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Fast Initiating Furan-Containing Hoveyda-Type Complexes: Synthesis and Applications in Metathesis Reactions

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Abstract: Two new ruthenium complexes with chelating-ether benzylidene ligands bearing a furan moiety were synthesized and characterized, including X-ray crystallography. They initiated fast, also at 0 °C, and were found to be highly active in a variety of ring-closing, ene-yne, and cross-metathesis reactions, including an active pharmaceutical ingredient (API) model, which makes them good candidates for the transformation of complex polyfunctional compounds that require mild reaction conditions.

Keywords: homogeneous catalysis; olefin metathesis; ring-closing metathesis; ruthenium; ligands

Citation: Nadirova, M.; Zieliński, A.; Malinska, M.; Kajetanowicz, A. Fast Initiating Furan-Containing Hoveyda-Type Complexes: Synthesis and Applications in Metathesis Reactions. *Chemistry* **2022**, *4*, 786–795. https://doi.org/10.3390/chemistry4030056

Academic Editors: Maria Luisa Di Gioia, Luísa Margarida Martins and Isidro M. Pastor

Received: 30 June 2022
Accepted: 3 August 2022
Published: 9 August 2022

1. Introduction

In just a few decades, the olefin metathesis evolved from a chemical curiosity discovered accidentally in the 1960s to a useful methodology known to virtually every chemist [1,2]. This was possible due to understanding its mechanism [3], as well as the development of well-defined catalysts based on tungsten, molybdenum, and ruthenium [4–7]. The latter owe their popularity to their high stability in the presence of moisture and oxygen, tolerance to most known functional groups, mild reaction conditions, and the possibility of fine-tuning their structure to control chemical properties. In this context, N-heterocyclic carbenes (NHCs) [8,9] and their analogues, *viz.* unsymmetrical N-heterocyclic carbenes (uNHCs) [10] and cyclic (alkyl) (amino) carbenes (CAACs) [11] have received the most attention (Figure 1a). Modifications of the benzylidene ligands in Hoveyda–Grubbs-type complexes also offer wide possibilities to control the catalytic properties. Therefore, the introduction of electron-withdrawing [12,13] or bulky substituents (the latter in the *ortho* position to the O*i*Pr group) [14] to the aromatic ring of the benzylidene ligand accelerates the initiation rate, while the replacement of the chelating oxygen atom with sulfur [15–17], selenium [18,19], or nitrogen [20–22] results in latent catalysts activated by light [23,24] or temperature [24]. The structure of the substituent on the chelating oxygen atom also plays an important role. Replacement of the isopropyl substituent with the smaller methyl group (**Ru5**, Figure 1b) had a significant impact on the activity and stability of the resulting complex [25,26]. The larger isopropyl substituent not only facilitates the dissociation of the oxygen atom from Ru during initiation, but also allows for the more effective protection of the metal center from undesirable side reactions leading to catalyst decomposition. On the other hand, replacement of the *i*Pr group with the phenyl one reduced the steric bulk and, at the same time, decreased the donation of diaryl ether oxygen atoms, leading to stable and rapidly initiating catalysts (**Ru6**) [27]. Recently, this structural motif has been applied to fast initiating *Z*-selective catalysts developed by Grubbs [28,29]. Further modifications of the alkyl substituent were independently conducted by Grubbs [30], Diver [31], and Grela [32]. Grubbs et al. studied complexes bearing various small to large substituents at the chelating oxygen (e.g., **Ru7**) and observed their impact on the strength and length of the Ru-O bond, as well as the catalyst initiation rate [30].

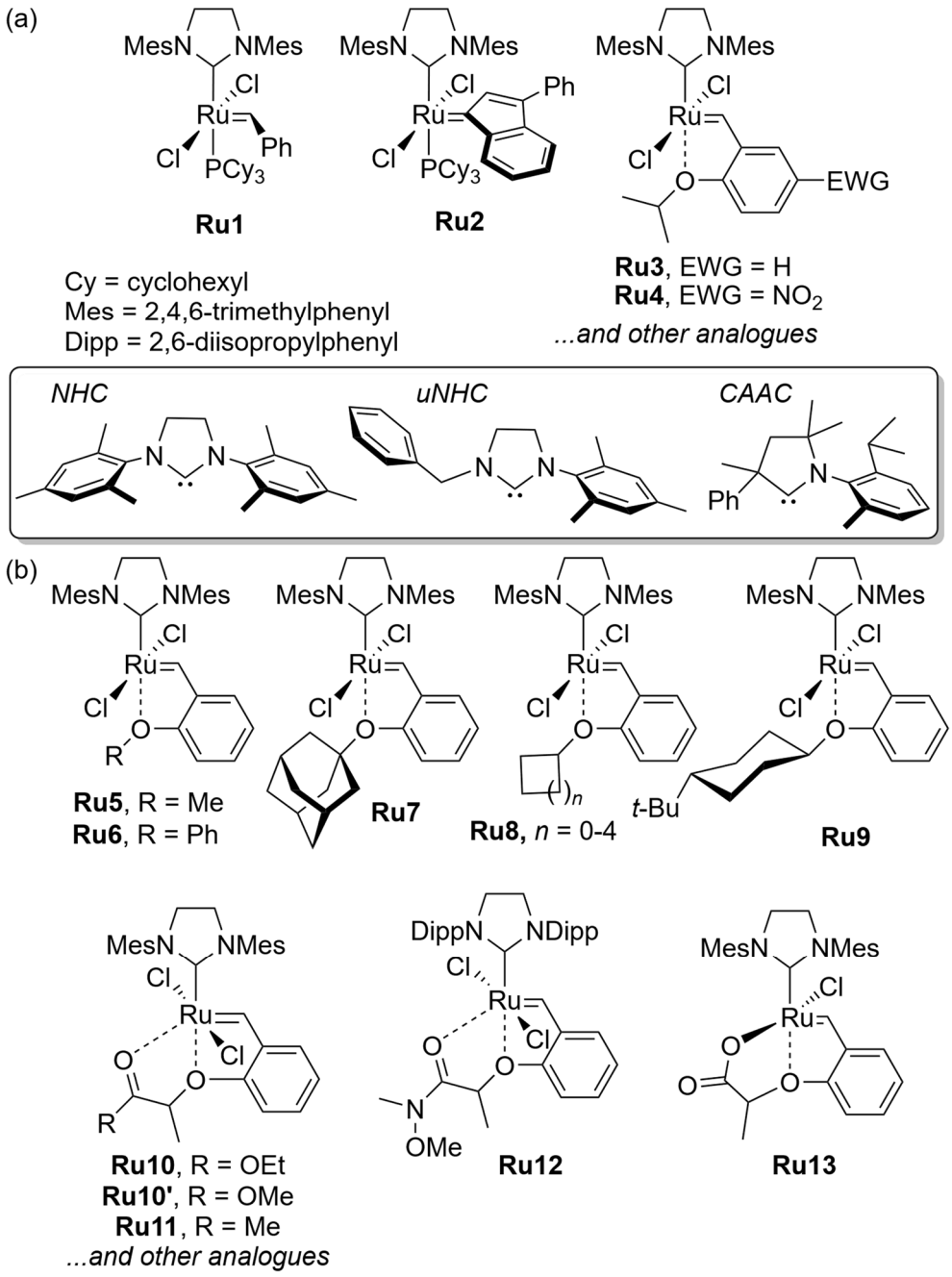


Figure 1. Selected (**a**) commercially available ruthenium-based general-purpose olefin metathesis catalysts and the structures of NHC, uNHC, and CAAC, and (**b**) selected ether-modified chelating benzylidene complexes.

In a similar set of complexes possessing a cyclic fragment (such as **Ru8**), Grela and co-workers observed an influence of ring size on catalyst activity [32], while Diver noted a significant influence of the axial or equatorial conformation of the differently substituted cyclohexyl ethers (e.g., **Ru9**) on the initiation rate in ring-closing metathesis reactions [31]. A different approach was presented by Grela et al. [33–35], who, by introducing an electron-withdrawing group as a terminal substituent of the 'leaving' benzylidene ether group (**Ru10**, **Ru11**), boosted the activity of Hoveyda catalysts. At the same time, the authors noted that substituents such as an ester, ketonic, or a malonic group work, as there is an additional coordinating functionality binding to the metal center. In addition, an analogue of **Ru11** that contains free carboxylic acid in the ether moiety easily undergoes cyclisation to

form a complex **Ru13** containing a chelating carboxylate ligand [36], which can be activated in situ by acids and has found some applications in metathesis reactions [37]. Subsequently, the same concept was creatively developed by Skowerski and Olszewski [38], Liu and Wang [39], Matsuto [40], and Al-Awadi [41]. The ethereal substituent in the benzylidene ligand can also serve as a platform to increase the solubility of catalysts in polar media [42] or to allow the immobilization of the resulting complexes [43–45]. This short and inevitably fragmentary introduction to a waste collection of olefin metathesis catalysts shows that the ligand engineering within the coordination sphere of the Ru atom is an important field of research, as it can bring about the control of catalyst initiation and productivity and introduce new traits such as solubility in given solvents, immobilization handles, etc., [46,47].

Understanding the influence of the modification of the chelating alkoxy-benzylidene ligand on the structure and catalytic activity of the resulting ruthenium complexes, we decided to synthesize a catalyst containing an oxomethylenefuran group as the ethereal-chelating fragment (the idea is presented as a prototypical structure **Ru16** in Figure 2). This design was inspired by a promising catalytic profile exhibited by **Ru14** and **Ru15** that featured benzyl-ether fragments in the chelating benzylidene ligand [48].

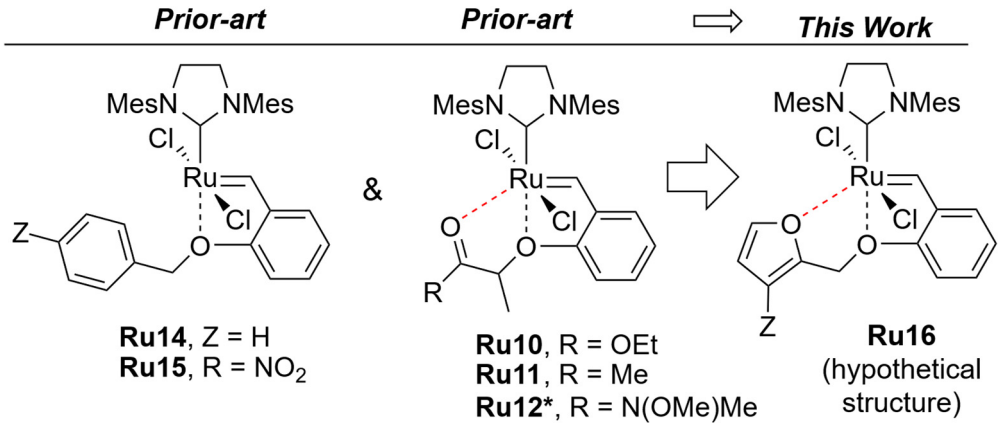
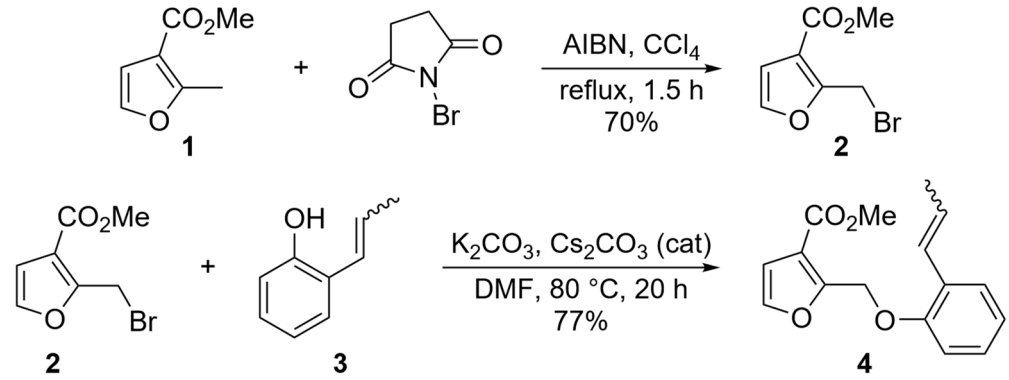


Figure 2. Combined structural characteristics leading to development of a new system. * NHC with Dipp substituent instead of Mes. (For **Ru14** and **Ru15**, see [48]; for **Ru10** and **Ru11**, see [33–35]; for **Ru12**, see [38]).

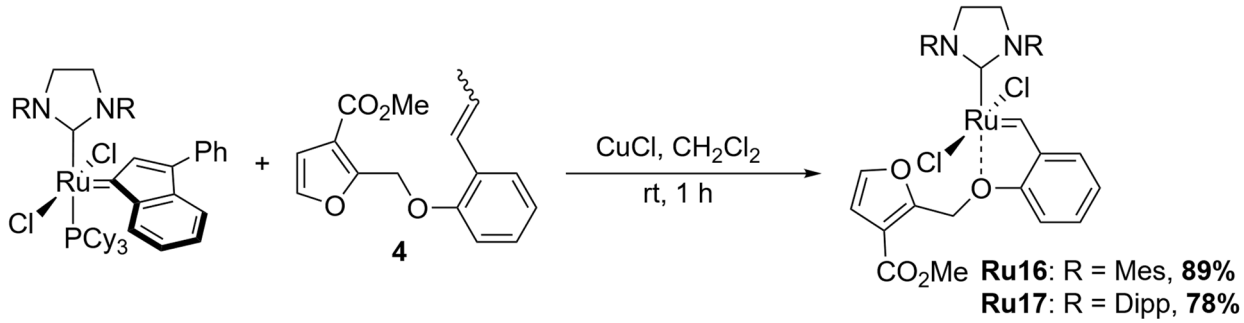
2. Results

We first approached the synthesis of the ligand precursor **4** (Scheme 1). The rationale behind selecting this structure was the known stability of brominated furan **2** and the general reliability of this reaction. In this regard, we performed the bromination of methyl 2-methyl-3-furancarboxylate (**1**) using NBS in the presence of AIBN and obtained product **2** in 70% yield. We then reacted the resulted bromide with 2-propenylphenol (**3**) and obtained the desired ligand precursor **4** in 77% yield (Scheme 1). In the alternative approach, propenylbenzene derivative **4** was prepared in a two-step procedure; first, a reaction of **2** with salicylaldehyde was performed, followed by Wittig reaction, giving the desired product with 32% yield (for details, see Supplementary Materials).



Scheme 1. Two-step synthesis of ligand precursor **4**.

With propenylbenzene derivative **4** in hand, we prepared two versions of Hoveyda–Grubbs type complexes containing SIMes and SIPr NHC ligands, respectively. To do so, the reactions between the corresponding indenylidene-type complex, namely **Ru2** and its SIPr analogue, and **4** were carried out in DCM at room temperature in the presence of CuCl used as a phosphine scavenger (Scheme 2). In both cases, the desired catalysts were obtained as green crystals in high yields, around 80%.



Scheme 2. Synthesis of complexes **Ru16** and **Ru17**.

The new catalysts **Ru16** and **Ru17** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as elemental analysis, MS, and IR spectroscopy. The signals of the benzylidene protons in the NMR spectra appeared at 16.54 and 16.34 ppm, which is typical of Hoveyda-type complexes. A single crystal of catalysts **Ru16** was grown and also analyzed using XRD (Figure 3). The studied complex crystallizes in $P2_1/c$ monoclinic space with one molecule in the asymmetric unit. The coordination sphere of the ruthenium atom is slightly distorted from the trigonal bipyramid. The geometrical features of the catalyst were compared with previously reported Hoveyda–Grubbs complex (**Ru3**) [48]. Most of the bond distances between the metal center and the atom in the first coordination sphere do not differ more than 3σ with the exception of the Ru1-O1 distance that is significantly elongated from 2.256(1) Å for Hoveyda to 2.282(1) Å for **Ru16**. This bond is even shorter for **Ru10′** molecule with methyl ester moiety. Unfortunately, we have not observed any interactions between the oxygen atom, neither in the furan ring nor in the ester group, and the ruthenium center, as the Ru1-O2 distance is 3.352(2) Å, and it is much longer in comparison to 2.536(2) Å for **Ru10′**.

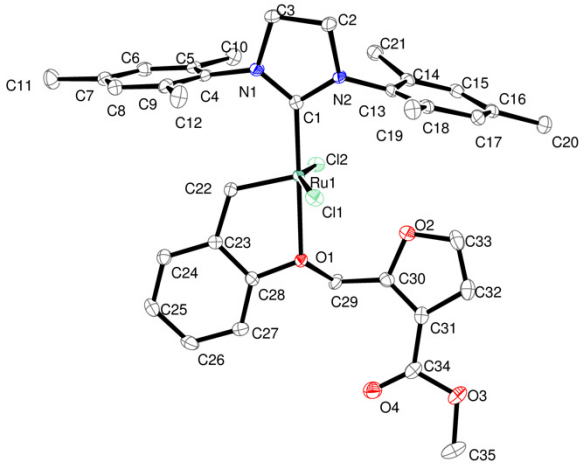


Figure 3. ORTEP diagram (50% probability ellipsoids) of complexes **Ru16**. Hydrogen atom omitted for clarity.

The molecular overlay presented in Figure 4 revealed differences in the position of the benzylidene and NHC ligand due to the bulky substituent replacement of the isopropoxy ligand. The torsion angle of Ru1-O1-C29-C30 is 69.1(2)° compared to the analog angle of 19.5(4) ° for **Ru10′** and −18.2(2)° in Hoveyda–Grubbs catalyst. It can also explain the change in the position of the benzylidene ligand that is pushed back and the Ru1-C22-C23-C24 torsion angle is positive (174.1(1)° for **Ru16** and 171.5(3)° for **Ru10′**) compared to Hoveyda–Grubbs negative value (−173.8(1)°). Additionally, the NHC ligand is twisted in such a way that the methyl groups pointing towards the viewer in Figure 4a are closer to one another by 2 Å comparing the distance between the C21 and C10 atoms equal to 3.908(3) Å for **Ru16**, 4.292(6) Å for **Ru10′** vs. 5.732(2) Å for Hoveyda–Grubbs.

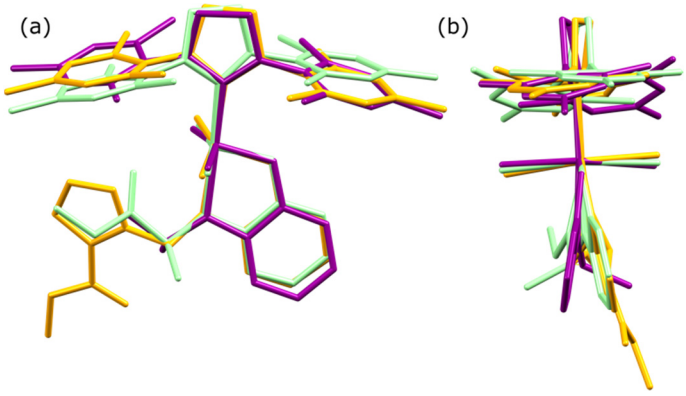


Figure 4. Front view (**a**) and side view (**b**) of molecular overlay for Hoveyda–Grubbs (violet), **Ru10′** (light green) and **Ru16** (orange) catalysts. Molecules represented by sticks, and hydrogen atom omitted for clarity.

With both complexes in hand, we investigated their activity in model metathesis reactions to check the profile of their applications. The results were compared with two known catalysts, the commercially available Hoveyda–Grubbs complex **Ru3** and its analogue with the ester group, **Ru10**. First, we carried out a model ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (**5**, Figure 5) in the presence of 1 mol% of the examined complexes at 0 °C. Such a low temperature is rarely used in olefin metathesis reactions, because only the most active catalysts allow satisfactory conversions, but we believed that the system we designed was capable of such a challenging task [33,49].

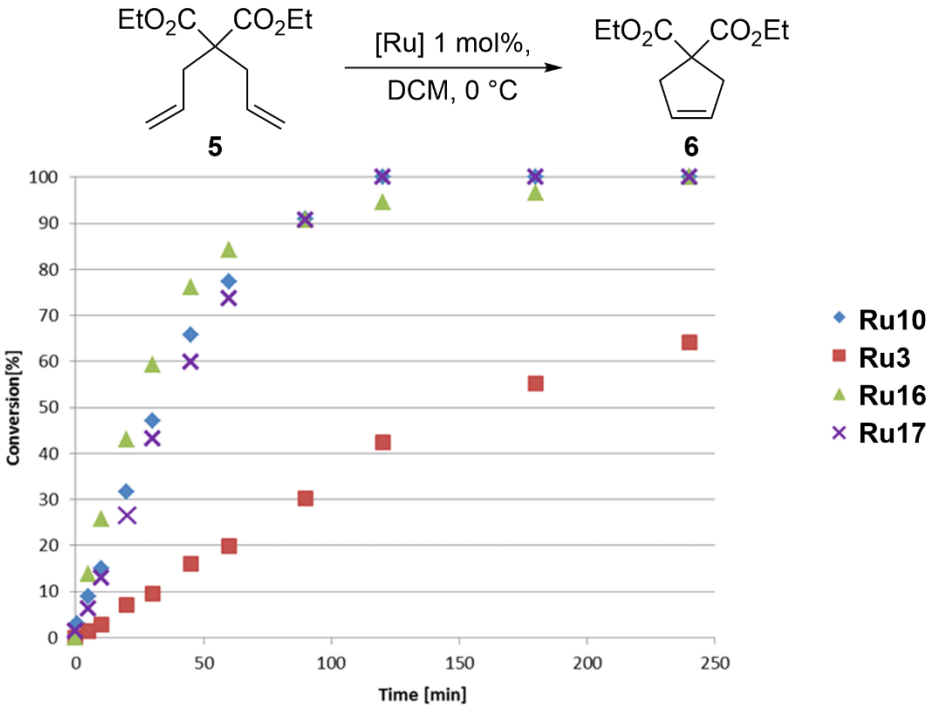


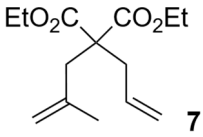
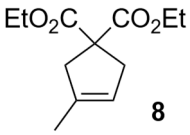
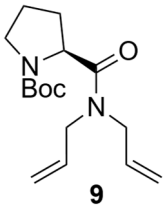
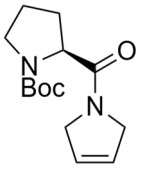
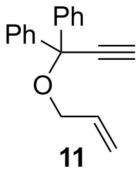
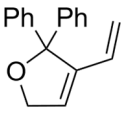
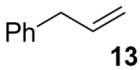
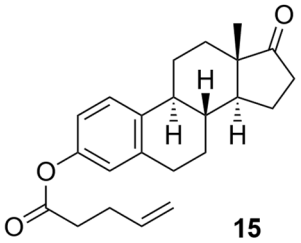
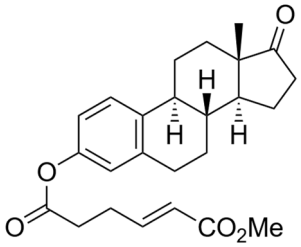
Figure 5. Relative conversion rates for a model RCM reaction of **5** using 1 mol% of the catalyst.

As expected, the Hoveyda–Grubbs complex **Ru3** initiates the slowest and also gives the lower conversion, only 64% after 4 h. All other complexes, viz. **Ru10** (18-electron double-chelated complex), new **Ru16**, and **Ru17**, behaved in a similar way, each of them initiated relatively fast and reached almost full conversion within 120 min.

Based on this preliminary study, we selected **Ru10** as a reference point for further comparison of the activity of newly obtained catalysts.

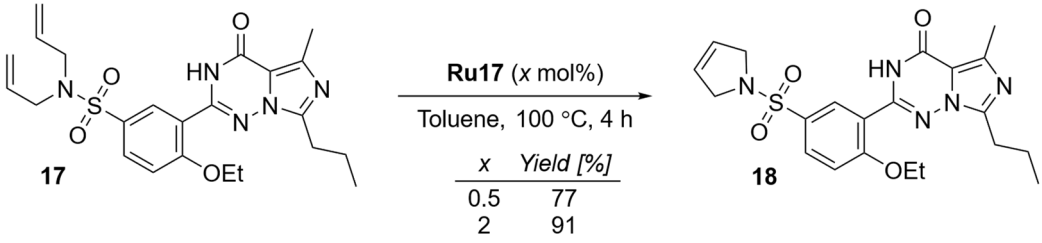
First, we examined the RCM of a more demanding substrate with a substituted double bond, namely diethyl 2-allyl-2-(2-methylallyl)malonate (**7**, Table 1, entry 1). When the reaction was performed at room temperature in the presence of 1 mol% of catalyst, in all cases, the conversion was quantitative or almost quantitative; however, **Ru10** required three or nine times more time than the furan-containing compounds **Ru16** and **Ru17**. When the catalyst loading was decreased to 0.2 mol% the conversion dropped significantly, but new complexes still allowed for reaching around 60% yield. **Ru10** provided the desired product with a 40% yield that only slightly increased to 49% when the catalyst loading was increased to 0.5 mol%. A similar trend was observed in the case of the next RCM reaction, this time a proline derivative **9** (Table 1, entry 2). Moreover, the best result was obtained when the SIPr version of the furan-containing complex was used, meaning that an almost quantitative yield was reached after two hours at room temperature. **Ru16** was slightly worse and provided the desired product **10** in 85% yield, while **Ru10** reached only 49% of yield, but only when a higher catalyst loading of 0.5 mol% was used. The situation slightly changed in the case of the ene-yne reaction of allyl 1,1-diphenylpropargyl ether (**11**). Here, all complexes exhibited high activity, **Ru10** and **Ru17**—used in 0.2 mol% loading—reached almost full conversion in 2 h while **Ru16** gave a similar result (92%) in only 15 min (Table 1, entry 3). When the loading was raised to 1 mol%, all complexes provided the desired product in 100% yield, but after varying periods of time. In a cross-metathesis reaction between allyl benzene (**13**) and *cis*-1,4-diacetoxy-2-butene, the best result was obtained when **Ru16** was used as a catalyst while the remaining complexes provided product **14** in a less than 80% yield (Table 1, entry 4). On the other hand, when estrone derivative **15** and methyl acrylate were used as substrates, all catalysts gave similar results, reaching an over 90% yield (Table 1, entry 5).

Table 1. Catalytical activity of **Ru16** and **Ru17** in comparison with **Ru10**.

Entry	Substrate	Product	Catalyst (mol%)	Temp (°C)	Time (min)	Yield (%) [a]
1	 **7**	 **8**	**Ru10** (1.0)	23	90	(92)
			Ru16 (1.0)	23	10	(97)
			Ru17 (1.0)	23	30	(100)
			Ru10 (0.2)	23	120	(40)
			Ru16 (0.2)	23	90	(59)
			Ru17 (0.2)	23	90	(60)
			Ru10 (0.5)	23	120	(49)
2	 **9**	 **10**	**Ru10** (0.5)	23	120	49
			Ru16 (0.2)	23	120	85
			Ru17 (0.2)	23	120	96
3	 **11**	 **12**	**Ru10** (0.2)	23	120	(100)
			Ru16 (0.2)	23	15	(92)
			Ru17 (0.2)	23	120	(98)
			Ru10 (1.0)	23	90	(100)
			Ru16 (1.0)	23	10	(100)
			Ru17 (1.0)	23	90	(100)
4 [b]	 **13**	 **14**	**Ru10** (1.0)	30	60	70
			Ru16 (1.0)	30	60	91
			Ru17 (1.0)	30	60	79
5 [c]	 **15**	 **16**	**Ru10** (1.0)	23	120	93
			Ru16 (1.0)	23	120	97
			Ru17 (1.0)	23	120	98

Conditions: [a] Isolated yields after silica gel chromatography. In parentheses are yields determined by GC. [b] Reaction with two equivalents of *cis*-1,4-diacetoxy-2-butene. [c] Reaction with two equivalents of methyl acrylate.

Encouraged by these results, we turned our attention to compounds with potential biological activity. This time, it was an analogue of Vardenafil, a popular drug utilized in the treatment of erectile dysfunction and pulmonary arterial hypertension, sold *inter alia* under the trade name Levitra [50]. From a synthetic point of view, the structure of the substrate can cause some problems during a metathesis reaction, as it contains a number of Lewis basic centers that can chelate the propagating ruthenium species, decreasing the activity of the catalyst. After a short optimization, including finding the best solvent, temperature, and reaction time (for details, see Supplementary Materials), we were able to obtain the desired product **18** in 77% yield (Scheme 3). This result is slightly worse than the best one known in the literature [51]; however, in the latter case, 1.5–2 mol% of catalyst bearing an unsymmetrical NHC ligand with thiophene moiety was used to achieve a 91% yield. Nevertheless, when the reaction was repeated in the presence of 2 mol% of **Ru17**, we were able to achieve the same result, 91%, as reported previously.



Scheme 3. Preparation of Vardenafil analogue **18** in RCM reaction catalyzed with **Ru17**.

3. Conclusions

The straightforward reaction between the easily accessible furan-containing benzylidene ligand precursor **4** and second-generation indenylidene complexes gave two new Hoveyda–Grubbs type catalysts in high yields (≥80%). These new complexes were fully characterized, and their catalytic activity was examined using a diverse set of olefin metathesis reactions. The new complexes were found to be fast initiating and highly efficient. Among others, they exhibited high activity in RCM, ene-yne, and cross-metathesis reactions in low catalyst-loading (0.2–1 mol%), including the transformation of a derivative of the known Vardenafil (Levitra™) API. Interestingly, in a model RCM of diethyl diallylmalonate substrate (**5**) conducted at 0 °C, the new complexes have shown visibly higher activity than the one exhibited by standard Hoveyda–Grubbs catalyst (**Ru3**), successfully rivaling with the 18-electron, double-chelated complex **Ru10**.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemistry4030056/s1. Detailed experimental procedures and copies of NMR spectra [51–59].

Author Contributions: Conceptualization, A.K.; formal analysis, M.N., A.Z. and M.M.; investigation, M.N. and A.Z.; data curation, M.N. and A.K.; writing—original draft preparation, A.K.; writing—review and editing, M.N., M.M. and A.K.; visualization, M.N., M.M. and A.K.; supervision, A.K.; project administration, A.K.; funding acquisition, A.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research performed within SONATA BIS project and was funded by National Science Centre, Poland, grant number DEC-2021/42/E/ST4/00187.

Data Availability Statement: Data supporting reported results of this study are available in the supplementary material of this article and can be obtained from the corresponding author.

Acknowledgments: The study was carried out at the Biological and Chemical Research Centre, University of Warsaw, established within the project co-financed by European Union from the European Regional Development Fund under the Operational Program Innovative Economy, 2007–2013.

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

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