

Ligand Influence on Metathesis Activity of Ruthenium Carbene Catalysts: A DFT Study

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Dedicated to Prof. Dr. Peter Hofmann on the occasion of his 60th birthday.



Supporting information for this article is available on the WWW under <http://asc.wiley-vch.de/home/>.

Abstract: A survey of the concept of active and inactive ligand conformations in ruthenium alkene carbene complexes of the Grubbs catalyst type is presented. This concept is extended to a variety of anionic ligand atoms. Density functional theory calculations at the B3LYP/LACV3P**+//B3LYP/LACVP* level of theory were performed on the pre-catalyst, 14 valence-electron intermediate, alkene carbene conformers and ruthena(IV)cyclobutane model intermediates for several ligands, such as methoxide, methanethiolate, fluoride, mesylate, water, and ammonia. The rule of the superiority of metathesis catalysts with small and electron-withdrawing halogens does not apply to fluoride ligands.

Alkoxides and thiolates also destabilize active carbene conformations, while mesylate ligands lead to a balanced energetic relation of active and inactive carbene orientations. Cationic ruthenium carbene species with aqua or ammine ligands are limited by unfavored ligand dissociation to 14 valence-electron intermediates. A guideline for the design of novel ligand systems for ruthenium carbene complexes as metathesis catalysts is proposed.

Keywords: carbene ligands; conformation analysis; density functional calculations; ligand effects; metathesis; ruthenium

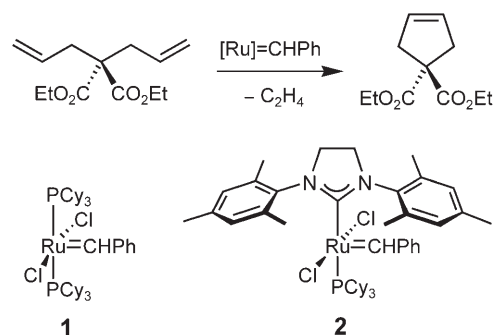
Introduction

Three main investigators in the field of alkene metathesis shared the Nobel Prize in chemistry of the year 2005 for their decisive contributions towards a general understanding of this reaction and for the development of highly active catalysts.^[1] Ruthenium carbene catalysts, known as Grubbs catalysts, have the advantage of high kinetic stability towards air, water, and tolerance towards “hard” functional groups (Scheme 1).^[2] The first generation catalysts **1** with two phosphine ancillary ligands are intrinsically less active than the Grubbs catalysts of the second generation **2** with one N-heterocyclic carbene ligand (NHC).^[3]

Already in 1998, the Grubbs group had put forward a fundamental rule, stating that “phosphines, which are larger and more electron-donating, and likewise halogens, which are smaller and more electron-withdrawing, lead to more active catalysts.”^[4] This rule is in full accordance with the later development of the second-generation catalysts, since N-heterocyclic car-

bene ligands behave as if they were particularly strongly electron-donating.

Decisive NMR experiments by Sanford and Grubbs unraveled the fundamental kinetic data of all relevant ruthenium catalysts.^[5] Of course, the mechanism is in



Scheme 1. Alkene metathesis (here RCM) by Grubbs catalysts of the first generation (**1**) and the second generation (**2**).

full accordance with the general Chauvin mechanism,^[1b] but some kinetic results were unexpected. Phosphine dissociation barriers are low for the least catalytically active iodo complexes of the first generation, while the catalytically highly active second-generation catalysts possess a high phosphine dissociation barrier (Scheme 2). This is in sharp contrast to prior expectations, since NHC ligands are known for their strong *trans* influence.^[6]

The reason for the unexpected anomaly in the *trans* influence has been traced back to the strong steric repulsion of the PCy₃ ligands with the halide ligands.^[7] Although NHC ligands appear to be more sterically demanding than PCy₃, the chloride ligands fit in between the two *N*-aryl substituents. From a strictly electronic point of view, NHC ligands do in fact favor dissociation of *trans* ligands, but steric repulsion seems to be of more importance for phosphine dissociation in first-generation catalysts.^[8]

Second-generation catalysts are significantly more efficient in alkene substrate coordination and productive intramolecular [2+2] cycloaddition to ruthena(IV)cyclobutanes.^[5] The question arises whether partitioning between phosphine coordination and alkene coordination (k_{-1} versus k_2) or the rearrangement of the alkene complex to the ruthenacyclobutane (k_3) is the reason of the different efficiencies.

The striking efficiency differences between the 14 valence-electron intermediates of various Grubbs catalysts, however, is of electronic origin.^[7] An assumed partitioning between phosphine and alkene coordination to the 14 valence-electron intermediates is questionable. The coordination processes at diamagnetic unsaturated transition metal complexes (with 12 or 14 valence electrons at the metal center) are usually diffusion-controlled if the free coordination site is not sterically blocked. In other words, there is no enthalpic barrier for ligand coordination, but only an entropic barrier due to two molecules combining to one.

We thus searched for an alternative explanation for the partitioning between phosphine and alkene coordination

to the 14 valence-electron species LRuX_2 ($=\text{CHPh}$) that could account for the observed differences in catalyst efficiencies (see k_{-1}/k_2 in Scheme 2). We believe that k_3 is inversely proportional to this parameter. The Grubbs catalysts thus differ in their intramolecular rate to transform alkene carbene intermediates into ruthena(IV)cyclobutanes. Since considerable barriers for carbene ligand rotation had already been established (Figure 1),^[9] our initial hypothesis to explain barrier differences for the intramolecular cycloaddition reaction was connected with carbene ligand rotation.

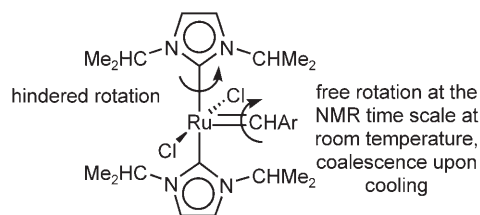
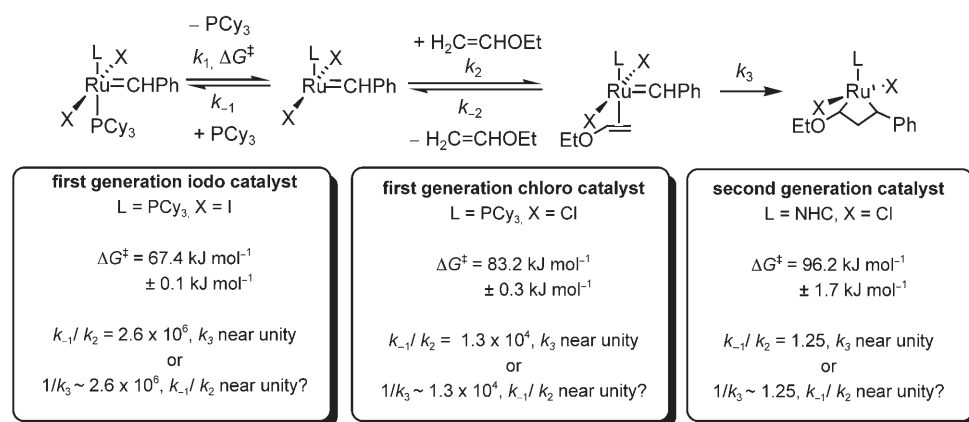


Figure 1. Carbene ligand rotation observed by W. A. Herrmann's group.^[9]

With an inactive alkene ligand orientation and an inactive carbene ligand orientation, a cycloaddition cannot take place in alkene complex intermediates (red traffic lights row in Figure 2). Both the alkene ligand (left side of the yellow traffic lights row) as well as the carbene ligand (right side of the yellow traffic lights row) have to rotate into an active conformation, so that the cycloaddition to the ruthenacyclobutane can take place without further ligand rotations (green traffic lights row in Figure 2).^[7]

In order to understand the influence of ancillary ligands on the energetic preferences of ligand orientations, it is mandatory to understand the basic electronic and geometric structures. Diamagnetic complexes of transition metals with partially occupied *d*-orbitals (d^2 to d^8) generally maintain their geometry



Scheme 2. Sanford's and Grubbs' NMR spectroscopic determination of mechanistic parameters in alkene metathesis.

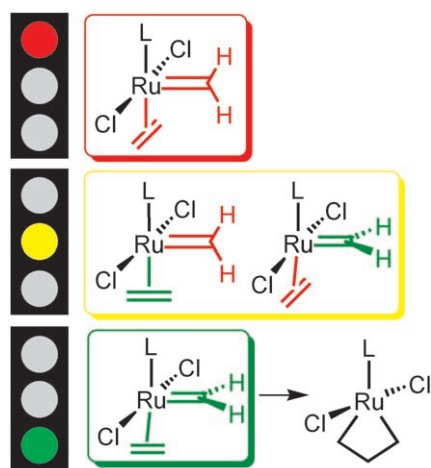


Figure 2. “Traffic lights” concept of active and inactive ligand conformations in ruthenium alkene carbene complexes: STOP for inactive (red) conformations, GO for active (green) conformations.

upon ligand removal. The free coordination site remains at the position of the ideal polyhedron of the corresponding saturated 18 valence-electron parent complex ($d^8\text{-ML}_5$ is derived from a triangular bipyramid; an exception for $5d$ -row, $4d$ -row, and some $3d$ -row late transition metals are the square-planar geometries of $d^8\text{-ML}_4$ complexes, because their 16 valence-electron count essentially means electronic saturation; $d^6\text{-ML}_6$ is octahedral; $d^4\text{-ML}_7$ can be pentagonal bipyramidal). From this point of view, the ruthenium(II) intermediates in metathesis catalysis can be classified as pseudo-octahedral, with a free coordination site occupying the sixth vertex (left side in Figure 3). From a first estimate point of view, the L-Ru-L angle and the X-Ru-X angle are close to 180° .

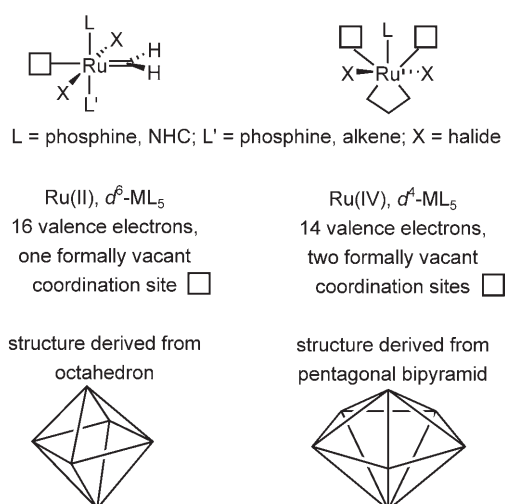


Figure 3. Electronic classification and geometry of ruthenium complexes in alkene metathesis: precatalyst and alkene complexes (left) and ruthena(IV)cyclobutane (right).

The structure of the 14 valence-electron $d^4\text{-ML}_5$ ruthena(IV)cyclobutane intermediates is best described as a pentagonal bipyramid with two free coordination sites in the pentagon close to the spectator ligand L (right side in Figure 3). This structural origin accounts for the local C_{2v} symmetry of the ruthenium coordination environment. The increased distance of the ligand L to the ruthenacyclobutane carbon atoms rationalizes the difficulty to sterically control E/Z specificity in today's ruthenium metathesis catalysts.^[10]

The σ donor strength of the ancillary ligands in Grubbs catalysts strongly influences the geometry, the relative energies of intermediates and conformers, and the activity of ruthenium carbene catalysts. In a linear Cl-Ru-Cl fragment, the interaction between the chloride donor orbitals and the occupied ruthenium $4d$ orbitals is non-bonding (Figure 4). A decrease

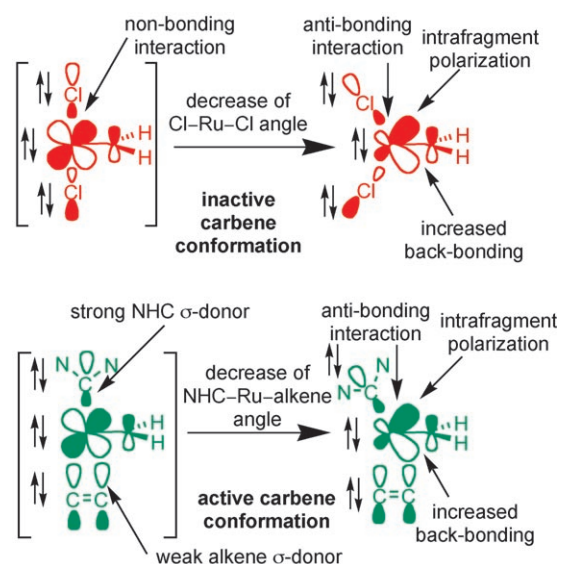


Figure 4. Molecular orbital interactions in Grubbs' ruthenium(II) complexes with inactive (red) and active (green) carbene ligand conformation. The ruthenium fragment has been rotated by 90° between the first, “red” line and the second, “green” line. The interaction of the other occupied p orbitals of the halide with metal d orbitals will certainly play a significant role for small fluoride ligands.

of the Cl-Ru-Cl leads to an anti-bonding orbital interaction. The ruthenium $4d$ -orbital mixes with an empty ruthenium $5p$ orbital (=intrafragment polarization), and increases the overlap to the π acceptor orbital of the carbene ligand (first, red row of Figure 4). As a consequence, the inactive carbene conformation is stabilized.^[7,11] If, however, the ruthenium fragment is rotated by 90° , the same line of argumentation predicts a stabilization of the active carbene conformation (second, green row of Figure 4). The NHC ligand is a particularly effective σ donor, and thus compensates the weak σ donor capability of the alkene

ligand. Phosphine ligands are worse σ donors, but better π acceptors. Instead of bending back and increasing the back-bonding to the active carbene moiety, a phosphine ligand even withdraws electron density from the ruthenium orbital that stabilizes the ruthenium π bond to the active carbene.

This result of the differences in electronic behavior of NHC and phosphine ligands is apparent in Figure 5. The stabilization of the active carbene orientation in structure **8** and transition state **10** by NHC ligands makes the rotation from the inactive carbene conformers **6** and **7** electronically degenerate. In phosphine complexes, the inactive carbene orientation is preferred, and an additional barrier for the rearrangement to an active carbene conformer exists. Thus, the main origin of the high activity of second-generation Grubbs catalysts ($L = \text{NHC}$) compared to their first generation analogues ($L = \text{PCy}_3$) lies in the electronic stabilization of active carbene conformations in second-generation complexes (green arrows in Figure 5). Other factors contribute to the overall energetic picture. The larger *trans* influence of the NHC ligand electronically stabilizes the 14 valence-electron species **5**, and the significant steric repulsion between PCy_3 ligands and halide ligands in precatalysts **3** or **4** favor phosphine dissociation in first-generation catalysts.^[7] As a consequence, the rate-limiting step in first-generation Grubbs catalysts is the cycloaddition step, the rate-limiting step in second-generation Grubbs catalysts is phosphine dissociation. If sterically possible,^[7] either structure **6** or structure **7** is an intermediate in the catalytic cycle, because struc-

ture **5** possesses an inactive carbene ligand. Coordination of an alkene substrate, however, electronically facilitates carbene ligand rotation into an active orientation.

The quantum-chemical prediction of the most stable isomer or conformer is in agreement with experimentally characterized complexes. First-generation complex **6** ($L = \text{PCy}_3$) with inactive carbene and active alkene ligand is predicted to be more stable than the other conformations – and has indeed been structurally characterized by Snapper's group (Figure 6).^[12] Second-generation ruthenacycle **11** is predicted to be more stable than the isomeric alkene carbene conformers – and indeed, it has been detected in solution by Piers' group.^[13]

Chloride ligands are the standard anionic ligands in ruthenium carbene catalysts. Anionic ligands superior to chloride have not yet been found. Theoretical

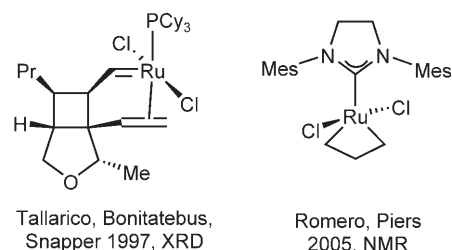


Figure 6. X-ray diffraction characterization of a first generation alkene carbene complex (*left*) and NMR spectroscopic characterization of a second-generation ruthenacyclobutane (*right*).

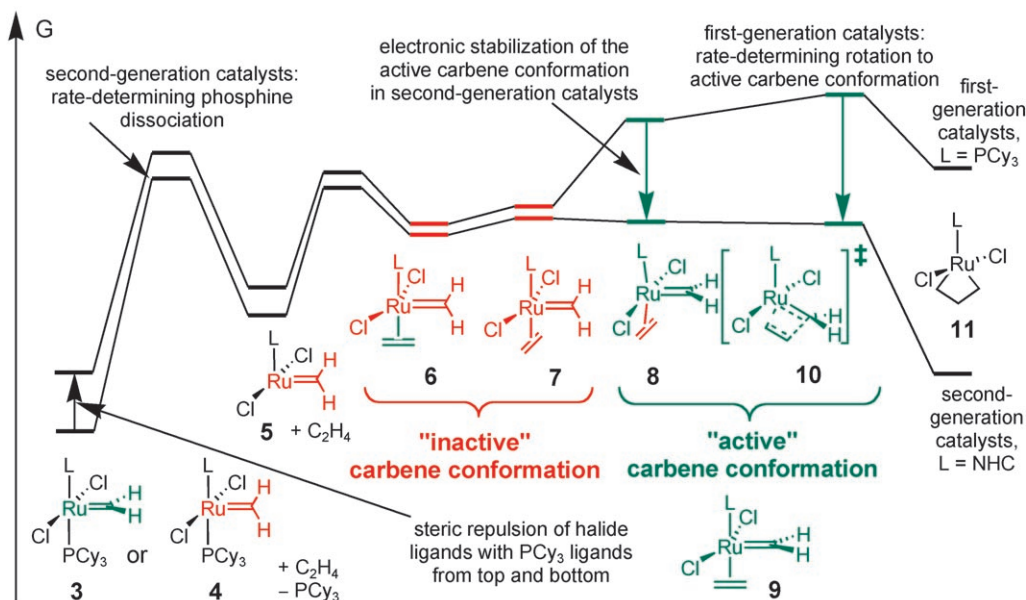


Figure 5. Semiquantitative Gibbs free energy diagram of mechanistic pathways of first- and second-generation Grubbs catalysts. Intrinsic electronic carbene rotation barriers are in the order of magnitude of 10 kJ mol^{-1} , but will be strongly influenced by sterically demanding substituents. Not all possible interconnections between alkene carbene complexes are shown.

model investigations have studied several aspects of alkene metathesis.^[7,11,14,15] However, the influence of anionic ligands on the relative stability of carbene ligand conformations was limited to chloride and iodide.^[7] We here present quantum-chemical calculations directed towards the evaluation and understanding of ruthenium carbene complexes with other ancillary ligands.

Results and Discussion

Although metathesis catalysts are highly active – the 14 valence-electron second-generation Grubbs catalysts even operating at diffusion-control rate – *E/Z* specificity remains a challenging goal. Within the accepted mechanism of ruthenium carbene catalysts in alkene metathesis, other ancillary ligand environments are of high interest. To avoid “trial and error” catalyst syntheses and screening, we attempt to obtain guidelines for rational ligand design by quantum-chemical methods within our concept of active and inactive carbene conformations. Four ruthenium carbene complex types are possible, of which the Grubbs type has proven most valuable so far. Grubbs catalysts are characterized as uncharged complexes with a *trans* ruthenium dihalide fragment (Table 1).

We computed the relative energies of intermediates of several anionic ligands X within the Grubbs complex type. Our goal is to evaluate the influence of X on the formation of 14 valence-electron intermediates, on the predicted stability of active carbene conformers, and on the overall barrier for [2+2] cycloaddition to ruthenacyclobutanes. It is not imperative that the cycloaddition step is the rate-limiting step: The ligand dissociation towards the active 14 valence-electron

Table 1. Four types of ruthenium carbene catalysts (L = uncharged donor ligand such as phosphine or N-heterocyclic carbene NHC; X = anionic ligand such as halide, alkoxide, thiolate, sulfonate etc.).

	Uncharged ruthenium center	Cationic ruthenium center
<i>trans</i> X-Ru-X or <i>trans</i> L-Ru-L'		
	Grubbs type	
<i>cis</i> X-Ru-X or <i>cis</i> L-Ru-L'		
		Hofmann type

species may well be decisive. In this manuscript, however, we wish to focus on the cycloaddition efficiency, directed towards a better understanding of the role of active and inactive ligand conformations.

For a better comparison of the effects of different ligands, the “gold standard” is again presented in Figure 7. The computed Gibbs free energy diagram of a *trans* ruthenium dichloride fragment with an *N,N'*-dimethyl-substituted saturated N-heterocyclic carbene (NHC) ligand reflects the similar stabilities of active and inactive carbene conformations, and the high stability of the ruthena(IV)cyclobutane.

A mechanistic alternative by isomerization of the *trans* ruthenium dichloride fragment to a *cis* dichloride system is shown in Figure 8. Vyboishchikov et al.

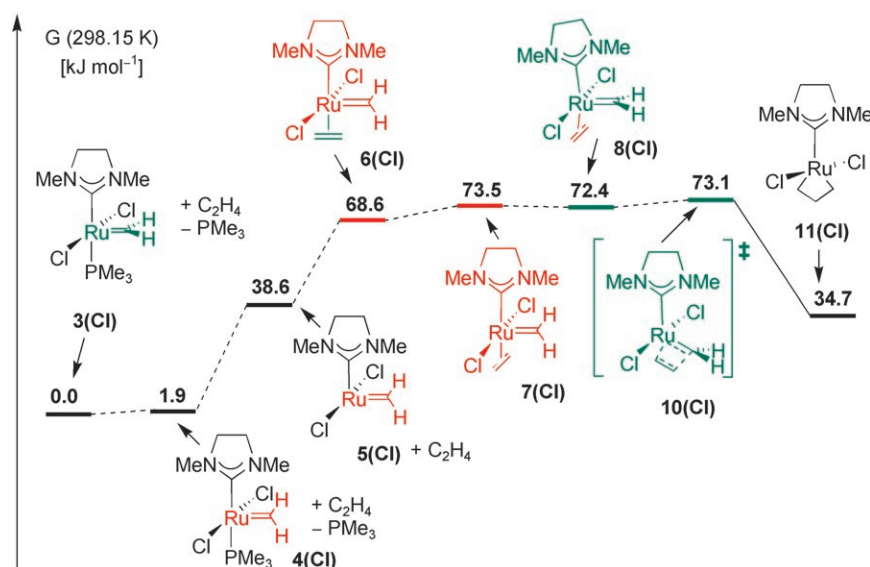


Figure 7. Gibbs free energy diagram of ruthenium dichloride model intermediates.

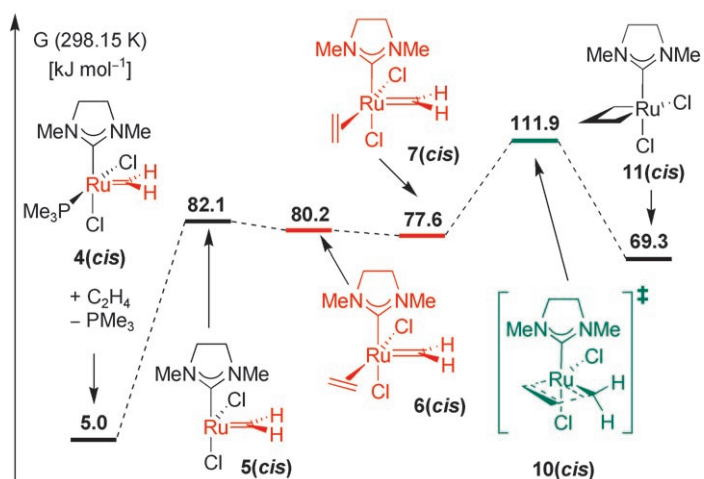


Figure 8. Gibbs free energy diagram of *cis*-dichlororuthenium model intermediates.

have already compared *cis* and *trans* pathways quantum-chemically, and proposed a *trans* mechanism as the more favorable path.^[14c] We wish to evaluate the *cis* alternative from a carbene conformation point of view.^[14]

Electronically, the ruthenium *cis*-dichloride fragment has a similar stability as the *trans*-dichloride fragment in the precatalysts. The model complexes **3(Cl)**, **4(Cl)**, and **4(cis)** feature only small energy differences. Of course, the non-simplified ligand PCy₃ and an *N*-mesityl-substituted NHC ligand will avoid a *cis*-relationship due to steric reasons. The rearrangement of the 14 valence-electron species **5(Cl)** to its *cis*

isomer **5(cis)** is very endergonic. The electronic reason is that the strong σ donor possesses a strong *trans* influence: Ligands *trans* to the NHC are thermodynamically more labile, and free coordination sites are favored in this *trans* position. This is indeed the case for **5(Cl)**, where both chlorides are *cis* to the NHC ligand. For the isomer **5(cis)**, however, a chloride is in a *trans* position to the NHC ligand. Already here, the *cis* pathway is higher in Gibbs free energy than the transition state **10(Cl)** of the *trans*-dichloride pathway. Coordination of a free alkene substrate causes extra entropic costs, which makes metathesis mechanisms relying on **5(cis)** and its experimental, real-world counterparts unreasonable.

Alkene carbene complexes with a *cis*-dichloride fragment are also not competitive with their *trans*-dichloride analogues. This is particular true for species with an active carbene orientation, since it is both disfavored electronically as well as sterically. One of the active carbene substituents interacts repulsively with one of the *N*-substituents of the NHC ligand. Electronically, the NHC ligand and its *trans* chloride ligand are better σ donors than the *cis* chloride and the alkene ligand. As a consequence, the [2+2] transition state **10(cis)** of the *cis*-dichloride pathway is almost 40 kJ mol⁻¹ higher in Gibbs free energy than the *trans* analog **10(Cl)**. Thus, mechanistic proposals that suggest *cis*-dichloride pathways for second-generation Grubbs catalysts should be accompanied with good suggestions how these strong steric and electronic challenges are supposed to be overcome.

In Figure 9, the role of substituents at the NHC ligand is investigated. NHC ligands without *N*-sub-

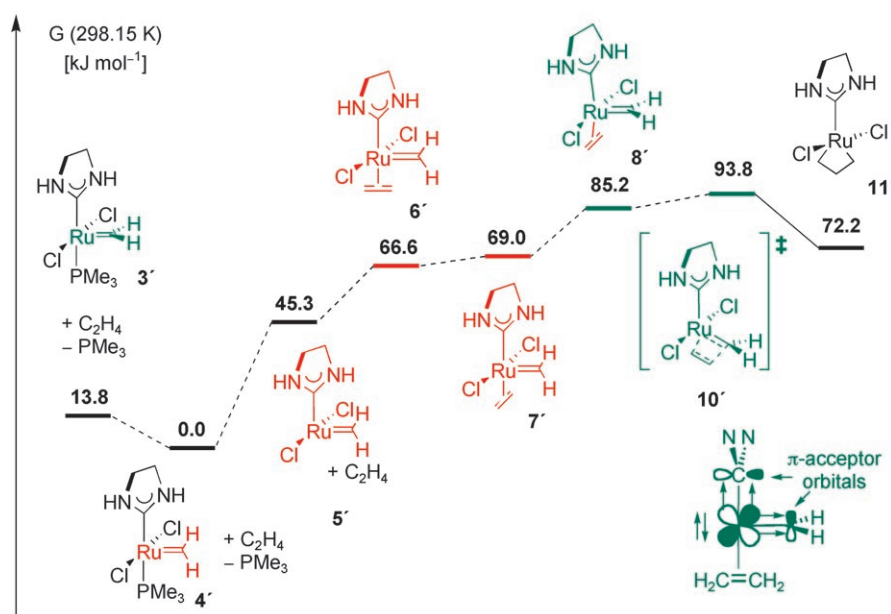


Figure 9. Gibbs free energy diagram of imidazolynylidene ruthenium dichloro model intermediates. Deactivation of the active carbene conformation due to competition with an NHC orientation that bonds back to the same *d* orbital.

stituents are oversimplified model ligands for ruthenium metathesis catalysts, which fail to reproduce observed structures and energetic tendencies. In “real” catalysts, the NHC π acceptor orbital is in plane with the halide ligands. The simplified $C_3N_2H_6$ fragment, however, adopts an orientation with the π acceptor orbital directed towards the carbene. The immediate consequence is that electron-density is withdrawn from the same ruthenium d -orbital which stabilizes the active carbene conformation (Figure 9, bottom right). The existence of an electronic effect of the NHC π acceptor orbital has already been mentioned by Tsepis et al.^[15a] Although NHC ligands are only weak π acids, such an undesired orbital interaction significantly destabilizes the active carbene conformation by up to a 20 kJ mol⁻¹.

The predicted energy differences for the *N*-methyl-substituted NHC complexes on the one hand (Figure 7), and the unsubstituted NHC complexes on the other hand (Figure 9) are thus not a random artifact of the ligand periphery, but originate in the electronic situation at the ruthenium center itself.^[15]

Furthermore, a route to irreversible intramolecular carbene dimerization is rendered possible (Figure 10). In an active conformation such as in **3'**, the NHC ligand and an active carbene ligand point their p -orbitals towards each other. A decrease of the C–Ru–C angle towards transition state **12'** causes an overall Gibbs free activation energy of 110.5 kJ mol⁻¹, and leads to a C–C coupling product **13'** (Figure 11). Thus, this reaction leads to catalyst decomposition. While an active carbene orientation is desired in

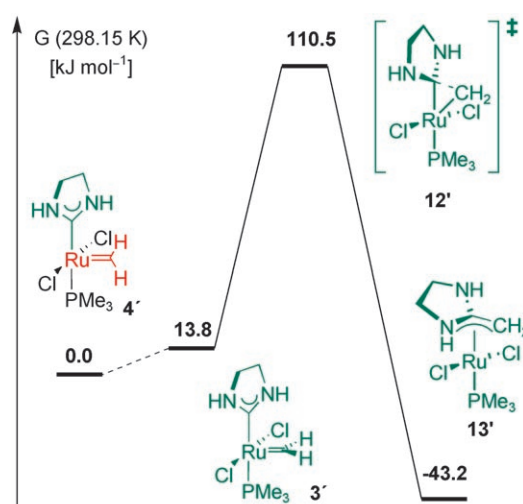


Figure 10. Gibbs free energy diagram of carbene dimerization to ruthenium alkene complex.

order to achieve high metathesis activity, the inactive NHC conformation is helpful to suppress an undesired catalyst decomposition pathway. Indeed, an inactive NHC orientation is enforced by sterically demanding *N*-(2,6-xylyl) derivative substituents in “real” second-generation Grubbs catalysts (Scheme 1, structure 2).

At the first glance, this rearrangement may appear artificial. However, there is the danger of ligand coupling for all ancillary ligands with sp^2 carbon atom – and possibly even for all sp^2 element ligands. Since this rearrangement concerns the 16 valence-electron

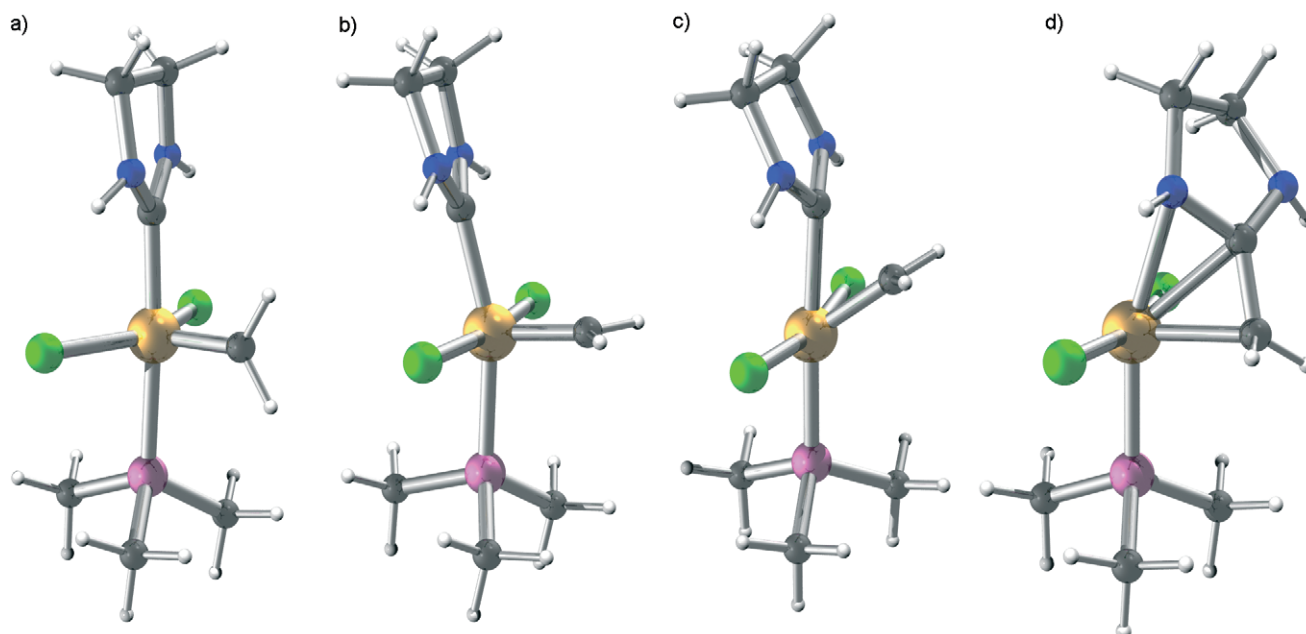


Figure 11. Ball-and-stick model structures of carbene complexes **4'** and **3'**, transition state **12'**, and decomposition product **13'**. Color code: hydrogen (gray), carbon (black), nitrogen (blue), phosphorus (violet-red), chlorine (green), ruthenium (orange).

precatalyst storage complex, any ligand design of new or even novel ligand systems has to recognize the challenge of maintaining the equivalence of ancillary ligands as “spectator” ligands.

In Table 2, the ligand influence on the energetics of the catalyst intermediates is listed. The dichloride complex has already been shown in the energy diagram of Figure 7. The difluoride, dimethoxide, dimesanethiolate, dimesylate, and the cationic chloro-aqua as well as the chloro-ammine ruthenium complex have been investigated. For energy diagrams, see the Supporting Information. The structure assignments of **3** to **11** refer to Figure 5.

Fluorine has a high electronegativity and has therefore been proposed as a better alternative to chloride-based Grubbs catalysts. Grubbs-type precatalysts with one fluoride ligand have indeed been synthesized and successfully employed. Whether the fluoride ligand remains coordinated at the ruthenium in the catalytic cycle, is unclear.

Due to their small size, second row elements are characterized by a very efficient overlap with their binding partners. This behavior causes several anomalies in inorganic chemistry, be it the low acidity of HF compared to HCl, the lower electron affinity of F compared to Cl, or the low bond energy of F₂. Fluoride ligands interact strongly with ruthenium *d*-orbitals. Anti-bonding orbital interactions (see Figure 4) are the basis for switching between carbene ligand orientations. In difluoride model complexes, the carbene ligand is predicted to strongly prefer an inactive conformation. This effect of fluoride ligands is even larger than that of the electropositive, but large, iodide in diiodide complexes. The previously expected catalyst activity row F₂(L)Ru=CH₂ > Cl₂(L)Ru=CH₂ > Br₂(L)Ru=CH₂ > I₂(L)Ru=CH₂ thus has to be revised to Cl₂(L)Ru=CH₂ > Br₂(L)Ru=CH₂ > I₂(L)Ru=CH₂ > F₂(L)Ru=CH₂. Chloride appears to be the best compromise of small electron-donating character and diffuse orbital shape.

Due to the apparent low fluorophilicity of ruthenium(II), fluoride precatalysts may well exchange fluoride ligands with substrate, water etc. and lead to cationic ruthenium complexes. In Figure 4, some frag-

ment molecular orbital interactions have been visualized, which show the interaction of angle changes with the orientation of the carbene π acceptor orbital. This interaction can be summarized in a short phrase: back-bending results in better back-bonding; and back-bonding leads to increased back-bending. In Table 3, angles at ruthenium are listed. For inactive

Table 3. Angle distortion from 90° due to carbene orientation.

X = F or Cl	$\alpha(\text{C}=\text{Ru}-\text{X})$	$\alpha(\text{C}=\text{Ru}-\text{C}^{\text{NHC}})$	$\alpha(\text{C}=\text{Ru}-\text{P})$
3(F):	95.1°/90.0°	103.2°	96.1°
4(F):	107.8°/108.0	89.2°	94.8°
3(Cl):	94.3/94.3	107.8°	93.7°
4(Cl):	110.3°/100.6°	92.3°	93.2°

carbene conformers, the halide ruthenium fragment bends back, thereby increasing $\alpha(\text{C}=\text{Ru}-\text{X})$ from the range of 90°–95° towards a range of 100°–110°. The NHC bends back in active carbene conformers, from $\alpha(\text{C}=\text{Ru}-\text{C}^{\text{NHC}}) < 93^\circ$ to angles larger than 103°. Interestingly, $\alpha(\text{C}=\text{Ru}-\text{P})$ remains almost constant. Since a phosphine ligand is both a σ donor as well as a π acceptor, an increase of the phosphine–ruthenium carbene angle would lead both to an anti-bonding interaction $\sigma(\text{P})$ to $d(\text{Ru})$ as well as to the loss of back-bonding $d(\text{Ru})$ to $\sigma^*(\text{P}-\text{C})$.

The differences in $\alpha(\text{C}=\text{Ru}-\text{X})$ angles are already present in the sterically simplified model system. In experimental X-ray diffraction studies on Grubbs catalysts with a sterically demanding ligand system, steric restrictions may cover electronic effects.^[16] Furthermore, only the most stable conformer can be isolated, rendering structural comparisons of both active and inactive carbene conformers essentially impossible.

Furthermore, a rotation of the NHC ligand into an active NHC conformation would be less unfavorable as in the chloride analogues due to the small size of the fluoride ligands and an intramolecular carbene coupling might become a problem.

Table 2. Ligand influence on carbene ligand orientation. Gibbs free energies in kJ mol^{−1}. The most stable precatalyst **3** or **4** is normalized to 0.0 kJ mol^{−1} for each anionic ligand choice. L = *N,N'*-dimethylimidazolidin-2-ylidene.

	3	4	5	6	7	8	9	10⁺	11
(Cl–Cl)	0.0	1.9	38.6	68.6	73.5	72.4	-	73.1	34.7
(F–F)	20.8	0.0	37.2	55.5	57.7	89.5	-	96.5	69.9
(OMe–OMe)	45.2	0.0	2.4	52.2	59.1	111.8	-	110.7	81.6
(SMe–SMe)	22.7	0.0	11.4	66.9	74.2	97.4	-	101.5	69.0
(OMs–OMs)	0.0	-	19.3	69.9	72.8	-	62.0	66.7	36.4
(Cl–OH ₂)	0.0	31.2	102.6	-	-	97.8	-	93.8	58.1
(Cl–NH ₃)	0.0	31.1	96.1	-	-	98.2	-	93.0	59.6

Alkoxide ligands result in tetracoordinated ruthenium species (Figure 12).^[17] Their catalytic activity is low. With HCl, first generation alkoxide complexes are converted to highly active metathesis catalysts.^[17a]

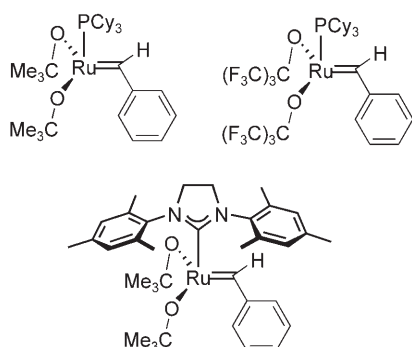


Figure 12. Catalytically inactive ruthenium carbene dialkoxide complex.^[17]

The low catalyst activity of ruthenium alkoxides can easily be deduced from the extreme stabilization of the inactive carbene conformation. Between 45 kJ mol⁻¹ and 60 kJ mol⁻¹ are required to overcome the electronic preference of the inactive carbene conformation over species with an active carbene orientation. Besides that, the high relative stability of the formal 14 valence-electron species **5(OMe)** is remarkable. The binding energy of a phosphine ligand to the ruthenium center roughly amounts to the entropic costs for the association of two molecules to one 16 valence-electron complex such as **4(OMe)**. This quantum-chemical result is in perfect agreement with the isolation of Grubbs dialkoxides depicted in Figure 12. With methoxide ligands, the catalyst system is predicted to feature only a very poor activity. With a more sterically demanding NHC ligand and bulky *tert*-butoxide ligands, alkene substrate coordination will be even more hindered and the low activity of the experimental ruthenium complexes is logical.

The comparison of oxygen and sulfur ligand atoms reveals that thiolate ligands have a positive influence on catalyst activity compared to the alkoxide analogues. Thiolates and alkoxides parallel chloride and fluoride in their tendency for predicted overall catalyst activity and stabilization of the active carbene orientation. Generally, third-row element ligand atoms are superior in their influence on inactive and active carbene conformations. Nevertheless, neither alkoxide ligands nor thiolate ligands, nor fluoride ligands can be regarded as viable alternatives for chloride.

Next, we were interested in the contrary effects of oxygen ligand atoms and electron-withdrawing acyl substituents at these oxygens. Mesylate (H₃CSO₃⁻) ligands combine these features perfectly. Indeed, the σ donor character of the oxygen ligand atom is strongly

weakened. As a consequence, there appears to exist no local minimum **4(OMs)** with an inactive carbene conformation – in sharp contrast to the methoxide analogue **4(OMe)**, which is about 45 kJ mol⁻¹ more stable than **3(OMe)**. The facile phosphine dissociation from **3(OMs)** is mainly due to the $\kappa^2\text{O}$ coordination of one of the mesylate ligands at the ruthenium center in **5(OMs)**, making the latter an almost saturated 16 valence-electron species. The predicted overall Gibbs activation energy of less than 70 kJ mol⁻¹ is the lowest cycloaddition barrier we have encountered so far. The rate-limiting step for mesylate catalysts is expected to be ligand dissociation from **3(OMs)** or alkene substrate coordination to structures analogous to **6(OMs)**. Even though **9(OMs)** is more stable than **6(OMs)**, the inactive carbene ligand conformation of structure **5(OMs)** is initially preserved, but will easily rotate into an active orientation. Transition state **10(OMs)** represents an even lower overall cycloaddition barrier than its chloride analogue **10(Cl)**. This is due to a balanced relative stability of active and inactive carbene conformations. Although we did not find a local minimum **8(OMs)** with active carbene and inactive alkene conformation, we succeeded in the characterization of a local minimum **9(OMe)** with carbene and alkene both in an active orientation. In most cases, such species exist only as transition states such as **10(OMs)**, immediately collapsing into ruthena(IV)-cyclobutane structures such as **11(OMs)**. Nevertheless, the barrier for the rearrangement of **9(OMs)** to **11(OMs)** amounts to only about 5 kJ mol⁻¹. The predicted high activity of ruthenium carbene mesylate complexes relies on intact mesylate coordination at the ruthenium. However, metal sulfonates tend to ionize, and saturate the free coordination site with water, other solvents, or functional groups of alkene substrate. Carboxylate ligands and pentafluorophenolate ligands have been employed successfully.^[18]

Cationic ruthenium carbene complexes have first been prepared and investigated by Peter Hofmann's group (Figure 13).^[11,19] A chelating diphosphine resulted in *cis*-diphosphine ruthenium carbene chloride complexes. Cationic derivatives featured high ROMP activity, though however, functional group tolerance is low.

For Grubbs-type catalysts, we computed the influence of the positive charge of the complex, and the role of uncharged ligands on the energies of the intermediates. Therefore, we replaced one chloride ligand by H₂O or NH₃.

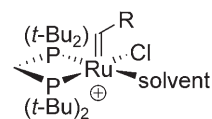


Figure 13. Cationic Hofmann ruthenium carbene complexes.^[11,19]

Aqua ligands reveal a tremendous stabilizing effect in favor of the active carbene conformation. This is true both for the precatalyst **3**(Cl-OH₂) versus **4**(Cl-OH₂) as well as for the alkene carbene isomers. For these isomers, we were unable to find local minima for inactive carbene conformations. Thus, the coordination and subsequent cycloaddition of an alkene to the ruthenium carbene fragment is extremely facile. The comparison of the oxygen atom ligands alkoxide, sulfonate, and water clearly shows the potential for ligand tuning.

The ammine ligand in cationic ruthenium carbene complexes displays a very similar influence on the energetics of intermediates compared to the aqua ligand. The weak donor capability of H₂O and NH₃ renders these ligands ideally suited for stabilizing active carbene conformations and demonstrates the importance of substituents at the ligand atoms. The challenge of cationic ruthenium carbene catalysts appears to be the dissociation of the phosphine ligand (or the counter ion, or a functional group of the substrate) from the precatalyst **3**(Cl-OH₂) or **3**(Cl-NH₃) to the 14 valence-electron intermediate **5**(Cl-OH₂) or **5**(Cl-NH₃). This effect reveals cationic ruthenium carbene complexes as an only mediocre synthetic goal for a functional group tolerant and highly active metathesis catalyst. However, amine or ether ligands may well be suited neutral ligand fragments for uncharged catalysts with a *cis* X-Ru-X' fragment (X = anionic ligand, see Table 1).

Conclusions

Regrettably, the amount of stabilization of ancillary ligands towards active carbene ligand orientations does not appear to be linearly additive. Nevertheless, a qualitative estimate of the ligand capability to influence the carbene ligand conformation is given below. The first ligands in the series below stabilize carbene π acceptor orbitals in plane with ruthenium atom and the respective ligand. The last ligands in the series stabilize a carbene π acceptor orthogonal to the ruthenium center and this ligand.

Alkyl > aryl > NR₂ > OR > SR \approx F \approx NHC > I > Br > Cl > O₃SR > R₃P > NR₃/NH₃ \approx OR₂/OH₂ > alkyne or alkene \gg free coordination site.

The introduction of the concept of second-generation catalysts has been the last major step in the development of ruthenium carbene complexes for alkene metathesis. Numerous new derivatives of the Grubbs-type have been synthesized and tested in recent years. The design of novel ligand environments, e.g., with *cis*

anionic ligands at ruthenium (Table 1), might benefit from the conclusions of this study.

Firstly, the fast and thermodynamically facile formation of active 14 valence-electron species from a 16 valence-electron precatalyst is a mandatory prerequisite. Uncharged catalysts are generally better suited to form electron-rich ruthenium centers that easily dissociate a labile ligand and do not bind functional groups of the substrate.

Secondly, similar to the original rule of Grubbs,^[4] strong σ donors have to be located *trans* to the alkene. Poor σ donor ligands have to be in a *cis* relationship to the alkene ligand. By this strategy, the active carbene conformation can be stabilized and the intrinsic reactivity of alkene carbene complexes towards rearrangement to ruthenacyclobutanes is maximized.

Thirdly, the ligand sphere has to be inert towards the electrophilic carbene moiety. Unsaturated ligands in an active conformation (as in Figure 10) bear the danger of opening the path for catalyst decomposition.

Experimental Section

Computational Methods

The B3LYP/LACV3P**+//B3LYP/LACVP* level of theory as implemented in the Jaguar 6.5 quantum chemistry program package^[23] has been utilized throughout this study.^[20–22] For C, N, O, P, S, Cl and H, the 6–31G* basis set of Pople and co-workers was used for structure optimizations. For ruthenium, a Hay–Wadt small-core effective potential replaces the 28 innermost core electrons. Full geometry optimizations and vibrational frequency calculations have been performed for all model compounds at the B3LYP/LACVP* level of theory. Exactly zero imaginary frequencies characterize minima; transition structures are characterized by exactly one imaginary frequency. Visual inspection of imaginary frequencies was performed with the Molden program package^[24] and geometry optimizations from slightly distorted transition state structures ensured the assignment of the two corresponding local minima. Single point energies were computed analytically with the LACV3P**+ basis set, which is characterized by the 6–311G**+ basis set for main group elements and by a diffuse d function for ruthenium (coefficient 0.042). The Gibbs free energies *G* refer to 298.15 K and 1 atm and are based on unscaled molecular vibrations and ideal gas phase conditions. Overall free activation energies of investigated catalytic cycles are based on Gibbs free energy differences between the rate-limiting transition state structure and the catalyst resting state. Free activation energies of single steps are based on Gibbs free energy differences between the respective transition state structure and the originating local minimum. Deviations of Gibbs free energies from previous calculations with an older Jaguar program package are due to different Gibbs energy corrections based on new frequency calculations.

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