



Olefin Metathesis

Ruthenium-Catalysed Olefin Metathesis in Environmentally Friendly Solvents: 2-Methyltetrahydrofuran Revisited

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Abstract: Application profiles of a set of popular second-generation ruthenium catalysts were experimentally investigated in an environmentally friendly solvent, 2-methyltetrahydrofuran (2-MeTHF), and compared with the activity of the same catalysts in toluene, a popular solvent used in industrial olefin metathesis. It was found that a catalyst containing a 2-isopropoxy-5-nitrobenzylidene moiety and a symmetrical N-heterocyclic (NHC) ligand with 2,6-diisopropylphenyl substituents (SIPr) ex-

Introduction

Catalytic olefin metathesis^[1] utilising modern, well-defined catalysts is a powerful transformation in organic chemistry allowing to form carbon-carbon double bonds selectively and in practically unlimited structural arrangements, thus offering great promises for fine chemical and pharmaceutical synthesis.^[2] Historically, olefin metathesis reactions were carried out in toxic solvents, such as dichloromethane (DCM), 1,2-dichloroethane (DCE), chloroform, benzene and other aromatic solvents.^[1] As pointed out recently by Sherwood, the use of chlorinated solvents soon will be banned (or are prohibited already) and the society of chemists must adapt to.^[3] This is especially the case in the pharmaceutical production, which is not truly material-efficient (high E-factor values)^[4] and uses large amounts of solvents.^[5] Therefore, finding more environmentally friendly equivalents of these solvents in order to fulfil the principles of green chemistry is of highest importance.[6-9]

A number of reports proving the compatibility of modern ruthenium olefin metathesis catalysts with alternative reaction media, such as water,^[10] ethanol,^[11] ionic liquids,^[12] supercritical carbon dioxide (scCO₂),^[13–15] glycerol,^[16] polyethylene glycol,^[17] dimethyl carbonate (DMC),^[18–20] methyl decanoate,^[21] ethyl acetate (EtOAc),^[22] cyclopentyl methyl ether (CPME)^[22] and other solvents appeared in the recent literature.^[23] Surpris-

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hibits the highest catalytic activity in 2-MeTHF also at a lower temperature (30 °C). *Ab initio* studies showed that initiation rates of Ru catalysts bearing NHC ligands in 2-MeTHF can be correlated with partial charges and bond lengths between selected crucial atoms in the studied ruthenium complexes. The results demonstrate that aromatic or chlorinated solvents, typically used in metathesis reactions, can be successfully replaced in many cases by 2-MeTHF.

ingly, despite such a big deal of academic research on the application of green solvents has been done, the pharmaceutical companies are very slow in transforming these results into industrial practice. Specifically, from almost 30 metathesis-made drug candidates listed by Hughes, Wheeler and Ene in their recent review,^[24] all were prepared in non-green solvents, usually in DCM, DCE or toluene. Similarly, all examples of active pharmaceutical ingredients (API) larger scale olefin metathesis production, reviewed recently by Pederson et al.^[25] were conducted either in chlorinated ICH Class 1 solvents^[26] or in toluene (ICH Class 2 solvent). Only one example of pharmaceutically-relevant larger scale (1.5 kg) metathesis reaction performed in a green solvent (in EtOAc, ICH Class 3) know to us is the synthesis of IDX320, a hepatitis C virus protease inhibitor by Idenix Pharmaceuticals Inc. (Figure 1).^[27]

In the context of the newly EC-introduced "circular economy" policies, the use of renewable resources (incl. solvents) in chemical manufacturing is of key importance.^[28,29] These new policies tighten up the already existing legislation for reduction of CO₂ emissions. In this context, one of the promising green solvents, that can be obtained from various renewable materials and agricultural wastes such as corn cobs and oat hulls, is 2methyltetrahydrofuran (2-MeTHF).^[30,31] Because of its reduced carbon footprint (incineration of 2-MeTHF does not increase the CO₂ concentration in the atmosphere as it simply returns the CO₂ captured by the previous year's crop from the air),^[32] 2-MeTHF constitutes an economic^[33] and sustainable alternative to common organic solvents, and it has already found some applications in organic chemistry.^[34–37]

Some time ago, we have reported preliminary results showing that olefin metathesis can be successfully conducted in this solvent using SIMes-bearing Ru complexes **1** and **3a–c** (Figure 2) at 30 or 50 °C.^[38] In contrast, in a later report, Skowerski et al. showed that 2-MeTHF is visibly inferior at 40 °C as com-

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Figure 1. Selected examples of APIs and drug candidates prepared by olefin metathesis (RCM = ring-closing metathesis; DCM = dichloromethane; DCE = 1,2-dichloroethane; PhMe = toluene).



Figure 2. Ruthenium metathesis catalysts already tested in 2-MeTHF (Ref. 22 and 38).

pared to other classical (DCM, PhMe) and green solvents (AcOEt, DMC and CPME) and requires at least 70 °C to operate.^[22] Sadly, with exception of this (partially negative) recommendation,^[22] there are no further reports on use of 2-MeTHF with popular Ru olefin metathesis catalysts.^[39]

Results and Discussion

Therefore, in the present work we decided to test in 2-MeTHF seven (six of them are commercially available) complexes belonging to two established families of olefin metathesis catalysts (Figure 3): Umicore Grubbs[™] Catalyst M1 (**13**) developed by Nolan,^[40] Umicore Grubbs[™] Catalyst M2 (**8**),^[41] Umicore Grubbs[™] Catalyst C627 (**1**) developed independently by Hoveyda^[42] and Blechert,^[43] Apeiron Nitro-Catalyst (**6**),^[44] the SIPr versions of the above (**2** and **7**) and in addition electron donating group (EDG) bearing Hoveyda–Grubbs catalyst (**12**).^[45]



Figure 3. Ru catalysts used in this work (popular commercial catalysts are marked with a dollar sign $\$

The role of the electron-withdrawing group (EWG) in Nitro-Catalyst 6 is to weaken the strength of the Ru–O chelation and thus increase the catalytic activity of the complex.^[44,46] Accordingly, the analogous catalysts substituted with EDG are initiating more slowly than parent 1.^[47,48] In our previous 2-MeTHF study^[38] we noted, however, that in the case of functionalised catalysts 3a-c, the most strongly EWG-activated complex (3b) initiated more slowly than 1. On the other hand, in DCM and toluene the order of initiation rates was $3b > 3c \approx 3a > 1$, what is in accordance with previously published results on the electronic activation of Hoveyda–Grubbs type complexes.^[47] Because the previously used catalysts were rather "exotic" and with limited application record,^[38] we decided to revisit the study on the utility of 2-MeTHF as a solvent, also at lower temperature,^[22] but this time using a set of more popular, general purpose catalysts (Figure 3) and combine the experimental results with the *ab initio* calculations.

Comparative Activity Study of General Purpose Catalysts 1–2, 6–8, 13, and Complex 12 in 2-MeTHF and a Classical Solvent

To compare the catalytic activity of the selected catalysts, the standard model ring-closing metathesis reaction (RCM) of di-





ethyl diallylmalonate (**14**) was selected (Scheme 1, Figure 4 and Figure 5).



Scheme 1. RCM of diethyl diallylmalonate (14) (0.1 м).



Figure 4. Reaction profile of RCM of diethyl diallylmalonate (**14**) (c = 0.1 M) with catalysts **1–2**, **6–8**, **12–13** (1 mol-%) in dry and degassed toluene at 30 °C under argon. Lines are visual aid only.



Figure 5. Reaction profile of RCM of diethyl diallylmalonate (**14**) (c = 0.1 m) with catalysts **1–2**, **6–8**, **12–13** (1 mol-%) in dry and degassed 2-MeTHF at 30 °C under argon. Lines are visual aid only.

The conversion-time profiles of complexes **1–2**, **6–8**, **12–13** at 30 °C in toluene displayed significant differences in catalysts' activity. The following catalysts reach the full conversion of diene **14**: **7**, **6**, **1**, **12**, **2** and their order is ranked from the most active. As we expected, the SIMes and SIPr nitro-substituted **6** and **7** were found to be the most active, while the H- and MeO-substituted complexes were initiating at slower pace. Interestingly, the electron-donating group substituted complex **12** was

found to be faster-initiating than **2**, which is not in full agreement with general theory concerning Hoveyda-like SIMes catalysts.^[47] To address this issue we performed additional computational analysis, presented in the Computational Study section. Both indenylidene catalysts **13** and **8** did not reach the full conversion under these conditions, even after 1 h (Figure 4).

The observed trend was roughly preserved also in 2-methyl tetrahydrofuran, under identical conditions (Figure 5). However, it shall be noted that all studied complexes required a slightly longer time to reach full conversion (approximately 1 h instead of 30 minutes in PhMe). As previously, **13** and **8** were not able to catalyse efficiently the RCM reaction of **14** under the given conditions. Again, complex **7** appeared to be the most active catalyst, but its SIMes analogue **6** was this time less productive, being unable to reach full conversion (Figure 5).

In the next step we have tested only the SIPr-bearing EWG and EDG substituted ruthenium complexes **2**, **7**, **12** at 50 °C in toluene and then at the same temperature in 2-MeTHF in order to have a closer look at their relative activities in these solvents. All catalysts **2**, **7** and **12** were found to achieve almost full conversion in toluene after only 6 minutes (Figure 6). Again, the EWG substituted **7** was the fastest, while the complex with an EDG group **12** was the slowst one in toluene. In contrast, the activity of the complexes **2** and **12** was slightly decreased in 2methyltetrahydrofuran, but the complex **7** was still very active, like in toluene (Figure 6).



Figure 6. Reaction profile of RCM of diethyl diallylmalonate (**14**) (c = 0.1 m) with catalysts **2**, **7** and **12** (1 mol-%) in dry and degassed toluene (continuous line) and 2-methyltetrahydrofuran (dashed line) at 50 °C under argon. Lines are visual aid only.

Next, we examined the activity of 2-alkoxybenzylidene-type catalysts **2**, **7** and **12** in a more diverse set of RCM reactions in 2-methyltetrahydrofuran. All reactions were performed in non-degassed 2-MeTHF (Sigma-Aldrich) at 30 °C under air.^[49] Pleasurably, **2**, **7** and **12** were characterized in this solvent by a very good activity, as high conversions were reached with all tested substrates, including the nitrile containing diene (Table 1, entry 2) and the pharmaceutically relevant barbituric derivative (entry 3). Among examined complexes, **7** turned out to be the most active, allowing to accomplish all metathesis transformations in



less than 30 minutes. Surprisingly, the activity of catalyst bearing the EDG substituent (**12**) was again slightly higher than its unsubstituted analogue **2** (Table 1).

Table 1. Application of catalysts ${\bf 2},\,{\bf 7},\,and\,\,{\bf 12}$ in RCM and ene-yne reactions in 2-MeTHF under air. $^{[a]}$

Entry	Substrate	Product	Catalyst	Time (min)	Conversion
1	EtO ₂ C CO ₂ Et	EtO ₂ C CO ₂ Et	2 (1)	180	95
I	14	15	7 (1)	30	98
			12 (1)	120	97
2	Ph_CN I	Ph_CN	2 (1)	30	99
	6 7 16	17	7 (1)	5	>99
			12 (1)	30	>99
3	0 L		2 (2)	240	99
			7 (2)	10	>99
	18	\ <u>19</u>	12 (2)	60	>99
4	07-	Ph_	2 (2)	180	98
	Ph Ph 20		7 (2)	30	98
			12 (2)	120	99

[a] All reactions were performed in non-degassed 2-methyltetrahydrofuran (Sigma-Aldrich) at 30 °C under air. [b] Conversion was determined by gas chromatography using durene as internal standard.

The results presented in Table 1 demonstrate the efficiency of the SIPr bearing complexes **2**, **7** and **12** to perform metathesis reactions in the environmentally friendly 2-methyltetrahydrofuran under air.

Computational Studies

To gain more insight into the different initiation/activation rates of studied complexes we decided to additionally perform a computational study using DFT approach. Experimental investigations of the initiation mechanisms performed for a number of different Hoveyda catalysts and using different olefins as substrates showed that this reaction may simultaneously follow two parallel pathways, dissociative and interchange, depending on the electronic/steric properties of both the catalyst and the substrate.^[50] It was also established that sterically demanding olefins (including diethyl diallylmalonate **14** and all other olefins discussed in the experimental part of this investigation) initiate preferentially via the dissociative pathway, while simple olefins such as ethylene prefer the interchange one. Since all



olefins used in the experimental part of this study are definitely sterically demanding, we decided to explore only the dissociative pathway for this reaction, which is also in agreement with recent kinetic data.^[51] Moreover, it was found earlier that the dissociative mechanism consists of two steps: the dissociation of the Ru–O bond and the association of the olefin. In all known cases the first stage is, however, the rate-determining step of the entire process. Therefore, in our studies, we only evaluated the Gibbs free energy barriers (ΔG^{\ddagger}) of the first step of the dissociative mechanism.

Recently Grubbs et al. suggested also a simpler quantity to describe the initiation rates for Hoveyda-like complexes, namely the Ru–O bond strength.^[52] In his work he suggested two definitions of the bond strength; one (BS1) being the difference in Gibbs free energy between the activated catalysts and the precatalyst and the second one (BS2) as the difference in Gibbs free energy between the 14-electron Fischer carbene complex and the precatalyst. The second quantity, BS2, gave a particularly good correlation with experimental initiation rates for a large set of Hoveyda-like complexes. In view of these results, we decided to also evaluate these two quantities using diethyl diallylmalonate (**14**) as the model olefin in the case of BS2.

Before conducting the calculations for complexes 2, 7 and 12 we decided to first verify if there is any correlation between the experimental and computational data for systems 3a-c, which were synthesized earlier but not studied computationally.^[38] As stated above we noticed earlier that in 2-MeTHF at 50 °C the order of initiation rate for this group of catalysts was $3c \approx 3a > 3b > 1$. Our computational results follow the same trend, as the calculated ΔG^{\ddagger} are equal to 19.5 kcal/mol (**3c**), 20.8 kcal/mol (3a), 20.9 kcal/mol (3b) and 20.9 kcal/mol (1), respectively. It is worth mentioning, though, that the differences in computed ΔG^{\ddagger} values are relatively small given the expected accuracy of our method, estimated at \approx 1 kcal/mol. On the other hand bond strength defined as either BS1 or BS2 does not give such correlation with experimental data, as in both cases complex **3b** is characterized by the lowest bond strength of all four considered systems (Table 2). Interestingly though, these results are in agreement with the electron-withdrawing properties of the $-OSO_2C_6H_4NO_2$ moiety, which is apparently able to weaken the Ru-O bond.

Table 2. Gibbs free energy barriers and bond strengths (as defined as in the text of the manuscript) for complexes 1 and 3a-c (all in kcal/mol).

Complex	ΔG^{\ddagger}	BS1	BS2	
1	20.9	13.3	25.6	
3a	20.8	10.0	32.5	
3b	20.9	6.1	24.7	
3c	19.5	9.1	25.5	

The results for the **2**, **7**, **12** series investigated in this work are presented in Table 3 and are also in a relatively good agreement with the experimental data, though also, in this case, the differences in ΔG^{\ddagger} values are small. The lowest values of Gibbs free energy of activation were found for **7** and **12** which may be quite surprising since the latter complex bears an electron donating $-OCH_3$ moiety. This result is, however, in agreement with experimental data presented earlier in this study. As ex-





pected **2** gives the highest activation barrier, while the lowest one was found for **6**. A good correlation with the experimental results was also found for the BS2 quantity, for which the order of complexes is 6 < 1 < 7 < 2 < 12.

Table 3. Gibbs free energy barriers and bond strengths (as defined as in the text of the manuscript) for complexes 1, 6 and 2, 7, 12 (all in kcal/mol).

ΔG^{\ddagger}	BS1	BS2
20.9	13.3	25.6
19.9	10.2	20.8
20.9	8.3	31.5
20.3	10.6	29.2
20.2	13.2	32.2
	ΔG [‡] 20.9 19.9 20.9 20.3 20.2	ΔG^{\ddagger} BS1 20.9 13.3 19.9 10.2 20.9 8.3 20.3 10.6 20.2 13.2

We can justify these results by analysing Mulliken partial charges on selected atoms and crucial bond lengths in precatalyst with the premise that electron-withdrawing groups in the benzylidene part of the catalysts lead to a smaller negative partial charge on the isopropoxy oxygen atom and, in turn, to a weaker interaction with the ruthenium atom, making the Ru-O distance longer. As expected the longest Ru-O bond length (2.377 Å) was found for the fast-initiating nitro 6 complex and the shortest (2.324 Å) for the relatively slow Hoveyda-Grubbs 1 system (Table 4). Complexes 3b and 7 bearing the -OSO₂C₆H₄NO₂ and -NO₂ groups also show relatively long Ru-O distances, which correlates well with their fast initiation, while the slowly-initiating 2 complex has one of the shortest Ru–O distances. The weakening and lengthening of the Ru–O bond for fast initiating complexes can also be correlated with the lower partial charge on the isopropoxy oxygen atom due to the electron-withdrawing effect of the -NO₂ moiety. This is indeed the case, as partial charges on the O atom for all such complexes (6 = -0.519 e, 3b = -0.520 e and 7 = -0.513 e) are smaller than those without electron-withdrawing groups (with the average partial charge of -0.525 e). The opposite is, however, not true for the weaker electron withdrawing moieties such as $-OSO_2C_6H_4OMe$ in **3c** or electron donating -OMe in **12**, even though we could expect the strengthening and shortening of the Ru–O bond. The partial charge on the chelating O atom for these two systems is almost identical to the partial charge of the oxygen atom of complexes 3a and 2. More importantly, the Ru-O bond lengths of 3c and 12, while slightly shorter than for 3b/7, are definitely longer than for 3a/2 suggesting faster initiation of -OMe vs. -H complexes, in agreement with experimental data presented earlier.

Table 4. Ru–O bond lengths and Mulliken partial charge of the isopropoxy oxygen atom for complexes 1, 6, 3a–c and 2, 7, 12.

Complex	Ru–O [Å]	O partial charge [e]	
1	2.324	-0.525	
6	2.377	-0.519	
3a	2.341	-0.523	
3b	2.370	-0.520	
3c	2.366	-0.521	
2	2.340	-0.524	
7	2.356	-0.513	
12	2.355	-0.527	

Conclusions

In summary, we re-investigated the application profiles of selected general purpose second generation ruthenium catalysts bearing symmetrical NHC ligands in environmentally friendly 2methyltetrahydrofuran under argon and in air. The time-conversion profiles were compared with the results of the same reactions made in toluene. It was found that catalyst **7** containing 2isopropoxy-5-nitrobenzylidene moiety and a symmetrical NHC ligand with 2,6-diisopropylphenyl substituents (SIPr) has shown the highest catalytic activity. These results demonstrate that in metathesis reactions typically used aromatic or chlorinated solvents can be successfully replaced by 2-methyltetrahydrofuran.

Computational results reveal a correlation between the obtained values of Gibbs free energy barriers of activation and experimental initiation rates, but their in-depth analysis is difficult due to very small differences in the computational results. A good correlation, particularly for complexes **2**, **7** and **12b**, was also found between the Gibbs free energies of activation and bond strengths, as defines by Grubbs in his recent work. Unfortunately, the small differences in their Gibbs free energies of activation make the computational predictions of energy barriers little useful in investigating sets of complexes of so similar initiation profiles. On the other hand, the detailed analysis of partial changes and Ru–O bond lengths reveals useful information which can be used in the future design of more efficient catalysts.

Experimental Section

General Remarks: All reagents and catalysts were purchased from Sigma-Aldrich company and used as received without further purification. HPLC grade toluene 99.9 % containing the following impurities (≤ 0.0005 % non-volatile matter, ≤ 0.0005 % thiophene, ≤ 0.001 % free acid, ≤ 0.02 % water) and dry 2-methyltetrahyrofuran stored over molecular sieve were purchased from Sigma-Aldrich company. Dry toluene was taken from a solvent drying system MBRAUN SPS-800 installed in a drybox model MBRAUN UNILab 1950/780. Thin-layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization of TLC plates was performed by UV light (254 nm) and/or in KMnO₄ aq. solution. Flash column chromatography was performed using silica gel 60 (230–400 mesh).

Pre-catalyst **12** was prepared according to Wagener's procedure.^[53] N^{1} -(2,6-diisopropylphenyl) ethane-1,2-diamine was prepared according to Marshall's procedure.^[54]

General procedure for metathesis reactions (Table 1): Comparative RCM and ene-yne experiments with model compounds were performed in 2-methyltetrahydrofuran under air at 30 °C with a concentration of substrates c = 0.1 M and catalysts loading 1 mol-% (entry 1 and 2) or 2 mol-% (entry 3, 4).

To a stirred solution of the substrate (1 equiv.) and durene (1 equiv., used as internal standard) in 2-methyltetrahydrofuran, a solution of the catalyst in 2-methyltetrahydrofuran was added at 30 °C in a single portion. Aliquots (50 μ L) of the reaction mixture were taken at given intervals and ethyl vinyl ether (100 μ L) was added immediately to quench the reaction sample. Then HPLC grade toluene (500 μ L) was added and such prepared reaction mixture samples were analysed by GC chromatography.





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Olefin Metathesis

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Popular SIPr-bearing Hoveyda-type catalysts were investigated both experimentally and computationally. It was proved that metathesis reactions

can be performed in green 2-MeTHF, which can successfully replace more toxic solvents typically used in the pharmaceutical industries.

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