DOI: 10.1002/adsc.201200385

Catalytic and Structural Studies of Hoveyda–Grubbs Type Pre-Catalysts Bearing Modified Ether Ligands

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Received: May 3, 2012; Published online: October 4, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200385.

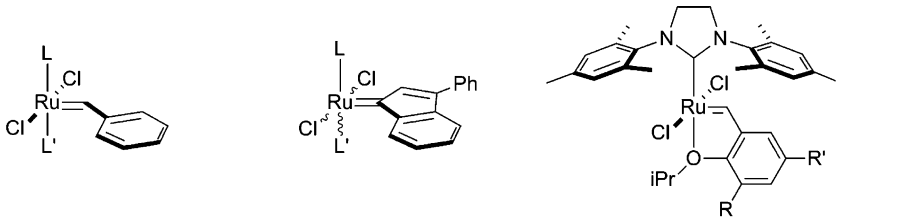
Abstract: Catalytic and crystallographic studies of Hoveyda–Grubbs type pre-catalysts **M51**™ and **M52**™ were performed. These two new instruments in the olefin metathesis catalyst toolbox were shown to be active at ambient temperature and at low loading, leading to clean formation of ring-closing, ring-closing enyne and cross metathesis products.

Keywords: N-heterocyclic carbenes; olefin metathesis; ring-closing metathesis; ruthenium

Introduction

Olefin metathesis is a powerful tool for carbon-carbon double bond formation with important applications in synthetic organic and pharmaceutical chemistry.[1] Numerous pre-catalyst types have been developed in the last 20 years.[2] Ruthenium-based pre-catalysts have gained popularity because of their stability and tolerance to various functional groups.[2c] Well-known 1st and 2nd generation benzylidene (**G-I** and **G-II**) and indenylidene (**Ind-I** and **Ind-II**) complexes have been extensively studied showcasing the enormous potential of these systems (Figure 1).[3] In order to further improve the activity/stability of such pre-catalysts, various modifications have been implemented by several research groups.[4]

The first example of a phosphine-free (NHC bearing) complex **Hov-II** (known as Hoveyda–Grubbs type pre-catalyst) was reported independently by Hoveyda and Blechert (Figure 2).[5] The isopropoxy moiety on the benzylidene ring which acts as a fifth ligand in the metal coordination sphere is a key feature of this class of complexes. The coordination of the oxygen atom is believed to be influenced by the electronic density in the aromatic ring.[6b] Attempts to tune the steric and electronic properties of the car-



G-I	L=L'=PR_3	**Ind-I**	L=L'=PR_3	**Hov-II**	R=R'=H,
G-II	L=NHC, L'=PR_3,	**Ind-II**	L=NHC, L'=PR_3	Blechert	R=Ph, 2-O^{i}Pr-naphthyl, R'=H
G-II-P(OR)$_3$	L=NHC, L'=$P(OR)_3$	**Caz-I**	L=NHC, L'=$P(OR)_3$	Grela	R=H, R'=NO_2

Figure 1. Ruthenium pre-catalysts for olefin metathesis reactions.

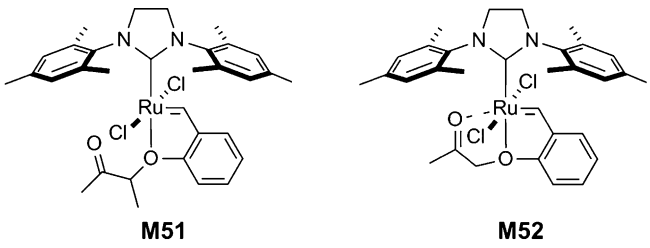


Figure 2. Hoveyda–Grubbs type pre-catalysts examined in this study.

bene moiety were carried out by Blechert and Grela (Figure 1).[6] Grela's complex with an electron-withdrawing group in the *para* position relative to the isopropoxy moiety is one of the most active pre-catalysts of this class.[6b] All such complexes are highly active in catalysis and their potential recyclability is claimed in the literature.[7] The reactivity of these complexes has been clarified with kinetic studies reported by the Plenio group.[8]

Recently, further functionalized Hoveyda–Grubbs type pre-catalysts have been reported by Grela and co-workers.[9] Several complexes with both higher thermal stability and catalytic activity than **Hov-II** were obtained by adding electron-withdrawing groups at the isopropoxy moiety. Some of these complexes adopt an octahedral geometry due to coordination of a carbonyl moiety positioned at the functionalized isopropoxy unit.

In this context, complexes **M51**™ and **M52**™ are now gaining attention as efficient Hoveyda–Grubbs type pre-catalysts.[10] Herein we report the first detailed study on their catalytic activity in olefin metathesis reactions (Figure 2).

Results and Discussion

Catalytic Performance

In order to compare the catalytic activity of **M51** and **M52** with **Hov-II** and **Ind-II**, the room temperature ring-closing metathesis (RCM) of diethyl diallylmalonate using 1 mol% of catalyst was first monitored. While **M51** and **M52** display a similar kinetic profile, the reaction is slightly to drastically slower with **Hov-II** and **Ind-II** (Figure 3).

The effect of the solvent and temperature on this reaction using **M51** and **M52** was next examined (Table 1). In order to obtain reliable data, all reactions were carried out at 30 °C. At this temperature, in dichloromethane, **M51** is more active than **M52** (97% and 77% conversion obtained using 0.05 mol% Ru). Reactions carried out in toluene led to slightly lower catalyst performance for both **M51** and **M52** (Table 1, entries 11 and 16). At very low catalyst loading (100 ppm), increasing the temperature led to an essentially similar catalyst activity as that obtained at 30 °C (Table 1, entries 4, 5, 12 and 13).

The scope of the RCM reaction leading to other five-membered ring compounds was next investigated (Table 2). Pre-catalysts **M51** and **M52** afforded di- and trisubstituted five-membered ring products at low catalyst loading at 30 °C (Table 2, entries 1–4 and 10–23). Poor conversions were observed when using more challenging substrates such as tetrasubstituted dienes (Table 2, entries 5–9, 24 and 25). Complex **M51** shows similar (Table 2, entries 1, 2, 10–14 and 18–21) to higher catalytic activity than **M52** (Table 2, entries 3, 4, 15-17, 22 and 23).

Further reactions with more challenging substrates were carried out with pre-catalyst **M51** only (Table 3) because of its higher activity compared to **M52**. Di-

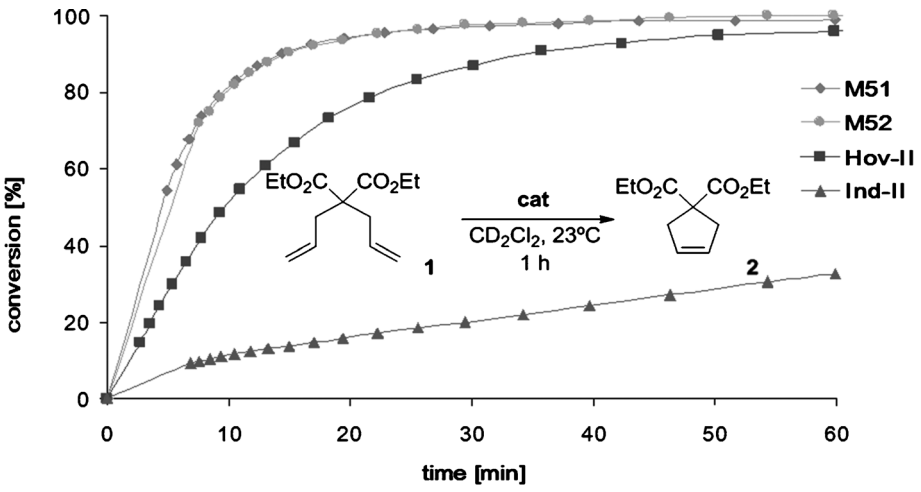
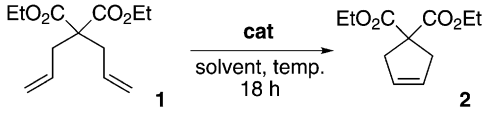


Figure 3. Reaction profiles of RCM of diethyl diallylmalonate promoted by **Ind-II** (▲), **Hov-II** (■), **M51** (◆) and **M52** (●) determined by ^{1}H NMR in CD_2Cl_2 (at 23 °C).

Table 1. Ring-closing metathesis reactions of diethyl diallylmalonate with pre-catalysts **M51** and **M52**.[a]



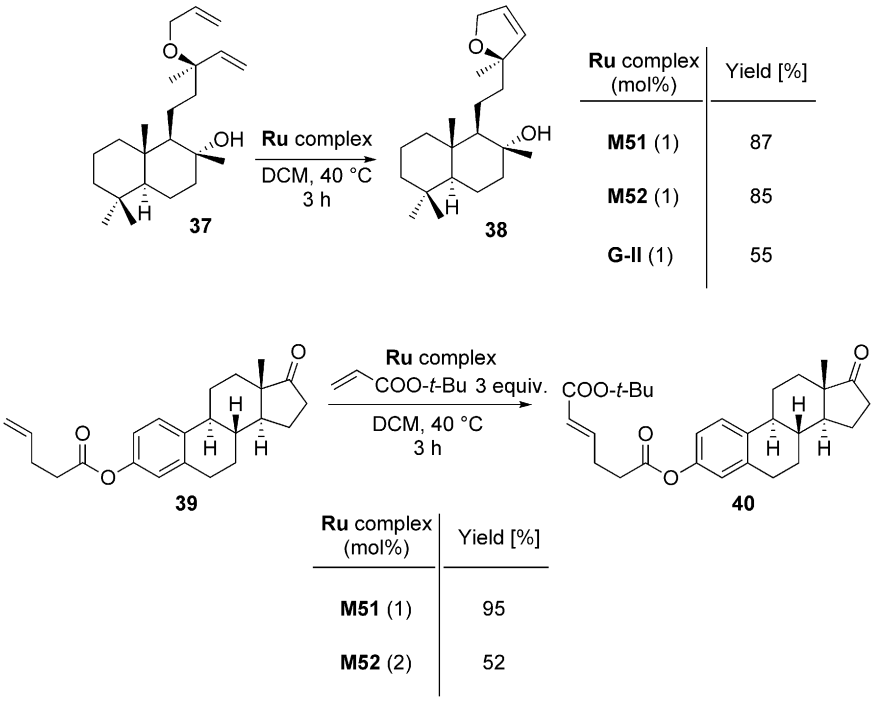
Entry	Solvent	Pre-catalyst (mol%)	Temperature [°C]	Conversion [%][b]
1	CH_2Cl_2	**M51** (1)	30	>99
2	CH_2Cl_2	**M51** (0.1)	30	98 (94)
3	CH_2Cl_2	**M51** (0.05)	30	97
4	CH_2Cl_2	**M51** (0.01)	30	4
5	CH_2Cl_2	**M51** (0.01)	50	5
6	CH_2Cl_2	**M52** (1)	30	>99
7	CH_2Cl_2	**M52** (0.1)	30	92 (88)
8	CH_2Cl_2	**M52** (0.05)	30	77
9	toluene	**M51** (1)	30	>99
10	toluene	**M51** (0.1)	30	96
11	toluene	**M51** (0.05)	30	90
12	toluene	**M51** (0.01)	30	10
13	toluene	**M51** (0.01)	80	10
14	toluene	**M52** (1)	30	>99
15	toluene	**M52** (0.1)	30	88
16	toluene	**M52** (0.05)	30	67

[a] *Reaction conditions:* substrate (0.25 mmol), pre-catalyst (0.01 to 1 mol%), solvent (0.5 mL), 18 h.
[b] Conversion determined by GC; isolated yield in parentheses.

and trisubstituted six-membered rings were obtained in high yields (Table 3, entries 1–3, 6 and 7). Reactions forming seven-membered rings are more difficult due to the eventual homo-cross metathesis between two substrate molecules (Table 3, entries 4, 5 and 8, 9). Ring-closing enyne metathesis of **29** was performed at very low catalyst loading (0.05 mol%) and produced a high yield of product **30** (Table 3, entry 10). Pre-catalyst **M51** catalyzes cross metathesis reactions between methyl acrylate and different functionalized olefins (Table 3, entries 12 and 13). The benzoate derivative **35** gave lower conversion than the *tert*-butyldimethylsilyl ether **33**, and both of these show the same *E*/*Z* ratio (20/1) as determined by ^{1}H NMR spectroscopy.

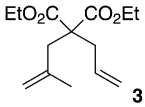
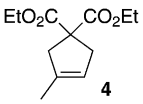
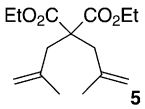
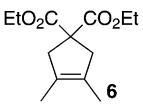
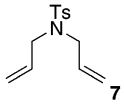
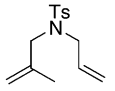
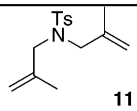
Furthermore, catalytic reactions focusing on the use of pre-catalysts **M51** and **M52** in the formation of two selected bio-active compounds were performed (Scheme 1). First, a rather straightforward RCM of sclareol (fragrant compound naturally occurring in *Salvia sclarea*) derivative **37** was performed with 1 mol% of **M51** leading to five-membered product **38** in good isolated yield (87%). Interestingly, the same reaction catalyzed by **M52** under identical conditions gave almost the same isolated yield (85%) of **38**. These results show that both **M51** and **M52** can be successfully used in easily ring-closed substrates.

In order to provide additional examples of the catalytic performance of **M51** and **M52** in more challenging transformations involving biologically active compounds, the cross metathesis (CM) reaction of estrone derivative **39** was examined. Reaction of **39** with equivalents of *tert*-butyl acrylate initiated by 1 mol% of **M51** led to the desired product **40** in excellent isolated yield (95%). However, pre-catalyst **M52** was



Scheme 1. RCM and CM reactions with bioactive compounds.

Table 2. Scope of the reaction affording five-membered rings.[a]

Entry	Substrate	Product	Solvent	Pre-catalyst (mol%)	Conversion [%][b]
1	 3	 4	CH_2Cl_2	**M51** (0.1)	96 (95)
2			toluene	**M51** (0.1)	74
3			CH_2Cl_2	**M52** (0.1)	79
4			toluene	**M52** (0.1)	56
5	 5	 6	CH_2Cl_2	**M51** (0.5)	5
6			toluene	**M51** (0.5)	8
7			CH_2Cl_2	**M51** (2)	8
8			toluene	**M51** (2)	12
9			toluene	**M51** (5)	21[c]
10	 7	 8	CH_2Cl_2	**M51** (0.1)	97
11			toluene	**M51** (0.1)	96
12			CH_2Cl_2	**M51** (0.01)	84
13			toluene	**M51** (0.01)	94 (88)
14			MTBE	**M51** (0.01)	86
15			CH_2Cl_2	**M52** (0.01)	84
16			toluene	**M52** (0.01)	93
17			MTBE	**M52** (0.01)	79
18	 9	 10	CH_2Cl_2	**M51** (0.1)	97 (92)
19			toluene	**M51** (0.1)	96
20			CH_2Cl_2	**M51** (0.05)	94
21			toluene	**M51** (0.05)	92
22			CH_2Cl_2	**M52** (0.1)	95
23			toluene	**M52** (0.1)	85
24	 11	 12	CH_2Cl_2	**M51** (0.5)	28
25			CH_2Cl_2	**M51** (2)	36

[a] *Reaction conditions:* substrate (0.25 mmol), pre-catalyst, solvent (0.5 mL), 30 °C, 18 h. MTBE is methyl *tert*-butyl ether.
[b] Conversion determined by GC, isolated yields in parentheses.
[c] At 70 °C for 20 h.

shown to be less active in the same transformation, leading to lower yield (52%) of **40**, despite the use of higher catalyst loadings.

Crystallographic Analysis

In order to understand the varied behaviour of the pre-catalysts, X-ray structural studies were conducted for both complexes. Pre-catalyst **M51** was crystallized from three different mixtures of solvents resulting in three types of solvates and, as a consequence, three different crystal structures have been obtained for this compound.[11] For example, **M51** crystallized from benzene/*n*-pentane and benzene/*n*-hexane mixtures in the triclinic P-1 space group (Figure 4, **M51A**) with two molecules of the catalyst and two molecules of benzene in the asymmetric part of the unit cell. However, when this compound was crystallized from a mixture of dichloromethane (CH_2Cl_2/pentane), the crystal lattice accommodates one independent molecule of CH_2Cl_2 (see **M51B**). For more polar mixtures (CH_2Cl_2/MeOH), the solvent molecules are absent from the crystal lattice.

In the case of **M51A**, the geometry of the molecule in the crystal lattice revealed a five-coordinated ruthenium atom and disorder in the isopropoxy

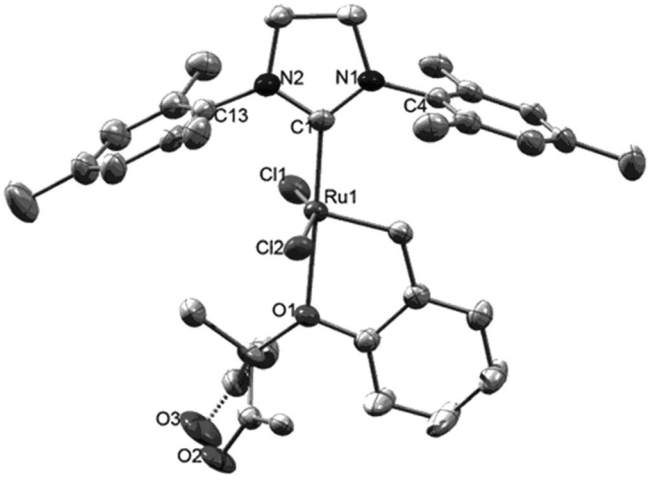
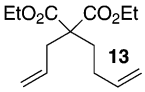
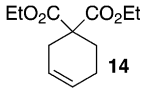
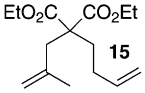
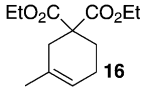
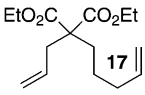
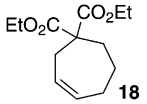
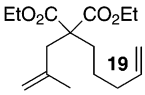
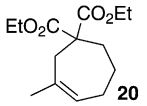
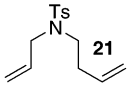
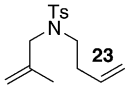
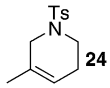
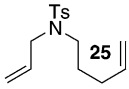
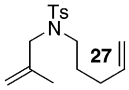
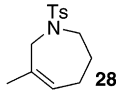
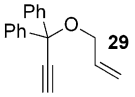
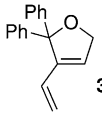
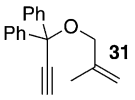
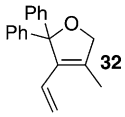
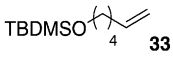
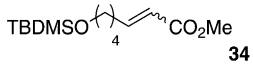
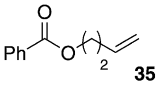
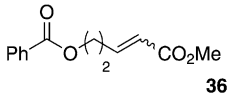


Figure 4. Molecular structure of **M51A** crystallized from benzene/*n*-pentane and benzene/*n*-hexane (solvent molecules and hydrogen atoms are omitted for clarity). Thermal ellipsoids are shown at the 50% probability level.

Table 3. Scope of RCM reactions affording larger rings, ring-closing enyne and cross metathesis products.[a]

Entry	Substrate	Product	Catalyst (mol%)	Conversion [%][b]
1			**M51** (0.1)	96 (95)
2			**M52** (0.1)	93 (86)
3			**M51** (1)	98 (98)
4			**M51** (1)	70 (54)
5			**M51** (1)	82 (85)
6			**M51** (0.1)	>99 (98)
7			**M51** (0.5)	97 (97)
8			**M51** (1)	80 (67)
9			**M51** (1)	75 (60)
10			**M51** (0.05)	>99 (97)
11			**M51** (5)	(89)[c]
12			**M51** (1)	85 (82)[d]
13			**M51** (2)	76 (75)[d]

[a] *Reaction conditions:* substrate (0.25 mmol), pre-catalyst, dichloromethane (0.5 mL), 30 °C, 18 h.
[b] Conversion determined by GC; isolated yields in parentheses.
[c] In toluene at 70 °C for 20 h.
[d] Methyl acrylate (2 equiv.) as coupling partner, *E*/*Z* ratio 20/1 determined by ^{1}H NMR.

moiety with two positions occupied close to 50% (the open conformer).

Single crystals of **M51** grown from a CH_2Cl_2/*n*-pentane mixture adopt the monoclinic *C*2/*c* space group symmetry. There are two conformers present in this crystal: the open conformer and the closed one (see Figure 5, **M51B**). The conformers are found with 70% and 30% occupancies, respectively. The open form is similar to **M51A**, whereas the closed conformer contains a six-coordinated ruthenium atom directly interacting with the oxygen atom from the carbonyl group as the sixth ligand. The geometry of the ruthenium catalyst with six ligands surrounding the ruthenium atom is almost unchanged compared to the ruthenium complex with five ligands. The geometry of the rest of the molecule with the exception of the extra Ru–O bond is practically the same as the other conformed (for a more detailed description of crystals packing, see the Supporting Information).

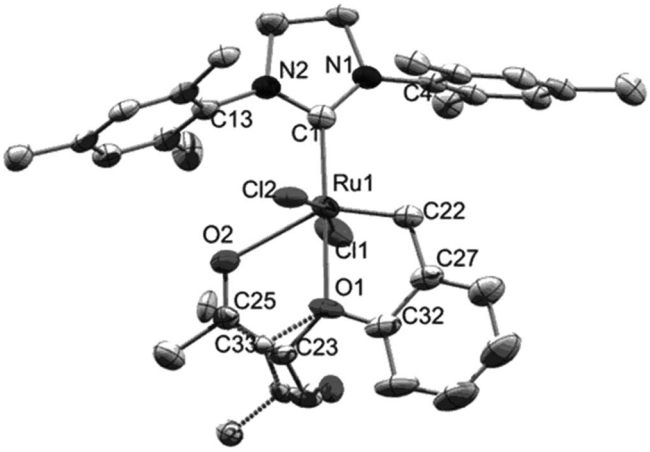


Figure 5. Molecular structure of **M51B** crystallized from CH_2Cl_2/*n*-pentane mixture. All solvent molecules and hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level. The closed form is shown with gray bonds and the open form with dotted bonds.

Pre-catalyst **M51** crystallized from a solution of CH_2Cl_2 and MeOH forms a triclinic P-1 structure with two molecules of the pre-catalyst in the asymmetric unit (**M51C**, Figure 6). Both of these are in the open form, with a five-ligand coordination around the ruthenium center. The pre-catalyst molecules form dimers connected by weak π-π interactions between two carbon atoms in the NHC ligands [the length of the C(56)–C(58) [1−*x*, 1−*y*, 1−*z*] contact is 3.782(7) Å, see the Supporting Information).

The structure of **M52** which has already been reported,[9b] was measured again at low temperature to permit comparison with the other structures examined in this study.[11] **M52** crystallizes in the P-1 triclinic

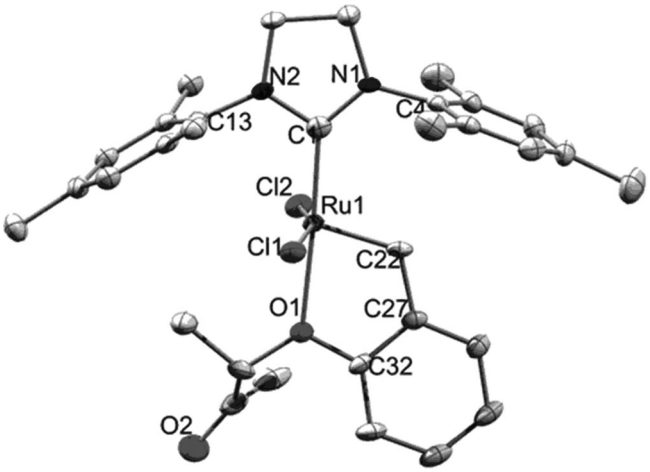


Figure 6. Molecular structure of **M51C** crystallized from CH_2Cl_2/MeOH mixture. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

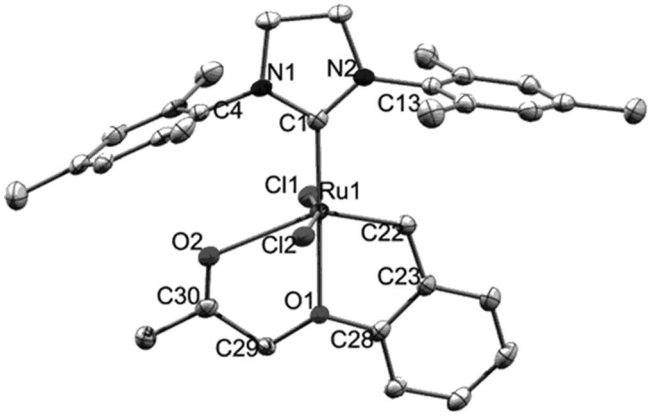


Figure 7. Molecular structure of **M52** crystallized from CH_2Cl_2/*n*-pentane mixture. All solvent molecules and hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

space group with one disordered molecule of CH_2Cl_2 (Figure 7). The **M52** molecule forms the closed conformer in the crystal structure with the O(2) oxygen atom as the sixth ligand. The crystal packing reveals the layered arrangement of molecules with one layer consisting of the NHC ligands and the second of the rest of the molecules (see the Supporting Information).

The most striking differences between crystal forms of the **M51** pre-catalyst are the molecular geometry and molecular packing in the crystal lattices. As we have already mentioned, **M51** can form either the six- or the five-coordinated structures. In the crystal lattices of **M51A** and **M51C**, only the open form of the complexes occurs, whereas in the case of **M51B** both forms are present.

For **M52**, the closed form is found with the ruthenium atom coordinated by six ligands. A comparison of all structures reveals that the formation of the closed form leads to an elongation of bonds between the Ru(1) and C(1), C(22), Cl(1) and Cl(2) atoms. The bond distances Ru(1)–C(1), Ru(1)–C(22) are 1.978(2) Å and 1.819(3) Å for **M51A** and 1.959(5) Å, 1.815(5) Å for **M51C**, while in **M51B** and **M52** respective values are 1.985(3), 1.827(3) Å and 1.983(3) Å, 1.836(2) Å. A similar relationship is present for the bond lengths between the ruthenium and the chloride atoms. However, the opposite trend occurs for the Ru(1)–O(1) bond length where values of 2.271(2) Å for **M51A**, 2.243(3) Å for **M51C** are found but for **M51B** is measured as 2.200(2) and 2.225(2) Å for **M52**. For the Ru(1)–O(2) bond, lengths of 2.458(3) Å and 2.511(2) Å for **M51B** and **M52** are measured, respectively. Moreover, the six-coordinated ruthenium complexes have wider angles between the chloride ligands: 166.25(3)° for **M52**, 164.25(3)° for **M51B** and 158.63(3)° for **M51A**, 161.51(4)° for **M51C**. However,

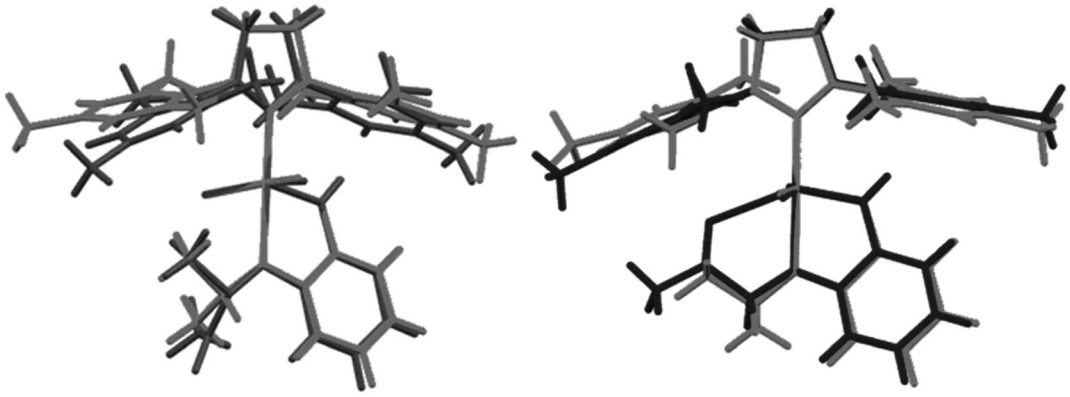


Figure 8. *Left*: Overlay of molecules from the **M51A** structure (dark) and the **Hov-II** (light) one; RMS = 0.026. *Right:* Overlay of molecules from the **M52** structure (dark) and **Hov-II** (light); RMS = 0.087.

the most significant differences are found in torsion angles. The **M52** molecule forms a non-planar five-membered ring based on the Ru(1), C(22), C(23), C(28) and O(1) atoms. The torsion angle C(22)–Ru(1)–O(1)–C(28) is 16.2(3)° for **M52** while the corresponding values for **M51A**, **M51B**, **M51C** are 2.8(2)°, −8.0(2)° and 7.4(3)°.

The root mean square (RMS) analysis, taking into account the following six atoms: Ru(1), C(1), C(22), O(1), Cl(1) and Cl(2), reveals similarities with the reported structure of pre-catalyst **Hov-II**.[12] The RMS values are 0.026, 0.067, 0.078 and 0.087 for **M51A**, **M51B**, **M51C** and **M52**, respectively, see Figure 8. **M51A** has the most closely related molecular geometry to that of **Hov-II** and the small values of the RMS indicate a possible presence of several molecular conformers.

The molecular structure of **M51** varies in different crystalline environments. This means that the molecule is flexible and can adjust its geometry. This suggests that the flexibility of the pre-catalyst is strongly dependent on polarity and size of the solvent molecules used for crystallization and weak interactions within the crystal lattice. It may also help explain some catalytic behaviour.

Stability of Pre-Catalysts in Solution

Catalytic performance of any given pre-catalyst is always affected by its stability in solution. In order to highlight this factor, we performed a comparative stability study of **M51** and **M52** in dry CD_2Cl_2 solution under argon at 22 °C in sealed NMR tubes. Pre-catalyst **M51** shows progressive decomposition, however after 10 days still a large amount of catalyst was present (54% of the initial amount, according to ^{1}H NMR, using durene as internal standard). Its analogue, **M52**, in contrast, underwent visibly faster decomposition during the first day (after 20 h, only 30% of the initial catalyst remained), although complete decomposition was not observed even after 10 days (10% of **M52** was still present after 240 h). This lower stability of **M52** must have an important impact on its overall catalytic performance, especially in reactions requiring longer time and higher temperatures. In such cases better results are obtained with **M51** (see CM in Scheme 1).

Conclusions

The efficiency in olefin metathesis reactions of the modified Hoveyda–Grubbs type pre-catalysts **M51** and **M52** has been described. Both pre-catalysts can be used with di- and trisubstituted dienes in ring-closing metathesis achieving high yields at room temperature. Nevertheless, these complexes are not thermally stable enough to perform efficiently ring-closing metathesis leading to products with a tetrasubstituted double bond. **M52** does not exhibit high solution phase stability. Enyne cyclization and cross metathesis reactions can be performed and products are obtained in good yields. In the case of easily ring-closed substrates, **M51** and **M52** provide similar results. However, in more challenging transformations, **M51** exhibits higher catalytic activity than **M52**. This is a result of poorer solution phase stability of **M52** when compared to **M51. M51** exhibits the typical Hoveyda–Grubbs type configuration (five-coordinated ruthenium) while **M52** possesses six-coordination and octahedral geometry. While the crucial bond lengths are rather similar in both complexes, the torsion of the five membered ruthenacycle [C(22)–Ru(1)–O(1)–C(28)] is much more significant in **M52** than in **M51**. Although geometries obtained in the solid state can hardly provide information about existing solution conformations, the X-ray studies show that the geometry of **M51** is strongly dependent on solvent of crystallization polarity and size. We propose that the

higher activity of **M51** with more difficult substrates is related to its higher stability.

Experimental Section

All reactions were carried out under an inert atmosphere of argon.

RCM of Diethyl Diallylmalonate (Figure 3)

An NMR tube was charged with **1** (0.16 mmol, 38.6 mg) dissolved in CD_2Cl_2 (0.7 mL) and a stock solution (100 μL) of the catalyst (0.016 mmol dissolved in 1 mL) in CD_2Cl_2. The reaction was followed by ^{1}H NMR spectroscopy (Varian 200 MHz) at 296 K.

General Procedure for Olefin Metathesis Reactions (Table 1, Table 2, Table 3)

A 5-mL screw-cap vial fitted with a septum and equipped with a magnetic stirring bar was charged with the substrate (0.25 mmol), methyl acrylate if appropriate (45 μL, 0.5 mmol), the appropriate solvent (0.5 mL) and a stock solution of the pre-catalyst. The reaction mixture was stirred at the indicated temperature for 18 h. The crude product was analyzed by GC and purified by column chromatography (SiO_2, Et_2O/pentane, see the Supporting Information for details).

RCM Reaction Leading to 38 (Figure 4)

In a Schlenk tube, substrate **37** (140 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (2 mL) under an argon atmosphere, **M51** (3 mg, 1 mol%) was added in one portion as a solid. The reaction mixture was heated to reflux temperature for 3 h. The solvent was removed under vacuum and the crude product was purified by column chromatography (SiO_2, EtOAc:cyclohexane 1:9). Product **38** was obtained as a viscous oil; yield: 111 mg (87%); mp 67–69 °C. IR (film): ν = 3447, 2925, 1459, 1387, 1366, 1347, 1191, 1110, 1084, 1041, 1014, 938, 805, 712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.80 (dt, J = 6.0 Hz, J = 1.4 Hz, 1H), 5.80 (dt, J = 6.0 Hz, J = 2.4 Hz, 1H), 4.67–4.59 (m, 2H), 1.85 (dt, J = 12.2 Hz, J = 3.2 Hz, 1H), 1.75–1.61 (m, 6H), 1.56 (tt, J = 13.5 Hz, J = 3.4 Hz, 1H), 1.46–1.29 (m, 6H), 1.27 (s, 3H), 1.13 (s, 3H), 1.06 (t, J = 4.1 Hz, 1H), 0.96–0.89 (m, 2H), 0.86 (s, 3H), 0.78 (s, 3H), 0.77 (s, 3H); ^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 134.1 (CH), 125.1 (CH), 90.6 (C), 74.5 (CH_2), 74.2 (C), 62.1 (CH_3), 59.2 (CH_3), 44.4 (CH_2), 43.9 (CH_2), 42.0 (CH_2), 39.7 (CH_2), 39.2 (C), 33.4 (CH_3), 33.2 (C), 26.1 (CH_3), 24.0 (CH), 21.5 (CH), 20.5 (CH_2), 19.5 (CH_2), 18.4 (CH_2), 15.3 (CH_3); HR-MS (EI) m/z = 320.2721, calcd. for $C_{21}H_{36}O_2$: 320.2717; elem. anal. calcd. for $C_{21}H_{36}O_2$: C 78.70, H 11.32; found: C 78.55, H 11.11.

CM Reaction Leading to 40 (Figure 4)

Estrone derivative **39** (142 mg, 0.4 mmol) and *tert*-butyl acrylate (155 mg, 1.2 mmol) were charged in a Schlenk tube and dissolved in CH_2Cl_2 (2 mL). **M51** (1 mol%) was added in one portion and the reaction mixture was heated to reflux temperature for 3 h. The solvent was removed under vacuum and the crude product purified by column chromatography (SiO_2, EtOAc:cyclohexane 1:4) and recrystallized from cold *n*-hexane. **40** was obtained as a colorless solid; yield: 172 mg (95%); mp 134–136 °C. IR (film): ν = 2932, 1757, 1739, 1712, 1653, 1494, 1454, 1368, 1291, 1223, 1151, 1140, 1084, 1007, 978, 849, 820 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29 (d, J = 8.1 Hz, 1H), 6.90 (dt, J = 15.6 Hz, J = 6.7 Hz, 1H), 6.85 (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 6.80 (d, J = 2.5 Hz, 1H), 5.85 (dt, J = 15.7 Hz, J = 1.6, 1H), 2.93–2.88 (m, 2H), 2.71 (dt, J = 7.9 Hz, J = 1.3 Hz, 2H), 2.64–2.58 (m, 2H), 2.55–2.47 (m, 1H), 2.44–2.37 (m, 1H), 2.28 (dt, J = 10.7 Hz, J = 4.0 Hz, 1H), 2.15 (dt, J = 19.1 Hz, J = 8.9 Hz, 1H), 2.09–1.93 (m, 3H), 1.68–1.52 (m, 5H), 1.48 (s, 9H), 1.47–1.42 (m, 1H), 0.91 (s, 3H); ^{13}C-{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 220.7 (C), 171.1 (C), 165.6 (C), 148.4 (C), 144.7 (CH), 138.0 (C), 137.5 (C), 126.4 (CH), 124.3 (CH), 121.5 (CH), 118.6 (CH), 80.3 (C), 50.4 (CH), 47.9 (C), 44.1 (CH), 37.9 (CH), 35.8 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 29.3 (CH_2), 28.1 (CH_3), 27.1 (CH_2), 26.3 (CH_2), 25.7 (CH_2), 21.5 (CH_2), 13.8 (CH_3); HR-MS (ESI) m/z = 475.2445, calcd. for $C_{28}H_{36}O_5Na$: 475.2455; elem. anal. calcd. for $C_{28}H_{36}O_5$: C 74.31, H 8.02; found: C 74.28, H 8.19.

Acknowledgements

The authors gratefully acknowledge the Royal Society (University Research Fellowship to CSJC), the EC (CP-FP 211468-2 EUMET) and the Polish Ministry of Science and Higher Education (grant number NN204404940) for funding. Additionally, CS acknowledges personal fellowship from the "START-2012" grant for young researchers, which was given by The Foundation for Polish Science.

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