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Sulfoxide-Chelated Ruthenium Benzylidene Catalyst: a Synthetic Study on the Utility of Olefin Metathesis

Karolina Żukowska,*[a] Łukasz Pączek,[a] and Karol Grela[a, b]

We provide an experimental summary of selected advances in olefin metathesis methodology that were reported over the past decades. A stable and universal sulfoxide-chelated ruthenium olefin metathesis catalyst [$RuCl_2$(SIMes)(=CH–C_6H_4–S(O)Ph)], SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene, was introduced and its application profile was studied in detail. A range of model substrates of natural origin was developed and successfully metathesized with variants of the reaction, such as ene–yne, cross, or ring-closing metathesis. All reported reactions were performed in non-pretreated solvents and in air to demonstrate the user-friendliness of the system. Besides the great functional group tolerance exhibited by the reported complex, its compatibility with multiple solvents was determined along with its air and moisture stability. Additionally, an interesting effect increasing the reaction efficiency was observed, if reactions were performed at temperatures around the solvent boiling point.

Introduction

The growing importance of catalysis is evident in the chemical processes reality.[1] This is particularly visible in the industry, where a growing number of catalytic methods became virtually irreplaceable.[2] Application of catalysis has several advantages, which constitute decrease of generated waste, overall time, and cost reduction and, consequently, production in the spirit of green chemistry, which considers catalysis one of its key points. Additional benefits come from the ease of compound modification or diversification enabled by catalytic process, resulting in shorter synthetic routes leading to high-value products of increased complexity.

Olefin metathesis[3] is among the most commonly employed catalytic methods of C=C bond formation. It is a fairly mature field of science that has been finding its way to industrial processes over recent decades.[4] There are numerous examples of applications in both industry and fine-chemicals synthesis.[5] A great advantage of this method is that it gives access to straightforward derivatization leading to compound libraries with potentially diverse activity making it ideal for pharmaceutical research.[6]

This fine methodology requires transition-metal complexes to promote the catalytic cycle. Various compounds based on molybdenum, tungsten, and ruthenium[7] were found suitable to perform this task, however, the last class is assumed to be the most user-friendly. The most beneficial characteristics of ruthenium-based complexes are their air and moisture stability making them easy to handle.[8] Over the years many catalyst classes have been developed to serve different purposes (Figure 1).

Complexes **1**–**6**[9] were among the first obtained structures and served as a basis for further modifications. Many interesting classes of compounds have been obtained, for example, containing two N-heterocyclic carbenes such as **7**,[10] but compounds bearing bidentate alkylidene ligands are perhaps the

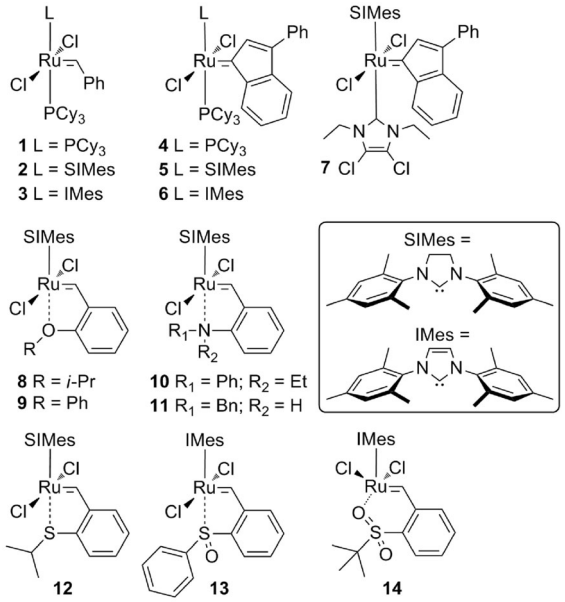

Figure 1. Selected ruthenium-based metathesis complexes.

[a] K. Żukowska, Ł. Pączek, Prof. K. Grela
Institute of Organic Chemistry
Polish Academy of Sciences
Kasprzaka 44/54
01-224 Warsaw (Poland)
E-mail: karolina.zukowska@gmail.com

[b] Prof. K. Grela
Biological and Chemical Research Centre, Faculty of Chemistry
University of Warsaw
Żwirki i Wigury 101
02-089 Warsaw (Poland)

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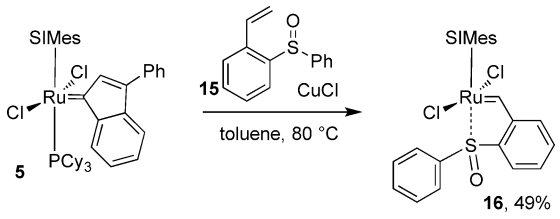
most interesting for further applied research nowadays.[11] The excellent performance of complex **8**[12] triggered various studies on optimization of oxygen substituents (**9**),[13] other types of heteroatoms (**10**–**11**),[14] or oxidation level of thereof (**12**–**14**).[15]

Variety of those complexes turned out to be stable and promising (e.g., **7**, **9**, **10**, **13**), but reports on their applications towards advanced synthetic targets are still quite scarce, even though such catalysts are known to be easily scalable.[16] Most reports contain only a brief description of their activity in model reactions. Tests of solvent compatibility and more advanced substrates remain mostly unavailable thus discouraging the use of novel complexes. Finding one of our complexes in such a situation motivated us to provide a more detailed study.

Compound **13** was a very promising member of a sulfoxide-chelated catalyst series, unfortunately, the original study[15b] did not entirely reveal the advantages of the catalyst class. Therefore, we decided to conduct a more thorough investigation.

Results and Discussion

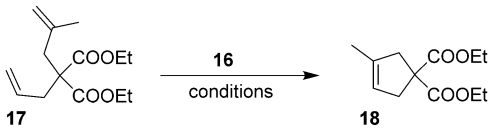
Based on the reported study,[15b] we initially believed that the *p*-nitrophenyl derivative of complex **13** was the most promising member of the sulfoxide complex family, but the high catalyst loading in that study prevented accurate comparison. A recent study on the same class of compounds revealed that the phenyl-substituted complex performed almost two times better in low loadings.[17] It was also indicated that the catalyst bearing a saturated N-heterocyclic carbene initiates faster than its unsaturated congener providing very similar end results. Therefore, we decided to synthesize complex **16** that would combine those beneficial structural features (Scheme 1).



Scheme 1. Synthesis of the studied complex **16**.

The obtained system was preliminarily checked in ring-closing metathesis (RCM) of a known model compound **17** (Scheme 2). This reaction leads to formation of a trisubstituted double bond, providing a good basis for screening metathesis systems. As one of the project aims was to get a user-friendly system, the initial screening included runs in predried degassed toluene under argon flow followed by runs in non-pretreated HPLC-grade solvent on air. The results are presented in Table 1.

The first run was conducted in typical metathesis conditions such as toluene, 80 °C. To stress the system, it was performed in air- and moisture-containing environment. Although only 0.5 mol% of the studied complex was used, 90% conversion



Scheme 2. Model RCM reaction.

Table 1. Initial screening of RCM conditions.

Ru loading [mol%]	Temperature [°C]	Conditions	Conversion [%][a]
0.5	80	toluene as received, on air	90
0.5	100	anhydrous toluene, argon atmosphere	98
0.5	100	toluene as received, on air	99
0.1	100	anhydrous toluene, argon atmosphere	79
0.1	100	toluene as received, on air	22

[a] Conversion determined by GC after 1 hour.

was reached. To push the system even further we elevated the temperature of the transformation to 100 °C.[7] Irrespective of the reaction conditions, maximum conversions were achieved in 1 h, and over time (8 h heating) no decomposition or isomerization of the formed product was observed. Subsequently, the loading was decreased by five times to 0.1 mol%. Only in this conditions the application of the pretreated solvent in inert conditions proved significantly better than the non-pretreated one (79 vs. 22%). Interestingly, in all cases the maximum conversion was reached within an hour of the reaction start and no side reactions were observed during prolonged heating time.

As toluene is not a particularly difficult solvent to conduct metathesis reactions, we selected a number of solvents that tend to be more challenging and typically require pretreatment.[18] Usually, the aim of such operation is to evacuate any stabilizers, possibly formed decomposition products, or traces of water that may be detrimental to the metathesis reaction. The solvents were selected to enable working with polar compounds. Additionally, the screening took into consideration the current regulatory situation[19] unfavorable for typically utilized metathesis solvents such as DCM or toluene. Emphasis was put on the environmental aspects so the chosen solvents can be described as green.[20,21] Considering the already reported compatibility with other ruthenium systems we selected dimethyl and diethyl carbonates (DMC and DEC),[22] alcohols (1-butanol), ethers such as 2-methyltetrahydrofurane (2-MeTHF),[23] cyclopentyl methyl ether (CPME),[18b] and dimethyl glycol (DMG). All of those were used as obtained, without any purification with the tested ruthenium system. The results are presented in Figure 2.

The outcome of this experiment was very interesting. Over 80% conversion was achieved in both tested carbonates and

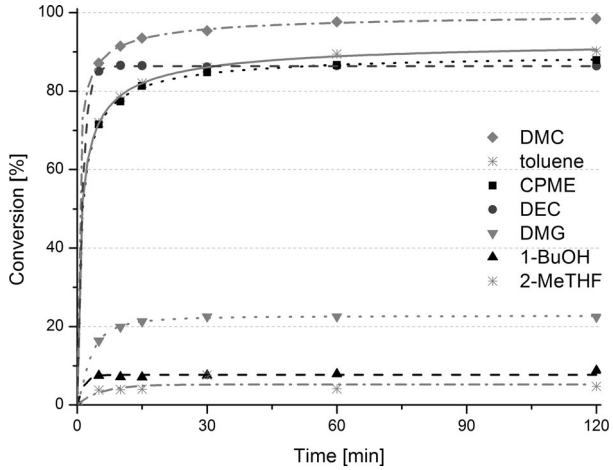


Figure 2. RCM of **17** conducted in various solvents (0.5 mol% **16**, 80 °C).

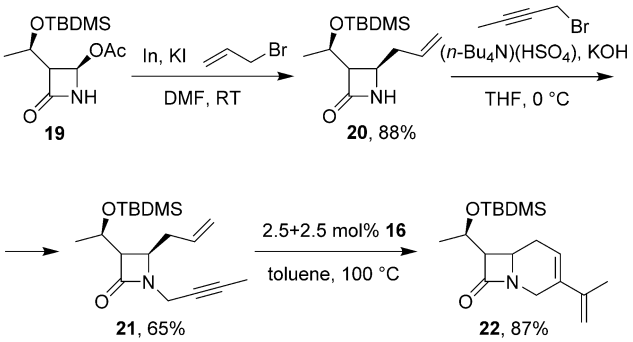
CPME, whereas other tested ethers (2-MeTHF and DMG, 5% and 22%, respectively) and 1-buthanol (9%) turned out to be very poor. The very pronounced difference between CPME (88%) and 2-MeTHF, which are known to be very similar in their properties, drew our attention. As the reactions were performed in a relatively low ruthenium loading, we have considered the potential presence of inhibiting stabilizers, such as butylated hydroxytoluene (BHT) and the tendency of both solvents to form peroxides as a possible source of this discrepancy. Both of these issues can be excluded by additional solvent purification, but the reactions run in distilled and degassed 2-MeTHF and CPME gave the same tendency.

The difference between methyl and ethyl carbonate was also interesting. The first of those gave the product in the highest nearly quantitative conversion (98%), whereas the second led to a noticeably lower conversion (86%).

This pronounced difference cannot be explained by the temperature, which was the same in both experiments. A different type of interaction with the reacting system is also highly unlikely because of the similar chemical character of considered solvents (DMC and DEC). We presume that the difference may lie in the boiling points of the studied solvents. The conditions utilized temperature near the boiling point of methyl carbonate (90 °C) and that may have aided the ethylene removal[24] from the reaction media, and as no flow of inert gas was applied, the difference may be pronounced. This effect would not be observable in the case of the diethyl carbonate which boils at 126 °C. To explore this possibility we decided to conduct an additional run under reflux with CPME (b.p. = 106 °C) and toluene for comparison purpose. The yields after 1 h at 110 °C were 88% for CPME and 53% for toluene, providing a hint that the described effect may be in operation.

Having obtained satisfactory results with the model diene **17** in non-innocent conditions we decided to utilize the developed catalytic system in the synthesis of selected, more challenging molecules containing pharmaceutically relevant fragments. Our aim was to perform the study in conditions that would reveal complex **16** as a user-friendly tool in target-oriented organic synthesis. We decided against the application of pretreated solvents, high vacuum, or inert gas atmosphere. Moreover, we focused on reporting isolated yields, because isolation of the polar compound from the crude mixture may also be difficult.

The first chosen model substrate, **21**, is a precursor of a bicyclic member of β-lactam family of antibiotics. This class of compounds is heavily used in medicine thanks to its broad spectrum of antibacterial and antifungal activity combined with a relatively low toxicity.[25] Our target molecule was the known β-lactam-containing compound **22**, which can be obtained by a short sequence involving ene–yne metathesis (Scheme 3).

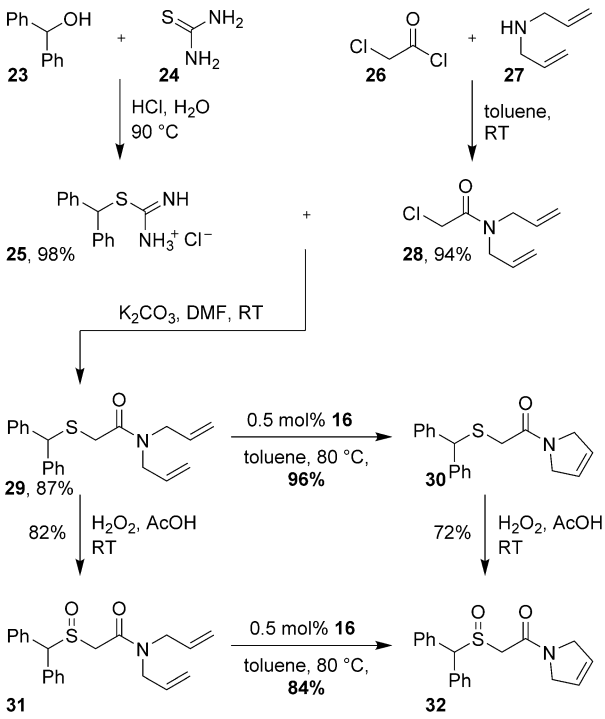


Scheme 3. Synthesis of compound **22** containing a β-lactam core.

The metathesis substrate **21** was obtained from commercially available **19** by utilizing a two-step pathway.[26] The previously reported metathesis of this substrate utilized 10 mol% of ruthenium complex **1** under completely inert conditions.[27] Aware of the challenges, we initially employed 2.5 mol% of complex **16**, but this led only to 33% conversion after 1 h. In another run, applied 2.5 mol% and after 1 h reaction time we added the same dose of the Ru complex. Such treatment led to a nearly complete conversion and allowed us to isolate the desired compound in 87%. This success allowed us to employ more challenging substrates to ensure that it is compatible with more structurally diverse compounds.

As another model system, we selected a compound bearing a strongly chelating sulfoxide moiety:[28,29] modafinil, a pharmacologically active agent commonly used in treating of sleep disorders.[30] We envisioned a derivative of the parent compound containing two allylic groups that through metathesis would form a substituted pyrroline ring. To obtain the desired model we utilized benzhydrylisothiouronium chloride **25**[31] and *N*,*N*-diallyl-2-chloroacetamide[32] as the substrates (Scheme 4). Combining those compounds in a final alkylation reaction resulted in the formation of a molecule that required a final oxidation stage. Once it was completed two structurally similar models, **29** and **31**, were available for us to test in the metathesis reaction, a thioether and its monooxidated version.

We decided to run metathesis on both of them to evaluate the influence of sulfoxide and sulfide functional groups. We adapted the initial conditions, non-pretreated toluene in 80 °C, and gladly observed that both compounds underwent metathesis readily allowing isolation of pure products in very good yield. The studied thioether derivative resulted in quantitative



Scheme 4. Synthesis of a modafinil derivative **32**.

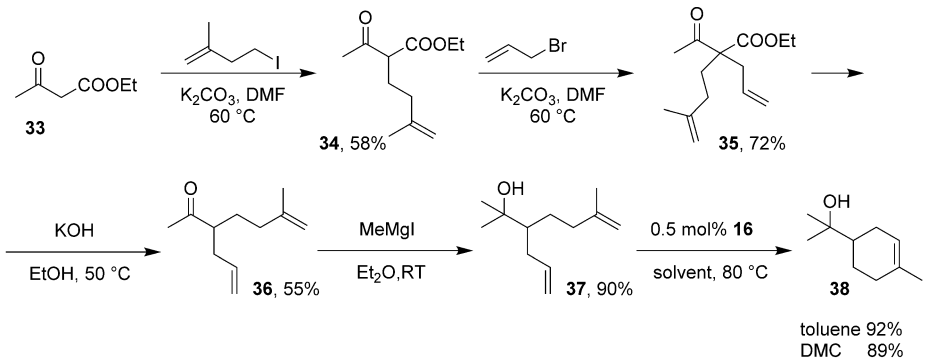
conversion and 96% isolated yield. The sulfoxide compound was also quantitatively converted to the product but because of its high polarity its isolated yield was lower (84%). To enable comparison with other known catalytic systems, reactions in similar conditions were performed utilizing complex **2**. In both cases the results were inferior—the thioether **30** was obtained with 88% yield and the sulfoxide **32** with 82% yield.

Interestingly, the sequence of metathesis and oxidation can be performed equally successfully irrespective of the order. Applying RCM after the oxidation step results in 69% yield of a two-step sequence. This approach has the advantage of using the minimal quantity of the ruthenium compound, as the catalytic step is the last one in the synthetic pathway. On the other hand, conducting RCM prior to oxidation allows an identical 69% yield of the sequence. The additional beneficial aspect of the metathesis-then-oxidation is that the latter step facilitates removal of ruthenium residues in the final product making it more suitable for pharmaceutical applications.[33]

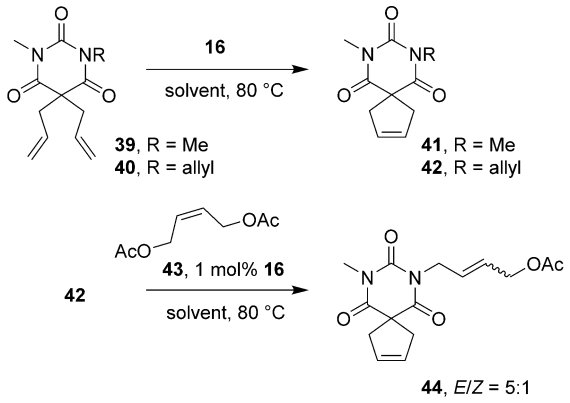
The next selected model was α-terpineol (**38**, Scheme 5), a natural compound containing a substituted double bond. One of its main characteristics is a very pleasant odor of this compound, often associated with lilac, making it a very common ingredient in the production of cosmetics and perfume.[34] Owing to the high demand from the industry, many large-scale methods of synthesis have been developed.[35] We did not envision metathesis becoming one of those for cost reasons, but it remained a valid research model for evaluating our catalytic system in metathetic reactions leading to a substituted double bond. We visualized a synthesis starting from ethyl acetoacetate which after subsequent alkylation, saponification,[36] and a Grignard reaction[37] yielded the model for the metathesis study. Subjecting the substrate **37** to standard conditions utilized in this study, we managed to obtain very good yields irrespective of whether the reaction was conducted in toluene or DMC.

Another class of compounds examined in our study were the allyl barbiturate derivatives already explored in metathesis reactions.[38] We prepared two models with different number of allyl functionalities. The first was the simple diallyl derivative **39**, and the other molecule (**40**) had an additional allyl moiety substituted at the nitrogen atom (Scheme 6). By comparing how those models undergo metathesis we wanted to check the selectivity of the resulting process. A summary of the conducted experiments is presented in Table 2.

The experiment series begun with subjecting both compounds to 1 mol% of catalyst **16** in toluene. Quantitative conversion of the dimethyl compound led to the isolation of **41** in 99% yield, whereas in a previously published report[38] 10 mol% of complex **1** were used to provide product **41** with only 88% yield. The molecule bearing the additional allyl moiety yielded the RCM product in only 70% proving the reaction more challenging as a result of the lower selectivity. Decreasing the catalyst loading was the next step of the research. The spiro compounds **41** and **42** were then obtained in 84% and 67%, respectively. Interestingly the decrease of loading was far less detrimental to the substrate bearing three allyl moieties. Presumably owing to the lower concentration of the active ruthenium species, the number of unproductive turn-



Scheme 5. Metathesis step en route to α-terpineol.



Scheme 6. Synthesis of chosen barbituric acid derivatives.

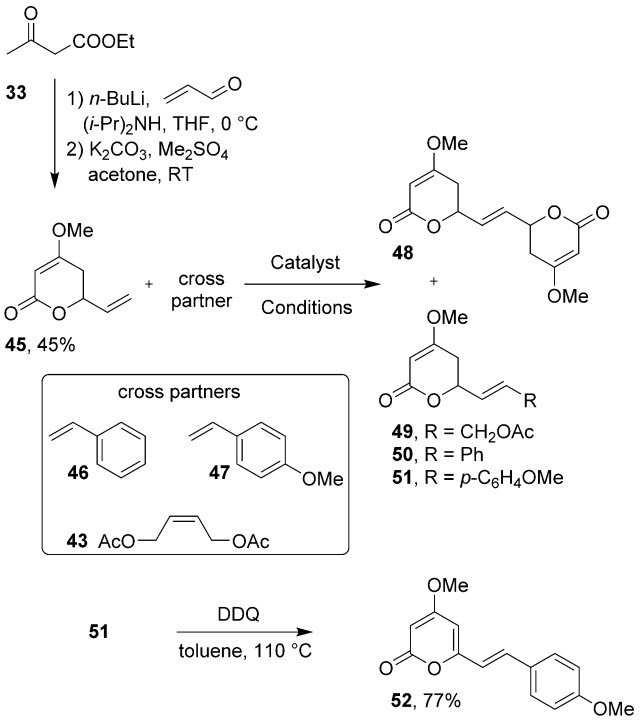
Table 2. Conditions utilized in metathesis of barbiturate derivatives. [C] = 0.1 M.

Product	Loading [mol%]	Solvent	Isolated yield [%]
41	1	toluene	99
42	1	toluene	70
41	0.5	toluene	84
42	0.5	toluene	67
42	0.5	DMC	81
44	1	toluene	55
44	1	DMC	59

overs was reduced. Having in mind the beneficial effect of dimethyl carbonate discussed before, we decided to employ it in the described reaction. As a result we isolated the RCM product **42** in very high, 81% yield. Having this compound in hand, we decided to subject it into cross metathesis employing *cis*-1,4-diacetoxy-2-butene as a cross partner. Utilizing 1 mol% of the catalyst, we managed to isolate 55% of the substituted product **44**. Changing the solvent to DMC resulted in improved yields of 59%. The results may stem from the very high polarity of the product, making it relatively difficult to purify by column chromatography.

The next group of studied compounds were members of the kavalactone family. Compounds belonging to this class were isolated from the Kava shrub and popularized because of their healing properties. They are used for treating a range of conditions, such as stress disorders, nervous tension, and restlessness, with minimal side effects.[39] The pharmacological potential made them interesting targets for the synthesis with complex **16** (Scheme 7). The first step to obtain the substrate was aldol condensation of ethyl acetoacetate with acroleine and a subsequent methylation of the resulting compound.[40] The obtained compound **45** was then coupled with various compounds in metathesis reactions and the results are summarized in Table 3.

Subjecting **45** and styrene to previously utilized metathesis conditions resulted in only minor conversion. After isolation of the obtained product and analysis it was determined to be the result of the



Scheme 7. Synthetic pathway towards selected kavalactones.

substrate self-cross metathesis (**48**) in 7% yield. Increasing both the catalyst loading and the temperature increased the yield to 18%, but the result was still the isolation of **48**. To determine if cross metathesis is a feasible method of obtaining a cross product with **45** we decided to further increase the loading to 2.5 mol% added twice and change the cross partner. In the reaction with *cis*-1,4-diacetoxy-2-butene we observed the formation of the expected cross product in 75% yield. To check if a change of catalyst may provide better results we examined a known complex **2**. Unfortunately it performed in the examined reaction quite poorly leading to 56% yield. In another attempt to increase the yield of the reaction we conducted a run in toluene (110 °C) and utilized CPME in the very same conditions. We were hoping to observe a higher yield in the reaction conducted in CPME, whereas we obtained 78% yield in toluene and only 64% yield in CPME. This result seemed to be a bit out of place until we realized that the uti-

Table 3. Conditions of cross metathesis (CM) leading to kavalactone derivatives.

Cross partner	Loading [mol%]	Catalyst	Solvent	Temperature [°C]	Isolated yield [%] dimer	CM
46	0.5	**16**	toluene	80	7	0
46	2.5	**16**	toluene	100	18	0
43	2.5+2.5	**16**	toluene	100	0	75
43	2.5+2.5	**2**	toluene	100	0	56
43	2.5+2.5	**16**	toluene	110	0	78
43	2.5+2.5	**16**	CPME	110	0	64
46	2.5+2.5	**16**	toluene	110	13	48
46	2.5+2.5	**16**	CPME	110	8	56
47	2.5+2.5	**16**	CPME	110	0	55

lized cross partner (**43**) had a boiling point of 120 °C. As a result the boiling CPME facilitated not only the removal of ethylene, but also of **43** decreasing the concentration of the cross partner in the reaction mixture and overall diminishing the yield.

Having in hand the conditions suitable to perform cross metathesis we returned to the styrene as a cross partner to obtain the desired kavalactone. In 110 °C and toluene we observed a very high conversion. After purification we observed 48% of the cross product and 13% of the self-CM product. Repeating the reaction with CPME as a solvent improved the ratio, resulting in 56% of kavain and 8% of the dimer.

As the last applied conditions proved to be the best we utilized them to obtain the yangonin precursor (**51**). In this reaction we did not observe any trace of substrate dimerization. The cross product was obtained selectively in 55%. Subsequent reaction of **51** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) resulted in the desired kavalactone–yangonin with 77%.

Conclusions

This work summarizes the advances in olefin metathesis methodology that were reported over the past decades. A new member of sulfoxide-chelated class of ruthenium catalysts was obtained and fully characterized as an emphasis of numerous improvements in catalyst structure. To illustrate the user-friendliness of the system along with application versatility, we demonstrated the compatibility of our sulfoxide-chelated ruthenium catalyst [$RuCl_2$(SIMes)(=CH–C_6H_4–S(O)Ph)] (SIMes = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene) with multiple solvents, along with its air and moisture stability. To prove that olefin metathesis is up to the rising challenges of organic synthesis, we successfully employed the new catalyst in several metathesis reactions leading to derivatives of natural compounds with good to excellent outcomes. A significant functional group tolerance of the catalyst was determined. Additionally, the facilitation of ethylene removal by application of a boiling solvent was presented as a tool for optimization of metathesis reactions conducted without inert gas flow.

Experimental Section

Preparation of complex 16

Complex **5** (0.4 mmol, 380 mg), copper(I) chloride (0.48 mmol, 47.5 mg), and compound **15** (0.6 mmol, 138 mg) were placed in a Schlenk tube under argon and dissolved in anhydrous toluene (20 mL). The mixture was heated at 80 °C for 20 minutes. After that it was cooled down to room temperature and evaporated. The residue was redissolved in ethyl acetate and passed through a Pasteur pipette containing a cotton pad. and evaporated to dryness. The crude product was purified by column chromatography (cyclohexane : ethyl acetate 5:95 to 50:50 (v:v)). After evaporation of the solvents, the resulted solid was dissolved in DCM and washed with cold *n*-heptane. Complex **16** was obtained as dark green crystals (137 mg, 0.2 mmol) with 49% yield. ^{1}H NMR ($CDCl_3$): δ = 2.41 (d, J = 18.2 Hz, 12H), 2.55 (s, 6H), 4.11 (s, 4H), 6.77 (d, J = 7.6 Hz, 1H), 6.97 (s, 2H), 7.05 (s, 2H), 7.08–7.12 ppm (m, 2H), 7.20- 7.25 (m, 2H), 7.27–7.36 (m, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.56–7.61 (m, 1H), 16.75 ppm (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 21.3, 22.8, 29.1, 32.0, 52.2, 121.0, 127.0, 127.5, 127.7, 129.7, 130.0, 130.2, 130.7, 134.2, 138.0, 138.5, 138.8, 139.0, 142.3, 156.3, 206.1 ppm. IR (KBr) $\tilde{\nu}$ = 3495, 3058, 2951, 2916, 2853, 1697, 1606, 1581, 1478, 1442, 1397, 1306, 1284, 1264, 1226, 1125, 1112, 1065, 1034, 996, 852, 798, 746, 688, 632, 593, 579, 539, 516, 493, 449, 419 cm^{-1}. MS (ESI) m/z: [(M-Cl^+)] 657.13. Anal. calcd. for $C_{34}H_{36}Cl_2N_2ORuS$ (692.70): C, 58.95; H, 5.24; N, 4.04; S, 4.63. Found: C, 58.88; H, 5.24; N, 3.79; S, 4.48.

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Keywords: alkenes · homogeneous catalysis · metathesis · natural products · ruthenium

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K. Żukowska, Ł. Pączek, K. Grela*

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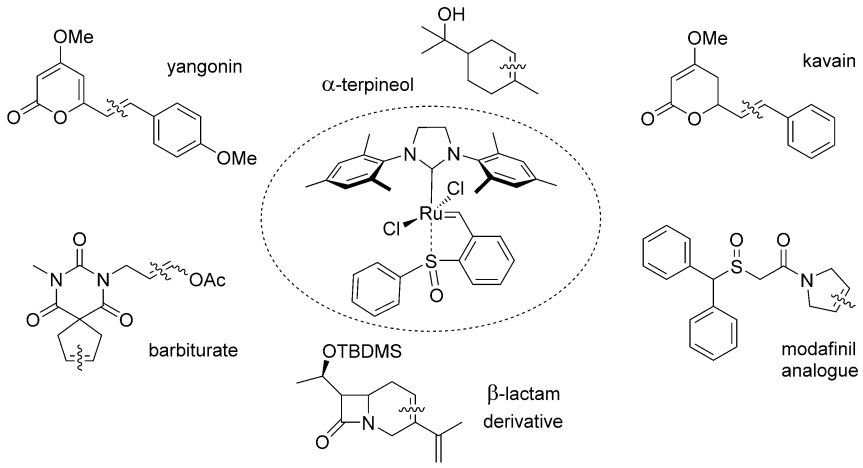
Sulfoxide-Chelated Ruthenium Benzylidene Catalyst: a Synthetic Study on the Utility of Olefin Metathesis



A new industry's darling? The stable and universal sulfoxide-chelated ruthenium olefin metathesis catalyst [$RuCl_2$(SIMes)(=CH–C_6H_4–S(O)Ph)] is introduced and its application profile in metathesis with respect to relevant target natural compounds studied. The catalyst offers great functional group tolerance, compatibility with multiple solvents, and air and moisture stability.