# Sterically Tuned *N*-Heterocyclic Carbene Ligands for the Efficient Formation of Hindered Products in Ru-Catalyzed Olefin Metathesis

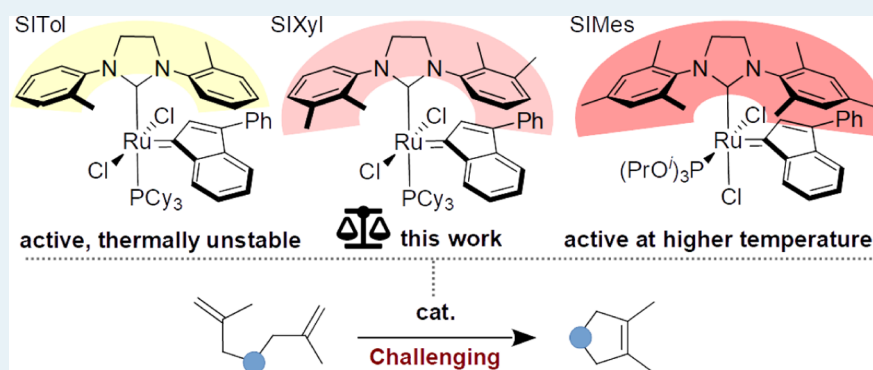Sebastian Planer, Paweł Małecki, Bartosz Trzaskowski, Anna Kajetanowicz,* and Karol Grela*

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**ABSTRACT:** Formation of tetrasubstituted C−C double bonds via olefin metathesis is considered very challenging for classical Ru-based complexes. In the hope to improve this condition, three ruthenium olefin metathesis catalysts bearing sterically reduced *N*-heterocyclic carbene (NHC) ligands with xylyl "arms" were synthesized, characterized using both computational and experimental techniques, and tested in a number of challenging reactions. The catalysts are predicted to initiate much faster than the analogue with mesityl *N*-substituents. We also foreboded the rotation of xylyl side groups at ambient temperature and the existence of all four atropoisomers in the solution, which was in agreement with experimental data. These catalysts exhibited high activity at relatively low temperatures (45−60 °C) and at reduced catalyst loadings in various reactions of sterically hindered alkenes, including complex polyfunctional substrates of pharmaceutical interest, such as yangonin precursors, chrysantemic acid derivatives, analogues of cannabinoid agonists, α-terpineol, and finally a thermally unstable peroxide.

**KEYWORDS:** *olefin metathesis, ruthenium, ligands, sterically reduced N-heterocyclic carbenes, catalysis, tetrasubstituted double bonds*

## INTRODUCTION

Well-defined ruthenium olefin metathesis catalysts are widely utilized in modern organic chemistry due to their universality and good stability toward air and moisture.[1−4] Despite the fact that the most popular ruthenium catalysts **Ru1−Ru4** (Figure 1a) enabled the synthesis of a variety of products with differently substituted double bonds, the effective and economically viable synthesis of crowded alkenes still remains a challenge.[5,6] Compared to Schrock's highly active molybdenum alkylidenes (e.g., **Mo1**),[7] the formation of sterically hindered C−C double bonds was always the Achilles' heel of ruthenium metathesis catalysts. The introduction of the so-called second generation of ruthenium metathesis complexes, containing *N*-heterocyclic carbene (NHC) ligands (such as SIMes, Figure 1a),[8] partially revoked this limitation. However, the reactivity of SIMes-bearing catalysts such as **Ru2−Ru4** in the formation of tetrasubstituted C−C double bonds still remained imperfect. In the following years, extensive modification of catalysts' structure was conducted to ameliorate the reactivity of Ru-based catalysts toward sterically hindered C−C double bonds.[5,6]

Importantly, Grubbs[9,10] and Schrodi[10] proposed that Ru complexes containing NHCs with at least one ortho position of the *N*-aryl ring unsubstituted (such as **Ru5**) should provide the space required for the formation of the more sterically demanding metalacyclobutene *en route* to a tetrasubstituted olefin. This key observation led to the development of other catalysts bearing sterically reduced NHC ligands (Figure 1b).[5,6,11−13] Unfortunately, in many cases, the improved activity in the formation of substituted C−C double bonds was at the expense of the catalyst's thermal stability. The reason for limited stability was thoroughly explored by Grubbs[9] and Blechert[14] and attributed to facilitated C−C and C−H activation and carbene insertion reactions (e.g., as in **Ru7**, Figure 1c), leading finally to
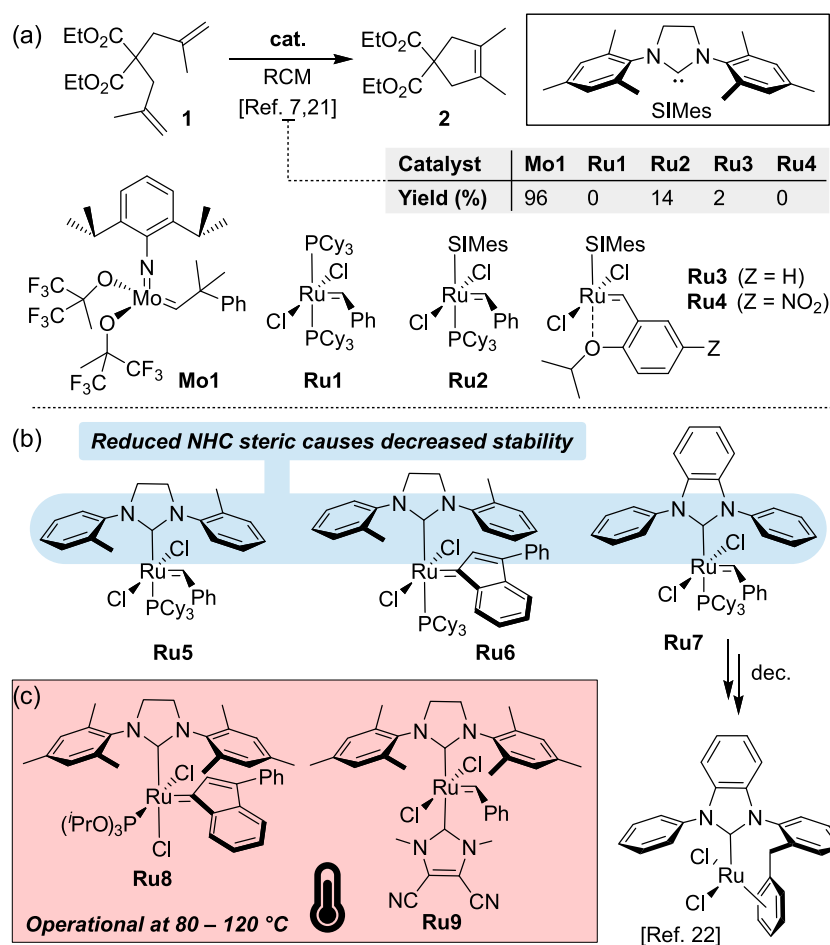
**Figure 1.** (a) Performance of classical olefin metathesis catalysts in RCM of **1**.[7,21] (b) Selected catalysts bearing sterically reduced NHC ligands exhibiting enhanced activity toward hindered olefins and one of the multiple pathways of their decomposition.[22] (c) Selected Ru complexes giving good results in the formation of tetrasubstituted olefins at higher temperatures.

various Ru complexes inactive in metathesis.[9,14] Thus, apparently in this case, the remedy became a poison: the reduced steric bulk around the Ru catalytic center, necessary to allow the metathesis of crowded olefins, made at the same time the catalysts much less stable. Numerous solutions for this fundamental problem have been proposed, which have been recently reviewed.[5,11]

In their landmark discovery, Cazin et al. replaced the tricyclohexylphosphine (PCy$_3$) ligand, typical for many ruthenium metathesis catalysts, with a phosphite one.[15,16] This seemingly small change had important consequences, as the thermodynamically stable product of this exchange, complex **Ru8** (Figure 1c),[15] had a unique *cis* arrangement of chloride ligands (initially, a *trans* product was formed, which isomerized to a more stable *cis* form). It also exhibited latent behavior, being activated at relatively high temperatures (80−120 °C). Importantly, **Ru8** efficiently transformed a number of sterically crowded dienes into products bearing tetrasubstituted C−C double bonds.[15] Later, a related phosphite-containing cationic Ru complex was obtained, which was also shown to be privileged in the metathesis of sterically crowded olefins.[17] Plenio et al. decided to follow a slightly different path, as they developed a series of (NHC)(NHC$_{EWG}$) ruthenium complexes, in which two NHC ligands differ in electronic properties (e.g., **Ru9**, Figure 1c).[18,19] Such bis(NHC) catalysts also required higher temperatures to operate (80−100 °C) and enabled the synthesis of

various olefins bearing tetrasubstituted double C−C bonds. Elevated temperatures of operation can be paired with other factors, as in the work of Lemcoff and Tzur, who developed a series of S-chelated ruthenium catalysts that are thermal- and light-activated and that effectively catalyze the metathesis of hindered substrates.[20]

Despite the fact that extensive research on ruthenium complexes capable of catalyzing the metathesis of sterically hindered olefins has been made, in our opinion, there is still a need for catalysts (at least in some cases) that are thermodynamically stable but at the same time can operate at ambient conditions. The need for such lower-temperature active catalysts is illustrated in the present organic syntheses. For example, Koide et al. reported on the synthesis of FR901464[23] and its analogues, such as meayamycin,[24] based on cross metathesis of two advanced olefinic partners **3** and **4** (Scheme 1).[25] Unluckily, formation of the key C−C double bond utilizing CM at the very last step of the synthesis was not a trivial task, as the fragile nature of **3** prevented using any more forcing reaction conditions. Because it was found that **3** quickly decomposes above 47 °C, the CM step had to be done below this temperature, thus limiting the catalyst choice. Finally, Koide used standard SIMes-bearing catalysts at temperatures not exceeding 43 °C to obtain FR901464 but in only 40% yield (Scheme 1).[25] Similar examples, where the application of sterically reduced NHC catalysts was for some reasons

**Scheme 1. Temperature Limitation Encountered in the Last Step of FR901464 Total Synthesis (ref 25)**



**Scheme 2. Synthesis of Complexes Ru11−Ru13 from Xylidenes 5a−c**
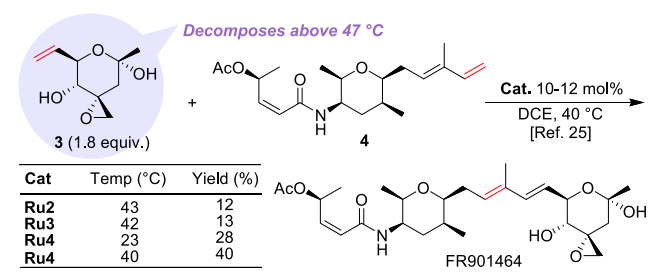


impossible or unprofitable and the standard SIMes catalysts were also suboptimal,[26] leading to low yields of the target products or requiring high catalyst loading have been published.[3,27,28] This problem is obviously even more serious in the context of larger-scale applications of the metathesis reaction in pharmaceutical production.[29]

In this work, we opted to check whether aromatic NHC "arms" smaller than the most frequently used mesityl (2,4,6-trimetylophenyl, Mes) or 2,6-(diisopropyl)phenyl (DIPP) substituents[8] but larger than phenyl or o-tolyl fragments (e.g., in **Ru5−Ru7**) allow us to obtain more robust catalysts. As a result, we report herein on the synthesis and characterization of indenylidene-type Ru-complexes stabilized by new NHC ligands bearing N-xylene NHC side groups, as well as their characterization supported by computational methods (DFT B3LYP-D3 for geometry optimization, M06-D3 for Gibbs free energy evaluation, and SAPT2+3 for very accurate interaction energy, see the Supporting Information) and catalytic activity evaluation in a set of challenging metathesis reactions, including complex polyfunctional substrates.

## ■ RESULTS AND DISCUSSION

**Synthesis and Characterization of the Complexes.** The synthesis of the NHC precursors was completed in a sequence of three simple and economical reaction steps (Scheme 2). Condensation of corresponding xylidines **5a−c** with glyoxal was performed to provide diamines **6a−c** in 83−85% yields. Next, reduction with sodium borohydride followed by hydrochloric acid addition allowed obtaining dichlorides **7a−c**, which were then utilized in a reaction with triethyl orthoformate to produce imidazoline salts **8a−c** in good to excellent yields (89−98%). Upon treatment with base, the in situ generated carbenes were then subjected to a reaction with commercially available first-generation indenylidene catalyst **Ru10**. Initially, KHMDS was used as a base, leading to satisfying results only in the case of **Ru12**, yielding the desired complex in 53% yield but failing to provide a satisfactory yield with the two other compounds. In the next attempt, inspired by a recent work of Skowerski,[30] LiHMDS was used for carbene generation, affording complexes **Ru11−Ru13** in good yields (63−70%, Scheme 2).

In solution, each of these complexes exists as a mixture of four conformers, which is clearly visible in both ^{1}H and ^{31}P NMR spectra (for details, see the SI), consistent with our previous observation of the o-tolyl system (SITol),[31] as well as with the previous study by Delaude on related systems featuring benzimidazol o-tolyl NHC ligands.[32] On the other hand, in the cases of **Ru11** and **Ru13** (we were, unfortunately, not able to grow single crystals suitable for X-ray diffraction from the third isomer, **Ru12**), only syn conformers were found in the X-ray diffraction analysis (Figure 2). The ORTEP diagram of **Ru11**
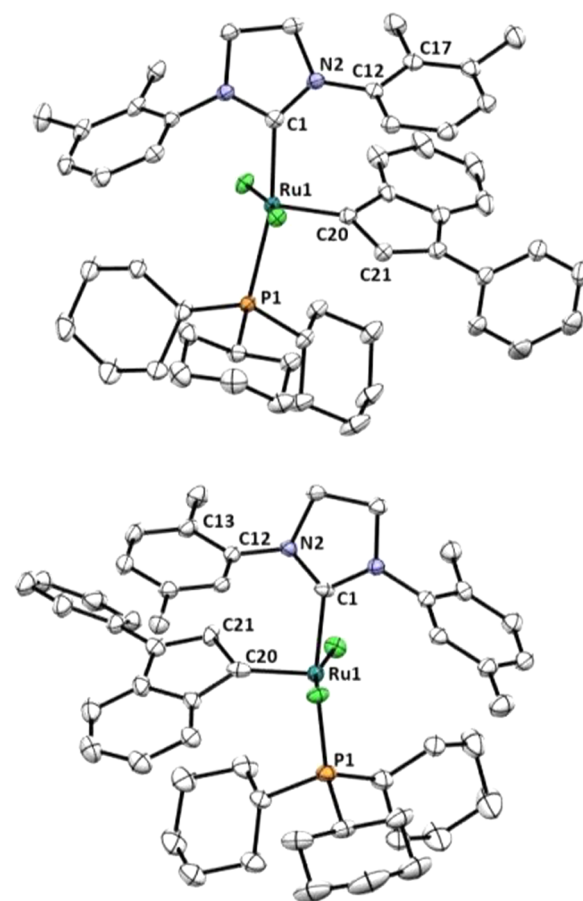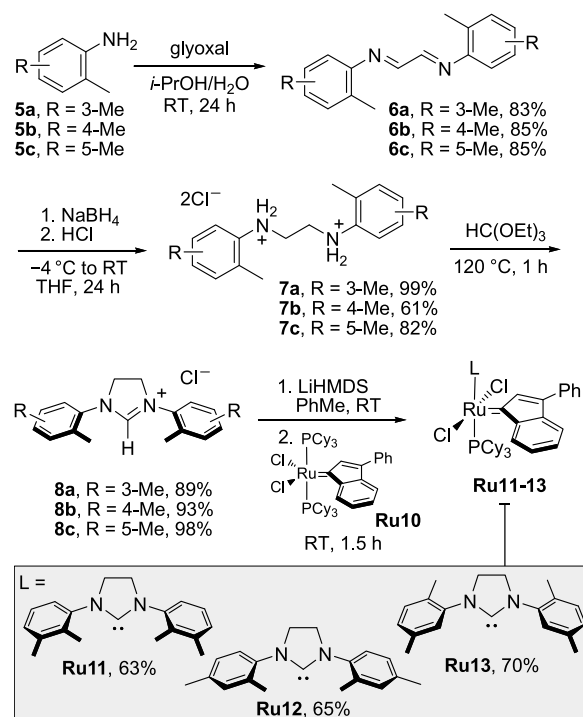


**Figure 2.** Molecular structures of **Ru11** (top) and **Ru13** (bottom). Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

displays the methyl groups of the xylene substituents on the opposite side as the phenyl group of the indenylidene moiety. Consequently, the metal center is considerably less sterically shielded on one side of the complex. Thereby, the structure differs distinctly from **Ru13**, where both sides of the complex are protected by the methyl groups of xylene substituents. As a result, **Ru11** is expected to be more effective in metathesis reactions with demanding substrates than **Ru13** (vide infra). Furthermore, the indenylidene moiety and the *N*-xylyl substituents in **Ru11** and **Ru13** complexes display different torsion angles (see Figure 2 and Table 1). Of course, because it is

**Table 1. Selected Bond Lengths and Angles of Ru11 and Ru13**

|  | parameter | Ru11 | Ru13 |
|---|---|---|---|
| $d$ [Å] | Ru1−C1 | 2.073(2) | 2.054(3) |
|  | Ru1−C20 | 1.856(2) | 1.851(4) |
|  | Ru1−P1 | 2.4911(5) | 2.4904(9) |
| $\alpha$ [deg] | C20−Ru1−C1 | 97.81(9) | 94.31 |
|  | C17(13)−C12−N2−C1 | 129.8(2) | −124.7(4) |
|  | C21−C20−Ru1−C1 | 118.85(18) | 62.0(3) |

well known that solid-state structures do not necessarily reflect the conformations mostly present in solutions, the above prediction about reactivity shall be treated only as an indication and verified experimentally.

**DFT Computations.** As complex **Ru12** did not yield in suitable crystals for X-ray diffraction analysis, we decide to seek aid in computational methods to get a closer look into structural and energetic differences between isomers of **Ru11−Ru13**. The DFT-optimized geometries of complexes **Ru6**, **Ru11−Ru13**, and **Ru14** are presented in detail in the Supporting Information.

While **Ru14** has only one major conformation, catalysts **Ru6** and **Ru11−Ru13** exist as four atropoisomers depending on the position of the tolyl/xylyl moieties with respect to each other (see Figure 3). Therefore, we considered each of them in the DFT calculations. For **Ru6**, four signals in the $^{31}$P NMR spectrum have been reported earlier with an intensity ratio of 8.3:3.7:1.4:1, corresponding to two *syn* (**Ru6a−Ru6b**) and two *anti* (**Ru6c−Ru6d**) isomers.[31] A similar analysis performed earlier for Grubbs-type catalysts bearing benzimidazol *o*-tolyl carbene yielded a 3:1:5:1 ratio, suggesting also the formation of a mixture containing four atropoisomers.[32] In that study, however, no assignment of each NMR signal to a particular structure was performed, although the obtained ratio suggests very similar energies for all atropoisomers. Our computational analysis shows that all four isomers are very close in the Gibbs free energy

(Table 2). The lowest free energy isomer **Ru6a** (*syn*) is only 0.9 kcal/mol more favorable than the *anti* isomer **Ru6c**. However, **Ru6b** (*syn*) and **Ru6d** (*anti*) are 3.2–3.4 kcal/mol less stable than **Ru6a**. These values correspond to a ratio of 312:68:1.4:1 (**Ru6a/Ru6c/Ru6b/Ru6d**) at room temperature and are in good agreement with the experimental data considering the expected accuracy of the DFT approach of approx. 1−2 kcal/mol. Similar to that, **Ru11a** and **Ru13a** appear to be the most stable conformations among their respective atropoisomers, which is also emphasized in NMR analysis, where one conformer accounts for the majority. This is also in agreement with the X-ray diffraction analysis where the *syn* isomers **Ru11a** and **Ru13a** were detected exclusively (Figure 2). However, **Ru11** in particular shows conformer distinctions among the *o*-toluene/xylene complexes. While for **Ru6** and **Ru12-13** the major conformer shows a share of around 50%, the distribution for **Ru11** is more than 70% concentrated on one atropoisomer (please find a more detailed discussion in the SI). Overall, energetic differences between the four atropoisomers are larger for **Ru13** with up to 6.9 kcal/mol for **Ru13b** (relative to **Ru13a**). The results for **Ru12** differ from **Ru11/13**, predicting conformer **Ru12c** as the most stable. Nevertheless, we observe a similar signal pattern in $^{31}$P NMR spectra for **Ru12** to that for **Ru11/Ru13**, indicating the same conformer distribution. Former experimental studies suggest quick rotation of tolyl and mesityl substituents at elevated temperatures.[33−37] Our computational approach estimates tolyl/xylene rotation barriers for **Ru6** and **Ru11−Ru13** between 21.8 and 29 kcal/mol (Table 2), respectively, suggesting a rather modest tolyl/xylene rotation at room temperature and an effortless rotation at elevated temperatures. By increasing the temperature during the NMR experiment, a shift in conformer distribution was already observed at 30 °C for **Ru11**, indicating exchange between all four atropoisomers (please see the SI for more information). As the lowest rotation barrier is predicted for the unhindered xylene moiety of **Ru11** with 21.8 kcal/mol, we assume in advance fast conformational adaptation for **Ru11** toward bulky olefins, leading possibly to lower sterically shielding of the ruthenium center and therefore higher catalytic efficiency with respect to **Ru12/13**. In contrast to that, the calculated rotation barriers for **Ru14** are much higher (>45 kcal/mol), resulting in no rotation of the mesityl substituents, even at high temperatures. We can also claim at this point that, due to the almost free rotation of the tolyl/xylyl moieties, the rate of the metathesis initiation is likely to be independent of the relative population of the atropoisomers but rather depend on the Gibbs free energy of the lowest-barrier transition state, in accordance with the Curtin−Hammett principle.[38]
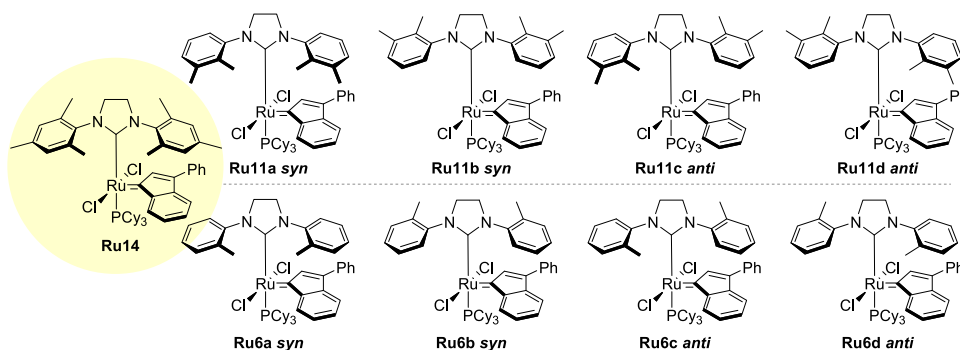


**Figure 3.** Schematic representation and naming scheme of the four possible conformers for **Ru11** and **Ru6**.

**Table 2. Selected Parameters for Ru6 and Ru11−Ru14 Obtained from the DFT Calculations[a]**

| parameter | Ru6 | Ru11 | Ru12 | Ru13 | Ru14 |
|---|---|---|---|---|---|
| Ru−P distance (Å) | 2.52 | 2.52 | 2.50 | 2.53 | 2.50 |
| Ru−C$_{carbene}$ distance (Å) | 2.08 | 2.08 | 2.08 | 2.08 | 2.10 |
| relative stability of isomers (kcal/mol) | **Ru6a**: 0.0 | **Ru11a**: 0.0 | **Ru12a**: 1.2 | **Ru13a**: 0.0 | |
| | **Ru6b**: 3.2 | **Ru11b**: 3.0 | **Ru12b**: 4.5 | **Ru13b**: 6.9 | |
| | **Ru6c**: 0.9 | **Ru11c**: 0.2 | **Ru12c**: 0.0 | **Ru13c**: 2.1 | |
| | **Ru6d**: 3.4 | **Ru11d**: 1.4 | **Ru12d**: 3.6 | **Ru13d**: 2.2 | |
| side group rotation barrier (kcal/mol) | 1: 22.5 | 1: 21.8 | 1: 23.9 | 1: 23.2 | 1: 45.0 |
| | 2: 25.2 | 2: 29.0 | 2: 26.2 | 2: 25.1 | 2: 48.9 |

[a]Side group rotation refers to the rotation around the N−Ar bond separately for the aromatic group opposite to the indenylidene moiety (1) and next to the indenylidene moiety (2)

**Table 3. Predicted Gibbs Free Energies of Activation for Investigated Complexes at the DFT Level of Theory[a]**

| activation mechanism | Ru6 | Ru11 | Ru12 | Ru13 | Ru14 |
|---|---|---|---|---|---|
| dissociative (kcal/mol) | **Ru6a**: 26.8 | **Ru11a**: <u>24.1</u> | **Ru12a**: <u>20.0</u> | **Ru13a**: 30.9 | <u>27.6</u> |
| | **Ru6b**: 28.8 | **Ru11b**: 25.9 | **Ru12b**: 25.4 | **Ru13b**: 24.4 | |
| | **Ru6c**: 25.2 | **Ru11c**: 25.9 | **Ru12c**: 26.2 | **Ru13c**: 27.4 | |
| | **Ru6d**: <u>23.3</u> | **Ru11d**: 28.0 | **Ru12d**: 23.2 | **Ru13d**: <u>24.1</u> | |
| interchange (kcal/mol) | **Ru6a**: 28.8 | **Ru11a**: 30.7 | **Ru12a**: 27.2 | **Ru13a**: 30.8 | 30.1 |
| | **Ru6b**: 26.1 | **Ru11b**: 28.4 | **Ru12b**: 29.3 | **Ru13b**: 26.9 | |
| | **Ru6c**: 30.8 | **Ru11c**: 31.4 | **Ru12c**: 28.2 | **Ru13c**: 31.9 | |
| | **Ru6d**: 25.2 | **Ru11d**: 27.4 | **Ru12d**: 24.1 | **Ru13d**: 28.0 | |
| associative (kcal/mol) | **Ru6a**: - | **Ru11a**: - | **Ru12a**: - | **Ru13a**: − | 32.3 |
| | **Ru6b**: - | **Ru11b**: - | **Ru12b**: - | **Ru13b**: 27.1 | |
| | **Ru6c**: - | **Ru11c**: - | **Ru12c**: - | **Ru13c**: - | |
| | **Ru6d**: - | **Ru11d**: - | **Ru12d**: - | **Ru13d**: −- | |

[a]The lowest barriers for each atropoisomer of each studied complex are underlined.

During the analysis of new metathesis catalysts, many groups are looking for various correlations between the structural parameters of catalysts and their initiation rates.[39] For example, a stronger interaction between the tolyl/xylyl/mesityl moiety and the indenylidene part could lead to a shorter Ru−C$_{carbene}$ distance and an extended Ru−P bond due to the known *trans* effect.[40,41] The results of the SAPT2+3 calculations (see the Supporting Information) show, however, that the strength of the tolyl/xylyl/mesityl-indenylidene interaction does not correlate with the computed Ru−C$_{carbene}$ distance, which is almost constant for all investigated complexes (Table 2). In addition, no correlation between the calculated Ru−C$_{carbene}$ and Ru−P bond lengths can be observed either (Table 2). On a side note, predictions on catalytic activity based on structural parameters are often difficult as proven for Hoveyda−Grubbs catalysts, where no correlation between the initiation rates and Ru−O bond lengths was found.[42]

Most indenylidene ruthenium catalysts initiate according to the well-known dissociative mechanism, although small changes in the catalysts, conditions, or substrates can favor an associative or interchange initiation pathway instead.[43−45] To shed more light on the probable initiation mechanisms of **Ru6** and **Ru11**−**Ru14**, we performed calculations for all three possible mechanisms including again all four atropoisomers (see Table 3). According to mechanistic and kinetic studies reported in the literature, the dissociation of the phosphine ligand leading to the formation of the active 14-electron complex is the rate-determining step for the entire catalytic cycle in the dissociative mechanism.[43] However, initiation rates via the associative mechanism are limited by the formation of an 18-electron species through olefin association. In the case of the interchange

mechanism, the transition state leading to the 16-electron species is considered as the rate-limiting step.

The experimental initiation rate for **Ru14** ($k < 0.01$ s$^{-1}$ at 353 K) is much lower than initiation rates for the first- and second-generation Grubbs-type catalysts.[42,46,47] As such, our predictions for the Gibbs free energy initiation barrier of **Ru14**, estimated at 32 kcal/mol for associative, 30.1 kcal/mol for interchange, and 27.6 kcal/mol for dissociative pathways, meet our expectations of high thermal stability. Based on these results, **Ru14** is predicted to activate via the dissociative mechanism and the Gibbs free energy of 27.6 kcal/mol is consistent with the experimental data, indicating very slow activation of this complex. A similar pattern of results was obtained for **Ru6** and **Ru11**−**Ru13**, although with lower Gibbs free energy barriers, suggesting a much faster activation of these catalysts with respect to **Ru14**. With a few exceptions (**Ru6b**, **Ru11d**, and **Ru13a**), the free energy barrier for dissociative activation is the lowest for all conformers and all studied complexes, suggesting initiation via the dissociative mechanism. As a matter of fact, we were not able to find stable 18-electron intermediates for most of the atropoisomers, with the exception of **Ru13b**, since during geometry optimization ethylene spontaneously dissociates from the complex. As a result, we excluded the associative mechanism as a possible initiation pathway for our catalyst systems, especially considering the fact that we focused our research on sterically demanding olefins, for which the associative mechanism is highly unlikely.[44] For small olefins, however, the differences between Gibbs free energies are in some cases (**Ru6**) predicted to be below 2 kcal/mol, potentially allowing initiation via both dissociative and interchange mechanisms simultaneously, similarly to Hoveyda−Grubbs catalysts.[44] It is also worth mentioning that, unlike for similar systems studied

earlier,[12,13] the lowest initiation barriers were found both for *syn* atropoisomers (**Ru11**, **Ru12**) and *anti* atropoisomers (**Ru6**, **Ru13**). This finding is, however, of little consequence to the catalytic activities of these complexes and their initiation rates, as for all studied complexes, the atropoisomers are in close equilibrium and can thermally interconvert into each other due to relatively low barriers of side group rotations (Table 2). The practical conclusion from the results presented in Table 3 is that the computational part of this study predicts fast activation of **Ru12**; relatively fast activation of **Ru6**, **Ru11**, and **Ru13**; and slow activation of **Ru14**.

**Catalytic Activity Studies.** Since we were interested in the practical potential of new complexes in the metathesis reaction of hindered olefins, we circumvented the typical activity test with unsubstituted diethyl 2,2-diallylmalonate and 2,2-diallyltosylate and focused directly on the difficult cases, starting with the RCM of diethyl 2,2-di(2-methylallyl)malonate (**1**) (see also Figure 1a). The reaction was performed at 0.1 M concentration at 60 °C in toluene with 1 mol % respective catalyst. For comparison, commercially available **Ru14** (bearing a mesityl-decorated NHC ligand, SIMes) and **Ru5** (with a smaller tolyl bearing SITol) and SITol indenylidene complex **Ru6**, previously reported by us,[31] were comparatively screened under identical conditions (Figure 4).
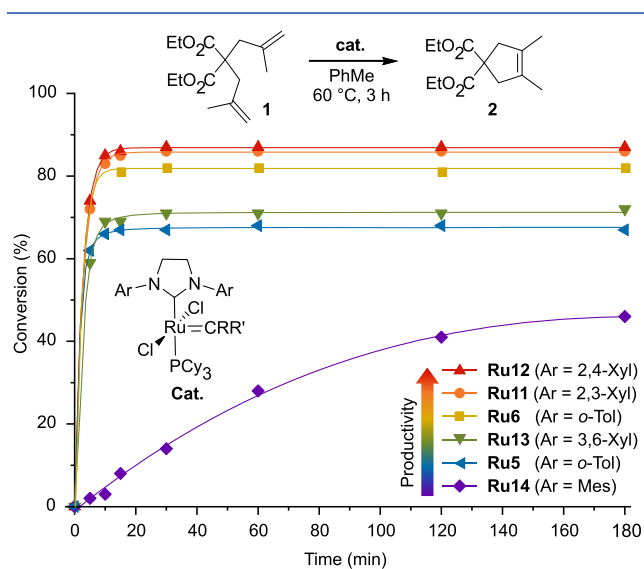


**Figure 4.** Time/conversion curves for the RCM reaction of **1** with 1 mol % Ru complexes at 60 °C (monitored by GC). For complexes **Ru6** and **Ru11**–**Ru14**, CRR' stands for the indenylidene ligand. For complex **Ru5**, CRR' stands for the benzylidene ligand. Lines are visual aids only.

All catalysts with sterically reduced NHC ligands initiated rapidly, with **Ru11** and **Ru12** providing the highest conversions. The third catalyst in the xylyl series, **Ru13**, exhibited visibly lower activity in the RCM of **1**. A commercial standard— benzylidene catalyst **Ru5** led to lower conversion than **Ru11** and **Ru12**, possibly because of the lower protection of sterically smaller *o*-tolyl NHC ligand toward its more sensitive benzylidene ligand. In comparison, the indenylidene analogue of the latter, complex **Ru6**,[31] was visibly more productive in this transformation, however, providing still 5 percentage points lower conversion than the SIXyl complex (**Ru12**). One can state that the improvement of 5 percentage points is not a significant difference, but in the history of olefin metathesis applied toward

the synthesis of biologically active and natural products,[3,27,28] such a small difference noted for a simple model can often translate to much higher improvement in the case of real polyfunctional complex targets.[48] This was also the case here, as one can observe in scheme 4–6 later.

Nevertheless, all of these small-NHC complexes out-performed in this challenging RCM reaction the SIMes-bearing complex, **Ru14**, which is known as a popular general-application olefin metathesis catalyst (Figure 4).
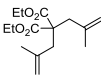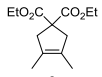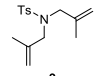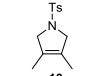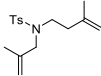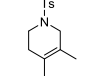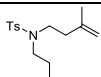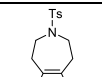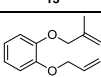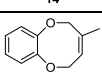
Based on the above results, complex **Ru11** bearing 2,3-xylyl-decorated NHC ligand has been chosen for further tests. The decision was made based in part on the highest activity exhibited in the model RCM reaction of **1** and in part because this complex was the most convenient in purification and the price of *o*-xylidine was most affordable.

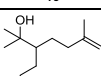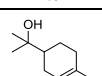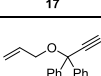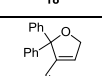The results presented in Table 4 illustrate the general high catalytic activity of **Ru11** as, except for substrate **13** (entry 4), all RCM reactions were effectively performed with less than 1 mol % catalyst.

As the previously used benchmark 2,2-di(2-methylallyl)-malonate (**1**) is known as one of the most challenging model substrates, we returned to it once more, this time checking whether its cyclization would be possible with less than 1 mol % catalyst. We were pleased to obtain the RCM product **2** in an isolated yield of 77% in the presence of only 0.5 mol % **Ru11** catalyst (Table 4, entry 1). Also, the RCM reactions of tosylamine derivatives **9** and **11** were performed with 0.1 or 0.2 mol % catalyst loading, respectively, leading to practically quantitative yields (Table 4, entries 2 and 3). In comparison, RCM of substrates **1**, **9**, and **11** catalyzed by **Ru8** prepared by Cazin et al. led to similarly good results but required higher temperatures (120 °C) and longer reaction times (8 h) according to the published report.[15] In the case of tosylamine derivative **13**, a precursor of seven-membered ring product **14**, catalyst **Ru11** gave complete conversion and a high isolated yield of 94%, although a loading of 1 mol % was necessary (the catalyst was added in four separated portions of 0.25 mol % each) (Table 4, entry 4). A constant argon flow to remove the resulting ethylene efficiently encouraged product formation and sup-pressed the catalyst decomposition.[49] The same experiment with **Ru5** afforded **14** in only 43% yield, which highlights the superiority of the **Ru11** complex.

Trisubstituted olefin **16** was synthesized in a high yield by the use of only 0.4 mol % **Ru5** or **Ru11** (Table 4, entry 5). Interestingly, the undesired process of dimerization of **15** via the CM reaction on the sterically less hindered double bond was not observed in the presence of any of the tested catalysts, which is in contradiction to some previous reports.[50,51] The next selected target was α-terpineol (**18**), a natural compound containing a substituted double bond. One of its main characteristics is a very pleasant odor, often associated with lilac, making it a very common ingredient in the production of cosmetics and perfumes. We used this compound as a valid research model for comparative evaluation of **Ru5** and **Ru11**. No negative influence of the free OH group in **17** on the yield of the RCM reaction was observed, as both catalysts led to satisfactory results at only 0.01 mol % catalyst loading, with **Ru11** giving again slightly better results. It shall be noted that previously we executed the same RCM using a SIMes-bearing catalyst and obtained α-terpineol in 92% yield, yet using a five-time higher catalyst loading at 80 °C.[52] At last, the enyne metathesis of **19** (Table 4, entry 7) was performed with a catalyst loading of only 0.05 mol %, leading to a conversion of 90% for **Ru11** and 70% for

## Table 4. Results of RCM and Enyne Metathesis Reactions

| Entry | Substrate | Product | Catalyst [mol%] | Time [h] | Yield [%] |
|-------|-----------|---------|-----------------|----------|-----------|
| 1 | 1 | 2 | **Ru11** (0.5)<br>**Ru5** (1.0) | 2<br>2 | 77<br>67[b] |
| 2 | 9 | 10 | **Ru11** (0.1)<br>**Ru5** (0.1) | 1<br>1 | 95<br>79 |
| 3 | 11 | 12 | **Ru11** (0.1)<br>**Ru11** (2 × 0.1)<br>**Ru5** (0.1) | 1<br>3<br>1 | 88<br>95<br>58 |
| 4 | 13 | 14 | **Ru11** (4 × 0.25)<br>**Ru5** (4 × 0.25) | 8<br>8 | 94<br>43 |
| 5 | 15 | 16 | **Ru11** (4 × 0.1)<br>**Ru5** (4 × 0.1) | 4<br>4 | 95<br>92[a] |
| 6 | 17 | 18 | **Ru11** (0.01)<br>**Ru5** (0.01) | 1<br>1 | 93[a]<br>72[a] |
| 7 | 19 | 20 | **Ru11** (0.05)<br>**Ru5** (0.05) | 1<br>1 | 90[a]<br>70[a] |

Conditions: 0.1 M, 60 °C, toluene [a]The conversion is determined by NMR spectroscopy. [b]Conversion is determined by GC using durene as an internal standard.
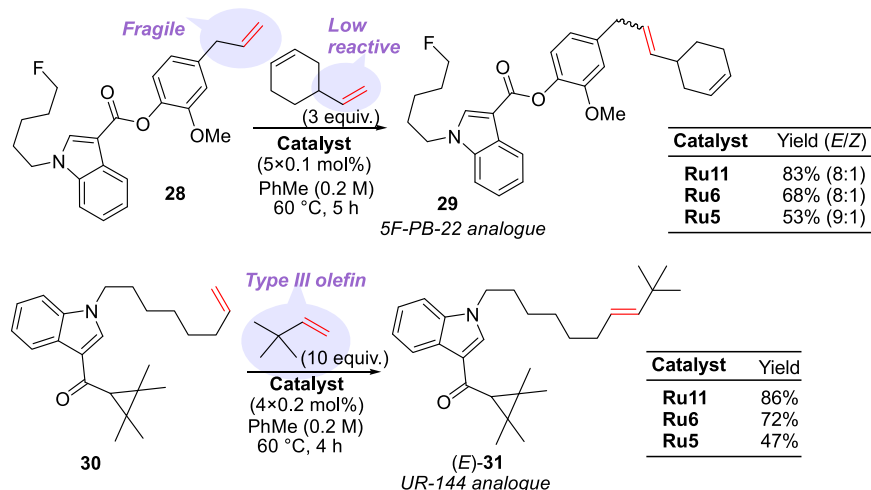
**Ru5**. Despite the fact that this substrate is not that challenging, the above results are one of the best achieved using phosphine-containing catalysts reported up to date. Only the highly active bis(cyclic alkyl amino carbene)−ruthenium complexes presented by Skowerski et al. in 2017 and the phosphite-containing complexes presented by Cazin et al. combine a lower catalyst loading with consistent high conversions.[30,53,54] The results presented in Table 4 show that xylene-based catalyst **Ru11** in each case outperformed SITol-based **Ru5**, although the latter can also effectively yield desired products at acceptable catalyst loadings.

To fully expound the scope and limitations of the studied catalyst, several challenging cross-metathesis reactions were investigated (Scheme 3). First, the reaction between a low reactive trisubsituted C−C double bond of ethyl chrysanthemate (**21**) and (Z)-but-2-ene-1,4-diyl diacetate (**22**) in the presence of 3 × 1 mol % **Ru5** and **Ru11** was performed. Both catalysts showed high isolated yields of **23**, significantly outperforming the previously reported result, where under more harsh conditions (20 mol % **Ru14**, C₆F₅CF₃, MW, 120 °C) the desired product was isolated in 51% yield (Scheme 3a).[55] When challenging 4-methylene-1-tosylpiperidine (**24**) was employed with (Z)-but-2-ene-1,4-diyl diacetate (**22**), the CM reaction afforded **25** in 86 or 75% yield, depending on the catalysts used. It shall be noted that the same substrate has been studied previously, giving with standard SIMes-based catalyst an almost twice lower yield (47%) of product **25** (Scheme 3b).[21] Next example, the CM reaction between **26** and p-methoxystyrene shows the true limits of xylyl catalyst **Ru11** (Scheme 3c). In our hands, the expected product **27** was obtained in 45% yield, thus finishing the formal total synthesis of yangonin, a

## Scheme 3. Comparative Study on CM Reactions Catalyzed by Ru11 and Other Catalysts[a]
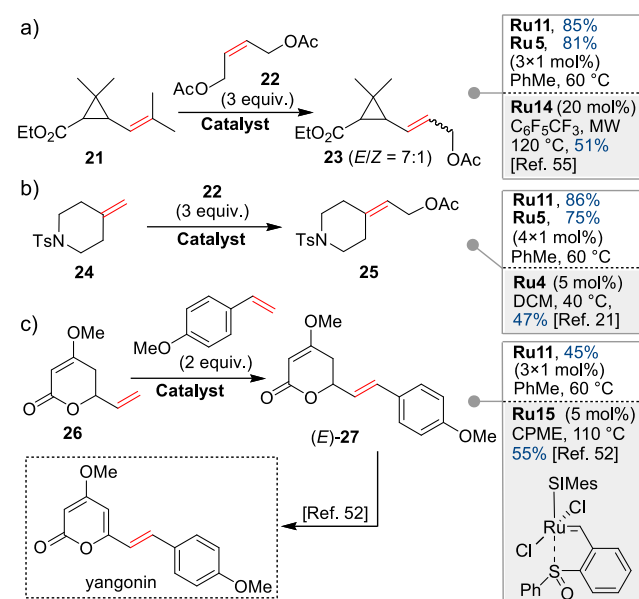


[a]MW = microwave irradiation, DCM = Dichloromethane, CPME = cyclopentyl methyl ether.

member of kavalactone family of natural products. So far, this ambitious CM was tried only once, providing **27** in 55% yield while using more forcing CM conditions (110 °C, 5 mol % SIMes-bearing **Ru15**, a member of Cazin's and Lemcoff's groups of thermally activated catalysts).[52]
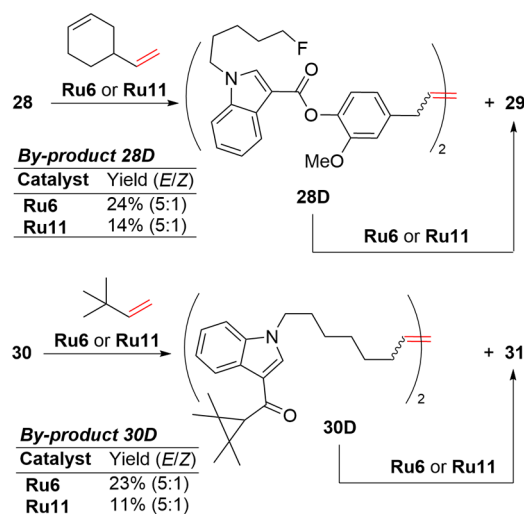
**Scheme 4. Catalysts Ru5, Ru6, and Ru11 in CM Leading to New Analogues of Cannabinoid Agonists 29 and 31[a]**



| Catalyst | Yield (E/Z) |
|---|---|
| Ru11 | 83% (8:1) |
| Ru6 | 68% (8:1) |
| Ru5 | 53% (9:1) |

| Catalyst | Yield |
|---|---|
| Ru11 | 86% |
| Ru6 | 72% |
| Ru5 | 47% |

[a]Catalysts were added portionwise during the reaction.

Until now, our investigation has provided a proof of concept that ruthenium complexes bearing xylene-based NHC ligands can be indeed effective in the metathesis reaction of sterically hindered olefins. This encouraged us to test them in the synthesis of more sophisticated polyfunctional compounds of complexity level typical for medicinal chemistry targets (Scheme 4). To do so, we attempted the synthesis of two new analogues of psychoactive cannabinoid agonists, 5F-PB-22[56] and UR-144[57,58] bearing fragments derived from neohexene and vinylcyclohexene, that are known to be of very low reactivity in CM.[59] Until now, these substrates were tested with much simpler cross partners (belonging to type I or II olefins according to Grubbs' classification)[59] and required at least 1 mol % catalyst to obtain good yields.[60] We were therefore satisfied to obtain high yields in the presence of only 0.5−0.8 mol % Ru11, particularly since 5F-PN-22 substrate (28) contains a rather fragile eugenol fragment[60,61] and substrate 30 was reacted with neohexene, a low reactive type III olefin (Scheme 4). Nota bene, in both of these cases, the xylyl-derived catalyst Ru11 gave 14−15 percentage points higher yields then SITol-based Ru6 reported by us previously.[31] Importantly, the commercial benchmark, Ru5, also gave with these demanding targets slightly inferior results in terms of the isolated product yields (Scheme 4). Because in multistep total syntheses the olefin metathesis transformation is often used as one of the very last synthetic steps,[3,27,28,62] 14−39 percentage points higher yield obtained due to the application of Ru11 is not to be scorned.
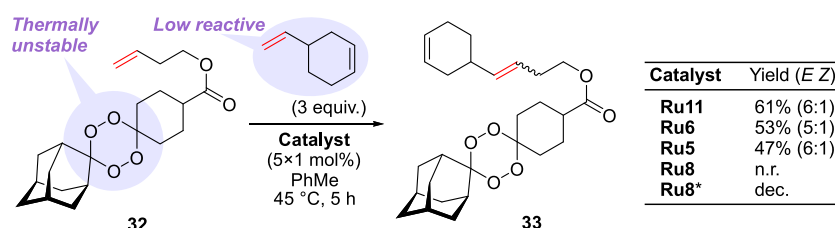
While studying the above CM reactions of cannabinoid agonists analogues, we noted another important difference between the behaviors of indenylidene SITol (Ru6) and SIXyl (Ru11) catalysts. In both cases, the formation of some amounts of byproducts ("homodimers") resulted from self-cross metathesis (self-CM)[63] of substrates 28 and 30, as observed by thin layer chromatography (TLC). To quantify the amounts of these byproducts, we attempted to isolate them. Interestingly, catalyst Ru6 produced as large as 23−24% of 28D and 30D "homodimers" (thus limiting the yield of the expected CM products 29 and 31), while the use of Ru11 led under exactly the same conditions to the reduction of this parasitic process almost two times (Scheme 5). This result shows that Ru11 is overall much more effective in a difficult CM reaction than structurally

**Scheme 5. Homodimer 28D and 30D Formation Observed during CM of Cannabinoid Agonists 28 and 30; for Reaction Conditions, see Scheme 4**



**By-product 28D**

| Catalyst | Yield (E/Z) |
|---|---|
| Ru6 | 24% (5:1) |
| Ru11 | 14% (5:1) |

**By-product 30D**

| Catalyst | Yield (E/Z) |
|---|---|
| Ru6 | 23% (5:1) |
| Ru11 | 11% (5:1) |

similar complex Ru6, leading to less homodimer formation and overall higher yields of the desired products.

As the final experiment, tetraoxane derivative 32 was examined in cross metathesis (Scheme 6).[64] The choice of this CM partner was made based on a known low thermal stability of the tetraoxane fragment and its importance in medicine.[65,66] Therefore, the CM reaction was performed at 45 °C only due to the fragile nature of peroxide 32. Despite the nonforcing conditions used, we were pleased to see that the desired product 33 was obtained in 61% isolated yield with 5 mol % Ru11. It shall be noted that SITol-based indenylidene complex Ru6 gave the same product in a lower yield (53%). The benchmark Ru5 allowed us to obtain 33 in a slightly lower yet still acceptable yield of 47%. Finally, we attempted the same transformation utilizing otherwise very successful Cazin's catalyst Ru8. Unfortunately, at the temperature safe for this fragile substrate,[64,67] complex Ru8 did not initiate the reaction, while at the temperature optimal for this catalyst,[15] full decomposition of the substrate was observed (Scheme 6).

**Scheme 6. Activity of catalysts Ru5, Ru6, Ru8, and Ru11 in CM Functionalization of Tetraoxane 32[a]**



| Catalyst | Yield (E Z) |
|----------|-------------|
| **Ru11** | 61% (6:1) |
| **Ru6** | 53% (5:1) |
| **Ru5** | 47% (6:1) |
| **Ru8** | n.r. |
| **Ru8\*** | dec. |

[a]Catalysts were added in five consecutive portions every hour. *Reaction at 120 °C (oil bath temperature). n.r. = no reaction, dec. = decomposition.

## CONCLUSIONS

An efficient synthesis of three new olefin metathesis catalysts bearing xylene-based, sterically reduced NHC ligands has been described, starting from inexpensive xylidines as starting materials. Resulting complexes were fully characterized using both experimental and computational techniques. Our computational studies predict a relatively fast initiation of all newly synthesized complexes in metathesis as well as almost free rotation of the xylyl side groups at ambient temperature and the existence of four atropoisomers, in agreement with experimental data. Based on theoretical results, we predict that all new catalysts initiate via the dissociative mechanism. Two of these complexes were shown to be effective catalysts in ring-closing metathesis of hindered diene **1**. An *o*-xylidine-derived **Ru11**, the best representative of the family, was in detail examined in a set of challenging RCM and CM reactions, providing usually better yields of the respective products and smaller byproduct formation than the known small-NHC complexes **Ru5** and **Ru6**. Performing a number of challenging transformations with low loadings, catalyst **Ru11** exhibited activity comparable to the powerful Cazin's phosphite catalyst[15,17] and the specialized (NHC)(NHC)$_{EWG}$ complexes by Plenio[19] but with the advantage of working at lower reaction temperatures.[68] This feature allows it to be used with a thermally unstable peroxide and other types of fragile substrates. Therefore, we believe that the newly obtained *o*-xylyl complex can be a valuable addition to a group of olefin metathesis catalysts capable to form tetrasubstituted crowded C−C double bonds.

## ASSOCIATED CONTENT

**Ⓢ Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c02770.

> Experimental, X-ray crystallographic, and computational methods and data (PDF)
>
> 3D rotatable images of all geometry-optimized structures (XYZ)

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**Notes**

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

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