

Modelling of structures and reactions paths of ruthenium complexes, potential olefin metathesis catalysts



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Summary of scientific achievements in relation to habilitation procedure

Warszawa, 06.04.2017

1. Name and surname.

Bartosz Trzaskowski

2. Diploma and degrees.

Ph.D. degree in chemistry, Faculty of Chemistry, University of Warsaw (Warszawa, Poland), 12th of October 2005, „Theoretical model of the nonenzymatic and enzymatic solvolysis of cytidine 5'-monophospho-N-acetylneuraminic acid”.

Ms.C. degree in chemistry, Faculty of Chemistry, University of Warsaw (Warszawa, Poland), 26th of June 2001, „Octahedral manganese complexes - an introduction to the modeling of inhibitors of the small cell lung cancer”.

3. History of employment

since 01.2013	Centre of New Technologies, University of Warsaw, Warszawa, Poland – assistant professor (adjunct)
02.2012 – 12.2012	International Institute of Molecular and Cell Biology in Warsaw, Warszawa, Poland – computer programmer
09.2011 – 12.2012	Faculty of Chemistry, University of Warsaw, Warszawa, Poland – assistant professor (adjunct)
09.2010 – 08.2011	Faculty of Chemistry, University of Warsaw, Warszawa, Poland – researcher
07.2008 – 08.2010	Department of Chemistry, California Institute of Technology, CA, USA – postdoctoral scholar
10.2005 – 06.2008	Department of Chemistry, University of Arizona, Tucson, AZ, USA – postdoctoral scholar
12.2000 – 06.2001	Nałęcz Institute of Biocybernetics and Biomedical Engineering Polish Academy of Sciences, Warszawa, Poland - assistant

4. Indication of achievement resulting from Article 16 Section 2 of the Act on University Degrees and the University Title and on University Degrees and the University Title in the Field of Fine Arts of March 14, 2003 (Journal of Laws No. 65, item 595, with later amendments):

a) title of scientific achievement

Modelling of structures and reactions paths of ruthenium complexes, potential olefin metathesis catalysts

b) list of publications constituting the scientific achievement

* - corresponding author	IF	Number of citations Web of Science/Scopus
<p>H1. K. Żukowska, A. Szadkowska, B. Trzaskowski*, A. Pazio, Ł. Pączek, K. Woźniak, K. Grela, “3-bromopyridine as a sixth ligand in sulfoxide-based hoveyda complexes: A study on catalytic properties”, <i>Organometallics</i>, 32, 2192-2198 (2013).</p> <p>My contribution to this work consisted of designing and performing the computational part of the study, data processing, as well as preparing the computational of the Supporting Information file and writing the computational of the manuscript. I estimate my contribution to be equal to 25%.</p>	4.253	15/19
<p>H2. B. Trzaskowski*, K. Grela, “Structural and mechanistic basis of the fast metathesis initiation by a six-coordinated ruthenium catalyst”, <i>Organometallics</i>, 32, 3625-3630 (2013).</p> <p>My contribution to this work consisted of designing and performing the entire study, data processing, as well as preparing the Supporting Information file and writing and publishing manuscript. I estimate my contribution to be equal to 80%.</p>	4.253	11/13
<p>H3. A. Pazio, K. Woźniak, K. Grela, B. Trzaskowski*, “Conformational flexibility of Hoveyda-type and Grubbs-type complexes bearing acyclic carbenes and its impact on their catalytic properties”, <i>Organometallics</i>, 34, 563-570 (2015).</p> <p>My contribution to this work consisted of designing and performing most of the study, data processing, as well as preparing the Supporting Information file and writing and publishing manuscript. I estimate my contribution to be equal to 70%.</p>	4.186	8/9
<p>H4. A. Pazio, K. Woźniak, K. Grela, B. Trzaskowski*, “Nitrenium ions and trivalent boron ligands as analogues of N-heterocyclic carbenes in olefin metathesis; a computational study”, <i>Dalton Transactions</i>, 34, 20021-20026 (2015).</p> <p>My contribution to this work consisted of designing and performing most of the study, data processing, as well as preparing the Supporting Information file and writing and publishing manuscript. I estimate my contribution to be equal to 70%.</p>	4.177	3/4
<p>H5. B. Trzaskowski*, K. Ostrowska, “Structural analogues of Hoveyda-Grubbs catalysts bearing 1-benzofuran moiety or isopropoxy-1-benzofuran derivatives as olefin metathesis catalysts”, <i>RSC Advances</i>, 6, 21423-21429 (2016).</p> <p>My contribution to this work consisted of designing and performing the entire study, data processing, as well as preparing the Supporting</p>	3.289	1/2

Information file and writing and publishing manuscript. I estimate my contribution to be equal to **80%**.

H6. B. Trzaskowski*, K. Grela, “Hoveyda-Grubbs complexes with boryl anions are predicted to be fast metathesis catalysts”, *Catalysis Communications*, 86, 133-138 (2016).

3.389

0/1

My contribution to this work consisted of designing and performing the entire study, data processing, as well as preparing the Supporting Information file and writing and publishing manuscript. I estimate my contribution to be equal to **80%**.

H7. B. Trzaskowski*, K. Ostrowska, “A computational study of structures and catalytic activities of Hoveyda-Grubbs analogues bearing coumarin or isopropoxycoumarin moiety”, *Catalysis Communications*, 91, 43-47 (2017).

3.389

0/0

My contribution to this work consisted of designing and performing the entire study, data processing, as well as preparing the Supporting Information file and writing and publishing manuscript. I estimate my contribution to be equal to **80%**.

H1-H7. Σ

26.936

38/48

c) brief description of the scientific goal and the results described in the publications constituting scientific achievement

1. Scientific goal

The scientific objective of my work was the use of computational quantum chemistry methods to describe the mechanisms of reactions catalyzed olefin metathesis ruthenium catalysts and the rational design of new ruthenium-based catalysts.

Olefin metathesis reaction (Fig. 1) of forming new C-C bonds is one of the most important reactions in organic synthesis. The first observation of the metathesis of propene at high temperature was reported in 1931, but due to lack of known catalysts for this reaction and the requirements of very high temperatures (700-800°C) it attracted very little interest.¹ The first catalyzed metathesis reactions were found in the 1950's when industrial chemists at Du Pont reported that propene led to ethylene and 2-butenes when it was heated with molybdenum (in the form of the metal, oxide or $[\text{Mo}(\text{CO})_6]$).² The use of the catalyst allowed for the reduction of the required temperature to 150-500 °C, depending on the substrate. In 1960 Eleuterio et al. performed the first polymerization reaction based on metathesis in the presence of $\text{WCl}_6/\text{AlEt}_2\text{Cl}$, but it was recognized only in 1967 that ROMP and the disproportionation of acyclic olefins were the same reaction.³

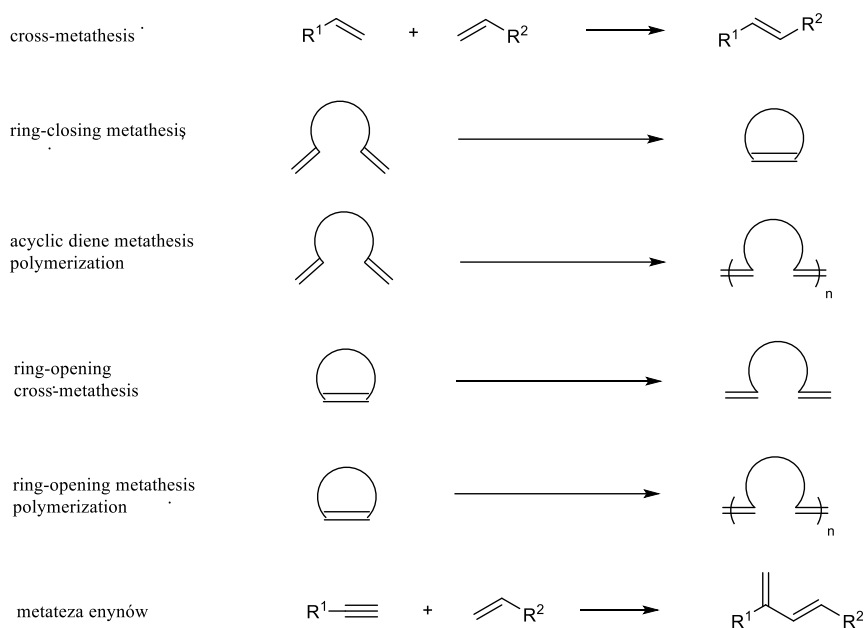


Fig. 1. Different types of olefin metathesis.

The same period saw first attempts to explain the mechanism of olefin metathesis reactions catalyzed by the $\text{M}(\text{CO})_6$ type of complexes. The most important attempts were published by Calderon (1968), Pettit (1971), Herrison and Chauvin (1971) and Grubbs (1972). The experimental results presented by Chauvin in 1971 and in several other works in later years proved that the mechanism proposed by this author is the correct mechanism of the metathesis olefin.⁴ This mechanism (Fig. 2) postulates that instead of a direct [2+2] cycloaddition between the two olefins, which has a high activation energy, the cycloaddition occurs between one of the olefins and the catalyst to form an unstable metallocyclobutane intermediate. In the next step, a second [2+2] cycloaddition takes place to yield the formation of a new C-C bond and the recovery of the catalyst. Yves Chauvin was awarded the Nobel Prize in 2005 for the elucidation of the mechanism of olefin metathesis reactions.

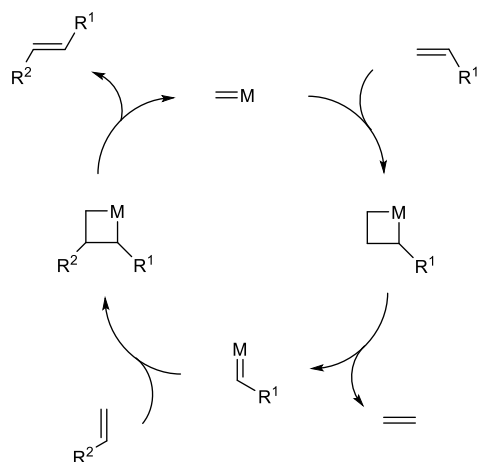


Fig. 2. Olefin metathesis catalytic cycle proposed by Chauvin. M – transition metal.

In 1980 Richard Schrock synthesized the first metathesis catalysts based on tantalum $[Ta(=CH-*t*-Bu)Cl(PMe_3)(O-*t*-Bu)_2]$ and a similar niobium complex, followed by a series of very efficient molybdenum and tungsten catalysts with the structure $[M(=CHCMe_2Ph)(=N-Ar)(OR_2)]$.⁵ In the 80s and 90s his group designed and synthesized a large series of similar molybdenum and tungsten complexes with excellent catalytic profiles, which could be also used in asymmetric catalysis (Fig. 3).⁶ Many of these catalyst are used commonly today and have a great commercial potential and very efficient and fast catalysts. Richard Schrock is the second recipient of the 2005 Nobel Prize in chemistry.

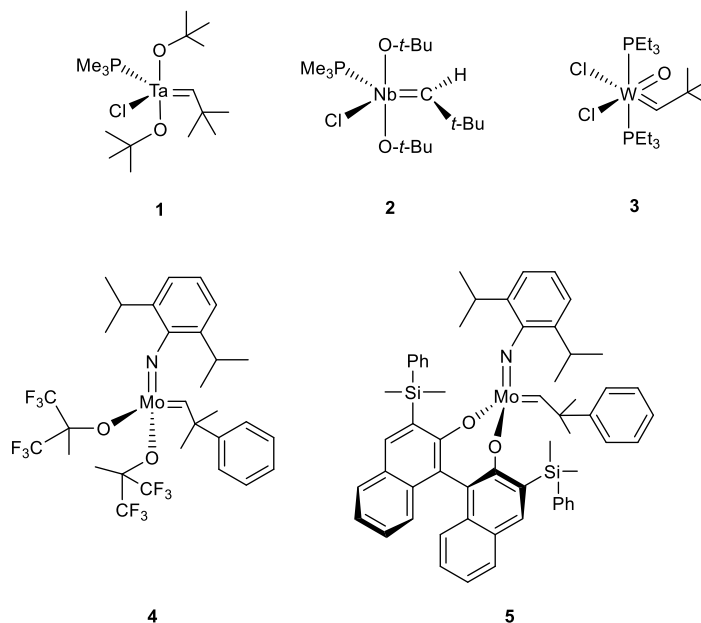


Fig. 3. Selected Schrock catalysts. **1**, **2**, **3** – early tantalum, niobium and tungsten catalysts; **4** – commercially available molybdenum catalyst; **5** – Schrock's first asymmetric molybdenum catalyst.

The third recipient of the 2005 Nobel Prize in chemistry for the development of the metathesis method in organic synthesis has been Robert H. Grubbs. In 1992 Grubbs showed a very efficient olefin catalysts based on ruthenium core $[RuCl_2(PPh_3)(=CH-CH=CPh_2)]$.⁷ Three years later Grubbs synthesized a similar complex $[RuCl_2(PCy_3)(=CH-Ph)]$ (named later 1st generation Grubbs catalyst), which was a great commercial success and for many years one of the most used metathesis catalysts.⁸ In 1999 Grubbs, Nolan, Herrmann and Furstner prepared independently a similar complex, called later 2nd generation

Grubbs catalyst) which had one of the PCy_3 groups replaced by a N-heterocyclic carbene, SIMes.⁹ To these days this system remains the most commonly used metathesis catalysts due to a very good efficiency and the possibility of performing metathesis at low temperatures. The structure of this complex allows also multiple and easy-to-introduce structural modifications which may alter its catalytic properties depending on the substrate, solvent and type of metathesis. In the next 17 years literally hundreds ruthenium-based catalysts based on 2nd generation Grubbs catalyst have been prepared and described in the scientific literature. Two of the most successful ones were the Hoveyda-Grubbs catalyst, where the PCy_3 group has been replaced by a propoxybenzylidene moiety and Grela catalyst, which through simple introduction of a nitro group made the catalysts exponentially faster and more active (Fig. 4).¹⁰

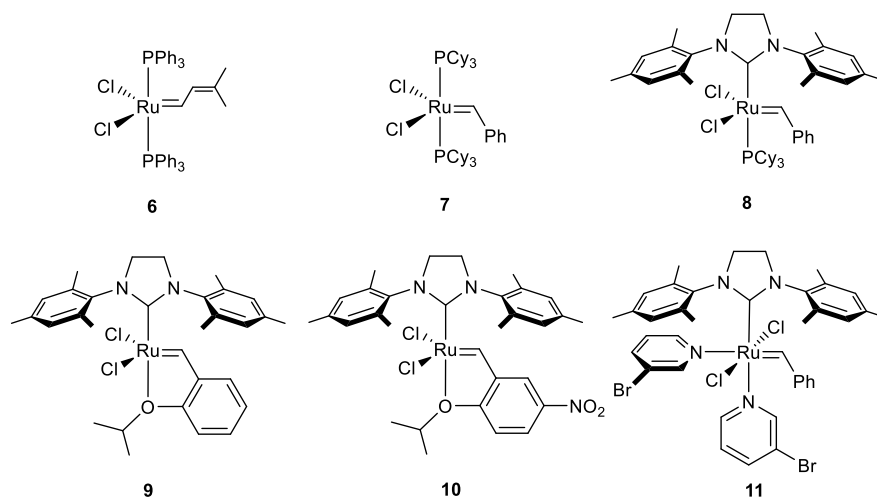


Fig. 4. Selected Grubbs-type catalysts. **6** – first ruthenium-based metathesis catalyst; **7** – first generation Grubbs catalyst; **8** – second generation Grubbs catalyst; **9** – Hoveyda-Grubbs catalyst; **10** – Grela catalyst; **11** – third generation Grubbs catalyst.

Metathesis catalysts can be studied not only using the experimental methods but also via theoretical/computational approaches. This task requires, however, very accurate computational methods which are able to describe rigorously the electronic structure of transition metal complexes and subtle van der Waals interactions between different parts of complexes. The last 30 years saw a very rapid development of methods based on density functionals (DFT), which replaces the intractable many-body problem of interacting electrons with a tractable problem of non-interacting electrons moving in an effective potential. In this method the total energy of the system is equal to the sum of kinetic energy of non-interacting electrons $T[\rho]$, electrostatic energy of attraction between electrons and nuclei $E_{\text{ne}}[\rho]$, electrostatic repulsion of electrons $J[\rho]$ and the exchange-correlation energy $E_{\text{xc}}[\rho]$, where all these quantities are a function of three-dimensional electron density. While the first three quantities can be obtained in a relatively easy manner, the exact functionals $E_{\text{xc}}[\rho]$ are not known and different DFT methods try to approximate its values using different approaches and equations. A relatively low complexity of the DFT method, very good description of transition metals systems and good description of electronic correlation made the DFT one of the most important computational methods for description of relatively large (more than 50 atoms) organometallic systems.

Among the large number of available DFT methods the B3LYP method definitely warrants to be mentioned. This very popular hybrid exchange-correlation functional uses a mixture of exchange and correlation energies obtained using the VWN local density approximation, Becke88 exchange energies, Lee, Yang and Parr correlation energies and exact exchange energies obtained using Hartree-Fock

approach. The B3LYP functional gives excellent results for a broad range of molecular systems (though often fails in proper description of non-covalent interactions) and is one of the most commonly used computational methods, with over 90,000 citations of the two original papers.¹¹ The last 10 years saw, however, the development of new exchange-correlation functionals which addressed the problem of the inaccurate description of the intermolecular interactions, such as π - π stacking, π -cation interactions and hydrophobic interactions. From the many new functionals published recently the M05-M06-M08 class of Truhlar functionals gained large popularity. These functionals are based on a large number of parameters which are fitted to accurate experimental data, including the MGAE109 database (atomization energies of 109 simple molecules), IP13 (ionization energies of 13 atoms and simple molecules), EA13 (electron affinities of 13 atoms and simple molecules), PA8 (proton affinities of 8 simple molecules), DBH76 (barrier heights for 76 reactions), NCCE31 (interaction energies of 31 non-covalent complexes), TMML30 (atomization energies of 9 transition metals and bond energies of 21 transition metal complexes), ABDE4 (dissociation energies of 4 small organic systems), AE17 (total energies of 17 atoms) and piTC13 (thermochemical data of organic compounds with pi bonds). Benchmark show that these functionals give average errors which are several times lower than those for B3LYP functionals when estimating the energies of non-covalent interactions, while performing as good in the description of geometries of molecular systems.¹²

The rapid development of both experimental methods of organic chemistry and computational methods allowed for detailed understanding of metathesis reaction mechanism catalyzed by Schrock and Grubbs catalysts and, in particular, the mechanism of precatalyst initiation (the mechanism of the rest of the catalytic cycle follows the Chauvin mechanism described earlier). In the case of first and second generation Grubbs catalyst the initiation mechanism has been proposed by Grubbs in 1997.¹³ This mechanism, presented in Figure 5, starts with the dissociation of the PCy₃ group and the formation of an active, 14e complex (**int1**, Fig. 5) which immediately coordinates the olefin (substrate) and starts the metathesis catalytic cycle. The dissociation of the PCy₃ moiety has the largest free energy barrier of the entire catalytic cycle, hence is the rate-limiting step of the reaction. Grubbs measured the reaction rate constant for a number of his catalysts which allowed him to estimate their free energy ΔG^\ddagger , enthalpy ΔH^\ddagger and entropy ΔS^\ddagger of activation, presented in Table 1.

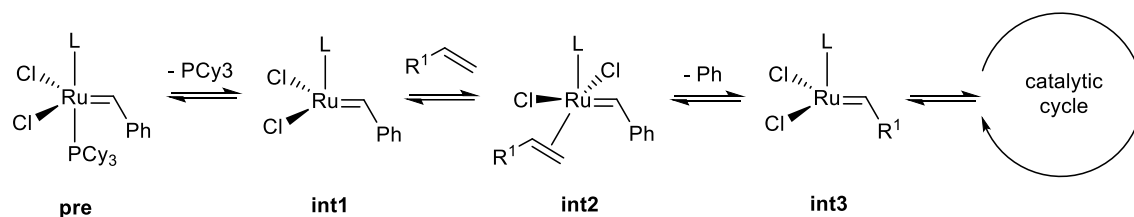


Fig. 5. Initiation/activation mechanism for first and second generation Grubbs catalysts. **L** = PCy₃ or PPh₃ or IMES.

Table 1. Reaction rate constants k_{init} , free energies of activation ΔG^\ddagger , enthalpies of activation ΔH^\ddagger and entropies of activation ΔS^\ddagger for selected Grubbs catalysts.

catalyst	temperature (°C)	k_{init} (s ⁻¹)	ΔG^\ddagger (kcal/mol)	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (cal/mol)
6	25	$1,0 \pm 0,1 \cdot 10^{-3}$	-	-	-
7	10	$1,0 \pm 0,1 \cdot 10^{-3}$	+19,88	-23,6	-12
8	35	$4,6 \pm 0,4 \cdot 10^{-4}$	+23,0 ± 0,04	+27 ± 2	-13 ± 6
9	2	$4,3 \cdot 10^{-4}$	+20,69 ± 0,2	+15 ± 2	-19 ± 3

In the case of Hoveyda-Grubbs catalysts **9** a similar, dissociative mechanism (with the entire catalytic cycle starting with the Ru-O bond dissociation) was believed to be true for many years. A relatively recent paper by Ashworth et al. from 2011 questioned, however, the dissociative mechanism of the initiation step of Hoveyda-type catalysts and recent experimental studies by Plenio validated these findings. Both groups considered three possible initiation mechanisms for the pre-catalyst, termed dissociative, associative and interchange have been discussed (Fig. 6). The simplest initiation mechanism (dissociative) involves rupture of the Ru-O(alkoxy) bond to create a vacant Ru binding site for the incoming olefin substrate. This behavior resembles the mechanism favored for the first and second generation Grubbs complexes, which is supported by evidence from computational and solution experimental studies. Alternative mechanisms involve the olefin itself. In the associative mechanism the olefin forms a six-coordinate intermediate with the Ru complex, while the interchange mechanism involves simultaneous olefin binding and alkoxy dissociation. The result of computational study suggested that the third option (interchange mechanism) is the most favorable from the energetics point of view.¹⁴ These theoretical findings were later partially confirmed experimentally. The group of Plenio showed in two seminal works that this reaction may simultaneously follow two parallel pathways: dissociative and interchange, depending on the electronic/steric properties of both the catalyst and the substrate.¹⁵ In general small olefins follow the interchange mechanism only, while larger ones follow mostly the dissociative mechanism.

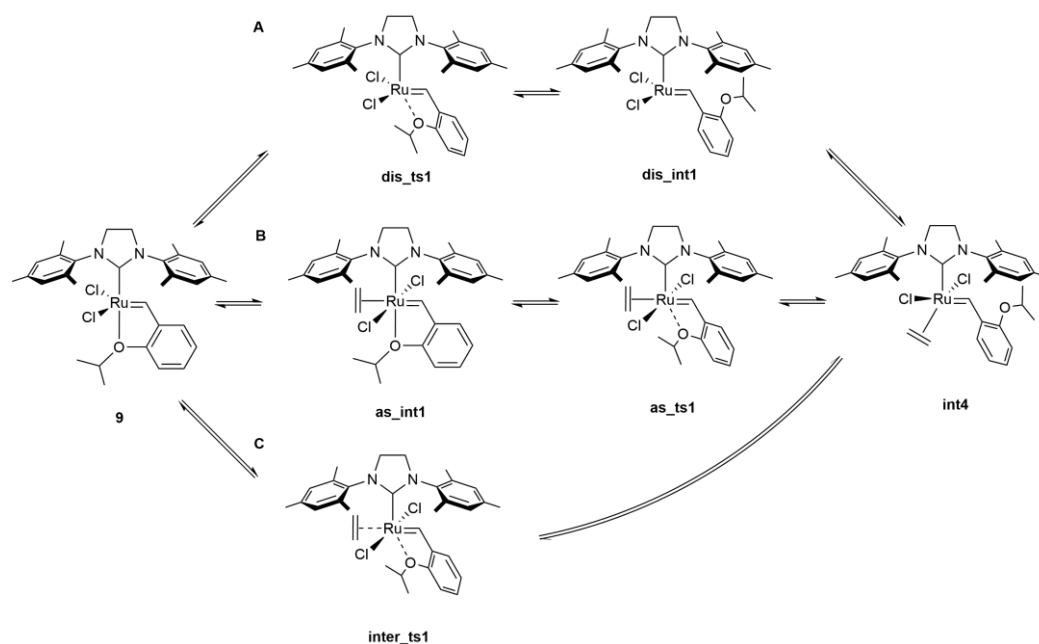


Fig. 6. Theoretically possible initiation mechanisms for the Hoveyda-Grubbs catalyst. **A** – dissociative mechanism; **B** – associative mechanism; **C** – interchange mechanism.

The year 2011 is also the time in which I moved into the field of olefin metathesis. The results of my research are presented in the next section.

2. Results

Third generation Grubbs catalyst (**11**) is one of the fastest initiating metathesis catalysts with the initiation rate constant (4 s^{-1} at 5°C) being six orders of magnitude larger than the initiation rate constant of **8** and three orders of magnitude larger than the initiation rate constant of **9**.¹⁶ Due to these findings we asked ourselves a question: what is the initiation mechanism of this catalysts and what is the effect

of the additional ligand (3-bromopyridine) on the reaction rate of this and similar systems. To explore this problem Karol Grela and his group synthesized a series of sulfoxide-based Hoveyda-Grubbs catalyst with and without the 3-bromopyridine (Fig. 7).

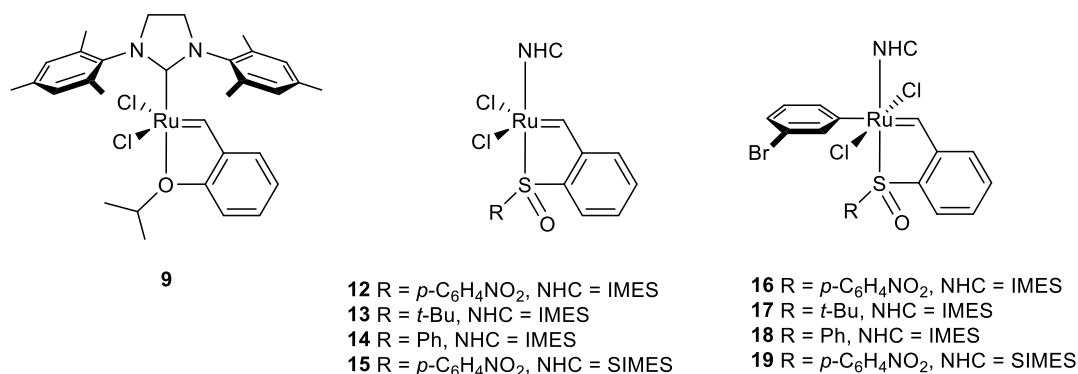


Fig. 7. Structure of Hoveyda-Grubbs catalyst (**9**) and new catalysts studies in paper **H1**. IMES = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene.; SIMES = 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene

Experimental studies of the metathesis reaction rates using this series of catalysts showed large differences between them. In the ambient temperature complexes without 3-bromopyridine were completely inactive, while complexes with 3-bromopyridine were partially active in ring-closing metathesis. At 40°C both complexes were partially active, but the 3-bromopyridine-substituted catalysts reached the maximum conversion much faster. A similar trend was observed at higher temperatures (50°C, 60°C and 80°C), where the 3-bromopyridine-substituted catalysts were both much faster and catalyzed the reaction much more efficiently.

The computational studies of catalysts initiation were performed by me for catalysts **12**, **16** and **19** and described in paper **H1**. In the computational part of this study we used a well-established protocol which was successfully used to describe reaction paths and transition states of similar five-coordinated Hoveyda type with good accuracy. We have used an all-atom model for the catalyst and an ethylene molecule to model the substrate of olefin metathesis. For each system we have performed full geometry optimizations of all theoretically possible and chemically feasible stationary points using B3LYP/lacvp**. To evaluate accurate free energies of all stationary points, we used M06/lacv3p+** single-point calculations and to add solvent contribution, we used Poisson-Boltzmann self-consistent polarizable continuum method. For each stationary point we have confirmed that all vibration frequencies are positive for minima and that only one is imaginary for transition states. Free energies were defined as the sum of electronic energy (from single-point M06/LACV3P+** calculations), solvation energy, zero-point energy correction, thermal correction to enthalpy, and the negative product of temperature and entropy (at 298 K).

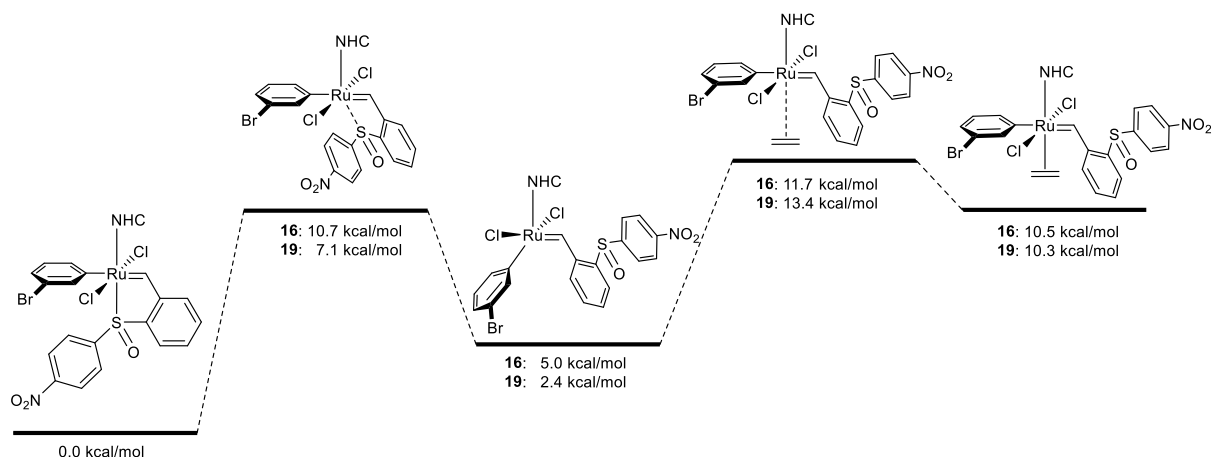


Fig. 8. Initiation mechanism for catalysts **16** and **19** and Gibbs free energies for selected stationary points.

We include all three theoretically possible mechanisms (dissociative, associative, interchange) in all calculations performed in this study. For system **12** the lowest value of ΔG^\ddagger was found for interchange mechanisms at 17.4 kcal/mol, but for the interchange mechanism this value was only slightly higher (18.5 kcal/mol). For complexes **16** and **19** the first step of the reaction is the dissociation of the Ru-O bond ($\Delta G^\ddagger = 7.1$ kcal/mol for **19** and 10.9 kcal/mol for **16**) which can be followed by three different scenarios: 3-bromopyridine dissociation, olefin association or simultaneous occurrence of both of these actions. Our calculations showed that olefin association is the most energetically-favorable scenario ($\Delta G^\ddagger = 11.7$ kcal/mol for **16** and 13.4 kcal/mol for **19**) followed by 3-bromopyridine dissociation in a second, separate step. The difference in Gibbs free energy of activation (ΔG^\ddagger) between **16** and **12** of approximately 6 kcal/mol explains the experimentally found fast initiation of **16** and relatively slow initiation of **12**.

It is worth noticing that the mechanism of initiation of third generation Grubbs catalyst **11** was not known at that moment. In our next investigation we decided to study this system and all theoretically possible initiation mechanisms to find the one with the lowest Gibbs free energy of activation (paper **H2**). The reaction rate constant for this catalyst of more than 4 s^{-1} (at $5 \text{ }^\circ\text{C}$) can be translated (using Eyring equation) to $\Delta G^\ddagger < 15.5$ kcal/mol. In this work we used the same computational protocol, but used dichloromethane as the model solvent and two different models of olefin, ethylene and 2-*trans*-butene.

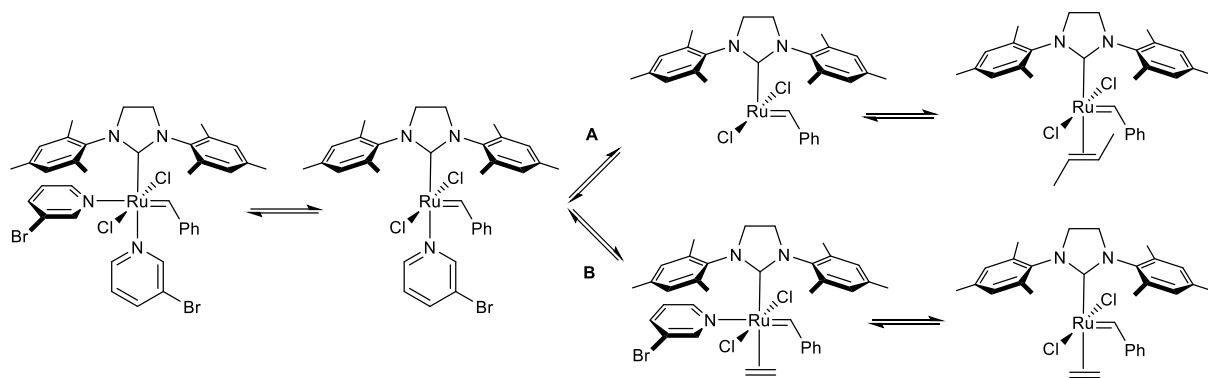


Fig. 9. The most plausible initiation mechanism of third generation Grubbs complexes for large olefins (A) and small olefins (B).

In this work we considered a total of four different mechanisms of initiation of **11** and a derivative of this complex bearing pyridine moieties instead of 3-bromopyridine (**20**) and using M06 functional for both geometry optimization (in lacvp** basis set) and energy calculation (in lacv3p++** basis set). After performing the calculations we suggested two different initiation mechanisms, depending on the size of the olefin. Both reaction paths start with the dissociation of one of the 3-bromopyridine or pyridine moiety in *cis* position with respect to the benzyldiene group. The second step of initiation depends on the size of the olefin. For small olefins the next step is the olefin association followed by the dissociation of the second (3-bromo)pyridine moiety. For larger olefins the most energetically favorable path involves first the dissociation of the second (3-bromo)pyridine moiety followed by the olefin association. The obtained values of 11.4 kcal/mol for **11** and 12.4 kcal/mol for **20** are in perfect agreement with the experimental data.

Most Hoveyda-Grubbs-like catalysts contain a N-heterocyclic carbene coordinating the ruthenium atom/ion. There is, however, also a relatively unknown class of catalysts with an acyclic carbene responsible for ruthenium coordination. The most studied example of such system is the N,N'-dimesityl-N,N'-dimethylformamidin-2-ylidene (Fig. 10). It's a very interesting and flexible system which can occur in three different conformation as a free carbene or in four different conformations when coordinating ruthenium in a Hoveydy-Grubbs catalyst analogue. It was found experimentally that in solution this system adopts only one conformation both as the free carbene (*amphi* conformation) and in Hoveydy-Grubbs catalyst analogue (*amphi-L* conformation).¹⁷ In our next study, **H3**, we investigated the conformational flexibility of this system and its impact on the reactivity of the ruthenium complex.

The results of this computational study showed that the *amphi* conformation of carbene **20** and catalysts **21** and **22** is indeed to lowest-energy conformation, though energy differences between various conformations are relatively small, on the level of a few kcal/mol. These differences come from interactions between phenyl and/or methyl groups of the acyclic carbene. In the case of free/unbound groups the interactions strength follows the pattern: benzene-benzene (approx. -3 kcal/mol), benzene-methane (approx. -1.5 kcal/mol), methane-methane (approx. -0.5 kcal/mol) which would suggest that the *anti* conformation should be the most favorable one from the energy point of view.¹⁸ We have shown that the propensity of the acyclic carbene **20** and catalysts **21** and **22** to adopt the *amphi* conformation is a result of a favorable benzene-methyl interaction and an example of a -CH₂... π -driven structure stabilization. Due to the specific geometry constraints in the acyclic carbene such interaction is stronger than the possible pi-pi stacking of two mesityl rings in the *anti* conformation. We also estimated the rotation energy barrier for **20**, **21** and **22** to be approximately 21 kcal/mol.

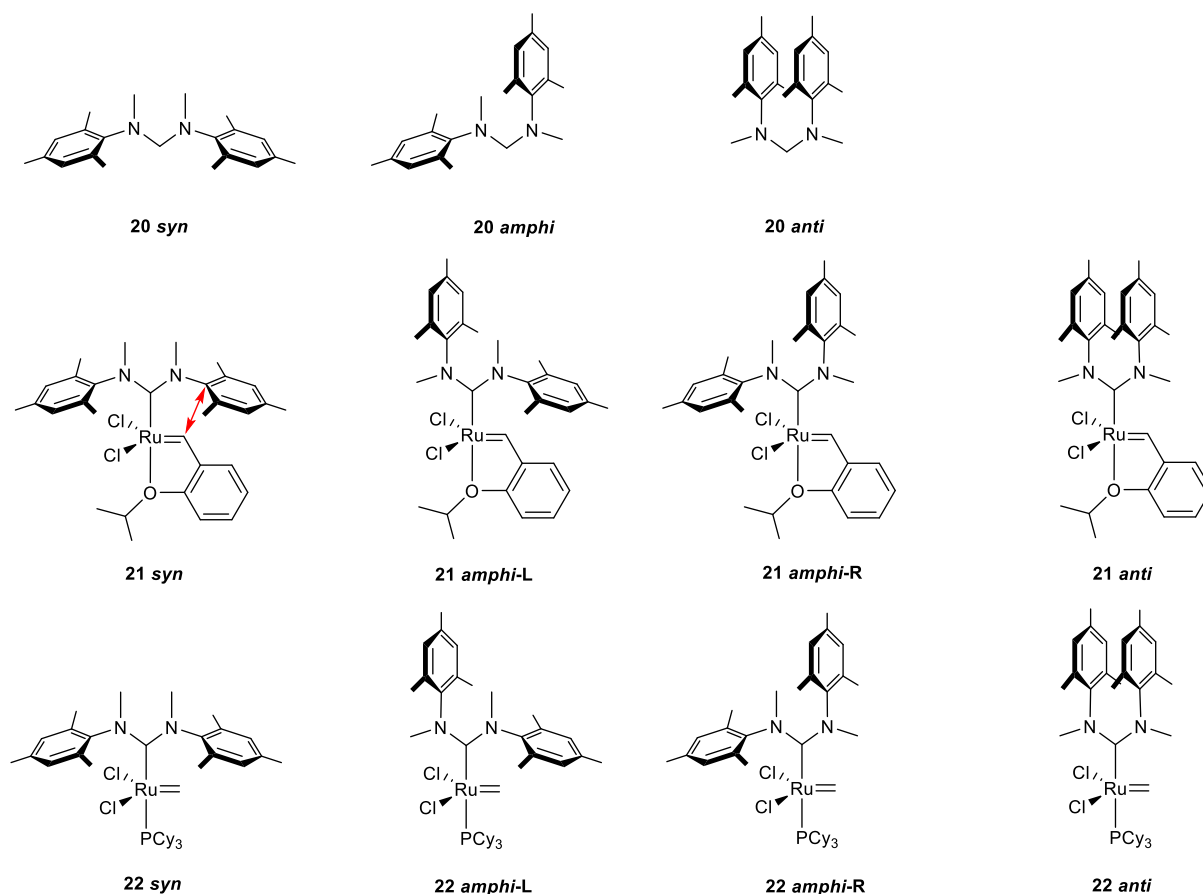


Fig. 10. Acyclic carbene **20** and catalysts incorporating this carbene studies in paper **H3**. Red arrow shows the important interaction between C_{benzylidene} and C_{ipso} carbon atoms.

In the case of Hoveyda-Grubbs catalyst two groups have earlier postulated the existence of an interesting interactions between the C_{benzylidene} and C_{ipso} carbon atoms (Fig. 10).¹⁹ Interestingly both groups suggested that this interactions does not stabilize the structure of the precatalyst. Our calculations support this hypothesis, since both total energies of the *amphi-R* and *amphi-L* conformers are identical as are the rotation barriers of the mesityl groups. The presence of the four possible conformations of system **21** allows, however, also to estimate the impact of this subtle interaction on the Gibbs free energies of activations of this system. The results presented in Figure 11 show that for both the dissociative and interchange mechanism the activation barrier is lowest for the *amphi-L* conformation. We can therefore draw the conclusion that while the C_{benzylidene}-C_{ipso} doesn't indeed stabilize the precatalyst, it does stabilize both the activation transition state and the activated catalyst to produce a relatively low activation energy and a relatively fast catalytic cycle. These results also show that the mesityl group located on the same side as the benzylidene moiety is vital for obtaining an efficient Hoveyda-Grubbs-like catalyst.

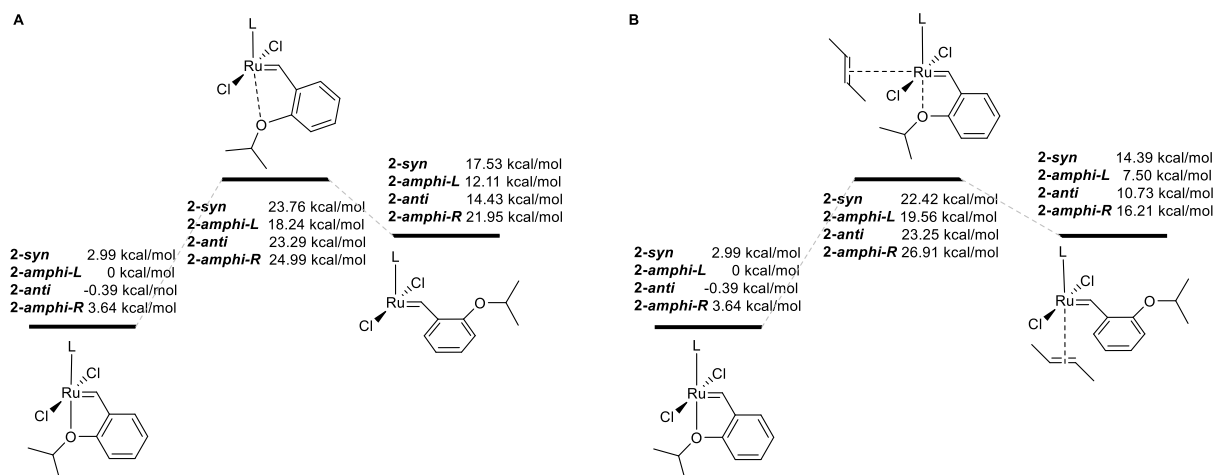


Fig. 11. Relative Gibbs free energies of catalyst **21** activation for the dissociative (**A**) and interchange (**B**) mechanisms.

In the next five papers we decided to use computational methods to rationally design new candidates for metathesis catalysts based on Hoveyda-Grubbs and Grela catalysts, but introducing new analogues of either N-heterocyclic carbenes or new analogues of benzylidene moiety. In these studies we have used either the M06 or M06-D3 functionals; the latter one includes an empirical correction to the dispersion energy.²⁰

In the **H4** paper we performed computational study of a series of Hoveyda-Grubbs analogues with the N-heterocyclic carbene replaced by derivatives of either N-heterocyclic trivalent boron anions or N-heterocyclic nitrenium ions (Fig. 12). The starting point for designing these systems were the recently synthesized transition metal complexes with the N-heterocyclic nitrenium ion²¹ and the boryl analogue.²² In all cases we characterized the structure of the new, hypothetical complexes as well as estimated Gibbs free energies of their activation for the dissociative and interchange mechanisms. Additionally we performed identical calculations for the nitrenium ion system modified with enolates, resulting in neutral systems and the boron derivative interacting with the Na⁺ ion, which also produces a system with the total charge of zero.

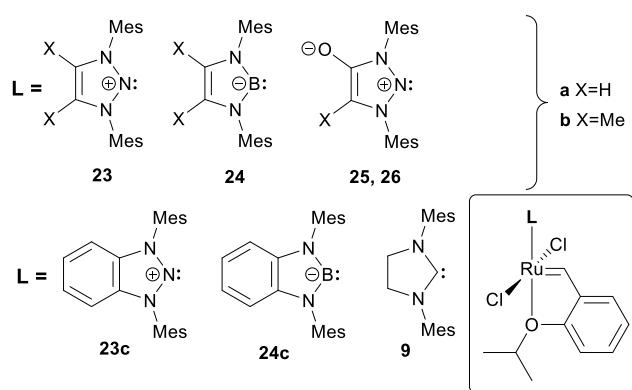


Fig. 12. New analogues of Hoveyda-Grubbs catalyst studies in paper **H4**. Complexes **25** and **26** have an identical N-heterocyclic ligand, but different position of the enolate with respect to the benzylidene moiety.

The structural differences introduced with the change of the C carbene into N or B, between Hoveyda catalyst derivatives are relative small and negligible apart from the elongation of the Ru-N bond in the nitrenium ion modified systems. This is an expected result taking into the account the formal charge of the N atom (+1) and Ru atom (+2) in the complex. The elongation of the Ru-N bond impacts also the length of the Ru-O bond making it shorter. In agreement with the known *trans* effect the shorter/stronger Ru-B bond weakens the Ru-O bond and vice versa, the longer/weaker Ru-N bond shortens the Ru-O bond. This effect influences also Gibbs free energies of activation of these systems and our calculations confirm that hypothesis. Gibbs free energies of activation for nitrenium ion-modified systems are in the range of 25-30 kcal/mol (5-10 kcal/mol than for original Hoveyda-Grubbs catalyst) and 12-20 kcal/mol for boron-substituted systems (a few kcal/mol lower than for Hoveyda-Grubbs catalyst). As a result, the nitrenium ions-modified precatalysts are poor candidates for fast metathesis catalysts, but potentially good candidates for latent catalysts. On the other hand boron-modified precatalysts, possessing strong Ru1-B1 bond, are excellent candidates for very fast and efficient metathesis catalysts.

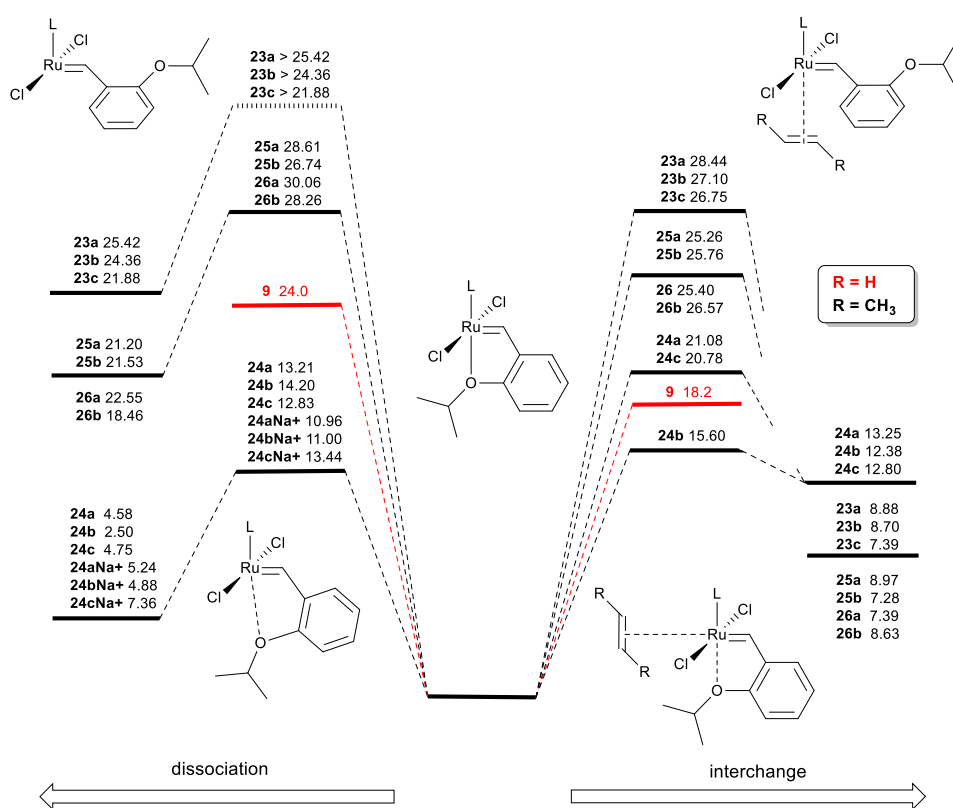


Fig. 13. Gibbs free energies of activation for systems **9** and **23-26** for both the dissociative and interchange mechanisms.

In our next paper (**H5**) we turned our attention to the modification of the benzylidene moiety of the Hoveyda-Grubbs catalyst and replaced them by 1-benzofuran derivatives. Earlier, other groups synthesized several series of similar catalysts bearing 2,3-dihydrobenzofuran and chromane derivatives.²³ The use of natural products and/or biologically-active compounds and ligands as building blocks of new Ruthenium-based olefin metathesis catalysts is an interesting approach that provides readily available and well characterized precursors. Our preliminary results for a model Grubbs-like catalyst revealed that the interaction energy between this complex and benzofuran moiety is approximately -16 kcal/mol, on the level of Gibbs free energy of activation of standard Hoveyda-Grubbs

catalyst. For this study we have chosen 11 different ruthenium complexes bearing benzofuran or propoxybenzofuran derivatives (Fig. 14).

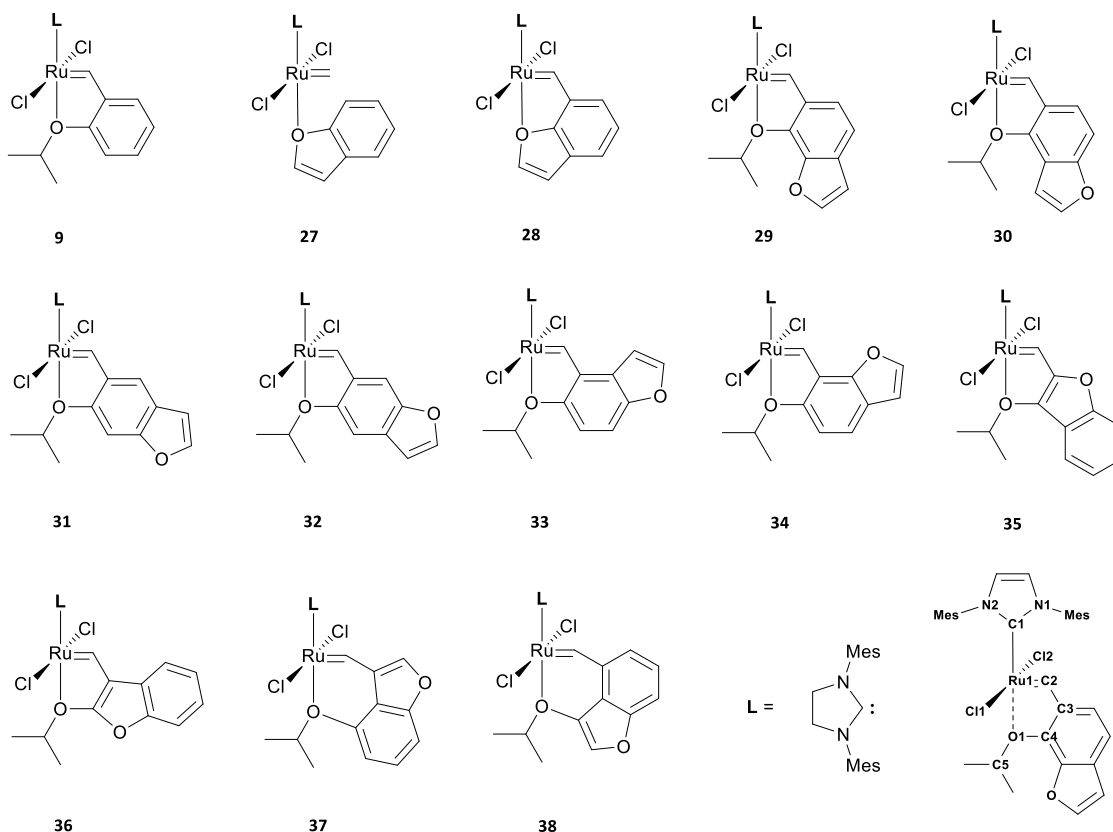


Fig. 14. Structure of ruthenium complexes studied in paper **H5**.

The results of the computational investigations of these complexes are presented in Figure 15. Complex **28** with only the benzofuran moiety seems to be a poor candidate for an efficient catalysts due to a very low Gibbs free energy of activation and the resulting low stability in solution. Amongst all other studies systems there are some interesting differences between pairs of complexes of similar structure. We noticed e.g. that the **31/32** pair has a relatively low ΔG^\ddagger (14.4 – 14.6 kcal/mol), particularly when compared to a structurally similar **29/30** pair (17.6 – 20.0 kcal/mol). Such a difference can be translated to a relatively fast activation of the first pair, when compared to the second one. A similar feature has been described experimentally earlier in a series of Hoveyda-Grubbs-like complexes with the benzylidene moiety replaced by a vinylonaphthalene group.²⁴ In this work authors noted that complexes bearing a group similar structurally to phenantrene (including two naphthalene rings and one ring formed by the Ru-O bond) are completely inactive as metathesis catalysts, while complexes bearing a group similar to anthracene show activity on the level of the activity of Hoveyda-Grubbs catalyst. Authors of that work postulated that it's a result of aromatic stabilization of phenantrene (coming from a larger number of possible resonance structure of this system). In the case of benzofuran complexes we postulated a similar effect, which could explain the slow activation of the **29/30** pair versus the fast activation of the **31/32** pair.

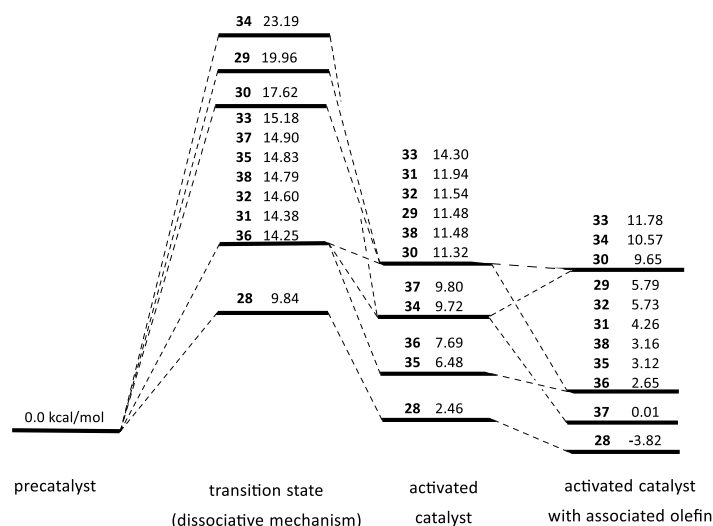


Fig. 15. Gibbs free energies of activation for complexes **28-38** and the dissociative mechanism.

To summarize this investigation, some of the studied complexes (**30-33** and **35-38**) seem to be good candidates for metathesis catalysts due to the relatively low Gibbs free energy of activation. Their initiation barriers are 2-5 kcal/mol lower than for Hoveyda-Grubbs catalyst, suggesting 10-1000 times faster initiation.

Simultaneously we decided to continue our studies of Hoveyda-Grubbs-like complexes with carbene derivatives bearing a formal -1 charge. The goal of paper **H6** was to show if the N-heterocyclic carbene derivatives of boryl anions are good candidates for ruthenium ligands and can produce efficient metathesis catalysts. New ruthenium complexes studied in this work were based on known, stable boryl anions synthesized in the Curran group.²⁵ Similarly to the **H4** paper we decided to perform calculations for both complexes bearing a formal -1 charge and containing a Na⁺ ion (total charge equal to zero). Additionally, both new complexes (**40** and **41**) have two stable conformations we performed all calculations independently for both of them.

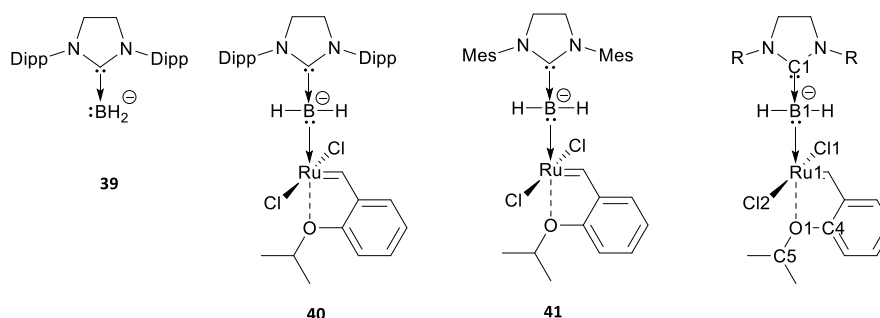


Fig. 16. Structures of boryl anion **39** and ruthenium complexes **40** and **41** studied in paper **H6** as well as the atom numbering scheme.

Similarly to the results of the **H4** paper the structures of all complexes are similar and also similar to the Hoveyda-Grubbs structure, with the exception of the shortening of Ru1-B1 bond and lengthening of the Ru1-O1 bond, in agreement with the previously described *trans* effect. As a result, both candidates for catalysts show a relatively low Gibbs free energy of activation, between 11 and 18 kcal/mol. On the basis of our results we believe that these new, hypothetical complexes are good candidates for fast and

efficient metathesis catalysts, as are other complexes based on ionic analogues of N-heterocyclic carbenes.

In the meantime we decided to continue the topic from the **H5** paper and suggested a new set of Hoveyda-Grubbs catalyst modifications, with the benzylidene moiety replaced by coumarin (2H-chromen-2-one) and its derivatives. Similarly to benzofuran derivatives these compounds are very well known and has been very thoroughly studied. Before performing a thorough study we decided to estimate the Ru-O bond dissociation energy for a model system consisting of standard 1st generation Grubbs catalyst but with coumarin molecule replacing the PCy₃ moiety. The M06-D3/lacvp** calculations gave us an estimated binding energy of -16.2 kcal/mol, comparable to the activation free energy of the initiation reaction for Hoveyda-Grubbs catalyst. In this work we designed a series of 12 new ruthenium complexes bearing coumarin derivatives (complexes **43-54**, Fig. 17).

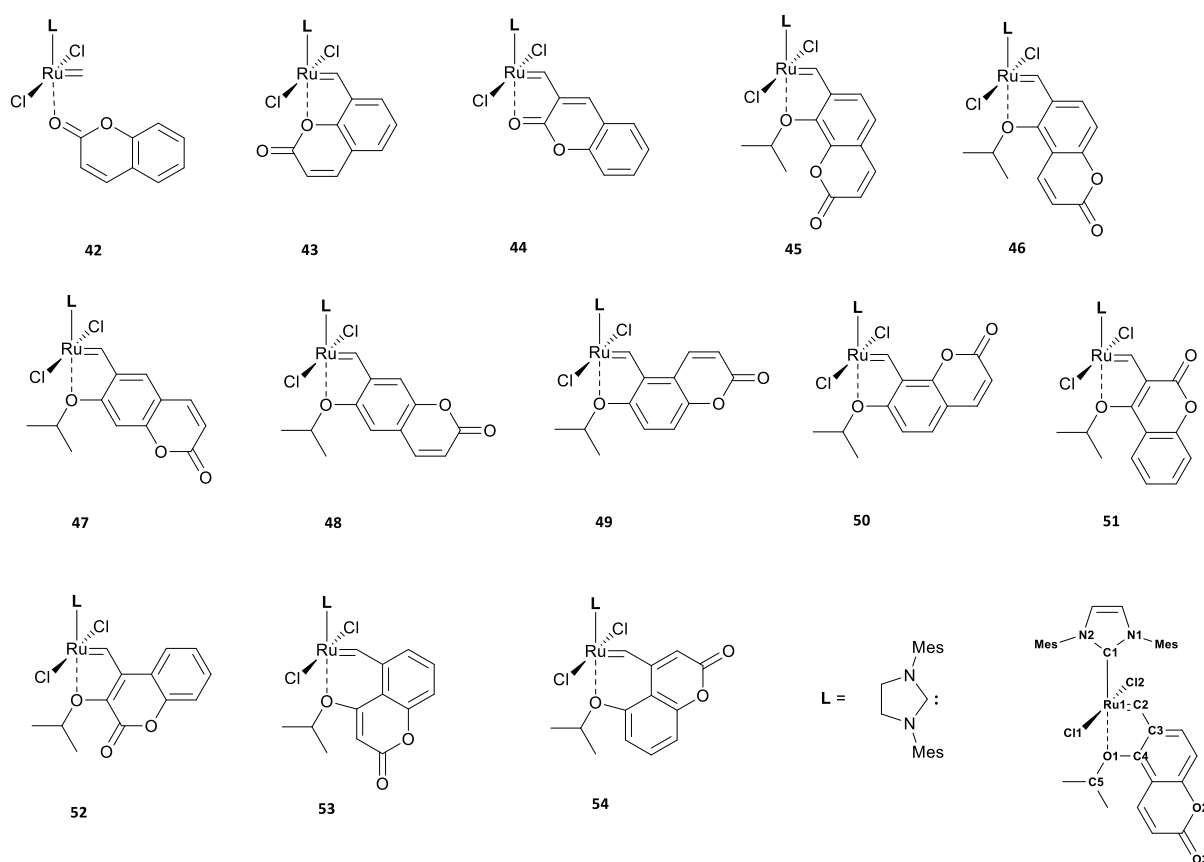


Fig. 17. Structure of ruthenium complexes investigated in paper **H7**.

Figure 18 presents the results of our computational study and shows a large variety of calculated Gibbs free energies for this group of complexes which depends on their structure. Complexes **43**, **44**, **45**, **46** and **54** show a very low initiation Gibbs free energy barriers (below 14 kcal/mol) and are probably not stable in the solution. Complexes **47**, **48** and **50** have Gibbs free energy of activations on the level of the original Hoveyda-Grubbs catalyst, which makes them uninteresting from the application point of view. On the other hand complexes **49**, **51**, **52** and **53** have estimates of Gibbs free energy of activation between 15.17 and 16.26 kcal/mol, making them interesting from the practical point of view, since these results suggest their fast initiation. One of these complexes (**51**) has been rejected due to the fact that upon its activation and rotation around the Ru1-O1 bond a new bond/interaction between Ru1 and O3

atoms is formed, making the olefin attack impossible. The other three complexes seemed to be good candidates for fast and efficient olefin metathesis catalysts.

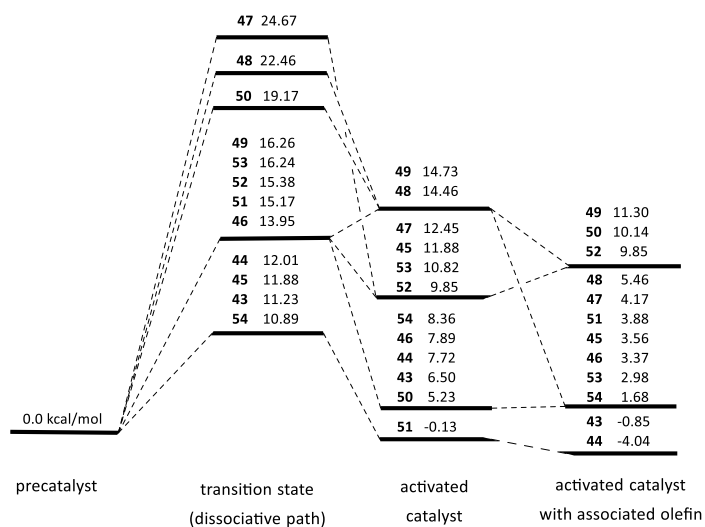


Fig. 18. Gibbs free energies of activation for complexes **43-54** and the dissociative mechanism.

It is worth pointing out, however, that the low ΔG^\ddagger initiation values of **49**, **52**, and **53** do not necessarily translate to low ΔG^\ddagger values of the entire catalytic cycle. Previous computational studies show that for Hoveyda-Grubbs catalyst the next step following the initiation, the formation of the metallocycle intermediate, has the second largest free energy barrier, equal to 17.2 kcal/mol, while all other steps have much lower barriers.¹⁴ For complexes with the ΔG^\ddagger initiation of 15-19 kcal/mol it is, therefore, questionable to assume that the catalyst activation is the rate-limiting step of the catalytic cycle. To better estimate free energy barriers of these systems verify if precatalyst activations is indeed the rate-limiting step of the entire catalytic cycle we performed additional calculations of the free energy barrier of the formation of the metallocycle intermediate. The results presented in Figure 19 suggest that for all three complexes precatalyst initiation is no longer the rate-limiting step of the catalytic cycle as the metallacyclobutane formation has a higher overall free energy barrier. In the case of complex **53** the overall barrier of 27.23 kcal/mol is very high, making this system completely unsuitable for olefin metathesis. The ΔG^\ddagger value for **49** and **52** (19.70 kcal/mol and 18.94 kcal/mol, respectively) suggest that these systems are, however, good candidates for catalysts faster than the original Hoveyda-Grubbs catalyst.

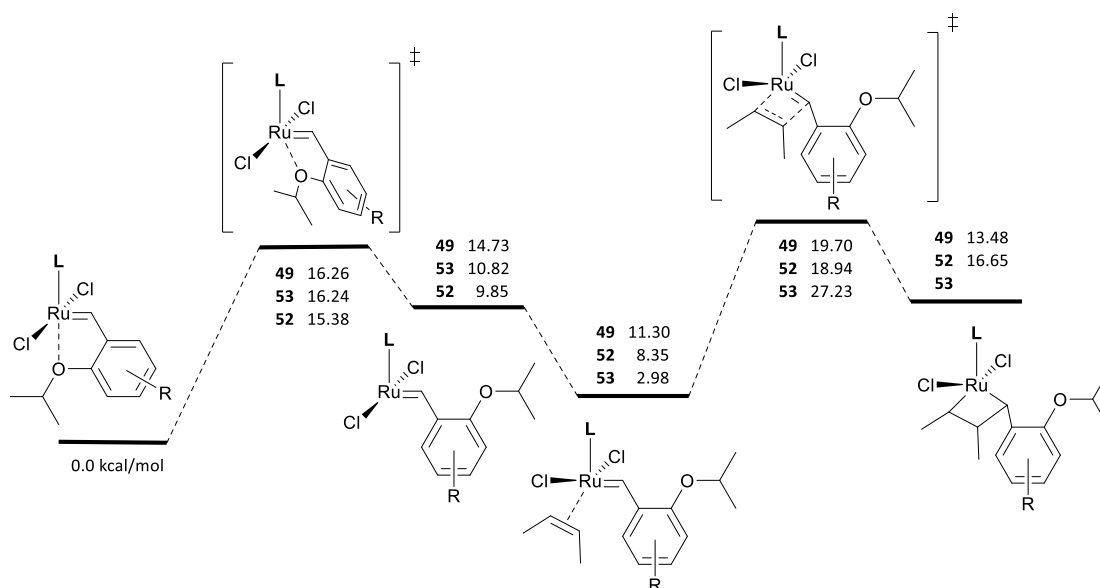


Fig. 18. Gibbs free energies of the early stages of the catalytic cycle for complexes **49**, **52** and **53** and the dissociative mechanism.

3. Impact

Results of our studies described in the previous section were aimed at understanding the mechanisms of initiation of selected metathesis catalysts and the use this knowledge to design new metathesis catalysts based on ruthenium complexes with better catalytic properties. The results of my work shows that advanced computational methods based on density functional method can accurately describe both geometries of modelled ruthenium complexes as well as Gibbs free energies, enthalpies and entropies of stationary points in entire metathesis catalytic cycle. Excellent accuracy of the results and their compliance with the experimental data allows not only for a full description of the mechanism of catalyzed reaction, but also to *in silico* design new candidates for efficient catalysts.

The main achievements of this dissertation are:

- mechanistic explanation of the rapid activation of Hoveyda-Grubbs catalysts containing sulfoxide groups and 3-bromopyridine as an additional ligand (**H1**),
- mechanistic explanation of a fast activation of the 3rd generation Grubbs Catalyst (**H2**),
- mechanistic explanation of how the conformational flexibility of the acyclic carbenes affects the Gibbs free energies of activation of acyclic Hoveyda-Grubbs catalysts (**H3**),
- design of new Hoveyda-Grubbs-like complexes containing carbene derivatives with the total charge of -1 and explanation of the charge impact on the fast activation of these candidates for catalysts (**H4**, **H6**),
- design of new Hoveyda-Grubbs-like complexes containing carbene derivatives with the total charge of +1 and explanation of the charge impact on the slow activation of these candidates for catalysts (**H4**),
- design of novel derivatives of Hoveyda-Grubbs catalyst with 1-benzofuran or coumarin derivatives and explanation of their fast/slow activation depending on their the electronic properties (**H5**,**H7**),
- new insight into the rational design of ruthenium complexes, candidates for efficient olefin metathesis catalysts (**H4-H7**).

4. Bibliography

1. V. Schneider and P.K. Frolich, Mechanism of formation of aromatics from lower paraffins, *Ind. Eng. Chem.*, 1931, 23, 1405-1410.
2. R. L. Banks and G. C. Bailey, Olefin disproportionation: A new catalytic process, *Ind. Eng. Chem. Prod. Res. Dev.*, 1964, 3, 170-173.
3. H. S. Eleuterio, German Pat. 1072811 (1960).
4. Y. Chauvin and J.-L. Herisson, Catalyse de transformation des oléfines par les complexes du tungstene. II. Télomérisation des oléfines cycliques en présence d'oléfines acycliques, *Makromol. Chem.*, 1971, 141, 161-176.
5. R. R. Schrock, S.M. Rocklage, J. H. Wengrovius, G. Rupprecht and J. Feldmann, Preparation and characterization of active niobium, tantalum and tungsten metathesis catalysts, *J. Mol. Catal.*, 1980, 8, 73-83.
6. (a) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare and M. O'Regan, Synthesis of molybdenum imido alkylidene complexes and some reactions involving acyclic olefins, *J. Am. Chem. Soc.*, 1990, 112, 3875-3886; (b) G. C. Bazan, E. Khosravi, R. R. Schrock, W. J. Feast, V. C. Gibson, M. B. O'Regan, J. K. Thomas and W. M. Davis, Living ring-opening metathesis polymerization of 2,3-difunctionalized norbornadienes by $\text{Mo}(\text{CH}-t\text{-Bu})(\text{N}-2,6\text{-C}_6\text{H}_3\text{-}i\text{-Pr}_2)(\text{O}-t\text{-Bu})_2$, *J. Am. Chem. Soc.*, 1990, 112, 8378-8387; (c) G. C. Bazan, J. H. Oskam, H. N. Cho, L. Y. Park and R. R. Schrock, Living ring-opening metathesis polymerization of 2,3-difunctionalized 7-oxanorbornenes and 7-oxanorbornadienes by $\text{Mo}(\text{CHCMe}_2\text{R})(\text{N}-2,6\text{-C}_6\text{H}_3\text{-}i\text{-Pr}_2)(\text{O}-t\text{-Bu})_2$ and $\text{Mo}(\text{CHCMe}_2\text{R})(\text{N}-2,6\text{-C}_6\text{H}_3\text{-}i\text{-Pr})(\text{OCMe}_2\text{CF}_3)_2$, *J. Am. Chem. Soc.*, 1991, 113, 6899-6907.
7. S. T. Nguyen, L. K. Johnson, R. H. Grubbs and J. W. Ziller, Ring-opening metathesis polymerization (ROMP) of norbornene by a Group VIII carbene complex in protic media, *J. Am. Chem. Soc.*, 1992, 114, 3974-3975.
8. P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, A Series of Well-Defined Metathesis Catalysts—Synthesis of $[\text{RuCl}_2(=\text{CHR}')(\text{PR}_3)_2]$ and Its Reactions, *Angew. Chem. Int. Ed. Engl.*, 1995, 34, 2039-2041.
9. (a) J. Huang, E. D. Stevens, S. P. Nolan and J. L. Petersen, Olefin metathesis-active ruthenium complexes bearing a nucleophilic carbene ligand, *J. Am. Chem. Soc.*, 1999, 121, 2674-2678; (b) M. Scholl, T. M. Trnka, J. P. Morgan and R. H. Grubbs, Increased ring closing metathesis activity of ruthenium-based olefin metathesis catalysts coordinated with imidazolin-2-ylidene ligands, *Tetrahedron Lett.*, 1999, 40, 2247-2250; (c) L. Ackermann, A. Furstner, T. Weskamp, F. J. Kohl and W. A. Herrmann, Ruthenium carbene complexes with imidazolin-2-ylidene ligands allow the formation of tetrasubstituted cycloalkenes by RCM, *Tetrahedron Lett.*, 1999, 40, 4787-4790.
10. (a) S. Gessler, S. Randl, and S. Blechert, Synthesis and metathesis reactions of phosphine-free dihydroimidazole carbene ruthenium complex, *Tetrahedron Lett.*, 2000, 41, 9973-9976; (b) S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts, *J. Am. Chem. Soc.*, 2000, 122, 8168-8179; (c) K. Grela, S. Harutyunyan and A. Michrowska, A Highly Efficient Ruthenium Catalyst for Metathesis Reactions, *Angew. Chem., Int. Ed.*, 2002, 41, 4038-4040.
11. (a) C. Lee, W. Yang and R. G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev. B*, 1988, 37, 785-789; (b) A. D. Becke, Density-functional thermochemistry. III. The role of exact exchange, *J. Chem. Phys.*, 1993, 98, 5648-5652.
12. (a) Y. Zhao and D. G. Truhlar, The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06 Functionals and Twelve Other Functionals, *Theor. Chem. Acc.*, 2007, 120, 215-241; (b) Y. Zhao and D. G. Truhlar, Density Functionals with Broad Applicability in Chemistry, *Acc. Chem. Res.* 2008, 41, 157-167.
13. E. L. Dias, S. T. Nguyen and R. H. Grubbs, Well-Defined Ruthenium Olefin Metathesis Catalysts: Mechanism and Activity, *J. Am. Chem. Soc.*, 1997, 119, 3887-3897.
14. I. W. Ashworth, I. H. Hillier, D. J. Nelson, J. M. Percy and M. A. Vincent, What is the initiation step of the Grubbs-Hoveyda olefin metathesis catalyst?, *Chem. Commun.*, 2011, 47, 5428-5430.
15. (a) V. Thiel, M. Hendann, K.-J. Wannowius and H. J. Plenio, On the Mechanism of the Initiation Reaction in Grubbs-Hoveyda Complexes, *J. Am. Chem. Soc.*, 2012, 134, 1104-1114; (b) T. Vorfalt, K.-J. Wannowius and H. J. Plenio, Probing the Mechanism of Olefin Metathesis in Grubbs-Hoveyda and Grela Type Complexes, *Angew. Chem.*, 2010, 122, 5665-5668.

16. J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, A Practical and Highly Active Ruthenium-Based Catalyst that Effects the Cross Metathesis of Acrylonitrile, *Angew. Chem. Int. Ed.*, 2002, 41, 4035-4037.
17. E. L. Rosen, D. H. Sung, Z. Chen, V. M. Lynch and C. W. Bielawski, Olefin Metathesis Catalysts Containing Acyclic Diaminocarbenes, *Organometallics* 2010, 29, 250-256.
18. (a) Y. Zhao and D. G. Truhlar, Benchmark Databases for Nonbonded Interactions and Their Use To Test Density Functional Theory, *J. Chem. Theory Comput.* 2005, 1, 415-432; (b) M. O. Sinnokrot, E. F. Valeev and C. D. Sherrill, Estimates of the Ab Initio Limit for π - π Interactions: The Benzene Dimer, *J. Am. Chem. Soc.* 2002, 124, 10887-10893.
19. (a) B. F. Straub, Origin of the High Activity of Second-Generation Grubbs Catalysts, *Angew. Chem. Int. Ed.* 2005, 44, 5974-5978; (b) I. Fernández, N. Lujan and G. Lavigne, Effects of Attractive Through Space π - π^* Interactions on the Structure, Reactivity, and Activity of Grubbs II Complexes, *Organometallics* 2012, 31, 1155-1160.
20. S. Grimme, J. Antony, S. Ehrlich, and S. Krieg, A consistent and accurate ab initio parametrization of density functional dispersion correction (dft-d) for the 94 elements H-Pu, *J. Chem. Phys.*, 2010, 132, 154104.
21. (a) Y. Tulchinsky, M. A. Iron, M. Botoshansky and M. Gandelman, Nitrenium ions as ligands for transition metals, *Nat. Chem.*, 2011, 3, 525-531; (b) Y. Tulchinsky, S. Kozuch, P. Saha, M. Botoshansky, L. J. W. Shimon and M. Gandelman, Cation-cation bonding in nitrenium metal complexes, *Chem. Sci.*, 2014, 5, 1305-1311.
22. (a) Y. Segawa, M. Yamashita, K. Nozaki, Boryllithium: Isolation, Characterization, and Reactivity as a Boryl Anion, *Science*, 2006, 314, 113-115; (b) R. Kinjo, B. Donnadiou, M. A. Celik, G. Frenking and G. Bertrand, Synthesis and characterization of a neutral tricoordinate organoboron isoelectronic with amines, *Science*, 2011, 333, 610-613; (c) J. Cid, H. Gulyás, J. J. Carbó and E. Fernández, Trivalent boron nucleophile as a new tool in organic synthesis: reactivity and asymmetric induction, *Chem. Soc. Rev.*, 2012, 41, 3558-3570;
23. (a) M. Barbasiewicz, M. Bieniek, A. Michrowska, A. Szadkowska, A. Makal, K. Woźniak and K. Grela, Probing of the Ligand Anatomy: Effects of the Chelating Alkoxy Ligand Modifications on the Structure and Catalytic Activity of Ruthenium Carbene Complexes, *Adv. Synth. Catal.*, 2007, 349, 193-203; (b) A. Hryniewiecka, J. W. Morzycki and S. Witkowski, New efficient ruthenium metathesis catalyst containing chromenyl ligand, *J. Organomet. Chem.*, 2010, 695, 1265-1270; (c) A. Hryniewiecka, J. W. Morzycki, L. Siergiejczyk, S. Witkowski, J. Wojcik and A. Gryf-Keller, Hindered Rotation in New Air-Stable Ruthenium Olefin Metathesis Catalysts with Chromanylmethylidene Ligands, *Aust. J. Chem.*, 2008, 62, 1363-1370; (d) A. Hryniewiecka, A. Kozłowska and S. Witkowski, New nitrochromenylmethylidene-containing ruthenium metathesis catalyst, *J. Organomet. Chem.*, 2012, 701, 87-92.
24. M. Barbasiewicz, A. Szadkowska, A. Makal, K. Woźniak and K. Grela, Is the Hoveyda-Grubbs Complex a Vinylogous Fischer-Type Carbene? Aromaticity-Controlled Activity of Ruthenium Metathesis Catalysts, *Chem.-Eur. J.*, 2008, 14, 9330-9337.
25. A. Solovyev, Q. Chu, S. J. Geib, L. Fensterbank, M. Malacria, E. Lacote and D. P. Curran, Substitution Reactions at Tetracoordinate Boron: Synthesis of N-Heterocyclic Carbene Boranes with Boron-Heteroatom Bonds, *J. Am. Chem. Soc.*, 2010, 132, 15072-15080.

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