ChemPubSoc Europe

DOI: 10.1002/chem.201904549

CHEMISTRY A European Journal Full Paper

Olefin Metathesis

In a Quest for Selectivity Paired with Activity: A Ruthenium Olefin Metathesis Catalyst Bearing an Unsymmetrical Phenanthrene-Based N-Heterocyclic Carbene

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Abstract: Robust, selective, and stable in the presence of ethylene, ruthenium olefin metathesis pre-catalyst, {[3-benzyl-1-(10-phenyl-9-phenanthryl)]-2-imidazolidinylidene}dichloro(*o*-isopropoxyphenylmethylene)ruthenium(II), **Ru-3**, bearing an unsymetrical *N*-heterocyclic carbene (uNHC) ligand, has been synthesized. The initiation rate of **Ru-3** was examined by ring-closing metathesis and cross-metathesis reactions with a broad spectrum of olefins, showing an unprecendented selectivity. It was also tested in industrially relevant ethenolysis reactions of olefinic substrates from renewable feedstock with very good yields and selectivities.

Introduction

'If your only tool is a hammer, then every problem looks like a nail'—A. H. Maslov.[1] For this reason, a professional toolbox should be well-equipped with specialized instruments. This does not affect only mechanics or instrumental work but is also significant when applied to chemical catalysis. Today well-defined organometallic complexes can successfully mediate many of the chemists' desired transformations. However, a universal-the "jack of all trades"-catalyst does not exist yet.[2]

Olefin metathesis is a powerful tool used for the formation of new carbon–carbon double bonds.[3,4] Its significance was acknowledged by the awarding of the Nobel Prize to Schrock, Grubbs, and Chauvin.[5–8] Olefin metathesis is well-established, in polymer chemistry and in the synthesis of natural products and drugs.[3,4,9–12] However, the "tools" portfolio of the ruthenium olefin metathesis catalyst consists mostly of *N*-heterocyclic carbene (NHC, second generation) and PCy_3 (first generation) derivatives of benzylidene (Grubbs type, Figure 1, **A**),[13–15] 2-*i*PrO-benzylidene (Hoveyda type, Figure 1, **C**),[16–18] and indenylidene (Figure 1, **B**)[19,20] complexes. These "general use" complexes mediate a range of standard transformations, but they lack selectivity and utility in the case of more demanding substrates or specialist applications (i.e. ethenolysis).[21]

One of the strategies affording ruthenium complexes with fine-tuned selectivity is modification of NHC.[3,22–27] This has led to increasing interest in the use of various unsymmetrical NHC (uNHC) ligands in olefin metathesis (Figure 1).[28,29]

One of the earliest mentions of *N*-alkyl-*N*′-aryl NHC based ruthenium complexes, are catalysts published by the Blechert (Figure 1, **L4-C**)[30] and Verpoort groups (Figure 1, **L5-A**,**C**).[31,32] The authors of the first group prepared a series of different Grubbs- and Hoveyda-type complexes, bearing *N*-methyl and ethyl moieties, together with the *N*′-mesityl group. In the case of the Verpoort group, alkyl moieties such as methyl, cyclohexyl, or camphor were used together with Mes (mesityl) and DIPP (2,6-diisopropylphenyl) substituents. In 2007, Bertrand together with Grubbs presented ruthenium pre-catalysts with cyclic alkyl amino carbene (CAAC) ligands which are, to date, the best catalysts for the ethenolysis of oleic acid derivatives (Figure 1, **L6-C**).[33,34] More recently, Gawin et al., published series of bis(CAAC) complexes of enhanced selectivity.[35] Also in 2007, Vougioukalakis and Grubbs published series of complexes bearing NHC ligands with fluorinated aryl moieties (Figure 1, **L7-A**,**C**).[36]

Similarly, Copéret group published in 2016 an uNHC Grubbs-type complex bearing a trifluoromethyl group (Figure 1, **L8-A**).[37] This catalyst showed very high selectivity in the ethenolysis of ethyl oleate. Moreover, Copéret group showed usage of uNHC, as anchor spot for covalent bonding of ruthenium catalyst to a solid support.[38,39] Unsymmetrical NHCs were also used by the Grubbs group for the synthesis of *Z*-selective catalysts by a C–H activation of an *N*-alkyl substituent.[40] Recently, the Mauduit group have presented indenylidene-type complexes with a cyclopentyl or cyclododecyl group on one of the

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Supporting information and the ORCID identification numbers for the authors of this article can be found under:
https://doi.org/10.1002/chem.201904549.

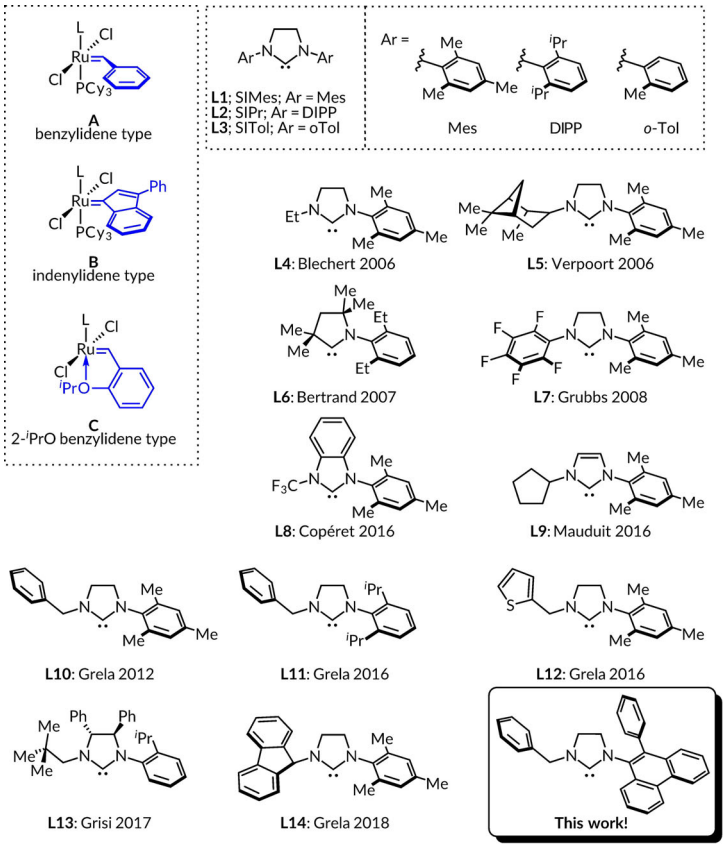


Figure 1. Selected ruthenium complexes **A**–**C** which are commercially available (with ligands **L1** to **L3**) and bearing unsymmetrical NHC (**L4-L12**).

nitrogen atoms in the NHC, finding applications in the metathesis of α-olefins in low-catalyst loading (Figure 1, **L9-B**).[41] uNHCs were also used by Paradiso et al. in an investigation of backbone steric hinderence influence on the reactivity of ruthenium alkylidene complexes (Figure 1, **L13-A**,**C**).[42–45] *N*-Cyclohexyl derivative was succesfully used in alternating ring-opening metathesis polymerisation (AROMP),[46] similarly to that previously published by the Plenio group *N*-pentiptycenyl ruthenium complex.[47]

In line with the trend of investigating uNHC as ligands for olefin metathesis, our group published a series of works on *N*-aralkyl-*N*′-aryl NHC-based complexes. These proved useful as olefin-metathesis precatalysts, not only, in standard conditions under an argon atmosphere, but also in commercial grade nondegassed solvents (Figure 1, **L10-B**).[48,49] Importantly, those complexes were successfully applied in the ethenolysis of ethyl oleate (Figure 1, **L12-B**,**C**)[50] and afforded low isomerization in self-metathesis of α-olefins (Figure 1, **L11-C**).[51] They were also used in reactions with 1 ppm pre-catalyst loading yielding 232 735 TON (Figure 1, **L14-B**).[52] However, despite all their virtues, such catalysts in general show slower propagation rates and require higher temperatures to operate as compared with standard symmetrical-NHC-based complexes (Figure 1, **L1**,**2**,**3-A**,**B**,**C**).

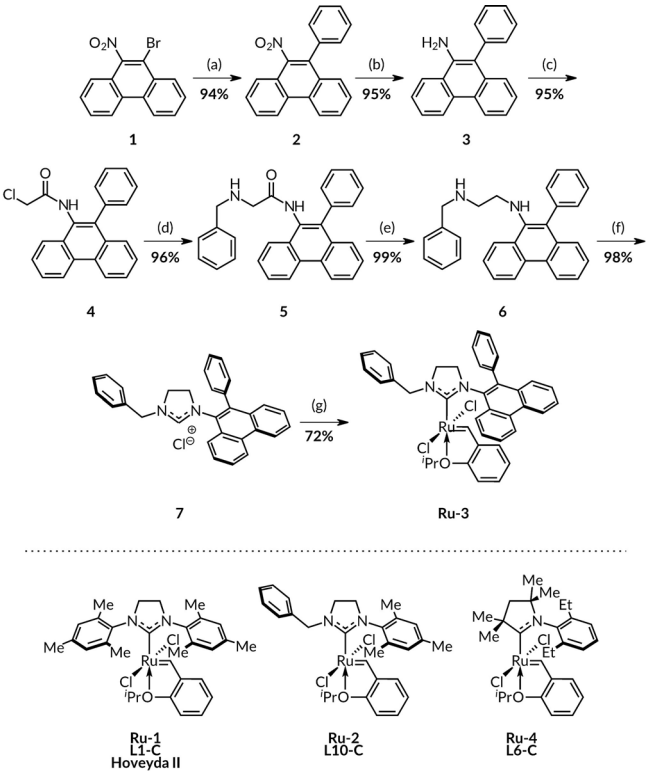
Herein, we present the synthesis of a new phenylphenanthrene-derived uNHC precursor and corresponding second-generation Hoveyda complex. Its higher reactivity is demonstrated and unique utility in challenging transformations, such as the ethenolysis of renewable feedstock.

Results and Discussion

Synthesis and structure of Ru-3

Ru-3 catalyst was synthesized in seven steps (Scheme 1). Known 9-bromo-10-nitrophenanthrene (**1**)[53] was used in Suzuki–Miyaura coupling with phenylboronic acid affording 94% of nitroaryl **2**, which was subsequently catalytically reduced with hydrazine hydrate in the presence of Pd/C yielding amine **3** (95%) which readily undergoes acylation (**4**, 95%). Alkylation of benzylamine with amide **4** afforded compound **5** (96%), which was subsequently reduced to diamine **6** in quantitative yield. The corresponding imidazolidynium salt **7** was obtained in 98% yield and was used to synthesize **Ru-3** with 72% yield after 20 min of the reaction at 70 °C.

Ru-3 is a dark-brown, powdery solid. Single-crystals suitable for X-ray diffraction studies were ob-



Scheme 1. Synthesis of **Ru-3** and structures of known complexes used for comparison. (a) 2 mol% $[Pd(PPh_3)_2Cl_2]$ Cs_2CO_3, $PhB(OH)_2$, THF/H_2O (20:1), reflux, overnight; (b) 5 mol% Pd/C, $N_2H_4{\cdot}H_2O$, EtOH, reflux, overnight; (c) $CH_2ClCOCl$, K_2CO_3, THF, rt, 2 h; (d) $BnNH_2$, K_2CO_3, THF, reflux, overnight; (e) $LiALH_4$, THF, reflux, 4 h; (f) $HC(OEt)_3$, NH_4Cl, 120 °C, 2 h; (g) KO*t*Am, rt, PhMe, 3 min then Hoveyda I, 20 min, 70 °C.

tained by slow diffusion of *n*-heptane into concentrated DCM solution of the complex. The structure of **Ru-3** was determined by single-crystal X-ray diffraction analysis.

The investigated compound crystallizes in a triclinic *P*-1 space group with one molecule of the compound in the asymmetric part of the unit cell (Figure 2). The details of crystallographic data and refinement parameters are summarized in the Supporting Information. Selected bond lengths and valence angles are presented in the description of Table 1.

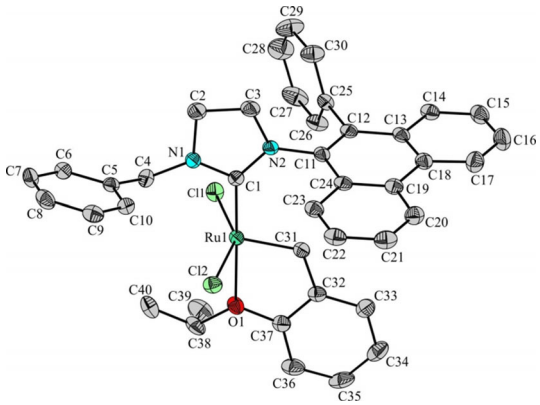


Figure 2. Molecular structure of **Ru-3** with atom labeling. Displacement ellipsoids are drawn at the 50% probability level. The hydrogen atoms were omitted for clarity.

Table 1. Selected, corresponding bond lengths [Å] and angles [°] in **Ru-2** and **Ru-3**.

Bond lengths [Å]	Ru-2	Ru-3
C1–N1	1.357(2)	1.354(3)
C1–N2	1.343(2)	1.350(3)
C2–C3	1.521(3)	1.521(3)
C14–N1 (**Ru-2**)/C4–N1 (**Ru-3**)	1.457(2)	1.457(3)
C14–N2 (**Ru-2**)/C11–N2 (**Ru-3**)	1.432(2)	1.433(3)
C22–C23 (**Ru-2**)/C31–C32 (**Ru-3**)	1.451(3)	1.457(3)
C24–O1 (**Ru-2**)/C37–O1 (**Ru-3**)	1.381(2)	1.376(3)
Ru1–C1	1.9676(18)	1.969(2)
Ru1–C22 (**Ru-2**)/Ru1–C31 (**Ru-3**)	1.8393(18)	1.835(2)
Ru1–Cl1	2.3415(5)	2.3304(5)
Ru1–Cl2	2.3456(4)	2.3170(5)
Ru1–O1	2.2666(12)	2.2480(14)
Valence angles [°]	**Ru-2**	**Ru-3**
C1–Ru1–C22 (**Ru-2**)/C1-Ru1-C31 (**Ru-3**)	102.75(8)	101.78(9)
C1–Ru1–Cl1	93.27(5)	89.27(6)
C1–Ru1–Cl2	86.84(5)	92.33(6)
C1–Ru1–O1	177.31(6)	178.81(7)
Cl1–Ru1–Cl2	153.121(17)	148.34(2)
N1–C14–C15 (**Ru-2**)/N1–C4–C5 (**Ru-3**)	111.11(15)	112.74(17)
N2–C1–N1	107.34(15)	107.17(17)
Ru1–O1–C24 (**Ru-2**)/Ru1–O1–C37 (**Ru-3**)	110.19(10)	110.74(12)

The metallic centre in **Ru-3** is pentacoordinate and the geometry of ligands is close to square pyramid with two *trans*-oriented chlorine atoms in the corners of the basal plane (Figure 2). The other two corners of this plane are occupied by the oxygen atom and the alkylidene carbon atom from the NHC ring system. The geometry of the oxygen atom is typical for the sp^2-hybridization type. The apical position of the aforementioned pyramid is occupied by the methylidene carbon atom.

Generally, the geometrical parameters describing the molecular skeleton of **Ru-3** well correlate with those of **Ru-2** (Figure 1, **L10-C**), which may be treated as the reference compound (Figure 3, Table 1).[51] Based on angles between ruthenium ligands, geometry index (τ_5) was calculated for **Ru-3** and **Ru-2**,[54] to quantify the square-pyramid distortion. In both complexes $\tau_5 > 0$, 0.51 for **Ru-3** and 0.40 for **Ru-2**. In this case, the length of the Ru1–C1 bond does not differ by more than three estimated standard deviations in both of the investigated structures. The same can be said about the length of the bond between rutenium and methylidene carbon atom (Ru1–C22 (**Ru-2**)/Ru1–C31 (**Ru-3**)). On the other hand, the Ru1–Cl1, Ru1–Cl2, and Ru1–O1 bonds are slightly shorter in the case of **Ru-3** (respectively: 0.011(1), 0.028(59), 0.018(6) Å). Regarding the C1–Ru1–O1 and Cl1–Ru1–Cl2 angles, which may be considered to be descriptors of the accessibility of the metallic centre, the value of the first one (C1–Ru1–O1) is similar in both compounds (difference of 1.50(1)°); however, the value of the Cl1–Ru1–Cl2 angle is a bit higher in the case of **Ru-2** (difference of 4.77(9)°). The most noticeable difference in spatial arrangement is observed in the change of orientation of the benzyl substituent and the benzylidene moiety respective to the plane of the NHC ring system. The mean planes, delineated by the nonhydrogen atoms of the benzyl substituent phenyl ring and the NHC moiety, are inclined by the angle of 91.03(7) in **Ru-2** and 82.22(8)° in **Ru-3**. In turn, the mean planes defined by the carbon atoms of the phenyl moiety of the benzylidene

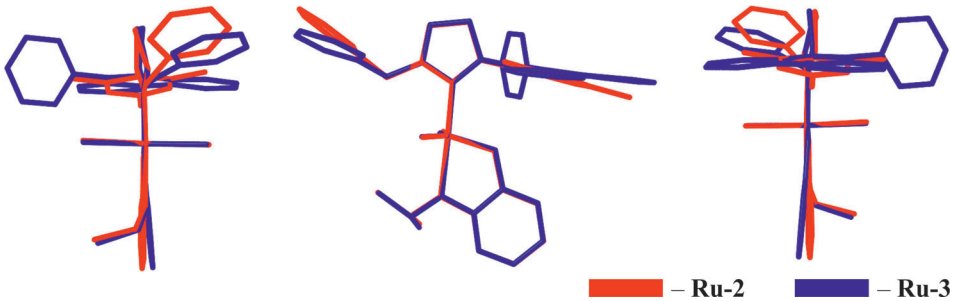


Figure 3. Superimposed X-ray structures of compounds **Ru-2** and **Ru-3**. The hydrogen atoms were omitted for clarity.

and the nonhydrogen atoms of the NHC ring system in **Ru-2** and **Ru-3** are oriented to each other, respectively, by an angle of 9.07(7) and 4.36(9)°. The presence of the phenylphenantrene substituent instead of the mesityl group does not affect significantly the geometry of the NHC ring system. The phenantrene and the NHC moieties in **Ru-3** are inclined to themselves by the angle of 95.84(7)°, and the phenyl ring described by the C25–C30 atoms is inclined by the angle of 85.40(7)° to the mean plane delineated by the nonhydrogen atoms of the aforementioned phenantrene.

Using the data obtained from diffraction studies, we have calculated the buried volume ($V_{bur\%}$) for the uNHC derived from **8** by using SambVca 2 software developed by the Cavallo group.[55] Comparing values of $V_{bur\%}$ for commercially available **Ru-1** (33.7) and complex **Ru-3** (32.3), the overall steric demand of **Ru-3** is slightly lower despite the relatively bulky phenanthrene moiety when partnered with smaller benzyl substituent. It is caused by overall smaller, in contrast to mesityl group, steric bulk of the benzyl moiety. Moreover, it is clearly visible on Figure 4 that, in the case of **Ru-3**, the phenanthrene core creates a flat cavity, which further decreases overall steric demand of the ligand.

Reactivity and stability studies

As a next step of characterization of **Ru-3**, we investigated its activity in the RCM reaction of diethyldiallyl malonate (**DEDAM**, Figure 5 a,b), diethylallylmethallyl malonate (**DEAMAM**, Figure 5 c), and diallyltosyl amide (**DATA**, Figure 5 d).

Initiation rates of **Ru-1** and **Ru-3** in all cases are very similar (Figure 5). In contrast, under our reactions conditions (40 °C, CD_2Cl_2, C = 0.1 M), **Ru-2** has a very low rate of initiation. It is known that the *N*-alkyl-substituted Hoveyda-type complexes, require higher temperatures to initiate.[51,56] This clearly shows that **Ru-3** shows deviation in reactivity from previously published *N*-benzyl-substituted catalysts,[51] exhibiting initiation rates equal to commercially available catalyst **Ru-1**.

Having established the activity of **Ru-3** in the RCM of benchmark substrates we investigated its stability in CD_2Cl_2 (Figure 6). After 30 days at 40 °C under argon, less than 10% decomposition was observed for all compounds. Significantly, **Ru-3** was 96% intact after one month, whereas both **Ru-1** and **Ru-2** were below 94%.

Scope and limitations of the study

With stability and initiation rate data in hand, **Ru-3** was examined in more detail in a series of more diverse olefin metathesis reactions. As **Ru-2** activity in **DEDAM**, **DEAMAM**, and **DATA** reaction profiles was inferior in comparison to **Ru-1** and **Ru-3**, we have decided to not use it in further examination of the reactivity of **Ru-3**. First, we investigated a range of RCM substrates leading to products of different ring size, as well as bearing substituents with various steric and electronic factors. Results are collected in Table 2.

Similarly to simple RCM reactions discussed previously (Scheme 2), in the case of enyne **S-1** cycloisomerisation, **Ru-3** exhibits reactivity akin to commercially available **Ru-1**. Another enyne substrate (**S-1′**) was selected based on Fogg's observation[59] explaining why acetylenic enynes with minimal propar-

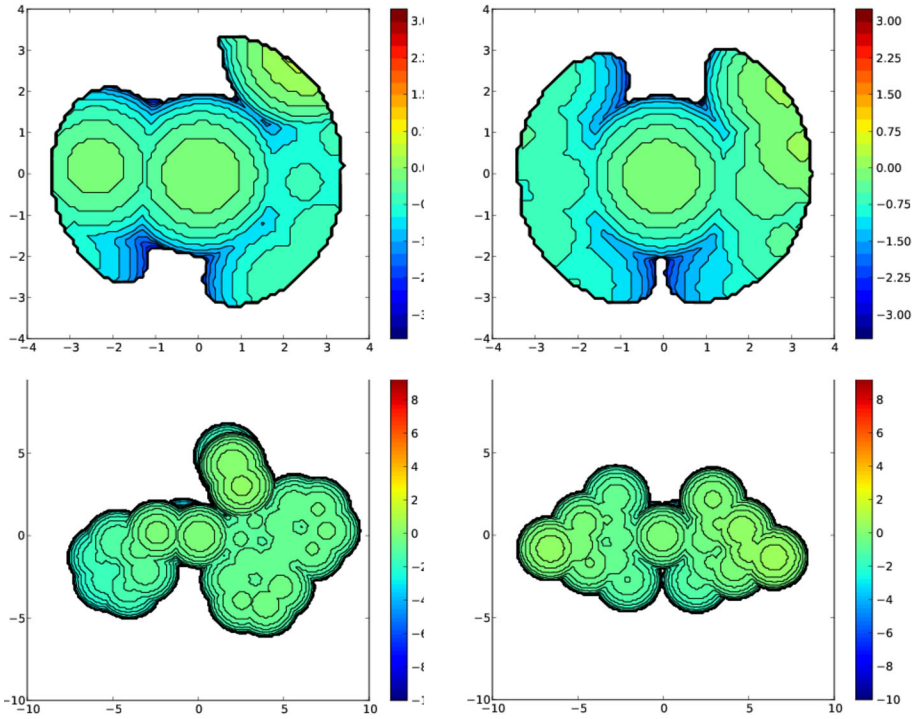


Figure 4. Steric maps calculated in SambVca software for **Ru-1** (right) and **Ru-3** (left). Standard (3.5) and enlarged (10) radi were used.

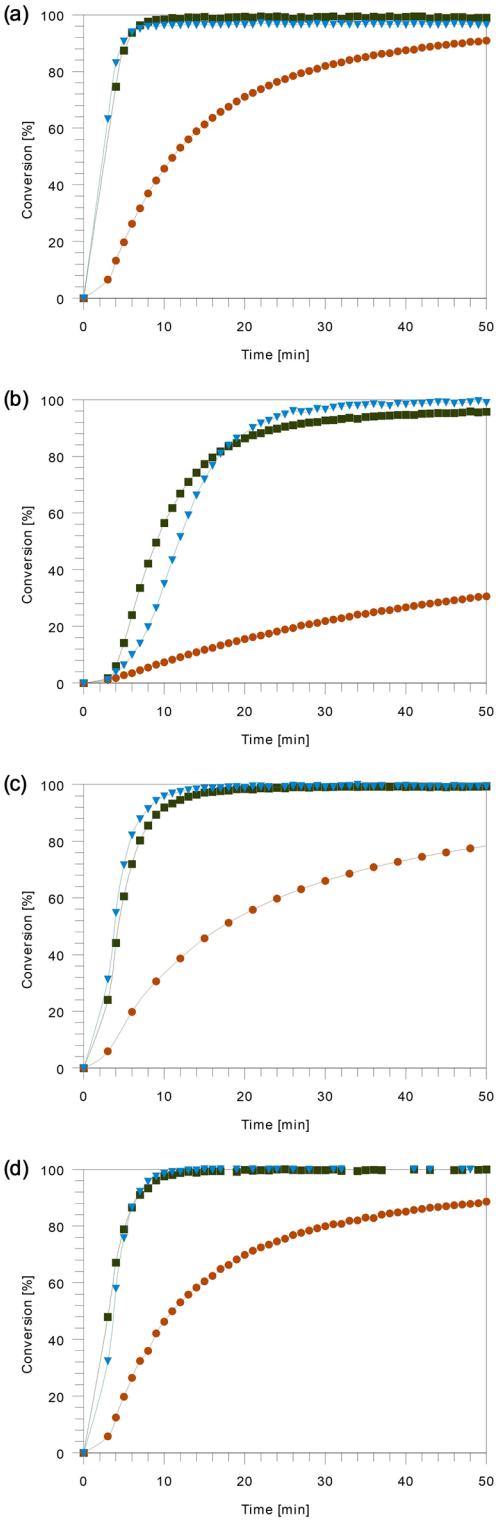


Figure 5. Reaction profiles of DEDAM 1 mol% (a) and 0.1 mol% (b), DEAMAM (c) and DATA (d). Reactions were monitored by ^{1}H NMR spectroscopy (lines are visual aids and not curve fits; ■: **Ru-1**, ●: **Ru-2**, ▼: **Ru-3**).

gylic bulk perform poorly in ethylene-free cycloisomerisation. We opted to try if the unique steric properties of **Ru-3** would have the potential to block yne–yne dimerization, which kills productive metathesis in this case.[67] Unfortunately, no reaction was observed, and instead of the expected **P-1′**, the substrate was recovered (conversion below 5%) and only traces of other unidentified compounds were visible on the GC chromatogram. It shall be noted, that the same behaviour was observed by us also for **Ru-1**, thus in this regard, the new catalyst **Ru-3** follows the general trend observed by Fogg.[59]

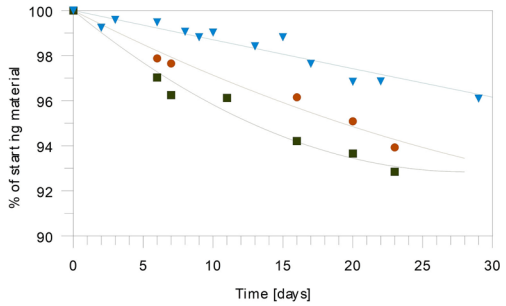


Figure 6. Stability test of investigated complexes. Measurements were made by ^{1}H NMR spectroscopy (benzylidene proton signal in reference to aromatic signal from trimethoxybenzene). Conditions: CD_2Cl_2, 40 °C, C = 18 mM, argon atmosphere. Reactions were monitored by ^{1}H NMR spectroscopy (lines are visual aids and not curve fits; ■: **Ru-1**, ●: **Ru-2**, ▼: **Ru-3**).

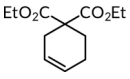
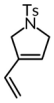
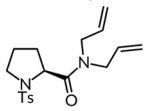
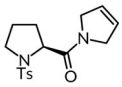
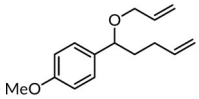
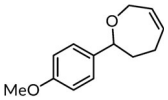
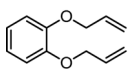
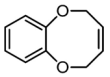
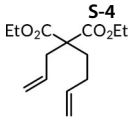
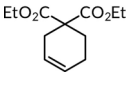
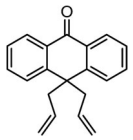
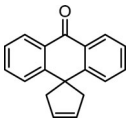
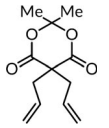
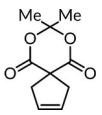
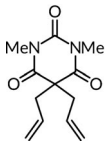
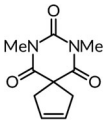
While the five-membered ring of **P-2** forms efficiently, the difference in reactivity emerges in the case of RCM leading to seven and eight-membered rings (**P-3** and **P-4**). In the case of **P-3**, reaction with **Ru-1** was not selective, leading to a complicated mixture of products. Purification of the reaction mixture yielded 49% of **P-3** as well as comparable in mass fraction of byproducts with complicated ^{1}H NMR spectra. The same reaction proceed cleanly in the case of **Ru-3**. Low reactivity of **Ru-1** towards medium-sized rings (seven–eight) was also observed for the RCM reaction of **S-4**, in which not only **P-4** but also linear and cyclic oligomers were observed.[60,61] It is worth noting that in the reactions catalyzed by **Ru-1**, even after prolonged reaction times (20 h), substrate was still present. In case of **Ru-3**, we have observed full conversion of substrate to closed products with 82% yield of **P-4**.

Unexpectedly, poor reactivity towards substrates containing 1,3-dicarbonyl moieties (**S-7**, **S-8**) was observed for **Ru-3**. In both cases, the major constituent of the reaction mixture was the unreacted substrate. This astonishing, and previously not reported for this class of substrates, drop in reactivity prompted us to expand the scope of tested compound to different 1,3-diones and ketone **S-12** (Table 3).

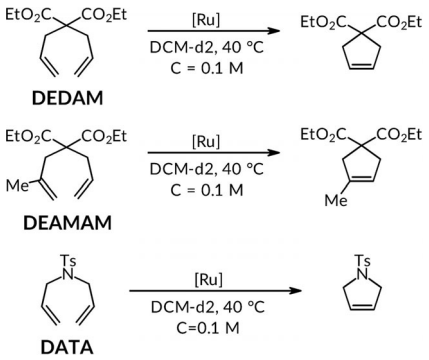
The lowest yields were observed for substrates with increasingly flat structures. When rotation of carbonyl groups is fully possible, (like in substrate **S-9**), there is no decrease in reactivity, and isolated yields are very similar for both **Ru-1** and **Ru-3** catalysts.

With increasing planarity of carbonyl groups and compound skeleton, conversion of substrate decreases. It is worth noting that in the case of **S-12** containing only one carbonyl group, we also observed only traces of product. Further testing of observed effect, by conducting the RCM reaction with equimolar amounts of **DEDAM** and **S-11** (Scheme 3), showed that reaction with **S-11** is preferred over **DEDAM** (Figure 7a,c).

Table 2. Simple and more challenging enyne and RCM.[a]

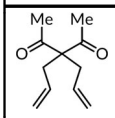
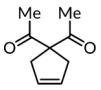
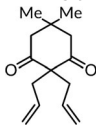
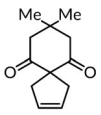
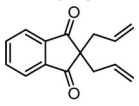
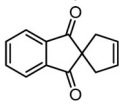
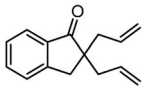
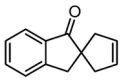
Substrate	Product	[Ru]	Isolated yield [%]
 **S-1**	 **P-1**	**Ru-1** **Ru-3**	97 98
 **S-1′**	 **P-1′**	**Ru-1** **Ru-3**	$<5^{[b,c]}$ $<5^{[b,c]}$
 **S-2**	 **P-2**	**Ru-1** **Ru-3**	99 99
 **S-3**	 **P-3**	**Ru-1** **Ru-3**	49 80
 **S-4**	 **P-4**	**Ru-1** **Ru-3**	$53^{[b,d]}$ $82^{[d]}$
 **S-5**	 **P-5**	**Ru-1** **Ru-3**	99 99
 **S-6**	 **P-6**	**Ru-1** **Ru-3**	95 95
 **S-7**	 **P-7**	**Ru-1** **Ru-3**	98 $70^{[b]}$
 **S-8**	 **P-8**	**Ru-1** **Ru-3**	99 $56^{[b]}$

[a] Conditions: 0.5 mol% cat., DCM, C = 0.1 M, 40 °C, 5 h, reactions quenched using 45 μM solution of 1,4-bis(2-isocyanopropyl)piperazine (SnatchCat Metal Scavenger).[57,58] [b] Substrate was recovered. [c] Conversion. [d] C = 0.04 M, 20 h.

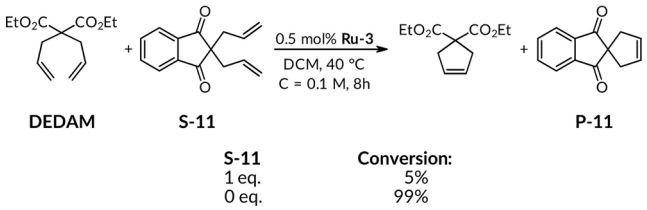


Scheme 2. RCM of model substrates.

Table 3. The specific case of RCM reaction of different bisallyl ketones.

Substrate	Product	[Ru]	Yield/Conv.[%]
 **S-9**	 **P-9**	**Ru-1** **Ru-3**	95 92
 **S-10**	 **P-10**	**Ru-1** **Ru-3**	96 22
 **S-11**	 **P-11**	**Ru-1** **Ru-3**	96 $5^{[b]}$ $>99^{[b,c]}$
 **S-12**	 **P-12**	**Ru-1** **Ru-3**	93 $4^{[b]}$ $>99^{[b,c]}$

[a] Conditions: 0.5 mol% cat., DCM, C = 0.1 M, 40 °C, 5 h, reactions quenched using 45 μM solution of 1,4-bis(2-isocyanopropyl)piperazine (SnatchCat Metal Scavenger).[57,58] [b] Conversion were determined by GC in accordance to internal standard (durene). [c] Reaction conducted in toluene at 80 °C.



Scheme 3. RCM reaction of DEDAM in the presence of **S-11**.

Next, we performed the RCM of **DEDAM** and after five minutes of reaction we added **S-11** (Scheme 4). Under these conditions, **S-11** behaves as a peculiar metathesis quenching reagent, blocking ruthenium center from further metathesis giving 13% conversion over one hour (Figure 7b). Under the same conditions, but without addition of **S-11**, over 90% conversion was observed (Figure 7c).

We assume that a carbonyl moiety in the γ-position to a C–C double bond as well as flat structure of molecule, are necessary conditions to block **Ru-3** reactivity. The most probable cause of the decrease in reactivity can be coordination of the carbonyl moiety to ruthenium,[62–65] in which the rigid skeleton imposes a conformation where oxygen lone pair is in proximity to the metallic center. The proposed, stable **Ru-3** intermediate (Figure 8) does not undergo new catalytic cycles in conditions of performed reactions. Interestingly, this coordination seems to be permanent for *N*-benzyl-type complex under 40 °C (no

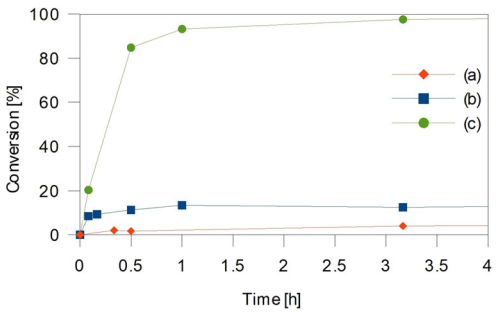
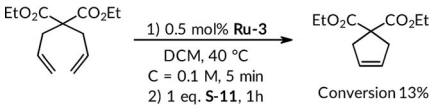


Figure 7. RCM reaction of DEDAM in the presence of **S-11**: (a) Mixed together before addition of catalyst; (b) **S-11** added after 5 min of reaction; (c) RCM of pure DEDAM. Conditions: DCM, 40 °C, 1 mol% (lines are visual aids and not curve fits).



Scheme 4. Quenching effect of 1,3-dicarbonyl compound **S-11**.

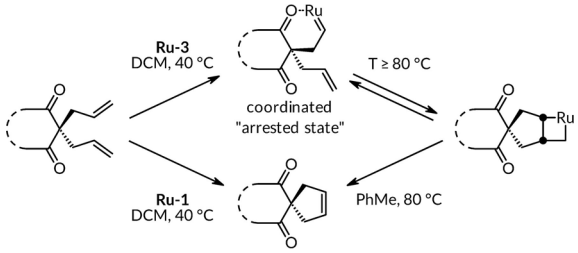


Figure 8. Proposed "arrested state" blocking further RCM.

change in conversion was observed in 4 hours after initial reaction, Figure 7a,b) but disappears when the reaction is performed at 80 °C. Despite being well-known that formation of strong chelates can block further metathesis,[66] such a drastic difference in reactivity between **Ru-3** and **Ru-1** at ambient temperatures towards the "planar" 2-allyl 1,3 diketones is really interesting and probably worth a deeper examination.[67]

In contrast, almost quantitative conversion is achieved in the first 10 minutes of the reaction (Figure 9). This change of "reactivity" can be explained not only by temperature increase giving more energy to transition states, but also by an aromatic solvent effect, which probably can destabilize substrate–catalyst complex.[68]

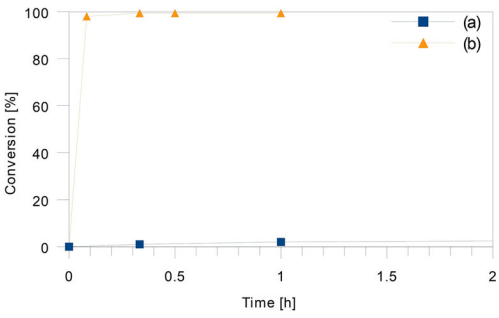
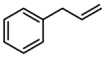
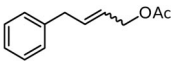
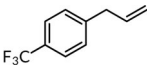
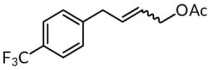
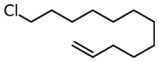
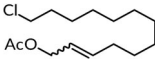
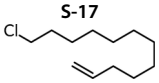
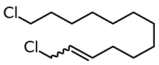
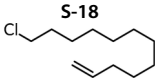
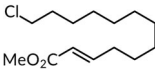
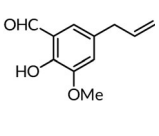
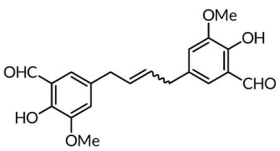


Figure 9. RCM reaction of **S-11**: (a) DCM, 40 °C, 1 mol%; (b) PhMe, 80 °C, 1 mol% (lines are visual aids and not curve fits).

Next the reactivity of **Ru-3** was investigated in a series of cross- and self-metathesis reactions (Table 4). The complex gives high yields and high *E/Z* ratios in most of the performed reactions. When methyl acrylate was used as a cross-metathesis partner (**S-15**), we observed a decrease in yield of the desired cross product and an increased tendency for self-metathesis reaction. It is known that electron-deficient olefins are in general difficult partners for uNHC-based catalysts.[3,30–32,69]

Table 4. Preparative Cross-Metathesis reactions.[a]

Substrate	Product	[Ru]	Yield [%]	*E/Z*
 **S-13**		**Ru-1**	87	10.9
 **S-17**	**P-13**	**Ru-3**	91	9.9
 **S-14**		**Ru-1**	84	9
 **S-17**	**P-14**	**Ru-3**	85	8.6
 **S-15**		**Ru-1**	86	8
 **S-17**	**P-15a**	**Ru-3**	87	7.5
 **S-15**		**Ru-1**	81	7.32
 **S-18**	**P-15b**	**Ru-3**	89	7.26
 **S-15**		**Ru-1**	95	*E* only
 **S-19**	**P-15c**	**Ru-3**	87	
 **S-16**	 **P-16**	**Ru-1**	59	6.8
		Ru-3	63	9

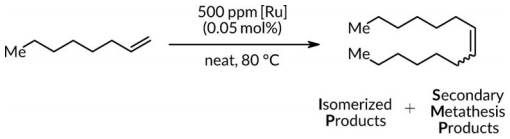
[a] Conditions: 1 mol% cat., DCM, $c = 0.1$ M, 3 equiv of CM partner 40 °C, 20 h, reactions quenched using 45 μM solution of 1,4-bis(2-isocyanopropyl)piperazine (SnatchCat Metal Scavenger).[57,58]

Therefore, we were happy to see that, in the case of **Ru-3**, the decrease of reactivity was only very small (87 vs. 95%).

Isomerisation susceptibility and stability in the presence of ethylene

As we mentioned earlier for RCM of **S-3**, we did not observe isomerisation products with catalyst **Ru-3**. The same reaction catalyzed by **Ru-1** was low yielding and effected by the isomerisation of products. We decided to investigate **Ru-3** isomerisation susceptibility further.

It has been reported for years, that isomerisation is related to ruthenium hydride complexes which emerge from a bimolecular decomposition of the propagating ruthenium complexes.[70–72] Later, in a series of detailed studies by Fogg,[73–77] Nelson and Percy[78] it has been shown that non-hydride Ru-complexes, shall be considered. Recently, one of the commonly suspected Ru-hydride species,[71,79] was shown to be kinetically incompetent to account for isomerization during metathesis.[80] Various methods have been proposed to stop undesired olefin isomerisation processes, such us addition of quinones[81,82] or by using catalysts bearing a quinone fragment in their structure.[79] Different steric and electronic NHC surroundings can alter reactivity of a ruthenium catalyst making it less prone to undergo decomposition.[41] Therefore, we decided to use self metathesis (SM) of 1-octene as a model reaction for an isomerisation susceptibility test (Scheme 5).



Scheme 5. Self-metathesis reaction of 1-octene.

Results of performed experiments are shown on Figure 10. For the reaction catalyzed by **Ru-1**, we observed instantaneous ethylene generation which ended after approximately three minutes. In opposition, reaction with **Ru-3** was still producing bubbles of gas after 15 minutes. As we have shown on Figure 10, commercially available **Ru-1** almost immediately gives full conversion (blue line). Fast decomposition of Hoveyda catalyst led to formation of large quantity of byproducts, rendering this reaction nonselective (green line). To our surprise, reactions catalyzed by **Ru-3**, achieved maximum content of SM product (82%) in the first 30 minutes of reaction exhibiting a much lower level of isomerisation (Figure 10).

Diminished isomerisation during a metathesis process is usually connected with higher stability of a given Ru alkylidene propagating species.[73–77] One of the factors affecting the rate of decomposition is the presence of ethylene, as it is known that ruthenium methylidenes are the least stable active species.[71,83–87]

Taking the above into account we decided to perform an ethylene-stability test of selected complexes based on a mea-

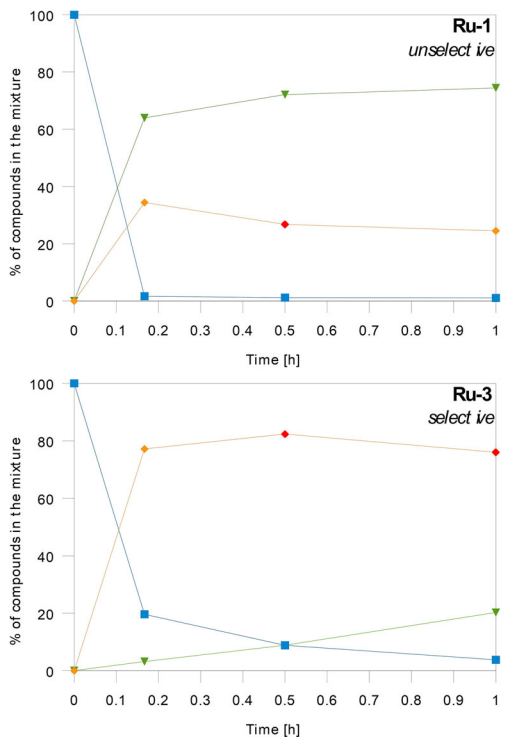
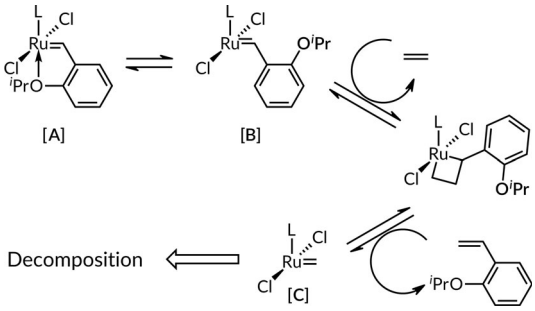


Figure 10. SM/isomerisation of 1-octene with **Ru-1** and **Ru-3**. Measurements were made by GC with tetradecane as internal standard. Conditions: 500 ppm (0.05 mol%) [Ru], neat, 80 °C (lines are visual aids and not curve fits; ■: 1-octene, ◆: 7-tetradecene, ▼: other products).



Scheme 6. Ethylene-based [Ru] initiation and decomposition pathway.

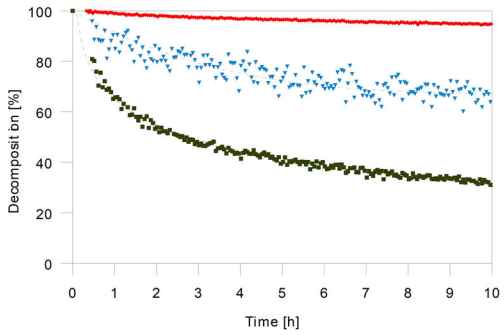


Figure 11. Stability test of studied complexes in an ethylene atmosphere. Measurements were made by ^{1}H NMR spectroscopy. Conditions: CD_2Cl_2, 40 °C, C = 18 mM. Reactions were monitored by ^{1}H NMR spectroscopy using trimetoxybenzene as an internal standard (lines are visual aids and not curve fits; ■: **Ru-1**, ▼: **Ru-3**, ◆: **Ru-4**).

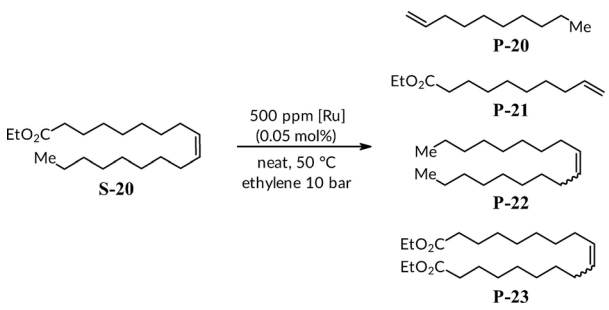
surement of amount of catalyst resting state (Scheme 6 [A]) as a function of time. To do so, we treated a solution of the respected ruthenium complex solution with 20 bars of dynamic pressure of ethylene for 20 minutes. Afterwards, the sample was monitored by ^{1}H NMR spectroscopy at 40 °C for 10 hours. The decrease of precatalyst amount in time is shown on Figure 11.

Interestingly, we observed that after 10 hours, the amount of nondecomposed **Ru-3** is almost twice as big as the sum of **Ru-1**, demonstrating the higher ethylene stability of uNHC-containing complex over the general purpose catalysts, which is also in agreement with self-metathesis results (Figure 10). However, as expected known for its superior results in ethenolysis reactions, CAAC complex **Ru-4**,[21,34] was the most stable one (Figure 11). It is worth noting that the methodology used herein is uncomplicated and easy to perform. Alternative approaches are known in the literature, which are based on performing the DEDAM RCM in an atmosphere of ethylene or with the use of ethylene pretreated catalyst solution.[87]

Ethenolysis of olefinic substrates from renewable resources

Utilization of renewable resources by the use of olefin metathesis reactions is a research topic of many groups[88] including ours.[89–91]

In the light of recent publications, ethenolysis emerges as a great method for valorisation of oleic acid derivatives.[21,35,92–94]



Scheme 7. Ethenolysis of ethyl oleate (**S-20**).

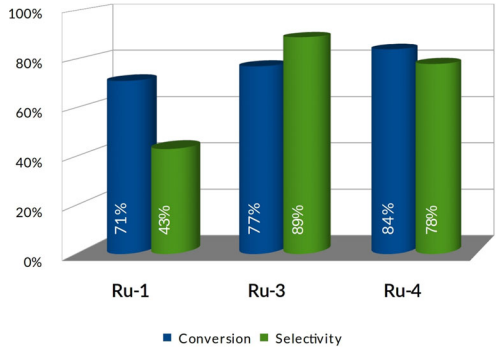


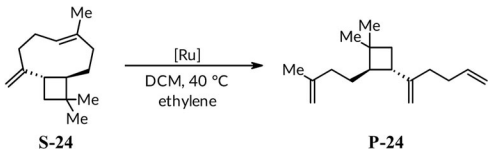
Figure 12. Ethenolysis of ethyl oleate (**S-20**). Conversion and selectivity was calculated from GC chromatogram. Conversion = 100−[(final moles of **S-20**)×100/(initial moles of **S-20**)]; Selectivity = 100×(moles of **P-20**+**P-21**)/[(moles of **P-20**+**P-21**)+(2×moles of **P-22**+**P-23**)].

Logically, we decided to explore possible use of **Ru-3** in the ethenolysis reaction of ethyl oleate (**S-20**, Scheme 7, Figure 12).

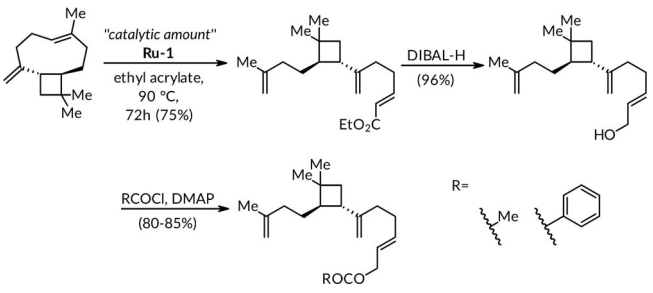
As presented above, **Ru-1** exhibits low selectivity and moderate conversion, which is in agreement with the literature.[34] Comparing ethenolysis results (Figure 12) and initiation rate in an ethylene atmosphere (Figure 11), we can see that conversion is in correlation with stability in the presence of ethylene. We were pleased to see, that under chosen conditions (ethylene grade 99.9%, all manipulations were conducted on air and the key ethenolysis process was conducted outside of the glovebox)[21] both uNHC-bearing **Ru-3** and CAAC-based **Ru-4** showed a comparable level of selectivity (89 vs. 78%) and activity (77 vs. 84%). It is worth noting, that Nascimento et al. published recently CAAC indenylidene chloride-bridged dimer catalyst.[95] Authors describe the positive impact of the quaternary carbon flanking on robustness of ruthenium complex in ethenolysis.

Encouraged by these results, we have decided to expand the scope of the reaction to different, naturally occurring compounds.

β-Caryophyllene is one of the bicyclic sesquiterpenes present in many essential oils.[96] It is one of the active ingredients of hops[97,98] and Cannabis sativa.[99] It is widely used as an additive in the food industry (characteristic spicy, pepper-like, woody, camphoraceous taste with a citrus background at 50 ppm concentrations),[100] as well as fragrance component (woody, spicy aroma).[101,102] This makes it a cheap, generally available, renewable sesquiterpene. It has an anti-inflammatory effect in mice, as well as neuroprotective, antinociceprive, and antidepressant activity in in vitro studies.[99,103–105] β-Caryophyllene is selective agonist of type-2 cannabinoid receptor (CB_2) but it is worth noting that it is not binding to type-1 receptors (CB_1). This renders it devoid of psychoactive effects. Because of those bioactive properties, its seems interesting to find an easy, scalable, and flexible method for the derivatization of β-caryophyllene. In our opinion, ethenolysis and CM of the obtained open-chain product is a viable option (Scheme 8). More-



Scheme 8. Ethenolysis of β-caryophyllene (**S-24**).



Scheme 9. **P-24** derivatives synthesized by Chicca et al..[107]

over, up to date, the only other metathetic transformation of **S-24** is ring-opening metathesis polymerisation (ROMP),[106] and ring-opening cross metathesis (RO-CM) with neat ethyl acrylate under unspecified conditions (Scheme 9).[107,108]

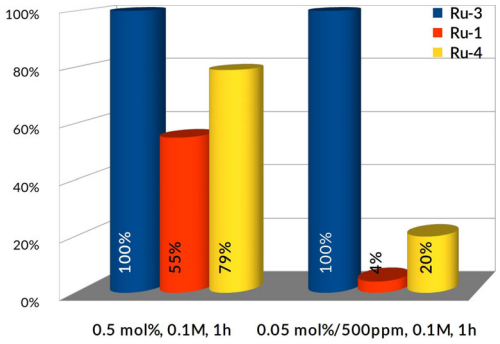
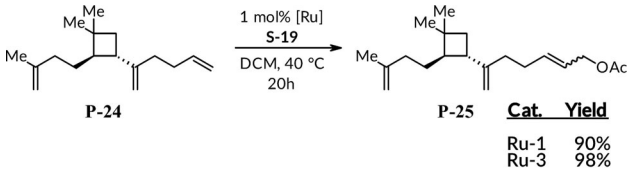


Figure 13. Ethenolysis of β-caryophyllene (**S-24**). Reactions were monitored by ^{1}H NMR spectroscopy.

We decided to use as a starting point conditions analogous to ones that we used before in RCM reactions (0.5 mol% of [Ru], C = 0.1 M, 40 °C). To our delight, after an hour under 10 bars of ethylene pressure, with **Ru-3** we achieved full conversion as well as no sign of possible dimers or other byproducts, while both **Ru-1** and **Ru-4** exhibited lower activity (55 and 79%, respectively, Figure 13). Next, we were able to further lower the loading of **Ru-3** to 500 ppm (0.05 mol%) level, in contrast to catalysts **Ru-1** and **Ru-4**, we still observed complete conversion to the expected product (TON 1797, Figure 13). However, the same reaction was not possible in neat conditions, and a further decrease of **Ru-3** loading to 250 and 100 ppm (0.025, 0.01 mol%) resulted in decreased conversions, to 68 (TON 2715) and 32% (TON 2876), respectively, even despite the use of ethylene of higher priority (Table 5).

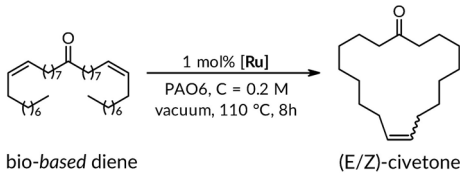
Recently Copéret et al. connected selectivity in the ethenolysis of cyclic olefins with an unsymmetrical NHC ligand bearing ruthenium catalysts.[109]



Scheme 10. Cross-metathesis of **P-24** with **S-19**.

Having optimized conditions and synthesized product (**P-24**) in hand, we performed the CM reaction of the ethenolysis product with **S-19** (Scheme 10). Choice of this derivative was connected with its role in the research of Chicca et al.[107] Those authors obtained a series of derivatives by amidation and esterification of the allylic alcohol derivative of **P-24** (Scheme 9) and proved that these derivatives are not only CB_2 agonists but also inhibits fatty acid amide hydrolase (FAAH). This type of activity is important, because FAAH is one of the primary enzymes responsible for endocannabinoid hydrolysis.[107]

Taking in account that product **P-25** was obtained in excellent isolated yield (90% for **Ru-1** and 98% in the case of **Ru-3**), we think that the ethenolysis/CM sequence (Schemes 9 and 10) is a superior and more universal method for further derivation of β-caryophyllene. Taking into account the outstanding stability of **Ru-3** under metathesis reaction conditions, and its low tendency to isomerise C–C double bonds, we tested it in



Ru-1: Yield: 31%; Selectivity: 36%; (E)/(Z): 2.5
Ru-3: Yield: 73%; Selectivity: 83%; (E)/(Z): 3.1

Scheme 11. Comparison of standard NHC catalyst **Ru-1** and uNHC bearing **Ru-3** in high-concentration RCM (HC-RCM) leading to (*E*/*Z*)-civetone.

Table 5. Ethenolysis of β-caryophyllene.[a]

[Ru]	Conditions	Conv. [%]	TON	TOF [1/h]
Ru-3	0.5 mol%, 10 bar,[b] 40 °C, 0.1 M, 1 h	100	200	200
Ru-1	0.5 mol%, 10 bar,[b] 40 °C, 0.1 M, 1 h	55	92	92
Ru-4	0.5 mol%, 10 bar,[b] 40 °C, 0.1 M, 1 h	79	154	154
Ru-3	0.5 mol%, 10 bar[b], rt, 0.1 M, 1 h	100	188	188
Ru-3	0.1 mol%, 10 bar,[b] 40 °C, 0.1 M, 1 h	100	953	953
Ru-3	0.1 mol%, 10 bar,[b] rt, 0.1 M, 1 h	72	686	686
Ru-3	0.05 mol% (500 ppm), 10 bar,[b] 40 °C, 0.1 M, 1 h	100	1797	1797
Ru-1	0.05 mol% (500 ppm), 10 bar,[b] 40 °C, 0.1 M, 1 h	4	81	81
Ru-4	0.05 mol% (500 ppm), 10 bar,[b] 40 °C, 0.1 M, 1 h	20	404	404
Ru-3	0.05 mol% (500 ppm), 10 bar,[b] rt, 0.1 M, 1 h	47	845	845
Ru-3	0.01 mol% (100 ppm), 10 bar,[b] 40 °C, 0.1 M, 1 h	32	2876	2876
Ru-3	0.025 mol% (250 ppm), 10 bar,[b] 40 °C, neat, 1 h	oligomeric products observed	–	–
Ru-3	0.01 mol% (100 ppm), 10 bar,[b] 40 °C, neat, 1 h	oligomeric products observed	–	–
Ru-3	0.025 mol% (250 ppm), 10 bar,[c] 40 °C, 0.4 M, 3 h	68	2715	905

[a] Conversion was determined by ^{1}H NMR spectroscopy. [b] Ethylene purity 99.9%. [c] Ethylene purity 99.995%.

recently discovered high-concentration RCM (HC-RCM).[110] Importantly, under harsh conditions required for the HC-RCM, **Ru-3** was giving much higher selectivity than standard symmetrical NHC bearing **Ru-1**, yielding the valuable musk macrocycle in good isolated yield (Scheme 11). As the diene substrate used in this reaction was prepared entirely from a biosourced substrate-methyl oleate,[111] it creates also the first example of use of **Ru-3** in the sustainable preparation of a macrocyclic ketone, (*E*/*Z*)-civetone, under high-concentration RCM conditions.[110]

Conclusion

An 2-isopropoxybenzylidene ruthenium complex featuring new uNHC ligand containing phenanthrene N-substituent has been successfully synthesized from the corresponding azolium salt. The new complex (**Ru-3**) has been fully characterized and tested in a number of metathesis reactions. **Ru-3** exhibits the same initiation rate and activity in the model RCM reactions as commercially available Hoveyda–Grubbs II-generation complex (**Ru-1**), which is in contrast to other uNHC-based Ru catalysts. Interestingly, it contrasted from **Ru-1** by being nonreactive at low temperature towards some 2-allyl-1,3-diketones, and it is substantially less prone to double-bond isomerisation in homometathesis of the α-olefin–1-octene, as well as affords improved yield in the formation of challenging, medium-sized rings (7,8-membered).

Importantly, **Ru-3** was significantly more stable than standard general-purpose catalyst in the presence of ethylene. As such, **Ru-3** outperformed **Ru-1** in the ethenolysis of biorenewable feedstock, ethyl oleate, and β-caryophyllene, delivering results comparable or better to the state of the art CAAC-based **Ru-4**. The improved selectivity and high robustness of **Ru-3** in ethylene facilitated the first ethenolysis of naturally occurring caryophyllene affording useful derivatives in outstanding yields. The above properties seem to be unique and may open practical applications of this complex.[112]

Finally, **Ru-3** gave much better results in high-concentration RCM (HC-RCM) synthesis of *E*/*Z*-civetone, exhibiting outstanding selectivity as compared with **Ru-1**.[110]

Experimental Section

General information

If not noted otherwise, all reactions were carried out under argon atmosphere in oven dried glassware (overnight, 135 °C) with magnetic stirring. Commercially available chemicals were used without further purification. Hoveyda II (**Ru-1**) catalyst was purchased from STREM Chemicals. **Ru-2** and **Ru-4** were synthesized by known protocols.[32,46] Solvents were purified by Solvent Purification System, Mbraun MB-SPS-800. Analytical TLC was performed on Merck silica gel 60 with fluorescent indicator UV254 TLC plates. The flash column chromatography was performed using Merck silica gel 60 (particle size: 0.040–0.063 mm, 230–400 mesh) typically using *n*-hexane/ethyl acetate the eluent system. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer with diamond ATR accessory, wave numbers are in cm^{-1}. Elemental Analyses (EA) were provided by the EA analytical laboratory at the Institute of Organic Chemistry, Polish Academy of Sciences (PAS). HRMS were provided by the Faculty of Chemistry University of Warsaw or analytical laboratory at the Institute of Organic Chemistry, PAS. NMR spectra were recorded on an Agilent 400-MR DD2 400 MHz spectrometer. NMR chemical shifts are reported in ppm downfield from solvent residual peak ($\delta = 7.26$ and 77.16 ppm for ^1H and ^{13}C in $CDCl_3$, $\delta = 5.32$ and 54.00 ppm for ^1H and ^{13}C in CD_2Cl_2). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, qui: quintuplet, m: multiplet), coupling constant (*J* in Hz) and integration. Deuterated solvents were purchased from Sigma–Aldrich, stored over molecular sieves used without further purification (chloroform) or distilled under inert atmosphere from CaH_2 (dichloromethane). ^{13}C NMR spectra were recorded at 100 MHz using broadband proton decoupling and chemicals shifts are reported in ppm using residual solvent peaks as a reference.

Further details of experimental procedures and characterization data are presented in the Supporting Information.

[3-Benzyl-1-(10-phenyl-9-phenanthryl)]-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium (Ru-3)

A 50 mL Schlenk flask was charged with 213.4 mg of imidazolidinium salt **7** (0.47 mmol, 1.1 equiv) and dried under vacuum in 70 °C for 30 min. Next, it was cooled to room temperature and 20 mL of toluene were added. To the resulted suspension, a solution of 0.3 mL 25% KO*t*Am was added and after disappearance (≈2–3 min), 259 mg of Hoveyda I (0.43 mmol, 1 equiv) was added and the Schlenk flask was inserted into a preheated oil bath (70 °C). The reaction was monitored by TLC and after ≈20 min (full conversion) the Schlenk flask with the mixture was inserted into an ice bath. After cooling the mixture below room temperature, *n*-hexane was added (1 part for 2 parts of mixture) and the solution was chromatographed with 0→10→20% EtOAc/*n*-hexane. A greenish–brown band was collected and after evaporation, the solid was recrystallized from DCM/MeOH affording 230 mg as a brownish-green microcrystalline solid (72%). ^1H NMR (400 MHz, $CDCl_3$) $\delta =$ 16.60 (s, 1H), 8.92 (d, $J = 8.3$ Hz, 1H), 8.80 (d, $J = 8.3$ Hz, 1H), 8.13 (d, $J = 8.2$ Hz, 1H), 7.79 (dt, $J = 16.0$, 8.1 Hz, 3H), 7.71–7.62 (m, 3H), 7.56 (dt, $J = 16.7$, 7.5 Hz, 3H), 7.44 (t, $J = 6.6$ Hz, 4H), 7.40–7.29 (m, 3H), 6.86 (d, $J = 8.3$ Hz, 1H), 6.64 (t, $J = 7.5$ Hz, 1H), 6.24 (d, $J =$ 7.5 Hz, 1H), 5.81–5.50 (m, 2H), 5.21–5.04 (m, 1H), 3.80 (q, $J = 11.2$, 9.9 Hz, 1H), 3.47–3.33 (m, 2H), 3.10 (q, $J = 12.8$, 11.1 Hz, 1H), 1.75 ppm (d, $J = 6.1$ Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) $\delta =$ 289.8, 210.6, 152.8, 143.4, 138.2, 136.2, 135.9, 135.0, 133.3, 131.8, 130.9, 130.7, 129.8, 129.7, 129.5, 129.3, 129.2, 128.8, 128.5, 128.3, 127.9, 127.9, 127.8, 127.4, 127.1, 125.8, 122.8, 122.5, 122.3, 122.3, 112.8, 75.3, 56.2, 53.0, 47.6, 22.3, 22.2 ppm; IR (diamond tip) $\tilde{\nu} = 3059$, 2987, 2889, 1587, 1572, 1472, 1436, 1419, 1381, 1263, 1214, 1110 cm^{-1}; M.p. 230.5 °C, decomposition; HRMS: calcd: ($C_{40}H_{35}N_2ORu^+$): 661.1798; found: 661.1795; Difference: $\delta =$ 0.45 ppm; m.p. 230.5 °C, decomposition; EA: elemental analysis calcd (%) for $C_{40}H_{36}Cl_2N_2ORu$: C, 65.57; H, 4.95; Cl, 9.68; N, 3.82; found: C, 65.53; H, 5.06; Cl, 9.66; N, 3.85.

Acknowledgements

We wish to thank the National Science Centre (Poland) for the NCN MAESTRO Grant No. DEC-2012/04A/ST5/00594. The study was carried out at the Biological and Chemical Research Centre, University of Warsaw, established within the project co-

financed by the European Union from the European Regional Development Fund under the Operational Programme Innovative Economy, 2007–2013. Authors want to thank: Dr. P.I. Jolly, Dr. K. Grudzień, Dr. A. Sytniczuk, Dr. G. Szczepaniak, M. Milewski, and Dr. M. Michalska for manuscript proofreading and helpful advice.

Conflict of interest

The authors declare no conflict of interest.

Keywords: caryophyllene · catalysis · ethenolysis · isomerization · ruthenium

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[110] Although the synthesis and full characterisation of Ru-3 is described for the first time here, it shall be noted that **Ru-3** has been previously tested in HC-RCM synthesis of valuable musk-smelling macrocyclic lactones with very good results. See: A. Sytniczuk, M. Dąbrowski, Ł. Banach, M. Urban, S. Czarnocka-Śniadała, M. Milewski, A. Kajetanowicz, K. Grela, *J. Am. Chem. Soc.* **2018**, *140*, 8895 – 8901. However, the synthesis of macrocyclic ketone with **Ru-3** (Scheme 11) was not reported previously.
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Manuscript received: October 4, 2019
Revised manuscript received: December 2, 2019
Version of record online: ■■ ■■, 0000

FULL PAPER

Olefin Metathesis

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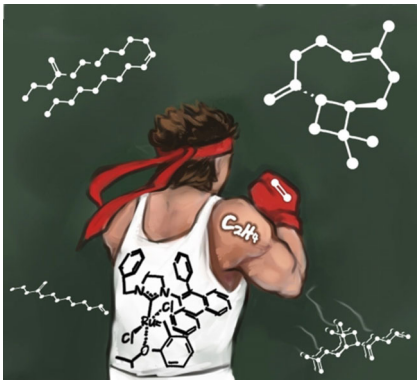
■■ – ■■

In a Quest for Selectivity Paired with Activity: A Ruthenium Olefin Metathesis Catalyst Bearing an Unsymmetrical Phenanthrene-Based N-Heterocyclic Carbene



Selective, but still active! A ruthenium catalyst containing phenanthrene-based unsymmetrical *N*-heterocyclic carbene ligand has been synthesized. Its anomalous reactivity at 40 °C contrasts known *N*-benzyl Hoveyda-type complexes that need high temperatures to operate. Simultaneously, it keeps high selectivity towards olefin metathesis products (see graphic).