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

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 13C-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.
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 imidazolinium tetrafluoroborates (Scheme 1). Having both ligand precursors in hand, we obtained the Grubbs type second-generation complexes (Scheme 2). The deprotonation of the corresponding imidazolinium salts with tBuOK followed by the addition of the Grubbs first-generation precatalyst delivered the desired complexes Ru-2C6 and Ru-2C8 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 formation 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-3C6 and Ru-3C8 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-2C8 to a broad set of signals at 16.21 ppm for Ru-3C6, 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-3C6. 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$_2$)$_n$-OH or Br(CH$_2$)$_n$-OH, K$_2$CO$_3$, DMF, 80 °C, 16 h; (b) TsCl, Et$_3$N, CH$_2$Cl$_2$, 0 °C to RT, 16 h; (c) salicylaldehyde, K$_2$CO$_3$, DMF, 60 °C, 16 h; (d) N-mesitylethylenediamine, Na$_2$SO$_4$, HCOOH (cat.), MeOH, RT, 24 h then NaBH$_4$, MeOH, RT, 24 h; (e) NH$_4$BF$_4$, TEOF, 105 °C, 18 h. RT—room temperature, TOEF—triethylorthoformate.

Scheme 2. Synthesis of 2nd-generation Grubbs type precatalysts and polymeric species Ru-3$^{C6}$ and Ru-3$^{C8}$. Gru-I—benzylidene-bis(tricyclohexylphosphine)dichlororuthenium, RT—room temperature.
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-3C6 compared to Ru-4. The elevation of
the temperature to 80 °C significantly increased the activity of Ru-3C6 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-3C6 at 80 °C was comparable to the
one measured for Ru-4 at 40 °C (2.47 · 10⁻¹ s⁻¹ vs. 1.03 · 10⁻¹ s⁻¹, respectively) and very
similar to Ru-4 at 80 °C (1.03 · 10⁻¹ s⁻¹). This phenomenon can be explained by a very
low rate of depolymerization process of Ru-3C6 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-3C6
complex. Reactions were carried out using 1.0 mol% of Ru-3C6 at 80 °C in toluene (c = 0.2 M).

| Entry | Scale (mmol) | Mass of Ru Used in Reaction [21] | Conversion (%) a | Yield of Ru Recycling (%) b |
|-------|--------------|---------------------------------|-----------------|---------------------------|
| 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 com-
ounds (Scheme 3). We performed the reaction with a number of aromatic amides and
sulfonamides to produce 2,5-dihydropyrrolyl-containing products. N–tosyl dihydropyr-
role (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 bi-
ologically 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-3C6), we exploited this condition to purify the compound via simple filtration,
to obtain an analytically pure product without the utilization of column chromatography.
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) 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 contrast to polymeric ruthenium complex Ru-3C6), 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-3C6, toluene (c = 0.2 M), 80 °C, 18 h. The yields correspond to the isolated product. a 1 mol% of Ru-3C6, 2 h of reaction time. b 1 mol% of Ru-3C6. c 5 mol% of Ru-3C6.

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.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal12101087/s1, Table S1. Gas chromatography data. Table S2. Setup of recycling reactions with reagent amounts. Table S3. Gas chromatography data [25–33].

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