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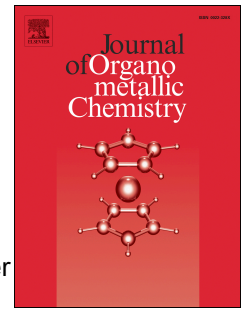

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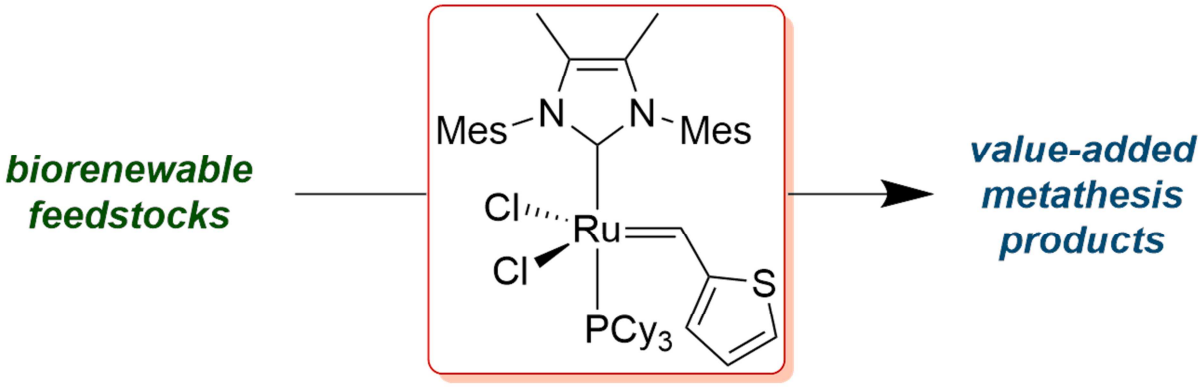

EXPLORING THE REACTIVITY OF A RUTHENIUM COMPLEX IN THE METATHESIS OF BIORENEWABLE FEEDSTOCKS TO GENERATE VALUE-ADDED CHEMICALS

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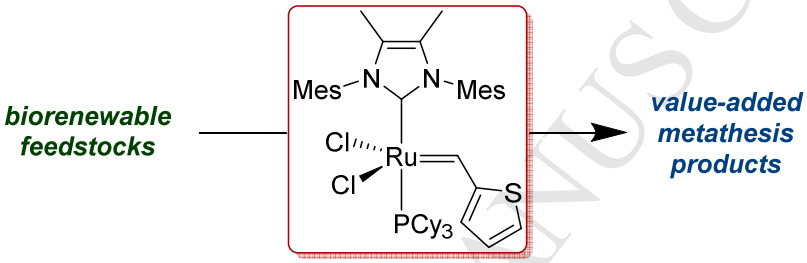
In memory of Professor the Lord Lewis of Newnham: Ph.D. advisor, mentor, and encourager



A ruthenium complex proves active for the ring-closing metathesis of linalool and citronellene, the self-metathesis of eugenol, and to some extent the ethenolysis of methyl oleate. Microwave heating and continuous-flow processing have been used as tools for performing the reaction.

KEYWORDS: Metathesis; Ruthenium; Biorenewable; N-Heterocyclic Carbene; Valorization

ABSTRACT

Tricyclohexylphosphine[4,5-dimethyl-1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene][2-thienylmethylene]ruthenium(II) dichloride proves active for the ring-closing metathesis of linalool and citronellene, the self-metathesis of eugenol, and to some extent the ethenolysis of methyl oleate. Microwave heating and continuous-flow processing have been used as tools for performing the reaction. For the ring-closing metathesis reactions, transition from batch to flow processing for scale-up of the reaction is possible, but it proves problematic in the case of cross-metathesis.

1. INTRODUCTION

The conversion of biomass into biofuels has been a topic of increasing research interest in the chemistry community. This has been driven by environmental concerns, political drivers, and commercial success [1]. Although they account for only around 2% of the biomass produced annually, fats and oils constitute approximately 35% of the renewable feedstocks currently used by the chemical industry [2,3]. They are most frequently converted into fatty acid monoesters (biodiesels) by means of transesterification reactions with low molecular-weight alcohols such as methanol and ethanol [4]. Alongside efforts focused around biofuels production, the valorization of biomass is also gaining momentum; that is the transformation of biorenewable feedstocks into value-added commodity chemicals [5,6]. Again, oleochemicals are attractive starting materials due to their availability on large scale at commodity prices and the fact that they contain multiple functional groups with which chemistry can be performed [7]. The presence of double bonds in fats and oils means that they are amenable to derivatization by means of alkene metathesis [8]. Transition-metal catalyzed alkene metathesis has proven to be a powerful tool in organic synthesis [9,10] but one of the issues with using biomass in these reactions can be the sensitivity of the catalyst to either the range of functional groups present or the purity of the feedstock. However, with the development of more rugged catalysts, these problems are being overcome. The ruthenium-based catalyst systems pioneered by Grubbs and coworkers have found particular application due to their tolerance to air, water, and polar organic functional groups [11,12].

It is possible to perform cross metathesis, ring-opening metathesis, ring-closing metathesis and ethenolysis (reaction with ethene) on biomass substrates depending on their structure. Most attention has focused on either self-metathesis [13] or ethenolysis [13,14] of methyl oleate or analogous monoglycerides, where the products are either long-chain internal alkenes or shorter-chain terminal alkenes, respectively. The ethenolysis of oils (triglycerides) has been less widely explored [15], as have metathesis reactions of terpenes such as citronellene [16,17] and linalool [18,19,20,21], and phenylpropenoids such as eugenol [19,22,23].

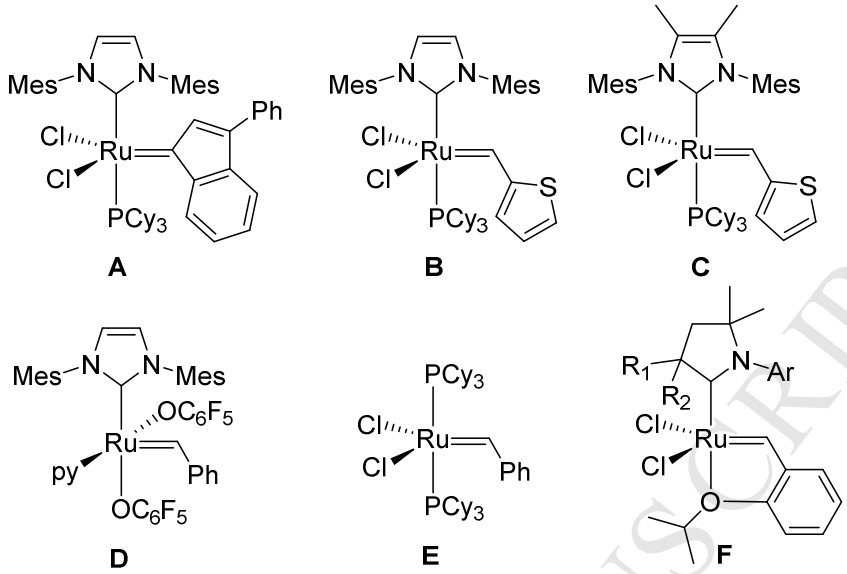
In our group, we have an interest in developing cleaner, greener synthetic methods and, as part of this endeavor, we use microwave heating and continuous-flow processing as enabling technologies. Microwave heating offers safe, easy, and highly reproducible access to elevated temperatures [24]. It is also possible to perform reactions under an atmosphere of reactive gases [25]. Conventionally heated continuous-flow processing is proving to be a viable alternative to the traditional batch methods for preparative chemistry [26,27]. Inherent advantages include enhanced safety, ease of scale-up, and efficient mixing of reagents. It is possible to control reaction parameters precisely and to affect chemistry across a wide temperature range successfully. As with microwave heating, reactive gases can be used as reagents in flow processing [28]. The small volumes of flow reactors ameliorate the hazards of high-pressure gas reactions and enable improved mixing with the liquid phase. We have recently turned our attention to the use of these tools for performing alkene metathesis reactions on bio-renewable feedstocks and present our results here.

2. RESULTS AND DISCUSSION

2.1. CATALYST SELECTION

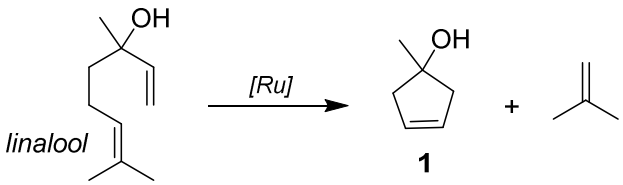
The selection of appropriate catalyst candidates was considered of key importance. Given the scale on which alkene metathesis reactions would need to be performed when using bio-renewable feedstocks as sources of value-added commodity chemicals, cost, availability, and licensing are important factors to take into account. Our attention turned to a series of three royalty-free catalysts that have become available in the last few years [29,30,31]. They are based on a second-generation Grubbs type motif, bearing *N*-heterocyclic carbene (NHC) and tricyclohexylphosphine ligands (Figure 1). The difference between the three complexes comes either in the nature of the alkylidene unit (**A** vs **B**) or the NHC group (**B** vs **C**). Of the three, **C** has seen particular application in metathesis so our attention focused on this complex.

Figure 1: Ruthenium complexes discussed in this study



2.2. RING-CLOSING METATHESIS OF LINALOOL

Our starting point was to study the ring-closing metathesis (RCM) of linalool to yield 1-methylcyclopent-2-enol (**1**) and isobutene, both of which are valuable precursors to high-energy fuels (Scheme 1) [32]. Although the RCM of linalool involves passing through a sterically-hindered intermediate, hydroxyl groups in an allylic position are known to accelerate the rate of carbene-exchange between the adjacent vinyl group and external ruthenium alkylidenes [19]. This enhancement is sufficient to overcome the significant steric deactivation. While generally, catalyst loadings of 1-5 mol% are used to achieve high product conversion efficiencies [18], one of the most effective catalysts to date is the pseudohalide-functionalized ruthenium complex **D** where 100% conversion can be obtained after 15 min heating in refluxing chloroform when using a loading of 0.5 mol% loading, or after 1 h at a loading of 0.05 mol% [21].



Scheme 1: Ring-closing metathesis of linalool

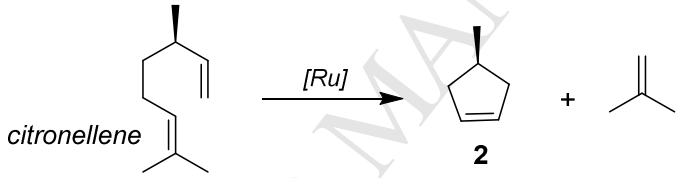
Using **C** as our catalyst, we decided to screen the reaction in two solvents: toluene and dimethylcarbonate (DMC). The latter was selected since it is classified as a green solvent [33]. Working at a catalyst loading of 0.1 mol% and after heating at 80 °C for 1 h, we obtained 40% and 43% conversions in DMC and toluene respectively (Table 1, entries 1&2). We also performed the reaction solvent-free under the same reaction conditions (entry 3). Although we were able to obtain a conversion of 70%, we also observed significant oligomer formation, presumably due to competing cross-metathesis reactions. Returning to toluene as the solvent, we probed the effects of temperature on the reaction, finding that 80 °C was optimal (entries 4-6). Complete conversion was obtained after heating at 80 °C for 20 min by increasing the catalyst loading from 0.1 mol% to 0.5 mol% (entry 7). We were able to reduce the reaction time to just 10 minutes and obtain quantitative conversion (entry 8). However, halving the catalyst loading to 0.25 mol% resulted in a concommitant drop in product conversion (entry 9). Thus, our optimized conditions were 0.5 mol% **C**, heating at 80 °C for 10 minutes.

Table 1: The ring-closing metathesis of linalool using **C**.

Entry	Solvent	Catalyst Loading (mol%)	Time (min)	Temperature (°C)	Conversion (%)
1	toluene	0.1	60	80	43
2	DMC	0.1	60	80	40
3	-	0.1	60	80	70
4	toluene	0.1	60	25	3
5	toluene	0.1	60	40	24
6	toluene	0.1	60	100	28
7	toluene	0.5	20	80	100
8	toluene	0.5	10	80	100
9	toluene	0.25	20	80	65

2.3. RING-CLOSING METATHESIS OF CITRONELLENE

There have only been relatively few reports of the RCM of citronellene to date (Scheme 2). A tungsten oxo-complex was used as the catalyst, with a 68% yield of 3-methylcyclopentene (**2**) being obtained after heating in 1,2,4-trichlorobenzene at 90 °C for 1 h using a loading of 2 mol% [16]. Moving to ruthenium, Grubbs Type 1 (**E**) has been employed in a relative reactivity study [19]. Citronellene was found to be significantly less reactive than linalool, thus confirming the "allylic alcohol effect". With conditions in hand for the RCM of linalool, we wanted to see if we could extend our protocol to citronellene as a substrate.



Scheme 2: Ring-closing metathesis of citronellene

Employing **C** as the catalyst and performing the reaction in toluene at 80 °C for 1 h with a loading of 0.5 mol%, complete conversion of citronellene to **2** was obtained (Table 2, entry 1). We performed the reaction using microwave heating in a sealed tube to avoid product loss since **2** has a boiling point of 64 °C. After the reaction was complete, **2** was isolated from the catalyst, solvent, and any unreacted starting material by trap-to-trap distillation. We probed the effects of catalyst loading, finding that quantitative conversion was obtained when using 0.2 mol% C but this dropped to 33% when further reducing the loading to 0.1 mol% (entries 2&3). The decreased reactivity of citronellal over linalool is

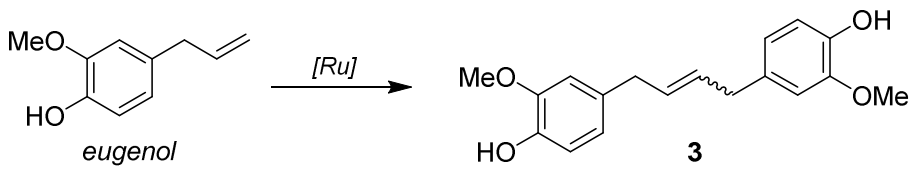
seen in this result when comparing identical reactions (Table 1, entry 1 vs Table 2, entry 3). We again probed the effects of reaction temperature and time, finding that complete conversion can be obtained in 20 mins at 80 °C when using a catalyst loading of 0.5 mol% (entries 4&5).

Table 2: The ring-closing metathesis of citronellal using **C**.

Entry	Solvent	Catalyst Loading (mol%)	Time (min)	Temperature (°C)	Conversion (%)
1	toluene	0.5	60	80	100
2	toluene	0.2	60	80	100
3	toluene	0.1	60	80	33
4	toluene	0.5	60	25	40
5	toluene	0.5	20	80	100

2.4. SELF-METATHESIS OF EUGENOL

Eugenol, a phenolic member of the phenylpropene family, is extracted from plants such as cloves. It has been used in a limited number of cross-metathesis reactions [19,22]. There is one report of self-metathesis in which 0.3 mol% **E** is used as the catalyst and the reaction is performed at room temperature for 24 h [23]. A 71% yield of stilbene **3** is obtained. We therefore decided to probe the activity of **C** in this reaction (Scheme 3).



eugenol **3**

Scheme 3: Ring-closing metathesis of eugenol

We started by performing the reaction at room temperature, using a catalyst loading of 0.5 mol% C and obtained a 48% conversion to **3** after 1 h (Table 3, entry 1). Performing the reaction at 80 °C increased the conversion to 60% (entry 2). Believing that the catalyst was being deactivated over time, we performed the reaction using a catalyst loading of 0.5 mol% and, after 60 mins, we added a second dose of 0.5 mol% **C**. By doing this, we were able to obtain a 93% conversion to **3** (entry 3). Changing from toluene to DMC as solvent had a deleterious effect on the reaction (entry 4).

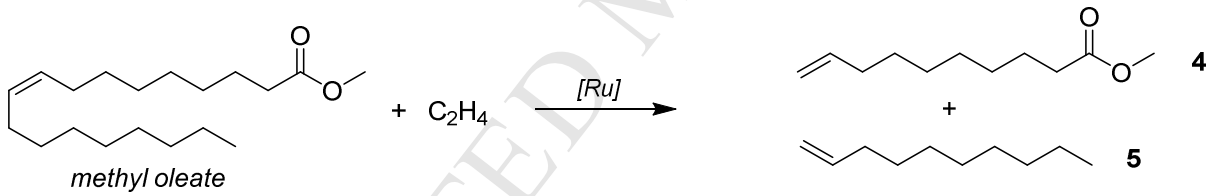
Table 3: The self-metathesis of eugenol using **C**.

Entry	Solvent	Catalyst Loading (mol%)	Time (min)	Temperature (°C)	Conversion (%)
1	toluene	0.5	60	r.t.	48
2	toluene	0.5	60	80	60
3	toluene	0.5 + 0.5	60 + 60	80	93
4	DMC	0.5	60	80	0

2.5. CROSS-METATHESIS OF METHYL OLEATE

Our final class of reaction for study was the cross-metathesis of methyl oleate and ethene to yield methyl 9-decenoate (**4**) and 1-decene (**5**) (Scheme 4). The formation of terminal alkenes from biorenewable feedstocks is particularly attractive. It would allow for the subsequent preparation of commodity chemicals from natural seed oils and their derivatives instead of petroleum products. Indeed, the products from the ethenolysis of methyl oleate find application in a range of industrial sectors including cosmetics, detergents, and soaps, [34] as well as being a potential renewable biofuel source [35].

Ethenolysis reactions involve the formation of metal methylidene species as key intermediates in the catalytic cycle. Most metathesis catalysts are unstable as methylidene complexes and also as the corresponding unsubstituted metallocyclobutane, and so undergo rapid decomposition [36]. Therefore, the ethenolysis of methyl oleate is a good gauge for the relative activity of **C** compared to other alkene metathesis catalysts. A range of ruthenium complexes have been used for the reaction [37], with those bearing NHC ligands being amongst the most active [38]. Perhaps the best currently known catalysts in this class are a series of *N*-aryl, *N*-alkyl NHC ruthenium complexes [39]. They exhibit high selectivity and catalyst loadings as low as 500 ppm can be used. Cyclic alkyl amino carbene complexes (**F**) also prove to be highly active catalysts, operating at loadings as low as 3 ppm [40].



Scheme 4: Cross-metathesis of methyl oleate and ethene

We started our investigations using a catalyst loading of 0.1 mol% **C** and performing the reaction in a microwave unit interfaced with a gas-loading accessory [41,42]. We have used this tool previously for performing reactions involving gaseous reagents [43]. It is possible both to flush reaction vessels with inert gas as well as load up to 17 bar of gas. Operating at an ethene pressure of 7 bar and performing the reaction solvent-free, we obtained a 25% conversion to **4** and **5** after 20 min at 60 °C. (Table 5, entry 1). Performing the reaction in toluene or DMC as a solvent increased the conversion to 27% and 32%

respectively (entries 2&3). Using DMC as the solvent and increasing the catalyst loading to 0.5 mol% resulted in a 45% conversion to **4** and **5** (entry 4). This was not improved upon by increasing the reaction time from 20 min to 60 min (entry 5) suggesting that the catalyst, while initially highly active, is quickly deactivated.

Table 4: The cross-metathesis of methyl oleate and ethene using **C**.[a]

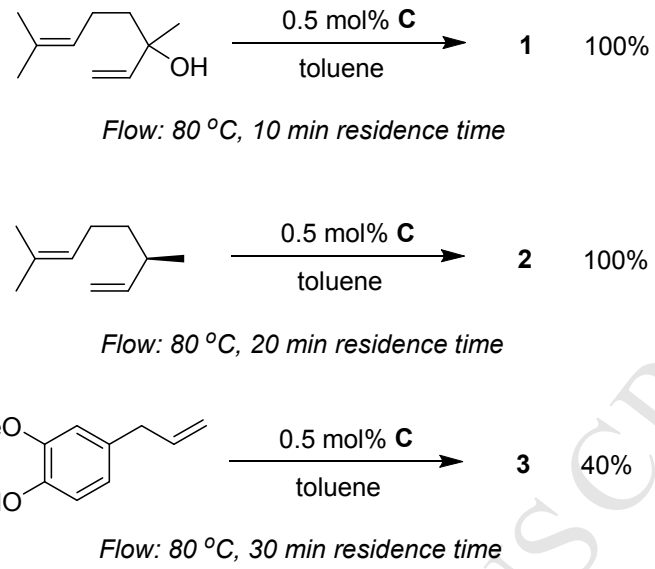
Entry	Solvent	Catalyst Loading (mol%)	Time (min)	Temperature (°C)	Conversion (%)
1	none	0.5	20	60	25
2	toluene	0.5	20	60	27
3	toluene	0.5	20	60	32
4	DMC	0.5	20	60	45
5	DMC	0.5	60	60	46

a) Reactions performed under 7 bar ethene pressure

2.6. REACTION SCALE-UP

Having performed reaction scouting and optimization studies, we wanted to turn our attention to the scale-up of the ring closing metathesis of linalool and citronellene, and the self-metathesis of eugenol. We decided to employ continuous-flow processing as a tool in this endeavor. Flow processing has been used before for metathesis reactions [44]. Most attention has been focused on cross-metathesis and self-metathesis [45,46,47,48], along with examples of ethenolysis [45,49]. In our case, we wanted to probe the effectiveness of flow processing as a tool primarily for ring-closing metathesis, a process that has been less studied in flow mode [46,47].

Since the reaction takes place in a narrow gauge tube and is under a positive pressure (back-pressure regulator at the exit of the flow stream), a concern was that since they could not escape from the reactor as they were generated, the gaseous byproducts formed in the ring-closing metathesis could react with the product or with each other to compromise the efficiency of the process. However, we found this not to be the case when performing the ring-closing metathesis of linalool and citronellene (Scheme 5). Passing the reaction mixture of substrate, 0.5 mol% **C** in toluene through a 10 mL volume coil heated to 80 °C at a flow rate of 1 mL min^{-1} (corresponding to a residence time of 10 min) we observed complete conversion of linalool to **1**. The buildup of the isobutene byproduct was clearly observable as the course of the reaction proceeded, bubbles of gas forming between slugs of liquid. In the case of citronellene, **2** was formed quantitatively when performing the reaction under the same conditions, the only change being that the flow rate was halved, giving a residence time of 20 min. The transition from batch to flow was not as smooth when performing the self-metathesis of eugenol. Operating at 80 °C, using a catalyst loading of 0.5 mol% **C**, and with a residence time of 30 min, a conversion of only 40% was obtained (Scheme 5). In this case, we do believe that the back-reaction could pose a problem. Not only would it reduce the effectiveness of the process but also the ethenolysis reaction has already been shown to deactivate the catalyst over time.



Scheme 5: Metathesis reactions performed using flow processing

3. CONCLUSION

In summary, we have probed the activity of a ruthenium NHC complex, C, in a number of metathesis reactions using biorenewable feedstocks as substrates. It proves active for the ring-closing metathesis of linalool and citronellene, the self-metathesis of eugenol, and to some extent the ethenolysis of methyl oleate. For the ring-closing metathesis reactions, transition from batch to flow processing for scale-up of the reaction is possible, but it proves problematic in the case of cross-metathesis.

4. EXPERIMENTAL SECTION

4.1. General experimental

Chemicals were used as purchased, unless stated otherwise. Ruthenium complex **C** (Tricyclohexylphosphine[4,5-dimethyl-1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene][2-thienylmethylene]ruthenium(II) dichloride; catMETium® RF 3) was purchased from Strem Chemicals. NMR Spectra (^{1}H, ^{13}C) were performed at 298 K on either a Brüker Avance Ultra Shield 300 MHz NMR, Brüker DRX-400 400 MHz NMR, or Brüker Avance 500 MHz NMR. ^{1}H-NMR Spectra obtained in $CDCl_3$ were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent. ^{13}C- NMR Spectra obtained in $CDCl_3$ were referenced to chloroform (77.3 ppm).

Reactions employing microwave heating were performed using a CEM Discover microwave unit and, where appropriate, equipped with a gas-loading accessory. Reactions using continuous-flow processing were performed using either a Uniqsis FlowSyn or a Vapourtec R-Series unit.

4.2. Ring-closing metathesis of linalool

To a 10 mL glass tube equipped with a Teflon-coated stirbar was added linalool (69 mg, 0.45 mmol), **C** (2 mg, 0.5 mol%), and toluene (1 mL, 0.45 M). The tube was then placed in an oil bath that had been heated to 80 °C. The solution was allowed to stir uncapped for 10 min. The reaction mixture was then cooled to room temperature and transferred to a round-bottom flask. The reaction tube was then rinsed twice with diethyl ether (2 mL),

adding the washings to the round bottom flask. The solvents were removed in vacuo by rotary evaporation. The residue was dissolved in $CDCl_3$ and filtered in to a clean round-bottom flask through a pipet filled with a small volume of Celite. The product mixture was analyzed by NMR spectroscopy and GC-MS.

4.3. Ring-closing metathesis of citronellene

To a 10-mL capacity glass microwave tube equipped with a Teflon-coated stir bar was added citronellene (69 mg, 0.45 mmol), **C** (2 mg, 0.5 mol%), and toluene (1 mL, 0.45 M). The tube was sealed with a septum and placed into the microwave cavity. The reaction mixture was heated to 80 °C using an initial microwave power of 100 W and setting a pressure cut-off of 250 psi for safety purposes. Once at temperature, the contents of the tube were maintained at 80 °C for 20 min. After completion of the heating time, the reaction vessel was cooled to room temperature before removing from the microwave unit. Due to the volatility of the product (**2**), conversion was assayed by ^{1}H NMR spectroscopy of an aliquot of the crude reaction mixture.

4.4. Self-metathesis of eugenol

The reaction was performed in an analogous manner to that for linalool, but using eugenol (74 mg, 0.45 mmol) as the substrate, and heating the reaction mixture at 80 °C for 30 min. The product mixture was analyzed by NMR spectroscopy and GC-MS.

4.5. Cross-metathesis of methyl oleate

To a 10-mL capacity glass microwave tube equipped with a Teflon-coated magnetic stir bar was placed methyl oleate (139 mg, 0.47 mmol), **C** (2 mg, 0.5 mol%), and toluene (1 mL, 0.47 M). The reaction vessel was placed into the microwave cavity, the gas-loading accessory connected. The tube was loaded with a pressure of 7 bar of ethene. The reaction mixture was heated to 60 °C using an initial microwave power of 100 W and setting a pressure cut-off of 250 psi for safety purposes. Once at temperature, the contents of the tube were maintained at 80 °C for 20 min. After completion of the heating time, the reaction vessel was cooled to room temperature before releasing the pressure, removing the tube from the microwave unit, and transferring the contents to a round-bottom flask. The reaction tube was then rinsed twice with diethyl ether (2 mL), adding the washings to the round bottom flask. The solvents were removed in vacuo by rotary evaporation. The residue was dissolved in $CDCl_3$ and filtered in to a clean round-bottom flask through a pipet filled with a small volume of Celite. The product mixture was analyzed by GC-MS.

4.6. Scale-up of the ring-closing metathesis of linalool

A 50 mL glass bottle was charged with linalool (1.84 g, 12 mmol), **C** (50 mg, 0.5 mol%), and toluene (25 mL, 0.48 M). The solution was thoroughly mixed until it became a completely homogenous clear dark green solution. The flow reactor was readied using the equipment manufacturer's suggested start-up sequence, followed by heating the reactor coil to 80 °C. The reaction mixture was then loaded into the reactor. Product collection commenced immediately after this switch. After the reaction mixture had been completely loaded into

the reactor, the reactor pump was set back to pumping solvent. After the product had been fully discharged from the reactor coils, the resulting green solution could then be purified.

Toluene was carefully removed using rotary evaporation at room temperature leaving the crude product. The crude product was dissolved in a small amount of 90:10 by volume mixture of hexanes to ethyl acetate and loaded onto a plug of silica. The plug was then rinsed thoroughly with 90:10 by volume mixture of hexanes to ethyl acetate and the solvent was stripped in vacuo in a room temperature water bath. The product was assayed by NMR spectroscopy, relative to an internal standard. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.30 (s, 3 H), 1.83 (m, 2 H), 2.22 (m, 1 H), 2.38 (m, 1 H), 2.59 (br, 1 H), 5.66 ppm (m, 2 H).

4.7. Scale-up of the ring-closing metathesis of citronellene

A 50 mL glass bottle was charged with (69 mg, 0.45 mmol), **C** (2 mg, 0.5 mol%), and toluene (1 mL, 0.45 M). The solution was thoroughly mixed until it became a completely homogenous clear dark green solution. The flow reactor was readied using the equipment manufacturer's suggested start-up sequence followed by heating the reactor coil to 80 °C. The reaction mixture was then loaded into the reactor. Product collection was commenced immediately after this switch. After the reaction mixture had been completely loaded into the reactor, the reactor pump was set back to pumping solvent. After the product had been fully discharged from the reactor coils, the product conversion was first assayed by ^{1}H NMR spectroscopy of an aliquot of the crude reaction mixture. The product was then isolated by a trap-to-trap distillation of **2** from the crude reaction mixture. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1.02 (d, 3H), 1.30 (m, 1H), 2.05 (m, 1H), 2.30 (m, 2H), 2.73 (m. 1H), 5.66 (m, 2H).

4.8. Scale-up of the self-metathesis of eugenol

A 50 mL glass bottle was charged with eugenol (1.864 g, 12 mmol), **C** (50 mg, 0.5 mol%), and toluene (25 mL, 0.48 M). The reaction was performed using the same protocol as that for linalool. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 6.82 (d, 2H), 6.71 (2H, m), 6.69 (2H, s). 5.66 (2H, m), 5.52 (2H, s), 3.86 (6H, s), 3.31 (4H, d).

5. ACKNOWLEDGEMENTS

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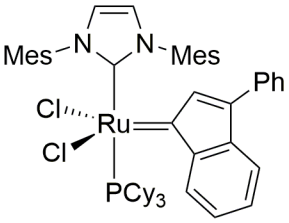

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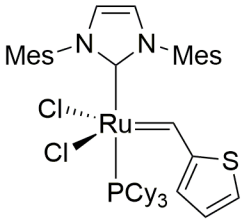

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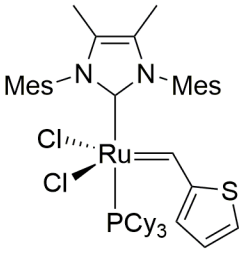

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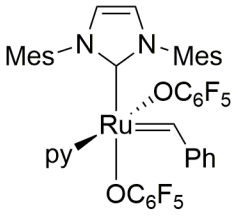

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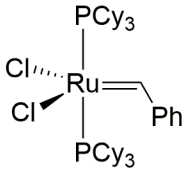

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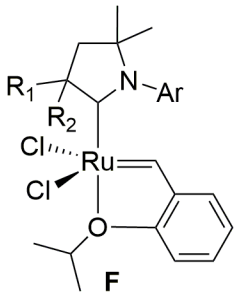

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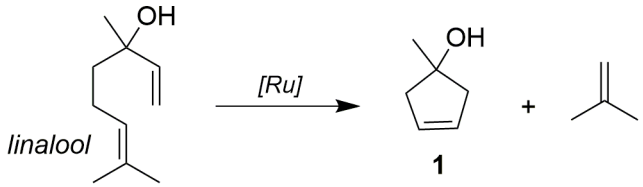

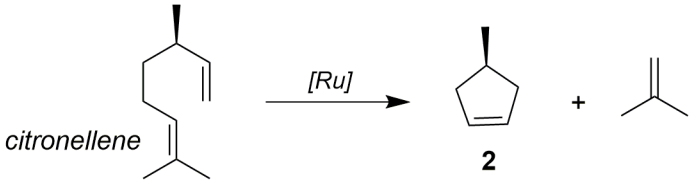

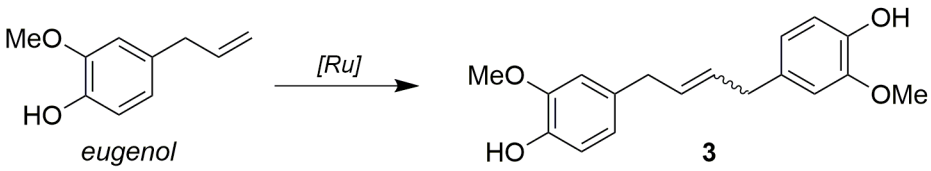

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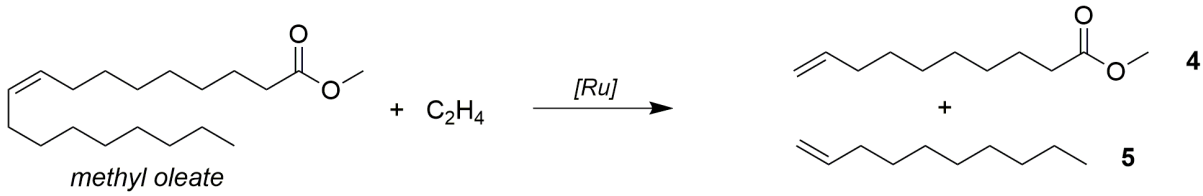

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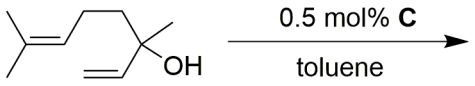

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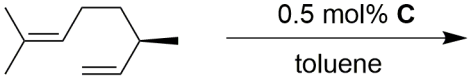

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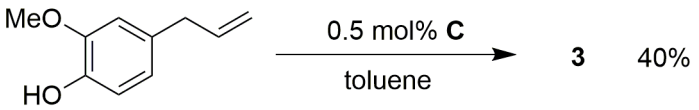

3 40%

Flow: 80 °C, 30 min residence time

HIGHLIGHTS

A ruthenium complex proves active for metathesis of biorenewable feedstocks.

Microwave heating and continuous-flow processing are used as tools for performing the reactions.

For the ring-closing metathesis reactions, transition from batch to flow processing for scale-up of the reaction is possible.