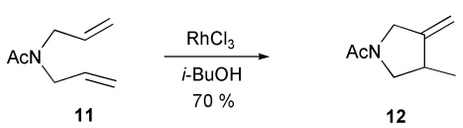


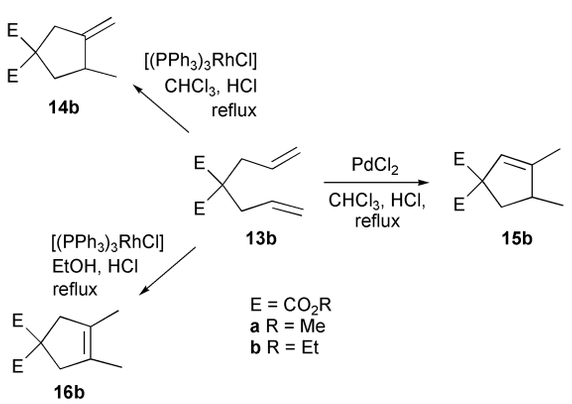
Scheme 2

which gave a host of products (the Rh-catalysed process being marginally more selective).[10] Interestingly, the acrylamide moiety participated extensively in the Pd-catalysed process (giving lactams) whereas the opposite outcome was apparent with Rh (giving pyrollidine isomers). When the complexity of substrate (and thus product range) was reduced from a triene to a 1,6-diene, in the form of *N*,*N*-diallyl amides (*e.g.* **11**) or *N*-alkyl-*N*-allyl acrylamides, much higher selectivities were observed.[11] For example, amide **11** gave *exo*-methylenepyrrolidine **12** in 70% yield, Scheme 3.



Scheme 3

Some while later, Grigg reported extensively on the cycloisomerisation of 1,6-dienes based on diallylated 1,3-dicarbonyl compounds, such as diallyl malonate **13b** which can give isomers **14b**, **15b** and **16b**, Scheme 4. With palladium chloride

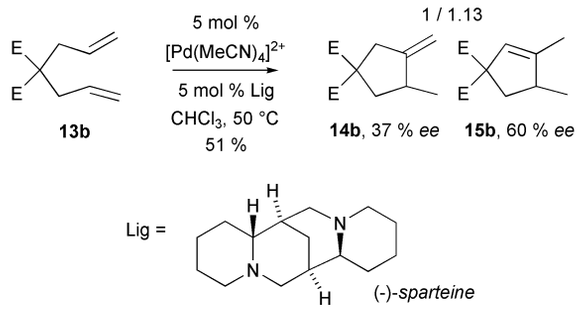


Scheme 4

as a (pro)-catalyst high regioselectivity for **15b** was observed.[12] The use of Wilkinson's complex [$(PPh_3)_3RhCl$] was also reported (other complexes, including $RhCl_3$ hydrate, were not effective) and choice of solvent ($CHCl_3$ *versus* EtOH) facilitated usefully selective cycloisomerisation to **14b** or **16b** respectively.[13] Thus through choice of catalyst and solvent, all three cycloisomers **14b**, **15b** and **16b** could be obtained with good regioselectivity.[14]

After this report by Grigg *et al.*, the field lay dormant for some 14 years. However, in 1998, coincident with the review by Trost and Krische,[2] interest revived and the readily synthesised and analysed diallyl malonate type substrate (**13**) was adopted as the 'benchmark' system for testing novel late-transition metal catalysts for 1,6-diene cycloisomerisation, giving 5-membered ring cycloisomers as products (**14**, **15** and **16**)

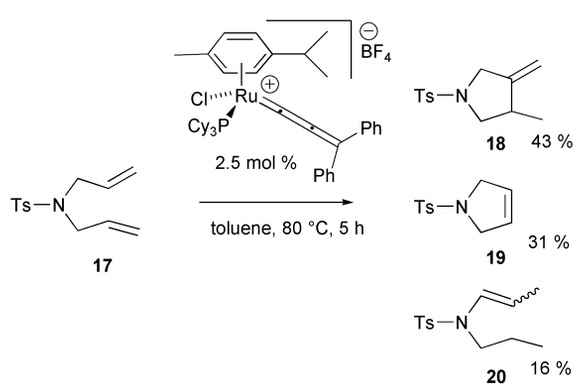
Radetich and RajanBabu reported on Ni- and Pd-catalysed cycloisomerisation of **13a**,[15] employing M-allyl type pro-catalysts and Heumann and Moukhliss reported on *asymmetric* cycloisomerisation of **13b** with cationic Pd catalysts bearing *N*,*N*-ligands,[16,17] Scheme 5.



Scheme 5

Later Itoh *et al.* reported the first Ru catalysts, with [$RuCl_2$-COD]$_n$ proving highly effective for selective isomerisation of **13a** to *exo*-methylene isomer **14a**.[18] Shortly after, a number of contributions were made by Widenhoefer *et al.*, including cationic allyl-Pd pro-catalysts for the selective isomerisation of **13** to the thermodynamically most stable cycloisomer **16**[19] and a cationic phenanthroline methyl palladium pro-catalyst for selective isomerisation of **13** to **15**,[20] thereby completing the suite of catalysts for highly controlled conversion of **13** to 5-ring products. More recently, Lloyd-Jones *et al.* reported that *neutral* chloride-bearing[21] palladium complexes (*e.g.* [(t-BuCN)$_2$PdCl$_2$]) are very convenient pro-catalysts for highly regioselective isomerisation of **13a** to **15a**,[22] and Lloyd-Jones *et al.* and Cozzi *et al.* have studied the mechanism[23] and activity[24] of cationic allyl palladium pro-catalysts for cycloisomerisation of **13a**.

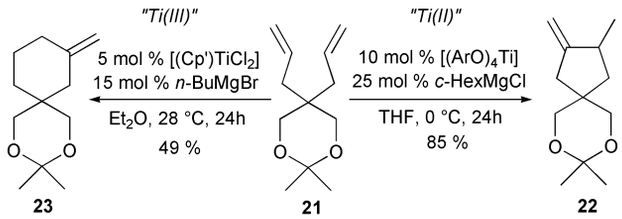
In parallel with these developments, Dixneuf *et al.*,[25,26] and Fürstner *et al.*,[7] were experiencing undesired cycloisomerisations competing rather effectively with ring closing metathesis (RCM) of 1,6-dienes catalysed by ruthenium allenylidene complexes, for example diene **17** gave substantial quantities of isomerised (**20**) and cycloisomerised (**18**) products in addition to the desired RCM product (**19**), Scheme 6.



Scheme 6

The good to excellent functional group tolerance and general ease of handling displayed by late transition metals has made their study more popular. Nonetheless, a number of early transition metal systems have been investigated for diene cycloisomerisation – although mostly involving 1,5- and 1,7-dienes.[27,28] Livinghouse has reported two types of Ti-catalyst systems, prepared *in situ* by reduction of Ti(IV) complexes with Grignard reagents, for cycloisomerisation of a range of 1,6-dienes.[29,30] The Ti(II) systems "$(ArO)_2Ti$" were found to be highly selective for generation of *exo*-methylene cyclopentane type products. Thus, for example, the 7,9-dioxaspiro[4.5]decane **22** is obtained from the diallyl-1,3-dioxane **21**, Scheme 7.[29]

With the Ti(III) systems generated from Cp_2TiCl_2, a mixture of 5- (*e.g.* **22**) and 6- ring (*i.e.* **23**) cycloisomers is generated. The latter can be favoured by using the bulky, chelating ethylene-bis(tetrahydroindenyl) ligand.[30] Thiele and Erker found that Cp_2ZrCl_2–methylalumoxane gives mostly the 6-membered ring



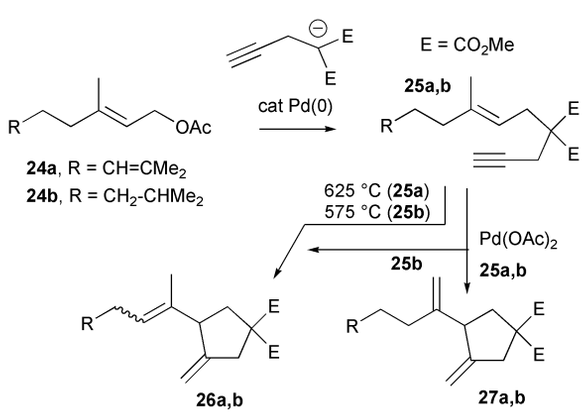
Scheme 7

isomer from the simplest 1,6-diene: hepta-1,6-diene.[31] Organolanthanides have also been explored as catalysts. For example, Bercaw *et al.* have reported very selective and rapid cycloisomerisation of simple 1,6-dienes to the corresponding methylene cyclohexane system. The extreme Lewis acidity of these complexes is undoubtedly the origin of their activity and thus why they also present "considerable, though not insurmountable, difficulties in their preparation and handling".[32]

2.2 1,6-Enynes

Unlike diene cycloisomerisation, the area of enyne cycloisomerisation and metathesis has been reviewed extensively,[2,5,33–35] and consequently, we will only chart the development of this much more developed reaction class in a brief and non-comprehensive manner here.

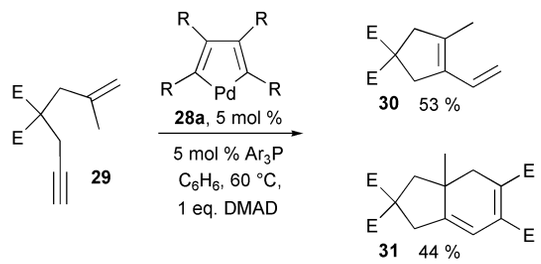
The transition metal catalysed cycloisomerisation of 1,6-enynes was first described in 1985 by Trost and Lautens.[36] Serendipity again played a key role: during studies to develop the synthesis of 1,6-enynes by Pd(0) catalysed addition of dimethyl propargyl‡ malonate to allylic acetates, it was found that the presence of Pd(II) salts resulted in cycloisomerisation of the products. On examining a range of Pd(II) complexes, both $Pd(OAc)_2$ and $[(PAr_3)_2Pd(OAc)_2]$ were found to be effective catalysts for this process. The reaction is sometimes described as a catalysed "Alder-ene" reaction, but can give very different regiochemical or stereochemical outcomes to the conventional thermal process, which in some cases fails to proceed at all. For example, the 1,6-enyne **25a** (generated by Pd(0) catalysed reaction of geranyl acetate **24a** with dimethyl propargyl malonate gives an 83% yield of 1,4-diene **26a** on flash vacuum thermolysis (625 °C) whereas, regioisomeric 1,4-diene **27a** is obtained in 80% yield on $(Pd(OAc)_2)$ catalysed cycloisomerisation, Scheme 8.[37]



Scheme 8

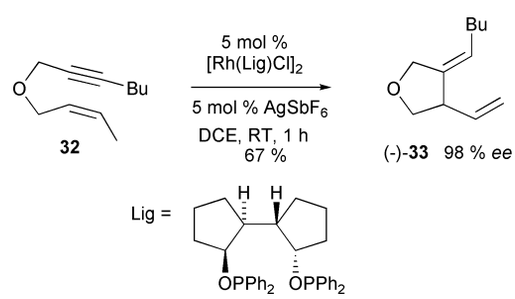
Interestingly, when PPh_3 was added the selectivity dropped (**26a**–**27a** *ca.* 1–3) and when the dihydro analogue **25b** was employed, selectivity for **26b**–**27b** was negligible in the Pd-catalysed process, but remained essentially perfect (for **26b**) in the FVP process (575 °C). The selectivity in the Pd-catalysed process was ascribed to chelation by the alkene in the proposed palladacyclopentene Pd(IV) intermediate, *vide infra*. Some 15 years later, Mikami rendered the Pd(II)-catalysed reaction asymmetric by applying chiral chelating ligands. However, the key to attaining suitable reactivity was switching from $Pd(OAc)_2$ to $Pd(O_2CCF_3)$ and ultimately to $[Pd(MeCN)_4]^{2+}$.[38]

In 1987, Trost and Tanoury introduced a combination of palladacyclopentadiene (**28a**, R = CO_2Me) and tri-*o*-tolyl phosphite as a catalyst system for 1,6-enyne cycloisomerisation. The ligand was added to 'break down the insoluble palladacyclopentadiene polymer' and reaction proceeded smoothly at 60 °C to give 'Alder-ene' type diene products. In the case of enyne **29**, in the presence of dimethyl acetylenedicarboxylate (DMAD), the major product (53%) was found to be **30** in which there has been a skeletal rearrangement,[39] this being the first example of a 1,6-enyne metathesis reaction,[35,34] Scheme 9.



Scheme 9

Trost and Tour also described a mixed Cr–Ni system which cycloisomerised 1,6-enynes to 1,2-bismethylene cyclopentanes in good yield.[40] The Rh-catalysed cycloisomerisation of 1,6-enynes was first described in 1988 by Grigg and co-workers. Wilkinson's catalyst was found to be effective, provided that neither alkene nor alkyne were substituted at the termini, and gave *exo*-methylene cyclohex-2-enes with very high selectivity.[41] Zhang later explored chelating ligands for this process and employed cationic Rh species generated *in situ* (using $AgSbF_6$). Cycloisomerisation proceeded with terminally substituted alkenes, providing they were of *Z*-geometry, to give cyclopentene type products.[42] Application of chiral ligands resulted in good to excellent asymmetric induction. For example, **32** was isomerised to **33** in 98% *ee*. Scheme 10.[43,44]

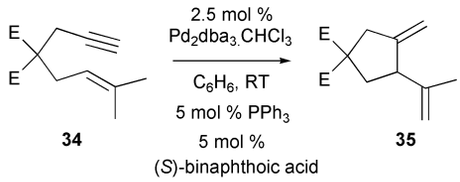


Scheme 10

The use of Ru-based catalysts for 1,6-enyne cycloisomerisation (without skeletal rearrangement) was reported by Mori in 1998.[45] Later reports from Trost and Toste in 1999 demonstrated access to 7-[46] or 5-[47] membered rings. The success of the latter catalyst system relied on improvements made to Ru-based catalyst systems for the intermolecular Alder-ene reaction.[48,49] The Ru-catalysed,[50] Pd catalysed[51] and Pt catalysed[52–54] cycloisomerisation of 1,6-enynes in which the 'ene' component is part of an aromatic ring has also been reported.[55] A titanocene based catalyst system, reported by Buchwald, is a rare example of early transition metal *catalysis* of enyne cycloisomerisation.[56]

‡ The IUPAC name for propargyl is prop-2-ynyl.

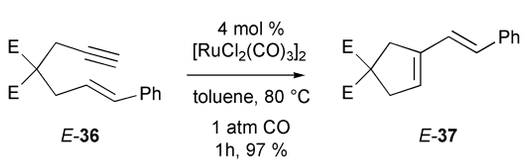
In 1989 Trost reported the design of a "Pd-H" catalyst system for enyne cycloisomerisation. The combination of Ar_3P, $Pd_2dba_3.CHCl_3$ (a Pd(0) source) and AcOH was very effective for a large range of 1,6-enynes.[57,58] Adaptation of these conditions also led to the earliest example of an asymmetric transition metal catalysed 1,6-enyne cycloisomerisation: use of enantiomerically pure (*S*)-binaphthoic acid instead of acetic acid resulted in the generation of 1,4-diene **35** from 1,6-enyne **34** in 33% *ee*, Scheme 11.[57] Later studies demonstrated



Scheme 11

promising levels of asymmetric induction by use of a chiral diphosphine ligand,[59] and that replacement of acetic acid with formic acid led to higher catalyst activity.[60]

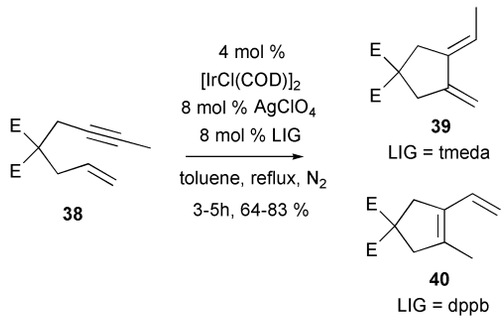
In 1994, Mori broadened the scope of the pioneering studies on enyne metathesis involving carbene-based catalysts by Katz and Sivavec[61] to include 1,6-enynes. Extending earlier studies,[62,63] chromium Fischer carbene complexes were shown to catalyse the enyne metathesis of 1,6-enynes in which the alkene terminus bears an alkoxy group.[64,65] The early generation Grubbs type catalyst[66] was found to be more broadly applicable.[67,68] The decade also saw a growth in non-carbene based catalysts for 1,6-enyne metathesis and cycloisomerisation with skeletal rearrangement. Murai reported $[RuCl_2(CO)_3]_2$ as a very efficient catalyst for 1,6- (and 1,7-) enyne cycloisomerisation to afford vinyl cyclopentenes (and vinyl cyclohexenes) with high stereoselectivity.[69] For example, *E*-**36** is very efficiently isomerised to *E*-**37** by this Ru pro-catalyst, Scheme 12.



Scheme 12

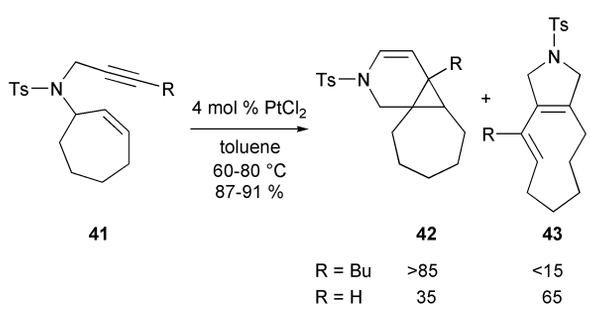
Crucial to high catalyst activity was the use of a CO atmosphere. Indeed, a range of other complexes were tested and it was found that the presence of both a halide and a carbonyl ligand and the absence of phosphine ligands were essential for catalyst activity.[69] It was also noted that halide complexes of Rh, Re, Ir, Pt and Au were active for these transformations. Murai later reported on analogous Ir-based systems where the presence of a CO ligand was also essential, but a CO atmosphere reduced turnover rates. Intriguingly, halide was not essential and halide abstraction (with Ag^+) followed by addition of *N*,*N*- or *P*,*P*- chelating ligands allowed essentially perfect tuning between generation of dienes **39** and **40** from 1,6-enyne **38**, albeit in moderate yields – Scheme 13. The use of $[IrCl(COD)]_2$ with AcOH was also found to be highly effective for enynes in which the alkyne is internal.[70]

Recently, it has emerged that the use of simple platinum salts and complexes provides for some spectacular molecular reorganisations during enyne cycloisomerisations. The first report of Pt-catalysed ($PtCl_4$) enyne cycloisomerisation was from Blum *et al.*[71] who showed that allyl propargyl ethers were cycloisomerised to 3-oxabicylo[4.1.0]hept-4-enes in moderate yields. Subsequently, Murai,[72] Fürstner[73] and Echavarren[74] and their co-workers reported extensively on the use of $PtCl_2$ to catalyse formation of vinyl cyclopentenes and vinyl methylene pentanes from 1,6-enynes. Oi *et al.* found that although addition of phosphine ligands inhibited catalysis, the activity could



Scheme 13

be regained if the halide (Cl) was abstracted.[75] Indeed, using pure cationic Pt complexes (*e.g.* $[Pt(dppe)(PhCN)_2][BF_4]_2$) enyne cycloisomerisation reactions could then be conducted at room temperature in $CHCl_3$, as opposed to at 70–80 °C in acetone or toluene with $PtCl_2$. All three groups observed 'anomalous bond connections during skeletal reorganisation' and Fürstner[76] later reported that allyl propargyl amine type substrates gave 3-azabicylo[4.1.0]hept-4-enes in a manner analogous to the reactions described by Blum. For example, tosyl amide **41** (R = Bu) gave an 87% yield of tricycle **42** (R = Bu), in a reaction that substantially increases the 'molecular complexity' despite the application of a very 'low-tech' catalyst system, Scheme 14.[76,77] Interestingly, when R = H, the major product from **41** is diene **43**.



Scheme 14

2.3 Current state of development

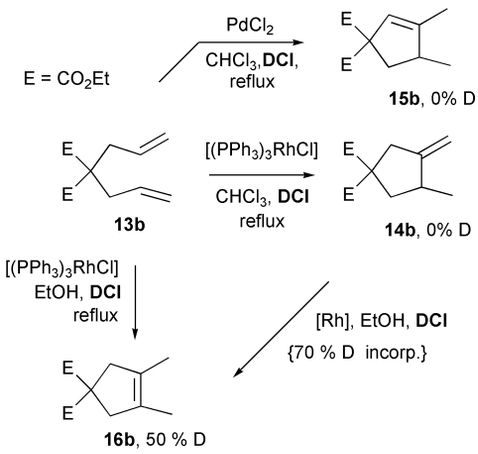
Taking into consideration the section above, it is evident that significant advances have been made in recent years and that the modern portfolio of catalysts allow highly selective cycloisomerisation of 1,6-dienes and 1,6-enynes in excellent yield. Despite being a more recent innovation, the 1,6-enyne cycloisomerisation reaction has been developed to a much greater extent than the 1,6-diene cycloisomerisation. This may be attributed to a) the ready chemo-differentiation between alkene and alkyne functionalities usually resulting in one product isomer, b) the diene nature of the product facilitating a wider applicability to synthesis and c) the reactivity of the alkyne moiety allowing a wider base of effective catalysts. Thus it is not surprising that, unlike 1,6-enynes, the transition metal catalysed cycloisomerisation of 1,6-dienes has not yet been applied in target synthesis. Furthermore, there is only one report on enantioselective 1,6-diene cycloisomerisation[17] and the selectivities, whilst promising, are probably not yet high enough[78] to arouse the interest of the synthetic community.

3 Mechanistic studies

3.1 1,6-Diene cycloisomerisation

3.1.1 Preliminary studies. Preliminary mechanistic studies in this area were performed by Grigg on the Rh- and Pd-based catalyst systems he pioneered for diallyl malonate type substrates, **13**, Scheme 4.[14] As described earlier, catalytic $Pd(OAc)_2$

in HCl pre-saturated chloroform at reflux effects clean cycloisomerisation of **13b** to **15b**. As noted by Grigg, it is 'hard to envisage a mechanism which does not involve hydride intermediates'. However, analysis of cyclopentene **15b** generated when DCl replaced HCl indicated that there was no D-incorporation in the product, Scheme 15.



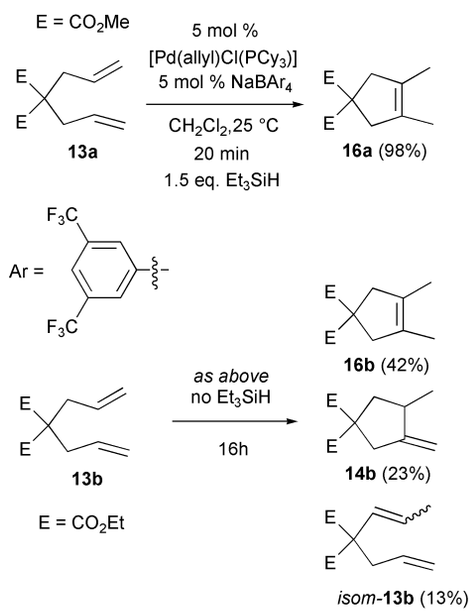
Scheme 15

Thus, it was concluded that interaction of HCl with Pd does not generate an active hydride and that any hydride intermediates must have rather transient lifetimes or undergo surprisingly slow exchange with DCl. Generation of a Pd-hydride was thus proposed to arise by reaction of $PdCl_2$ with **13b** and a mechanism suggested for the cycloisomerisation which was based on precedented (Pd, Ni, Nb, Pt, W) individual steps. It is known that Wilkinson's complex ([$(PPh_3)_3RhCl$]) reacts with HCl to generate [$(PPh_3)_2Rh(H)Cl_2$]), a clear candidate for cycloisomerisation catalysis. However, Grigg found that catalytic [$(PPh_3)_3RhCl$] in DCl pre-saturated chloroform at reflux cycloisomerised **13b** to **14b** with no observable D-incorporation. In stark contrast, analogous reaction in EtOH gave **16b** with *ca.* 50% D-incorporation at the methyl groups (30% D_1, 9% D_2). Under identical conditions, **14b** was isomerised to **16b** with *ca.* 70% D-incorporation. Based on these results, the known generation of [$(PPh_3)_2Rh(H)Cl_2$]) from [$(PPh_3)_3RhCl$] on dissolution in $CHCl_3$–EtOH and the precedented Rh-catalysed isomerisation of alkanes *via* addition–elimination a simpler mechanism (**Ii**, *vide infra*) was suggested for the reaction in EtOH. However, to account for the different results in chloroform, it was concluded that either there was no exchange of D with H between [$(PPh_3)_2Rh(H)Cl_2$]) and DCl in chloroform (but that there is in EtOH, due to charged intermediates being involved) or that a different mechanism was operative. A mechanism analogous to that involved in Ta- and Nb-catalysed olefin dimerisation was proposed as a possibility.

Thus, three different mechanisms (**I**, **II** and **III**, *vide infra*) were suggested to account for the different outcomes from Pd-catalysis (**15b**) *versus* Rh-catalysis (**14b** and **16b**) and the non-exchange of H with D when reactions were conducted in $CHCl_3$ pre-saturated with DCl. It is perhaps salient that the lifetime of DCl in refluxing chloroform is likely to be fairly short, whereas in ethanol, rapid exchange with DCl will generate HCl + EtOD and thus charge the reaction medium with a much more persistent source of deuterons.

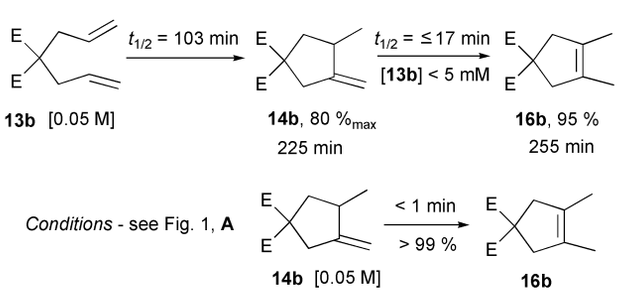
3.1.2 Palladium-allyl pro-catalyst systems. RajanBabu,[15] Widenhoefer[19,79] and Lloyd-Jones[23] and their co-workers have all reported on the use of Pd-allyl cations as pro-catalysts for the cycloisomerisation of dialkyl diallyl malonate. In the latter two cases, detailed mechanistic investigations were performed.

In the RajanBabu system the pro-catalyst is generated *in situ* by chloride abstraction (AgOTf) from [Pd(allyl)Cl]$_2$ in the presence of Ar_3P (Ar = *o*-tolyl). 5 mol% of the resultant complex cycloisomerises dimethyl diallyl malonate **13a** to a mixture of **14a** (22%) and **16a** (78%) in 24 h at RT. As part of extensive studies into Pd(II)-catalysed reactions of 1,6-dienes,[80] Widenhoefer later reported the serendipitous discovery that under rather similar conditions (halide abstraction with $NaBAr_4$ (Ar = 3,5-$(CF_3)_2$-C_6H_4) from [Pd(allyl)Cl(PCy_3)]), the presence of silane had a very beneficial effect on rate and selectivity. For example in the presence of 1.5 equivalents of Et_3SiH, **13a** was completely converted to **16a**–**14a** (98% **16a**) in 20 minutes. Bulky silanes were found to be less effective, and in the absence of a silane, cycloisomerisation of **13b** only proceeded to 78% in 16 h (to give a 1.8 : 3.2 : 1.0 mixture of **14b**, **16b** and isomerised substrate *isom*-**13b**), Scheme 16.



Scheme 16

A detailed kinetic study by Widenhoefer[79] revealed some rather curious features for the cycloisomerisation reaction of **13b** [0.05 M] in CH_2Cl_2 promoted by Et_3SiH [0.075 M] and catalysed by $NaBAr_4$–[Pd(allyl)Cl(PCy_3)] [2.5 mM] at 0 °C. The consumption of **13b** followed a pseudo zero-order kinetic regime (k_{obs} = 8.1 × 10^{-5} s^{-1}) for over 3 half lives to give **14b**, with no detectable **16b** (<3%). However, on reaching a maximum (*ca.* 80% after 225 minutes) **14b** was then completely isomerised to **16b** at a rate over six-fold greater (k_{obs} = 5 × 10^{-4} s^{-1}) than that by which it was initially generated, Fig. 1, left hand graph.



Scheme 17

Thus after a further 30 minutes the product mixture consisted of >95% **16b**. This dramatic acceleration of turnover rate was linked to the depletion of the substrate (**13b**) which thus acts as a very effective inhibitor when [**13**] > 5 mM. Indeed, in the absence of **13b**, but under otherwise identical conditions, pure samples of **14b** were quantitatively isomerised to **16b** in less than one minute.

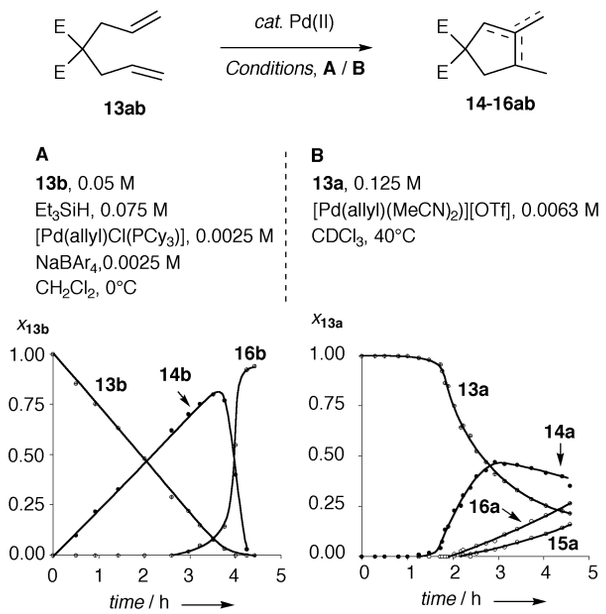
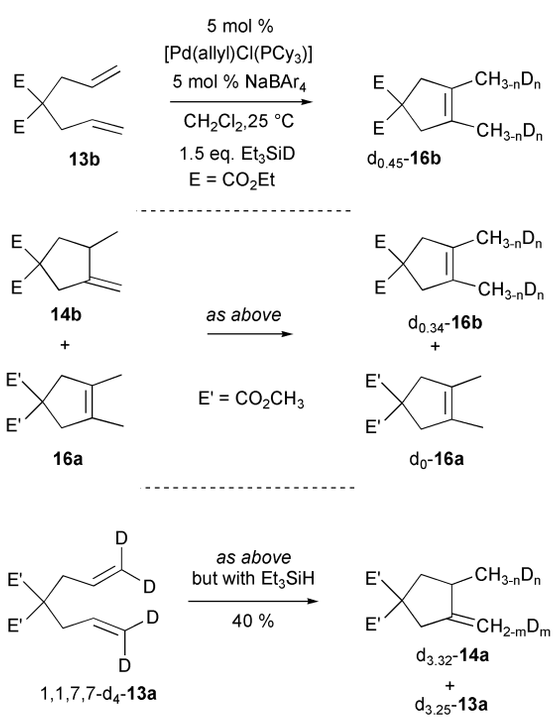


Fig. 1 Evolution profiles for the cycloisomerisation of dimethyl diallyl malonate (**13a**) and diethyl diallyl malonate (**13b**) catalysed by two different Pd(II)-allyl pro-catalysts (conditions **A** and **B**). See text for full details. Under conditions **B**, the length of the induction period varies substantially from run to run, being rather long in the case shown. In both graphs, the lines running through the data points are merely added as aids to the eye.

When the cycloisomerisation of **13b** was conducted in the presence of Et_3SiD instead of Et_3SiH, there was a noticeable induction period. Indeed, the full pseudo zero-order kinetic regime was not reached for *ca.* 30 minutes, in contrast to the unlabelled system where no induction period was evident. However, although with Et_3SiD there was significant deuterium incorporation into the methyl groups of **16b** (d_0–d_3 isotopomers, average 0.45 D per molecule) the turnover rates for the two systems were essentially identical (k_{obs} = 8.8 × 10^{-5} s^{-1} with Et_3SiD). Co-reaction of a 1 : 1 mixture of **14b** and **16a** in the presence of Et_3SiD gave **16b** as a mixture of d_0–d_3 methyl isotopomers (average 0.34 D per molecule) with no incorporation of D into **16a**, Scheme 18.



Scheme 18

In addition to the silane, substrate deuterium labelling studies were also conducted. In a similar manner to Et_3SiD, these experiments were also complicated by scrambling. For example, 2,6-d_2-**13a** gave **16a** as a d_0–d_3 mixture of isotopomers (average 1.28 D per molecule) Consequently, the isomerisation of **13** to **14** was studied separately. Nonetheless, scrambling was still extensive and intermolecular: a 1 : 1 mixture of **13b** and 2,6-d_2-**13a** gave d_0–d_3 mixtures of isotopomers of both **13** and **14**, whilst 1,1,7,7-d_4-**13a** gave d_0–d_6 mixtures of isotopomers, Scheme 18. In all cases, turnover was accompanied by significant 'leakage' of deuterium from the reaction manifold, but the deuterons were located exclusively at C(1) and C(7) in **13** and exocyclic methyl–methylene groups in **14**. Two mechanisms (**Ii** and **II**, Figs 2 and 3 respectively) were considered for the

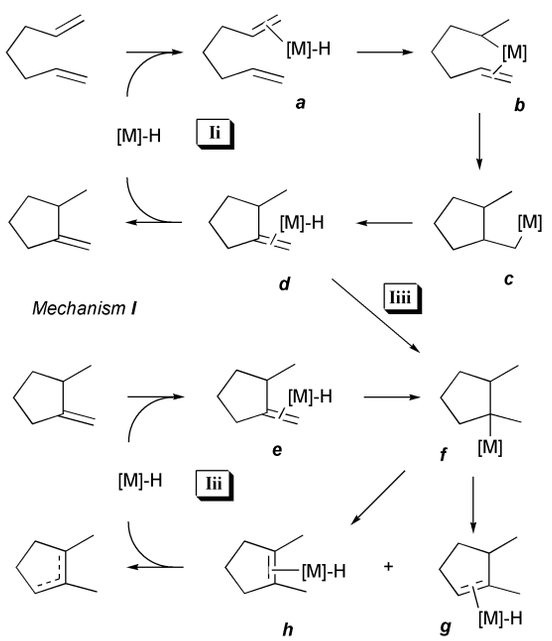


Fig. 2 Mechanism **I**; a generic hydrometallation mechanism for 1,6-diene cycloisomerisation.

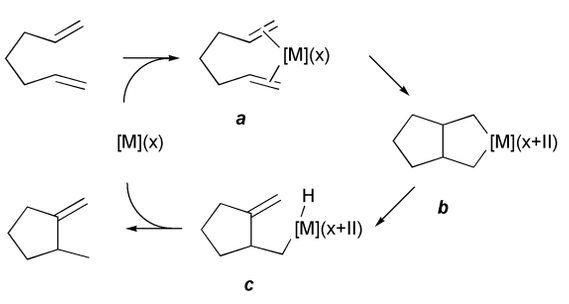


Fig. 3 Mechanism **II**; a generic oxidative cyclometallation mechanism for 1,6-diene cycloisomerisation

process whereby **13** is converted to kinetic product **14**: a hydropalladation–carbopalladation–β-hydride elimination sequence (**Ii**) or an oxidative cyclisation–β-hydride elimination–reductive elimination sequence (**II**). The extensive scrambling of D–H at the *termini* of the alkenes in **13** during reaction is consistent with a reversible hydropalladation (**Iiab**).

In contrast, reversible oxidative cyclisation–β-hydride elimination (**II**) would scramble D–H at the *internal* position of the alkenes (which is not observed).

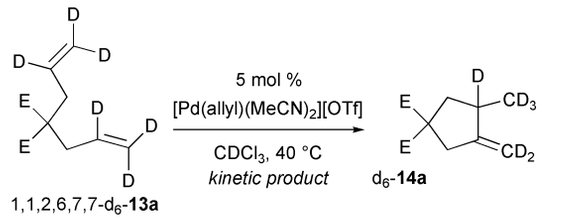
Thus, overall the findings were interpreted to support mechanism **Ii** as outlined in Fig. 2. The Et_3SiH was ascribed a dual role: to both convert the pro-catalyst $[Pd(allyl)(Cl)(PCy_3)]^+$ into the active catalyst (a "Pd-H" species – or a Pd-D species with Et_3SiD) and to stabilise it by weak coordination. However, no direct or indirect evidence could be obtained for either process

through extensive spectroscopic analysis. Additionally, the weak binding of Et_3SiH to a Pd–D species would also provide a mechanism by which 'leakage' of D can occur from the reaction manifold. The induction period observed with Et_3SiD, but identical turnover frequency under the saturation kinetics regime suggests that catalyst activation is quantitative in both cases. The extensive D–H scrambling is indicative that hydropalladation is reversible (**Ii*a*** ⟶ **Ii*b*** ⟶ **Ii*a***) and thus the saturation kinetics would have to arise from a catalyst resting state at stage **Ii*c*** or **Ii*d***. An analogous hydropalladation–β-hydride elimination sequence (cycle **Iii**) was suggested to account for the rapid isomerisation of the kinetic product **14** into the thermodynamic product **16**. Again with reversible hydropalladation (**Iii*e*** ⟶ **Iii*f*** ⟶ **Iii*e***) and under a saturation kinetics regime, when [**13**] drops below *ca.* 5 mM, thus with **Iii*f*** or **Iii*g*/*h*** as resting states.

In many ways, the studies of the Pd-allyl pro-catalyst system by Lloyd-Jones *et al.*[23] complement those of Widenhoefer. In contrast to the clear kinetics observed by Widenhoefer, complex and non-reproducible kinetics were observed by Lloyd-Jones and co-workers for the cycloisomerisation of **13a** employing 5 mol% $[Pd(allyl)(MeCN)_2]^+$ as pro-catalyst in $CHCl_3$ at 40 °C. However, silane was not employed as a promoter and although the reaction is no longer highly selective, the extensive scrambling of labels that had complicated the Widenhoefer study did not interfere. The kinetics of the system with $[Pd(allyl)(MeCN)_2]^+$ as a pro-catalyst are characterised by a pronounced induction period that varies from minutes to hours between runs. An evolution profile demonstrating a long induction period is given in Fig. 1, right hand graph, and it can be seen that the kinetic product is again **14** but the saturation kinetics and accumulation-depletion phenomenon observed under the Widenhoefer conditions are not apparent. Thus, in addition to the major kinetic product **14a**, the thermodynamic products **15a** and **16a** are evident soon after induction commences and grow smoothly in a *ca.* 1 : 2 ratio. Material balance, independent isomerisation of **14a** and co-addition of ^{13}C-labelled **14a** during turnover[81] demonstrate that two pathways generate **15a**. One involves isomerisation of **14a** (and also generates **16a** in a *ca.* 1 : 3 ratio) the other involves generation *directly* from **13a**. The addition of excess MeCN was found to favour the direct generation of **15a**. Due to the complications of the latter processes, experiments employing a range of symmetrical and non-symmetrically labelled variants of **13a**[82] were conducted such that reaction samples were analysed during the early stages of reaction when the kinetic product **14a** was dominant. In contrast to the use of GC-MS required in the Widenhoefer study, the reactions were generally amenable to detailed ^{1}H, ^{2}H and ^{13}C-NMR study and two other mechanisms (**III** and **IV**, Fig. 4) which had been earlier proposed for cycloisomerisation or co-dimerisation were also considered in addition to mechanisms **I** and **II**.

Reaction of a hexadeuterated substrate 1,1,2,6,7,7-d_6-**13a**, cleanly gave d_6-**14a** in which the allylic methylene groups remained unlabelled – Scheme 19 upper section.

This result eliminated the allylic C–H insertion mechanism **III**; *cf.*(**III*a*** ⟶ **III*c***), leaving **I**, **II** and **IV** partially consistent with the result obtained by reaction of 2,6-d_2-**13a**. In the latter experiment, 15% incorporation of D at the methylene carbon in **14a** was traced to a competing process that led to *ca.* 15% deuteration of the terminal methylene in the substrate d_2-**13a**-but did not scramble the internal alkene D with H. In contrast to **IV**, mechanisms **I** and **II** both involve β-hydride elimination steps (**Ii*c*** ⟶ **Ii*d*** and **II*b*** ⟶ **II*c***). To test for these, *E*,*E*-1,7-d_2-**13a** and *Z*,*Z*-1,7-d_2-**13a** were employed as stereochemical probes, Scheme 20. The resulting d_2-**14a** were obtained with high, but not perfect, geometric purity whose 'reversed' identities supported a β-hydride elimination step and mechanism **IV** (*cf.* **IV*a*** ⟶ **IV*c***, which proceeds with 'retention') could therefore be eliminated from consideration.



Scheme 19

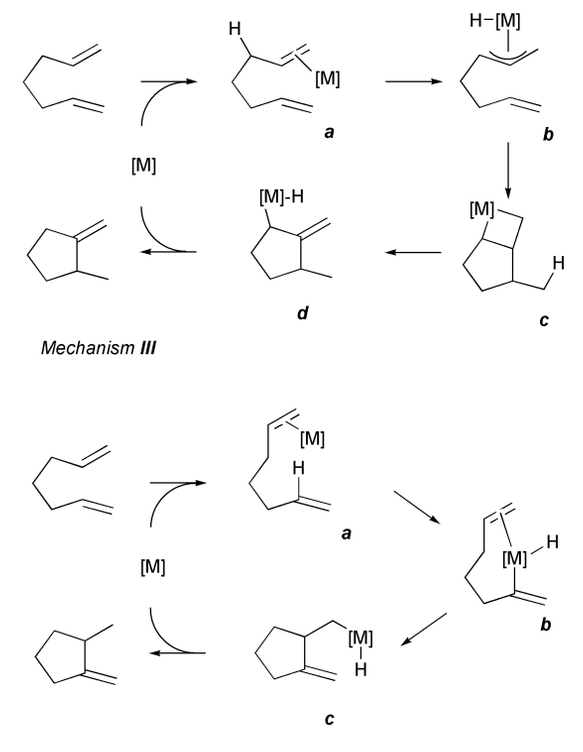
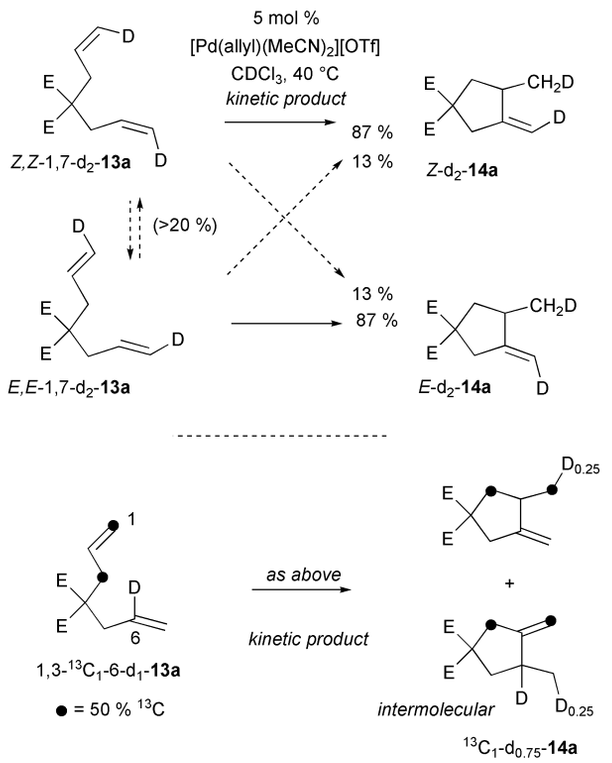
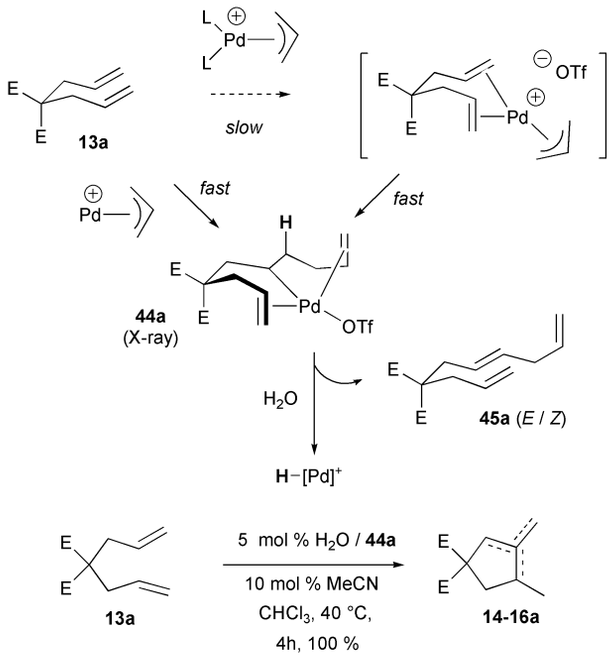


Fig. 4 Mechanisms **III** and **IV**; generic allylic C–H insertion (**III**) and vinylic C–H insertion (**IV**) mechanisms for 1,6-diene cycloisomerisation.

The geometric purity of the substrates were found to be eroded during reaction with full equilibration between *E*,*E*; *E*,*Z* and *Z*,*Z*-**13a** isomers evident by 80% conversion, but without external exchange of D or H. However, careful analysis of the product obtained in the very early stages of reaction *before* substrate isomerisation was apparent indicated that the cycloisomerisation process itself involved *ca.* 13% isomerisation onto which was then superimposed the degree of isomerisation of the substrate later in the reaction evolution. ^{13}C-NMR analysis of products **14a** derived from isotopically desymmetrised 6-d_1-(1,3)-^{13}C-**13a** confirmed that the H (or D) at C(6) in **13a** is formally transferred to what was C(1) and becomes the *exo*-methyl group in **14a**, Scheme 20. Both mechanisms **Ii** and **II** are consistent with this observation. However, the clean generation of some d_2-**14a** in which the second D-label is on a *non*-labelled carbon and adjacent to a site of >95% D, suggests that the transfer is inter- (as in [M]–H ⟶ **Ii*a***) and not intra-molecular (as in **II*c*** ⟶ [M]). This was tested by co-reaction of $^{13}C_2$-labelled **13a** with 2,6-d_2-**13a** which demonstrated the clean intermolecular transfer of a single D (55%) to the methyl group



Scheme 20



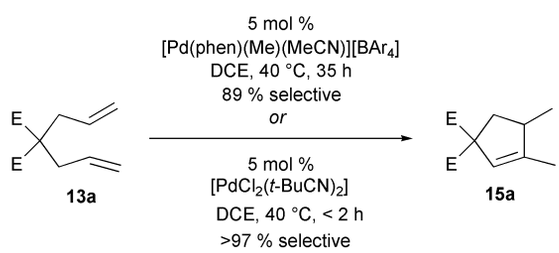
Scheme 21

in **14a** derived from C(1). The data thus strongly supported the operation of mechanism **Ii** with a Pd-H species also effecting the exchange and isomerisation processes that compete with cyclisation to **14a**. The induction period could be accounted for by slow generation of the Pd-H species. However, the mode of generation of the Pd-H in the absence of silane and the variability in the induction period remained unexplained.

Stoichiometric reactions between **13a** and the pro-catalyst at ambient temperature were followed by ^{1}H NMR which revealed that the generation of a transient species prefaced reasonably rapid and complete cycloisomerisation of **13a**, with most of the $[Pd(allyl)(MeCN)_2]^+$ remaining unreacted. The use of ^{2}H- and ^{13}C-labelled **13a** in conjunction with 2D NMR experiments allowed the identity of the transient intermediate to be assigned as allyl-palladation complex **44a**, Scheme 21.

The complex is likely to be generated in a multi-step process of which displacement of one or both MeCN groups was proposed as being rate-limiting. Consequently, $[Pd(allyl)(Cl)]_2$ was reacted with **13a** in the absence of MeCN, by halide abstraction with AgOTf, and this facilitated isolation of **44a** whose structure was confirmed by X-ray crystallography.[83] Given its transience when generated *in situ* by stoichiometric reaction between **13a** and $[Pd(allyl)(MeCN)_2]^+$, the Pd-σ-alkyl complex **44a** proved surprisingly stable when isolated and indeed was found to be inert when exposed to a $CHCl_3$ solution of **13a** and MeCN. Of course, this suggests that **44a** is not related to the process by which the genuine catalyst is generated. However, the key to engendering activity was eventually found to be the addition of water – whose presence in trace but variable quantities was considered as a possible cause of the variability of the induction periods. Stoichiometric reaction of **44a** with water, triggers *syn* β-hydride elimination to generate triene **45a** and, in principle, a Pd-H species which has not been observed but instead undergoes rapid decomposition to Pd-black (and TfOH).[83] Adding catalytic quantities of water to a stable system (no turnover over a period of hours) comprising **13a**, 10 mol% MeCN and 5 mol% **44a**, engendered quantitative cycloisomerisation (to give **14a**, **15a** and **16a**), with no induction period and demonstrated that β-hydride elimination in **44a** is a plausible and likely route by which the $[(L)Pd\text{-}H]^+$ species (L = unspecified ligand(s)) is generated when $[Pd(allyl)(MeCN)_2]^+$ is used.

3.1.3 Palladium(II)-alkyl and halide pro-catalyst systems. In contrast to the Pd-allyl pro-catalyst systems described above, which give **14a** as the kinetic product, use of 5 mol% of the cationic complex $[(phen)Pd(Me)(MeCN)][BAr_4]$ (phen = 1,10-phenanthroline; Ar = 3,5-$(CF_3)_2$-C_6H_4) in DCE at 40 °C gives **15a** as the kinetic product in good yield and with fair selectivity (89%), Scheme 22.[20,84] Reaction is somewhat slower than the



Scheme 22

allyl-palladium systems, taking around 35 h. to proceed to completion (compare with *ca.* 4 h with $[Pd(allyl)(PCy_3)(OEt_2)][BAr_4]$ in CH_2Cl_2 at 0 °C). Simple catalysts also effect the regioselective generation of **15b** from **13b** – for example $[PdCl_2]_n$ in HCl-sat. $CHCl_3$ (92–94% selectivity, 8 h at reflux) or $[(MeCN)_3PdCl]^+$ in $CHCl_3$ (>90% selectivity, 18 h at reflux). The selectivity for **14b** on use of $[(MeCN)_4Pd]^+$, led Heumann and Mouhklis to suggest that the charge (1^+ *versus* 2^+) controlled selectivity.[17] However, Lloyd-Jones *et al.* later reported that $[(MeCN)_3PdCl]^+$, which is generated *in situ* from the neutral complex $[(MeCN)_2PdCl_2]$, is in equilibrium with the halide exchange products $[(MeCN)_2PdCl_2]$ and $[(MeCN)_4Pd]^+$. It was subsequently found that the *neutral* complex $[(MeCN)_2PdCl_2]$ is in fact far more active and selective for isomerisation of **13a** to **15a** than the cationic mono-chloro complex[21] and the chloride ion is proposed as being the origin of the selectivity, *vide infra*. Optimisation led to the use of simple, stable and readily prepared catalyst systems, such as $[(t\text{-}BuCN)_2PdCl_2]$, which are capable of near-perfect regioselectivity (97–99%) for **15a**, and analogous 1,6-diene substrates, with reaction proceeding quantitatively in just a few hours, Scheme 22.

A kinetic investigation of the cycloisomerisation of **13a** to **15a** by [(*t*-BuCN)$_2$PdCl$_2$] in DCE at 40 °C revealed complex but reproducible behaviour.[22] Pronounced induction periods which often extended into a number of half-lives were always observed, as well as catalyst termination with a maximum of *ca.* 80 turnovers. This combined 'trickle-feed' of catalytically active species which has a transient existence leads to a phase of apparent pseudo-zero order in the central portion of the evolution profiles, Fig. 5. A simple kinetic model, incorporating these features was able to satisfactorily simulate the real data over a wide range of initial substrate and pro-catalyst concentrations.

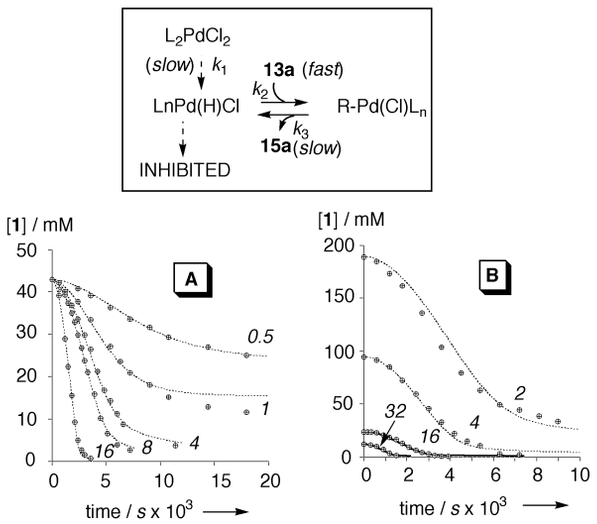
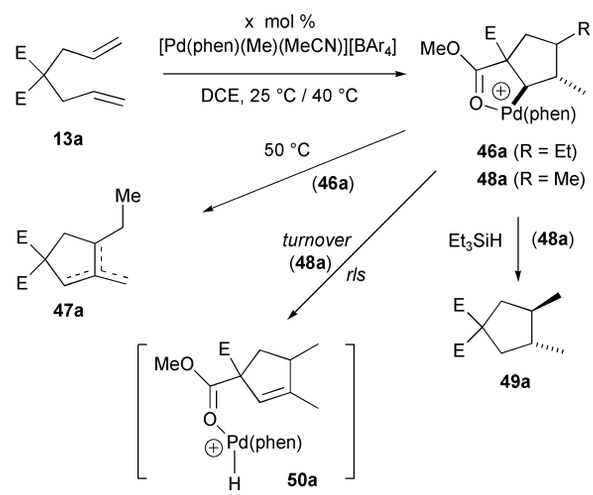


Fig. 5 A series of evolution profiles for the Pd-catalysed cycloisomerisation of dimethyl diallyl malonate (**13a**) in DCE at 40 °C and employing [(*t*-BuCN)$_2$PdCl$_2$] as *pro*-catalyst. Series 'A': constant [**13a**]$_0$ and variable [Pd]$_0$; series 'B' constant [Pd]$_0$ and variable [**13a**]$_0$. Lines passing through data points are predicted concentrations of **13a** according to the simple kinetic model shown in the inset.

From these studies it became clear that the standing concentration of active intermediates is always very low and this explains earlier failures to observe any of them spectroscopically.[21] The active species is again proposed to be a Pd-H complex of the type [(L)Pd(H)(Cl)n] with the Cl essential for selectivity, *vide infra*. However, the mechanism of pro-catalyst activation has yet to be determined for this system.

In both of the pro-catalyst systems [(L)$_2$PdX$_2$] (L = nitrile or sulfoxide, X = halide) and [(phen)Pd(Me)(MeCN)][BAr$_4$], traces (<0.5% in the former and up to 4% in the latter system) of **14a** are observed and thus one might consider that, like the Pd-allyl pro-catalyst systems, *vide supra*, **14a** is the kinetic product. This would then require a rapid isomerisation, *via e.g.* **Iii**, with unusual regioselectivity in the β-H elimination step such that **Iii*f*** ⟶ **Iii*g*** gives **15a** rather than thermodynamically favoured **16a**. However, further studies reveal that in the [(*t*-BuCN)$_2$PdCl$_2$] system, *exo*-methylene cyclopentane **14a** not only acts as a powerful inhibitor (reducing turnover rate by an order of magnitude), but is isomerised, at a rate approximately 0.3 that of 1,6-diene **13a**, to >90% **16a** and not **15a**.[22]

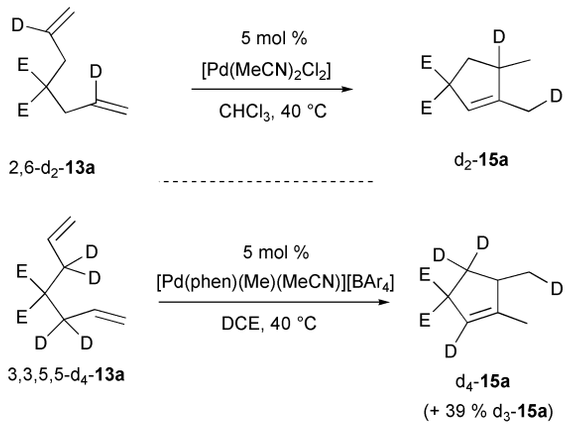
In the [(phen)Pd(Me)(MeCN)][BAr$_4$] system, analysis of [**14a**], [**15a**] and [**16a**] *versus* conversion revealed negative, zero and positive deviations respectively and co-reaction of equimolar diethyl malonate diene **13b** and dimethyl malonate product **14a**, resulted in only 20% conversion of **14a** (to a 1 : 2.5 mixture of **15a** : **16a**) but 90% cyclisation of the diene **13b** to **15b**. Further study with co-mixtures of **13b** and **15a** suggested that isomerisation of **15** to **16** occurred at a 190-fold lower rate than that at which it is generated.[84] Much like the [Pd(allyl)(PCy$_3$)(OEt$_2$)][BAr$_4$] pro-catalyst system, Widenhoefer found that the [(phen)Pd(Me)(MeCN)][BAr$_4$] system displayed clean and reproducible pseudo zero-order kinetics. However, the accumulation–consumption phenomenon observed with the former was not present in the latter due to the very slow isomerisation of the kinetic product **15a** to the thermodynamic product **16a**. The pseudo zero-order kinetics (k_{obs} = 7.1 × 10^{-7} s^{-1} at 40 °C in DCE) were established soon after initiation (*i.e.* rapid induction) and were evident for *ca.* 80% of the reaction evolution. Further studies also revealed that in addition to a zero order dependence on [**13a**], the reaction also has a zero-order dependence on [MeCN]. Product analysis in the early stages of reaction identified carbocycle **47a** (as a mixture of isomers) and material balance correlated this with the catalyst stoichiometry and demonstrated that it was produced within two turnovers of initiation, Scheme 23.



Scheme 23

A stoichiometric reaction between the pro-catalyst and 1,6-diene **13a** at 25 °C was followed by ^{1}H NMR and found to yield (>90%) chelate complex **46a** (2 : 1 ratio of diastereoisomers). No intermediates were observed for this process and one diastereoisomer of the complex was isolated (26% yield) and its structure confirmed by X-ray as the *trans-trans* isomer. Thermolysis of complex **46a** (DCE, 50 °C, 2h) yielded carbocycle **47a** and the complex also functioned as a pro-catalyst. It was also possible to observe complex **48a** (> 10 : 1 ratio of diastereoisomers) in the ^{1}H NMR spectrum of cycloisomerisation of **13a** undergoing *turnover* (the assignment being aided by reference to **46a**). The stereochemical identity of the complex as *trans-trans* was deduced by cleavage *in situ* with Et$_3$SiH to give, amongst other products, the *trans*-dimethyl cyclopentane **49a**. The data strongly support the catalyst resting state being **48a** with an unimolecular, rate-limiting, breakdown. The zero order dependence on [MeCN] led to the suggestion that the ester carbonyl serves as an associative ligand in this process to give **50a**, which subsequently releases **15a** and generates [(phen)Pd(H)(MeCN)]$^+$ upon reaction with MeCN.

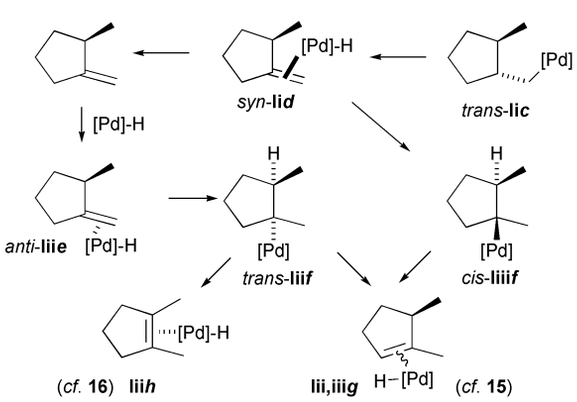
To account for the switch in kinetic product from **14** to **15** on the use of pro-catalyst systems of type [(L)$_2$PdX$_2$] (L = nitrile or sulfoxide, X = halide) and [(phen)Pd(Me)(MeCN)][BAr$_4$], Lloyd-Jones[23,22] and Widenhoefer[20,84] have independently suggested essentially identical mechanisms which extend mechanism (**Ii**) described above for both of the Pd-allyl pro-catalyst systems to *directly* couple **Ii** with **Iii**, *via* step **Iiii**. The Widenhoefer mechanism incorporates reversible access to the resting state **48a** from **Iiii*g*** (the step-wise generation of a Et$_3$Si-analogue of this complex has subsequently been observed by NMR)[85] whereas although kinetic data for the [(L)$_2$PdX$_2$] system suggest a resting state that also breaks down in a unimolecular manner, the 'trickle-feed' catalyst generation-termination has so far precluded its identification by spectroscopic analysis. Extensive isotopic labelling studies[21,84,86] fully support the mechanism in both systems. For example, the pro-catalyst [PdCl$_2$(MeCN)$_2$] in CHCl$_3$ at 40 °C converted 2,6-d$_2$-**13a** to d$_2$-**15a** (>95% d$_2$) and [(phen)Pd(Me)(MeCN)][BAr$_4$] in



Scheme 24

DCE at 25 °C converted 3,3,5,5-d_4-**13a** to d_4-**15a** : d_3-**15a** (72 : 28), Scheme 24. Co-reaction of dimethyl malonate based 3,3,5,5-d_4-**13a** with diethyl diallyl malonate **13b** resulted, at 50% conversion, in cross-over to generate partially labelled **15b** (73 : 27 ratio of d_0 : d_1).

The key to the high and unusual (**15**) regioselectivity in these systems is thus suggested to be two-fold: firstly the presence of a strong σ-donor ligand on the Pd (Cl, phen, RCN *etc.*) increases the back-bonding in intermediate *syn*-**Iid**, whose stereochemistry is proposed as arising from β-H elimination from *trans*-**Iic**, as would be consistent with the observations made for complexes **44a**, **46a** and **48a**. This then engenders re-addition of the Pd-H unit *without* dissociation from the alkene (*i.e.* pathway **Iiii**), see Fig. 2 and Scheme 25.

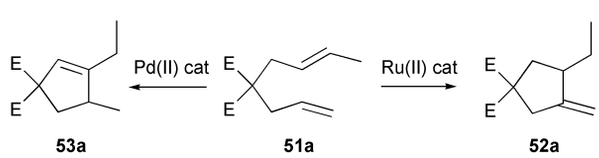


Scheme 25

This generates *cis*-**Iiii*f*** in which *syn*-β H elimination *can only* proceed to give a Pd(H) complex of **15**. In contrast, by the same mechanism, but in which the Pd-H carrier is electron poor or bulky (*e.g.* cationic or coordinated by phosphines), rapid dissociation from *syn*-**Iid** gives the opposite kinetic product **14**. When the substrate (**13**) is depleted, re-coordination of the more hindered alkene **14** occurs from the opposite face to that from which it formally departed to give *anti*-**Iiie**. Now, hydropalladation generates *trans*-**Iii*f*** from which *syn*-β H elimination can proceed in either direction to give a Pd(H) complex of **15** (*cf.* **Iii*g***) or **16** (*cf.***Iii*h***). The latter *product* (**16**) is preferred thermodynamically and is also consistent with the selectivities observed when independent samples of **14** are isomerised under the conditions that generate **15** from **13**.

From the mechanistic proposals outlined above, the switching between selectivity for **14** *versus* **15** with Pd(II)-allyl *versus* Pd(II)-methyl or Pd(II)-halide pro-catalysts appears to be solely ligand determined. Good supporting evidence for this comes from the reactions where pro-catalyst system **44a**, known to generate "Pd-H" on addition of water, can be induced to switch from generating **14a** (>90%) as the kinetic product from **13a** to generating **15a** (>90%) as the *kinetic* product by addition of the σ-donating chloride ligand.[87]

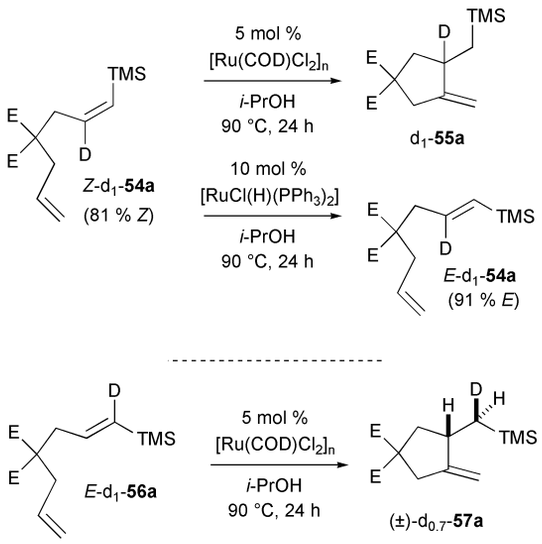
3.1.4 Ruthenium(II) chloride pro-catalyst systems. In 1999, Itoh and co-workers reported on the serendipitous discovery of a highly selective Ru pro-catalyst for cycloisomerisation.[18] In the course of developing Ru-based catalyst systems for intermolecular cycloaddition between diynes and alkenes, it was found that [Cp*Ru(COD)Cl] co-catalysed the ring opening metathesis polymerisation (ROMP) of norbornene. On attempting to expand this to RCM, it was found that **13a** gave the *exo*-methylene cycloisomerisation product **14a** and *not* the expected cyclopentene RCM product on heating to 80 °C with 10 mol% of the Ru complex in EtOH. Subsequent studies revealed a range of Ru(II) complexes were active for this transformation.[88] Optimisation led to the use of the *polymeric* and essentially insoluble pro-catalyst system $[Ru(COD)Cl_2]_n$ in *i*PrOH at 90 °C with which selectivity was near perfect for **14a**. Using 0.5–5 mol% of this catalyst, a wide range of hepta-1,6-dienes can be converted to the analogous *exo*-methylene cycloisomer. Two features differentiate the Ru(II) catalyst system from the Pd(II) catalyst systems described above: i) with Ru(II), especially with the more soluble complex $[RuCl_2(COD)(MeCN)_2]$, a secondary catalyst cycle isomerises **14a** to **15a** – with Pd(II) this isomerisation gives the more stable isomer **16a** with high selectivity, and ii) octa-1,6-diene type substrates **51a** are cycloisomerised with opposite regioselectivities: Ru(II) (⟶ **52a**) *versus* Pd(II) (⟶ **53a**), Scheme 26.[79,89]



Scheme 26

No kinetics studies for the Ru(II) system have been reported, but a variety of experiments have been conducted which allow some insight into the mechanistic possibilities. Firstly it was found that with **13a** and $[Ru(COD)Cl_2]_n$ as pro-catalyst, a primary or secondary alcohol (*e.g.* EtOH or i-PrOH) was essential as reaction medium. Reaction did not proceed in *tert*-butanol, which lacks an α-hydrogen, DCE, toluene or acetonitrile. This requirement for an alcoholic solvent which bears an α-hydrogen strongly suggests that $[(L)_nRuCl_2]$ is converted to a ruthenium hydride species by β-hydride elimination in a ruthenium alkoxide and this is supported by the observation that when benzyl alcohol was employed as solvent, traces of benzaldehyde dibenzyl acetal were isolated. Ruthenium(II) chloro complexes such as $[RuCl_2(PPh_3)_2]$ and $[Cp^*RuCl_2]_2$ that do not bear a readily displaceable ligand (*e.g.* NBD or COD) were found to be inactive as catalysts, as was the Ru(0) complex $[(C_6Me_6)Ru(COD)]$. However, the latter complex *was* active when DCE was employed as solvent, but not in chlorobenzene, toluene or MeCN. The oxidative addition of DCE to the Ru(0) complex, followed by β-hydride elimination would provide a route to a chloro-Ru(II) hydride. All of this data supports the active species being a ruthenium hydride complex, but it was also found that a range of known hydride complexes $(RuCl(H)(CO)(PPh_3)_3]$, $[CpRu(H)(PPh_3)_2]$ and $[Cp^*RuH_3(PPh_3)]$ were *inactive*! This was attributed to the presence of the strongly coordinating PPh_3 ligand and ultimately the complex $[Ru(Cl)(H)(piperidine)_2]$ was prepared and proved to be active in toluene, albeit with lower selectivity (79%), for conversion of **13a** to **14a**.

In terms of tracking hydrogen migrations in the conversion of **13a** to **14a** (as catalysed by $[Ru(COD)Cl_2]_n$ in i-PrOH) isotopic labelling was not informative, presumably due to exhaustive H/D exchange with the solvent (*i*-PrOH).[90] However,



Scheme 27

two reactions employing D-labelled TMS-dienes **54a** and **56a** were informative.

Reaction of **54a** (as a 1 : 4.3 ratio of *E* : *Z* isomers) gave **55a** as a single isotopomer and when $[CpRu(H)(PPh_3)_2]$ was employed instead of $[Ru(COD)Cl_2]_n$, cycloisomerisation failed and instead *E*–*Z*-isomerisation of **54a** occurred. The cycloisomerisation of **56a** gave **57a** with partial retention of deuterium (7 : 3 d_1 : d_0) with the d_1-isotopomer generated as a single diastereoisomer.

In terms of mechanism, the requirement for the generation of a Ru-H, suggests a hydroruthenation–carboruthenation–β-H elimination sequence, as in mechanism **Ii**, Fig. 2. However, the hydroruthenation would be expected to occur with selectivity towards the least hindered alkene and thus **51a** would be expected to generate **53a** and not **52a** (Scheme 26) and furthermore, in the presence of PPh_3, cycloisomerisation, but not hydroruthenation, is inhibited (*cf.* isomerisation of **54a**). The selectivity for **52a** is consistent with the oxidative cyclisation–β-H elimination–reductive elimination sequence in mechanism **II**, in which the regioselectivity of metallacyclopentane fragmentation is driven by steric decompression. However, this mechanism does not require the generation of a ruthenium hydride to proceed. To account for the observations, Itoh has suggested a novel mechanism (**V**), Fig. 6, which might be considered a hybrid of mechanisms **I** and **II** *vide supra*.

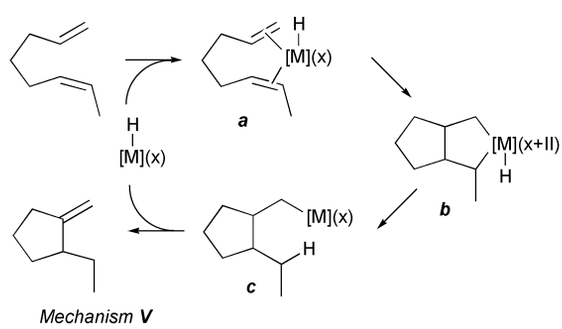


Fig. 6 Mechanism **V**; a generic oxidative cyclometallation mechanism for 1,6-diene cycloisomerisation.

The mechanism involves an oxidative cyclisation of the diene with a ruthenium hydride species. Reductive elimination, under control of steric decompression then cleaves the C–Ru at the more hindered site (*cf.* **V*bc*** ⟶ **V*c***) and then β-H elimination completes the sequence. In the presence of strongly coordinating ligands (*e.g.* PPh_3), it is suggested that insufficient vacant sites are available for the simultaneous coordination of both alkenes as required to commence the oxidative cyclisation. Nonetheless, a *non-productive* hydroruthenation–β-H elimination is still proposed as the origin of the isomerisation of **54a** and deuterium depletion from **56a** *en route* to **57a** and it is not clear why this does not then lead to a cycloisomerisation *via* mechanism **Ii** since a free coordination site should become available upon hydroruthenation.

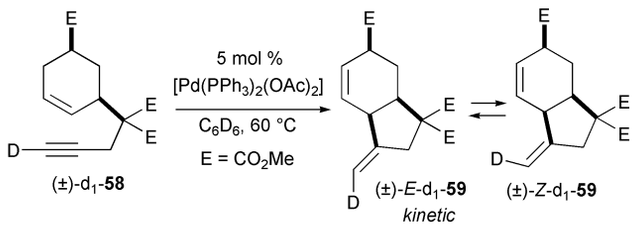
3.1.5 Early transition metal catalyst systems. Of the mechanistic investigations performed thus far on 1,6-diene cycloisomerisation,[23,80,88] all late transition metal catalysed reactions appear to proceed *via* the generation and then intermolecular propagation of a metallohydride species through mechanism **I** or the [**I**, **II**] hybrid mechanism **V**. Detailed mechanistic investigations into early transition metal catalysed 1,6-diene cycloisomerisations are lacking, but dependent on the oxidation state of the proposed active species and based on analogous processes,[91] both mechanisms **I** and **II** have been postulated. For example, a Ti(II) ⟶ Ti(IV) oxidative cyclisation then β-H elimination, reductive elimination (*i.e.* mechanism **II**) has been proposed by Livinghouse for 1,6-diene cycloisomerisation employing pro-catalysts of type $(ArO)_2Ti$ reduced *in situ* to "$(ArO)_2Ti$(II)" by cyclohexyl–MgCl.[29] In contrast, reduction of $CpTiCl_2$ with excess *n*BuMgBr is proposed to yield a "Cp_2Ti(III)-H" species[30] and proceed *via* mechanism **Ii**. The differentiation is largely based on the accompanying isomerisation (proposed to be mediated by "Ti-H") and the formation of 6-membered rings from 1,6-dienes occurring with the latter pro-catalyst system, especially when a bulky chelating bis-indenyl ligand is employed.

3.2 1,6-Enyne cycloisomerisation without skeletal reorganisation

3.2.1 Pd(II) and Pd(0) based pro-catalyst systems. As described earlier, $[(Ar_3P)_2Pd(OAc)_2]$ and $Pd(OAc)_2$ are some of the earliest effective catalyst systems for 1,6-enyne cycloisomerisation. Trost and Lautens considered three mechanisms (**VI**, **VII** and **VIII**) for the Pd-catalysed generation of 'Alderene' type products (**48** and **49**) from 1,6-enynes based on the allyl propargyl malonate skeleton.[92] Mechanism **VI**, involving C–H insertion into the allylic position of the alkene, was discounted on the basis that analogous reaction of 1,6-dienes would also be expected to proceed (they do not), that the absence of allylic C–H units in the substrate does not shut down cycloisomerisation and that the mechanism can only account for 1,4-diene products and not for the fact that sometimes both 1,3- and 1,4- type products are observed, Fig. 7.

Mechanism **VII** is analogous to 1,6-diene mechanism **I** and involves the generation of a metallo-hydride species, insertion across the alkyne, β-migratory insertion across the alkene and then β-H elimination. Mechanism **VIII** is analogous to 1,6-diene mechanism **II** and involves an oxidative cyclisation, β-H elimination, then reductive elimination. The lack of activity of Pd(0) complexes in the reaction suggested that the active catalyst is at the Pd(II) oxidation state and thus the oxidative cyclisation step in **VIII** would result in a Pd(IV) palladacyclopentene intermediate. Reaction of the labelled cyclohexenyl malonate d_1-**58** supported mechanisms **VII** and **VIII** in as much as the *kinetic* product was 1,4-diene *E*-d_1-**59** as would be predicted. Under the reaction conditions *E*-d_1-**59** is equilibrated with *Z*-d_1-**59**, without migration of either double bond, and there is no loss or gain of deuterium in either substrate (**58**) or product (**59**), Scheme 28.

The loss of stereochemical integrity of the deuterated alkene unit in **59** was ascribed to a 'side reaction unrelated to the cyclisation pathway'. Both mechanisms (**VII** and **VIII**) satisfactorily account for the high regioselectivity that is observed on $Pd(OAc)_2$ catalysed cycloisomerisation of the geranyl-based substrate **25a** (to give **27a**, see Scheme 8) and the loss of selectivity when either PPh_3 is added or the dihydro substrate



Scheme 28

25b is employed.[37] Trost, Lautens and co-workers concluded that,with the data in hand, they were unable to mechanistically distinguish between pathways **VII** and **VIII**. In later analysis of regioselectivity issues (with respect to the direction of β-H elimination), the Pd(II)-Pd(IV)-Pd(II) based mechanism **VIII** was assumed to be operative.[93] Supporting evidence for the oxidative cyclisation comes from studies involving the palladacyclopentadiene pro-catalyst, although this gives products arising from skeletal rearrangement, *vide infra*.

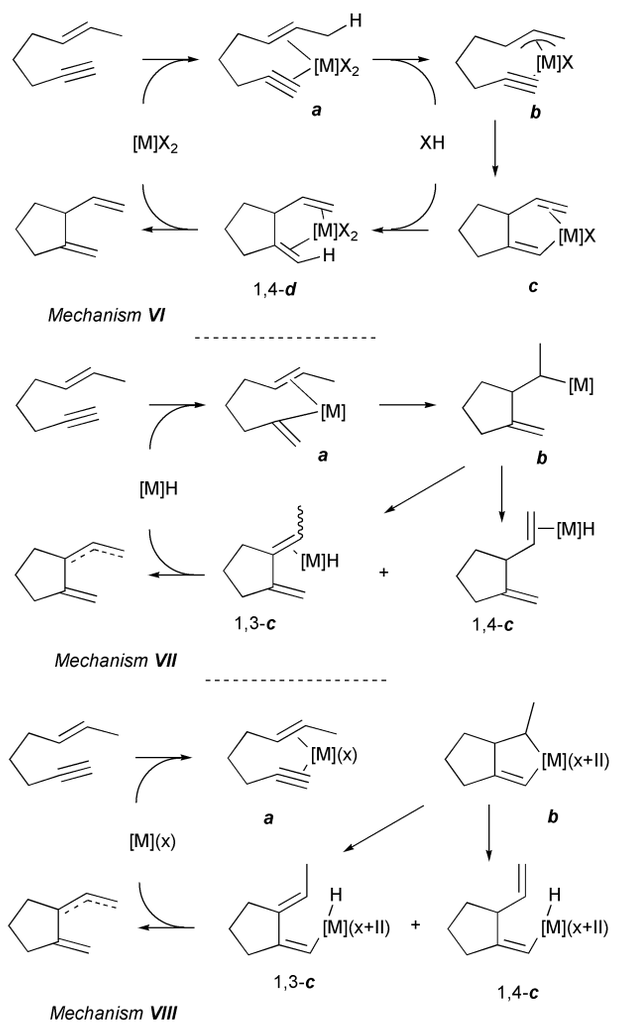
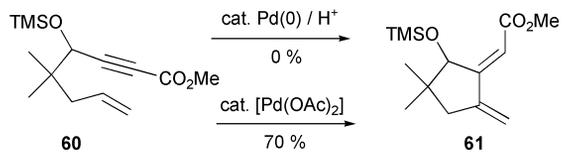


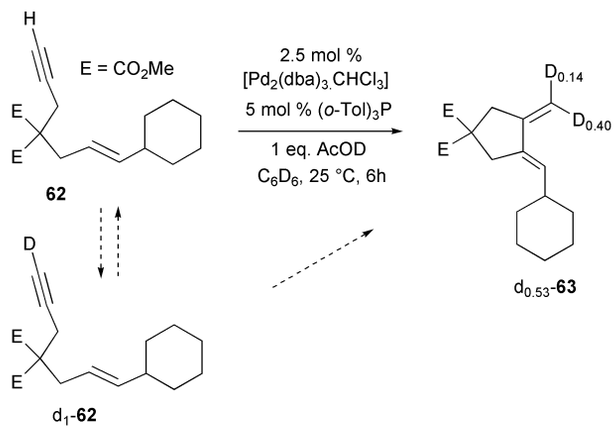
Fig. 7 Mechanisms **VI**, **VII** and **VIII**; generic allylic C–H insertion (**VI**), alkyne hydrometallation (**VII**) and oxidative cyclometallation (**VIII**) mechanisms for 1,6-enyne cycloisomerisation of oct-2-ene-7-yne type substrates.

The *in situ* generation of a "Pd-H" species by protonation of palladium would facilitate mechanism **VII** and consideration of this prompted the successful testing of Pd(0)–acid combinations for generating enyne cycloisomerisation catalysts.[57] Although NMR analysis of mixtures of AcOH and Pd_2dba_3 in $CHCl_3$ gave no evidence for the formation of a "AcO–Pd-H" species, the combination is very effective for cycloisomerisation of 1,6-enynes to 1,2-dimethylene cyclopentane derivatives (*i.e.* 1,3-dienes). The lack of reactivity of enyne **60** towards the Pd(0)–AcOH combination, yet its ready cycloisomerisation to **61**, Scheme 29, by $Pd(OAc)_2$ reinforced the conclusion that the two pro-catalysts operate by different mechanisms (**VII** and **VIII** respectively).



Scheme 29

Both mechanisms would predict that the geometric identity of an internal alkene unit in a 1,6-enyne substrate should be 'reversed' on formation of the 1,3-diene product due to the β-H elimination and this is indeed observed with the Pd(0)–AcOH system, *e.g.* as in Scheme 30. Some support for mechanism **VII**

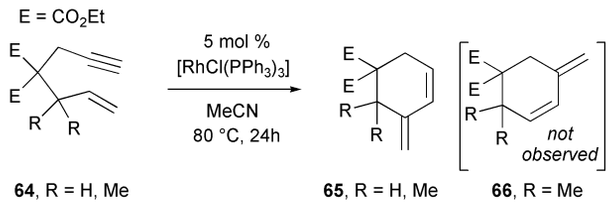


Scheme 30

comes from the reaction of enyne **62** in the presence of 1 equiv. AcOD[94] which gives the cycloisomer **63** as a mixture of d_0 (54%), d_1 (39%; *ca.* 5 : 1 *Z* : *E*) and d_2-(7%) isotopomers according to MS/NMR analysis. Although exchange of H with D at the alkyne terminus of **62** was confirmed as a side reaction, the generation of the d_2-isotopomer must be through addition of a deuterium during cyclisation. The interpretation of the excess of the *Z*-d_1 isotopomer is that it is the *Z*-deuterium that is introduced during cyclisation *via* deuteropalladation of the alkyne with a [Pd]-D species generated by exchange of [Pd]-H with AcOD.

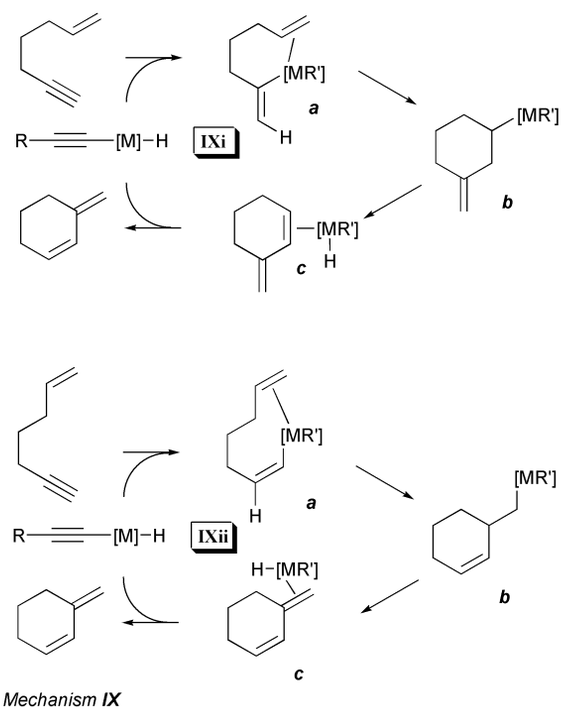
It should be noted that mechanism **VIII** would also facilitate such D-incorporation if there is exchange between R-Pd-H and AcOD after β-H elimination, but prior to reductive elimination. The analogous incorporation of D in the site *Z*-related to the new C–C bond was reported by Mikami for asymmetric 1,6-enyne cycloisomerisation with $[Pd(CF_3CO_2)_2]$–BINAP in d_6-benzene (and also in d_6-DMSO) in the presence of 6 equiv. D_2O. Interestingly, Mikami favoured the hydropalladation mechanism (**VII**) over the cyclopalladation mechanism (**VIII**) suggested by Trost for Pd(II) pro-catalyst systems and rationalised the asymmetric induction in terms of either neutral five coordinate intermediates in benzene and four coordinate ionised intermediates in DMSO.[38]

3.2.2 Rh(I)- and Ni–Cr based pro-catalyst systems. There is a paucity of mechanistic information for both of these pro-catalysts systems.[40–43] The Rh-catalysed 1,6-enyne cycloisomerisation products reported by Grigg using Wilkinson's catalyst are unique with regard to other 1,6-enyne cycloisomerisations; for example 1,6-enyne **64** (R = Me) is converted to **65** with very high selectivity.[41]



Scheme 31

The restriction of the reaction to terminal alkynes led Grigg to suggest that insertion of Rh into a terminal alkyne C–H unit would generate a Rh(III)-H species. However, as noted by Grigg, the generation of **65** (R = Me) and not **66** (R = Me) rules out mechanism **IXi** which involves a 6-*endo*-trig type cyclisation of a vinylrhodium species generated by hydrorhodation of the alkyne, Fig. 8.



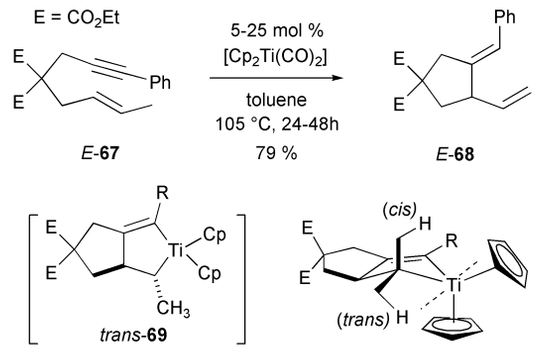
Mechanism ***IX***

Fig. 8 Mechanism **IX**; generic alkyne hydrometallation mechanisms for 1,6-enyne cycloisomerisation giving rise to methylene cyclohexene type products, *via* two routes (**IXi** and **IXii**).

Instead a *trans*-hydrorhodation of the alkyne is postulated to occur followed by 6-*exo*-trig carborhodation and then β-H elimination (mechanism **IXii**). It is interesting to note that Trost and Tour reported the generation of **65** (= **66**; R = H) as a side product (*ca.* 29%) on Ni–Cr catalysed cycloisomerisation of enyne **64** (R = H).[40] The more conventional 1,3- and 1,4- 'Alderene' type products (*e.g.*, **33** *vide supra*) obtained with the Rh-cation based pro-catalysts systems developed by Zhang and co-workers[42,43] and in particular their double bond geometry are suggestive of a mechanism analogous to **VII** or **VIII**, however, at this stage, Zhang *et al.* have made no suggestions regarding possible mechanisms.

3.2.3 Ti(II) pro-catalyst system. The presence of 5–25 mol% Cp_2TiCO_2 effects slow but very regioselective cycloisomerisation of *trans*-hept-2,7-enynes to 1,4-dienes without the competing, or sometimes dominant, formation of the 1,3-isomers that are observed with Pd-catalysis. For example, 1,6-enyne *E*-**67** is cycloisomerised to 1,4-diene *E*-**68** in 79% yield after 24–48 h at 105 °C in toluene, Scheme 32.[56]

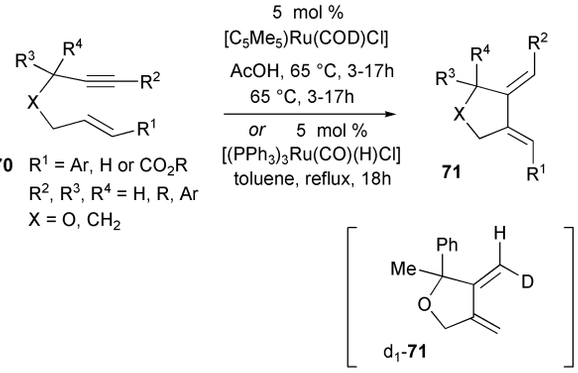
Buchwald suggested that the mechanism for this process is oxidative cyclisation (to a Cp_2TiCO fragment, with concomitant loss of CO), β-H elimination then CO-driven reductive elimination, *i.e.* mechanism **VIII**. Due to the relatively high



Scheme 32

temperature (105 °C) at which the process occurs, it proved possible to prepare the proposed metallacyclic intermediate *trans*-**69** by reaction of enyne *E*-**67** with $Cp_2Ti(PMe_3)_2$ at room temperature in C_6D_6. On heating, the complex decomposes and *E*-**68** is generated. Noteworthy was the observation that *cis*-alkene substrates, *e.g.* *Z*-**67** do not undergo the Ti-catalysed cycloisomerisation. Instead, they are recovered unchanged or with traces of cyclopentenone product derived from CO insertion. This latter process can be made efficient by employing a high CO pressure,[95] and suggests that it is the β-H elimination and not the oxidative cyclisation that inhibits the cycloisomerisation from proceeding. This was supported by non-productive thermal decomposition of the analogously prepared *cis*-**69**. Calculations (PM3) of model metallacycles in which a methyl group replaces the aryl ring of **69**, suggest that the β-H elimination cannot occur in *cis*-**69** due to the inappropriate geometric relationship of the methyl group to the $1a_1$ LUMO (see dashed line projecting through the Ti centre in inset to Scheme 32) requisite for the agostic interaction that prefaces β-H elimination. In the *trans* isomer, the methyl group is appropriately positioned and catalytic cycle is able to continue turnover.

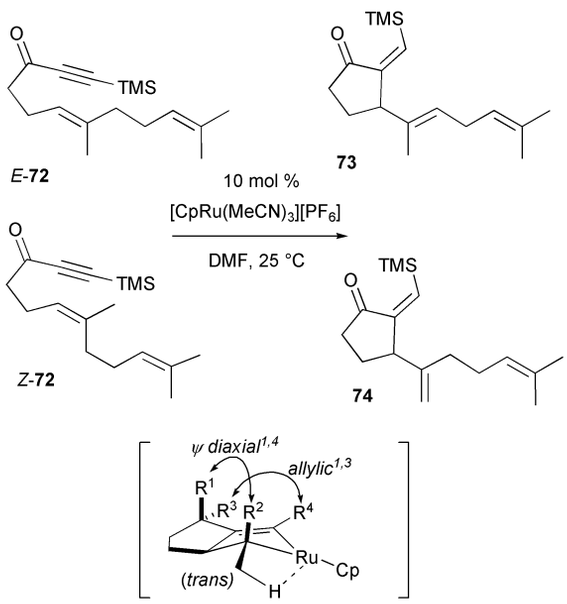
3.2.4 Ru(II) based pro-catalyst systems. The Ru-catalysed cycloisomerisation of 1,6-enynes has been reported by Mori *et al.*,[45,96] by Trost and Toste[46,47,97] and by Dixneuf *et al.*.[98] The catalyst systems reported by Mori ($[RuCl(H)(CO)(PPh_3)_3$ in refluxing toluene) and by Dixneuf ([Cp*RuCl(COD)] in AcOH at 60 °C or in EtOH at RT) both cycloisomerise simple enynes in which the alkene is non-alkylated (as in **70**, R^1 = H, Ph or CO_2R) to give 1,3-diene cyclopentane products of type **71** in which both R^1 and R^2 (the alkyne substituent in **70**), have *trans*-relationships to the new C–C bond, Scheme 33



Scheme 33

A simple hydroruthenation, carboruthenation, β-H elimination mechanism (mechanism **VII**) was proposed by both groups.[45,98] The Dixneuf conditions requires the use of AcOH or EtOH to generate the Ru-H species and the mechanism of the reaction was supported by use of AcOD to generate d_1-**71** (see inset to Scheme 33) in which the deuterium is *cis*-related to the new C–C bond.

The Ru-catalyst $[CpRu(MeCN)_3][PF_6]$ developed by Trost and Toste[99] demonstrates "mechanistic dichotomies"[97] in enyne cycloisomerisation. When simpler 1,6-enynes are employed,[47] the 1,4-diene type product is obtained with no trace of the 1,3-diene prevalent with Pd-catalysis. A number of observations, including the higher reactivity of *E*-alkenes over *Z* and a high, but substrate dependent, diastereoselectivity for 1,3-*cis* or 1,3-*trans* cyclopentane products, are suggested to support an oxidative cycloruthenation mechanism (as in mechanism **VIII**). The conclusions are somewhat analogous to those made for the Ti(II) catalyst system, *vide supra*, and are exemplified by the rationalisation of the regiodiversity in the reactions of isomeric of *E*-**72** *versus* *Z*-**72** which give **73** and **74** respectively, Scheme 34.

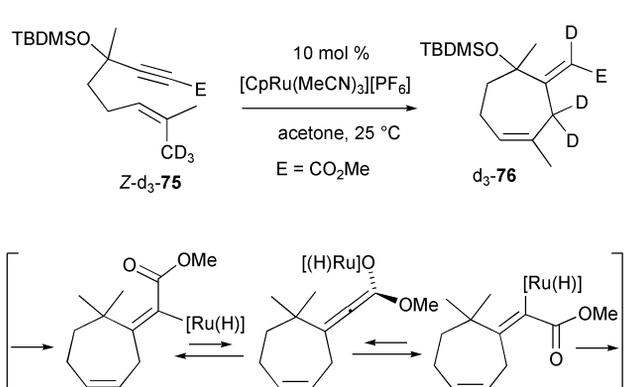


Scheme 34

The model suggests that on *approach* to cyclometallation the pseudo equatorial propargylic substituent (R^1) can develop 1,3-allylic strain with the alkyne substituent (R^2) whilst the pseudo axial propargylic substituent (R^3) can develop pseudo 1,4-diaxial strain with the alkene terminus (R^4, see inset to Scheme 34). Both of these factors are implicated in the observed diastereoselectivities.

However, the reaction course is rather substrate dependent and methylenecycloheptene type products are obtained when the 1,6-enyne is alkynoate in nature and the propargylic centre is quaternary, *e.g.* **75** is converted to **76**, Scheme 35.

As a corollary to the aforementioned 1,3-allylic and pseudo 1,4-diaxial strain, a quaternary propargylic centre will experience severe strain and cyclometallation is inhibited. Trost and Toste suggested that this then results in the onset of an alternative mechanism (**X**) in which the cationic Ru enyne complex undergoes allylic C–H insertion and thereby facilitates the formation of a seven membered ring (*e.g.* **76**) *via* allyl-ruthenation of the alkyne, Fig. 9.



Scheme 35

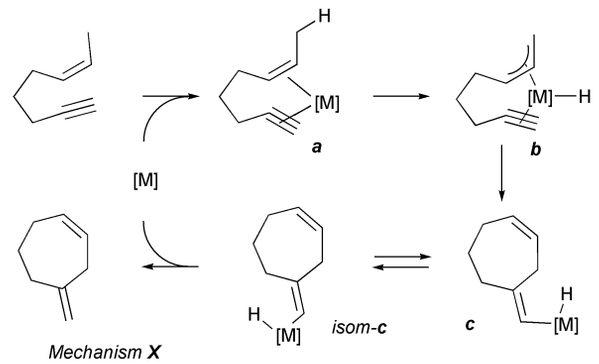
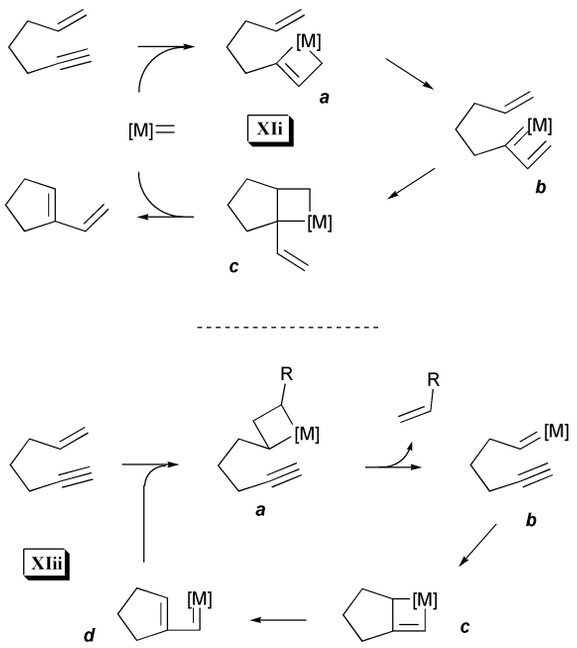


Fig. 9 Mechanism **X**; a generic allylic C–H insertion mechanism for 1,6-enyne cycloisomerisation of oct-2-ene-7-yne type substrates.

To account for the geometric identity of the *exo*-enoate, equilibration *via* a ruthenium allenolate prior to reductive elimination was suggested, see inset to Scheme 35. It is not clear what controls the resultant relative rates of reductive elimination/equilibrium populations, since both ester and Cp-ruthenium complex will suffer severe 1,3-allylic strain with the quaternary allylic centre. Observations that *Z*-monosubstituted alkene analogues of **75** underwent ready cyclisation (again to cycloheptenyl products) *versus* their *E*-isomers which instead underwent slow decomposition was interpreted as the preferential C–H insertion of Ru at the *cis* alkene alkyl group. This was probed with the deuterated substrate *Z*-d_3-**75** which cleanly gave d_3-**76** as a single regioisotopomer. The congestion of the transition state *en route* to cyclopentane formation was proposed as the reason for the predominant or exclusive generation of cycloheptene products.[97]

3.3 1,6-Enyne cycloisomerisation isomerisation with skeletal reorganisation

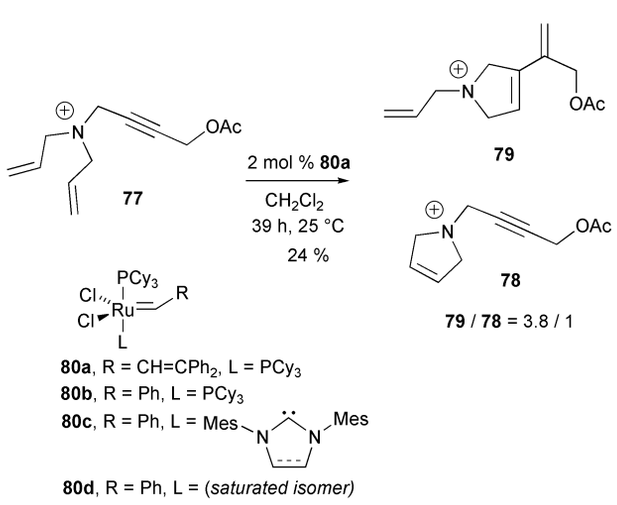
3.3.1 Catalysis propagating intermolecularly *via* alkylidene complexes.[100] Transition metal catalysed enyne metathesis (of 1,7-enynes) was first reported by Katz and Sivavec in 1985.[61] Catalytic quantities (1 mol%) of the Fischer carbene complex [Ph–C(OMe)=$W(CO)_5$] converted a range of 2-vinyl-2′-alkynyl biphenyls into 9-vinylphenanthrenes in yields that ranged from 18–31% after 18 h at 75 °C in toluene. Earlier studies by Katz on the co-polymerisation of alkenes with alkynes,[101] suggested that *non-stabilised* carbenes of the form [R–CH_2–CH=$W(CO)_n$] react more rapidly with alkenes than alkynes and *vice versa* for *stabilised* carbene complexes of the form [R–CH=CH–C(Ph)=$W(CO)_n$]. Thus, an 'yne-then-ene' carbene based metathesis mechanism (*cf.* **XIi**) was preferred over an 'ene-then-yne' mechanism (*cf.* **XIii**) for the cycloisomerisation of 2-vinyl-2′-alkynyl biphenyls. The cycloisomerisation of 1-ethoxy-1,6-enynes using Cr-based Fisher carbene catalyst of the form [Ph–C(OEt)=$Cr(CO)_5$],[62,63] as later developed by Mori, was again explained by consideration of the 'yne-then-ene' mechanism. The observation of side products derived from addition of the "Ph–C(OEt)=Cr" unit to the 'yne' moiety and subsequent diversion *via* benzannulation, strongly support this suggestion.[64,65] With the convenience and broad applicability of the Grubbs type catalyst systems (**80**), the application of enyne metathesis[102] in organic synthesis has developed rapidly.[103] Both the 'yne-then-ene' (**XIi**) and the 'ene-then-yne' (**XIii**) mechanisms have been suggested for this process and indeed the mechanism(s) that operate may well be substrate dependent, Fig. 10.



*Mechanism **XI***

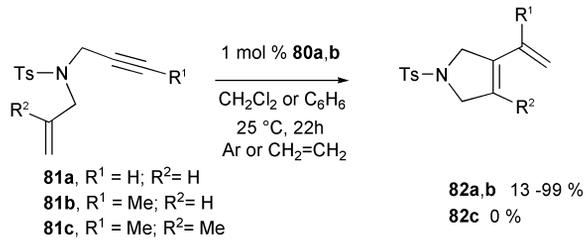
Fig. 10 Mechanism **XI**; generic [2+2] carbene–alkene/alkyne cycloaddition mechanisms (**Xi**, 'yne-then-ene' and **Xii**, 'ene-then-yne') for 1,6-enyne ring closing metathesis.

Mori has reported extensively on Ru-catalysed enyne metathesis using Grubbs type catalysts and favours an 'yne-then-ene' pathway on the basis that dieneyne ammonium salt **77** gives the RCM product (**78**) and enyne cycloisomerisation product (**79**) in a ratio of 1 : 3.8 (total yield 24%, catalysed by 'first generation' Grubbs type complex **80a**).[67] The interpretation was that this arises from the reaction of the alkyne moiety of **77** being faster than the alkene,[34] however, there appears to be some ambiguity since reaction of the alkene moiety first could give rise to both **78** and **79**, whilst reaction of the alkyne first can only give rise to **79**, Scheme 36.



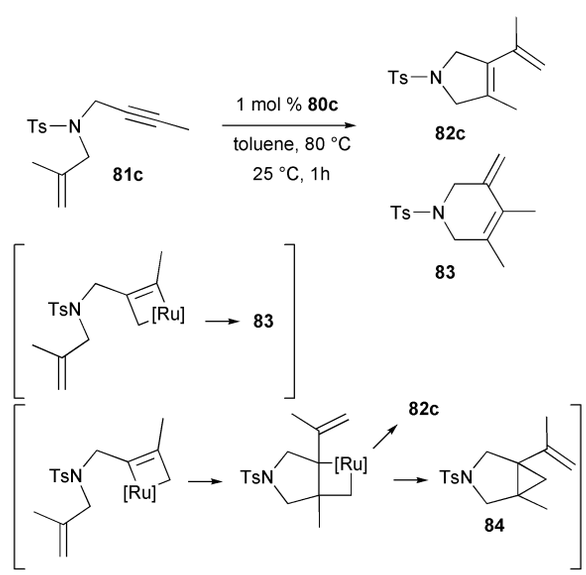
Scheme 36

During studies on the enyne metathesis reactions of a series of allyl propargyl tosylamines, some remarkable subtleties in reactivity were uncovered. For example, under an Ar atmosphere, enyne **81a** (R^1 = H; R^2 = H) undergoes low-yielding cycloisomerisation (13–21% **82a**) with the Grubbs type complexes **80b** whereas enyne **81b** (R^1 = H; R^2 = Me) reacts smoothly (89–91% yield **82b**). When the former reaction was carried out under an atmosphere of ethylene, essentially quantitative yields of **82a** were obtained, Scheme 37.



Scheme 37

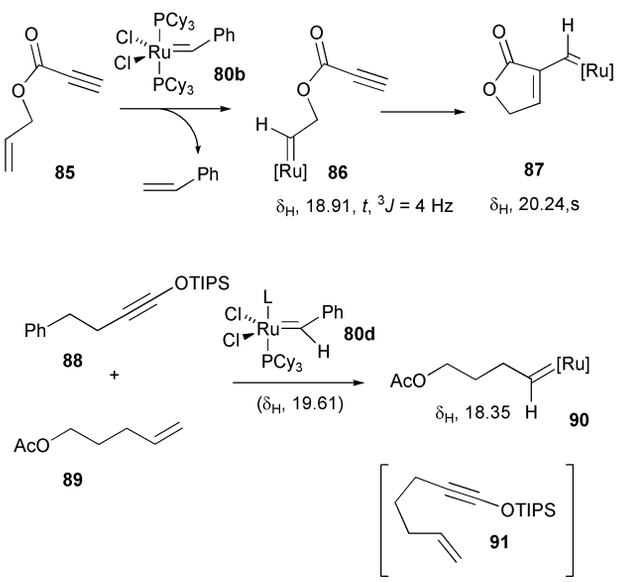
This was interpreted as a prophylactic effect of the ethylene with respect to degradation of the *product* (**82a**) by the intermolecular carrier of mechanism **XIi**, "$(L)_nRu{=}CH_2$". The ethylene was suggested to do this by reversible trapping of $(L)_nRu{=}CH_2$ in the form of ruthenacyclobutane.[104] However, since ethylene would merely have the effect of depleting the concentration of the active intermediate "$(L)_nRu{=}CH_2$" but would not affect its *relative* reactivity towards substrate (**81a**) and product (**82a**), a more satisfactory explanation may be that mechanism **XIii** ('ene-then-yne') is operative. Here then the ethylene may act as a surrogate alkene (in place of **81a**) to release the product **82a** from the vinylcarbene intermediate, diverting **XIii*d*** ⟶ **XIii*a*** to give the more reactive "$(L)_nRu{=}CH_2$" as carrier. More recently, Mori has reported that enyne **81c** (R^1 = R^2 = Me) which is inert to catalysts of the type **80a**,**b**, Scheme 37, undergoes smooth metathesis on exposure to the 'second generation' Grubbs type complex **80c**, Scheme 38.



Scheme 38

In addition to the expected product (**82c**), substantial quantities of diene **83** were also generated, as well as trace quantities of vinylcyclopropane **84**. The metathesis products were suggested to arise *via* generation of two regioisomers in the initial addition to the alkyne (see inset to Scheme 38) in an 'yne-then-ene' type cycle (**XIi**). The vinyl cyclopropane was proposed to be generated *via* reductive elimination in the 'normal' ruthenacyclobutane.[105] It is not clear however, why reversed regioselection would occur on addition of the carrier carbene to the alkyne of **81c**, whereas no trace of such products are obtained with **81b**, which bears a near identical alkyne unit. Of course, reversible addition and thus Curtin–Hammet conditions, may well dictate different outcomes on intermolecular attack of the vinyl carbene intermediates on the mono- (**81b**) *versus* di-substituted (**81c**) alkenes. The possibility of non-Chauvin type mechanisms, *e.g.* arising from catalytically active non-carbene complexes generated as co-products *via* methylene loss associated with generation of **84**, was not discussed.

Grubbs *et al*. have reported on studies of dieneyne metathesis in which a mechanism involving interception of a regular diene RCM by the alkyne is proposed.[68] The detection of *ca.* 3% of a cycloheptenyne co-product on reaction of a 5-alkynyloct-1,8-diene as well as *in situ* NMR spectroscopic studies support this mechanism.[106] Such conclusions would suggest that the simpler enyne systems would propagate *via* an 'ene-then-yne' mechanism (**XIii**). The viability of the latter mechanism is supported by the NMR spectroscopic studies of Hoye[107] on the Ru-catalysed metathesis of enyne **85**, Scheme 39. ^{1}H-NMR



Scheme 39

signals present *during turnover*, at 18.91 ppm (t, J = 4 Hz) and 20.24 ppm (s) were ascribed to the CH=R metallocarbene protons in proposed intermediates **86** and **87**, derived through metathesis with complex **80b**, Scheme 39. Indeed, styrene was observed as a co-product of the initiation of this cycle.

More recently, Kozmin and co-workers reported on an ^{1}H-NMR study of the co-reaction of alkene **88** and alkyne **89** with complex **80d**.[108] Addition of **88**/**89** to **80d** in C_6D_6 at 57 °C immediately resulted in the signal at 19.61 ppm, ascribed to the benzylidene proton in **80d**, being replaced by a single signal at 18.35 ppm, assigned as that arising from the alkene derived carbene **90**. In the absence of alkene **88**, the alkyne failed to react with complex **80d**. This was taken as evidence to support an 'ene-then-yne' pathway (**XIii**) for ring-closing enyne metathesis of a range of siloxyalkynes based on 1,6-enyne skeleton **91**.

3.3.2 Palladacyclopentadiene pro-catalyst systems. The combination of a palladacyclopentadiene with a phosphine resulted in the first examples of transition metal catalysed skeletal reorganisation of 1,6-dienes during cycloisomerisation, *vide supra*.[39] A mechanism (**XIIi**) involving an initial oxidative cyclisation (Pd(II) ⟶ Pd(IV)) as in **VIII*a*** ⟶ **VIII*b***, Fig. 7, to generate a 5-palladaspiro[4.4]nonatriene intermediate was suggested for the cycloisomerisation and this was tested by trapping with dimethyl acetylenedicarboxylate (DMAD). Under these conditions, enyne **29** gave a 44% yield of cyclohexadiene **31** together with 53% of **30**, Scheme 9. The possibility that **31** is generated by Pd-catalysed co-cyclisation of the alkynes, to generate a 5-palladaspiro[4.4]nonatetraene type intermediate, followed by insertion of the alkene was tested by reaction of a simple alkyne analogue of **29** which failed to generate any aromatic products (through trapping with a second molecule of dimethyl acetylenedicarboxylate). Thus both **30** and **31** were envisaged as arising from unimolecular (**30**) *versus* bimolecular (DMAD ⟶ **31**) decomposition of the Pd(IV) intermediate (**XII*a***) in mechanism **XIIi**, Fig. 11.

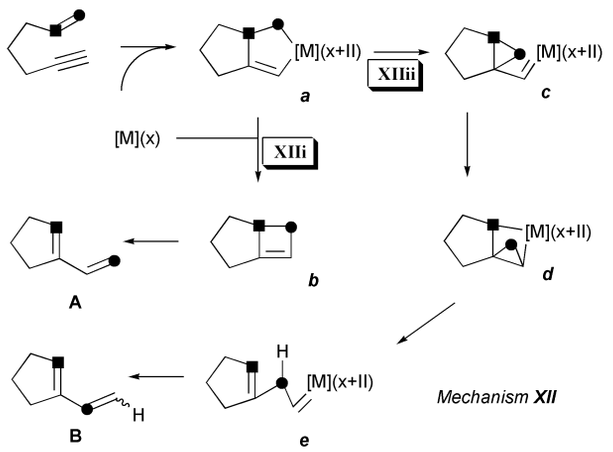
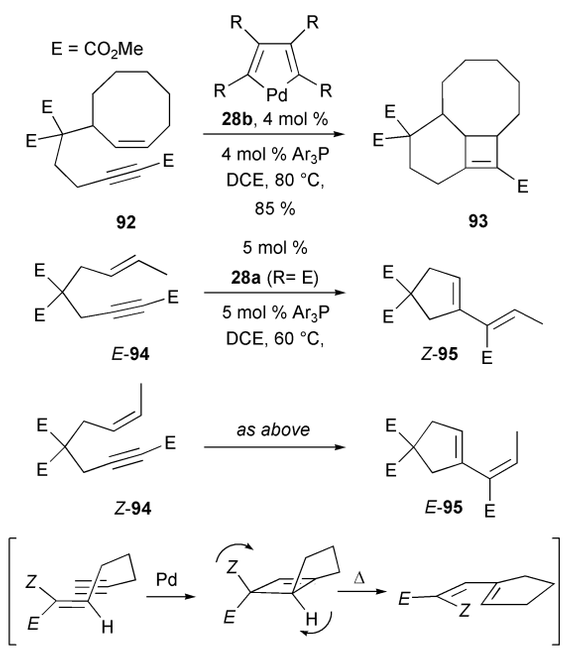


Fig. 11 Mechanism **XII**; a generic oxidative cyclometallation mechanism, involving cyclobutene (**XIIi**) and metallavinylcyclopropane (**XIIii**) intermediates, for 1,6-enyne cycloisomerisation with skeletal reorganisation, with (**B**) or without (**A**) anomalous bond connectivity.

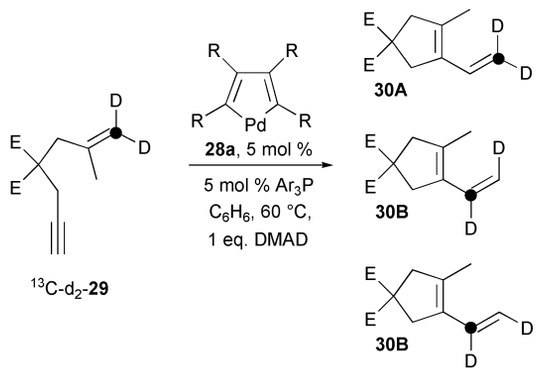
The cycloisomerisation pathway would thus involve reductive elimination to generate the cyclobutene (**XII*b***) which, because of its "*trans*-cycloheptene"§ character, is unstable and undergoes thermal, conrotatory, ring opening to give the enyne cycloisomerisation product (**A**) with skeletal reorganisation. Support for this mechanism came from isolation of the less strained cyclobutene **93** ("*trans*-cyclooctene" in character) from Pd-catalysed (**28b**, R = $CH_2C_3F_7$) cycloisomerisation of 1,7-enyne **92**[109] (Scheme 40), and the isolation of an *isomerised* cyclobutene from a 1,6-enyne.[110,111] Further support came from the stereospecific reactions of 1,6-enynes *E*-**94** and *Z*-**94** which, consistent with conrotatory ring-opening, gave *Z*-**95** and *E*-**95** respectively,[112] Scheme 40.



Scheme 40

However, all is not as simple as these results might suggest. On further investigation, it was found that ^{13}C-labelled **29**, gave not just the expected product ^{13}C-**30A**, but also ^{13}C-**30B** (in a 23 : 77 ratio) whilst reaction of d_2-**29** gave d_2-**30A** together with *E*-d_2-**30B** and *Z*-d_2-**30B** (17 : 18 : 65 ratio), Scheme 41.[112]

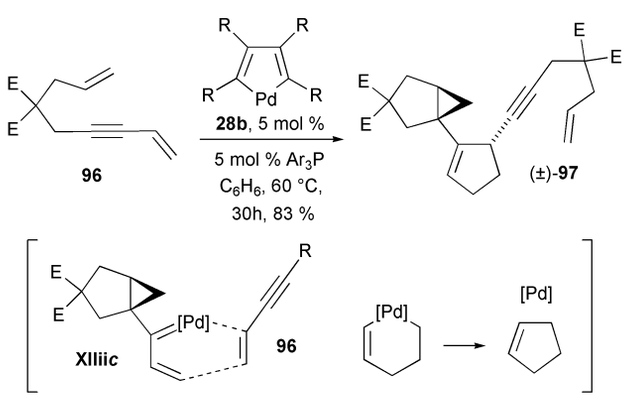
§ The term "*trans*-cycloheptene" is used by Trost *et al.* (see reference 109) to describe one perimeter of the bicyclo[3.2.0]hept-1(7)-ene core in an intermediate of type **XII*b***. Analogously, the term "*trans*-cyclooctene" refers to one perimeter of the bicyclo[4.2.0]oct-1(8)-ene core in **93**



(^{13}C / ^{2}H labelling performed in separate experiments)

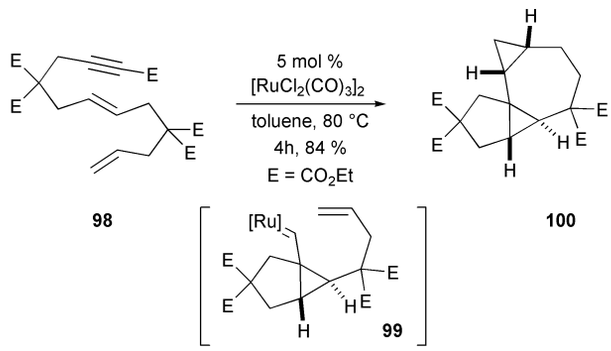
Scheme 41

The generation of the unexpected isotopomers (**B**) was accounted for by a rearrangement competitive with the reductive elimination (which would generate ^{13}C-**30A** and d_2-**30A** *via* cyclobutene **XIII*b***) at the stage of the 5-palladaspiro[4.4]-nonatriene¶ intermediate **XII*a***. The rearrangement was envisaged as proceeding *via* mechanism **XIIIi**, involving the generation of a palladavinylcyclopropane (**XIIIi*a*** ⟶ **XIIIi*c***) and subsequent ["2+2"] then retro ["2+2"] rearrangement leading to a palladium carbene intermediate **XIIIi*e*** *via* palladacyclobutane **XIIIi*d*** . The product (**30B**, which is degenerate with **30A** in the absence of labelling) would be released by a [1,2]-shift–elimination sequence. Later studies provided support for this mechanistic proposal through trapping of vinyl carbene analogues of the palladavinylcyclopropane (**XIIIi*c***) with alkenes.[113–115] For example, the palladacyclopentadiene catalyst system induced coupling of two molecules of vinyl-substituted 1,6-enyne **96** to give **97** as a single diastereomer in 83% yield *via* what is proposed to be a pallada-Diels-Alder reaction followed by 1,1-reductive elimination, Scheme 42.



Scheme 42

3.3.3 Ru(II), Rh(I) and Pt(II) pro-catalysts. $[RuCl_2(CO)_3]_2$ catalysed skeletal reorganisation of enynes analogous to, and including, the reaction **29** ⟶ **30** (94%, 80 °C, toluene, CO, 1 h) were reported by Murai and co-workers in 1994.[69] Analogies were drawn to the palladacyclopentadiene catalysed reaction pathway and labelling studies conducted but, as far as we are aware, never published.[116] Traces of anomalous bond reorganisation, analogous to **29**⟶**30B** *vide supra*, were also detected and in later work the involvement of a ruthenavinylcyclopropane (*cf*. **XIIIi*c***) was suggested and supported by intramolecular trapping of the metallocarbene with an alkene to generate a second cyclopropane ring. For example, under Ru (and even Rh and Pt) catalysis, dieneyne substrate **98** gave the remarkable tetracyclo[6.4.0.0.^{1,9}0^{2,4}]undecane product **100**, possibly *via* **99**, Scheme 43.[117]



Scheme 43

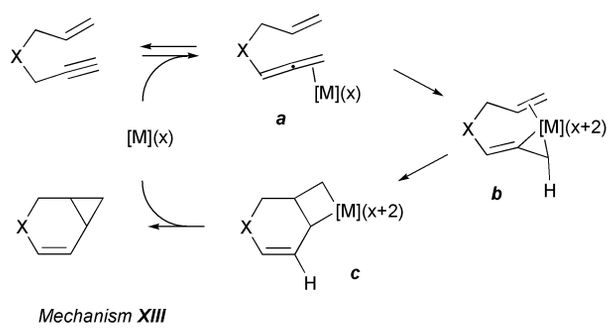
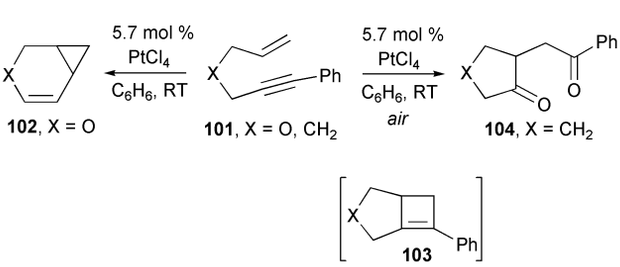


Fig. 12 Mechanism **XIII**; a generic mechanism, involving yne-to-allene tautomerisation then [2+1]-oxidative cyclisation, for 1,6-enyne cycloisomerisation.

An intriguing mechanism (**XIII**, Fig. 12) was suggested by Blum *et al.* for the Pt(IV)-catalysed cycloisomerisation of allyl propargyl ethers *e.g.* **101** X = O, to 3-oxabicyclo[4.1.0]heptenes. *e.g.* **102**, Scheme 44 .[71] Reaction was proposed to proceed by



Scheme 44

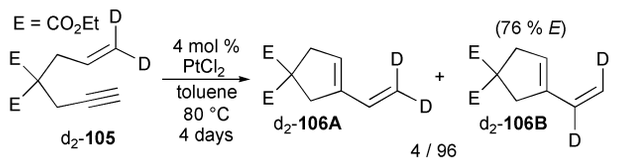
tautomerisation of the 1,6-enyne to a 1,2,6-triene (an eneallene) followed by complexation with Pt (to give **XIII*a***). Intramolecular capture by the allyl group then results in cycloaddition–prototropy to give metallacyclobutane **XIII*c*** and finally, reductive elimination generates the cyclopropyl ring in the product.

Simple hydrocarbons, such as 1-phenyl-hept-6-ene-1-yne (**101**, X = CH_2), also reacted but the products polymerised on work-up. Conducting the reaction under an atmosphere of air allowed the isolation of dione **104** which was suggested to arise from [2+2] cycloaddition-switched retro-cycloaddition of O_2 with cyclobutene **103**, a product reminiscent of Pd(II)-catalysed cycloisomerisation.[109]

Mechanism **XIII** does not account for why the course of reaction diverges on loss of the heteroatom. In light of the mechanistic interpretations of $PtCl_2$-catalysed reactions, *vide infra*, it is likely that the heteroatom is crucial. Shortly after the report by Blum, Murai reported that Pt(II) is a much more

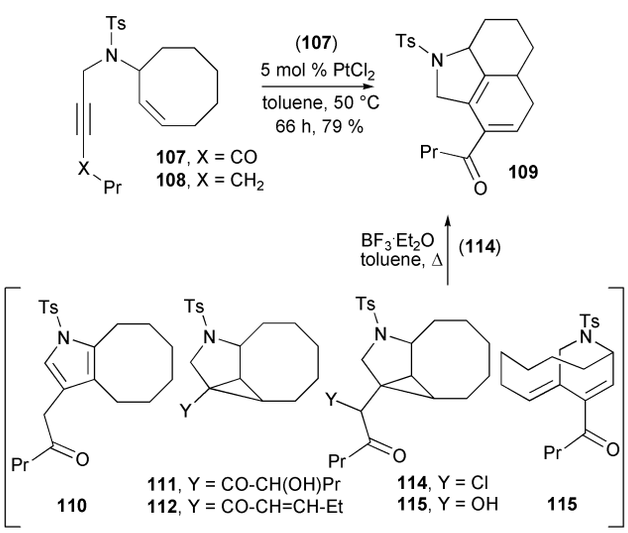
¶ The intermediate **XIIa** is, in this case, *spiro* because of the use of a catalyst of type **28**. Thus on oxidative cyclometallation a second ring is generated which is spiro-linked (through Pd) with the palladacyclopentadiene derived from **28**.

effective 1,6-enyne cycloisomerisation catalyst than Pt(IV). Furthermore, 'anomalous C–C bond formation' was detected in a number of the reactions studied and confirmed unambiguously by conversion of d_2-**105** into d_2-**106A**, *E*-d_2-**106B** and *Z*-d_2-**106B** (4 : 73 : 23 ratio), Scheme 45, and 'slipped η^1-alkyne complexes', *vide infra*, were suggested as potential intermediates.[72]



Scheme 45

Fürstner later reported on the application of the $PtCl_2$ catalyst system to the generation of macrocylic intermediates from 1,6-enynes *en route* to synthesis of metacycloprodigiosin and streptorubin B.[73] At lower temperatures (≤50 °C) the presence of an electron withdrawing group (ketone or ester) at the alkyne terminus was found to be essential. For example, 1,6-enynone **107** underwent cycloisomerisation to give **109** in 79% yield whereas the simpler 1,6-enyne **108** failed to react analogously, Scheme 46.



Scheme 46

The reaction of **107** was conducted on a large scale and this allowed the isolation and identification of a number of side products, including **110**–**115**. A mechanism involving a non-classical carbocation intermediate, *vide infra*, generated by attack of the alkene on a Lewis-acid activated alkyne was proposed to account for all of the products. The mechanism suggests that other Lewis and even Brønsted type acids should be sufficient to effect the metathesis. Indeed, $BF_3{\cdot}Et_2O$, HBF_4, $SnCl_4$, $AlCl_3$, $TiCl_4$ and $ZnCl_2$ were all found to be effective, whilst the 'less acidic' salts $NiCl_2$, $PdCl_2$, $CoCl_2$, $RhCl_3$, $CrCl_2$ and $MnCl_2$ were not. Further support comes from the $BF_3{\cdot}Et_2O$ catalysed dehalogenative rearrangement of **114** which gave **109** in 58% yield, presumably *via* the same non-classical carbocation manifold *vide infra*. The keto-group on the alkyne was suggested to facilitate enolate type intermediates, however it was later reported that on heating (80 °C) a broader range of heteroatom tethered 1,6-enynes, with or without electron withdrawing alkyne substituent, undergo analogous reaction, see *e.g.* Scheme 14.[76] A substrate-dependent exit (compare **41**, R = Bu with R = H, Scheme 14) from the non-classical carbocation manifold (**XIV*c*** ↔ **XIV*d*** ↔ **XIV*e***) shown in mechanism **XIV**, Fig. 13, neatly accommodates all of the results, including the rearrangements described by Blum.[71]

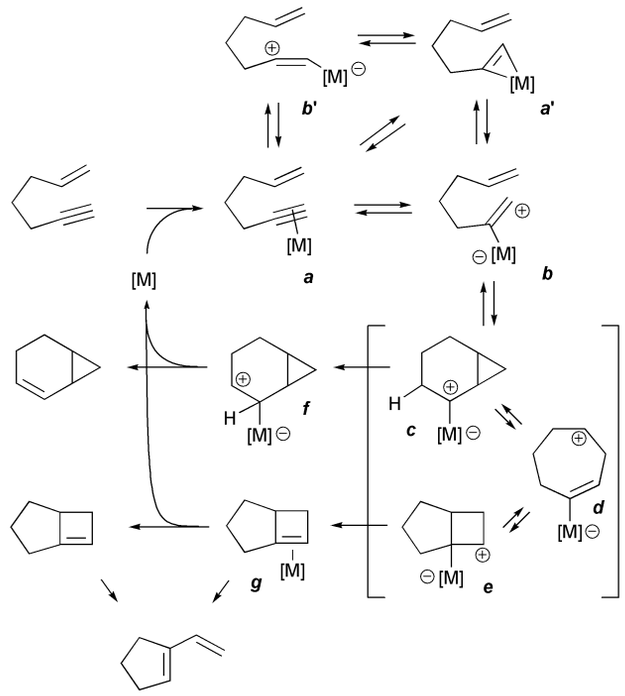
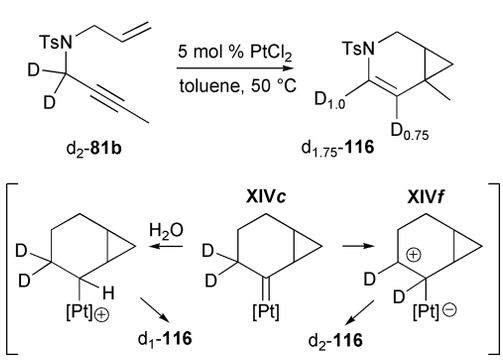


Fig. 13 Mechanism **XIV**; a generic mechanism, involving either a slipped polarised η^1-alkyne coordination (**XIV*b***), or a metallacyclopropane (**XIV*a'***), leading to a non-classical 'cyclopropyl methyl homoallyl cyclobutyl cation' manifold, for 1,6-enyne cycloisomerisation.

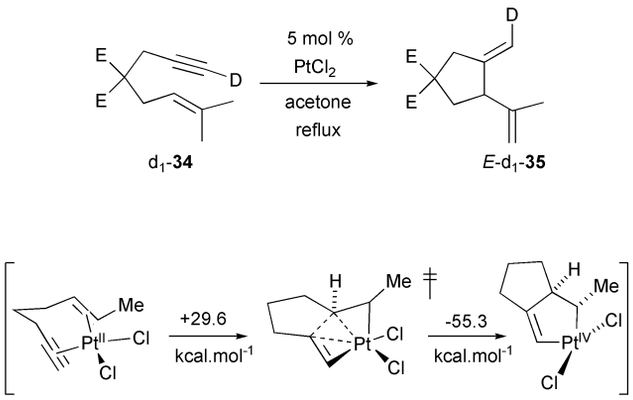
A carbenoid character is ascribed to the "cyclopropyl methyl cation" (**XIV*c***) which can thus undergo protonation (by traces of water) in competition with the major pathway involving [1,2]-shift-elimination. This then accounts for the partial loss (25%) of D on reaction of d_2-**81b** to give $d_{1.5}$-**116** (*i.e.* not all of intermediate **XIV*c***, converts *via* → **XIV*f*** → d_2-**116**), Scheme 47.



Scheme 47

Complementary results on reaction of d_0-**81b** in the presence of D_2O (to give $d_{0.25}$-**116** in which the D is located exclusively at the carbon adjacent to the cyclopropane) support this.[77] However, the 25% diversion, *even in the presence of excess D_2O*, suggests that the mechanistic divergence occurs before interaction with the water.

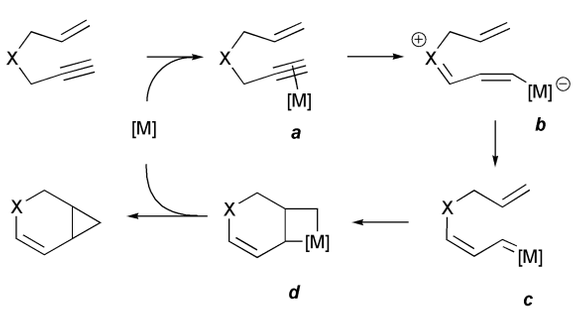
As part of a broader study on the $PtCl_2$-catalysed alkoxy- and hydroxy-cyclisation of enynes, Echavarren and co-workers also studied their cycloisomerisation in polar, non-nucleophilic, solvents such as 1,4-dioxane and acetone[74] instead of the toluene used as solvent by Murai *et al.*[72] and by Fürstner *et al.*[77] When the substrate does not contain a heteroatom as a tether between propargylic and allylic units, the conventional Alderene type products, and not products of skeletal reorganisation, are obtained. For example, d_1-**34** gives *E*-d_1-**35**, stereospecifically, Scheme 48.



Scheme 48

A conventional oxidative cyclisation, β-H elimination, then reductive elimination (mechanism **VIII**) is suggested and supported by DFT calculations on the generation of a platinacyclopentene starting from a generic [(η⁴-hept-1-ene-6-yne)$PtCl_2$] complex, see inset to Scheme 48. Cyclometallation was predicted to proceed *via* a shift of the alkene terminal carbon to an axial position and then, post transition state, a widening of the Cl–Pt–Cl angle from *ca.* 90° to 170°. The activation energy to reach the transition state (confirmed by study of internal reaction coordinates) was predicted to be 29.6 kcal mol^{-1} and the overall process exergonic (25.7 kcal mol^{-1}).

When the linker has a heteroatom, *e.g.* an ether or tosyl amide, then bicyclo[4.1.0]heptane products are obtained. Indeed, Echavarren noted that all reports of Pt-catalysed generation of bicyclo[4.1.0]heptanes from 1,6-enynes involve substrates with a heteroatom linking the propargylic with allylic sub-units. Consequently, a mechanism (**XV**) was proposed in which there is a lone-pair driven, [1,2]-shift of H from the propargylic position to generate a vinylalkylidene complex and then an intramolecular cyclopropanation of the tethered allyl unit, Fig. 14.

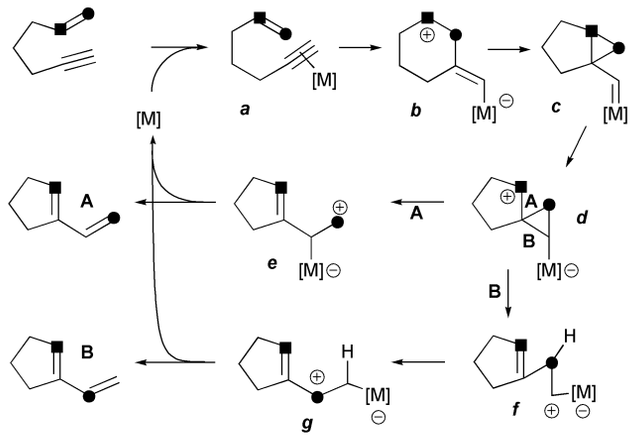


*Mechanism **XV***

Fig. 14 Mechanism **XV**; a generic mechanism, involving η²-alkyne coordination then heteroatom triggered generation of a vinylmetallacarbene intermediate, for 1,6-enyne cycloisomerisation.

DFT calculations on the alkyne complex [(η²-hept-1-ene-6-yne)$Pt(H_2O)Cl_2$] indicates that, despite the terminal carbon lying closer to Pt than the internal (2.086 and 2.195 Å, respectively) the coordination mode is best described as η²-coordinated alkyne (*cf.* **XIV*a*** and **XV*a***) and not an η¹-coordinated vinyl cation (the 'slipped η¹-alkyne complex' **XIV*b′***, Fig. 13).[53,74]

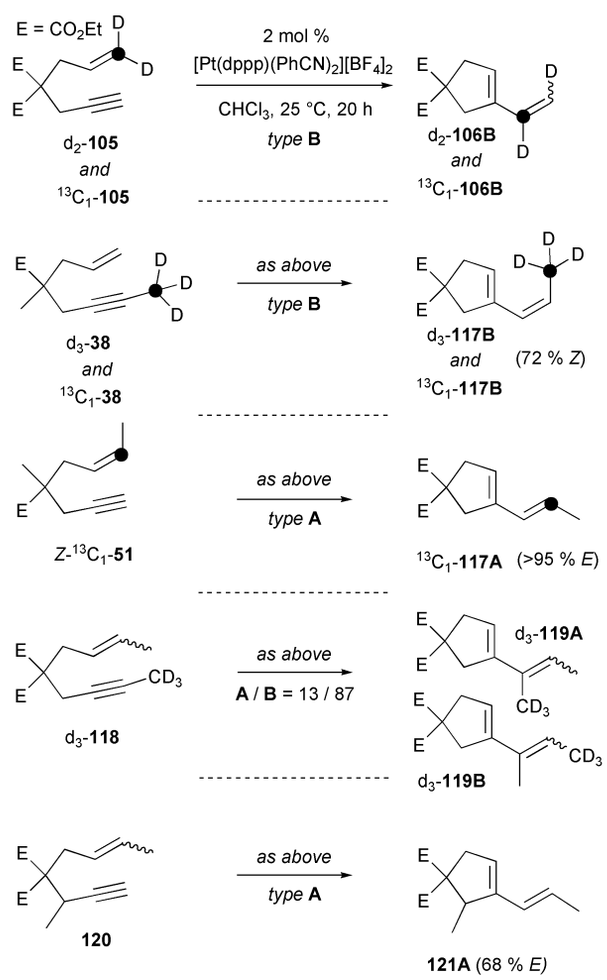
Switching from neutral ($PtCl_2$) to cationic Pt complexes bearing the chelating diarylalkyl phosphines (dppe, dppp or dppb), allows cycloisomerisation of malonate based 1,6-enynes to proceed smoothly in chloroform at ambient temperature, with skeletal reorganisation, to give 1,3-diene products.[75] Oi and co-workers conducted extensive ^2H and ^{13}C-labelling studies on this system, using $[Pt(dppp)(PhCN)_2][BF_4]_2$ as pro-catalyst. The bond relationships in the cycloisomerisation/skel-



*Mechanism **XVI***

Fig. 15 Mechanism **XVI**; a generic mechanism, involving metallavinylcyclopropane and metallated cyclopropyl methyl cation intermediates, for 1,6-enyne cycloisomerisation with skeletal reorganisation with (**XVIB**) or without (**XVIA**) anomalous bond connectivity.

etal rearrangement products thus identified were assigned as 'type A' and 'type B' (see Fig. 15). The following key observations were made. The simplest system, allyl propargyl malonate **105** undergoes 'type B' rearrangement to **106** (*cf.* ^{13}C-**106B** and d_2-**106B**), Scheme 49. The label distribution in d_2-**106**



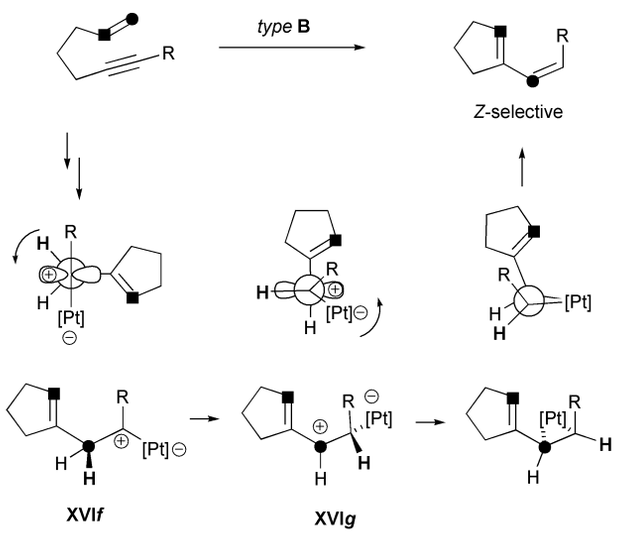
Scheme 49

is such that both carbons bear a single deuterium and thus transfer is *intramolecular*.

Addition of a methyl group to the terminus of the alkyne (^{13}C-**38**), does not affect the outcome which is again 'type B'

and gives **117B** with *Z*-selectivity (72%); reaction of d_3-**38** confirmed that the methyl protons were not involved. However, addition of a methyl group to the alkene terminus (*Z*-^{13}C-**51**) results in a 'type A' rearrangement (to give **117A**). The substrate in which *both* alkene and alkyne were methyl terminated (**118**) was thus tested. To distinguish one methyl group from the other, d_3-**118** was deployed and found to mostly give d_3-**119B**, *i.e.* a 'type B' product. Moving the alkyne methyl substituent from the terminus to the propargylic centre (**120**) gave cycloisomerisation product **121A**, a 'type A' product, and with *E*-selectivity (68%), in stark contrast to the 'type B' process, *vide supra*. To account for the products and label distributions, mechanism **XVI** involving the generation of a platinavinylcyclopropane intermediate was suggested, Fig. 15.

Echavarren and co-workers have conducted DFT calculations on such processes as intermediates in the Pt-catalysed alkoxy- and hydroxy-cyclisation of enynes and concluded that with $PtCl_2$ the generation of a platinavinylcyclopropane intermediate is competitive with oxidative cyclisation (*cf.* mechanism **VIII** and inset to Scheme 48, *vide supra*).[74] In the case of the electron deficient di-cationic platinum(II) systems, the oxidative cyclisation may be strongly inhibited and thus the platinavinylcyclopropane route becomes dominant. The final step in the overall reaction mechanism is suggested by Oi and co-workers to be rearrangement to a "cyclopropyl methyl cation" which can undergo ring-opening to give a homoallyl cation with Pt at the allylic or homoallylic position, dependent upon which cyclopropyl bond (A *versus* B) is broken. In 'type A', elimination of Pt^{2+} generates the products. In 'type B', in common with **XIIIi*i***, Fig. 11, elimination of the Pt^{2+} is prefaced by a [1,2]-H shift (**XVI*f*** ⟶ **XVI*g***). The elimination is proposed to be *Z*-selective, through the latter steps occurring rapidly and *via* minimum energy conformation changes,[118] as outlined in Scheme 50.



Scheme 50

4 Summary and outlook

1,6-Diene and enyne cycloisomerisation reactions are still in relative infancy and are undergoing rapid development in terms of catalyst discovery and novel substrate/product types. However, it is apparent that the long term utility and application of cycloisomerisation in synthesis will be dependent on the logical and predictable control of chemo- regio- and stereo-selectivity. The development of such selective processes, as well as the deliberate bypass, diversion or inhibition of cycloisomerisation reactions, will be dependent on an intimate mechanistic knowledge relating to catalyst activation and propagation processes. Although it is evident that significant inroads have been made into the mechanistic understanding of cycloisomerisation reaction of 1,6-dienes and 1,6-enynes, substantial endeavour will be required if all of the known systems are to be explored in full. Comparing 1,6-diene and 1,6-enyne cycloisomerisation reactions, it is interesting to note that virtually no kinetic studies have been performed on the latter, despite the wider variety of catalysts, greater applications to synthesis and greater diversity of products and thus mechanistic manifolds. Of the mechanistic investigations performed on the non-alkylidene skeletal rearrangements of 1,6-enynes, it appears that DFT studies might make major contributions to understanding the true nature of the intermediates that some authors consider more like conventional non-classical carbocations than organometallic intermediates. It is clear that the reaction manifold is open to catalysis by a large number of transition metal complexes, simple acids and main group halides (most recently gallium[119]) and that understanding how to control the capture and rearrangement of these cationic intermediates will lead to an even broader and more diverse range of products, hopefully with selectivity.

In conclusion, it is striking that the bulk of the mechanistic clues are currently derived from observations relating to subtle changes in substrate structure rather than more physical inorganic/organic studies involving isolation/characterisation, spectroscopic observation or trapping of intermediates, kinetic measurements, isotopic labelling, quantitative structure–activity relationships and high level computational chemistry. Further studies in these latter areas will make for interesting and worthwhile goals since there appears to be a wealth of mechanistic diversity: consider for example the 21 different mechanisms outlined in in this review.

Note added in proof: just after completion of the manuscript for this review, a full paper appeared from Mori *et al.* describing, in part, the effect of ethylene gas on the rate of reaction of enyne metathesis and the possibility of an ene-then-yne rather than yne-then-ene types mechanism. See ref. 120.

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