A General Approach to the Formation of Oxygen-Chelated Ruthenium Alkylidene Complexes Relying on the Thorpe-Ingold Effect.

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Ruthenium alkylidene complexes are prepared via enyne ring-closing metathesis relying on the exo and endo *gem*-dialkyl substituent effect. The structural features stabilizing oxygen-chelates are explored and confirmed by single crystal X-ray diffraction analyses. In stark contrast to the previously reported oxygen chelated Grubbs-type complexes, all chelates prepared through ring-closing enyne metathesis regime show the disposition of the chelated oxygen and the NHC ligand in cis relationship, which force the two chloride ligands in *cis*-orientation. The newly synthesized oxygen-chelated ruthenium alkylidene complexes are metathesis active only at elevated temperatures.

The coordination of an alkene or an alkyne of a substrate to the unsaturated ruthenium metal centre is required for the productive alkene and enyne metathesis catalysed by Grubbs type ruthenium alkylidene complexes.[1] However, the polar functional groups such as lone pair electrons near the reactive metal centre occasionally occupy the coordination site over the substrate of alkene or alkyne such that the catalytic cycle is preferentially arrested at various resting stages either temporarily or permanently in alkene and enyne metathesis.[2] It is critical to understand the structure and dynamic properties of trapped propagating ruthenium alkylidene species to minimize these non-productive metathesis events.[3] It should provide important information for selecting substrate that may overcome the resting stage problem. There are many known heteroatom-chelated ruthenium alkylidenes derived from prototype Grubbs complex **1a** and **1b**.[4,5] One of the most successful variations of **1a** and **1b** is the oxygen-chelated second-generation Grubbs-Hoveyda complex **1d** (Figure 1).[6] Fürstner and coworkers reported that treating an alkyne containing a silyloxy group at the propargylic position with the first-generation Grubbs-Hoveyda complex **1c** afforded oxygen-chelated ruthenium vinylcarbene complexes **2a**, which upon removal of the silyl group provided hydroxy-chelate **2b**.[7] More recently, other oxygen-chelated complexes such as **1e** and **1f** were derived from the Grubbs second-generation complex **1b**.[8] The structural characteristics of the new complexes containing multiple bidentate ligands allows for the selective formation of cis-alkenes. It is interesting to note that in **1e** the isopropyl ether ligand is trans to the NHC whereas in **1f** it is cis to the NHC ligand.

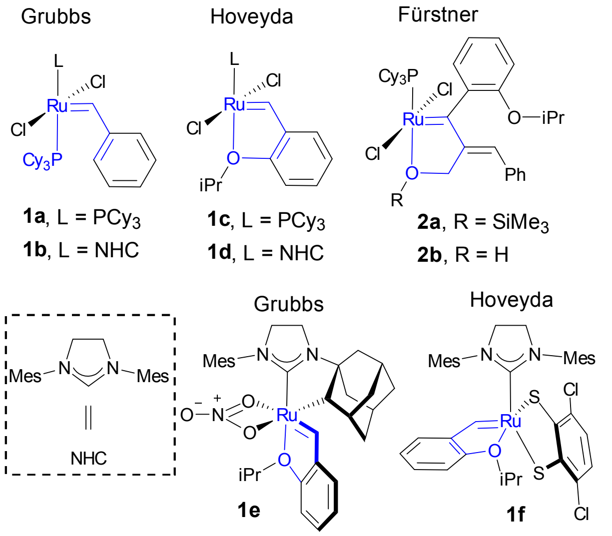

Figure 1. Ether- and hydroxy-chelated ruthenium alkylidene complexes

Identifying structural elements whereby a propagating ruthenium species chelated to oxygen functionality to become stable or unreactive during the metathesis is crucial because in many occasions substrates engaged in metathesis contain oxygen-based functional groups. To gain insight into the chelating behaviour of hydroxyl, ether, and ester functionality to ruthenium alkylidenes, we explored the structural factors in the substrates for metathesis (Scheme 1). In this regard, we envisioned that the ring-closing metathesis (RCM) of enynes

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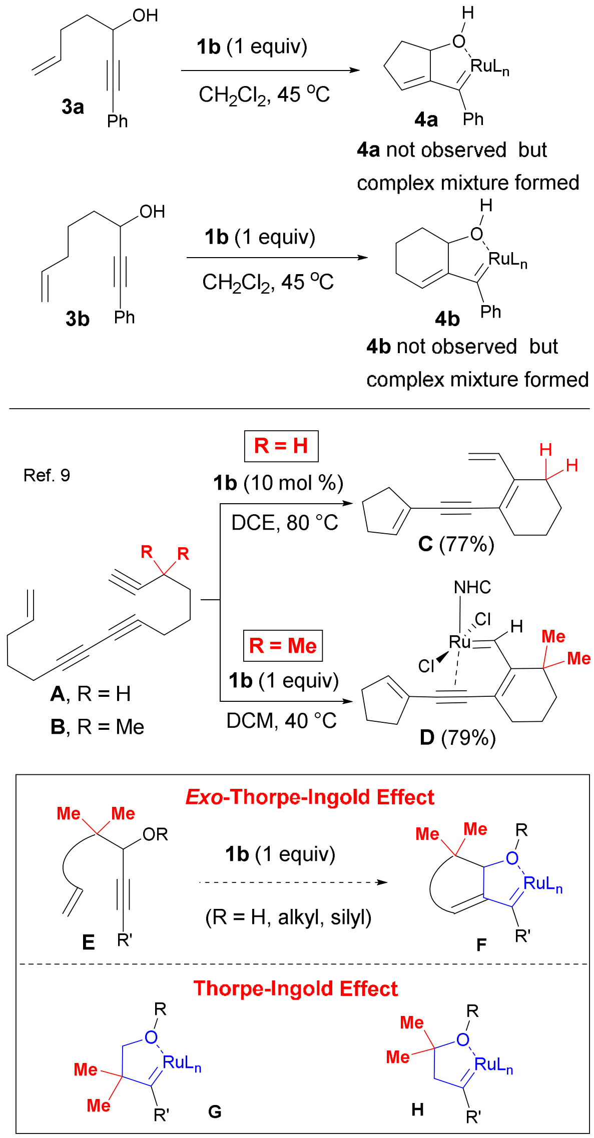
would be one of most effective method to position the ruthenium alkylidene moiety at an appropriate location such that the metal centre and the installed chelating group would interact to form the expected chelates. Based on this hypothesis, we have examined simple enyne substrates **3a** and **3b**. Upon ring-closing metathesis mediated by Grubbs-type complexes, the propagating species resulting from the ring-closure would provide hydroxy-chelated ruthenium alkylidene species **4a** and **4b**. However, when 1,6-enyne **3a** and 1,7-enyne **3b** were treated with a stoichiometric amount of the second-generation Grubbs catalyst **1b**, neither trapped propagating alkylidene **4a**/**4b** nor the ring-closed metathesis products were obtained.



Scheme 1. Structural motifs for chelate formation

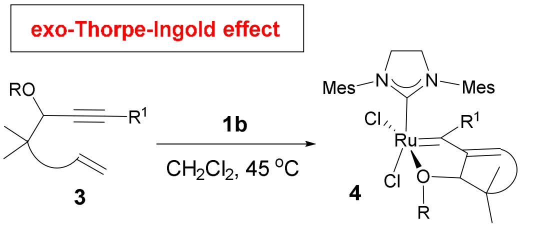
At this juncture, we turned our attention to the unusual *gem*-dimethyl substituent effect to promote the formation of ruthenium alkylidene complexes. For example, treating ene-triyne **A** with a catalytic amount of **1b** provided RCM product **C** in 77% yield whereas the corresponding *gem*-dimethylated enetriyne **B** afforded only the alkyne-chelated ruthenium alkylidene complex **D** in 79% yield upon treating a stoichiometric amount of **1b**.[9] We believe that this phenomenon is the manifestation of a steric effect of the *gem*-dimethyl substituents, which forces the ruthenium alkylidene moiety to be pointed toward the chelating alkynyl moiety to minimize steric interactions.[10,11] We surmised that this gem-dimethyl substituent effect could be resorted for the formation of oxygen chelated ruthenium complexes **F** from enyne **E**. The structural feature associated with this gem-dimethyl substituent effect in **D** and **F** is different from that of the conventional Thorpe-Ingold effect where the gem-dimethyl substituents should be within the incipient cyclic arrangements of the chelate to exert their effect. Thus, we termed this "*exo*-Thorpe-Ingold effect" because the gem-dimethyl substituents are not within the incipient cyclic structure. Herein, we report a general approach to the formation of various oxygen-chelated ruthenium alkylidene complexes relying on the "*exo*-Thorpe-Ingold effect" as well as the traditional Thorp-Ingold effect.

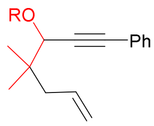
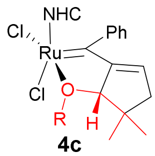
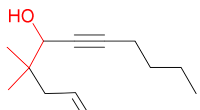
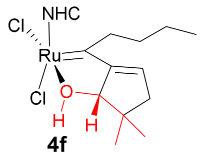
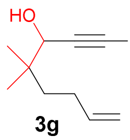
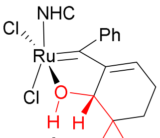
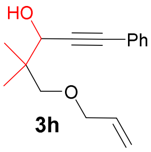
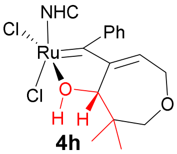
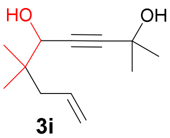
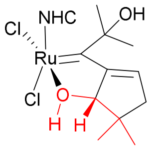
In order to prove the validity of *exo*-Thorpe-Ingold effect to promote oxygen-chelated ruthenium alkylidenes, the chelate-forming behaviours of alkenyl tethered propargylic alcohols containing *gem*-dimethyl substituents were explored (Table 1). First, *gem*-dimethyl substituents are installed on **3a** to generate the corresponding 1,6-enynes **3c**–**3e** bearing a propargylic alcohol, and its methyl and silyl ether derivatives. Upon treating these 1,6-enynes with a stoichiometric amount of Grubbs second-generation complex **1b** (CH_2Cl_2 at 45 °C), the expected oxygen-chelated ruthenium alkylidene complexes **4c**, **4d** and **4e** were isolated in 92%, 86% and 92% yield, respectively (entries 1 to 3). In contrast to the failure of forming **4a** with 1,6-enyne **3a** devoid of *gem*-dimethyl substituents, the efficient formation of **4c** and other related complexes **4d** and **4e** is remarkable. This clearly proves the strong stabilizing effect of the *gem*-dimethyl substituents on these complexes.

Having proven the validity of *exo*-Thorpe-Ingold effect to promote the formation of oxygen-chelates, we examined the effect of other structural elements. Replacing the phenyl group in **3c** with a butyl group in **3f** changed the chelation behaviour slightly, thus providing a 5:1 mixture of cis and trans chelates **4f** and **4f'** in 84% yield (entry 4). Although a significant ring-size-dependency was observed for the formation of alkynyl-chelates, the metathesis-induced chelate-forming behaviour of 1,7-enyne **3g** and 1,8-enyne **3h** is similar to that of 1,6-enyne **3c**, affording the expected hydroxy-chelated ruthenium alkylidene products **4g** and **4h** in 94% and 80% yield (entries 5 and 6). In case of diol containing substrate **3i**, there are two possible chelates **4i** and **4i'** to be formed, but only 5-membered chelate **4i** was obtained (entry 7). We believe that due to the geometrical constraint, the formation of 4-

membered chelate **4i'** is less favourable.

Table 1. Formation of oxygen-chelated ruthenium alkylidene complexes



entry	enyne	Product	yield (%)^a
1	 **3c**, R = H	 **4c**	92
2	**3d**, R = Me	**4d**	86
3	**3e**, R = SiMe$_3$	**4e**	92
4	 **3f**	 **4f**	84
5	 **3g**	 **4g**	94
6	 **3h**	 **4h**	80
7	 **3i**		82

^{a}Isolated yield. ^{b}Not observed.

One noteworthy structural feature of these oxygen-chelates was revealed from the X-ray structures of **4f** and **4g** (Figure 2).[12] Quite unexpectedly, these oxygen-chelates show unusual ligand geometry where the hydroxy and the NHC ligands are disposed in cis orientation, whereas they maintain a trans relationship in the Hoveyda complex **1d** and hydroxy-chelate **2b** observed by Fürstner. However, these cis-configured ruthenium complexes **4** exhibited catalytic activity only at elevated temperatures.[13]

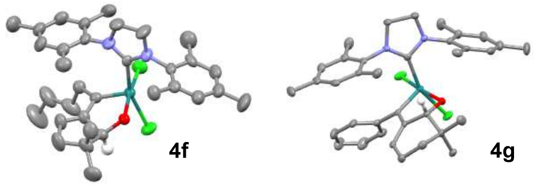
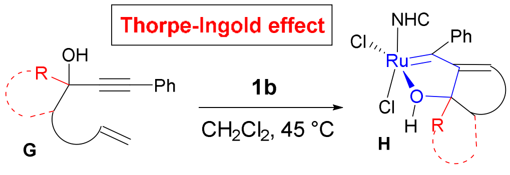
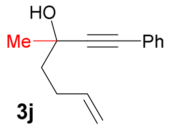
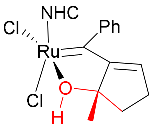
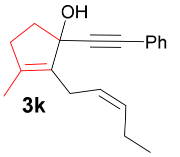
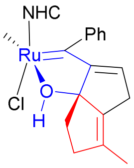
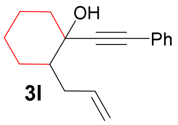
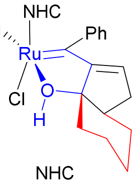
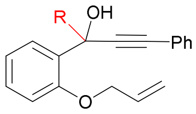
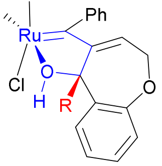


Figure 2. X-Ray structures of **4f** and **4g** (Hydrogen atoms are omitted for clarity except at the stereogenic carbon.)

Table 2. Hydroxy-chelate formation promoted by the Thorpe-Ingold effect

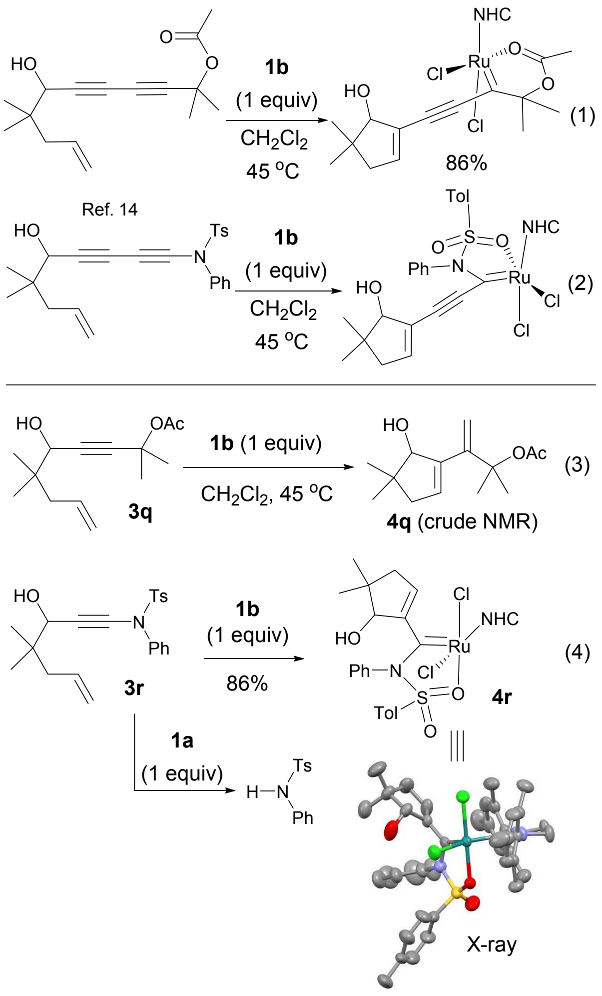


entry	enyne	product	yield (%)^a
1	 **3j**	 **4j**	88
2	 **3k**	 **4k**	91
3	 **3l**	 **4l**	90
4	 **3m** R=Me	 **4m**	58^b
5	**3n** R=H	**4n**	0

^{a}Isolated yield. ^{b}Based on the ^{1}H NMR of the crude material.

Based on the effectiveness of the *exo*-Thorpe-Ingold effect on the chelate formation, we next examined to the benefit of the Thorpe-Ingold effect for chelate formation. We hypothesized that enyne **G** resulting from enyne **3a** and **3b** by the addition of certain structural elements should have higher tendency to form oxygen-chelate **H** compared to the parent structures **4a** and **4b** because of the Thorpe-Ingold effect exerted by the substituent R or the extra cycle (Table 2). Although enyne **3a** containing 2° hydroxyl group did not form chelate **4a** enyne **3j** closely related to **3a** but containing 3°

hydroxyl and an extra methyl group readily formed ruthenium chelate **4j** in 88% yield (entry 1). Also, 1,6-enynes **3k** and **3l** smoothly converted to ruthenium chelate **4k** and **4l** in 91% and 90% yield (entries 2 and 3). Enyne **3m** containing a 3^{o} hydroxy group formed the chelate **4m** but it decomposed during purification (entry 4). On contrary, the 2^{o} alcohol **3n** did not afforded any desired product. These examples imply that the Thorpe-Ingold effect is less effective than the *exo*-Thorpe-Ingold effect for promoting ruthenium chelate formation.



Scheme 2. Competition between two different chelate forming event

Next, we explored the competition between two different chelate-forming events starting from a common enyne substrate (Scheme 2). In this vein, we have observed that ester (Eq 1) and sulfonamide functionality (Eq 2) ligate to the nearby ruthenium alkylidene more favourably over a hydroxyl group while the ruthenium alkylidene moiety can undergo metallotropic [1,3]-shift[14] between the competing polar functional groups. Compared to the efficient chelate formation from diyne (Eq 1),[15] it was quite surprising that enyne **3q** containing monoyne afforded only metathesis product **4q** in low yield together with decomposition product (Eq 3). On the other hand, ynamide **3r** provided sulfonamide chelate **4r** when treated with **1b** whereas forming toluenesulfonyl aniline with **1a** (Eq 4). The X-ray structure of **4r** clearly shows that the sulfonamide oxygen is ligated to the ruthenium centre not the hydroxyl group and the oxygen ligand is cis to the NHC like in other hydroxy-chelated structures. These examples suggest that despite the significant beneficial effect of the structural elements to stabilize the propagating ruthenium alkylidene species, even a small structural change in these ruthenium species can cause a significant change in the fate of the reactive intermediate.

In conclusion, we have defined the propensity of oxygen-chelate formation by capturing the propagating ruthenium alkylidene intermediates with nearby hydroxyl, ether, and ester functional groups. The formation of these oxygen-chelated ruthenium alkylidene complexes is significantly affected by the steric interactions exerted by *gem*-dialkyl substituents at a certain location. If the *gem*-dialkyl substituents are located outside of the incipient cyclic arrangement of the chelates, it is defined as "*exo*-Thorpe-Ingold effect" compared to the conventional "Thorpe-Ingold effect" wherein the *gem*-dialkyl substituents are within the cycle being formed. An unusual structural feature of these oxy-gen-chelates was revealed from the X-ray structures, which show that the hydroxy and the NHC ligands are disposed in cis-orientation as opposed to trans-geometry in many other oxygen-chelates including the Hoveyda complex and the hydroxy-chelate observed by Fürstner.

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13 The hydroxy- and ether-chelated ruthenium alkylidene complexes **4c**, **4d** and **4g** are metathesis-active only at elevated temperatures. Upon treating dimethyl-2,2-diallylmalonate with **4c**, **4d** and **4g** (5 mol %) in toluene-d_8 at 100 ^{o}C, the corresponding RCM product was obtained in 76%, 65%, and 78% yields (at ~90% conversion) after 16 h, respectively, but at 45 ^{o}C in $CDCl_3$, little product formation was observed after 24 h.

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