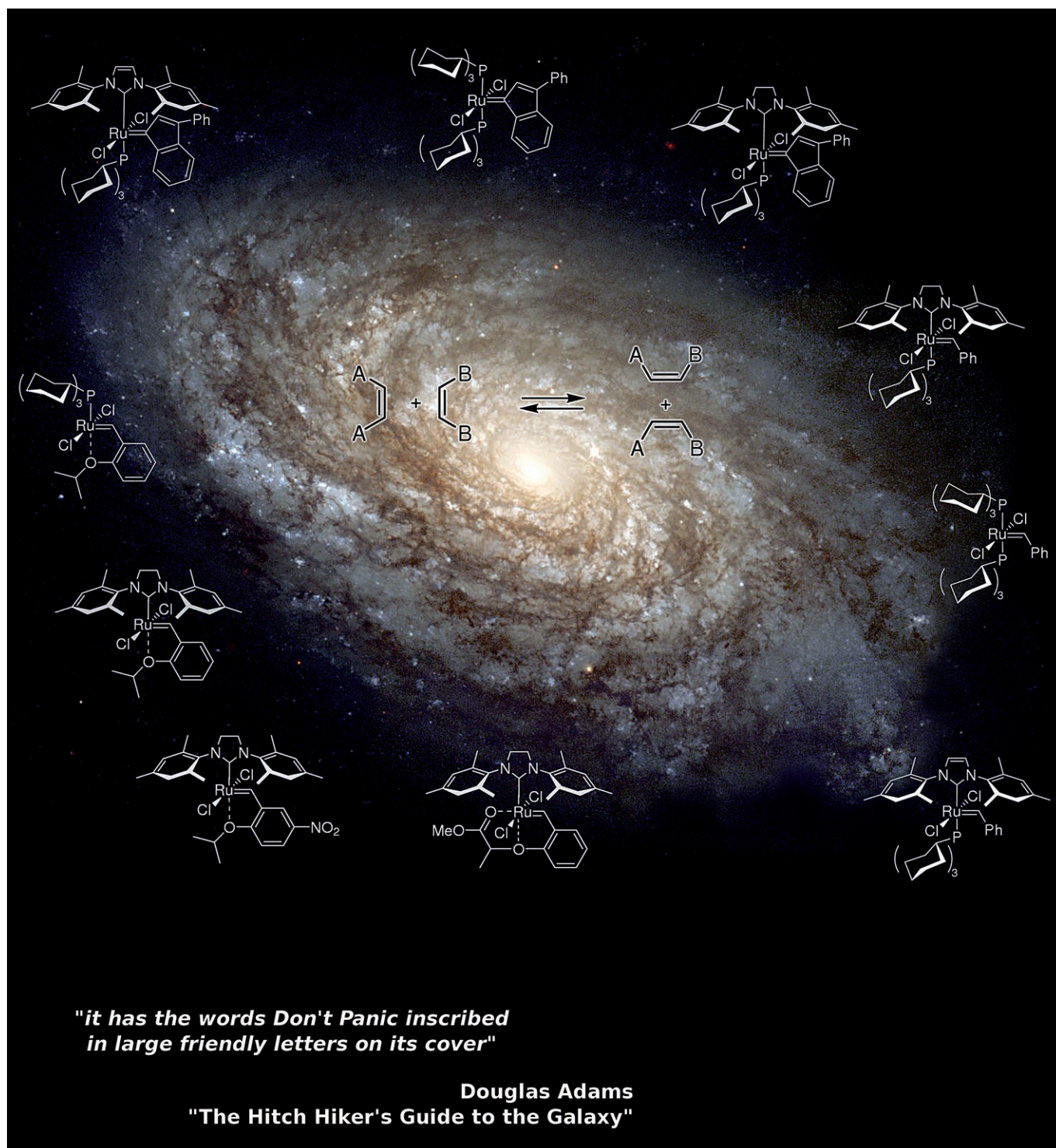


In an Attempt to Provide a User's Guide to the Galaxy of Benzylidene, Alkoxybenzylidene, and Indenylidene Ruthenium Olefin Metathesis Catalysts

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Abstract: The data reported in this paper demonstrate that great care must be taken when choosing an appropriate catalyst for a given metathesis reaction. First-generation catalysts were found to be useful in the metathesis of sterically unhindered substrates. Second-generation catalysts (under optimised conditions) showed good to excellent activities toward sterically hindered and electron-withdrawing group (EWG)-substituted alkenes that do not

react using the first-generation complexes. A strong temperature effect was noted on all of the reactions tested. Interestingly, attempts to force a reaction by increasing the catalyst loading were much less effective. Therefore, when possible, it is suggest-

Keywords: alkene metathesis • carbenes • homogeneous catalysis • phosphines • ruthenium

ed that metathesis transformations should be carried out with a second-generation catalyst at 70 °C in toluene. However, different second-generation catalysts proved to be optimal for different applications and no single catalyst outperformed all others in all cases. Nevertheless, some empirical rules can be deduced from the model experiments, providing preliminary hints for the selection of the optimal catalysts.

“it has the words Don’t Panic inscribed in large friendly letters on its cover”

Douglas Adams

“The Hitch-Hiker’s Guide to the Galaxy”

Introduction

The success of olefin metathesis has spurred the intense investigation of new catalysts for this transformation.^[1a,d] With the development and commercialisation of many different catalysts (Figure 1),^[1e] however, it becomes increasingly difficult to predict their efficiencies in a given metathesis process. The difference in reactivity patterns exhibited by first-generation and second-generation Grubbs complexes **Gru-I** and **Gru-II** is well established.^[2] On the other hand, the robust indenylidene catalysts **Ind-I**, **Ind-II**, and **Ind-II'** have not yet been compared in detail.^[3] The different reactivity of Grubbs (**Gru**)^[2] and Hoveyda (**Hov**)^[4] complexes within the same generation has also been documented.^[5] In a synthesis of the antiviral agent BILN 2061, a clinically validated inhibitor of the hepatitis C virus (HCV), several Ru pre-catalysts were screened, leading to distinctly different results.^[6] Recently, Barrett observed in his synthesis of viridofungin derivatives that the application of different second-generation complexes (**Gru-II**,^[2] **Hov-II**,^[4] **Ble-II**,^[7] and **Gre-II**^[8]) can also lead to quite diverse results.^[9] Some comparative studies have been reported, but the relative usefulness of various catalysts for a broader set of applications has not yet been comprehensively delineated.^[10,11] Selecting the best catalyst for a given olefin metathesis process is therefore often a

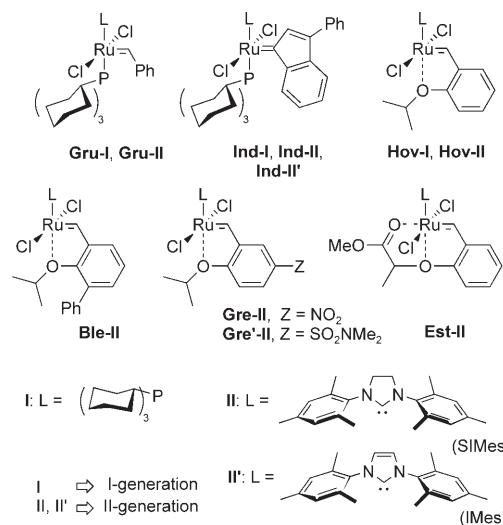


Figure 1. Selected ruthenium pre-catalysts for olefin metathesis.

trial-and-error process. This represents a serious drawback, especially when metathesis is applied at a late stage of a total synthesis of a natural or biologically active compound.^[12]

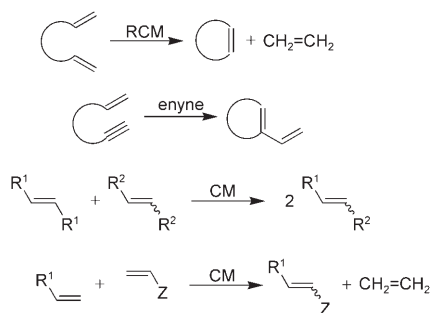
Results and Discussion

In this article, we present screening results for a series of catalysts applied to a set of carefully selected transformations conducted under optimised reaction conditions. The aim of this study was to reveal the relative efficacies of different catalysts and to provide guidelines that might allow the non-specialist a more rational choice of the reaction conditions.

Selection of the test reactions: To cover a wide range of reactivity and functionality within our assay, we selected three distinctly different reaction types: ring-closing metathesis of dienes (RCM), enyne cycloisomerisation (enyne), and alkene cross-metathesis (CM, Scheme 1).^[1] In particular, the RCM and enyne reactions in which a tetrasubstituted C=C

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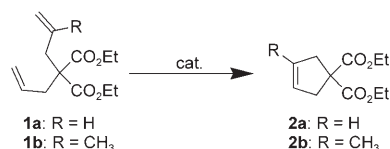


Scheme 1. Variations of the metathesis reaction tested in this study; Z = electron-withdrawing group.

double bond is formed, and CM leading to products containing a trisubstituted C=C double bond, are among the most difficult of metathesis reactions. The selected set of reactions was not meant to be exhaustive and was not extended to test catalysts for specific applications, such as polymerisation reactions or metathesis in aqueous media.^[13] The course of each reaction was monitored by GC with dodecane or tetradecane as an internal standard, measuring the increase in the amount of product with time. The reactions were performed in 4 mL sealed vials in parallel mode, using an automated Vantage unit. This device enables the simultaneous performance of up to 96 reactions at a specified temperature. All reaction mixtures were prepared in a drybox, and then charged vials with screw-cap septum tops were placed in the Vantage array. It is important to note that all reactions were performed in closed systems; when such reactions are carried out in open vessels, the results can be different. However, the conditions employed in this screening are valid for evaluating general differences between catalysts.^[10d] A full set of results in numerical form (presented here as Figures 2–8, and abridged in Tables 1–3 and 8–10) is provided in the Supporting Information.

Selection of the catalysts: Of the plethora of known modern Ru catalysts, the complexes **Gru-I**, **Gru-II**, **Ind-I**, **Ind-II**, **Ind-II'**, **Hov-I**, **Hov-II**, **Gre-II**, and **Est-II** were arbitrarily selected. The complexes **Gru**, **Ind**, and **Hov** are among the most commonly used Ru catalysts for olefin metathesis.^[2] Nitro catalyst **Gre-II** was chosen for this test to represent a class of activated Hoveyda catalysts, which have already been quite successfully deployed in syntheses of natural and bioactive products.^[14] Finally, the doubly oxygen-coordinated **Est-II** represents a promising new structural motif within Ru catalysts.^[15]

Straightforward ring-closing metathesis (RCM): This reaction class was chosen as the first assay in our set of reactions due to its high importance in synthetic chemistry.^[12] Two RCM substrates, namely diethylallyl malonate (**1a**) and diethylallylmethylallyl malonate (**1b**), were investigated (Scheme 2). The RCM formation of cyclopentenes incorporating di- and trisubstituted double bonds (**2a,b**) is a good



Scheme 2. Two models representing a straightforward RCM reaction.

first screening of catalyst efficiency, as it is one of the easiest catalysed RCM reactions.

The progress of the reaction of **1a** in the presence of the second-generation catalysts is shown in Figure 2, while Figure 3 shows the progress of the RCM of **1b**. Figures 2 and 3 illustrate that the Grubbs and Hoveyda-type catalysts show similar activities under these conditions (1 mol %, CH₂Cl₂, 30 °C), affording almost quantitative yields after 1 h, whereas the indenylidene complexes catalyse the reaction much more slowly. This difference became even more pronounced when the catalyst loading was reduced to 0.05 mol % (Figure 4). Under such exacting conditions, the indenylidene catalysts became completely impotent, while the best results were obtained with the activated Hoveyda catalysts **Gre-II** and **Est-II**, most likely due to a combination

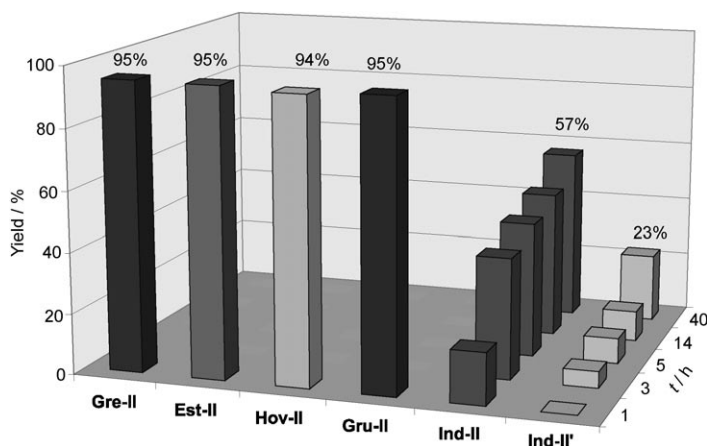


Figure 2. RCM of **1a**. Conditions: $c_{1a} = 0.02$ M, 1 mol % of catalyst, CH₂Cl₂, 30 °C, 40 h.

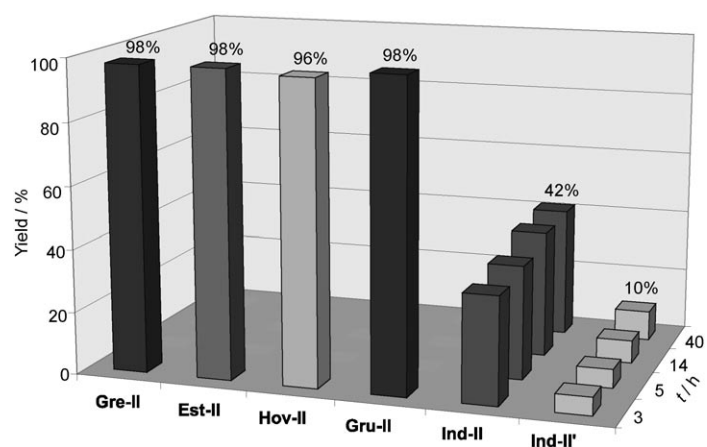


Figure 3. RCM of **1b**. Conditions: $c_{1b} = 0.02$ M, 1 mol % of catalyst, CH₂Cl₂, 30 °C, 40 h.

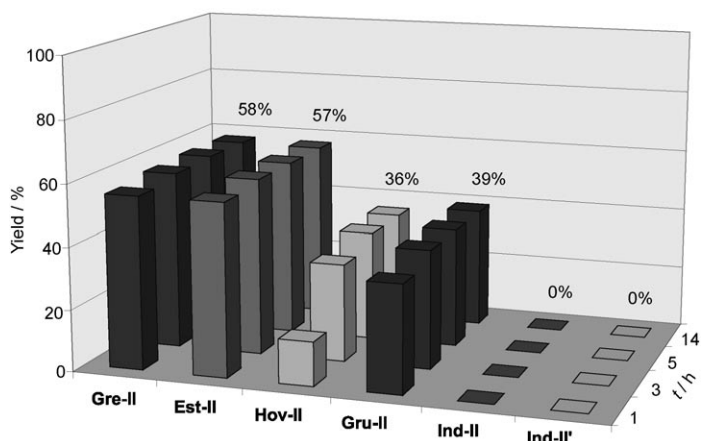


Figure 4. RCM of **1a**. Conditions: $c_{1a}=0.02$ M, 0.05 mol % of catalyst, CH_2Cl_2 , 30°C, 14 h.

of their fast initiation and fast propagation.^[8,15] However, it should be noted that the activities of all of the second-generation catalysts were dramatically increased by raising the temperature. In all cases, conducting the same reaction at 70°C in toluene led to very good to excellent yields after just 1 h. This temperature effect was most pronounced for indenylidene catalysts **Ind-II** and **Ind-II'**, the yields with which were increased from 0 to 97 and 84%, respectively (Figure 5).

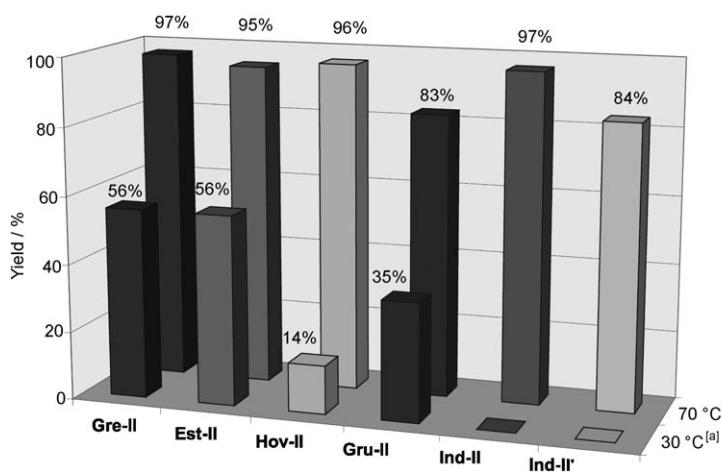


Figure 5. RCM of **1a**. Conditions: $c_{1a}=0.02$ M, 0.05 mol % of catalyst, 1 h, [a] 30°C, CH_2Cl_2 ; [b] 70°C, toluene.

A further decrease in the amount of catalyst (to 0.02 mol %) resulted in only slight decreases in the yields at 70°C (for example, from 97 to 81% for **Gre-II** and from 96 to 92% for **Hov-II**, Table 1). Using just 0.005 mol % of the catalyst, however, the limit for the cyclisation of **1a** was reached (under such conditions, **Gru-II** gave 6% of **2a**, while **Hov-II**, **Gre-II**, and **Est-II** gave 8, 4, and 8%, respectively). From the results presented above, one can conclude that for all second-generation catalysts tested, the increase of temperature has a much stronger effect on the reaction

Table 1. Observed yields [%] of **2a** in the RCM of **1a** after 1 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
0.05	97	95	96	83	97	84
0.02	81	85	92	80	79	49
0.005	4	8	8	6	0	0

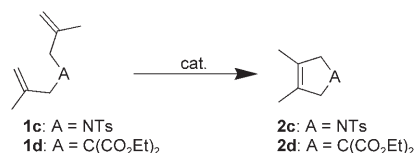
[a] Conditions: $c_{1a}=0.02$ M, 0.05–0.005 mol % of catalyst, toluene, 70°C, 1 h.

course than simply increasing the catalyst loading. Additionally, increasing the temperature allows a shortening of the reaction time. This was especially apparent with the indenylidene complexes **Ind-II** and **Ind-II'**. Since in many published syntheses 10–30 mol % or more of Ru has been used as a default minimal amount,^[12] we think that this observation is of great practical value.^[16]

The first-generation catalysts can still be used as a more economical alternative for metathesis reactions in which di- or trisubstituted C=C bonds are formed.^[1,12] In some reactions, it has been observed that first-generation catalysts are more selective as compared with their second-generation heirs.^[17] Previously, we have investigated the selectivity of the intramolecular enyne metathesis catalysed by representative first- and second-generation ruthenium alkylidenes.^[17a] To compare the activities of chosen first- and second-generation catalysts (**Gru-I**, **Ind-I**, **Hov-I**, **Gru-II**, **Ind-II**, **Ind-II'**, and **Hov-II**; 1 mol %), we utilised the relatively easy RCM of **1b**.^[20] According to the established mechanism,^[1,18] olefin metathesis with five-coordinate Ru pre-catalysts [Ru(=CHPh)(Cl₂)(L)(PCy₃)] proceeds by phosphane dissociation to generate the 14-electron (four-coordinate) active species [Ru(=CHPh)(Cl₂)(L)]. Interestingly, the phosphane dissociation in **Gru-I** is faster than that in second-generation **Gru-II**.^[1,18] Accordingly, we observed that **Ind-I** catalyses the reaction more rapidly than the corresponding second-generation catalysts, giving a 98% yield after 3 h as opposed to 34 and 6% with **Ind-II** and **Ind-II'**, respectively. The first- and second-generation Grubbs catalysts gave almost quantitative yields in the same model reaction (after 3 h, **Gru-I**: 94%; **Gru-II**: 98%). Interestingly, the Hoveyda catalyst **Hov-I** was found to be initiated much more slowly than its second-generation successor **Hov-II** (56 vs 96% after 3 h).

Challenging RCM: The formation of tetrasubstituted double bonds is one of the most challenging of transformations for Ru-based olefin metathesis catalysts. This transformation typically requires the application of second-generation catalysts at high loadings.^[1,19] Therefore, the metathetic formation of tetrasubstituted double bonds remains the domain of more active Schrock molybdenum catalysts^[1] and can be classified as an example of a currently unsolved problem in Ru-catalysed olefin metathesis. As a test case for our selection of Ru catalysts, RCM reactions of dienes **1c** and **d** were initially chosen (Scheme 3).

Unlike in the case of straightforward RCM reactions of **1a** and **1b** performed in CH_2Cl_2 , Grubbs and Hoveyda-type catalysts behave differently towards dienes **1c** and **1d**, with



Scheme 3. Two models representing a challenging RCM reaction.

Gru-II being noticeably more efficient at 30 °C. All the other catalysts are practically ineffective at low temperature in the RCM to form tetrasubstituted double bonds (Figures 6 and 7).^[20] This fact is in good accordance with our

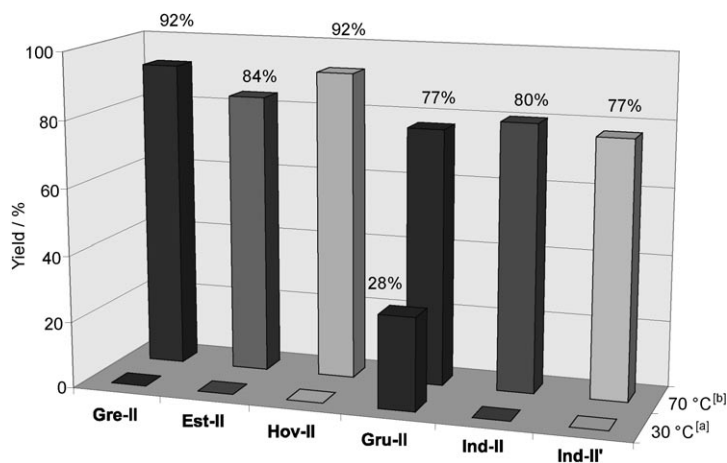


Figure 6. RCM of **1c**. Conditions: $c_{1c}=0.02$ M, 1 mol % of catalyst, 3 h, [a] CH₂Cl₂, 30 °C; [b] toluene, 70 °C.

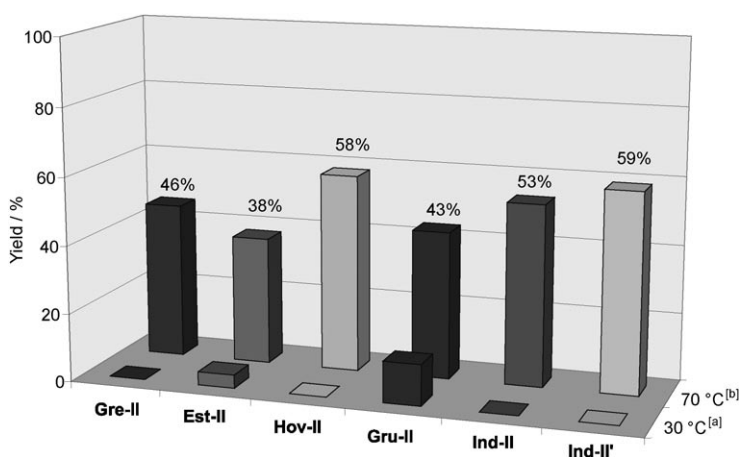


Figure 7. RCM of **1d**. Conditions: $c_{1d}=0.02$ M, 5 mol % of catalyst, 14 h, [a] CH₂Cl₂, 30 °C; [b] toluene, 70 °C.

previous observations.^[8b] In a desperate attempt to enhance the yield, we examined the effect of doubling or even tripling the catalyst loading (from 1 to 3 mol % for diene **1c** and from 5 to 10 mol % in the case of the more challenging RCM of **1d**). Although some improvements in yield were observed (see Tables 2 and 3), we consider that this benefit

Table 2. Observed yields [%] of **2c** in the RCM of **1c** after 3 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
1 ^[b]	0	0	0	28	0	0
3 ^[b]	6	6	0	43	6	0
1 ^[c]	92	84	92	77	80	77
0.5 ^[c]	75	74	89	60	72	63

[a] Conditions: $c_{1c}=0.02$ M, 3 h. [b] CH₂Cl₂, 30 °C. [c] Toluene, 70 °C.

Table 3. Observed yields [%] of **2d** in the RCM of **1d** after 14 h.^[a]

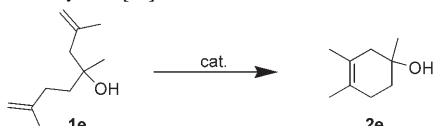
Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
5 ^[b]	0	4	0	12	0	0
10 ^[b]	0	8	0	22	4	0
5 ^[c]	46	38	58	43	53	59

[a] Conditions: $c_{1d}=0.02$ M, 14 h. [b] CH₂Cl₂, 30 °C. [c] Toluene, 70 °C.

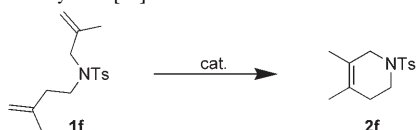
is outweighed by the cost of the precious metal added and the efforts that might be necessary to remove larger catalyst residues after the reaction.^[21] Therefore, we attempted to optimise this reaction by changing other parameters. Again, we observed that increasing the reaction temperature enhanced the yield much more markedly than merely increasing the amount of catalyst. Actually, in the case of **1c**, it was even possible to lower the catalyst loading, while still obtaining much higher yields. With 0.5 mol % of the catalysts in toluene at 70 °C yields in excess of 60% were obtained in all cases, whereas, except in the case of **Gru-II**, the same reaction run at 30 °C with 1 mol % catalyst loading afforded no yield at all (Table 2). It should be emphasised that employing just 0.5 mol % of the Hoveyda catalyst (**Hov-II**) at 70 °C was sufficient to produce **2c** in 89% yield (Table 2). Interestingly, unlike in the experiments conducted at lower temperature, **Hov-II** was clearly more efficient than **Gru-II** at 70 °C, especially when used in smaller loadings (Table 2). In the case of **1d**, which is one of the most demanding substrates for RCM, the best results were obtained with **Hov-II**, **Ind-II**, and **Ind-II'**.

To confirm the observed temperature-dependent efficiency of Ru catalysts toward challenging RCM, we also tested alcohol **1e**, another diene that is known to be reluctant to undergo RCM (Table 4).^[8b] While the use of 5 mol % of the nitro catalyst **Gre-II** led to only 29% of **2e** in CH₂Cl₂ (40 °C, 24 h),^[8b] application of the same catalyst in toluene (70 °C) gave a practically quantitative yield in a much shorter reaction time. The other catalysts, apart from **Gru-II** and **Ind-II'**, were similarly efficient (Table 4). Finally, another demanding diene, **1f**, was tested under these optimised conditions, which gave the expected product **2f** in generally good yields (Table 5). As in all of the previously attempted RCM reactions leading to the formation of tetrasubstituted double bonds, **Gru-II** again proved to be slightly less effective (Table 5).

From the results collated in Tables 2–5, one can conclude that for all second-generation catalysts tested, increasing the

Table 4. Observed yields [%] of **2e** in the RCM of **1e** after 3 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
5	98	96	97	84	98	56

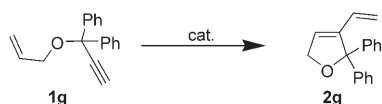
[a] Conditions: $c_{1e}=0.02$ M, toluene, 70 °C, 3 h.Table 5. Observed yields [%] of **2f** in the RCM of **1f** after 1 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
1	95	100	97	73	98	92

[a] Conditions: $c_{1f}=0.02$ M, toluene, 70 °C, 1 h.

temperature has a much greater effect on the reaction course than merely increasing the catalyst loading.

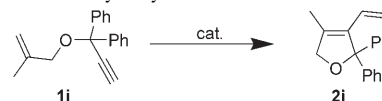
Straightforward enyne cycloisomerisation: The enyne metathesis reaction is a completely atom-economical transformation with great potential in organic synthesis and polymer chemistry (Scheme 1).^[22] Therefore, in the present study, enyne metathesis of **1g** was chosen as a first test for evaluating the different reactivities of the second-generation catalysts (see Table 6).

Table 6. Observed yields [%] of **2g** in the enyne cycloisomerisation of **1g**.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
0.1	94	95	97	96	94	94

[a] Conditions: $c_{1g}=0.02$ M, toluene, 70 °C.

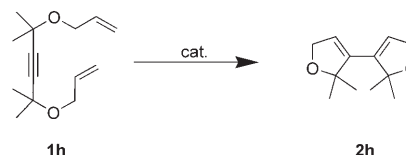
It has been reported that this straightforward substrate is easily cycloisomerised by 1 mol % of **Gre-II** at 0 °C in CH_2Cl_2 .^[8b] The data presented in Table 6 show that in toluene at 70 °C all of the NHC-bearing catalysts led to perfect results even when used at a ten times lower loading. Next, we tested

Table 8. Observed yields [%] of **2i** in the enyne cycloisomerisation of **1i** after 14 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
5 ^[b]	1	1	0	13	2	0
5 ^[c]	40	64	30	73	16	27
10 ^[c]	51	74	35	75	26	34

[a] Conditions: $c_{1i}=0.02$ M, 14 h. [b] CH_2Cl_2 , 30 °C. [c] Toluene, 70 °C.

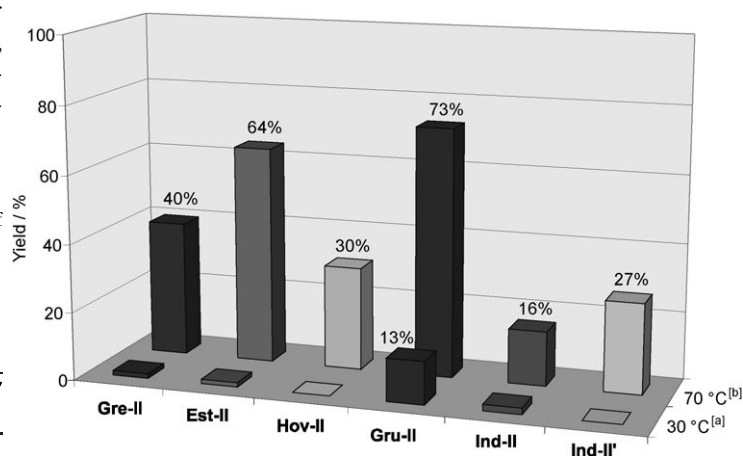
1h as a representative substrate for tandem enyne-RCM (Table 7).^[22] In this slightly more demanding case, some differences in the efficacies of the catalysts were observed (Table 7), with **Est-II** and **Gru-II** being distinctly more active than the other catalysts tested.

Table 7. Observed yields [%] of **2h** in the enyne-RCM tandem reaction of **1h** after 1 h.^[a]

Catalyst loading [mol %]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
1	69	98	68	88	68	63

[a] Conditions: $c_{1h}=0.02$ M, toluene, 70 °C, 1 h.

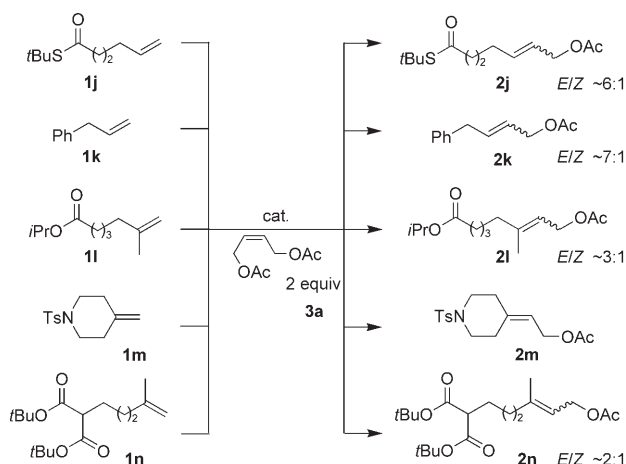
Challenging enyne cycloisomerisation: The challenging enyne **1i**^[10b] was chosen as a suitable substrate for evaluating the different reactivities of the second-generation catalysts (Table 8). Unlike in the previous straightforward cases, in the cycloisomerisation of **1i**, complex **Gru-II** outperformed all of the other catalysts at both 30 °C and 70 °C (Figure 8).

Figure 8. Enyne cycloisomerisation of **1i**. Conditions: $c_{1i}=0.02$ M, 5 mol % of catalyst, 14 h, [a] CH_2Cl_2 , 30 °C; [b] toluene, 70 °C.

Again, increasing the temperature had a very pronounced effect on the reaction, leading to a fivefold increase in yield in the case of the most active **Gru-II** catalyst and as much as a 64-fold increase in the case of **Est-II** (Table 8). The results compiled in Table 8 illustrate that a further doubling of the catalyst loading is not rewarding, giving only a slight increase in the yield.

Cross-metathesis (CM) between two olefinic partners: Functionalised alkenes are important building blocks for organic synthesis. Catalytic alkene CM (Scheme 1) is a convenient route to functionalized alkenes from simple alkene precursors.^[1,23] In view of the increasing importance of CM in syntheses of natural and biologically active products, we included this transformation in our study.

Cross-metathesis between (*Z*)-1,4-diacetoxy-2-butene (**3a**) and terminal alkenes **1j** and **1k**, as presented in Scheme 4, can be classified as a rather straightforward example of this transformation. The results of reactions conducted in toluene at 70 °C, as compiled in Table 9, indicate that all of the



Scheme 4. Olefin cross-metathesis reactions studied. Detailed data concerning the *E/Z* ratios for all products are available in the Supporting Information.

Table 9. Observed yields [%] of products in the CM of **1j–n** with **3a**.^[a]

Product	<i>t</i> [h]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
2j ^[b]	1	73	73	73	73	72	72
	3	73	74	73	73	72	73
	18	75	75	75	75	75	75
2k ^[b]	1	66	66	66	65	n.d.	66
	3	66	67	66	66	n.d.	66
	18	68	68	67	67	n.d.	68
2l ^[c]	1	26	45	29	40	40	39
	3	26	46	29	40	40	40
	18	25	45	28	40	40	40
2m ^[c]	1	50	55	n.d.	n.d.	n.d.	59
	3	50	55	n.d.	n.d.	n.d.	58
	18	49	54	41	52	n.d.	58
2n ^[c]	1	n.d.	42	22	39	39	36
	3	n.d.	42	20	37	38	39

[a] Conditions: $c_{1j-n} = 0.02$ M, toluene, 70 °C. [b] 1 mol % of catalyst. [c] 5 mol % of catalyst. n.d. = not determined.

complexes tested were almost indistinguishable in terms of their activity toward terminal alkenes **1j** and **k**.

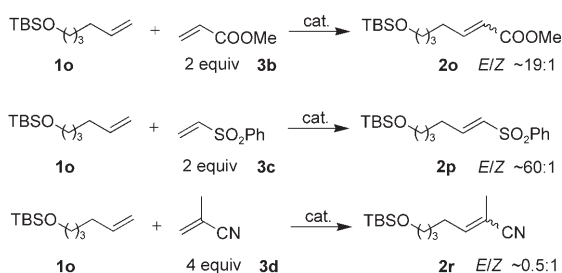
Next, we focused on more sterically demanding substrates, since previous comparative studies have dealt mainly with unhindered CM partners.^[10] As can be seen from Table 9, all of the NHC-containing complexes were effective in catalysing the cross-metathesis of geminally disubstituted alkenes^[24] **1l–n** with (*Z*)-1,4-diacetoxy-2-butene, although appreciable differences may be noted. Thus, the parent Hoveyda catalyst (**Hov-II**) generally afforded the lowest yields. Good results were obtained in reactions catalysed by phosphane-containing **Gru-II**, **Ind-II**, and **Ind-II'**. These results, although not fully understood, are consistent with our previously reported observation^[8b] that Grubbs-type alkylidenes are more potent than Hoveyda's catalysts in the formation of trisubstituted C=C double bonds by CM at lower temperatures. Interestingly, the present investigation has shown the doubly-stabilised complex **Est-II**, representing a new structural motif within Hoveyda's Ru–O chelates,^[15] to be much more potent than **Gre-II** and **Hov-II**, giving the highest yields with **1l** and **1n** of all of the catalysts tested. **Est-II** proved to be the second most active catalyst in the case of **1m**.

Cross-metathesis between an olefinic partner and an electron-deficient alkene:

One of the most appealing facets of the cross-metathesis transformation is that a carbon-carbon double bond of one of the cross-metathesis partners can be substituted with an electron-withdrawing group *Z* (Scheme 1).^[1] CM with electron-deficient alkenes leads to functionalisation of a C=C double bond in an olefinic substrate (a formal C–H activation)^[25] and therefore complements other methods, such as the Wittig, Horner–Wadsworth–Emmons, or Heck reactions.^[23] Exploitation of the CM of various electron-deficient alkenes is just beginning to emerge as a valuable synthetic tool for fine chemical synthesis.^[25] Grubbs and co-workers were the first to report that CM between α,β -unsaturated carbonyl compounds (esters, aldehydes, and ketones) and simple alkenes in the presence of **Gru-II** (5 mol %) in CH_2Cl_2 at 45 °C proceeded with good to excellent yields.^[26] Significantly, some electron-deficient partners, most notably vinyl sulfones and acrylonitriles, were initially found to be unreactive.^[26] Bleichert found that **Hov-II** was also active in CM reactions of α,β -unsaturated carbonyl substrates.^[4c] Later, the same group noted a markedly improved efficiency of **Hov-II** compared to that of **Gru-II** in CM of fluorinated electron-deficient alkenes $\text{C}_n\text{F}_{2n+1}\text{CH}=\text{CH}_2$ ^[27] and in CM of acrylonitrile derivatives.^[28] Hoveyda-type catalysts **Hov-II** and **Gre-II** have been used in CM of some unstable vinyl azulenes.^[29] Gouverneur and Grela have simultaneously reported a successful CM of vinyl phosphine partners catalysed by **Gru-II**.^[30] However, while the latter initiator was found to be ineffective in the more challenging self-CM of vinyl phosphane oxides,^[31] this transformation was accomplished with the phosphane-free complex **Gre-II**.^[31] Contrary to some previous reports,^[32] we have discovered that CM of vinyl sulfones can also be effectively

catalysed by **Gru-II**,^[33] although in the case of sterically congested substrates better results were achieved with the pre-catalyst **Gre-II**.^[34]

It is clear that more detailed study is needed to permit selection of the optimal catalysts for CM of electron-deficient partners. To this end, we selected three model CM reactions, these being representative of a relatively easy (**1o** + **3b**) and two more challenging cases (**1o** + **3c** and **1o** + **3d**, Scheme 5). Of the three CM partners bearing electron-withdrawing groups (**3b-d**), methyl acrylate (**3b**) is known to be the least reluctant to undergo this transformation and therefore just 0.2 mol % of catalyst proved sufficient to produce moderate yields (62–65 %). No difference in activity among all of the investigated catalysts was observed.



Scheme 5. Olefin cross-metathesis with electron-deficient alkenes: methyl acrylate, phenyl vinyl sulfone, and methacrylonitrile. Detailed data concerning the *E/Z* ratios for all products are available in the Supporting Information.

In the CM of terminal alkene **1o** with phenyl vinyl sulfone,^[33,34] which is a more reluctant substrate and was initially classified as an unreactive partner,^[26] a higher catalyst loading was employed (1 mol %). For this transformation, all of the Hoveyda-type complexes, **Gre-II**, **Est-II**, and **Hov-II**, were equally effective. Slightly lower yields were observed with **Gru-II**. Surprisingly, indenylidene complex **Ind-II'**, bearing an unsaturated NHC ligand, was much less effective than its saturated analogue **Ind-II**. However, care must be taken in generalising reactivity trends within this catalyst series. This became clear upon analysing the results obtained with the third electron-deficient partner tested.

Methacrylonitrile is one of the most reluctant substrates in CM,^[28] and therefore 5 mol % of catalyst was employed in this case. Table 10 shows that the corresponding product **2r** was formed only in moderate yields; in this demanding case, Hoveyda's family of complexes **Hov-II**, **Gre-II**, and **Est-II** proved to be unequivocally superior to the other catalysts tested. Interestingly, in this case, no significant differences between **Ind-II'** and **Ind-II** were noted.^[35]

Structure–activity relationship: The first-generation catalysts were found to still be useful in the metathesis of sterically unhindered substrates. As reported in the literature,^[1,12] the second-generation catalysts show much better activity toward sterically hindered and EWG-substituted alkenes that do not react using the first-generation Ru complexes.

Table 10. Observed yields [%] of products in the CM of **1o** with **3b-d**.^[a]

Product	<i>t</i> [h]	Gre-II	Est-II	Hov-II	Gru-II	Ind-II	Ind-II'
2o ^[b]	1	65	65	65	63	64	62
	3	65	66	65	60	60	59
	18	65	66	65	63	64	64
2p ^[c]	1	78	75	76	64	71	44
	3	78	75	78	65	71	n.d.
	18	79	75	79	64	70	47
2r ^[d]	1	58	56	52	13	11	15
	3	60	56	58	13	12	16
	18	60	57	59	13	12	17

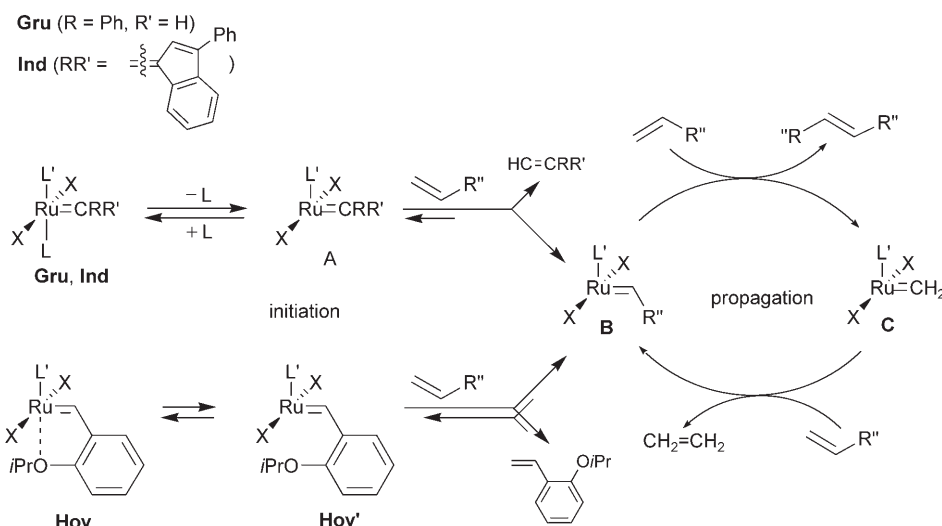
[a] Conditions: c_{1o} = 0.02 M, toluene, 70 °C. [b] 0.2 mol % of catalyst. [c] 1 mol % of catalyst. [d] 5 mol % of catalyst. n.d. = not determined

Different second-generation catalysts, however, have proved to be optimal for different applications and no single catalyst outperforms all others in all cases. The following preliminary rules can, however, be deduced from the model reactions:

- 1) in the case of straightforward RCM reactions performed at lower temperatures in CH_2Cl_2 , electronically activated Hoveyda-type catalysts **Gre-II** and **Est-II** are most suitable. The fast initiation and propagation of these complexes guarantee optimal results;
- 2) in the case of straightforward and moderately challenging RCM and CM reactions, all of the second-generation catalysts worked equally well at 70 °C in toluene, which can be recognised as the optimal conditions;^[36]
- 3) in enyne cycloisomerisation of more challenging substrates, the second-generation Grubbs catalyst, **Gru-II**, proved to be most effective. Unexpectedly, the doubly chelated complex **Est-II** was also found to be very efficient;
- 4) for the most demanding cases, such as the RCM formation of tetrasubstituted double bonds, **Hov-II** was found to be the most reliable catalyst, giving good to excellent results in all cases;^[37]
- 5) in the CM of demanding electron-deficient alkenes, such as α,β -unsaturated sulfones, nitriles, and phosphine oxides, the Hoveyda-type alkylidenes **Hov-II**, **Gre-II**, and **Est-II** were undoubtedly superior;
- 6) in spite of the initially observed lower activities of indenylidenes **Ind-II** and **Ind-II'** (see, for example, Figures 2 and 3), under optimised conditions these catalysts were found, in many cases, to be fully equivalent to **Gru-II** or **Hov-II**.

In the case of advanced natural product precursors, there are many other factors, such as template-directing^[38] and remote functional group control,^[39] that can influence the outcome of the metathesis step. These factors were not included in the test reactions that we have examined; however, in spite of this simplification, we believe that the observed substrate/catalyst structure–reactivity relationships should be of interest to synthetic chemists, and may also be helpful in the design of new, more efficient catalysts.

Preliminary mechanistic rationalisation: This study has revealed a distinct difference between the benzylidene, alkoxybenzylidene, and indenylidene families of metathesis catalysts in relation to the substrates used. According to the generally accepted mechanism, pre-catalysts of the type $[\text{Ru}(\text{=CRR}')(\text{L}')(\text{L})(\text{X}_2)]$ (**Gru**, **Ind**) are initiated by the dissociation of a PR_3 group (ligand **L**) to form the 14-electron complex **A**, while in the case of the Hoveyda-type complexes (**Hov**), where **L** is a tethered ether ligand, initiation requires breakage of the $\text{Ru}-\text{O}$ chelation as a first step (Scheme 6).^[40] This simple mechanistic scheme can be used to explain the observed differences between the second-gen-



Scheme 6. Plausible mechanism for the alkene CM reaction, catalysed by Grubbs, indenylidene, and Hoveyda-type initiators.

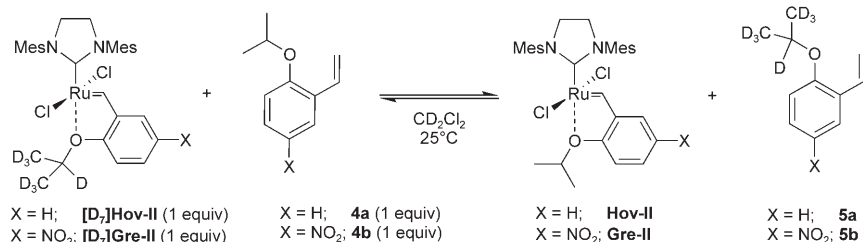
eration Grubbs and indenylidene complexes. The release of 1-methylene-3-phenyl-1*H*-indene and the formation of the common propagating species **B** and **C** proceeds much more slowly in the case of **Ind**, whereas **Gru** easily loses styrene in the analogous transformation. Therefore, pre-catalysts **Ind-II** and **Ind-II'** are initialised much more slowly than **Gru-II** and need a higher temperature to reach reasonable activity (Figures 2–8). However, the observed temperature effect requires some comments. It was initially noted by Fürstner and Nolan that some RCM reactions promoted by the second-generation catalyst $[\text{Ru}(\text{=CHPh})(\text{Cl}_2)(\text{IMes})(\text{PCy}_3)]$ in toluene at 80 °C are not only faster than those conducted in CH_2Cl_2 at 40 °C but also faster than reactions conducted in $\text{ClCH}_2\text{CH}_2\text{Cl}$ at 80 °C.^[10b] Therefore, we suggest that the observed increase in activity is not simply the effect of higher reaction temperature, but also a function of the solvent.^[41,42] A plausible explanation for the higher activity in the aromatic solvent (toluene) is based on the assumption that interactions between the aromatic *N*-mesityl groups of the NHC ligand^[43] and the aromatic solvent molecules may reduce the stabilising effect of the intramolecular $\pi-\pi$ stacking^[44] with the benzylidene or indenylidene fragments, which, in turn, may influence the rate of initiation of a metathesis reaction.^[10b] This intriguing *solvent effect* is currently

being studied in detail in our laboratory and the results will be published in due course. We have yet to find a clear and convincing explanation for the observed differences in the activities of **Ind-II** and **Ind-II'** towards different substrates. It has been shown for benzylidene complexes that saturated NHC ligands lead to more active catalysts as compared with unsaturated ligands.^[35] However, superior activity of an IMes-bearing catalyst, as we have observed in a few cases (see Figures 7 and 8), suggests that this picture is likely to be more complicated.

It is believed that both the Grubbs and Hoveyda-type pre-catalysts generate identical propagating species **B** ($[\text{Ru}(\text{=CH}_2)(\text{L}')(\text{X}_2)]$) and **C** ($[\text{Ru}(\text{=CRR}')(\text{L}')(\text{X}_2)]$) after a single turnover (Scheme 6).^[40] However, the well-documented differences in scope between these two catalysts (especially towards electron-deficient substrates) suggest that the mode of propagation might also be different, leading to the observed non-identical reactivities. In a recent publication, Farina and Wei reported on NMR analyses of some metathesis reactions promoted by 30 mol % of Hoveyda catalyst **Hov-I**; they observed no discrete intermediates of type **B**, which are typically present in the case of Grubbs pre-catalysts.^[6a] Therefore, it is reasonable to assume

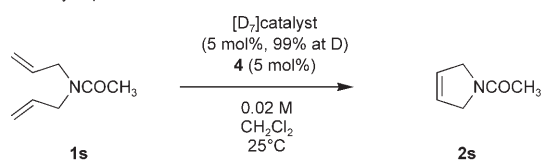
that reactions with Hoveyda catalysts proceed through the intermediacy of steady-state species (not observable by NMR), while the bulk of the Ru is sequestered in a resting state.^[6a,40c] To prove that this “sleeping” catalyst is not a bystander but actually takes part in the reaction,^[40,45] we carried out a simple crossover experiment. According to established procedures,^[46] the labelled complexes $[\text{D}_7]\text{Hov-II}$ and $[\text{D}_7]\text{Gre-II}$ (99% D atom) were prepared.^[47] First, we estimated the rate of “background” exchange by mixing equimolar amounts of the deuterated catalysts with non-deuterated styrene **4** in CD_2Cl_2 (Scheme 7a). As expected, pre-catalyst $[\text{D}_7]\text{Gre-II}$ equilibrated more rapidly (in 2 h), while the reaction with inactivated $[\text{D}_7]\text{Hov-II}$ required 48 h to reach equilibrium under identical conditions.^[48] The key crossover experiments, based on a simple RCM reaction, were carried out as detailed below (Scheme 7b). Two metathesis reactions of *N,N*-diallylacetamide were conducted independently with 5 mol % of $[\text{D}_7]\text{Hov-II}$ and $[\text{D}_7]\text{Gre-II}$ in the presence of the same amount (5 mol %) of the corresponding non-labelled styrene **4**. In each case, the reaction proceeded to >99% conversion, and the respective pre-catalysts were isolated by column chromatography. The remaining deuterium contents of the recovered catalysts were estimated by NMR to be 59% D atom for the Hoveyda cat-

a) background exchange experiments



X = H	t [h]	[D₂] Hov-II Hov-II	X = NO ₂	t [min]	[D₂] Gre-II Gre-II
	1	98 : 2		10	92 : 8
	2	94 : 6		20	84 : 16
	7	75 : 25		30	77 : 23
	24	61 : 39		40	69 : 31
	48	50 : 50		50	65 : 35
				120	50 : 50

b) catalyst recovery experiments



X = H	X = NO ₂
60 min, 100% conversion of 1s	15 min, 100% conversion of 1s
85% of [D₂] Hov-II recovered (59% at D)	67% of [D₂] Gre-II recovered (63% at D)

Scheme 7. Crossover experiment.

alyst and 63% D atom for the nitro catalyst. Since the background exchange reactions between these catalysts and styrenes **4** were in both cases too slow to be responsible for such significant losses in the deuterium atom content, we believe that during the RCM process the whole amount of the pre-catalyst applied was involved in the reaction and was then regenerated by the release-return mechanism proposed by Hoveyda.^[4b,40] Based on this preliminary experiment and the results obtained by Farina and Wei, it is reasonable to assume that in reactions promoted by Hoveyda pre-catalysts the propagation proceeds through a dynamic equilibrium involving the intermediacy of the self-regenerating 14-electron species **Hov'**, and that this is responsible for the observed differences in reactivity of these catalysts towards some substrates. However, the studies required to either corroborate or disprove this proposal are beyond the scope of the current investigation.

Conclusion

In summary, we have carried out a comparative study on some selected modern Ru metathesis catalysts. The data reported in this paper demonstrate the difficulty in anticipating the activity of pre-catalysts with respect to a specific substrate and highlight that, unfortunately, different catalysts prove to be optimal for different applications and no single

catalyst outperforms all others in all cases. Therefore, during optimisation of especially important (or industrial) metathesis processes, it is suggested that all major types of catalysts described in this study should be tested. However, based on the results of reactions described herein, in conjunction with data gleaned from the literature, some generalisations on structure–activity relationships can be made. Notably, a strong temperature effect was noted on all of the reactions tested. Therefore, when possible, we suggest that difficult metathesis transformations should be conducted at 70 °C in toluene, rather than simply by increasing the catalyst loading.^[36] Further studies aimed at rationalising the observed catalyst activities in terms of the metathesis transformation and substrate structure are currently ongoing in our laboratory and the results will be reported in due course.

Experimental Section

General: All stock solutions and reaction mixtures were prepared using drybox techniques. Reactions were carried out at 30 °C or 70 °C using a Vantage unit (a device that enables the simultaneous performance of up to 96 reactions at a fixed temperature). All aliquots for GC analysis were taken automatically at the specified time intervals using the same device. Gas chromatography (GC) was conducted using an HP 6890 equipped with an HP-5 capillary column. Anhydrous, oxygen-free toluene and dichloromethane were purchased from Aldrich and were used as received. Catalysts **Gru-I**, **Gru-II**, **Ind-I**, **Ind-II**, **Hov-I**, and **Hov-II** were purchased and used as received. Catalyst **Ind-II'** was provided by Degussa GmbH. Complexes **Gre-II**^[8] and **Est-II**^[15] were prepared according to literature methods. All other commercially available chemicals were used as received. Flash column chromatography was performed on silica gel 60 (E. Merck; 230–400 mesh). The compounds **2a**,^[49] **1b**,^[50] **2b**,^[50] **1c**,^[11] **2c**,^[51] **1d**,^[50] **2d**,^[50] **2e**,^[51] **1f**,^[11] **2f**,^[52] **1g**,^[11] **2g**,^[10a] **1h**,^[17a] **2h**,^[10] **1i**,^[53] **2i**,^[10a] **1j**,^[54] **2j**,^[8b] **1m**,^[55] **2m**,^[8b] **1o**,^[56] **2o**,^[8b] **2p**,^[57] **2r**,^[8b] **2s**,^[58] **4a**,^[4b] and **4b**,^[8a] have been described previously and were identified by comparison of their physical and spectroscopic data (¹H and ¹³C NMR; MS) with those in the cited references.

General procedure for kinetic studies: In a glovebox, 4 mL vials with screw-cap septum tops were charged with the required substrates and catalysts. The vials were then placed in the Vantage array and heated at 30 °C or 70 °C for at least 18 h. Aliquots were taken at the specified time intervals.

Stock solution preparation

Catalysts Gru-II, Ind-II, Ind-II', Hov-II, Gre-II, and Est-II: A single stock solution containing enough catalyst for at least a few series of metathesis reactions was prepared. In a glovebox, a volumetric flask was

charged with the catalyst (0.03 mmol), and the requisite solvent was added to prepare a stock solution (10 mL, $[c]=0.003\text{ M}$). In this way, solutions of all of the complexes (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**) in both of the required solvents (dichloromethane and toluene) were prepared. Such stock solutions should be used within a few hours because prolonged storage, even in a glovebox, can lead to partial decomposition of the catalysts.

Alkenes for RCM (1a–f), enyne metathesis (1g–i), and CM (1j–o): A single stock solution containing enough substrate for metathesis reactions with all six catalysts was prepared. In a glovebox, a volumetric flask was charged with the appropriate diene (**1a–f**), enyne substrate (**1g–i**), or alkene (**1j–o**) (0.6 mmol), along with dodecane (for alkenes **1a–i**) or tetradecane (for alkenes **1j–o**) (0.3 mmol) as an internal standard. The requisite solvent was then added to prepare a stock solution (10 mL, $[c]=0.06\text{ M}$). In this way, solutions of all of the alkenes (**1a–o**) in both of the required solvents (dichloromethane and toluene) were prepared. All of these solutions could be stored in sealed vials under Ar for extended periods of time.

Cross-metathesis (CM) partners (3a–d): In a glovebox, a volumetric flask was charged with the appropriate alkene (**3a–c**) (1.2 mmol) or (**3d**) (2.4 mmol), and then toluene was added to prepare a stock solution (10 mL, $[c]=0.12\text{ M}$) and (10 mL, $[c]=0.24\text{ M}$), respectively. All of these solutions could be stored in sealed vials under Ar for extended periods of time.

RCM of 1a–c, and f: In a glovebox, 4 mL vials were charged with alkene (**1a**, **b**, **c**, or **f**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and the required solvent (1.8 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 0.2 mL, 0.6 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in dichloromethane and six solutions in toluene were obtained with the following parameters: concentration of **1a**, **b**, **c**, or **f**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 1 mol%; solution volume: 3 mL. To obtain solutions with catalyst loadings of 0.05, 0.02, and 0.005 mol%, the appropriate catalyst stock solutions were diluted according to the following procedure. Aliquots of 0.5, 0.2, and 0.05 mL of the appropriate catalyst stock solution ($[c]=0.003\text{ M}$) were added by means of an adjustable-volume pipette to volumetric flasks and the appropriate solvent was added to prepare new stock solutions (10 mL) with catalyst concentrations $[c]=0.15$, 0.06, and 0.015 M, respectively. The thus prepared diluted catalyst stock solutions were used to prepare reaction mixtures with the required catalyst loadings of 0.05, 0.02, and 0.005 mol%, respectively.

RCM of 1d and e: In a glovebox, 4 mL vials were charged with alkene (**1d** or **e**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and the required solvent (1 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 1 mL, 3 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in dichloromethane and six solutions in toluene were obtained with the following parameters: concentration of **1d** or **1e**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 5 mol%; solution volume: 3 mL.

Enyne metathesis of 1h: In a glovebox, 4 mL vials were charged with alkene (**1h**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and the required solvent (1.8 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 0.2 mL, 0.6 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1h**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 1 mol%; solution volume: 3 mL.

Enyne metathesis of 1i: In a glovebox, 4 mL vials were charged with enyne substrate (**1i**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and solvent (1 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 1 mL, 3 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in dichloromethane and six solutions in toluene were obtained with the following parameters: concentration of **1i**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 5 mol%; solution volume: 3 mL.

CM of 1j or 1k with cis-1,4-diacetoxy-2-butene (3a): In a glovebox, 4 mL vials were charged with alkene (**1j** or **k**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol), cross-metathesis partner (**3a**) stock solution ($[c]=0.12\text{ M}$, 1 mL, 0.12 mmol), and toluene (0.8 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 0.2 mL, 0.6 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1j** or **k**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 1 mol%; solution volume: 3 mL.

CM of 1l, m, or n with cis-1,4-diacetoxy-2-butene (3a): In a glovebox, 4 mL vials were charged with alkene (**1l**, **m**, or **n**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and cross-metathesis partner (**3a**) stock solution ($[c]=0.12\text{ M}$, 1 mL, 0.12 mmol). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 1 mL, 3 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1l**, **m**, or **n**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 5 mol%; solution volume: 3 mL.

CM of 1o with methyl acrylate (3b): In a glovebox, 4 mL vials were charged with alkene (**1o**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol), cross-metathesis partner (**3b**) stock solution ($[c]=0.12\text{ M}$, 1 mL, 0.12 mmol), and toluene (0.96 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 0.04 mL, 0.012 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1o**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 0.2 mol%; solution volume: 3 mL.

CM of 1o with phenyl vinyl sulfone (3c): In a glovebox, 4 mL vials were charged with alkene (**1o**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol), cross-metathesis partner (**3c**) stock solution ($[c]=0.12\text{ M}$, 1 mL, 0.12 mmol), and toluene (0.8 mL). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 0.2 mL, 0.6 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1o**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 1 mol%; solution volume: 3 mL.

CM of 1o with 2-methylacrylonitrile (3d): In a glovebox, 4 mL vials were charged with alkene (**1o**) stock solution ($[c]=0.06\text{ M}$, 1 mL, 0.06 mmol) and cross-metathesis partner (**3d**) stock solution ($[c]=0.24\text{ M}$, 1 mL, 0.24 mmol). The appropriate catalyst stock solution ($[c]=0.003\text{ M}$, 1 mL, 3 μmol) was then added to each vial by means of an adjustable-volume pipette. As a result, six solutions in toluene were obtained with the following parameters: concentration of **1o**: $[c]=0.02\text{ M}$; catalyst loading (**Gru-II**, **Ind-II**, **Ind-II'**, **Hov-II**, **Gre-II**, and **Est-II**, respectively): 5 mol%; solution volume: 3 mL.

GC data analysis: Samples for GC analysis were obtained by adding aliquots of about 200 μL of the reaction mixtures to 500 μL of a 2 M solution of ethyl vinyl ether in dichloromethane.^[59] All aliquots were taken automatically at the specified times by the Vantage device. The samples were shaken and then analysed by GC. To obtain accurate yield data, the FID detector response factors were obtained for all the key products (ethylene excluded). Tetradecane was used as the internal standard for CM reactions, whereas for RCM and enyne metathesis dodecane was employed. The responses of the FID detector were calibrated using **2a**/dodecane, **2b**/dodecane, **2c**/dodecane, **2d**/dodecane, **2e**/dodecane, **2f**/dodecane, **2g**/dodecane, **2h**/dodecane, **2i**/dodecane, **2n**/tetradecane, **2o**/tetradecane, and **2r**/tetradecane standard solutions, respectively. All products required for this calibration were synthesised and isolated according to literature procedures.

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