Regio, Stereo and Chemoselectivity of 2nd Generation Grubbs Ruthenium-Catalyzed Olefin Metathesis.

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Graphical abstract

Highlights

- -Search for the origin of the chemo-, regio- and stereoselectivity in rutheniumcatalyzed
- olefin metathesis
- -Web server to facilitate the best combination catalysts/substrate
- -Predictive catalysis in olefin metathesis from DFT calculations

ABSTRACT

The examination of cross metathesis reactions leading to the desired product has been conducted to uncover computationally the origin of the chemo-, regio- and stereoselectivity. The comparison between the relative stabilities of all involved intermediates and products, together with the transition states, links to the probability for the respective pathway. Particularly, the respective transition states for each reaction tune the regio- and stereoselectivity because they lead to define the energy barriers needed to be overcome to form the new olefin as final product. The broad range of studied reactions with the 2nd generation Grubbs catalysts allows concluding in detail the points to pay attention and thus helps to understand the chemo-, regio- and stereoselectivity in new olefin metathesis reactions. Here, a web-server joins all these mechanistic insights which is intended to support future predictive olefin metathesis catalysis.

KEYWORDS: Olefin metathesis, predictive catalysis, mechanism, N-heterocyclic carbene, ruthenium

Supporting Information Placeholder

■ INTRODUCTION

Ru-catalyzed olefin metathesis certainly has a privileged position among the transition-metal catalyzed reactions with a bright future.[1,2,3,4] This reaction has great potential in a broad range of industrial applications spanning from basic transformations of raw materials in oil refinery and polymer chemistry, to sophisticated synthesis in the pharmaceutical industry. This potential would of course benefit from a thorough and comprehensive understanding of the basic mechanistic aspects involving reactivity of C=C double bonds. In addition to the overall activity, this also implies chemo-, regio- and stereoselectivity of the metathesis event. [5] Yet, we have a very good picture of many mechanistic details, both from the experimental[6,7,8,9,10,11,12,13,14,15,16,17,18,19,20] and theoretical[21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39] point of view. However, trying to correlate all these details into a single picture is complicated as the catalysts, the experimental conditions, or the computational approach, change from one work to the other,[40] apart from any decomposition that those olefin metatheses potentially suffer.[41,42,43,44,45,46,47]

Nevertheless, some general trends are by now well established. In terms of **reactivity/yields/turnover number (TON)**, fundamental studies (investigating metathesis events per unit of time) evidenced that the intrinsic capability of 2nd-generation N-heterocyclic (NHC) catalysts[48,49,50] is masked by the occurrence of non-productive (or degenerate) metathesis (Scheme 1).[51] An effective TON which is five times higher than those obtained with 1st generation catalysts was reached.[3,52]

Scheme 1. Productive versus non-productive cross metathesis products.

The **chemoselectivity** is mainly governed by the steric and electronic properties of the olefins: the olefin becomes more unreactive with higher steric protection. [53,54,55]

The **regioselectivity** derived from the product distribution for the simplest case of olefin metathesis, *i.e.* propene with a 2nd generation ethylidene Ru catalyst, was investigated by a computational approach. The role of both, reactivity and selectivity, was described based on the energetics of this basic CM reaction as a prototype of all terminal olefins finding out that 2,1-metathesis is generally favoured over 1-2 metathesis (see Scheme 2).[56] A similar trend was found in a kinetic ¹H NMR experiment monitoring the metathesis of unhindered, terminal CH₂=CHR olefins, such as 1-hexene, with the (PCy₃)₂Cl₂Ru=CHPh 1st generation catalyst. The initial formation of (PCy₃)₂(Cl)₂Ru=CHR, followed by the gradual and complete formation of (PCy₃)₂Cl₂Ru=CH₂ indicates a kinetic preference for 2,1-metathesis of a terminal CH₂=CHR olefin.[57] Furthermore, GC and TOF-MS monitoring of the metathesis of diethyl diallylmalonate and allylmethylmalonate with a series of NHC-based Ru catalysts indicated that non-productive cross metathesis (CM) can be competitive with ring-closing metathesis,[58] and that less hindered NHC ligands are more prone to undergo non-productive (2,1) CM. These findings highlight the relevance of understanding the factors controlling the regioselectivity of the metathesis event,[59] as in the formation of di-

and tri-substituted olefins most of the catalytic turnover events occur in non-productive metathesis that regenerates only the metathesis partners, but not the desired, productive cross metathesis products.[60]

Scheme 2. Potential olefin metathesis pathways for CM of **1** with **P** leading to regio- and stereoselective products *Z/E*-2-butene and propene.

The **stereoselectivity** of olefins with typical ruthenium based initiators, such as $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ gives almost exclusively *E*-olefins.[61] This implies that the formation of *E*-C=C bonds is favored over the formation of *Z*-C=C bonds. Several studies showed that changing selectivity towards the formation of *Z*-olefins is possible but involves the development of more advanced catalysts to regulate not simply the thermodynamics, but the kinetic barriers. Strategies have focused on protonation of the NHC ligand,[62,63] or the development of a new class of Ru-based metathesis catalysts with a C-H activated NHC ligand bond to the metal center[64,65,66,67] showing a remarkable selectivity for ring opening polymerization (ROMP),[68] and the formation of *Z*-olefins in CM, in particular adjusting the steric bulk.[69]

To understand how to control the activity and selectivity[70] in olefin metathesis, it is crucial to investigate the key steps of the olefin metathesis process which are (i) the generation of the 14e species, (ii) the coordination of the alkene, (iii) the generation of the metallacycle by [2+2] cycloaddition and (iv) the corresponding reverse steps.[71,72] In the current study, we invested a remarkable amount of resources in a comprehensive computational study to offer the chemical community a better and consistent understanding of various 2nd generation Ru based catalysts and their selectivity-determining steps in olefin metathesis.

Specifically, we built a set of 6 catalysts by combining two N-heterocyclic carbene ligands, **SIMes** and **SIPr**, with three alkylidenes $=\text{CH}_2$, $=\text{CH}(\text{Me})$ and $=\text{CMe}_2$ (Chart 1). The labels **0-2** on the Ru-species indicate the number of methyl groups on the alkylidene moiety, thus allowing for the immediate identification of the system discussed. The substrates (ethene **E**, propene **P**, *E*-2-butene **E-B**, *Z*-2-butene **Z-B**, iso-butene **iB**, 2-methyl-2-butene **3M** and 2,3-dimethyl-2-butene **4M**) have been chosen in order to cover systematically all possible carbon backbones that can occur in olefin cross metathesis (**chemoselectivity**). For olefins that can react with different **regiochemistry** – which is **P**, **iB** and **3M** – we considered the two possible regiochemical events (1,2- and 2,1-metathesis).[56] Additionally, we also examined which barriers are required to obtain **stereoselective** metallacycles leading to either to *Z*- or to *E*-olefins, respectively.

Chart 1. Labelling of catalysts and substrates under investigation.

As illustrative example, all possible combinations for **P** reacting with the Ru-ethylidene **1-SIMes** are sketched in Scheme 2. In case of the 1,2 pathway, *cis*- and *trans*-orientations of the methyl groups of the substrate and of the alkylidene moiety leading to *Z*- and *E*-butenes, respectively, have been considered. In case of the 2,1-pathway, both orientations of the two aforementioned methyl groups were included in our calculations, and the most favored pathway was used in the analysis.

Altogether, for both the **SIMes** and the **SIPr** systems we investigated 35 metathesis reactions, for a total of 70 complete pathways from reactants to products, as shown in Scheme 3 for the 1,2-*cis* pathway in case of propene **P** reacting with **1-SIMes**. To identify species along the pathway, we use the nomenclature reported in Scheme 3.[73]

Scheme 3. Olefin metathesis pathway on example of **1-SIMes** with **P** leading to Z-Bu.

Essentially, whatever olefins are used experimentally in a CM reaction, the basic skeleton around the C=C double bond of the substrates and around the Ru=alkylidene bond corresponds to one of the reactions we investigated. Considering the large number of reactions, 70, we do not describe each of them in detail. Instead, we discuss trends and focus on some specific paradigmatic cases only. Nevertheless, to give the reader the opportunity to better understand the specific energetic and geometric aspects of a given reaction, we have set up a web server where all the reactions are shown in detail, including the energy profiles and the geometries of all the species considered.

We believe that our study will offer a comprehensive understanding of fundamental issues related to olefin CM. Moreover, the web server should let the metathesis community to have easy access to the specific reaction needed.

■ RESULTS AND DISCUSSION

We investigated a total of 70 different reactions. The rather large number of profiles assembled requires a statistical analysis evidencing trends and general behavior. For this reason, the first part of this section comprises a description of the geometry and stability of the **14e** species and of the olefin coordinated complex **Co1** or **Co2** as a function of the alkylidene substitution, and of the metallacycle **MCY**, which is the key intermediate of olefin metathesis.[74] The following parts discuss preferences regarding the chemoselectivity on the basis of statistical analysis of all energy profiles. The final sections are devoted to clarify trends in the regio- and stereochemistry of metathesis reactions.

The role of alkylidene substitution up to olefin coordination. The first important particularity is the effect of alkylidene substitution on the binding energy of PCy₃. Moving from methyldiene **0** to ethyldiene **1**, the PCy₃ binding energies are similar, with a maximum difference of 0.2 kcal/mol for both **SIMes** and **SIPr** systems (see Table 1). The effect of the second methyl group on the alkylidene moiety, which means moving from propylidene to *iso*-propylidene, is approximately 2-3 kcal/mol in both systems, and results in easier PCy₃ dissociation.

Table 1. Dissociation energy, in kcal/mol, of PCy₃ from the SIMes and SIPr based precatalysts with different alkylidene units.

System	Ru=CH ₂	Ru=CH(Me)	Ru=CMe ₂
SIMes	11.0	10.9	8.2
SIPr	8.3	8.5	6.3

From a structural point of view this deviation can be explained by the following. In all the **14e** complexes the alkylidene moiety is rotated to bisect the Cl-Ru-Cl plane, which implies that for **2-SIMes** and **2-SIPr** one of the Me alkylidene groups is pointing toward the center of the nearby mesityl ring (Figure 1). To accommodate the second Me group the alkylidene moiety undergoes a severe deformation from the geometry it adopts in the **0** and **1** **SIMes** and **SIPr** analogues. This is compensated by a classical CH/π interaction between the positively charged Me group and the aromatic ring of the N-substituent.[75,76,77] The NHC-Ru=CR₂ angle increases by approximately 10°, which enables the formation of an agostic interaction (around 2.3 Å) between the nearest hydrogen of the methyl-group below the ruthenium center and the metal.

Figure 1. Geometries of the **14e** complexes for **0-SIMes**, **1-SIMes** and **2-SIMes**. Distances in Å, angles in °.

Additionally, the methyl substitution has no effect on the Ru=C bond distance, 1.79 ± 0.01 Å in the three complexes, while it has a strong effect on the polarity of the Ru=C bond. In **0-SIMes** this bond is almost non-polar, as shown by the similar Natural Population Analysis (NPA) charge on the Ru and C(alkylidene) atoms: -0.12e and -0.17e, respectively. In **1-SIMes**, this bond is slightly polarized (-0.14e and 0.06e) and becomes definitely polar in **2-SIMes** (-0.21e and 0.29e). The polarity of the Ru=C bond in **2-SIMes**, together with steric effects,[78] will induce preferential 2,1-metathesis with unsymmetrical olefins, such as **iB** (NPA charges on the dimethyl substituted C₁ and the unsubstituted C₂ atom: -0.01e and -0.42e, respectively). Minor but similar effects can also be expected for **P** and **3M**.

Focusing on the NHC ligand, the higher bulkiness of the SIPr ligand reduces the energy required to dissociate PCy₃ relative to the corresponding SIMes system. This conclusion is consistent with our previous analysis of the steric properties of these complexes with topographic steric maps.[79,80,81] They evidenced that the *iso*-propyl groups protrude into that part of the Ru coordination sphere, which is normally occupied by the PCy₃ ligand or the substrate.[82,83]

Metallacycle stability. The metallacycle **MCY** is the key intermediate of olefin metathesis and – aside from the **14e** complex – the most compact structure along the reaction pathway. Comparison of the relative stability of the metallacycle **MCY** deriving from metathesis of different substrates with the **14e** intermediate provides fundamental insights to understand the effects of alkyl substitution. The most stable metallacycle is the one of **E** with **0-SIMes**, laying at -10.4 kcal/mol below the starting **14e 0-SIMes** intermediate, a value reduced to -4.7 kcal/mol with **SIPr**. Methyl groups, either on the C_α or on the C_β atom, destabilize the metallacycle relative to **14e** intermediate and promote its reactivity. Double substitution on the C_α atom, as for the **MCY** of **0-SIMes** with **iB** results in a destabilization of 5.7 kcal/mol, as the corresponding **MCY** is only -4.7 kcal/mol below the **14e** intermediate. For the SIPr system the metallacycle with two methyls on the C_α atom is 3.6 kcal/mol above the **14e** intermediate, due to steric repulsion between the methyl substituents on the metallacycle and the *iso*-propyl groups of **SIPr**. Even higher destabilization was found for C_β-substituted metallacycles formed by 1,2-metathesis of **P** and **iB** with **0-SIMes** relative to the unsubstituted metallacycle (-4.2 and 0.5 kcal/mol). Moving to the **0-SIPr** system, the equivalent are laying at -

1.3 and 3.8 kcal/mol relative to the unsubstituted metallacycle, indicating that a bulkier NHC ligand destabilizes the metallacycle. Actually, the metallacycles deriving from 2,1-metathesis of **P** and **iB** with **0-SIMes** are 3.3 and 5.2 kcal/mol more stable than the corresponding 1,2-metathesis metallacycles (2.4 and 4.6 kcal/mol with **0-SIPr**). This clearly shows that methyl substituents on the C_α atom of the metallacycle have lower influence on the metallacycle stability than on the C_β atom. On the structural side, methyl substitution on the C_β atom results in a longer Ru- C_β distance, towards a more ideal tetrahedral geometry. Moving from the unsubstituted metallacycle to the metallacycle with one and two Me substituents on the C_β atom, the C_α - C_β - $C_{\alpha'}$ angle decreases from 117.6° to 115.5° and finally to 113.2° while the Ru- C_β distance increases from 2.24 Å to 2.27 Å and finally to 2.32 Å (see Figure 2). These results follow the trend in the force constant of the H-C-H, H-C-C and C-C-C vibrational bending modes, which result in a higher energy cost to deform a more substituted C atom from the ideal tetrahedral geometry. The longer Ru- C_β distance in the C_β substituted metallacycles also results in a weaker interaction between the atoms, a phenomenon suggested to destabilize the metallacycle.[84,85,86]

Figure 2. Geometries of the metallacycle **MCY** for **0-SIMes** with **E** and 1,2-coordinated **P** and **iB**. Distances in Å, angles in °.

During the synthesis of tri- and tetrasubstituted olefins, metallacycles presenting alkyl substituents at both the C_α and C_β atoms have to be formed. The substitution on both atoms clearly amplifies the effects previously discussed, as the repulsion increases with higher methyl substitution. Exemplary, the metallacycles deriving from 1,2-metathesis of **iB** with **1-SIMes** and **2-SIMes** are 3.0 and 8.8 kcal/mol above the **14e** intermediate (7.1 and 6.4 kcal/mol with **1-SIPr** and **2-SIPr**).

Statistical Analysis of Reaction Profiles.

Chemoselectivity. In this section, statistical trends regarding substitution effects are described using **SIMes** as example (see Figure 3a). At the end of this section, we also discuss significant deviations of the **SIPr** systems from the established trend. As stated before, dissociation of PCy_3 to reach the **14e** species costs approximately 10 kcal/mol both for **0-SIMes** and **1-SIMes**, while formation of the **14e** species of **2-SIMes** is 2 kcal/mol less unfavored due to the formation of a stabilizing agostic interaction (Figure 1). Moving to the coordination step **Co1**, it is a slightly favored step, average value of -0.3 kcal/mol relative to the **14e** species, with the extremes of the whiskers corresponding to coordination of **P** to **2-SIMes** and **4M** to **2-SIMes** at -2.3 and 3.7 kcal/mol, respectively. 50% of the binding energies is in the interquartile range (IQR) of 2.0 kcal/mol. The relatively small range covered by the olefin coordination energies suggests that the propensity of a given catalyst (NHC + alkylidene)

has scarce impact on determining the outcome of the metathesis reaction. Further, coordination of the olefins to **14e1** can be considered a substantially thermoneutral process, indicating that even tetrasubstituted olefins can approach the metal. **1-SIMes** has a slightly higher tendency to coordinate olefins relative to **0-** and **2-SIMes**. As expected, coordination to **SIPr** is always 2-3 kcal/mol disfavored relative to coordination to **SIMes**.

Moving to the stability of transition state **TS1** relative to the preceeding **14e** intermediate, 50% of the **TS1** energies scatter in a 5 kcal/mol range around the average value of 5.0 kcal/mol. The extremes of the whiskers correspond to the transition state for the metathesis of **E** with **1-SIMes**, laying at -2.0 kcal/mol, and for the metathesis of **4M** with **2-SIMes**, laying at 14.1 kcal/mol. The **TS1** energies follow a clear trend with the relative bulkiness of the substrate of the alkylidene group, in line with the well accepted idea that more hindered systems give less favored metathesis. In case of 1,2 and 2,1 metathesis of **P** and **iB**, the lower energy barriers always correspond to the 2,1 orientation, as it maximizes the distance between the methyl substituents on the olefin and the alkylidene, it results in the aforementioned more favorable orientation of the dipoles on the Ru=C and C=C bonds, and it leads to metallacycles less substituted at C_β atom. Similar considerations can be applied to **3M** metathesis.

Figure 3. Box plot of energy distributions for all intermediates/transition states during metathesis of substrates with the catalysts in Chart 1. The box contains 50% of the distribution (from the first to the third quartile) and the whiskers extend to the most extreme values of the distribution that are still within the inner fences (that is, one-and-a-half times the width of the box). Anything outside these whiskers is considered an outlier. The horizontal line separating the box in different colors represents the median of the distribution; the marker represents the average of the distribution. (a) blue: **SIMes**; (b) violet: **SIPr**.

In terms of reactivity, even the highest energy barrier, 14.1 kcal/mol corresponding to formation of a fully substituted metallacycle by metathesis of **4M** with **2-SIMes**, is easily accessible under the typical reaction conditions used in the field. This clearly supports that concept that the difficulty in achieving highly substituted olefins in cross metathesis is due to competitive nonproductive reactions.[1,3,60]

The metallacycle **MCY** is on average at the same energy level as the **14e** species, with a rather large interquartile range of 7 kcal/mol, and whiskers ending at -10.4 kcal/mol for **E** reacting with **0-SIMes** and at 14.7 kcal/mol for **4M** reacting with **2-SIMes**. This indicates that the stability of the metallacycle is the most variable parameter along the reaction pathway, with the already outlined trend that substituted metallacycles, particularly at the C_β atom, are less stable. On the other hand, no metallacycle is too much stable relative to the coordination intermediates to represent a dorming state for the system. A situation instead evidenced with Schrock catalysts.[87,88]

The aforementioned trends remain similar when **TS2** and **Co2** are considered, which is expected considering that the specific structures have been already considered at the **TS1** and **Co1** level. For instance, **TS2** along the reaction pathway corresponding to 1,2 reactivity of **iB** with **1-SIMes** corresponds to **TS1** along the reaction pathway of **3M** with **0-SIMes**. The slightly scattered values of **14e2**, instead, reflect the thermochemistry of the reaction, corresponding to the formation of a differently substituted olefin and of a differently substituted alkylidene.

At this point, we focused on probably the most relevant parameter to rationalize the products and the productive turn over numbers of cross metathesis, which is the energy difference between **TS1** and **TS2** (**TS2-TS1**), ΔG_{21} . ΔG_{21} expresses the formation of a given metallacycle via **TS1**, its forward evolution toward products via **TS2**, or the backward evolution to the reactants via **TS1**. A negative ΔG_{21} indicates that the metallacycle will move forward, a positive ΔG_{21} indicates that the metallacycle will move backward. All ΔG_{21} are summarized in Table 2.

Table 2. ΔG_{21} in the metathesis step, in kcal/mol, of **E**, **P**, **Z-B**, **E-B**, **iB**, **3M** and **4M** with the **SIMes** and **SIPr** based catalysts of Chart 1.

Olefin	0-SIMes ΔG_{Regio}	1-SIMes ΔG_{Regio}	2-SIMes ΔG_{Regio}
E	0.0	4.6	10.0
P (1,2)	0.0	1.2 / 1.1	5.7
P (2,1)	-4.6	0.0 / 0.0	2.6
Z-B	-1.1	0.0	2.3
E-B	-1.3	-1.9	-0.1
iB (1,2)	0.0	3.5	3.4
iB (2,1)	-10.0	0.0	0.0
3M (1,2)	-3.5	0.0	0.7
3M (2,1)	-5.6	2.3 / 0.0	0.0
4M	-3.4	-0.6	0.0
Olefin	0-SIPr	1-SIPr	2-SIPr
E	0.0	3.1	8.3
P (1,2)	0.0	5.0 / 4.9	6.5
P (2,1)	-3.0	0.0 / 0.0	4.4
Z-B	-4.9	0.0	2.4
E-B	-5.0	0.0	-1.0
iB (1,2)	0.0	3.0	5.3
iB (2,1)	-8.3	0.0	0.0
3M (1,2)	-4.0	0.0	-0.1
3M (2,1)	-6.5	-2.4 / 1.1	0.0
4M	-5.3	0.1	0.0

For **0-SIMes** all the ΔG_{21} are negative, from 0 kcal/mol for degenerate **E** and 1,2 metathesis of **P** and **iB**, to -10.0 kcal/mol for 2,1 metathesis of **iB**. Contrary, for **2-SIMes** all the ΔG_{21} are positive, from 0 kcal/mol for degenerate **4M** and 2,1 metathesis of **3M** and **iB**, to 10.0 kcal/mol for metathesis of **E**. This indicates that formation a more substituted alkylidene can be used as a rule of thumb to predict in which direction a metallacycle will evolve.

Finally, consistently with the low olefin bind energy discussed for intermediate **Co1**, release of the olefin from the **Co2** intermediate is not an energy demanding step.

Switching to **SIPr** catalysts, a similar trend was found (see Figure 3b). In general, all reaction steps exceed the **SIMes** pathway by approximately 3 kcal/mol (referring to the respective **14e1** species). This is not surprising, considering the higher bulkiness of the **SIPr** ligand.

Regioselectivity.

The impact of the different regiochemistry is illustrated by the energy profile of the metathesis of **1-SIMes** with **iB** as the substrate (Figure 4). This can be considered a typical case for the CM of a disubstituted and a monosubstituted olefin to give a trisubstituted olefin. The lower energy red pathway indicates that the most likely event is the non-productive exchange of the methylidene group between the Ru-alkylidene and the substrate. To point out that both pathways are slightly thermodynamically unfavourable. The regioselectivity, ΔG_{Regio} , is in this case evaluated as the energy difference between the highest in energy transition state along the reaction pathways corresponding to 2,1 and 1,2 metathesis. A negative value means that the 2-1 metathesis is favoured. In the presented example of **iB** with **1-SIMes** (Figure 4), 2,1-metathesis is clearly favoured, as $\text{TS}_{2,1}$ (4.8 kcal/mol) - $\text{TS}_{1,2}$ (-10.4 kcal/mol) resulting in a ΔG_{Regio} of -5.6 kcal/mol.

Figure 4. Reaction profiles (in kcal/mol) for 1,2- (green) and 2,1-metathesis (orange) of *iso*-butene **iB** with **1-SiMes**.

Given this background we discuss regioselectivity of **P**, **iB** and **3M**, because these (unsymmetrical) substrates can lead to the formation of two different products depending on which end of the substrate reacts with the alkylidene. For these substrates ΔG_{Regio} were calculated as indicated above. Positive values of ΔG_{Regio} imply that 1,2 metathesis is favored over 2,1 metathesis for **P** and **iB** (2,3 versus 3,2 for **3M**).

Table 3. Regioselectivity in the metathesis step, in kcal/mol, of **P**, **iB** and **3Me** with the SiMes and SiPr based catalysts of Chart 1. A negative value means that the formation of 2-1 metathesis is favoured.

Olefin	0-SiMes ΔG_{Regio}	1-SiMes ΔG_{Regio}	2-SiMes ΔG_{Regio}
P	-2.8	-0.8	-5.5
iB	1.1	-5.6	-3.4
3M	-0.1	-0.3	-0.1
Olefin	0-SiPr	1-SiPr	2-SiPr
P	-0.1	-0.9	-5.2
iB	-0.4	-3.7	-9.6
3M	1.4	1.5	-1.7

The ΔG_{Regio} values reported in Table 3 indicate that in case of **SiMes** nonproductive 1,2-reactivity is favored with catalyst **0** and substrate **iB** by 1.2 kcal/mol, productive 2,1-reactivity is favored with **P**, while reactivity of **3M** is substantially non-regioselective. For these examples, the regioselectivity is controlled at the metallacycle forming transition state **TS1**, as the metallacycle breaking transition state **TS2** is lower in energy. Increased bulkiness of the alkylidene group of the catalyst (**1-SiMes** and **2-SiMes**) shifts regioselectivity towards 2,1 reactivity, due to increased repulsion between the methyl substituents on the reacting alkylidene and olefin C atoms. Noteworthy, in these cases **TS2** is higher in energy than **TS1**, which indicates that the metallacycle would actually revert to reactants. As rule of thumb, less hindered alkylidenes, such as the methylidene group, is able to accommodate the bulkier tail of the substrate, thus reducing steric repulsion between the substrate and the NHC ligand. Bulkier alkylidenes, instead, are so bulky that it is better to place the bulkier tail of the substrate towards the NHC ligand. Further, 2,1 metathesis prevents the formation of a less substituted and less stable Ru-methylidene moiety.

The same tendency is found for the **SiPr** catalysts. The most sterically demanding substrate **3M** is more prone to undergo 3,2 metathesis with catalyst **0** and **1** due to reduced repulsion between the more substituted tail of **3M** and the alkylidene, rather than the SiPr ligands as in 2,3 metathesis. However, the bulkier alkylidene of **2-SiPr** reverses the trend, and favoring 3,2 nonproductive metathesis.

E/Z-Stereoselectivity.

Controlling the E/Z selectivity is one of the major issues in CM. Standard catalysts, as the SiMes and the SiPr based catalysts, considered in this work are biased toward *E*-selectivity.[89] Highly *Z*-selective catalysts have been developed by Grubbs, and are based on a rather different architecture, with a chelating N-heterocyclic carbene ligand.[90,91,92,93,94] In a previous work we already investigated the peculiarities of the 1,2 metathesis of **P** with the **1-SiMes** leading to **Z-B** and **E-B**. Our calculations indicated that, starting from the 14e species, the highest transition state along the productive 1,2-metathesis pathway was the metallacycle opening transition state, **TS2**. Surprisingly, the transition states for *Z*-selective products were located at slightly lower energy compared to *E*-selective products, which is frequently not in agreement with experiments.[56,95] Herein, we revise this mechanistic proposal of the reactivity of **1-SiMes** and **P**. The energy profile illustrated in Figure 5 shows 1,2- and 2,1 metathesis pathways. For 1,2-metathesis, the opposite pro-chiral faces of propene leading to *E*-butene and *Z*-butene are shown.[96] The methyl group of the Ru-ethylidene moiety is oriented as indicated in Figures 5a and

5b. Analysis of Figure 5 shows that 2,1-metathesis is favoured over 1,2-metathesis, as already discussed in the previous chapter (Table 3). The transition state for rotation around the Ru-alkylidene bond is at 5.8 and 10.7 kcal/mol for **Z-B** and **E-B**, respectively, indicating that alkylidene rotation is in both cases slower compared to metathesis events. Investigating the 1,2-metathesis, two events are possible – the coordination of propane with the methyl-tail *cis* (giving E-olefins) or *trans* (giving Z-olefins) towards the Ru-ethylidene tail as indicated in Figures 5a and 5b.

From the coordination intermediate **Co1**, **TS1** can be reached with rather low energy barriers (4.7 and 3.2 kcal/mol for **Z-B** and **E-B**, respectively). The formed metallacycles are C_β substituted and thus they are less stable (-2.0 and 1.0 kcal/mol for **Z-B** and **E-B**, respectively) compared to their C_α substituted (2-1) analogues. The metallacycles breaking **TS2** are at slightly higher energy values, leading to the respective Z- and E-olefin.

Figure 5. Reaction profiles (in kcal/mol) for cross metathesis of propene **P** with **1-SiMes**. (a) For the formation of *cis*- and (b) *trans*-2-butene (blue) the (c) overall reaction mechanism (1,2-metathesis and 2,1-metathesis) has to be considered.

Similar to the regioselectivity, also the stereoselectivity ΔG_{Stereo} , is evaluated. The energy difference between the highest in energy transition state along the reaction pathways corresponding to *E*-1-2 and *Z*-1-2 pathway. A negative value suggests that the formation of *E*-olefins are favoured. For the illustrated example **P** and **1-SiMes**, the difference between the highest TS of TS_{E1-2} (2.2 kcal/mol) – TS_{Z1-2} (3.6 kcal/mol) is -1.4 kcal/mol, indicating that the formation of an *E*-olefin is favoured. As shown in Table 4, we expect in all cases a preferred formation of the *E*-olefin as the kinetic product.

Table 4. Summary of ΔG_{Stereo} for substrates **P** and **3M** (relative energies in kcal/mol) for predicting the kinetic products. Negative values indicate a preferential formation of *E*-products.

Olefin	1-SiMes ΔG_{Stereo}	1-SiPr
P (1,2)	-1.4	-0.7
3M (2,1)	-1.1	-0.7

CONCLUSIONS

In this study, we have investigated computationally the origin of the chemo-, regio- and stereoselectivity in the cross metathesis of a library of second generation Ru-Grubbs catalysts by varying carbene-ligands (methylidene, ethylidene and *i*-propylidene) **0-2**, NHC-ligands (**SiMes** and **SiPr**), and substrates (**E**, **P**, **E-B**, **Z-B**, **iB**, **3M**, **4M**). While the chemoselectivity is controlled by electronic and steric factors of the intermediates and substrates, the regio- and stereoselectivity is controlled by the metallacycle forming and breaking transition states **TS1** and **TS2**, *i.e.* the energy barriers. To obtain all information about the kinetic product, the overall rate determining transition barrier has to be considered. This knowledge provides qualitative evidence for predicting preferred products of the reaction for testing newly designed catalysts.

To provide a clear picture of cross metathesis of 2nd generation Grubbs-catalysts and the special properties (as chemo-, regio- or stereoselectivity) of each reaction pathway, as already successfully done in the past,[78,79] we have installed a web-server to better visualize our mechanistic findings.[97] This is intended to support related predictive catalysis in future,[98,99,100] even though much more efforts must still be undergone in the future to further understand the Z/E isomer selectivity, as well as to expand the scope of the metathesis reactions, by means of other ligands and/or metals.[101,102,103,104,105]

■ COMPUTATIONAL DETAILS

DFT calculations were performed at the generalized gradient approximation (GGA) level with the Gaussian09 package,[106] using the M06 functional of Truhlar,[107] whose exchange functional is built based on the hybrid-meta generalized gradient approximation (HMA). The electronic configuration of the molecular systems was described with the standard split-valence basis set with a polarization function of Ahlrichs and co-workers for H, C, N and Cl (SVP keyword in Gaussian09).[108] For Ru we used the small-core, quasi-relativistic Stuttgart/Dresden effective core potential (standard SDD keywords in Gaussian09).[109] The geometry optimizations were performed without symmetry constraints, and the characterization of the located stationary points was performed by analytical frequency calculations, and transition states were further checked by intrinsic reaction coordinate (IRC) calculations, and the intermediates further checked from the latter IRC analyses. When two isomers were located for the same coordination intermediate, the transition state was further checked to be meaningless with energy barriers lower than 2 kcal/mol in all cases. The reported energies at 298.15 K have been obtained through single point calculations with the M06 functional and the electronic configuration of the molecular systems was described by a triple- ζ valence basis set with a polarization function for main group atoms (TZVP keyword in Gaussian09).[110] Solvent effects have been estimated in single point calculations on the gas phase optimized structures, based on the polarizable continuum model (PCM) using CH₂Cl₂ as the solvent.[111,112] Benchmark studies with the Solvation Model based on Density (SMD) were also conducted (see Table S4).[113] To state that the computational methods were chosen here as a compromise between accuracy and feasibility to provide more data for the web-server.

Credit Author Statement

Author Contributions

The manuscript was written through contributions of all authors.

Individual contributions

Eva Pump: Data curation; Formal analysis; Writing - original draft

Albert Poater: Data curation; Formal analysis; Conceptualization; Funding acquisition; Writing - review & editing

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Luigi Serra: Methodology; Software; Visualization

Vittorio Scarano: Methodology; Software; Visualization

Luigi Cavallo: Data curation; Formal analysis; Conceptualization; Funding acquisition; Writing - review & editing

ASSOCIATED CONTENT

Supporting Information

Computational details and all XYZ coordinates, energies and 3D structures of all species. This material is available free of charge via the Internet.

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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