

## Article

# Self-Supported Polymeric Ruthenium Complexes as Olefin Metathesis Catalysts in Synthesis of Heterocyclic Compounds

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**Abstract:** New ruthenium olefin metathesis catalysts containing N-heterocyclic carbene (NHC) connected by a linker tether to a benzylidene ligand were studied. Such obtained self-chelated Hoveyda–Grubbs type complexes existed in the form of an organometallic polymer but could still catalyze olefin metathesis after being dissolved in an organic solvent. Although these polymeric catalysts exhibited a slightly lower activity compared to structurally related nonpolymeric catalysts, they were successfully used in a number of ring-closing metathesis reactions leading to a variety of heterocyclic compounds, including biologically and pharmacologically related analogues of cathepsin K inhibitor and sildenafil (Viagra™). In the last case, a good solubility of a polymeric catalyst in toluene allowed the separation of the product from the catalyst via simple filtration.

**Keywords:** olefin metathesis; ruthenium; self-supported polymeric complex



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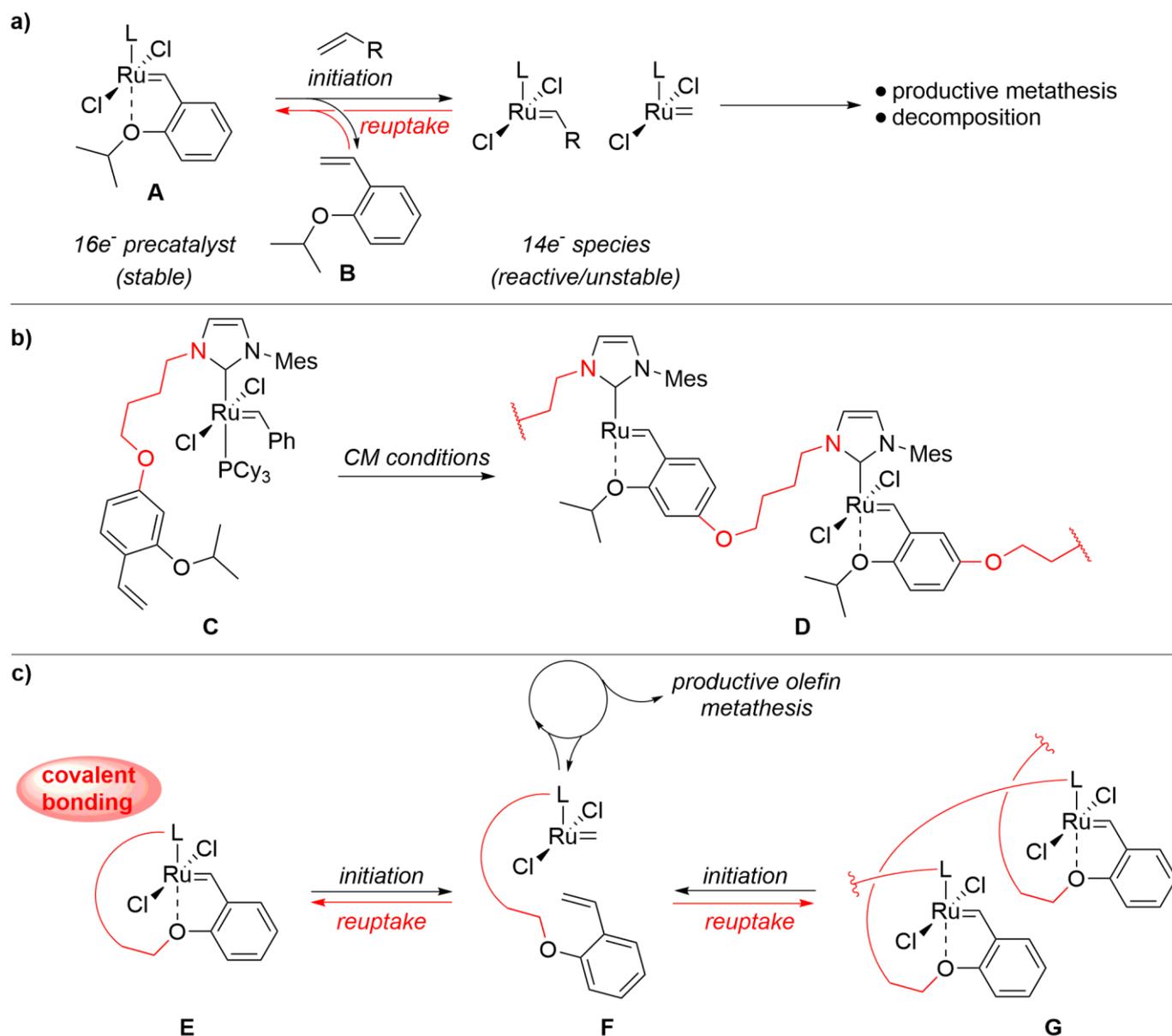
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## 1. Introduction

Unquestioned is the fact that ruthenium olefin metathesis precatalysts initiation requires first the dissociation of a neutral ligand, which after a single turnover leads to the release of  $14e^-$  propagating species [1,2]. An illustrious example of this process is the initiation step in Hoveyda–Grubbs catalysts, which concerns the dissociation of the 2-(isopropoxy)benzylidene ligand and the release of 2-(isopropoxy)styrene moiety [3,4]. In 1999, it was shown that the release of this styrene was reversible, meaning that the created  $14e^-$  species could reuptake the styrene back, leading to the re-creation of the former complex [5]. This process was called the release/reuptake (or “boomerang”) mechanism (Figure 1a) and since then, the effect has been carefully studied [6–11]. However, the results of experiments brought no consensus about the existence and importance of the effect. The studies from 2008 depicted an OM reaction in the presence of deuterium-labeled styrene leading to the reisolation of a Hoveyda–Grubbs type precatalyst containing the labeled benzylidene ligand with decent yield [7]. In 2014, Fogg carried out complementary experiments using a  $^{13}C$ -labeled Hoveyda–Grubbs catalyst and the results provided evidence of the existence of the boomerang effect [10]. On the other hand, the investigation of this effect in low-loading reaction conditions revealed the existence of the boomerang mechanism questionable. The utilization of a fluorophore-tagged Hoveyda–Grubbs complex by Plenio did not show evidence of the release–reuptake mechanism; however, it should be noticed that the complex he used belonged to the fast-activating EWG-substituted Hoveyda–Grubbs class of complexes [8]. In 2020, we described an application of the ammonium-group-tagged Hoveyda–Grubbs type catalyst immobilized on metal–organic frameworks (MOFs) [11]. The structure contained ammonium tags on both the NHC and benzylidene parts. To show the possibility of the boomerang effect, the MOF support was doped with an ammonium-tagged styrene derivative. The results showed an ambiguous behavior of this system in terms of a better stability at the cost of a decrease of reactivity in comparison to a nondoped MOF support.



**Figure 1.** Release/reuptake in olefin metathesis catalysts. (a) The schematic representation of the boomerang mechanism. (b) Polymeric self-supported ruthenium complex described by Sang-gi. (c) Idea of the boomerang effect in Ru complexes containing a covalent linker between NHC and benzylidene moieties.

In 2008, Sang-gi described a polymeric ruthenium structure that contained a covalent linker between NHC ligand and alkoxybenzylidene moiety based on an additional ether function in the aromatic part (Figure 1b) [12]. The authors claimed that during olefin metathesis with complex **C**, they obtained the polymeric, self-supported structure **D**. Considering the previous reports, we came up with an idea to investigate the boomerang mechanism based on the scaffold of a precatalyst containing the covalent bond between ligand L and alkoxybenzylidene (Figure 1c). Based on Sang-gi's results, we expected that this kind of structure upon reuptake process could lead to the polymeric complex (intermolecular complex **G**); however, the creation of a macrocyclic ruthenium complex (intermolecular complex **E**) was also possible, as described by Golder and co-workers [13,14].

Inspired by these results, we proposed the structure containing an aliphatic linker between the benzyl moiety on the NHC part and the benzylidene ligand via a ruthenium-

chelating oxygen atom (Figure 2). The choice of this kind of structure endeavored to reconcile the simplicity of the ligand synthesis and its activity [15–19]. We assumed that the length of six to eight carbons of linker could have been sufficient to furnish the macrocyclic structures; however, we did not reject the possibility of the creation of polymeric species.

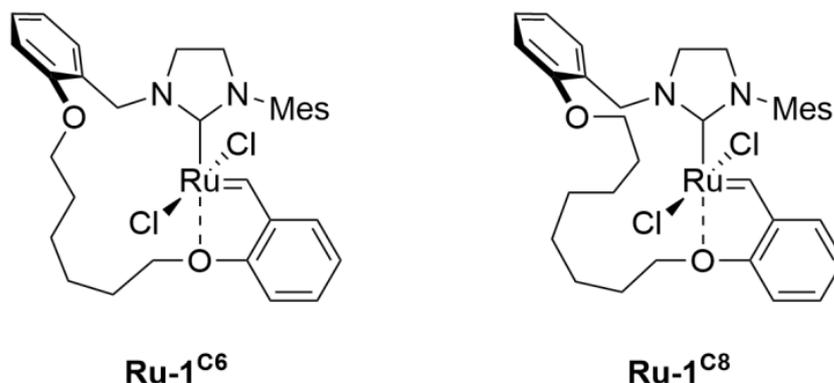


Figure 2. Proposed structures of macrocyclic ruthenium complexes.

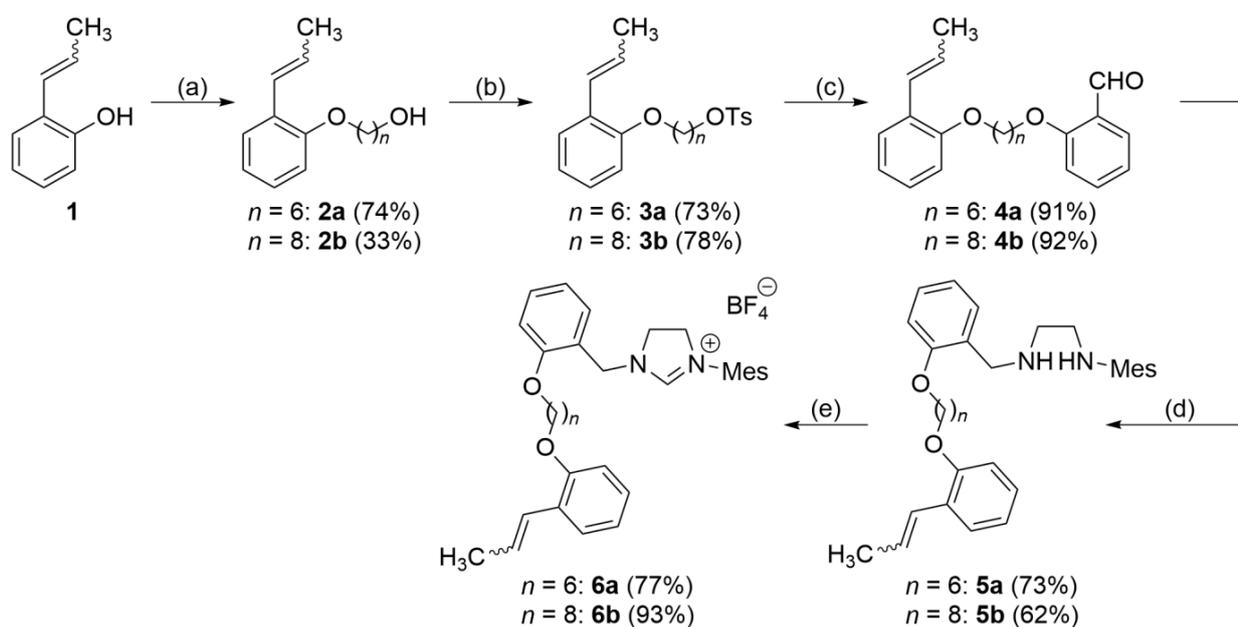
## 2. Results

The synthesis started from *O*-alkylation of 2-(prop-1-enyl)phenol (**1**) with corresponding terminal bromoalcohols (C6 and C8) providing the desired products **2a** and **2b** with moderate yields. The transformation of hydroxyl to tosyloxy function followed by another *O*-alkylation with 2-salicylaldehyde led to the formation of ethers **4a** and **4b** with good yields. The next steps provided an imidazoline core and utilized the hydroamination reaction with *N*-mesitylethylenediamine, furnishing the diamine products with good yields, followed by condensation with triethylorthoformate to provide the final ligand precursors **6a** and **6b** as imidazolium tetrafluoroborates (Scheme 1). Having both ligand precursors in hand, we obtained the Grubbs type second-generation complexes (Scheme 2). The deprotonation of the corresponding imidazolium salts with *t*BuOK followed by the addition of the Grubbs first-generation precatalyst delivered the desired complexes **Ru-2<sup>C6</sup>** and **Ru-2<sup>C8</sup>** with acceptable yields.

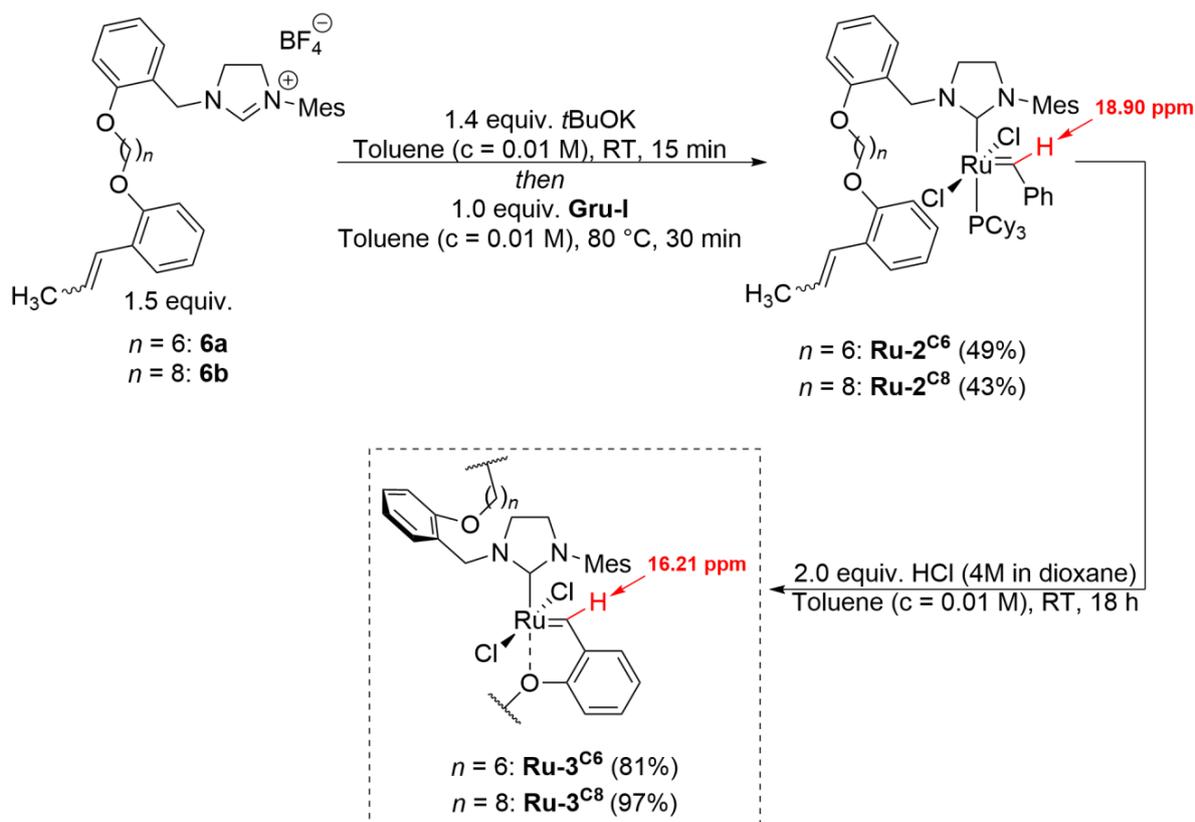
To create the proposed structure of ruthenium complexes, we decided to utilize common methods such as the addition of CuCl or submission under OM conditions; nevertheless, none of this led to the obtention of macrocyclic nor polymeric ruthenium species. Thus, we decided to use HCl, which we supposed could easily protonate the phosphine ligand and force the exchange of the benzylidene moieties. As we suspected, this approach converted the second generation precatalyst to produce the self-supported polymeric species **Ru-3<sup>C6</sup>** and **Ru-3<sup>C8</sup>** without any traces of macrocyclic ruthenium structures.

The polymeric Ru compounds exhibited a good solubility in many organic solvents such as toluene, chlorinated solvents, and ethyl acetate; however, it could easily precipitate from *n*-hexane or *n*-pentane. The nuclear magnetic resonance analysis of the obtained complexes showed a shifting of the benzylidene signal from 18.90 ppm for **Ru-2<sup>C6</sup>** to a broad set of signals at 16.21 ppm for **Ru-3<sup>C6</sup>**, which corresponds to *O*-chelated Hoveyda-Grubbs type second-generation complexes. The fact that this signal was broad and was composed of several singlet signals could be interpreted as undefined polymeric species.

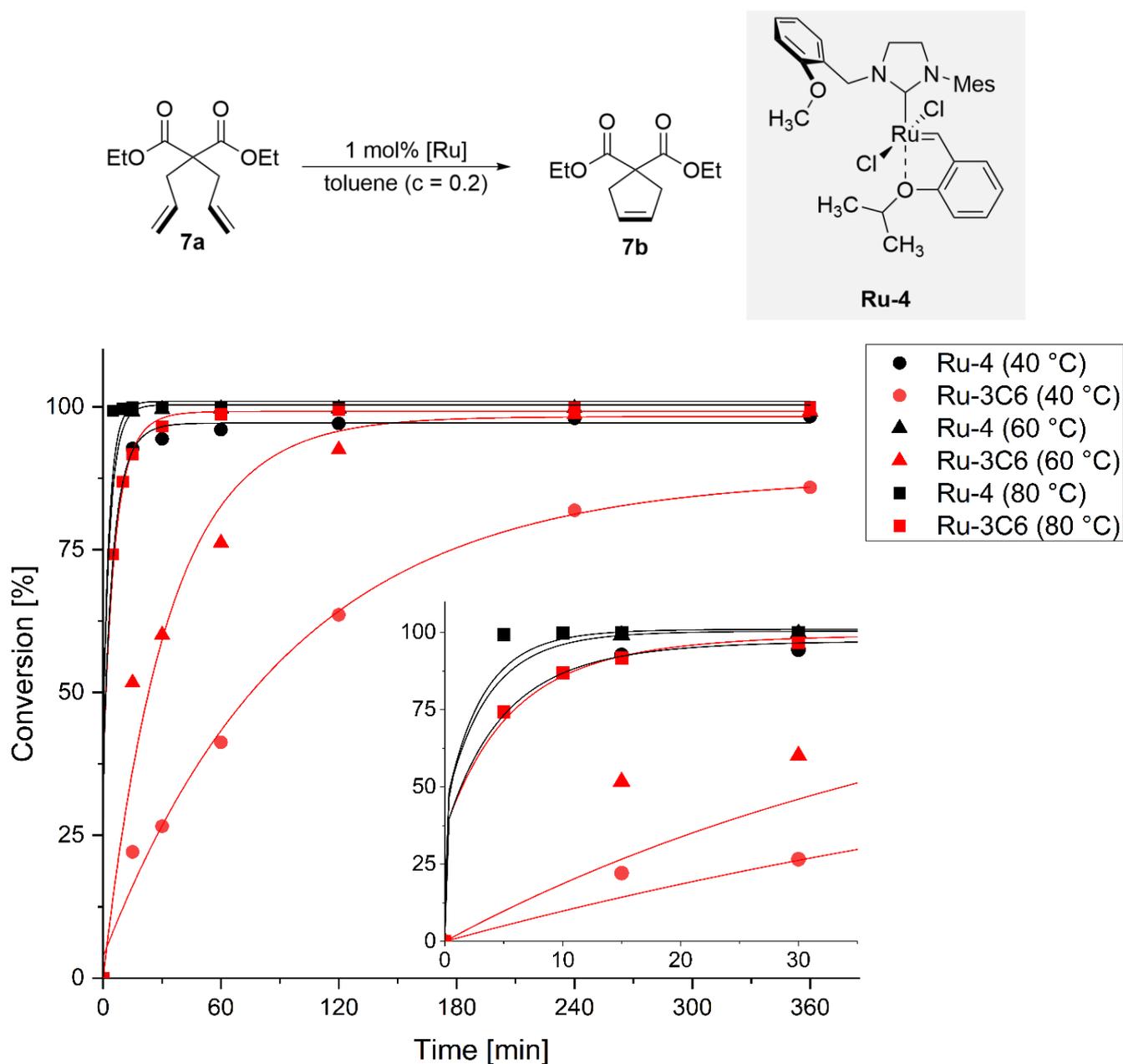
We compared the activity of the obtained polymeric ruthenium complexes with that of the closest structural analog, **Ru-4**. For further research, we chose the complex **Ru-3<sup>C6</sup>**. We performed the RCM reaction of diethyl diallylmalonate (**7a**) using 1 mol% of pre-catalyst (Figure 3) and calculated the turnover frequency (TOF) parameter to quantify and compare the activity of the complexes (Table 1).



**Scheme 1.** Synthetic pathways for the NHC ligand precursors. Conditions: (a) Br-(CH<sub>2</sub>)<sub>6</sub>-OH or Br-(CH<sub>2</sub>)<sub>8</sub>-OH, K<sub>2</sub>CO<sub>3</sub>, DMF, 80 °C, 16 h; (b) TsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to RT, 16 h; (c) salicylaldehyde, K<sub>2</sub>CO<sub>3</sub>, DMF, 60 °C, 16 h; (d) *N*-mesityl ethylenediamine, Na<sub>2</sub>SO<sub>4</sub>, HCOOH (cat.), MeOH, RT, 24 h then NaBH<sub>4</sub>, MeOH, RT, 24 h; (e) NH<sub>4</sub>BF<sub>4</sub>, TEOF, 105 °C, 18 h. RT—room temperature, TEOF—triethylorthoformate.



**Scheme 2.** Synthesis of 2nd-generation Grubbs type precatalysts and polymeric species **Ru-3<sup>C6</sup>** and **Ru-3<sup>C8</sup>**. **Gru-I**—benzylidene-bis(tricyclohexylphosphine)dichlororuthenium, RT—room temperature.



**Figure 3.** Reaction course time plot of RCM of diethyl diallylmalonate (7a). Black marks: **Ru-4**, red marks: **Ru-3C6**. Circles: reaction performed at 40 °C; triangles: reaction performed at 60 °C; squares: reaction performed at 80 °C. The inset shows the first 30 min period in detail. Lines are for visual aid only. Conversion was calculated by GC analysis with internal standard (1,2,4,5-tetramethylbenzene).

**Table 1.** Turnover frequency parameter calculated on the basis of reaction course time plot (Figure 3). For reactions performed at 40 and 60 °C, TOF is given after 15 min; for reactions performed at 80 °C, TOF is given after 5 min.

[Ru]	TOF (T = 40 °C, t = 15 min) (s <sup>-1</sup> )	TOF (T = 60 °C, t = 15 min) (s <sup>-1</sup> )	TOF (T = 80 °C, t = 5 min) (s <sup>-1</sup> )
<b>Ru-3C6</b>	$2.46 \cdot 10^{-2}$	$5.74 \cdot 10^{-2}$	$2.47 \cdot 10^{-1}$
<b>Ru-4</b>	$1.03 \cdot 10^{-1}$	$1.10 \cdot 10^{-1}$	$3.31 \cdot 10^{-1}$

The polymeric species exhibited a very low activity compared to the Hoveyda–Grubbs type complex **Ru-4**, which performed almost a quantitative conversion within 2 h at 40 °C

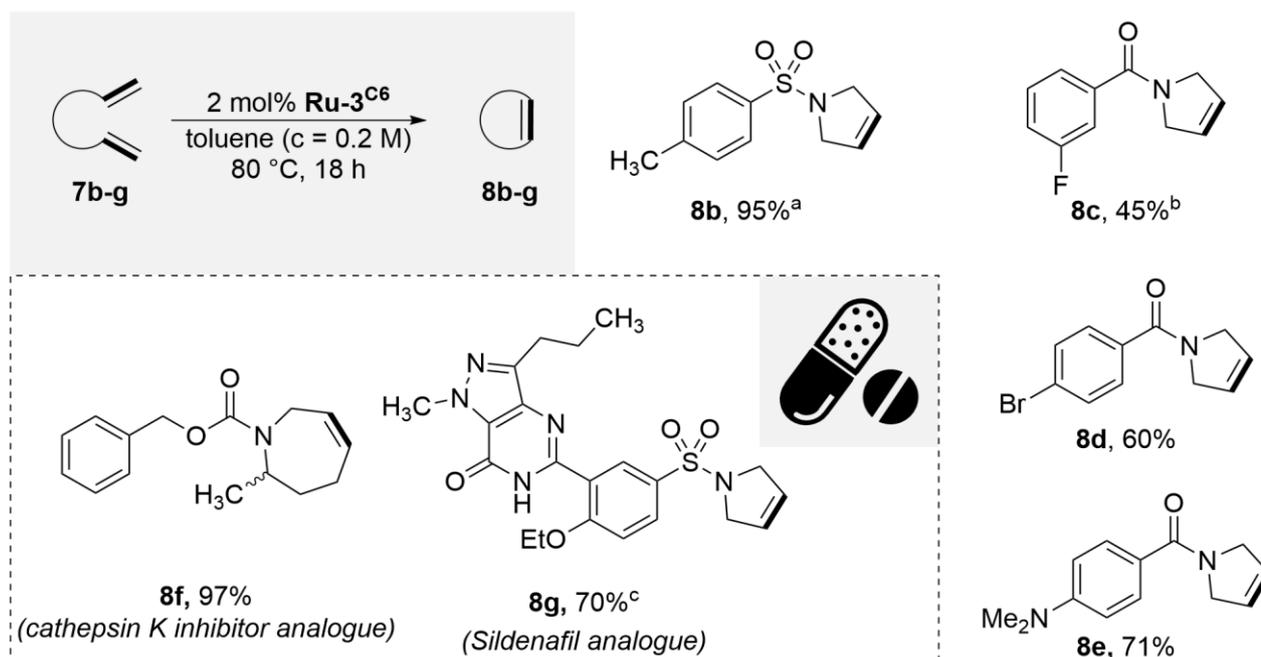
and in 15 min at 60 °C. The TOFs calculated for 15 min of reactions at 40 and 60 °C were an order of magnitude lower for the polymeric **Ru-3<sup>C6</sup>** compared to **Ru-4**. The elevation of the temperature to 80 °C significantly increased the activity of **Ru-3<sup>C6</sup>** as these conditions allowed to obtain a quantitative conversion in 2 h, which was comparable with that of **Ru-4** at 40 °C. Moreover, the TOF measured for **Ru-3<sup>C6</sup>** at 80 °C was comparable to the one measured for **Ru-4** at 40 °C ( $2.47 \cdot 10^{-1} \text{ s}^{-1}$  vs.  $1.03 \cdot 10^{-1} \text{ s}^{-1}$ , respectively) and very similar to **Ru-4** at 80 °C ( $1.03 \cdot 10^{-1} \text{ s}^{-1}$ ). This phenomenon can be explained by a very low rate of depolymerization process of **Ru-3<sup>C6</sup>** to metathetically active species at lower temperatures (for a process scheme: see Figure 1c, reaction G to F). It places the polymeric ruthenium species in a family of high-temperature activating ruthenium precatalysts.

As the properties of the ruthenium complex allowed to precipitate it from the reaction mixture, we decided to investigate the possibility of its recycling. To do so, we performed a standard RCM reaction of **7a** at 80 °C for 2 h followed by a precipitation of polymeric species with *n*-pentane. The first run provided almost full conversion, but the amount of recycled catalyst showed a significant loss of polymeric material as only 38% of the initial amount was recovered (Table 2, entry 1). In the next run, the conversion slightly decreased with a moderate improvement on Ru recycling (Table 2, entry 2). The third run showed a significant decrease in the activity (only 57% of the conversion) of the polymeric complex, therefore we did not perform further recycling runs (Table 2, entry 3). The results indicated that these conditions (including the polymeric nature of the complex) did not promote or support the boomerang effect. The first indication was that the recovery of Ru species was not quantitative, thus it was not possible to assert whether metathetically active monomeric species turned back into polymeric form (and also how much polymeric Ru formed a monomeric complex). Second, it seemed that the catalyst quickly decomposed since a low activity was noticed already in third run; however, it was still comparable with the recycling results obtained by Sang-gi [7,20].

**Table 2.** Catalyst recycling in ring-closing metathesis of diethyl diallylmalonate (**7a**) using **Ru-3<sup>C6</sup>** complex. Reactions were carried out using 1.0 mol% of **Ru-3<sup>C6</sup>** at 80 °C in toluene (c = 0.2 M).  
<sup>a</sup> Conversion was calculated by GC analysis with internal standard (1,2,4,5-tetramethylbenzene).  
<sup>b</sup> Yield of Ru recycling was calculated as a percentage ratio of precatalyst mass used compared to next run.

Entry	Scale (mmolL)	Mass of Ru Used in Reaction [21]	Conversion (%) <sup>a</sup>	Yield of Ru Recycling (%) <sup>b</sup>
1	5.00	32.7	>99	38
2	1.91	12.5	95	66
3	1.27	8.3	57	-

Despite the unsuccessful recovery of the polymeric Ru complex, we evaluated the synthetic utility of this catalyst in the ring-closing metathesis providing heterocyclic compounds (Scheme 3). We performed the reaction with a number of aromatic amides and sulfonamides to produce 2,5-dihydropyrrolyl-containing products. *N*-tosyl dihydropyrrole (**8b**) was obtained with an excellent yield and short reaction time (2 h). Moreover, benzoyl-substituted pyrroles containing functional groups such as fluorine (**8c**), bromine (**8d**), and dimethylamino substituent (**8e**) could be easily produced in moderate to good yields. More importantly, the polymeric complex could be utilized in the synthesis of biologically relevant heterocyclic structures. The seven-membered ring cathepsin K inhibitor analogue **8f** [22] was obtained with a very good yield and the sildenafil analogue **8g** was also synthesized in acceptable yield [23,24] (a higher catalyst loading was used—5 mol%). Moreover, since product **8g** was not soluble in toluene (in contrary to polymeric ruthenium complex **Ru-3<sup>C6</sup>**), we exploited this condition to purify the compound via simple filtration, to obtain an analytically pure product without the utilization of column chromatography.



**Scheme 3.** Scope and limitation studies on synthesis of heterocyclic compounds via ring-closing metathesis reaction. Standard condition: 2 mol% of **Ru-3<sup>C6</sup>**, toluene (c = 0.2 M), 80 °C, 18 h. The yields correspond to the isolated product. <sup>a</sup> 1 mol% of **Ru-3<sup>C6</sup>**, 2 h of reaction time. <sup>b</sup> 1 mol% of **Ru-3<sup>C6</sup>**. <sup>c</sup> 5 mol% of **Ru-3<sup>C6</sup>**.

### 3. Conclusions

This paper provided a design and synthesis of a new ligand containing a linker tethering the NHC precursor part with the benzylidene moiety. Applying the ligand on first-generation Grubbs type catalyst successfully provided a second-generation Grubbs type complex, which could be further transformed to a polymeric self-supported second-generation Hoveyda–Grubbs type. The polymeric species exhibited a lower activity compared to structurally similar nonpolymeric precatalysts; however, it could be successfully used in metathetical transformations such as ring-closing metathesis, providing a variety of heterocyclic compounds, also biologically and pharmacologically related, in which case the solubility properties of polymer allowed to ease the purification of products. Since these examples did not confirm a “boomerang” effect, further studies on the impact of a linker architecture and properties are under way.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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