Unexpected Results of a Turnover Number (TON) Study Utilising Ruthenium-Based Olefin Metathesis Catalysts

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Abstract: A turnover number (TON) study of ruthenium-based metathesis catalysts has been conducted for ring-closing metathesis (RCM) in dilute solution. Unexpectedly the results indicate that 1st generation metathesis catalysts can give higher TON in RCM of simple unsubstituted terminal olefins than their second generation counterparts. In particular, the 1st generation Hoveyda–Grubbs catalyst showed unexpectedly high activity, particularly when compared to the 2nd generation catalysts.

Keywords: alkenes; homogeneous catalysis; metathesis; ring-closing metathesis (RCM); ruthenium

Introduction

With the advent of efficient catalysts, the olefin metathesis reaction has emerged as one of the most powerful carbon-carbon bond forming methods in organic synthesis. This is primarily due to the disclosure of the Schrock molybdenum-based catalyst,[1] followed by the ruthenium-based catalyst **1** by Grubbs and co-workers in the mid 1990s,[2] which combined remarkable functional group tolerance and general stability. The replacement of one of the phosphine donors with a stronger σ-donating carbene ligand, in the belief that electron-deficient intermediates would be better stabilised, led to the 2nd generation ruthenium benzylidene complex **2**. In a systematic study of catalysts with the general formula $L^1L^2X_2$ Ru=CHR it was found that all ligands coordinated to the metal centre can individually and greatly influence the catalytic performance of a particular system.[3] It was shown that the 2nd generation catalysts (i.e., **2**), exhibit improved stability/functional group tolerance and the ability to efficiently form tri- and tetrasubstituted double bonds. Further developments led to the serendipitous discovery of (pre)catalyst **3**,[4] and later the phosphine-free alkylidene **4** bearing a chelating isopropoxybenzylidene ligand.[5] These (pre)catalysts display good recyclability properties and, in particular, **4** has been shown to perform particularly well in certain cross metathesis (CM) reactions of electron-deficient alkenes, where catalyst decomposition is an important issue.

The commercially available ruthenium-derived metathesis catalysts (Figure 1) have been used extensively in organic synthesis but the high cost and the high catalyst loadings that are typically used, generally 1–10 mol %, represent an uneconomic use of the catalyst systems. With emphasis on 'greener' chemistry it is desirable to utilise reduced catalyst loadings in order to reduce costs for industrial processes.

Of the many transformations involving olefin metathesis, most work has concentrated on the use of **1** and **2**, due to their commercial availability. Surprisingly, to the best of our knowledge no detailed reports exist comparing the activity of these (pre)catalysts to **3** and **4**, due in part to the same 14-electron intermediate being responsible for the metathesis activity of **1** and **3**, **2** and **4**. Intriguingly there have also been contradictory re-

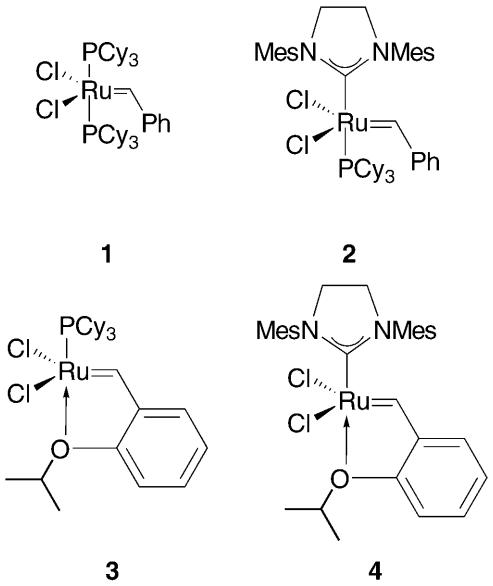

Figure 1. Ruthenium-based olefin metathesis precatalysts.

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ports in quantifying catalytic activity and efficiency of ruthenium-based olefin metathesis (pre)catalysts.[6]

Almost all previously published studies base the activity of (pre)catalysts on initiation rates with a few standard metathesis reactions.[7] As a counterpoint to these investigations we have focused on attempts to maximise the turnover number (TON) of a given RCM catalyst. In particular, we were interested to what extent the isopropoxystyrene ligand present in **3** and **4** affect TONs when compared to their phosphine-containing analogues **1** and **2**. The TON describes the degree of activity of a catalyst; and the catalyst efficiency is described though its turnover frequency (TOF in h^{-1}). Like all metathesis reactions, RCM is a reversible process. However when the by-product of the metathesis reaction (here ethene) is allowed to escape, the reaction is rendered essentially irreversible. These metathesis events cannot be followed and therefore the total turnover number for an individual catalyst molecule cannot be determined with any given accuracy. Therefore the TON represents *the average number of substrate molecules converted into the cyclised product per molecule of (pre)catalyst*.[8]

Studies by Grubbs and co-workers have shown that different phosphine-containing analogues of complexes **1** and **2** affect the rate of initiation,[9] and studies by Blechert and co-workers have uncovered basic rules for substitution of the isopropoxybenzylidene ligand to effect initiation in (pre)catalysts of type **3** and **4**.[10] We were particularly interested in the effect the substitution of this type of ligand by others would have on the TON, in particular we were interested in whether the activity of the catalyst could be influenced by steric or electronic effects incorporated into the chelating isopropoxystyrene ligand.

A point that is commonly overlooked is that the fastest initiating (pre)catalyst *does not necessarily* afford the highest chemical yield of a particular transformation with the lowest catalyst loading,[11] of course, the lifetime of the propagating species plays an important role. We were interested in investigating the lower catalyst limit to effect a ring closing metathesis transformation, to determine reactivity profiles and to provide a method for quantifying activity for the catalysts most commonly used in olefin metathesis reactions.

Results and Discussion

We first examined the activities of the catalysts **1**, **2**, **3** and **4** in RCM reactions of simple terminal alkenes. In order to obtain meaningful comparisons specific conditions were developed. Initial studies were concerned with the RCM of **5**, to yield the 5-membered ring product **6**. The specific conditions employed (0.05 M in CH_2Cl_2, N_2 atmosphere, reflux, 14 h) were chosen to reflect the conditions most commonly used in olefin metathesis reactions, and the conversions were monitored by HPLC. Substrate/catalyst mole ratio (S/C mole ratio) of between 5,000 and 10,000 [0.02–0.001 mol % (pre)catalyst] were chosen with the conversions being determined by HPLC, and the TON determined.

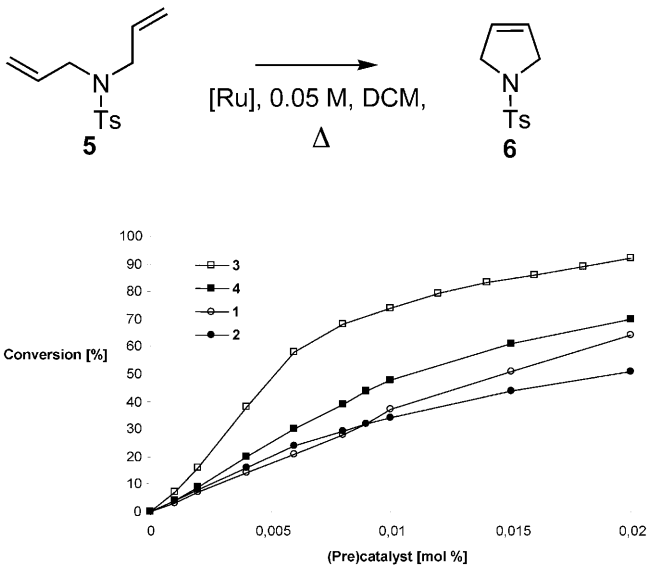


Figure 2. RCM of **5**: Conversion as a function of (pre)catalyst loading.

From the first results (Figure 2) it is clear that even when relatively small amounts of (pre)catalyst are used, high conversions can be obtained. When comparing the conversions obtained from the different (pre)catalysts utilising identical loadings it is clear that (pre)catalyst **3** delivers higher conversions at lower catalyst loadings in the RCM of **5** to **6**.

For example only 0.01 mol % of **3** is required to effect a 75% conversion whereas *at least twice* this (pre)catalyst loading is required to achieve the same conversion with the other (pre)catalysts. Furthermore, at a catalyst loading of 0.006 mol %, (pre)catalyst **3** delivers a conversion of 60% whilst the other (pre)catalysts require a *loading of at least twice this* to achieve the same conversion.

The TONs that were obtained during the RCM of **5** are shown in Figure 3. The activity of the catalysts follows the trend $\mathbf{3} > \mathbf{4} > \mathbf{1} > \mathbf{2}$. The trend is somewhat surprising since previous reports have shown **2** to display higher activity, however most previous studies have been based on efficiency or TOF. One trend already recognised by Grubbs et al., is that catalyst activity is often contrary to catalyst efficiency. Indeed, it is interesting to note that the order of catalyst efficiency has previously been measured as $\mathbf{1} \gg \mathbf{2} > \mathbf{4} \approx \mathbf{3}$.[10] What is clear is that higher TONs are obtained with the (pre)catalysts containing the *chelating isopropoxystyrene ligand*.

It is thought that the same catalytically active 14-electron species of **1** and **3**, **2** and **4** are operating and that the different activities of the (pre)catalysts can be reasoned

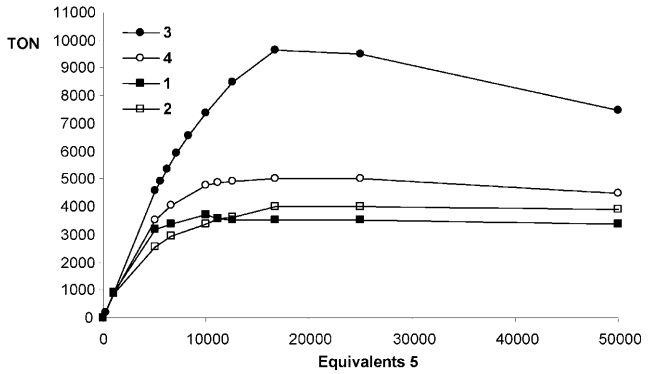


Figure 3. TON for RCM of **5** with (pre)catalysts **1**, **2**, **3** and **4**.

by different catalyst efficiencies. Studies by Grubbs et al. have shown that where the concentration of the propagating methylidene is high, decomposition of the complex is also increased.[12] In especially efficient catalysts (those with high initiation rates), the concentration of the active 14-electron species at any point is high, and this could be connected to faster decomposition rates, when compared to slower initiating species.[13]

With this in mind we examined the activities of sterically and electronically modified analogues of **3** and **4**. We proposed that the initiation of the modified analogues operate by the same mechanism. We expected (pre)catalysts **7** and **12**, that carry an electron-donating substituent and therefore have lower efficiency than unsubstituted analogues **3** and **4**, would display a higher activity than the unsubstituted variants.

Again RCM of **5** was used to test the hypothesis and the reactions were carried out in an identical manner as to those previously performed. To guarantee reproducibility the results were each repeated four times (Table 1).

Surprisingly, electronically modified (pre)catalysts **7**–**9** and **12**–**14** all delivered approximately the same TON as their unsubstituted counterparts (Table 2). Only sterically modified derivatives **10** and **15** showed any difference when compared to their unsubstituted analogues, delivering lower TON, presumably as a result of faster initiation rates. Complex **16** displayed no activity whatsoever.

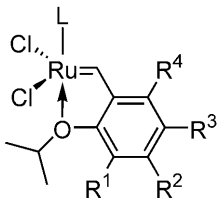
The electronically modified analogues delivered similar TONs to each other. In the case of the sterically modified (pre)catalysts, those that display higher initiation rates, lead to a higher concentration of the 14-electron active species at any point in time and therefore *exhibit a faster decomposition rate* resulting in lower TON.

In summary, electronic modification of the isopropoxystyrene led to (pre)catalysts that display different TOF and deliver similar TONs when compared to each other, and (pre)catalysts with steric modification of the isopropoxybenzylidene display greatly increased TOF and also show a decrease in TON, delivering values similar to their parent phosphine-containing systems. Therefore the general trend of activity is **3** = **12**, **13**, **14** > **4** = **7**, **8**, **9** > **1** ≈ **15** > **2** ≈ **10**.

Considering that the electronic effect of the chelating isopropoxybenzylidene had no great effect on the TON, we were interested in investigating whether the TON could be improved in the case of the 1st generation catalysts by exchange of the phosphine ligand. Two new (pre)catalysts were prepared (Figure 3) bearing different phosphine ligands. The phosphines chosen were $P(i\text{-}Pr)_3$, a sterically less demanding phosphine compared to $P(Cy)_3$, but electronically similar, and the more sterically demanding cyclohexyl phoban ligand.[14] Both catalysts were prepared in good yields using standard reaction conditions (see Experimental Section for details), and their activity tested in the RCM reaction of **5**.

From the results (Table 3) it can be seen that no significant differences in activity between the (pre)catalyst **18** and (pre)catalyst **3** were observed. These results suggest

Table 1. Parent ruthenium (pre)catalysts **3** and **4** and their sterically and electronically modified analogues.

L = IHMES							L = PCy_3				
Entry	R^1	R^2	R^3	R^4	(Pre)catalyst		R^1	R^2	R^3	R^4	(Pre)catalyst
1	H	H	H	H	**4**		H	H	H	H	**3**
2	H	O-*i*-Pr	H	H	**7**		H	O-*i*-Pr	H	H	**12**
3	H	H	O-*i*-Pr	H	**8**		H	H	O-*i*-Pr	H	**13**
4	H	O-*i*-Pr	O-*i*-Pr	H	**9**		H	O-*i*-Pr	O-*i*-Pr	H	**14**
5	OMe	H	H	H	**10**		OMe	H	H	H	**15**
6	H	H	H	O-*i*-Pr	**11**[a]		H	H	H	O-*i*-Pr	**16**

[a] Could not be synthesised.

Table 2. RCM of **5**: TON of modified metathesis initiators.

Entry	(Pre)catalyst	Conversion [%][a]					TON	TOF [h^{-1}][b]
		1st	2nd	3rd	4th	Average		
1	**1**	64	53	69	70	64	3200	3000
2	**2**	54	49	51	53	52	2600	130
3	**3**	93	91	92	92	92	4600	60
4	**15**	59	65	69	66	65	3250	214
5	**12**	88	88	87	85	87	4350	34
6	**13**	84	82	82	82	83	4150	103
7	**14**	86	86	86	86	86	4300	n/d
8	**16**	–	–	–	–	–	–	–
9	**4**	65	67	67	62	65	3250	60
10	**10**	48	50	47	51	49	2450	150
11	**7**	66	65	59	58	62	3100	11
12	**8**	60	56	63	60	60	3000	48
13	**9**	57	58	61	55	58	2900	n/d

[a] Determined by HPLC.
[b] See ref.[10]

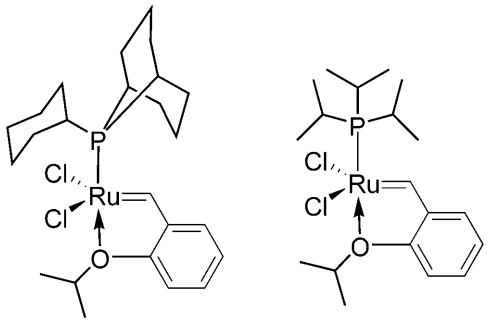


Figure 4. (Pre)catalysts **17** and **18**.

that the less sterically demanding P(*i*-Pr)$_3$ ligand[15] *does not* lead to increase in decomposition of the catalyst as very similar TONs were obtained when compared to (pre)catalyst **3**.[16] However, (pre)catalyst **17** displayed a slightly lower activity than **3**, delivering lower TONs presumably due to its higher initiation rate arising from the more sterically demanding cyclohexyl phoban ligand.[17]

Following these results we investigated different substrates for RCM in order to determine if the trends in catalyst activity were general. The electronically modified (pre)catalysts had been shown not to display increased TONs and the sterically modified catalysts displayed decreased TONs, so only (pre)catalysts **1**, **2**, **3** and **4** were investigated.

The next substrate investigated was **17** which yields an 8-membered system **18**, previously used to determine relative catalyst efficiencies.[10] Again, reactions were carried out utilising previously developed conditions. The first unexpected observation was that the 1st generation catalysts gave much high conversions (and therefore TON) than their 2nd generation counterparts (Figure 5).

Table 3. RCM of **5** with (pre)catalysts **1**, **3**, **17** and **18**.

Entry	Substrate	Catalyst	Loading [mol %]	Conversion [%][a]	TON
1	**5**	**1**	0.006	21	3500
2	**5**	**3**	0.006	59	9894
3	**5**	**17**	0.006	40	6667
4	**5**	**18**	0.006	62	10333
5	**5**	**1**	0.01	35	3581
6	**5**	**3**	0.01	76	7598
7	**5**	**17**	0.01	65	6500
8	**5**	**18**	0.01	80	8000
9	**5**	**1**	0.02	67	3372
10	**5**	**3**	0.02	92	4595
11	**5**	**17**	0.02	88	4400
12	**5**	**18**	0.02	90	4500

[a] Conversion determined by HPLC.

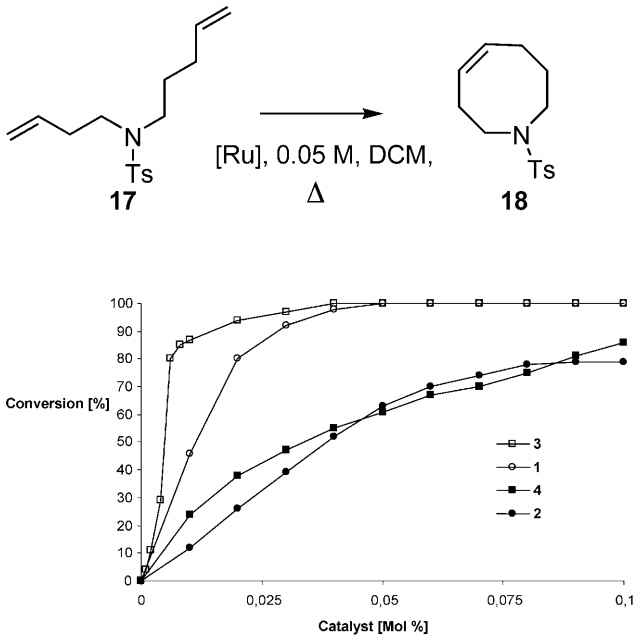


Figure 5. RCM of **17**: Conversion as a function of (pre)catalyst loading.

Interestingly, with (pre)catalysts **1** and **3** the conversion decreases by only approximately 10% when reducing the catalyst loadings from 0.1 to 0.01 mol %; however, precatalysts **2** and **4** show conversion losses of more than 60% over the same region. Below catalyst loadings of 0.025 mol % the superiority of (pre)catalyst **3** becomes obvious. Utilising a catalyst loading of 0.01 mol % delivers a conversion of 87%. To achieve the same conversion with the 2nd generation catalysts requires a loading of *over ten times this amount*.

Figure 6 displays the TON *vs.* S/C ratio. The catalysts **1**, **2** and **4** all reach their maximum TON at around 0.01 mol % (S/C = 10000), however catalyst **3** reaches its maximum TON (13000) at 0.006 mol %. With this substrate there is a clear trend in activity of the catalysts following the order **3** > **1** > **4** > **2**. Importantly, the *1st generation (pre)catalysts outperform the 2nd generation catalysts.*

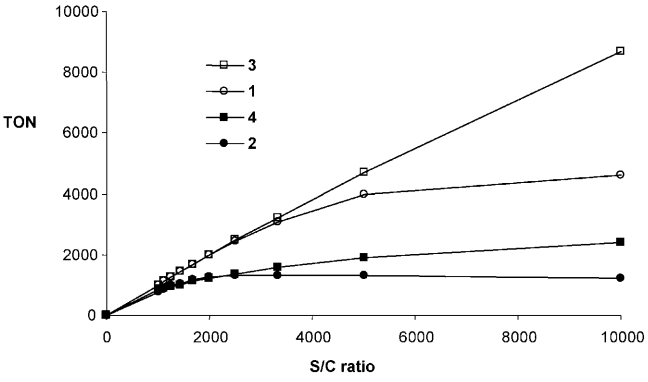


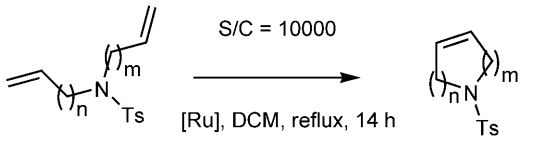
Figure 6. RCM of **17**: TON compared to substrate catalyst ratio.

Two further tosylamide substrates were investigated, **19** and **21**, both delivering a 7-ring product. Investigations were carried out under the same conditions, utilising 0.01 mol % of the corresponding catalyst. The results are listed in Table 4, for purposes of comparison the results for substrates **5** and **17** have been included.

The first point to note is that different substrates all deliver different TONs, even when the catalysts are compared at the same loading. When comparing the order of substrates delivering the highest TON the order follows **21** > **17** > **5** > **19**. The difference between the substrate reactivity of **19** and **21** and between that of **5** and **17** can be explained by considering the intermediate formed during the RCM reaction. In both substrates that show lower reactivity to RCM, **5** and **19**, an intramolecular coordination can occur as has previously been described.[10]

From these results a general sequence of relative catalyst activities can be derived. In the case of the substrates **5** and **19** the activity of the catalysts follows the trend **3** ≫ **4** > **2** ≈ **1**; and in the case of substrates **17** and **21** the trend of activity follows the order **3** ≫ **1** > **4** > **2**. In the case of substrates **17** and **21** the activity of the 1st generation Grubbs catalyst **1** is higher than that

Table 4. TON of (pre)catalyst **1**, **2**, **3** and **4** in the RCM of tosylamides **5, 17, 19** and **21**.



5 n = 1, m = 1
17 n = 2, m = 3
19 n = 1, m = 3
21 n = 2, m = 2

6 n = 1, m = 1
18 n = 2, m = 3
20 n = 1, m = 3
22 n = 2, m = 2

Entry	Substrate	Catalyst	Conversion [%][a]	TON
1	**5**	**1**	37	3700
2	**5**	**2**	36	3600
3	**5**	**3**	76	7600
4	**5**	**4**	49	4900
5	**17**	**1**	46	4600
6	**17**	**2**	12	1200
7	**17**	**3**	87	8700
8	**17**	**4**	24	2400
9	**19**	**1**	4	400
10	**19**	**2**	3	300
11	**19**	**3**	16	1600
12	**19**	**4**	5	500
13	**21**	**1**	60	6000
14	**21**	**2**	51	5100
15	**21**	**3**	80	8000
16	**21**	**4**	54	5400

[a] Conversion determined by HPLC.

of the 2nd generation catalysts, however, with substrates **5** and **19** it displays the lowest activity. The ruthenium complexes with isopropoxystyrene ligands afford higher TONs than their phosphine-containing counterparts and most importantly (pre)catalyst **3** in all cases *yields the highest TON* of all the (pre)catalysts.

We were also interested in testing more challenging substrates. The utilisation of RCM for the synthesis of cyclic amino acid derivatives was first reported by Grubbs et al.[18] and we were interested in utilising these more challenging substrates to examine the relative activities of the catalysts under investigation. As test substrates we chose the allylglycine derivatives **22**, **24** and **26** to furnish 6-, 7- and 8-membered ring systems. The compounds display a structural resemblance to the *N*-tosylamides, but contain an additional ester functionality which has frequently been reported to coordinate and deactivate the metal centre during the metathesis reaction.[19] Deactivation of the metal centre can occur through coordination of the ester carbonyl to the metal centre in the alkylidene intermediate.[20] The desired compounds were readily available through a three-step synthetic sequence, starting form commercially available allylglycine.[21]

The RCM of the allylglycine derivatives were carried out under the standard conditions and the results have been summarized in Table 5.

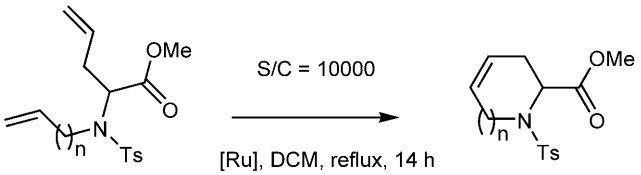
Interestingly the lowest TONs were obtained with catalyst **1**, suggesting poor tolerance to the ester functionality and a deactivation of the catalyst. (Pre)catalyst **3**, which previously displayed the highest activity in the RCM of substrates **5**, **17**, **19** and **21**, demonstrates comparable activity to catalysts **2** and **4**. Catalysts **2** and **4** also show comparable activity to each other, displaying similar TONs as were observed with the tosylamides, suggesting that the ester group has little effect on the activity of these catalysts. It is interesting to note that (pre)catalyst **4** performed slightly better than the other catalysts in these examples and again the (pre)catalysts with a chelating isopropoxystyrene *outperform their phosphine-containing counterparts in all cases.*

In the light of these results, we were interested to investigate why substitution of a PCy_3 ligand for a chelating isopropoxystyrene leads to catalysts displaying higher activity (**2** and **4**).

In order to measure the relative catalyst stability a study concerning the effect of temperature was undertaken. It was hoped that these investigations would deliver guidelines for the relative thermal stability of the precatalysts in solution in the presence of an RCM substrate. Utilisation of 0.01 mol % of catalyst with substrate **5** and conducting the reactions in refluxing 1,2-dichloroethane was investigated (Table 6). A sharp drop in TON was observed for **1** with conversion dropping from 66% to $<25\%$. The same trend was found, but to a lesser extent, for (pre)catalysts **2** and **3**. However at this elevated temperature (pre)catalyst **4** showed an identical result to the reaction in refluxing DCM, thus demonstrating the higher thermal stability of this complex and (pre)catalyst **2** in solution when compared to the other (pre)catalysts. These results suggest that the stability of the formed active species of the catalyst is not the only factor that effects the relative activities of the (pre)catalysts.

It has been suggested that the different activities of the (pre)catalysts **3** and **4** carrying the isopropoxystyrene ligand, compared to their phosphine containing counterparts **1** and **2**,[22] are due to the return of the disassociating ligand during the catalytic cyclic, e.g., PCy_3 in the

Table 5. RCM of allylglycine derivatives **22**, **24** und **26**.



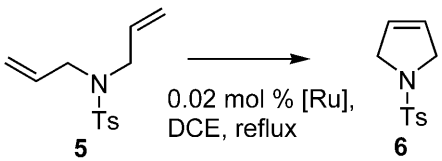
22 n = 1
24 n = 2
26 n = 3

23 n = 1
25 n = 2
27 n = 3

Entry	Substrate	Catalyst	Conversion [%][a]	TON
1	**22**	**1**	11	1100
2	**22**	**2**	17	1700
3	**22**	**3**	15	1500
4	**22**	**4**	16	1600
5	**24**	**1**	33	3300
6	**24**	**2**	42	4200
7	**24**	**3**	36	3600
8	**24**	**4**	48	4800
9	**26**	**1**	36	3600
10	**26**	**2**	49	4900
11	**26**	**3**	46	4600
12	**26**	**4**	54	5400

[a] Determined by HPLC.

Table 6. RCM of **5**: Influence of the reaction temperature on the activity of the (pre)catalysts **1**, **2**, **3** and **4**.



5 **6**

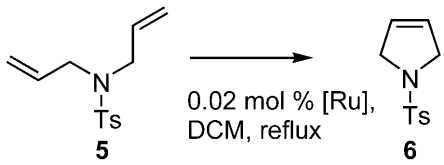
Entry	Catalyst	TON[a]	TON[b]
1	**1**	3200	1200
2	**2**[c]	10000	6500
3	**3**	2600	2300
4	**4**	3250	3450

[a] Determined after 14 hours in dichloromethane at 50 °C.
[b] Determined after 14 hours in 1,2-dichloroethane at 80 °C.
[c] 0.006 mol % (pre)catalyst utilised.

case of **1** and **2** and the isopropoxybenzylidene in the case of **3** and **4**. It was assumed that following its dissociation the free phosphine can then re-coordinate to the metal centre in preference to an olefin binding, and hence decrease activity. We recognise that the existence of free phosphine in solution under the reaction conditions could possibly account for the lower relative activity of **1** and **2** when compared to **3** and **4**. By carrying out the RCM of substrate **5** in the presence of excess CuCl, a phosphine scavenger, phosphine reassociation would be prevented, allowing the rebinding of phosphine during the reaction to be investigated through the TON obtained in the presence and absence of free phosphine. When reactions were run under the standard conditions in the presence of CuCl, the TON only differed minimally when compared to those experiments undertaken without CuCl present in the reaction, suggesting that under the conditions used to determine the TON the catalysts **1** and **2** are *not influenced* by the reassociation of the phosphine ligand during the catalytic cycle.

It has also been proposed that reassociation of the isoproxystyrene ligand during the catalytic cycle, regenerating the starting precatalyst, could be the reason for the increased activity of **3** and **4** when compared to **1** and **2**. To test this theory the RCM of substrate **5** with **1** and **2** was undertaken in the presence of an equimolar quantity of the isopropoxystyrene in the presence of CuCl (Table 7). It was thought that following dissociation of the PCy_3, which would be captured by the excess CuCl in the reaction mixture, the isopropoxystyrene ligand could coordinate and generate *in situ* (pre)catalysts **3** and **4**, and therefore afford increased TON. Interestingly, the same TONs were obtained as was seen when no additives were used. From these results it can be suggested that under the reaction conditions utilised reassociation of the chelating isopropoxystyrene has *no decisive influence* on the activities of the precatalysts **3** and **4**.

Table 7. RCM of **5**: Influence of the reaction conditions on the activity of the (pre)catalysts **1**, **2**, **3** and **4**.



Entry	Catalyst	TON	TON[a]	TON[a],[b]
1	**1**	3300	3150	3200
2	**2**[c]	10000	9667	–
3	**3**	2800	2650	2600
4	**4**	3300	3350	–

[a] Three equivalents CuCl added.
[b] One equivalent *ortho*-isopropoxystyrene added.
[c] 0.006 mol % (pre)catalyst utilised.

From the results obtained it can be suggested that, under the reaction conditions used, reassociation of neither the PCy_3 ligand nor the isopropoxybenzylidene occurs and that these pathways have no influence on the activity of the precatalysts. Assuming that the propagating species emerging from **1** and **3**, **2** and **4** are identical, what could the reasons be for their displayed differences in activity? One possible explanation could lie in different initiation mechanisms between **1** and **3**, **2** and **4**. Scheme 1 represents a mechanism for these events.

Firstly the activation of the precatalysts **3** and **4**, as postulated by Hoveyda et al.,[22] proceeds by opening of the Ru–O chelate and the development of a vacant coordination site and intermediates **3a** and **4a**. Concomitantly a rotation takes place around the C1–C2 bond and the isopropoxy group rotates into an orientation away from the metal centre. In the case of **3a**, we postulate that this forms a discrete intermediate. This suggestion is supported by complex **16**, which is readily synthesised from **1**, but displays no metathesis reactivity, presumably because upon rotation of the chelating isopropoxystyrene no open coordination site is available. However, the analogous 2nd generation complex **11** could not be isolated, presumably due to unfavourable steric interactions between the isopropoxy ether and the sterically demanding IHMES (Figure 7).

The formed species **3a** and **4a** are in equilibrium with stable precatalysts **3** and **4**. In contrast to the precatalysts **3** and **4**, activation of **1** and **2** proceeds directly following dissociation of the PCy_3 ligand to give intermediate **1a** or **2a**,[23] with decomposition of this intermediate in competition with olefin binding. The differences in the activities between both precatalysts with a chelating isopropoxystyrene and the analogous PCy_3-containing catalysts and between the 1st and 2nd generation (pre)catalysts can be explained by the different lifetimes and stabilities of the emerging intermediates, and the resulting concentrations of the 14-electron propagating species **29** or **30**.

While the alkylidene complexes **3a** and **4a** are in equilibrium with the stable precatalysts **3** and **4**, the coordination of the olefins to the complex is in competition with the decomposition of the 14-electron species **1a** and **2a**. We believe that **1** and **2** provide a higher concen-

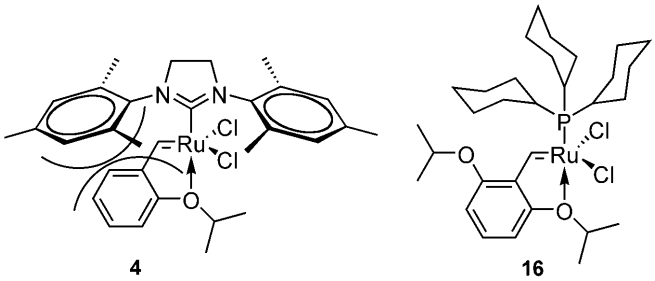
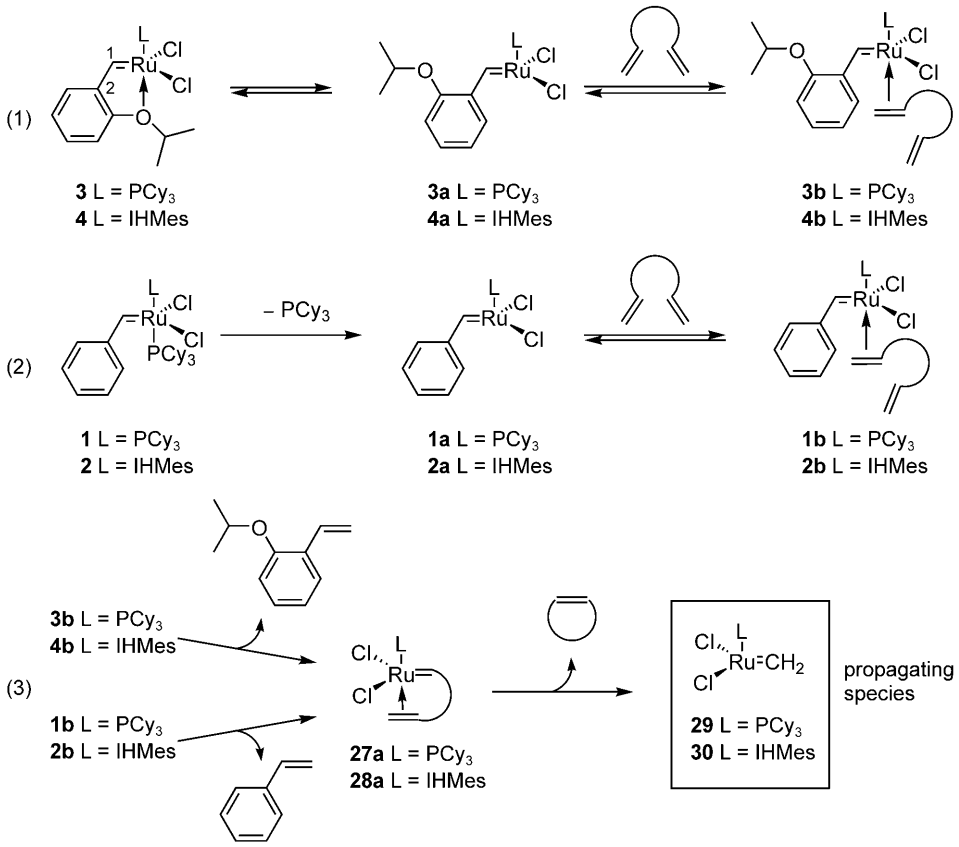


Figure 7. Diagram to represent sterically demanding IHMES compared to (pre)catalyst **16**.



Scheme 1. Mechanism for RCM of terminal alkenes.

tration of the propagating methylidene species and accordingly display a lower activity when compared to pre-catalysts **3** and **4**. The more sterically demanding IHMES ligand in comparison to PCy_3,[24] could also impede the coordination of olefins to intermediate **4a**, leading to higher decomposition rates of this ruthenium complex in comparison to **3a**.

Therefore (pre)catalysts **1** and **2** produce a higher concentration of the propagating methylidene, particularly when compared to (pre)catalyst **3**. The reason behind the increased activity of **4** compared to **2** can be understood by the decomposition pathway recently proposed.[1] With no phosphine present, (pre)catalyst **3** can display a longer propagating lifetime. (Pre)catalyst **3** can be regarded as a 'slow release' system, where the metal is delivered to the olefin, affording only small amounts of the propagating species at any one time and therefore minimising bimolecular decomposition pathways, therefore maximising TON.

Conclusion

A study of TON in solution utilising ruthenium-based olefin metathesis catalysts has been completed and provided unexpected results. In some examples presented the 1st generation catalysts gave higher TONs than the so-called more active 2nd generation catalysts although displaying very different initiation profiles, and consistently afford higher results with respect to TON.

The order of activity of the (pre)catalysts can be rationalised through the stability and the delivered concentration of the propagating species. The stability and activity of the intermediate reactive species is substantially altered by the steric and electronic characteristics of the neutral ligand remaining at the metal centre. In all examples *(pre)catalysts **3** and **4** displayed higher activity* than their phosphine-containing counterparts **1** and **2**. Further investigations including the synthesis of less sterically demanding NHC ligands are currently underway.

Experimental Section

General Remarks

All catalysts were prepared according to the previously published standard procedure.[10]

Synthesis of 17

The general procedure was followed using [(PhobCy)$_2$(Cl)$_2$-Ru=CHPh][17] (87 mg, 0.123 mmol), 2-isopropoxystyrene (40 mg, 0.246 mmol) and CuCl (12 mg, 0.121 mmol) in CH_2Cl_2 (7 mL). Column chromatography (CH_2Cl_2) gave **17** as a brown solid; yield: 45 mg (68%). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta =$ 17.64 (d, J = 1.5 Hz, 1H), 7.66 (m, 2H), 7.08 (m, 2H), 5.30 (m, 1H), 2.79 (m, 2H), 2.49–1.31 (series of multiplets, 29H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 283.3$ (CH), 152.7 (C), 144.7 (C), 129.9 (CHAr), 123.0 (CHAr), 122.8 (CHAr), 113.4 (CHAr), 75.6 (CH), 33.4 (CH), 29.0 (CH_2), 28.3 (CH_2), 27.7–20.9 (phoban ligand resonances); ^{31}P ($CDCl_3$, 200 MHz): $\delta =$ 37.64; IR (Nujol): $\nu = 2929, 2855, 1702, 1589, 1451$ cm^{-1}; HR-MS: calcd: 544.0996; found: 544.0991.

Synthesis of 18

The general procedure was followed using [(P-*i*-Pr$_3$)$_2$(Cl)$_2$-Ru=CHPh][25] (37 mg, 0.063 mmol), 2-isopropoxystyrene (20 mg, 0.127 mmol) and CuCl (6 mg, 0.063 mmol) in CH_2Cl_2 (4 mL). Column chromatography (CH_2Cl_2) gave **18** as a brown solid; yield: 15 mg (50%). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta =$ 17.39 (d, $J = 4.5$ Hz, 1H), 7.68–7.59 (m, 2H), 7.11–7.05 (m, 2H), 5.28 (pentet, $J = 6.5$ Hz, 1H), 2.70–2.59 (m, 3H), 1.81 (d, $J = 6.5$ Hz, 6H) 1.46, (q, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): $\delta = 279.6$ (CH), 153.0 (C), 144.0 (C), 129.7 (CHAr), 122.7 (CHAr), 122.6 (CHAr), 113.5 (CHAr), 25.7 (CHP), 20.1 (CH_3); ^{31}P NMR ($CDCl_3$, 200 MHz): $\delta = 57.51$; IR (Nujol): $\nu = 2963, 2932, 2874, 1588, 1475, 1452$ cm^{-1}; HR-MS: calcd: 480.0683; found: 480.0690.

General Procedure for RCM

All substrates were synthesised according to previously published methods,[26] and purified by column chromatography (twice) before kugelrohr distillation. All substrates were freshly distilled immediately before use.

An accurately weighed sample (six-figure analytical balance) of solid catalyst was dissolved in toluene to obtain a concentration of 1 mg/1 mL. Well determined volumes of these solutions were introduced *via* a Gilson Pipetteman under nitrogen to the preheated (50 °C) 0.05 M solutions of substrate in DCM under an inert atmosphere (N_2). The reaction mixtures were stirred at reflux for 14 hours and the progress of the metathesis reactions was measured by HPLC.

HPLC: Waters 600; Autosampler Waters 717; column: RP-7 C-18, (4 mm), particle size: 7 μm; PDA detector Waters 991, $\lambda = 254$ nm. MeOH/$H_2O = 8:2$; flow rate 0.8 mL/min; retention times (min): 3.49 (**6**), 4.59 (**5**), 5.88 (toluene). MeOH/$H_2O = 8:2$; flow rate 0.8 mL/min; retention times (min): 4.19 (**18**), 4.80 (toluene), 5.41 (**17**). MeOH/$H_2O = 7:3$; flow rate 1.5 mL/min; retention times (min): 3.52 (**20**), 4.87 (toluene), 6.23 (**19**). MeOH/$H_2O = 7:3$; flow rate 1.5 mL/min; retention times (min): 3.62 (**22**), 6.10 (**21**), 7.42 (toluene). MeOH/$H_2O = 8:2$; flow rate 1.2 mL/min; retention times (min): 3.30 (**23**), 4.39 (**22**), 5.56 (toluene). MeOH/$H_2O = 9:1$; flow rate 0.8 ml/min; retention times (min): 4.25 (**25**), 4.94 (**24**), 5.81 (toluene). MeOH/$H_2O = 9:1$; flow rate 0.8 mL/min; retention times (min): 4.58 (**27**), 5.14 (**26**), 5.73 (toluene).

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