Ruthenium(II)-catalysed cycloisomerisation of 1,6-dienes by focused microwave dielectric heating: improved rates and selectivities leading to *exo*-methylenecyclopentanes

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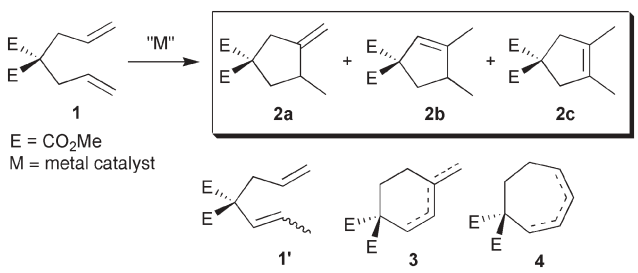
We herein report the effect of microwave dielectric heating in the Ru-catalysed cycloisomerisation of 1,6-dienes. Substantially improved reaction rates are attained for a series of 1,6-diene substrates, with equivalent or higher isomeric purity than conventional thermal heating.

Transition metal-catalysed cycloisomerisation of 1,6-dienes (**1** → **2a–c**) represents an extremely powerful, atom-economic and environmentally benign method for the rapid assembly of carbo- and heterocyclic compounds, suitable for target-oriented synthesis, *e.g.* in natural products, biological probes and inhibitors.[1] Although the 5-membered ring products (**2**) are most common, 6- and 7-membered ring products (**3** and **4**, respectively) may be formed. In some cases, regio-isomerisation of **1** to **1′** is seen. Generally, the formation of the ring system(s) involves hydrogen atom(s) migration with allied bond reorganisation; skeletal reorganisation is not observed in this specific process.[1c]

The first transition metal-catalysed 1,6-diene cycloisomerisation was reported by Shaw and co-workers in 1971,[2] which involved heating a solution of $RhCl_3{\cdot}3H_2O$ in diallyl ether containing a few percent of allyl alcohol, giving the *exo*-methylene isomer in good yield. Since these pioneering studies, many transition metals (Ti,[3] Rh,[4] Ru,[5] Ni,[6] Pd[7]) have been shown to promote 1,6-diene cycloisomerisation—elegant mechanistic studies by Lloyd-Jones and others have provided insights into the subtle interplay of the transition metal and the alkenes in ring-formation and in β-hydride elimination.[1c] The recent development of asymmetric 1,6-cycloisomerisation processes for Pd[8] and Ni[9] points to its emergence in synthesis.

In 1998, Itoh and co-workers reported that Ru pro-catalysts such as $RuCl_3{\cdot}H_2O$, Cp*Ru(cod)Cl and $[Ru(cod)Cl_2]_n$ promote the regioselective cycloisomerisation of **1** → **2a** in *i*-PrOH at 90 °C.[5a] The 1,6-diene substrate scope under these conditions is good, although some limitations are apparent for certain substrates (longer reaction times, up to 24 h; modest isomeric purity in some cases).[10] One could focus on improving catalyst activity through changes in catalyst structure, however other reaction conditions (photochemical, sonication, microwave *etc.*) could equally improve reaction efficiency. The development of microwave-assisted organic synthesis has been substantial in the past 20 or so years.[11] However, the application and exploitation of this technique in transition metal-mediated 1,6-diene cycloisomerisation reactions has not been investigated, which is surprising given that enhanced rates, higher reactivities towards awkward substrates and different product selectivities could be attained. The Ru-mediated process (and conditions) is perfectly suited to rate enhancement through use of microwave dielectric heating. The loss tangent value, related to the ability of the solvent to absorb energy in a microwave capacity, of *i*-PrOH is 0.799, which is relatively high and allows fast ramping of the reaction temperature—important for optimal heating of the reaction sample.[12] We herein report preliminary results from the first microwave-assisted 1,6-diene cycloisomerisation reactions.



Scheme 1 1,6-diene cycloisomerisation products.

The absence of kinetic studies on the Ru-mediated process led us to conduct some experiments on the conventially heated reaction (**1** → **2a**) using three pro-catalysts: $RuCl_3{\cdot}H_2O$, CpRu(cod)Cl and $[Ru(cod)Cl_2]_n$. Kinetic profiles for the reactions mediated by CpRu(cod)Cl, $RuCl_3{\cdot}H_2O$ and $[Ru(cod)Cl_2]_n$, are shown in Fig. 1.[13]

With 5 mol% $RuCl_3{\cdot}H_2O$ the reaction was complete in 3 h (**2a** : **2b** : **2c**, 93 : 3 : 4)—continued heating resulted in loss of isomeric purity (at 24 h, **2a** : **2b** : **2c**, 81 : 8 : 11). A significant induction period is only seen with CpRu(cod)Cl, which is indicative of it being a pro-catalyst species. Under microwave heating this reaction was quantitative after 0.25 h (**2a** : **2b** : **2c**, 93 : 3 : 4). In the conventionally heated reaction, mediated by 5 mol% $[Ru(cod)Cl_2]_n$, complete consumption of **1** was seen after 3 h, which was more selective for **2a** (**2a** : **2b** : **2c**, 97 : 2 : 1). Isomeric purity was again reduced on prolonged heating (at 24 h, **2a** : **2b** : **2c**, 94 : 4 : 2). Lowering the catalyst loading to 1 mol% provides similar yields and selectivity, although 24 h is required for complete consumption of **1**. Under microwave conditions (at 1 or 5 mol% Ru), **2a** was produced almost exclusively (98%) after 0.25 h, whereas $RuCl_3{\cdot}H_2O$, although highly active, exhibited lower selectivity (at 0.25 h, **2a** : **2b** : **2c**, 80 : 9 : 11). $[Ru(cod)Cl_2]_n$ thus appears the most efficient and selective pro-catalyst using microwave heating.

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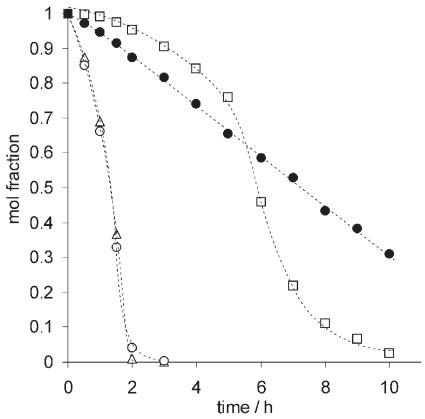
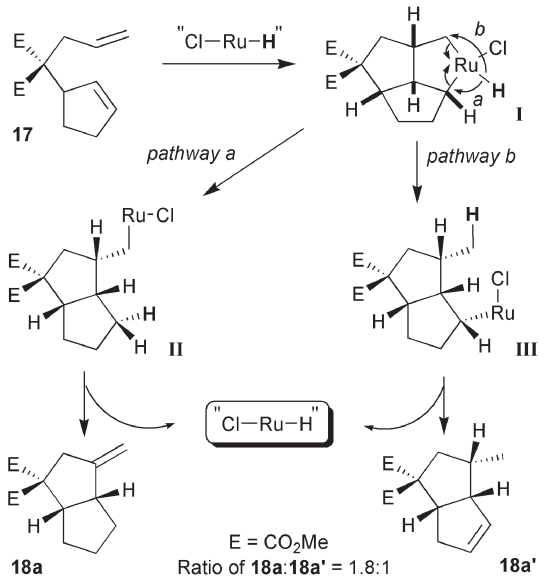


Fig. 1 A kinetic profile for reaction **1** → **2a**, mediated by [Ru] (using a 0.125 M solution of **1** in *i*-PrOH at 90 °C); □ = CpRu(cod)Cl (5 mol%); △ = $RuCl_3 \cdot H_2O$ (5 mol%); ○ = $[Ru(cod)Cl_2]_n$ (5 mol%); ● = $[Ru(cod)Cl_2]_n$ (1 mol%); monitored by GC analysis. Note that the dashed lines serve as a guide to the eye.



Scheme 2 Mechanism to account for the formation of **18a** and **18a**′.

A series of 1,6-dienes were assessed to test whether $[Ru(cod)Cl_2]_n$ was a generic pro-catalyst under microwave heating. Diethyl diallylmalonate **5** gave the *exo*-methylene isomer **6a** in 96% yield (98% purity). Selective cyclo isomerisations were recorded for pro-spirobicyclic 1,6-dienes **7** and **9**, proceeding to completion in 0.5 h. 1,6-Diene **11**, containing a cyanoester tether, cyclo isomerised to give **12a** as a mixture of diastereoisomers (3.1 : 1, (10)

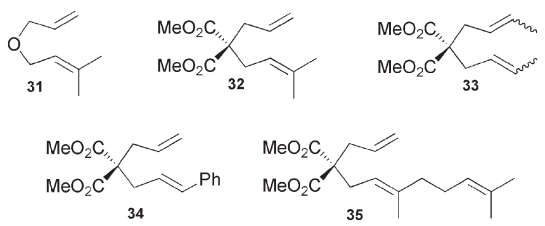
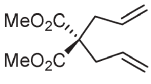
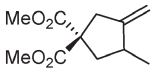
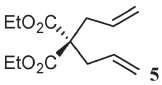
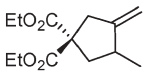
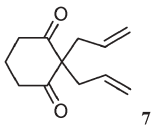
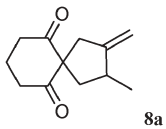
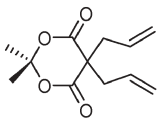
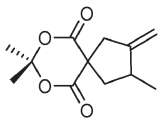
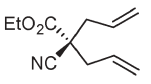
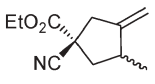
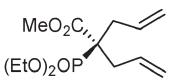
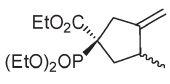
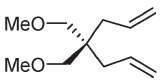
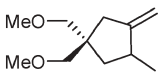
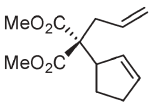
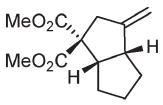
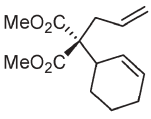
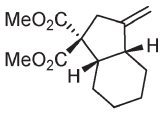
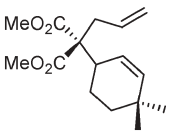
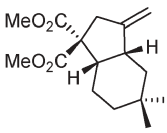
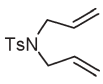
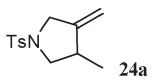
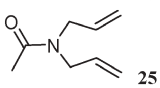
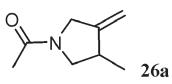
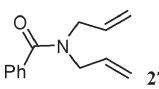
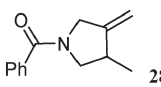
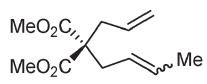
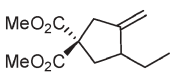


Fig. 2 1,6-dienes that failed to undergo cycloisomerisation.

Table 1 Microwave-assisted 1,6-diene cycloisomerisation reactions

1,6-Diene[a]	Product	% Yield/% Purity (h)[b]
 **1** (1)	 **2a**	98/98 (0.25)[c] 91/97 (24)[d]
 **5** (5)	 **6a**	96/98 (0.25)[c] 85/95 (24)[d]
 **7** (5)	 **8a**	99/98 (0.5)[c] 83/98 (24)[e]
 **9** (5)	 **10a**	92/97 (0.5)[c]
 **11** (5)	 **12a**	97/98 (0.5)[c] d.r. 3.1:1 (by NMR)
 **13** (5)	 **14a**	96/90 (0.5)[c] d.r. 4:3 (by NMR)
 **15** (5)	 **16a**	96/91 (0.25)[c]
 **17** (5)	 **18a**	94/64 (0.1)[c] 75/48 (24)[d]
 **19** (5)	 **20a**	30/50 (0.5)[c]
 **21** (10)	 **22a**	96/92 (0.25)[c] 90/80 (24)[e]
 **23** (5)	 **24a**	99/96 (0.5)[c] 65/86 (24)[d]
 **25** (5)	 **26a**	82/90 (0.25)[c] 62/83 (24)[e]
 **27** (5)	 **28a**	97/92 (0.5)[c]
 **29**	 **30a**	96/94 (1)[c] 92/76 (24)[d]

[a] Number in brackets is the mol% $[Ru(cod)Cl_2]_n$ employed. [b] Yield of product after column chromatography. Isomeric purity determined by ^1H NMR spectroscopy and/or GC. Number in brackets is the reaction time (h). [c] Microwave conditions: 300 W, 2 minutes to 90 °C; hold to the time indicated in brackets. [d] Conventionally heated reaction in *i*-PrOH at 90 °C for 24 h (identical conditions to those given in ref. 5a). [e] Yields and isomeric purity reported in ref. 5a.

determined by ^{1}H NMR spectroscopy). cycloisomerisation of **13** was less diastereo-selective (4 : 3, determined by ^{1}H NMR spectroscopy). The non-hindered dimethyl ether **15** is efficiently cyclo-isomerised to give **16a**. The unsymmetrrical 1,6-diene **17** was rapidly cyclo-isomerised to provide fused *exo*-bicycle **18a**, which was accompanied by the fused *endo*-bicycle **18a′** (see Scheme 2). In contrast, pro-bicyclic diene **19** was a poor substrate—only 30% conversion was recorded with extensive regio-isomerisation of **20a**. Pro-bicyclic diene **21**, possessing a *gem*-dimethyl group on the cyclohexene fragment, thwarts β-hydride elimination from the cyclohexyl ring, *i.e.* the *endo*-bicycle cannot be formed, providing **22a** as the sole cycloisomerisation product. Nitrogen-tethered 1,6-dienes (**23**, **25**, and **27**) undergo efficient cycloisomerisation. Here the greatest enhancement in yield and selectivity was observed. For example, yields for **24a** and **26a** were improved from 65 and 62%, from conventional heating, to 99 and 82% under microwave heating, respectively. Higher selectivity was seen using unsymmetrical 1,6-diene **29**.

Several 1,6-dienes failed to undergo microwave-assisted cycloisomerisation (Fig. 2). A co-mixture of **1** with **31** gave **2a** as the sole cycloisomerisation product after 0.25 h. The experiment confirms that **31** does not undergo cycloisomerisation in the presence of catalyst "Cl-Ru-H", propagated through cycloisomerisation of **1**.

The formation of **18a′** in the reaction of **17** → **18a** is intriguing as it indicates that a hydroruthenation/carboruthenation/β-hydride elimination process is not favoured, as hydroruthenation would occur on both hindered and non-hindered alkenes—the formation of *exo*-bicycle **18a** would occur through initial addition of "H-Ru-Cl" to cyclopentene, the more substituted alkene, which is kinetically less favoured. The oxidative ruthenation/reductive elimination/β-hydride elimination pathway provides a more adequate explanation, and supports the mechanistic proposal based on cycloisomerisation of **29**.[5a] Oxidative ruthenation gives Ru(IV) intermediate **I**, which then reductively eliminates to give **II** (*pathway a*) or **III** (*pathway b*). β-Hydride elimination reveals **18a** and **18a′**, respectively. *Pathway a* dominates to give **18a**.

In conclusion, we have shown that microwave heating accelerates Ru-mediated cycloisomerisation of 1,6-dienes. Enhanced rates are also seen in 1,6-enyne cycloisomerisation.[14] Generally, selectivity for the cycloisomerisation product is at least equal to or superior in several examples. Other cycloisomerisation processes, including alkene dimerisation leading to acyclic isomerisation products,[15] could benefit from microwave heating.

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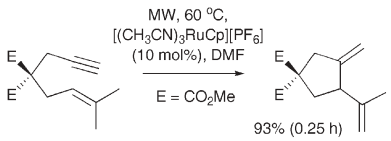

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