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Specialized Ruthenium Olefin Metathesis Catalysts Bearing Bulky Unsymmetrical NHC Ligands: Computations, Synthesis, and Application

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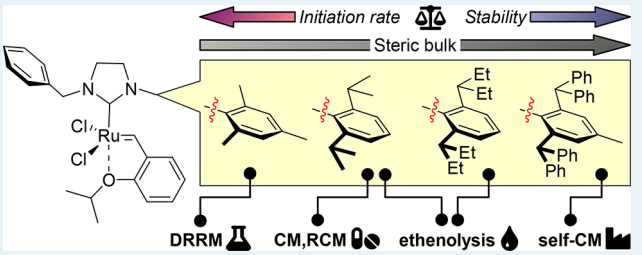
Supporting Information

ABSTRACT: Second-generation ruthenium olefin metathesis catalysts were investigated with systematic variation of the unsymmetrical uNHC ligands. Depending on the uNHC steric bulk, the catalysts exhibited different activity and selectivity in metathesis reactions. DFT calculations and X-ray crystallographic data were used to understand the influence of uNHC ligand structure on the catalyst properties. Furthermore, the catalysts were examined in the context of reactions that are problematic for general-purpose Ru catalysts, including industrially important self-cross metathesis of α-olefins and ethenolysis of ethyl oleate.



KEYWORDS: *olefin metathesis, ruthenium, ligands, N-heterocyclic carbenes, catalysis, selectivity, ethenolysis*

INTRODUCTION

Olefin metathesis is an important catalytic reaction that allows for preparation of various organic compounds.[1] The milestone enabling the introduction of metathesis methodology both for general laboratory practices and large-scale industrial production,[1c] was the introduction of well-defined catalysts, based on molybdenum, tungsten, and ruthenium. Peculiarly, the second-generation ruthenium catalysts **Ru1**−**Ru5**, in which one phosphine ligand was replaced by N-heterocyclic carbene (NHC) ligands (Figure 1, top), become very popular because of their satisfactory stability toward air and moisture, and good activity.[1]

The NHC moieties are among the most important ligands used not only in olefin metathesis catalysts but also in other transition-metals complexes commonly utilized in a variety of coupling reactions,[2−4] as well as in metal-free organocatalysis.[5,6] Such a high popularity of these ligands results from their modularity and easy fine-tuning of their steric and electronic properties, and thus the ability to modify the properties of the resulted catalysts.[7] Numerous ab initio and experimental trial-and-error studies probing the relationship between the structure of the NHCs and the stability and activity of the resulted catalysts were conducted.[8,9] In the context of Ru-catalyzed olefin metathesis, it was proven that the introduction of larger *N*-substituents (e.g., DIPP instead of Mes, Figure 1) in the NHC ligand core not only improves the stability of the resulted Ru alkylidene catalyst but also affects its activity. For example, many reports state that catalysts

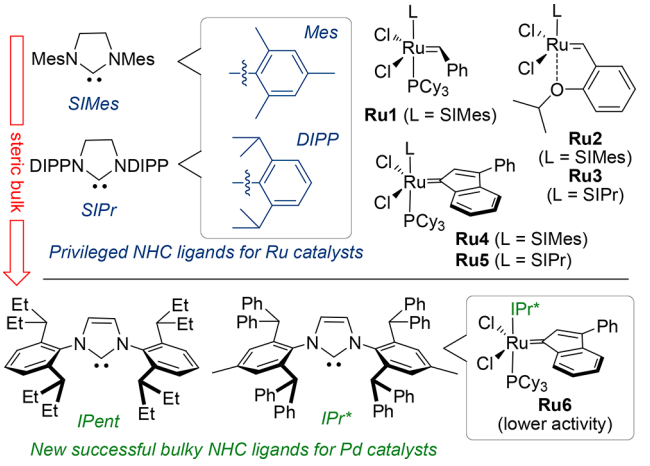


Figure 1. Selected popular second generation catalysts (**Ru1**−**Ru5**) bearing privileged SIMes and SIPr ligands and complex (**Ru6**) bearing more bulky IPr* ligand.

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bearing more bulky SIPr ligands are much more stable and productive than their SIMes analogues, although the latter usually work better in the case of more crowded or less reactive substrates.[10−14] Interestingly, further enlargement of the NHC ligand size does not always bring the improvement of the properties of the resulted Ru catalyst, as for example complex **Ru6** (Figure 1, bottom) bearing IPr* moiety[15] was shown to be less active than their analogues with smaller SIPr and IPr ligands.[16] This result is of great theoretical importance as it shows at its most extreme that when the bulk in the NHC ligand sphere is too significant, the olefin metathesis catalysts activity is reduced,[17] which suggests that a perfect NHC ligand shall combine enough bulkiness to protect the propagating 14-electron Ru species from decomposition, with sufficient flexibility to secure substrate unobstructed access. Herewith we are describing our efforts to find such a "perfect match" between the NHC ligand structure and efficiency of the resulted Ru-complex as olefin metathesis catalysts (Figure 2), first by ab initio and then by experimental methods.

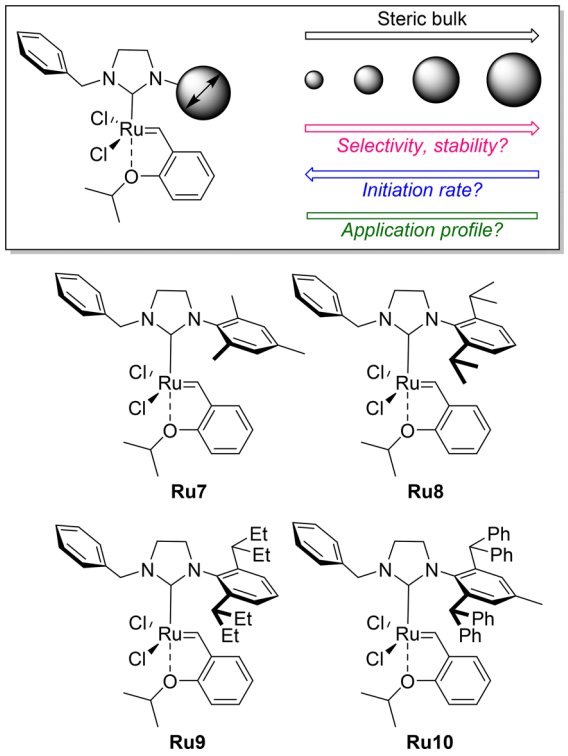

Figure 2. Structures of the uNHC Ru complexes used in this study.

RESULTS AND DISCUSSION

Recently we have synthesized two ruthenium 2-isopropoxybenzylidene complexes bearing *N*-aryl-*N*′-benzyl substituted unsymmetrical NHC (uNHC) ligands. These complexes, **Ru7**[18,19] and **Ru8**,[20] were found to be slower initiating but more selective comparing to general-purpose Hoveyda−Grubbs **Ru2** and **Ru3**. Especially, the *N*-DIPP bearing complex **Ru8**[20] was found to give promisingly good selectivity in demanding[21a] self-CM of α-olefins. This finding was somehow puzzling, as the more bulky, SIPr bearing catalysts (like **Ru3**) were described to be more prone to induce the unwanted C−C double bonds isomerization than their less sterically demanding SIMes variants (e.g., **Ru2**).[22]

In order to get a better picture of how the increasing size of uNHC ligand would influence the stability and activity of the corresponding catalysts, we envisioned a series of complexes bearing *N*-aromatic substituents of gradually increasing steric bulk in the uNHC ligand, while the other side kept small and constant (Figure 2). To complete the series, two complexes with never previously synthesized uNHC ligands, bearing 2,6-bis(diphenylmethyl)-4-methylphenyl (**Ru9**) and 2,6-di(3-pentyl)phenyl (**Ru10**) aromatic wings were proposed. Prior to entering into synthesis, we decided to use computational methods to predict performance in metathesis of these complexes.

Ab Initio Studies. In order to assess the stability and activity levels of the imagined complexes we performed state-of-art computational study of their activation using the B3LYP/DLPNO−CCSD(T) approach, described in detail in SI. We considered only the dissociative path of initiation, as it was shown that it is the only viable activation path for Hoveyda-like catalysts for substrates of medium and large size.[23] As shown in Figure 3 the lowest Gibbs free energy of

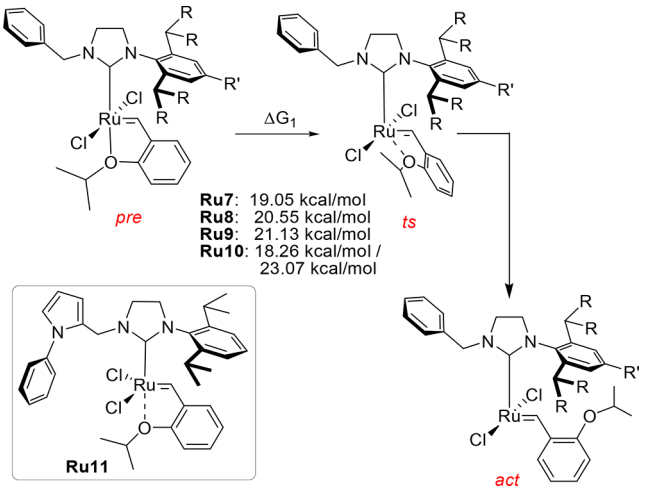

Figure 3. Gibbs free energies of activation of complexes **Ru7**−**Ru10** estimated at the B3LYP/DLPNO−CCSD(T) level.

activation was found for **Ru7** (19.05 kcal/mol), and the increase of the size of the aromatic substituent in the uNHC ligand increases the activation barrier, with the exception of **Ru10**. We can easily rationalize this results, as the larger uNHC substituent makes it harder for the isopropoxybenzylidene to rotate away in order to activate the complex due to steric hindrance. The relatively low free energy of the transition state for **Ru10** (of 18.3 kcal/mol) is, in this view, surprising and in disagreement with observed trends. The reason for this discrepancy is the fact that all transition states (defined as geometries with one imaginary frequency corresponding to Ru−O bond breaking) here are "early" with the average Ru−O distance of 3.4 Å, where the isopropoxy moiety is still relatively close to the ruthenium core. In order for the complex to activate the isopropoxybenzylidene part of it is required to rotate by another ∼90 deg from *ts* to *act* conformation and this rotation may be hindered by the bulky R groups. In order to verify this hypothesis, we have performed a relaxed potential energy scan of the isopropoxybenzylidene moiety rotation starting from the transition state geometry. In the case of **Ru7**, **Ru8**, and **Ru9**, the potential energy gets immediately lower when moving from

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ts to *act*, suggesting that the Gibbs free energy of the transition state is the true energy barrier of activation. In the case of **Ru10**, however, there is an additional barrier of 4.81 kcal/mol required to make the rotation around the bulky phenyl groups. As a result the true activation barrier of **Ru10** is equal to 23.07 kcal/mol, suggesting that **Ru10** is likely to be the slowest-activating complex out of those four studied. These results can be directly compared to the experimental $\Delta G^{\ddagger}$ of Hoveyda-Grubbs catalyst **Ru2** equal to 20.69 kcal/mol (at 275 K).[24] Given the obtained estimates we can predict that **Ru7** and **Ru8** should initiate with a similar rate to **Ru2**, while **Ru9** and **Ru10** are likely to initiate slower.

We also considered the possibility of the rotation of the benzyl moiety, which upon activation of complexes could inhibit olefin association, similarly to previously described catalysts bearing *N*-phenylpyrrol uNHC ligands (e.g., **Ru11**).[25] Unlike the latter system, for **Ru7**−**Ru10** the Gibbs free energy difference between the two conformations is around 5−6 kcal/mol, rendering the conformation with the possible Ru−π interaction unlikely from the energy point of view (Figure 4).

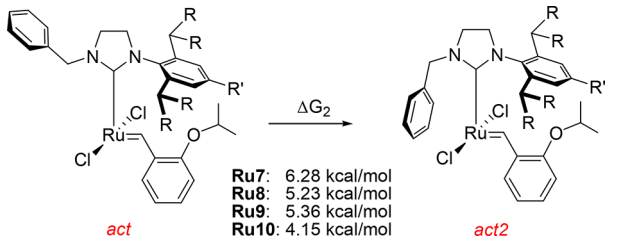


Figure 4. Gibbs free energies of *N*-benzyl moiety rotation estimated at the B3LYP/DLPNO−CCSD(T) level for complexes **Ru7**−**Ru10**.

The reason for the relatively high energy of this conformation is the unfavorable interaction between the benzyl moiety and Ru ion, estimated at +7.3 kcal/mol at the SAPT0 level of theory. Clearly, dissimilar to the phenylpyrrol derived NHC case,[25] the benzyl group is not sufficiently flexible to position the phenyl moiety close to the ruthenium to form a favorable interaction. As most Hoveyda-type catalysts exhibit a direct correlation between the initiation rate and their stability, we can speculate that **Ru10** is the most stable catalyst out of the four studied complexes, while **Ru7** is the least stable one (relatively).

The Gibbs free energy difference of initiation between **Ru8** and **Ru9** is below the expected accuracy of our calculations (~1 kcal/mol) so it is difficult to assess their relative stability, aside from the fact that they should be more stable than **Ru7** and less stable than **Ru10**. To better estimate the stabilities of new complexes, we also calculated the relative Gibbs free energies of their 14-electron methylidene intermediates (see Figure 5). We found that while the free energies of **Ru7**−**Ru9** are similar, and **Ru10** is more than 1 kcal/mol higher in energy

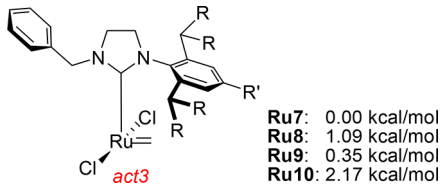
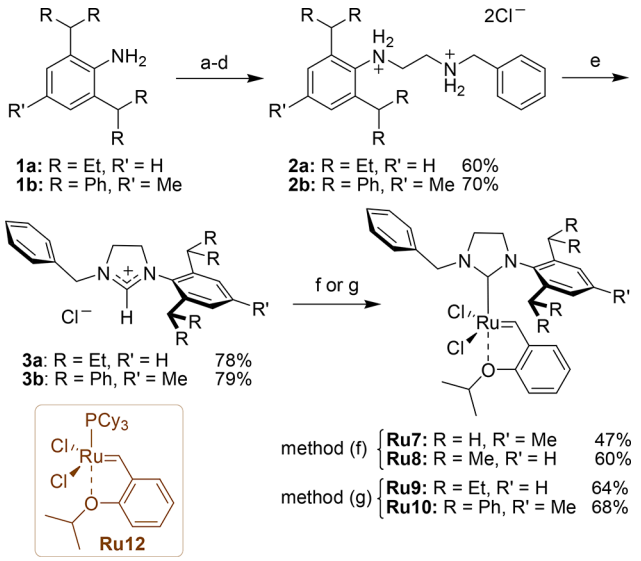


Figure 5. Relative Gibbs free energies of 14e methylidene intermediate for complexes **Ru7**−**Ru10**

suggesting that it is less likely to be produced during the catalytic cycle. Unfortunately the mechanism of Hoveyda−Grubbs catalyst degradation in the absence of the olefinic substrate and in nonpolar solvents is not fully understood, but it likely involves the formation of the 14e species (either benzylidene or methylidene), which are relatively unstable.[26] Therefore, we can expect that also in this case the larger barrier of initiation as well as higher energies of intermediates correlate with the higher stability in a solution.

Synthesis and Structural Characterization. Encouraged by the results of the ab initio study we decided to synthesize the predicted catalysts (**Ru9** and **Ru10**, Figure 2) and compare them with previously obtained complexes. Such resulted collection would compose of four structurally similar catalysts, in which the *N*-aryl substituents are of gradually increasing steric bulk, starting from Mes and DIPP in **Ru7** and **Ru8** and finishing with very spacious **Ru9** and **Ru10** (Figure 2). Unfortunately, the synthesis of new uNHC ligands carrying the bulkier *N*-aryl substituents (**3a**,**3b**) using the previously reported method[22] failed. Therefore, we worked out an alternative method based on the reaction between the appropriate aniline derivatives **1a**,**1b** and chloroacetyl chloride. The resulting amides were then subjected to the reaction with benzylamine and to subsequent reduction with lithium aluminum hydride (LAH) to produce diamines that were converted into the hydrochlorides **2a**,**2b** in overall yield 56 and 73%, respectively. In the next step, the imidazoline rings were formed upon reaction with triethyl orthoformate, to provide with the expected products **3a**,**3b** in almost 80% yields each (Scheme 1). With both ligand precursors in hand the synthesis of ruthenium complexes was attempted. In the first step, free carbenes were generated from imidazoline salts **3a**,**3b** in the presence of potassium *tert*-amylate as the base and then reacted

Scheme 1. Synthesis of uNHC and Ru Catalysts Ru7−**Ru10**[a]



[a]Reaction conditions: (a) chloroacetyl chloride, K_2CO_3, MeCN:DCM (1:1), 0 °C to RT, 2 h; (b) benzyl amine, K_2CO_3, MeCN/PhMe (1:1), reflux, 24 h; (c) LAH, THF, −20 to 60 °C, 8 h; (d) HCl, Et_2O, −40 °C; (e) $HC(OEt)_3$, 120 °C, 18 h; (f) *t*-AmOK, hexane, RT, 2−5 min, then **Ru12**, 65 °C, 25 min; (g) *t*-AmOK, toluene RT, 2−5 min, then **Ru12**, 75 °C, 5 min. NHC precursors for **Ru7** and **Ru8** prepared according to ref 20.

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with the first generation Hoveyda−Grubbs catalyst (**Ru12**). This process yielded **Ru9** and **Ru10** as greenish brown microcrystalline solids, in yield of 63 and 68%, respectively (Scheme 1). The ^{1}H NMR for **Ru9** showed a singlet peak at 16.23 ppm and for **Ru10** at 16.96 ppm, which is a characteristic region of the Hoveyda−Grubbs complexes, as well as other peaks conformed presence of uNHC ligands (N-CH_2-CH_2-N: for **Ru9** 3.61(dd); 3.99(dd) and for **Ru10** 2.00(dd); 2.77(dd)). First two complexes of the series, *N*-Mes bearing **Ru7** and *N*-DIPP substituted **Ru8** were obtained according to literature protocol,[20] although with some improvements (Scheme 1, method *f*) that allowed to shorten and simplify their preparation, and also to improve yield of **Ru7** from 28% (previously reported)[20] to 47% (see SI).

Single crystals, suitable for X-ray measurements, were obtained from a mixture of dichloromethane (DCM) and heptane. Both investigated catalysts, **Ru9** and **Ru10**, crystallize in, respectively, $P2_1/c$ and $P2_1/n$ space groups (with four molecules in the unit cell in each case) of the monoclinic crystal system. There are significant voids (V = 395 Å^3) in the structure of **Ru10** filled in with highly disordered DCM molecules. However, within the **Ru9** structure, such voids are not observed. To describe differences in conformation between the investigated compounds, we defined a specific torsion angle (T_1), $C_\alpha-C_\beta-C_\gamma-N_\delta$ (see Figure 6). This angle

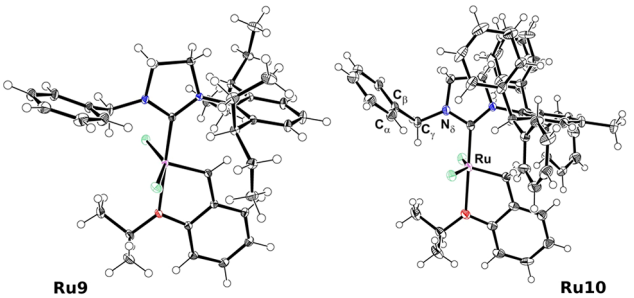

Figure 6. X-ray crystal structure of new catalysts with 50% probability ellipsoids, and specific torsion angle T_1 ($C_\alpha-C_\beta-C_\gamma-N_\delta$) parameters.

describes the position of the benzyl substituents with respect to the imidazolinium ring. Values of such defined angle are −80.3(5)° for **Ru9** and −44.32(15)° for **Ru10**, respectively. It shows that access to the metallic center is open (see values of this angle for similar catalysts in our previous paper).[22] In the case of **Ru10**, the phenyl rings substituted in the NHC ligand are slightly disordered, but only for one of four rings this disorder was so significant that it was possible to model it.

The overlay of four studied catalysts in a solid state visualizes the increasing steric bulk caused by the augmented *N*- aryl substituent (Figure 7). Importantly, the position of the second (benzyl) "arm" of the uNHC stays in general constant, in theory allowing for similarly unobstructed access to the metallic center in each case. These results are in agreement with computational data presented earlier, which suggest similarly large barriers of rotation of the benzyl moiety for all four studied systems (cf. Figure 4). As expected, the computationally obtained geometries of complexes **Ru7**−**Ru10** are very similar to their crystal structures.

Comparative Stability Tests. Before the activity studies of the uNHC Ru complexes were started, a set of standardized decomposition tests were conducted to check whether the introduced structural modifications improved the stability of

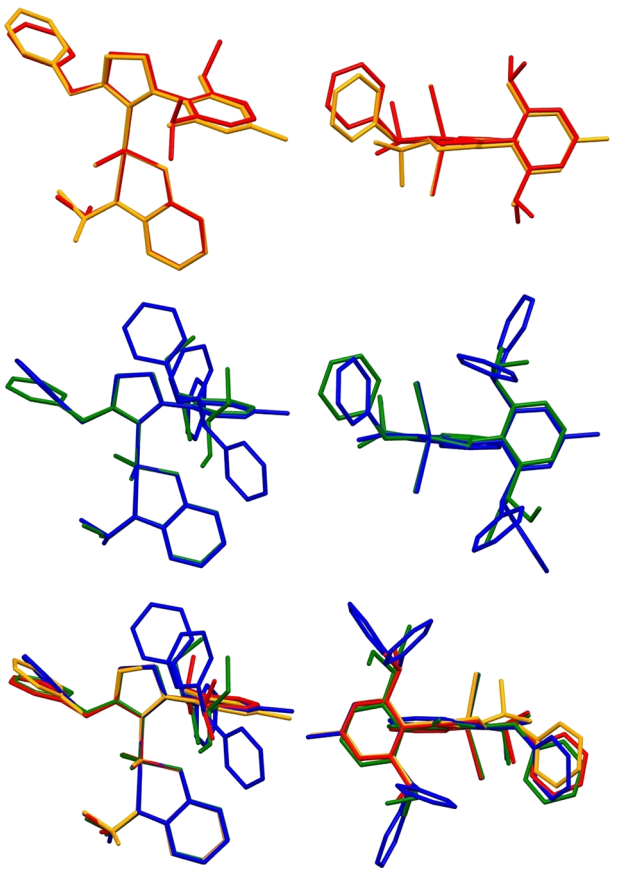

Figure 7. *Par deux* and all-four overlays of molecules: **Ru7** (yellow), **Ru8** (red), **Ru9** (green), and **Ru10** (blue). Hydrogen atoms have been omitted for clarity.

the resulted complexes. In addition, commercially available Hoveyda−Grubbs second-generation catalyst **Ru2** was added to this set, as the example of the popular general-purpose catalyst bearing a symmetrical NHC ligand. To quantify this important catalyst's property the following procedure for measuring the decomposition rate in solution was used: carefully weighed-out samples of the corresponding catalyst and 1,3,5-trimethoxybenzene (used as an internal standard) were dissolved in a CD_2Cl_2 in a glovebox and heated for 25 days at 40 °C. The ^{1}H NMR spectra were recorded every several days. The degree of degradation of the catalyst was determined on the basis of the integration of benzylidene signal coming from the complexes (peaks in the range of 16—17 ppm) and methoxy groups (6.15 ppm) coming from the internal standard (Figure 8). Notably, the most stable complex was **Ru10** bearing the larger *N*-aryl substituent: after almost a month in a solution warmed to 40 °C, only 1% of it was decomposed! Just a tiny bit less stable were two other complexes containing bulky aromatic substituents, namely, **Ru8** (with 2,6-diisopropylphenyl "wing") and **Ru9** (with 2,6-diisopentylphenyl), that under the same conditions decomposed 2% each. Slightly less stable was complex **Ru7** containing relatively the smallest substituent (mesityl), however also in this case 95% of the initial complex survived. For comparison, commercially available **Ru2** under the same conditions was visibly less stable, losing 25% of the initial amount after only 15 days (Figure 8).

In addition, solid-state stability tests were performed. For this purpose, catalysts samples were weighed into vials and left

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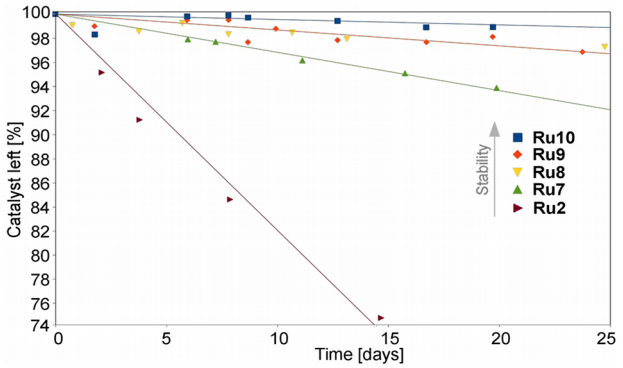


Figure 8. Degradation tests in CD_2Cl_2 solution at 40 °C under argon. Monitored by ^{1}H NMR spectroscopy with 1,3,5-trimetoxybenzene as an internal standard. Lines are visual aids only.

open on a shelf on air at ambient temperature (22 °C). After 3 weeks of such "lousy storage" test, ^{1}H NMR spectra were recorded to show that all complexes containing uNHC ligands (**Ru7** to **Ru10**) were not changed, while **Ru2** was partially decomposed.

Olefin Metathesis Catalytic Activity Studies. High stability, although welcome, is not enough to ensure a success of a chemical catalyst. Therefore, the application profile of complexes **Ru7** to **Ru10** in a diverse set of metathesis reactions was explored and compared to that of **Ru2**. In the first stage of this research the RCM reaction of the most commonly used model substrate, diethyl 2,2-diallylmalonate (**4**),[27] was examined in the presence of 1 mol % of a catalyst. Initially, the test reaction was performed at 50 °C (Figure 9a). As expected, the least active catalyst was the one containing the largest *N*-substituent in uNHC ligand (**Ru10**) as it reached only about 50% conversion after 3 h. The complex bearing second biggest substituent in this set (**Ru9**), gave almost twice as good result reaching after the same time (>80% conversion). All other catalysts, that is, **Ru2**, **Ru7**, and **Ru8**, reached full conversion within less than an hour. These results are in accordance with literature reports on other uNHC bearing 2-isopropoxybenzylidene complexes that were usually characterized as "thermally stable, latent".[28] To prove that the uNHC complexes are thermoswitchable, the same model reaction was repeated at higher temperature. Once the temperature was raised up to 80 °C, all tested catalysts reacted much faster and all of them achieved complete conversion within maximum 2 h, what renders these complexes of practical usefulness. The previously observed general trend of reactivity was preserved: the slowest complex was **Ru10**, then **Ru9**, while compounds containing less roomy mesityl and 2,6-diisopropylphenyl substituents (**Ru7** and **Ru8**, respectively) closed the five-membered ring of **5** in less than 5 min (Figure 9b). In our previous work[18,20] we adopted the diastereoselctive ring rearrangement metathesis reaction (DRRM) of cyclopentene derivative **6** as a test for catalysts selectivity. This transformation was previously studied in detail by Blechert et al.[29] who concluded that the first generation of Ru catalysts (e.g., **Ru12**) produced an equimolar mixture of diastereoisomers, while with the second generation complexes (**Ru1** and **Ru2**) the selectivity was slightly improved (up to *trans:cis* dr = 2:1). Blechert demonstrated also that the highest selectivity in this reaction (*trans:cis* dr = 9:1) may be obtained in the presence of the Grubbs-type catalyst bearing unsymmetrical NHC ligand based on tetrahydroquinoline moiety but at relatively low

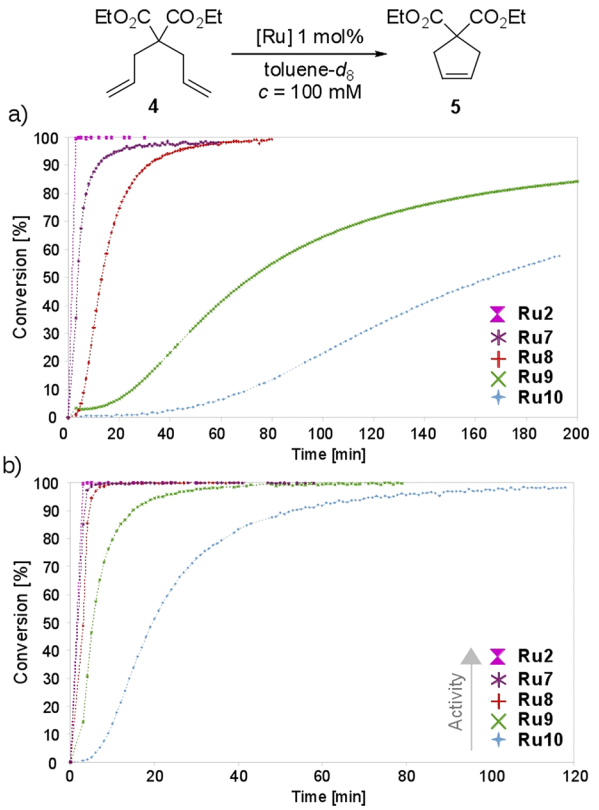
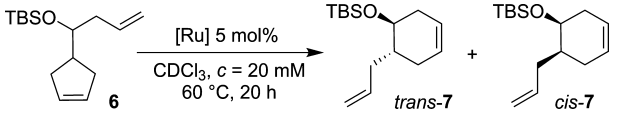


Figure 9. Time/conversion curves for the RCM reaction of **4** with 1 mol % of Ru complexes at 50 (a) and 80 °C (b) (monitored by ^{1}H NMR). Lines are visual aids only.

conversion of 58%.[29] Our previous studies on diastereoselective ring rearrangement metathesis of **6** showed that the application of indenylidene complexes containing unsymmetrical N-heterocyclic carbenes[18−20] can increase the selectivity of the reaction in comparison to standard second-generation complexes (*trans:cis* dr ≈ 4:1 versus 2:1) at the conversion exceeding 90−95%. Interestingly, similar result was obtained in the present work with the 2-isopropoxybenzylidene complex **Ru7** bearing *N*-benzyl-*N*′-mesityl substituted uNHC, which produced *trans:cis* isomers in dr 5:1 at full conversion (Table 1, entry 2). The decrease of selectivity was unfortunately observed in the case of more bulky uNHC complexes **Ru8** to **Ru10** that reached only 1.4:1 to 1.2:1

Table 1. Results of DRRM Reaction of 6[a]



entry	[Ru]	conversion [%]	*trans:cis*
1	**Ru2**	99	1.4:1
2	**Ru7**	>99	5.0:1
3	**Ru8**	>99	1.4:1
4	**Ru9**	>99	1.2:1
5	**Ru10**	96	1.2:1
6	**Ru3**	99	1.1:1

[a]Monitored by ^{1}H NMR spectroscopy and GC with durene as internal standard. Conditions: 5 mol % of [Ru], $CDCl_3$, *c* = 200 mM, 60 °C, 20 h.

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(*trans:cis*) while the conversion remained high (entries 3−5). When Hoveyda−Grubbs catalyst with symmetrical bulky SIPr NHC ligand (**Ru3**) was utilized, even lower selectivity was observed (*trans:cis* 1.1:1, Table 1, entry 6). On the basis of these results, one may conclude that while catalysts with small (**Ru2**) and enlarged (**Ru3**) symmetrical NHC ligands fail in providing good selectivity in DRRM, the catalyst bearing unsymmetrical NHC containing relatively small *N*- aromatic substituent, like Mes (**Ru7**) can led up to to 5:1 diastereoselectivity.

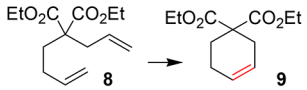
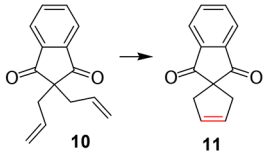
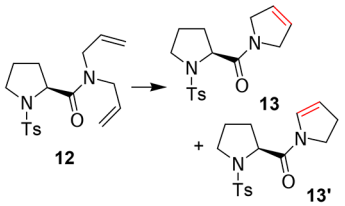
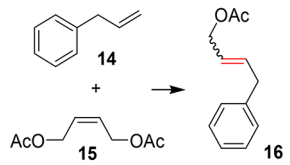
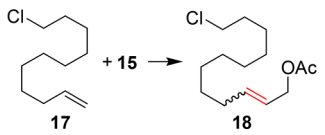
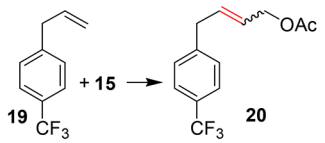
Looking for potential application areas of the studied catalysts, we decided to test them with a wider scope of substrates, used in practical RCM and CM reactions (Table 2). The comparison also included **Ru2**, one of the most popular commercially available Ru-catalysts. First, the selected contestants were tested in RCM reactions.

Diethyl 2-allyl-2-(but-3-en-1-yl)malonate (**8**) lead in 80−90% isolated yield to cyclohexene derivative **9** in the presence of all tested complexes. A slightly worse result was observed when **Ru10** was utilized; however, also in this case. the yield reached almost 80%. All ruthenium compounds worked also very well in the reaction of 2,2-diallyl-1*H*-indene-1,3(2*H*)-dione (**10**) leading to spiro-compound **11** in over 95% yield. So far, so normal. Somewhat different results, however, were achieved in the RCM reaction of (*S*)-*N*,*N*-diallyl-1-tosylpyrrolidine-2-carboxamide (**12**), leading to **13**—an analogue of promising prolyl endopeptidase inhibitor SUAM 1221.[30] Indeed, when **Ru2** were used in this transformation, some amount of a byproduct with a migrated double bond (**13′**) was formed as well. Importantly, uNHC-bearing catalysts **Ru7** to **Ru10** promoted the same reaction in a fully selective fashion, and no traces of byproduct **13′** were observed.

The unwanted formation of **13′** may be related to the presence of small quantities of the ruthenium hydride or other species, such as Ru dimeric complexes or even nanoparticles. Such compounds—products of catalyst's decomposition—are known to promote the migration of double bond.[22,31−33] Since **Ru2** was the least stable catalyst in the series (see Figure 4), it underwent degradation process the fastest; the other catalysts were apparently stable enough, and the isomerization product was not detected. Next, cross-metathesis reactions utilizing 1,4-diacetoxybut-2-ene (**15**) were carried out (Table 2, entries 4−6). With allyl benzene (**14**) as a cross-partner, it was found that the bigger substituent on uNHC was, the higher amount of (*Z*)-isomer was formed. Similarly, when the cross-partner was a long-chain terminal olefin, 11-chloroundec-1-ene (**17**), the most (*Z*)-selective catalysts was the most bulky **Ru10**. However, in the case of allyl *p*-trifluorobenzene (**19**), a relationship between the size of the *N*-substituent in the uNHC ligand and the (*Z*)-selectivity was not preserved, as relatively bulky **Ru8** and **Ru9** displayed (*E*)/(*Z*)-selectivity level similar to that one exhibited by standard, SIMes-bearing **Ru2**. We have no rationale for this observation, anyway, as in previous examples (Table 2, entries 4 and 5) the highest amount of (*Z*)-product was obtained for **Ru10**. (Table 2, entry 6). It shall be stressed that despite their latency, all tested uNHC complexes delivered the expected products in high isolated yield, similar or in some cases higher than the yield obtained for faster initiating **Ru2**.

Encouraged by the above results, we decided to test catalysts **Ru7** to **Ru10** in more demanding transformations. Functionalized allylbenzenes (phenylpropenoids), such as estragole, eugenol or safrole, readily available from essential oils, serve as

Table 2. Results of RCM and CM Comparative Study

Entry	Substrate → Product	[Ru]	Yield [%][a]
1		**Ru2**	95
		Ru7	93
		Ru8	87
		Ru9	90
		Ru10	79
2		**Ru2**	98
		Ru7	96
		Ru8	97
		Ru9	99
		Ru10	95
3		**Ru2**	87+5[b]
		Ru7	88
		Ru8	87
		Ru9	90
		Ru10	79
4[c]		**Ru2**	75 (8.4:1)
		Ru7	79 (7.6:1)
		Ru8	80 (8.0:1)
		Ru9	72 (4.5:1)
		Ru10	65 (3.3:1)
5[c]		**Ru2**	90 (5.6:1)
		Ru7	85 (6.5:1)
		Ru8	85 (5.3:1)
		Ru9	82 (3.4:1)
		Ru10	73 (2.8:1)
6[c]		**Ru2**	82 (5.7:1)
		Ru7	79 (3.3:1)
		Ru8	84 (6.0:1)
		Ru9	83 (6.0:1)
		Ru10	77 (3.0:1)

[a]Isolated yield. Conditions: 1 mol % of [Ru], toluene, c = 100 mM, 80 °C, 20 h. [b]Ratio **13**:**13′** = 87:5. [c]3 equiv of **15** were used. *E*:*Z* ratios are given in parentheses.

important precursors to the specialty chemicals.[34,35] Althought CM of these substrates is know, it is considered as difficult.[36] One of the challenges is the susceptibility of these substrates to isomerization of the double bond during metathesis. For example, a prior work aimed at the self-metathesis of estragole, using **Ru2** demonstrated that unintended isomerization of this substrate can compete with metathesis.[35,37] Being aware of this hazard, we hoped that the studied catalysts can promote this transformation more selectively. First, self-CM of 5-allyl-2-hydroxy-3-methoxybenzaldehyde (**21**) was examined (Scheme 2). Indeed, in the presence of **Ru2**, the desired self-CM product **22** was not observed, instead stilbene derivative **23**

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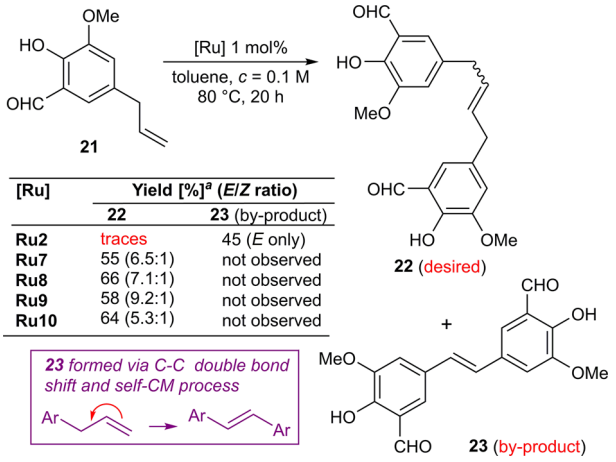
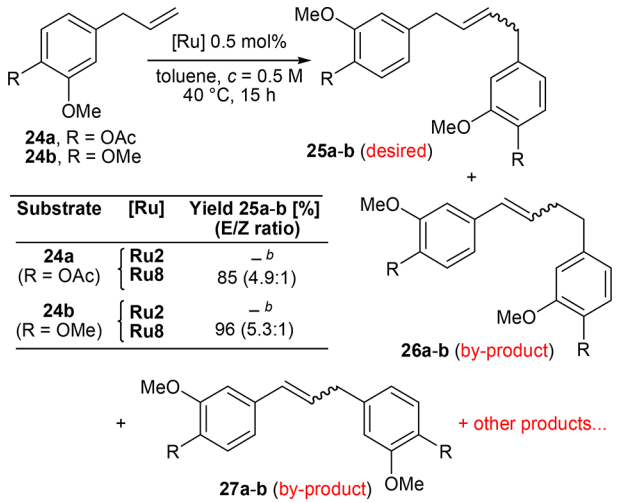
Scheme 2. Selectivity in Self-CM of Eugenol Derivative 21[a]



[Ru]	Yield [%][a] (*E*/*Z* ratio)	
	22	**23** (by-product)
Ru2	traces	45 (*E* only)
Ru7	55 (6.5:1)	not observed
Ru8	66 (7.1:1)	not observed
Ru9	58 (9.2:1)	not observed
Ru10	64 (5.3:1)	not observed

[a]Isolated yield.

Scheme 3. Self-CM of Eugenol Derivatives 25a,b[a]



Substrate	[Ru]	Yield 25a-b [%] (E/Z ratio)
24a (R = OAc)	**Ru2**	– [b]
	Ru8	85 (4.9:1)
24b (R = OMe)	**Ru2**	– [b]
	Ru8	96 (5.3:1)

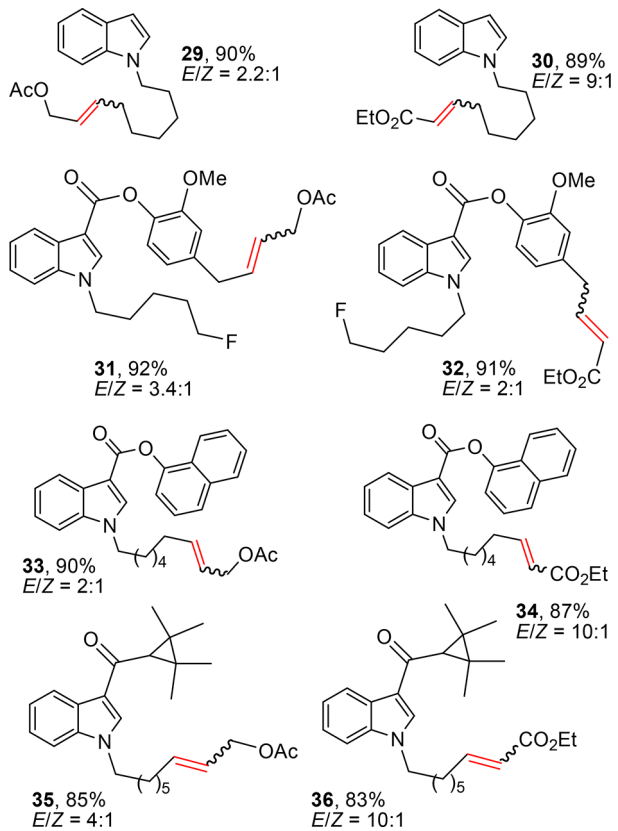
[a]Isolated yield. [b]Inseparable mixture of **25**, **26**, **27** and other products obtained.

(coming from self-CM reaction between two isomerized substrate molecules) was isolated as a single (*E*)-isomer in 45% yield. On the contrary, when complexes **Ru7** to **Ru10** were utilized in the same reaction, the only observed product was **22**, obtained in 55−66% isolated yields (Scheme 2). In all cases, (*E*)-isomer was obtained predominantly, and the highest (*E*/*Z*)-selectivity was observed for **Ru8** and **Ru9**, while **Ru10** was less selective. Additional experiments were conducted under milder conditions (40 °C; 0.5 mol % of catalyst) in a hope to make this reaction more selective also with nonspecialized catalysts, such as **Ru2**. While **Ru8** under these conditions still produced cleanly the expected product in 69% of isolated yield, the inseparable mixture of **22**, stilbene **23** and other isomerization products (e.g., coming from the cross-metathesis reaction between substrate and the isomerized substrate molecules) were obtained for **Ru2**.

In order to reveal whether such excellent selectivity of tested uNHC catalysts is limited to this particular compound or the trend is more general, a couple of additional eugenol derivatives, namely acetylated (**24a**) and methylated eugenol (**24b**) were tested (Scheme 3). In this examination, only **Ru8** was used (and compared with **Ru2**). Despite that mild conditions were used (40 °C; [Ru] 0.5 mol %), in the general-purpose **Ru2** catalyzed self-CM of **24a** an inseparable mixture of the desired product **25a**, its isomer having shifted C−C double bond **26a** as well as shorter analogue **27a** (coming from CM reaction between **24a** and isomerized **26a**) and traces of the corresponding stilbene were formed. The same complicated mixture was observed in the case of **24b**. In contrast, when **Ru8** was used as catalyst, the same reaction was fully selective, leading to expected self-CM dimers in high isolated yield (85 and 96% respectively), without formation of isomerized or shortened products (Scheme 3).

Having successfully demonstrated good properties of the new complexes in model RCM and CM reactions, we decided to apply the methodology to other compounds with potential biological activity. To do so, we attempted the CM reactions of selected indole derivatives in the presence of **Ru8**, the catalyst which exhibited so for the best balance between high activity and selectivity with eugenol derivatives. Previously, we found that modification of psychoactive indole derivatives that are characterized by a presence of longer fatty chain substituents is not always selective, leading to decrease of yields in some cases.[38] Therefore, we decided to reinvestigate the subject with a more selective catalyst. The study was started from modification of simple 1-(oct-7-en-1-yl)-1*H*-indole with 3 equiv of 1,4-diacetoxybut-2-ene (**15**) or ethyl acrylate (**28**) as CM partners, to deliver products **29** and **30** in high isolated yields (Chart 1). Next targets were compounds **31** and **32**—analogues of the designer drug 5F-PB-22.[39] Despite the

Chart 1. CM Reaction of Indole Derivatives[a]



[a]Conditions: 1 mol % **Ru8**, 3 equiv of **15** or **28**, toluene, *c* = 0.1 M, 80 °C, 8 h. Isolated yields.

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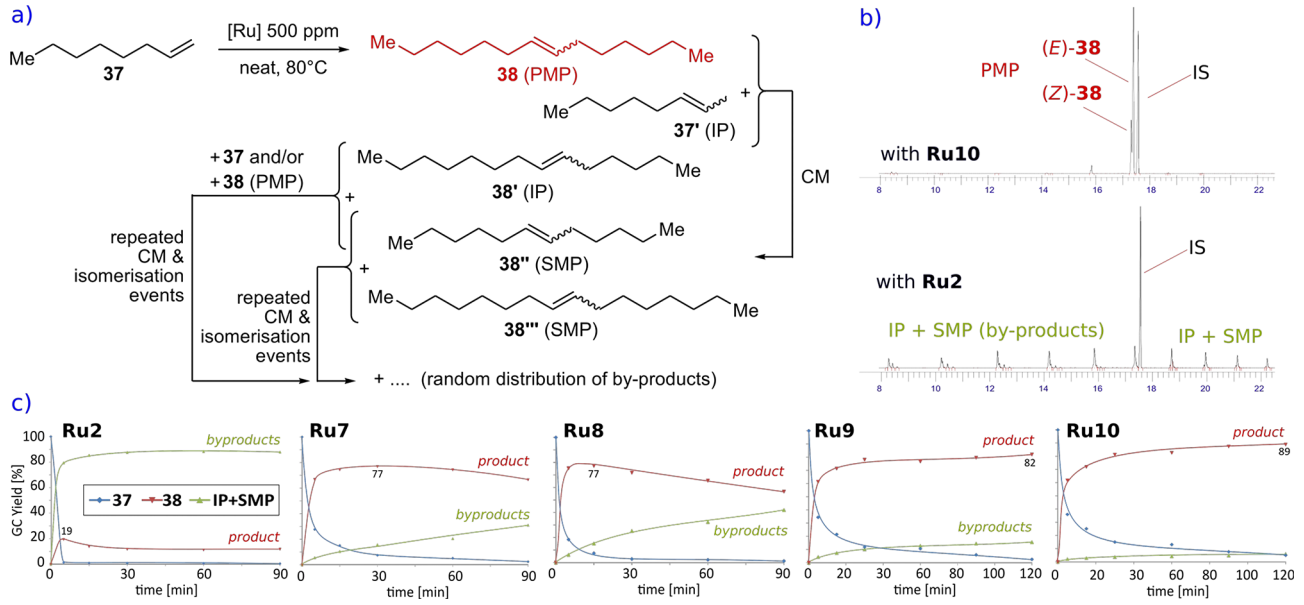

Figure 10. Self-metathesis of 1-octane (**37**). (a) Reaction scheme. PMP = primary metathesis product, IP = isomerization product, SMP = secondary metathesis product; (b) GC traces after reaction with **Ru10** vs **Ru2**. IS = internal standard (tetradecane); (c) Composition of the reaction mixtures over time recorded for catalysts **Ru2** and **Ru7** to **Ru10**. Lines are visual aids only.

planned modification required the CM reaction at the eugenol fragment, we were able to obtain more than satisfactory (>90%) isolated yield of both indole products **31** and **32**. Another analogue sharing a similar structural motif, a derivative of indole-based full agonist to CB1 and CB2 receptors named NM-2201,[40] was modified in CM with similar efficiency leading to **33** and **34**. Finally, **35** and **36**—two analogues of well-known UR-144, a drug invented by Abbott Laboratories, that acts as a selective full agonist of the peripheral cannabinoid receptor with general weak cannabinoid-like activity,[41] were obtained. It shall be noted that in all cases presented in Chart 1, the CM reactions catalyzed by **Ru8** were very clean, and the expected products were formed exclusively and in good isolated yields.

Next, we explored the industrially relevant self-metathesis reaction of α-olefins.[42] These substrates are known to be prone to migration of double bond along the carbon chain, especially when the second generation complexes are used (Figure 10a).[22] This usually undesired side process is invoked by the products of decomposition of the catalysts, mainly ruthenium hydrides,[43] dimers,[32] and nanoparticles.[33] The most common answer to this issue is the application of various additives, just to mention: metallic mercury,[33] quinones,[44] chlorocatechol-borane,[45] and phenylphosphoric acid;[46] however, none of them is universal in each case. Recent developments in this field have shown that the application of appropriate Ru catalysts bearing either unsymmetrical NHC ligands[21a,47,48] or quinone fragment present in the catalyst structure[49] can significantly reduce the double bond migration during the metathesis reaction, providing selectivity levels >90%.[21a] The suppressed isomerization of double bond may be related to the increased stability of the used complexes under the reaction conditions, and thus their lower susceptibility to the degradation to undesired ruthenium compounds. Encouraged by the results obtained until now, we decided to check how the newly obtained complexes would act in the self-CM reaction of 1-octene (**37**). All tests were carried out in the presence of 500 ppm of catalyst at 80 °C and without any solvent (in neat). The reaction mixture composition was monitored by gas chromatography (GC) during the reaction. The GC traces and product composition charts presented in Figure 10b,c show that the reaction outcome for standard Hoveyda−Grubbs second-generation catalyst and the new catalysts containing bulky uNHC ligands differ significantly. As expected, **Ru2** was the most active, as just after 5 min the full conversion of 1-octene was reached; however, unfortunately, the selectivity was very low. Practically from the very first minutes of the reaction, the desired product **38** and the by-products (SMP: homologues with shorter and longer carbon chain, and possibly other products) were formed almost simultaneously. The main product of the reaction (ca. 80%) was the unwanted SMP, while the maximum content of expected **38** was only 20% (Figure 10b,c). The reactions catalyzed by complexes containing enlarged substituent in the NHC ligand were slightly slower compared to **Ru2**, but up to 120 min was enough to obtain high conversion. On the other hand, all the catalysts bearing uNHC ligand showed better selectivity than **Ru2**. When **Ru7** or **Ru8**—containing the smallest *N*-aryl substituents in the tested series—were utilized in self-metathesis of 1-octene, the maximum amount of the desired (*E*)- and (*Z*)-isomers of the product **38** (77%) was obtained after 20 and 30 min, respectively. However, in both cases the side processes progressed too, unfortunately, which resulted in a decrease of selectivity over time (Figure 10c). In contrast, with **Ru9** and **Ru10** the reaction proceeded slower, but with much higher selectivity, and in the best case of **Ru10** product **38** was formed almost exclusively (Figure 10b,c). Therefore, the use of catalysts containing unsymmetrical NHC ligand seems to be preferential in the case of self-CM of α-olefins, allowing to reach high selectivity without need of using problematic additives.[50]

Fats and oils are very important renewable resources which have many applications in industrial chemistry. Among the many various metathesis-type reactions[51,52] of oils and fats, ethenolysis,[53,54] has become a very promising transformation which leads to terminal alkenes and unsaturated esters used in

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industry. Of the most commonly applied substrates are oleic acid esters that, after ethenolysis and saponification lead to dec-9-enoic acid (9-DA),[55] used for example in production of macrocyclic musks.[56,57] However, due to known instability of general purpose catalysts in ethylene, this process is not easy to be implemented and industrial scale, so the existing plants utilize 1-butene instead of ethylene.[58]

In order to reveal how the new uNHC catalysts might perform in ethenolysis, first we investigated the stability of **Ru7** to **Ru10** in the atmosphere of ethylene. The complexes were compared not only with **Ru2**, but also with CAAC Bertrand–Grubbs catalyst (**Ru13**, Figure 11) because the latter exhibits

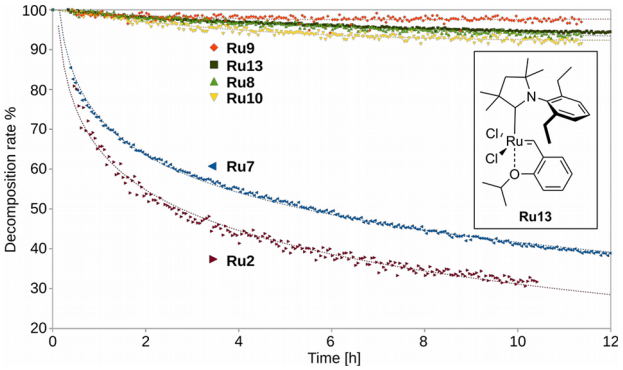

Figure 11. Degradation of catalysts **Ru2** and **Ru7** to **Ru10** and **Ru13** in CD_2Cl_2 at 40 °C under ethylene atmosphere. Monitored by ^1H NMR spectroscopy with 1,3,5-trimetoxybenzene as an internal standard. Lines are visual aids only.

one of the highest efficiency in ethenolysis noted so far.[59] To do so, the respective catalyst and 1,3,5-trimethoxybenzene (internal standard) were dissolved in CD_2Cl_2 in glovebox in a Young NMR tube. The tube was removed from the glovebox, placed in an autoclave, and pressurized with ethylene. Degradation of catalysts was conducted at 40 °C and monitored by ^1H NMR by comparing the integration of benzylidene signal coming from the catalyst and methoxy protons from the internal standard (formation of methylidene [Ru]=CH_2 signals were not observed. For the detailed procedure, see SI). Under these conditions, three complexes bearing the biggest unsymmetrical NHC ligands (**Ru8**, **Ru9**, and **Ru10**), and CAAC-type **Ru13** were characterized by practically the same high stability under an ethylene atmosphere, as after 12 h at the elevated temperature, more than 90% of each Ru-complex remained unchanged (Figure 11). As expected, Hoveyda–Grubbs second-generation catalyst was much less stable under these conditions and after 10 h only 30% of it remained unchanged. Notably, stability of **Ru7** (bearing the smallest uNHC ligand) was much lower than other tested uNHC complexes (after 6 h around half of **Ru7** decomposed), but still higher than **Ru2** (Figure 11).

In a model ethenolysis reaction complexes **Ru8** to **Ru10** were used (**Ru7** was excluded due to its low stability toward ethylene, vide supra), and the results were compared with those obtained in the presence of state-of-the art Bertrand–Grubbs catalyst **Ru13**. The challenge in the ethenolysis of ethyl oleate (**39**) is formation of by-products (diethyl octadec-9-enedioate, **42** and octadec-9-ene, **43**), being "homodimers" obtained in the unwelcome self-CM process that decrease the yield of expected products: ethyl dec-9-enoate, **40** dec-1-ene, **41** (Figure 12). The ratio between ethenolysis and self-CM

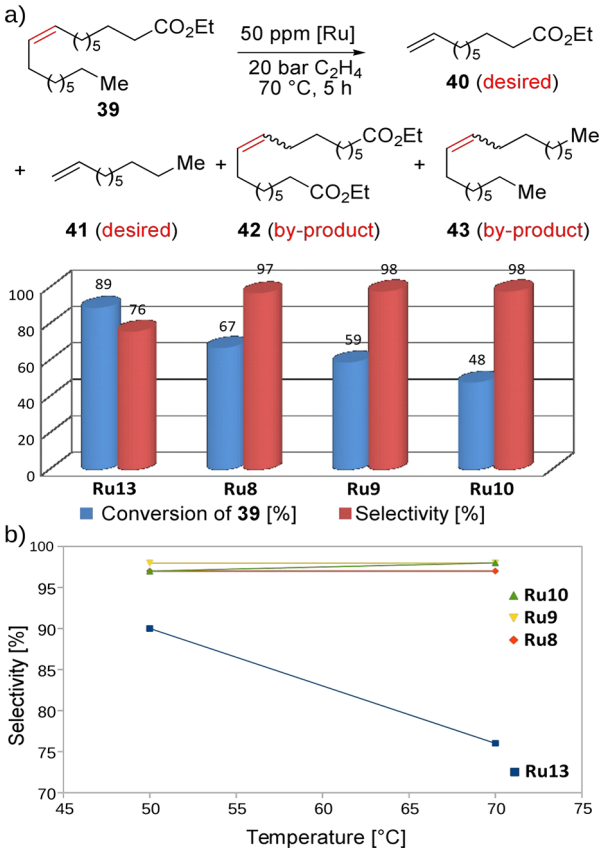

Figure 12. (a) Ethenolysis of **39**. (b) Selectivity-temperature dependence of various catalysts in ethenolysis of **39**. Selectivity = 100 × (moles of **40** + moles of **41**)/[(moles of **40** + moles of **41**) + 2 × (moles of **42** + moles of **43**)]. Lines are visual aids only.

products is usually defined as "reaction selectivity".[47,60] It is known that the nature of catalyst and conditions of the reaction have a great influence on the ratio of ethenolysis to self-CM.[61] In our tests, we decided to vary the temperature of the reaction, in order to map the catalysts thermal stability limits under real process conditions. To do so, ethenolysis reactions were carried out in the presence of 50 ppm of catalyst, under 20 bar of ethylene at temperature 50–70 °C. All tested uNHC complexes exhibited similarly high selectivity in this reaction (97–98%) regardless of temperature; however, they were less active then CAAC complex **Ru13**. Interestingly, selectivity exhibited by **Ru13** decreased with temperature to reach 87% at 70 °C (Figure 12). Under these conditions, **Ru8** to **Ru10** bearing unsymmetrical NHCs were still able to promote ethenolysis highly selectively, allowing to convert 67–45% of ethyl oleate (**39**) to expected products. Although the very recently developed Apeiron's bis(CAAC) indenylidene complexes were reported to work even better in this reaction,[62] the observed high thermal stability of the tested uNHC complexes is of interest.

CONCLUSIONS

A series of ruthenium catalysts containing in the unsymmetrical NHC ligand the *N*-aryl substituents of gradually increasing bulk (**Ru7** to **Ru10**) were studied computationally, synthesized, and fully characterized. DFT calculations and X-ray crystallographic data were used to understand the influence of uNHC ligand structure on the catalyst properties.

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Depending of the size of the *N*-substituent, these complexes are optimal to different applications. For example, while the Mes-substituted **Ru7** was giving best selectivity in the DRRM reaction, it displayed the lowest stability in the presence of ethylene. In contrast, **Ru9** and **Ru10** bearing much bulkier *N*-aromatic wings were preferred for self-CM of α-olefins, where they exhibited higher selectivity and thermal stability than their smaller uNHC siblings as well as the commercial general purpose catalyst **Ru2**. Similarly, the three most bulky uNHC complexes were found to be perfectly stable in the presence of ethylene and showed excellent selectivity in the ethenolysis of ethyl oleate, even at increased temperature. The improved selectivity of uNHC catalysts allows for metathesis reactions of various functionalized substrates that sometimes are problematic for the general purpose Ru catalysts. For example, when self-metathesis reactions of eugenol derivatives were carried out in the presence of the studied uNHC complexes, the desired products were exclusively obtained, while the same substrates with general SIMes-bearing catalyst led to non-selective reactions and formation of products with shifted C−C double bonds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b04783.

Experimental, X-ray crystallographic and computational methods and data (PDF)

3D rotatable images of all geometry-optimized structures (XYZ), CIF and CheckCIF files (ZIP)

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Notes

The authors declare no competing financial interest.
Crystallographic data (excluding structural factors) for the structures reported in this paper has been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers: CCDC 1556136 (**Ru9**) and CCDC 1556135 (**Ru10**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: (+44)-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk.

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■ REFERENCES

(1) (a) *Olefin Metathesis: Theory and Practice*; Grela, K., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2014. (b) *Handbook of Metathesis*, 2nd ed; Grubbs, R. H., Wenzel, A. G., O'Leary, D. J., Khosravi, E., Eds.; Wiley-VCH: Weinheim, 2014. (c) Higman, C. S.; Lummiss, J. A. M.; Fogg, D. E. Olefin Metathesis at the Dawn of Implementation in Pharmaceutical and Specialty-Chemicals Manufacturing. *Angew. Chem., Int. Ed.* **2016**, *55*, 3552−3565.

(2) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer: Berlin Heidelberg, 2007.

(3) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An Overview of N-Heterocyclic Carbenes. *Nature* **2014**, *510*, 485−496.

(4) *N-Heterocyclic Carbenes in Catalytic Organic Synthesis*; Nolan, S. P., Cazin, C. S. J., Eds.; Thieme Chemistry, 2017.

(5) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. N-Heterocyclic Carbenes as Organocatalysts. *Angew. Chem., Int. Ed.* **2007**, *46*, 2988−3000.

(6) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307−9387.

(7) Gomez-Suarez, A.; Nelson, D. J.; Nolan, S. P. Quantifying and Understanding the Steric Properties of N-Heterocyclic Carbenes. *Chem. Commun.* **2017**, *53*, 2650−2660.

(8) Chantler, V. L.; Chatwin, S. L.; Jazzar, R. F. R.; Mahon, M. F.; Saker, O.; Whittlesey, M. K. Stoichiometric and Catalytic Reactivity of the N-Heterocyclic Carbene Ruthenium Hydride Complexes [Ru(NHC)(L)(CO)HCl] and [Ru(NHC)(L)(CO)H(η^2-BH_4)] (L = NHC, PPh_3). *Dalton Trans.* **2008**, 2603−2614.

(9) Diez-Gonzalez, S.; Nolan, S. P. Stereoelectronic Parameters Associated with N-Heterocyclic Carbene (NHC) Ligands: A Quest for Understanding. *Coord. Chem. Rev.* **2007**, *251*, 874−883.

(10) Ivry, E.; Frenklah, A.; Ginzburg, Y.; Levin, E.; Goldberg, I.; Kozuch, S.; Lemcoff, N. G.; Tzur, E. Light- and Thermal-Activated Olefin Metathesis of Hindered Substrates. *Organometallics* **2018**, *37*, 176−181.

(11) Courchay, F. C.; Sworen, J. C.; Coronado, A.; Wagener, K. B. The Utility of Hoveyda-Type Catalysts in ADMET Chemistry: Sterics Versus Electronics. *J. Mol. Catal. A: Chem.* **2006**, *254*, 111−117.

(12) Skowerski, K.; Białecki, J.; Tracz, A.; Olszewski, T. K. An Attempt to Provide an Environmentally Friendly Solvent Selection Guide for Olefin Metathesis. *Green Chem.* **2014**, *16*, 1125−1130.

(13) Tracz, A.; Matczak, M.; Urbaniak, K.; Skowerski, K. Nitro-Grela-Type Complexes Containing Iodides − Robust and Selective Catalysts for Olefin Metathesis Under Challenging Conditions. *Beilstein J. Org. Chem.* **2015**, *11*, 1823−1832.

(14) Clavier, H.; Urbina-Blanco, C. A.; Nolan, S. P. Indenylidene Ruthenium Complex Bearing a Sterically Demanding NHC Ligand: An Efficient Catalyst for Olefin Metathesis at Room Temperature. *Organometallics* **2009**, *28*, 2848−2854.

(15) For applications of SIPr* ligand in Pd-catalyzed C−C couplings, see: (a) Meiries, S.; Chartoire, A.; Slawin, A. M. Z.; Nolan, S. P. [Pd(IPr*)(acac)Cl]: An Easily Synthesized, Bulky Precatalyst for C−N Bond Formation. *Organometallics* **2012**, *31*, 3402−3409. (b) Chartoire, A.; Frogneux, X.; Boreux, A.; Slawin, A. M. Z.; Nolan, S. P. [Pd(IPr*)(3-Cl-pyridinyl)Cl_2]: A Novel and Efficient PEPPSI Precatalyst. *Organometallics* **2012**, *31*, 6947−6951. (c) Chartoire, A.; Claver, C.; Corpet, M.; Krinsky, J.; Mayen, J.; Nelson, D.; Nolan, S. P.; Penafiel, I.; Woodward, R.; Meadows, R. E. Recyclable NHC Catalyst for the Development of a Generalized Approach to Continuous Buchwald−Hartwig Reaction and Workup. *Org. Process Res. Dev.* **2016**, *20*, 551−557. (d) Zinser, C. M.; Nahra, F.; Brill, M.; Meadows, R. E.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. A Simple Synthetic Entryway into Palladium Cross-Coupling Catalysis. *Chem. Commun.* **2017**, *53*, 7990−7993.

(16) Manzini, S.; Urbina Blanco, C. A.; Slawin, A. M. Z.; Nolan, S. P. Effect of Ligand Bulk in Ruthenium-Catalyzed Olefin Metathesis: IPr* vs IPr. *Organometallics* **2012**, *31*, 6514−6517.

(17) For another example of Ru catalysts bearing sterically augmented symmetrical NHC ligands, see: Fujihara, T.; Tomike, Y.;

DOI: 10.1021/acscatal.8b04783
ACS Catal. 2019, 9, 587−598

Ohtake, T.; Terao, J.; Tsuji, Y. Ruthenium-Catalyzed Ring-Closing Metathesis Accelerated by Long-Range Steric Effect. *Chem. Commun.* **2011**, *47*, 9699−9701.
(18) Ablialimov, O.; Kędziorek, M.; Malińska, M.; Woźniak, K.; Grela, K. Synthesis, Structure, and Catalytic Activity of New Ruthenium(II) Indenylidene Complexes Bearing Unsymmetrical N-Heterocyclic Carbenes. *Organometallics* **2014**, *33*, 2160−2171.
(19) Ablialimov, O.; Kędziorek, M.; Torborg, C.; Malińska, M.; Woźniak, K.; Grela, K. New Ruthenium(II) Indenylidene Complexes Bearing Unsymmetrical N-Heterocyclic Carbenes. *Organometallics* **2012**, *31*, 7316−7319.
(20) Małecki, P.; Gajda, K.; Ablialimov, O.; Malińska, M.; Gajda, R.; Woźniak, K.; Kajetanowicz, A.; Grela, K. Hoveyda−Grubbs-Type Precatalysts with Unsymmetrical N-Heterocyclic Carbenes as Effective Catalysts in Olefin Metathesis. *Organometallics* **2017**, *36*, 2153−2166.
(21) (a) For a discussion on selectivity problems in self-CM of α-olefins, see: Rouen, M.; Queval, P.; Borre, E.; Falivene, L.; Poater, A.; Berthod, M.; Hugues, F.; Cavallo, L.; Basle, O.; Olivier-Bourbigou, H.; Mauduit, M. Selective Metathesis of α-Olefins from Bio-Sourced Fischer−Tropsch Feeds. *ACS Catal.* **2016**, *6*, 7970−7976. (b) For synthesis of other unsymmetrical 2,6-diisopropylphenyl NHC precursors, see: Tarrieu, R.; Dumas, A.; Thongpaen, J.; Vives, T.; Roisnel, T.; Dorcet, V.; Crévisy, C.; Baslé, O.; Mauduit, M. Readily Accessible Unsymmetrical Unsaturated 2,6-Diisopropylphenyl N-Heterocyclic Carbene Ligands. Applications in Enantioselective Catalysis. *J. Org. Chem.* **2017**, *82*, 1880−1887.
(22) Nelson, D. J.; Percy, J. M. Does the Rate of Competing Isomerisation During Alkene Metathesis Depend on Pre-Catalyst Initiation Rate? *Dalton Trans.* **2014**, *43*, 4674−4679.
(23) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. On the Mechanism of the Initiation Reaction in Grubbs−Hoveyda Complexes. *J. Am. Chem. Soc.* **2012**, *134*, 1104−1114.
(24) Hejl, A. H. Controlling Olefin Metathesis Through Catalyst and Monomer Design. Ph.D. Thesis, California Institute of Technology, 2007.
(25) Grudzień, K.; Trzaskowski, B.; Smoleń, M.; Gajda, R.; Woźniak, K.; Grela, K. Hoveyda-Grubbs Catalyst Analogues Bearing the Derivatives of N-Phenylpyrrol in the Carbene Ligand - Structure, Stability, Activity and Unique Ruthenium-Phenyl Interactions. *Dalton Trans.* **2017**, *46*, 11790−11799.
(26) For a decomposition of Hoveyda−Grubbs catalysts in solution as a result of oxidation of the metal carbene, see: Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. A Recyclable Ru-Based Metathesis Catalyst. *J. Am. Chem. Soc.* **1999**, *121*, 791−799.
(27) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. In an Attempt to Provide a User's Guide to the Galaxy of Benzylidene, Alkoxybenzylidene, and Indenylidene Ruthenium Olefin Metathesis Catalysts. *Chem. -Eur. J.* **2008**, *14*, 806−818.
(28) Thomas, R. M.; Fedorov, A.; Keitz, B. K.; Grubbs, R. H. Thermally Stable, Latent Olefin Metathesis Catalysts. *Organometallics* **2011**, *30*, 6713−6717.
(29) Bohrsch, V.; Neidhofer, J.; Blechert, S. Diastereoselective Ring-Rearrangement Metathesis. *Angew. Chem., Int. Ed.* **2006**, *45*, 1302−1305.
(30) Kanai, K.; Erdoe, S.; Szappanos, A.; Bence, J.; Hermecz, I.; Szvoboda, G.; Batorii, S.; Heja, G.; Balogh, M.; Horvath, A.; Sipos, J.; Bartane Bodor, V.; Parkanyi, Z.; Lakics, V.; Molnar, P. Prolylendopeptidase Inhibitors. Patent US6191161B1.
(31) Bailey, G. A.; Lummiss, J. A. M.; Foscato, M.; Occhipinti, G.; McDonald, R.; Jensen, V. R.; Fogg, D. E. Decomposition of Olefin Metathesis Catalysts by Brønsted Base: Metallacyclobutane Deprotonation as a Primary Deactivating Event. *J. Am. Chem. Soc.* **2017**, *139*, 16446−16449.
(32) Higman, C. S.; Plais, L.; Fogg, D. E. Isomerization During Olefin Metathesis: An Assessment of Potential Catalyst Culprits. *ChemCatChem* **2013**, *5*, 3548−3551.
(33) Higman, C. S.; Lanterna, A. E.; Marin, M. L.; Scaiano, J. C.; Fogg, D. E. Catalyst Decomposition during Olefin Metathesis Yields Isomerization-Active Ruthenium Nanoparticles. *ChemCatChem* **2016**, *8*, 2446−2449.
(34) de Espinosa, L. M.; Meier, M. A. R., In *Organometallics and Renewables*, Meier, M. A. R.; Weckhuysen, B. M.; Bruijnincx, P. C. A., Eds. Springer Berlin Heidelberg: Berlin, Heidelberg, 2012; pp 1−44.
(35) Bilel, H.; Hamdi, N.; Zagrouba, F.; Fischmeister, C.; Bruneau, C. Eugenol as a Renewable Feedstock for the Production of Polyfunctional Alkenes via Olefin Cross-Metathesis. *RSC Adv.* **2012**, *2*, 9584−9589.
(36) Bantreil, X.; Nolan, S. P. Synthesis of N-Heterocyclic Carbene Ligands and Derived Ruthenium Olefin Metathesis Catalysts. *Nat. Protoc.* **2011**, *6*, 69.
(37) For an elegant example where olefin isomerization of essential-oil phenylpropenoids was deliberately used prior to metathesis step, see: Higman, C. S.; de Araujo, M. P.; Fogg, D. E. Tandem Catalysis Versus One-Pot Catalysis: Ensuring Process Orthogonality in the Transformation of Essential-Oil Phenylpropenoids into High-Vvalue Products via Olefin Isomerization-Metathesis. *Catal. Sci. Technol.* **2016**, *6*, 2077−2084.
(38) Małecki, P.; Kośnik, W.; Kajetanowicz, A., Grela, K., unpublished results.
(39) Banister, S. D.; Stuart, J.; Kevin, R. C.; Edington, A.; Longworth, M.; Wilkinson, S. M.; Beinat, C.; Buchanan, A. S.; Hibbs, D. E.; Glass, M.; Connor, M.; McGregor, I. S.; Kassiou, M. Effects of Bioisosteric Fluorine in Synthetic Cannabinoid Designer Drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS Chem. Neurosci.* **2015**, *6*, 1445−1458.
(40) Hess, C.; Schoeder, C. T.; Pillaiyar, T.; Madea, B.; Muller, C. E. Pharmacological Evaluation of Synthetic Cannabinoids Identified as Constituents of Spice. *Forensic Toxicol.* **2016**, *34*, 329−343.
(41) Pace, J. M.; Tietje, K.; Dart, M. J.; Meyer, M. D. 3-Cycloalkylcarbonyl Indoles as Cannabinoid Receptor Ligands. Patent WO2006069196.
(42) For an application in the paper industry, see: Czaban, J.; Schertzer, B. M.; Grela, K. Low Catalyst Loadings in Self-Metathesis of 1-Dodecene. *Adv. Synth. Catal.* **2013**, *355*, 1997−2006.
(43) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. Decomposition of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 7961−7968.
(44) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. Prevention of Undesirable Isomerization During Olefin Metathesis. *J. Am. Chem. Soc.* **2005**, *127*, 17160−17161.
(45) Moise, J.; Arseniyadis, S.; Cossy, J. Cross-Metathesis between α-Methylene-γ-butyrolactone and Olefins: A Dramatic Additive Effect. *Org. Lett.* **2007**, *9*, 1695−1698.
(46) Gimeno, N.; Formentin, P.; Steinke, J. H. G.; Vilar, R. Phenylphosphoric Acid as a New Additive to Inhibit Olefin Isomerisation in Ruthenium-Catalysed Metathesis Reactions. *Eur. J. Org. Chem.* **2007**, *2007*, 918−924.
(47) Thomas, R. M.; Keitz, B. K.; Champagne, T. M.; Grubbs, R. H. Highly Selective Ruthenium Metathesis Catalysts for Ethenolysis. *J. Am. Chem. Soc.* **2011**, *133*, 7490−7496.
(48) Rouen, M.; Borre, E.; Falivene, L.; Toupet, L.; Berthod, M.; Cavallo, L.; Olivier-Bourbigou, H.; Mauduit, M. Cycloalkyl-Based Unsymmetrical Unsaturated (U2)-NHC Ligands: Flexibility and Dissymmetry in Ruthenium-Catalysed Olefin Metathesis. *Dalton Trans.* **2014**, *43*, 7044−7049.
(49) Kajetanowicz, A.; Milewski, M.; Rogińska, J.; Gajda, R.; Woźniak, K. Hoveyda-Type Quinone-Containing Complexes − Catalysts to Prevent Migration of the Double Bond under Metathesis Conditions. *Eur. J. Org. Chem.* **2017**, *2017*, 626−638.
(50) For self-CM experiments showing problems related to quinone use at large scale, see SI (Figure S1).
(51) Kajetanowicz, A.; Sytniczuk, A.; Grela, K. Metathesis of Renewable Raw Materials-Influence of Ligands in the Indenylidene Type Catalysts on Self-Metathesis of Methyl Oleate and Cross-Metathesis of Methyl Oleate with (Z)-2-Butene-1,4-diol diacetate. *Green Chem.* **2014**, *16*, 1579−1585.

DOI: 10.1021/acscatal.8b04783
ACS Catal. 2019, 9, 587−598

(52) Sytniczuk, A.; Kajetanowicz, A.; Grela, K. Fishing for the Right Catalyst for the Cross-Metathesis Reaction of Methyl Oleate with 2-Methyl-2-butene. *Catal. Sci. Technol.* **2017**, *7*, 1284−1296.
(53) Nickel, A.; Ung, T.; Mkrtumyan, G.; Uy, J.; Lee, C. W.; Stoianova, D.; Papazian, J.; Wei, W.-H.; Mallari, A.; Schrodi, Y.; Pederson, R. L. A Highly Efficient Olefin Metathesis Process for the Synthesis of Terminal Alkenes from Fatty Acid Esters. *Top. Catal.* **2012**, *55*, 518−523.
(54) Ohlmann, D. M.; Tschauder, N.; Stockis, J. P.; Goossen, K.; Dierker, M.; Goossen, L. J. Isomerizing Olefin Metathesis as a Strategy To Access Defined Distributions of Unsaturated Compounds from Fatty Acids. *J. Am. Chem. Soc.* **2012**, *134*, 13716−13729.
(55) Miao, X.; Fischmeister, C.; Dixneuf, P. H.; Bruneau, C.; Dubois, J. L.; Couturier, J. L. Polyamide Precursors from Renewable 10-Undecenenitrile and Methyl Acrylate via Olefin Cross-Metathesis. *Green Chem.* **2012**, *14*, 2179−2183.
(56) Sytniczuk, A.; Forcher, G.; Grotjahn, D. B.; Grela, K. Sequential Alkene Isomerization and Ring-Closing Metathesis in Production of Macrocyclic Musks from Biomass. *Chem. -Eur. J.* **2018**, *24*, 10403−10408.
(57) Sytniczuk, A.; Leszczyńska, A.; Kajetanowicz, A.; Grela, K. Preparation of Musk-Smelling Macrocyclic Lactones from Biomass: Looking for the Optimal Substrate Combination. *ChemSusChem* **2018**, *11*, 3157−3166.
(58) For a more detailed discussion, see: Nickel, A.; Pederson, R. L. In *Olefin Metathesis. Theory and Practice*, Grela, K., Ed.; John Wiley and Sons, Inc.: Hoboken, NJ, 2014; pp 335−348.
(59) (a) Melaimi, M.; Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (Alkyl)(amino)carbenes (CAACs): Recent Developments. *Angew. Chem., Int. Ed.* **2017**, *56*, 10046−10068. (b) Ritter, T.; Hejl, A.; Wenzel, A. G.; Funk, T. W.; Grubbs, R. H. A Standard System of Characterization for Olefin Metathesis Catalysts. *Organometallics* **2006**, *25*, 5740−5745. (c) Gawin, R.; Tracz, A.; Chwalba, M.; Kozakiewicz, A.; Trzaskowski, B.; Skowerski, K. Cyclic Alkyl Amino Ruthenium Complexes—Efficient Catalysts for Macrocyclization and Acrylonitrile Cross Metathesis. *ACS Catal.* **2017**, *7*, 5443−5449. (d) Butilkov, D.; Frenklah, A.; Rozenberg, I.; Kozuch, K.; Lemcoff, N. G. Highly Selective Olefin Metathesis with CAAC-Containing Ruthenium Benzylidenes. *ACS Catal.* **2017**, *7*, 7634−7637. (e) Rozenberg, I.; Eivgi, O.; Frenklah, A.; Butilkov, D.; Kozuch, S.; Goldberg, I.; Lemcoff, N. G. Synthesis and Catalytic Properties of Sulfur-Chelated Ruthenium Benzylidenes Bearing a Cyclic (Alkyl)(amino)carbene Ligand. *ACS Catal.* **2018**, *8*, 8182−8191.
(60) Miyazaki, H.; Herbert, M. B.; Liu, P.; Dong, X.; Xu, X.; Keitz, B. K.; Ung, T.; Mkrtumyan, G.; Houk, K. N.; Grubbs, R. H. Z-Selective Ethenolysis with a Ruthenium Metathesis Catalyst: Experiment and Theory. *J. Am. Chem. Soc.* **2013**, *135*, 5848−5858.
(61) Bidange, J.; Fischmeister, C.; Bruneau, C. Ethenolysis: A Green Catalytic Tool to Cleave Carbon−Carbon Double Bonds. *Chem. -Eur. J.* **2016**, *22*, 12226−12244.
(62) Gawin, R.; Kozakiewicz, A.; Guńka, P. A.; Dąbrowski, P.; Skowerski, K. Bis(Cyclic Alkyl Amino Carbene) Ruthenium Complexes: A Versatile, Highly Efficient Tool for Olefin Metathesis. *Angew. Chem., Int. Ed.* **2017**, *56*, 981−986.

DOI: 10.1021/acscatal.8b04783
ACS Catal. 2019, 9, 587−598