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Extension of ring closing metathesis methodology to the synthesis of carbocyclic methyl and silyl enol ethers†

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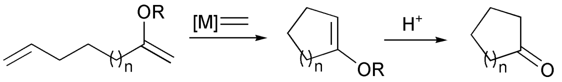
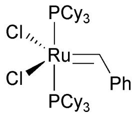
Carbocyclic methyl and silyl enol ethers (TBDMS is optimum) can be synthesised regiospecifically by ring closing metathesis using the 'second generation' Grubbs ruthenium carbene catalyst in combination with molecular sieves.

In recent times ring closing metathesis (RCM) has become a widely used and powerful tool in organic synthesis.[1,2] We considered the potential application of RCM to the synthesis of regiospecific carbocyclic enol ethers/cyclic ketones through cyclisation of a linear enol ether/alkene (Scheme 1). If this process could include the use of silyl enol ethers it would be of great synthetic utility because of the ease of preparation of the starting materials and the usefulness of the regiospecific silyl enol ether products. The recent development of the 'second generation' Grubbs ruthenium dihydroimidazole catalyst **2**,[3] which has increased reactivity with a broader range of substrates than **1**, further encouraged us to investigate this idea. Although there are a few examples of RCM of enol ether/alkene systems to give cyclic enol ether products,[4] at the start of our studies there were no examples of silyl enol ethers involved in metathesis. However, during the course of our work, Shibasaki and co-workers and Nakagawa and co-workers independently reported that **2** was capable of catalysing the RCM of alkene/silyl enol ether substrates.[5] These results will be discussed later, in conjunction with our own.



Scheme 1



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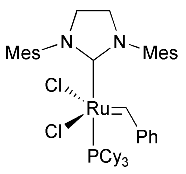
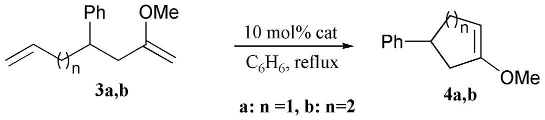


2

We initially synthesised the methyl enol ethers **3**[6] and investigated RCM. As expected catalyst **1** failed to effect cyclisation of substrate **3a** and complete decomposition to unidentified products was observed (Table 1, entry 1). However use of the second generation catalyst **2** gave low yields of cyclopentene **4a**. Simple variation of the reaction parameters showed that optimum conditions were refluxing benzene with a substrate concentration of 0.005 M. Under these conditions **4a** and **4b** were synthesised in 53 and 50% yield, respectively, after only 1 h. The remainder of the substrate appeared to decompose under the reaction conditions, however we did not make extensive further attempts to optimise the yield.

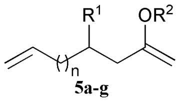
Table 1 RCM of methyl enol ethers[a]



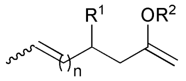
Entry	Substrate	Catalyst	Conc./M	Yield (%)
1	**3a**	**1**	0.005	0
2	**3a**	**2**	0.05	14
3	**3a**	**2**	0.005	53
4	**3b**	**2**	0.005	50

[a] For experimental details see Supporting Information.

We then wished to extend the methodology to the more easily accessible silyl enol ethers. Thus, we synthesised a range of silyl enol ethers **5a–g** to use as substrates for our investigations.[7] We initially exposed **5a** to 10 mol% **2** in refluxing benzene, but despite the substrate being completely consumed in 30 min the major product observed was in fact the isomerised alkene **6a** (as a mixture of isomers) (Table 2, entry 1).[8] We next examined the TES derivative **5b** due to the greater stability of this more hindered silyl enol ether, but similar behaviour was observed. However, this time a small amount (< 5%) of the cyclised product **7b** was formed (Table 2, entry 2). We also observed the

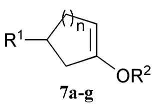


5a-g



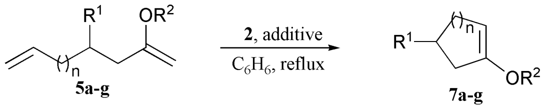
6a-g

	n	R¹	R²
a	1	Ph	TMS
b	1	Ph	TES
c	1	Ph	TBDMS
d	1	Ph	TIPS
e	1	Cy	TBDMS
f	2	Ph	TBDMS
g	3	Ph	TBDMS



7a-g

Table 2 RCM of silyl enol ethers[a]



Entry	Substrate	Conc./M	Mol% **2**	Method[b]	Yield of **6** (%)	Yield of **7** (%)
1	**5a**	0.01	10	A	31	0
2	**5b**	0.01	10	A	22	5
3	**5b**	0.01	10	B	15	15
4	**5b**	0.01	10	C	7	14
5	**5b**	0.005	20	C	5	54
6	**5c**	0.005	20	C	15	60
7	**5d**	0.005	20	C	< 5	37
8	**5e**	0.005	20	C	< 5	52
9	**5f**	0.005	20	C	—	65
10	**5g**	0.005	20	C	—	45[c]

[a] For experimental detail see ESI†. [b] A: catalyst and substrate heated in benzene at reflux; B: substrate added over 30 min to a solution of the catalyst in refluxing benzene; C: substrate added slowly over 30 min to catalyst and powdered 4 Å mol. sieves heated at reflux in benzene. [c] 23% of **7f**.

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† Electronic supplementary information (ESI) available: full experimental details. See http://www.rsc.org/suppdata/cc/b2/b208445g/

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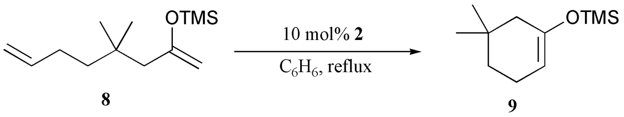
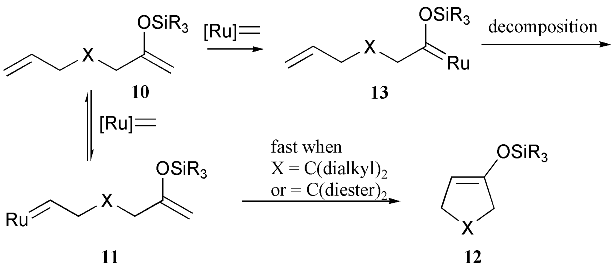
formation of some homodimer of the substrate and therefore experimented with slow addition of the substrate to a solution of the catalyst. Encouragingly, not only did this avoid the formation of homodimer but it also gave a 1 : 1 mix of **6b** and **7b** (Table 2, entry 3). At this stage we believed that the formation of the isomerised product **6** was mediated by a ruthenium hydride complex.[8] We were unsure as to the source of this complex but felt that the addition of molecular sieves to the reaction might have a beneficial effect. This was indeed borne out; addition of freshly activated 4 Å sieves to the reaction combined with slow addition of the substrate gave a 2 : 1 ratio of **7b** and **6b** in a combined yield of 21% at a substrate concentration of 0.01 M (Table 2, entry 4). The yield and product ratio were further increased to a practical 54% and 11 : 1 respectively, by raising the catalyst loading to 20 mol% and decreasing the concentration to 0.005 M (Table 2, entry 5).[9] When these optimised conditions were applied to **5a**, no improvement in yield was observed. We then turned to other silyl groups and were surprised to find *that increasing the steric bulk still further (TBDMS) led to an increase in yield to 60%* (Table 2, entry 6). Clearly the paradigm in RCM of decreasing efficiency with increasing steric bulk around the olefins did not apply in this case. Conventional wisdom prevailed in that further increases in bulk of the silyl enol ether then led to lower yields (Table 2, TIPS, entry 7). As TBDMS gave the highest yield, this group was employed with other substrates (**5e,f,g**) and was found to be generally useful. Replacing the phenyl group by a cyclohexyl group gave similar results (Table 2, entry 8). Ring closure to form six- and seven-membered ring enol ethers was also efficient although in the latter case a mixture of the seven-membered ring **7g** and six-membered ring **7f** (formed from isomerisation and subsequent ring closure)[8] was obtained.

As we were completing this study, Shibasaki and co-workers published a report of their investigations into RCM of alkene/silyl enol ether systems.[5a] Surprisingly they succeeded in cyclising trimethylsilyl enol ether/alkenes in generally > 90% yield using 7–10 mol% of **2** as catalyst. However, all of Shibasaki's substrates contained either *gem* diester substituents on the carbon backbone or a cyclic acetal linker. According to Jung these two groups in particular provide dramatically enhanced rates of cyclisation, greater even than a *gem* dialkyl group.[10] In light of this we synthesised trimethylsilyl enol ether **8** bearing a simple *gem* dialkyl group and gratifyingly it gave an 89% yield of the corresponding cyclised derivative **9** using only 10 mol% of **2**. Slow addition or molecular sieves were not required. This clearly shows the large *gem*-dialkyl effect observable in RCM and illustrates the importance of our discovery that molecular sieves, slow substrate addition and the use of TBDMS enable the cyclisation of alkene/silyl enol ethers which are not particularly prone to cyclisation using **2**.



We propose a possible rationalisation of these results (Scheme 2). Initial reaction of the metal carbene with **10** is most likely to occur with the less sterically hindered alkene to give **11** which can react with the silyl enol ether in a slow cyclisation step to give **12**. Cyclisation is slow because there is an inherent electronic preference for the enol ether to react with the metal carbene with the opposite regioselectivity to that required for ring closure.[11] This electronic bias was revealed in the intermolecular metathesis reaction of ruthenium alkylidenes with enol ethers which lead exclusively to the ruthenium Fischer carbenes; no cross metathesis product being formed.[11] If the substrate bears groups which enhance cyclisation rates (*e.g*, X = C(alkyl)$_2$, C(ester)$_2$), **12** is formed uneventfully but in the absence of such groups (*e.g*. X = CHPh) **11** can undergo reversion and give back **10**. The metal carbene can now react either with **10** in the same way as before or with the silyl enol ether moiety and give the Fischer carbene **13** which will not react further and may decompose. Indeed Grubbs has recently indicated that the thermal stability of species analogous to **13** is considerably lower than those such as **11**.[11] A decomposition process will not only consume the substrate but also the catalyst. TMS enol ethers, the least hindered of all, will react with the metal carbene fastest and this could account for the poor results obtained with **5a**. TBDMS enol ethers may provide the optimum steric hindrance to minimise reaction leading to **13** but still allow cyclisation of **11** to give **12**.[12]



Scheme 2

In summary we have successfully synthesised carbocyclic methyl enol ethers using RCM for the first time. We have also developed RCM conditions under which alkene/silyl enol ethers can be cyclised and have shown that for substrates with a high propensity for cyclisation, TMS enol ethers can be employed but for general substrates TBDMS enol ethers are optimum. The formation of regiospecific silyl enol ethers which have high synthetic utility renders this process very useful.

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