Highly selective macrocyclic ring-closing metathesis of terminal olefins in non-chlorinated solvents at low dilution

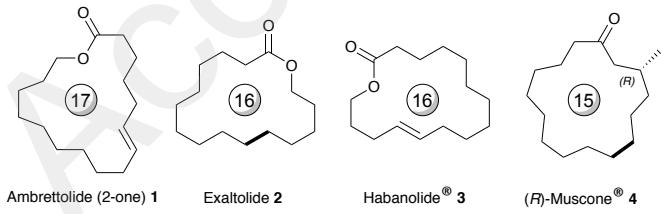
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A set of new ruthenium-indenylidene complexes bearing two unsymmetrical unsaturated *N*-cycloalkyl-NHC ligands was synthetised. These catalysts proved to be highly selective in the macrocyclic ring-closing metathesis performed in non-chlorinated solvents at low dilution (0.01M). *Without the requirement of benzoquinone derivatives to prevent the isomerisation side reactions*, this environmentally friendly catalytic process promoted the synthesis of macrocyclic odorant molecules of remarkable >99% purity.

Introduction

Since the development of well-defined, air-stable and easy to handle homogeneous Ru-arylidene complexes in the early 1990s,[1] olefin metathesis has become a powerful synthetic tool to efficiently build macrocyclic derivatives, surpassing in most cases traditional ring-closing methodologies such as Wittig reaction, lactonisation or lactamisation.[2] Advantageously, by limiting drastically the production of wastes, olefin metathesis is also considered as a greener technology.[3] Numerous macrocyclic products were successfully synthesised through this methodology,[4] notably macrolactones[5a], macrocyclic ketones[5b] or carbonates[6] which are frequently used in perfumery for their strong musk fragrance[7] (for instance: Ambrettolide (2-one) **1**,[8] Exaltolide **2**,[9] Habanolide® **3**[10] or (*R*)-Muscone® **4**[11]; see Figure 1). Although significant breakthroughs have been accomplished in the olefin metathesis area during the next decade, thanks to the catalyst design, three major drawbacks remain to be solved to make macrocyclic ring-closing metathesis (RCM) more attractive.[12]

Figure 1. Natural or synthetic macrocyclic derivatives frequently used in perfumery



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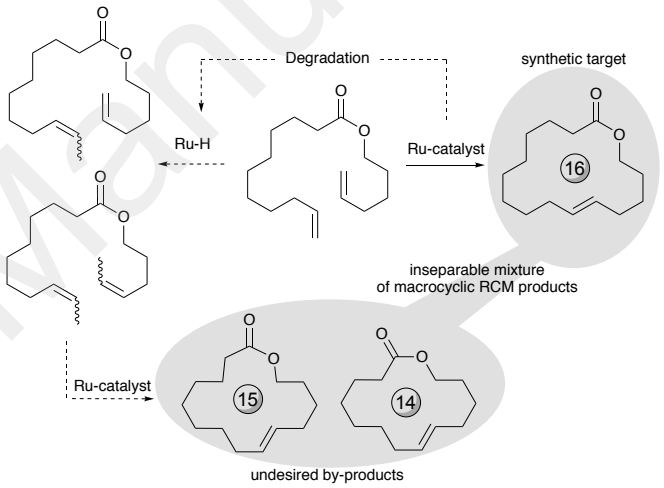


Figure 2. Ring contractions, which occur in macrocyclic ring-closing metathesis

The first one concerns the competitive migration of the terminal double bonds promoted by the presence of hydrido-complexes from the premature decomposition of the Ru-alkylidene species in the media,[13] leading to the formation of ring contraction by-products, which are difficult to separate from the targeted macrocycle (Figure 2). Various methods have been considered to inhibit isomerisation with varying degrees of success.[14-15] The use of toxic chlorinated solvents,[14] acid additives[15a,b] or toxic benzoquinone additives[15a] allowed reducing or trapping Ru-hydrides to prevent isomerisation during metathesis and afford higher selectivities. Nevertheless, these alternatives are not always efficient and could even appear in contradiction with a so-called environmentally friendly methodology. The second drawback is related to the high catalyst loading (1-5 mol% typically) often required to achieve attractive yields.[12b,16] Moreover a duality between activity and selectivity is usually observed. For instance, phosphine-based 1[st] generation Grubbs

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catalyst (**Ru-1**), have demonstrated remarkable level of selectivity but at the detriment of high catalyst loading to achieve acceptable yields.[17] In contrast, second generation complexes bearing *N*-heterocyclic carbene (NHC) ligands (**Ru-2**) gave excellent conversions at lower catalyst loading but the selectivity was seriously altered.[18] Last but not least, with currently available catalysts, moderate to high dilution conditions (typically 0.5 to 5 mM) are in most cases required in macrocyclic RCM to minimise self-metathesis and oligomerisation side reactions.[5a,12b,19] Obviously, the employment of large volumes of aromatic or chlorinated solvents seriously limits industrial productions, notably for low-value products.[12b] The quest for an efficient macrocyclic-RCM process involving greener solvents at low dilution/catalyst loading and without the requirement of any toxic additives remains a long-standing goal to chemists. *On this concern, we report herein an environmentally friendly and unprecedented highly selective ruthenium-catalysed macrocyclisation of terminal linear olefins in green solvents (ethyl acetate, Me-THF)[20] at 0.01M enabling to efficiently produce various macrocyclic odorant molecules of remarkable >99% purity.*

Experimental

General information

All reactions were carried out under an atmosphere of argon using standard Schlenk techniques. Toluene, diethyl ether, dichloromethane and tetrahydrofuran were purified using MBraun Solvent Purification Systems. Ethyl acetate was distilled over calcium hydride. Solvents used for catalysis were freeze-pump-thaw degassed prior to use. All commercial chemicals were used as received unless otherwise noted. The 1M solution of hydrogen chloride in ethyl acetate was purchased from Acros Organics with AcroSeal packaging. NMR spectra were recorded on a Bruker ARX400 spectrometer (^{1}H (400 MHz) and ^{13}C (101 MHz)) or Bruker 300 (^{1}H (300 MHz) and ^{13}C (75 MHz)) with complete proton decoupling for ^{13}C. ^{1}H and ^{13}C chemical shifts are reported in parts per million with the solvent resonance as the internal standard ($CDCl_3$, ^{1}H: δ 7.26 ppm, ^{13}C: δ 77.16 ppm). Coupling constants are reported in Hertz (Hz). Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, dd = double doublet, ddt = double double triplet, dq = double quartet, td = triple doublet, q = quartet, m = multiplet, br = broad. High Resolution Mass Spectrometry (HRMS) and elemental analysis were performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Université de Rennes 1.

GC methods

GC-2014 Shimadzu apparatus. GC column: TR5, 30m x 0.25 mm x 0.25 μm. Injector temperature: 280°C, FID: 340°C. Oven temperature: Starting temperature: 100°C, hold time: 0 minute. Ramp rate 10°C/min to 200°C, hold time: 10 minutes. Ramp rate 10°C/min to 300°C, hold time: 2 minutes. Carrier gas: Helium, u = 40 cm/sec. Injection volume: 1 μl. Split ratio: 20:1. Run time: 32 minutes.

Synthesis of complex Ru-**11a.**

In a glovebox, to a suspension of imidazolium salt **7a** (462 mg, 1.35 mmol, 2.5 equiv.) in dry toluene (2.7 mL) stored in a schlenk was added a 0.5 M solution of potassium bis(trimethylsilyl)amide (2.7 mL, 1.35 mmol, 2.5 equiv.). The mixture was stirred 30 minutes at room temperature. Commercial Ru-**3** (500 mg, 0.54 mmol, 1.0 equiv.) was then added in one portion to the schlenk and the resulting solution was allowed to stir at 40°C for 2 hours under an argon atmosphere outside the glovebox until TLC analysis showed complete conversion. After evaporation of the solvents, the crude material was purified on SiO_2 using the gradient of eluent: pentane/diethyl ether = 90/10 to 70/30. The desired complex Ru-**11a** was collected as a red solid (253 mg, 53% yield).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.97 (m, 1H), 7.88 – 7.81 (m, 1H), 7.75 – 7.66 (m, 1H), 7.59 – 7.49 (m, 1H), 7.48 – 7.36 (m, 3H), 7.24 – 6.99 (m, 5H), 6.92 – 6.77 (m, 2H), 6.74 – 6.65 (m, 2H), 6.43 (s, 1H), 6.31 – 6.24 (m, 1H), 3.69 – 3.49 (m, 1H), 2.74 – 2.60 (m, 3H), 2.57 (s, 1H), 2.42 (d, *J* = 5.6 Hz, 3H), 2.15 – 1.97 (m, 5H), 1.93 – 1.82 (m, 2H), 1.76 (d, *J* = 4.1 Hz, 6H), 1.68 (s, 2H), 1.55 (s, 3H), 1.50 (s, 3H), 1.42 – 1.31 (m, 2H), 1.30 – 1.16 (m, 3H), 1.10 – 0.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 296.2, 187.1, 144.7, 143.3, 141.0, 140.9, 140.2, 138.1, 137.9, 137.5, 137.2, 136.4, 136.2, 136.1, 136.0, 135.3, 129.8, 129.3, 128.9, 128.9, 128.3, 128.1, 128.0, 127.4, 127.3, 127.1, 126.5, 126.1, 126.0, 125.2, 122.9, 118.0, 117.6, 117.5, 115.2, 62.6, 59.2, 37.4, 35.3, 35.2, 32.3, 25.9, 24.9, 24.6, 24.1, 23.9, 21.5, 21.0, 20.1, 20.0, 19.4, 18.5, 18.4. HRMS (ESI) calcd. for $C_{49}H_{54}N_4{}^{35}Cl_2{}^{102}Ru$ $[M]^{+\cdot}$: m/z 870.27635, found: 870.2776 (1 ppm). Anal. calcd. for $C_{49}H_{54}Cl_2N_4Ru$: C, 67.57%; H, 6.25%; N, 6.43%; found: C, 67.74%; H, 5.93%; N, 6.04%.

Typical procedure for macrocyclic RCM.

A stock solution of Ru-**11a** complex (8.0 mg) in ethyl acetate (1000 μL) was prepared under argon. A two-necked flask equipped with a reflux condenser and a J Young valve was charged with a solution of diene **5** (133.0 mg, 0.5 mmol, 1.0 equiv.) in ethyl acetate (50 mL). 27.2 μL of the freshly prepared stock solution of complex was added. The reaction was initiated upon addition of a 1M HCl.EtOAc solution (12.5 μL, 0.0125 mmol, 0.025 equiv.) and was then placed in an oil bath set at 110°C to ensure a reflux for 4 hours. After cooling down to room temperature, the solution was quenched upon addition of ethyl vinyl ether (excess). The crude product was purified by chromatography on silica gel using pentane/diethyl ether = 95/5 as eluent to yield **6** as a pale-yellow oil (93 mg, 78% yield). >99% selectivity was found after GC measurement. ^{1}H NMR (400 MHz, $CDCl_3$) δ (*E*-isomer) 5.30-5.25 (m, 2H), 4.10 (t, *J* = 7.1 Hz, 2H), 2.35 - 2.26 (m, 2H), 2.07 - 1.97 (m, 4H), 1.67 - 1.54 (m, 4H), 1.45 - 1.15 (m, 12H). δ (*Z*-isomer) 5.42-5.29 (m, 2H), 4.12 (t, *J* = 6.3 Hz, 1H), 2.35 - 2.26 (m, 2H), 2.07 - 1.97 (m, 4H), 1.67 - 1.54 (m, 4H), 1.45 - 1.15 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ (*E*-isomer) 174.0, 131.9, 130.4, 64.0, 34.9, 32.1, 32.1, 28.5, 28.4, 28.3, 28.1, 27.3, 26.7, 25.6, 25.3. δ (*Z*-isomer) 174.0, 130.2, 129.9, 64.2, 34.0, 29.3, 28.5, 28.3, 28.1, 27.8, 27.3, 27.2, 26.7, 26.6, 25.4. The spectral data for both isomers were identical to those reported in the literature.[5a]

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Typical procedure for the hydrogenation of macrocycles.

A round-bottom flask was charged with macrocycle **6** (93 mg, 0.39 mmol, 1.0 equiv.) and ethyl acetate (7.8 mL). Palladium on activated carbon (9.8 mg, 0.00975 mmol, 0.025 equiv.) was added and a balloon of hydrogen was bubbled in the solution. The resulting mixture was allowed to stir at room temperature under an atmosphere of hydrogen for 16 hours. A balloon of argon was bubbled in the solution, the mixture was filtrated over a short plug of celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to yield the reduced macrocycle **2** (Exaltolide) as a white solid. (94 mg, 99% yield). >99% selectivity was found after GC measurement. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (t, *J* = 5.7 Hz, 2H), 2.31 (t, *J* = 6.9 Hz, 2H), 1.70 – 1.56 (m, 4H), 1.45 – 1.22 (m, 20H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 64.1, 34.6, 28.5, 27.9, 27.3, 27.2, 27.0, 26.8, 26.5, 26.2, 26.1, 26.0, 25.2, 25.1. The spectral data for this compound were identical to those reported in the literature. [5a]

Results and discussion

We started our investigation by evaluating a set of various commercially available Ru-catalysts[21] (figure 3 and Table 1) in the macrocyclic RCM of hex-5-enyl undec-10-enoate **5** performed in ethyl acetate (0.01 M) at 70 °C[22] over 4 hours. The resulting RCM macrocycle **6** was isolated in a 80/20 *E/Z* mixture and then reduced by a standard Pd/C-catalysed hydrogenation procedure to lead to the expected 16-membered macrocycle **2** (exaltolide) after silica gel purification.[5a] Although first generation catalysts (Ru-**1** and Ru-**3**) are known to be less prompt toward isomerisation, they were inefficient in our conditions as only traces of RCM products were detected (entries 1-2). Second generation complexes Ru-**2** and Ru-**4** gave the expected macrocycle product **2** in relatively good yields (83 and 79% respectively, entries 3-4). Nevertheless, significant amounts (5 and 3 % respectively) of a mixture of 14- and 15-membered macrocycles $\mathbf{C_{14}}$ and $\mathbf{C_{15}}$ were also detected. It is noteworthy that exaltolide **2** and related ring-contraction by-products cannot be separated, even after SiO_2 purifications, as depicted in figure 4 (chromatogram (a)). Unfortunately, similar levels of yields and selectivities were also observed with other commercially available phosphine-free catalysts (entries 5-9), even in the case of activated Hoveyda-Grubbs complexes Ru-**6** (Grela), Ru-**7** (M51) or Ru-**8-9** (M73) for which the purity dropped to 67%.

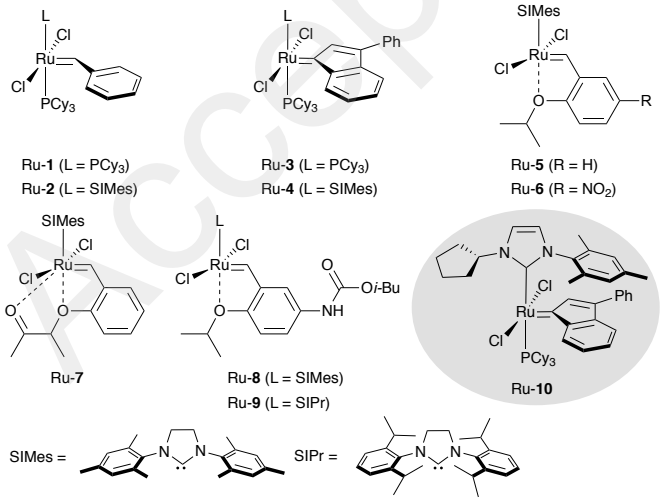
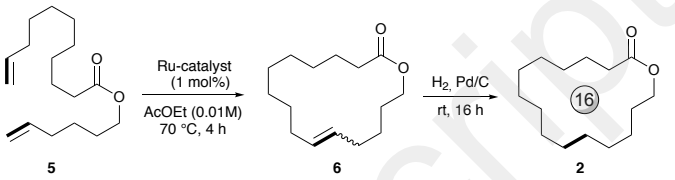


Figure 3. Selected Ru-metathesis complexes used in macrocyclic RCM

Table 1. Screening of Ru-metathesis complexes Ru-**1-10** for the macrocyclic RCM of hex-5-enyl undec-10-enoate **5** leading to Exaltolide **2** after hydrogenation[a]



Entry	Catalyst	**6** GC Yield (%)[b,c]	**2** Yield (%)[d]	Selectivity (%)[e]
1	Ru-**1**	<5	Nd[e]	Nd[e]
2	Ru-**3**	<5	Nd[e]	Nd[e]
3	Ru-**2**	83	99	95
4	Ru-**4**	79	99	97
5	Ru-**5**	79	99	93
6	Ru-**6**	42	99	77
7	Ru-**7**	43	99	67
8	Ru-**8**	70	99	84
9	Ru-**9**	76	99	96
10	Ru-**10**	31	99	>99

[a] Conditions: (1) Ru-catalyst (1 mol%), EtOAc (0.01 M), 70°C, 4h. (2) H_2 (1 atm), Pd/C (2.5 mol %), rt, 16h. [b] Determined by GC analysis with tetradecane as standard (see ESI for details). [c] E/Z selectivity: 8/2 (determined by GC). [d] Isolated yields after SiO_2 purification. [e]Determined by GC analysis of **2** (see ESI and *vide infra*, Fig. 4). [f] Not determined.

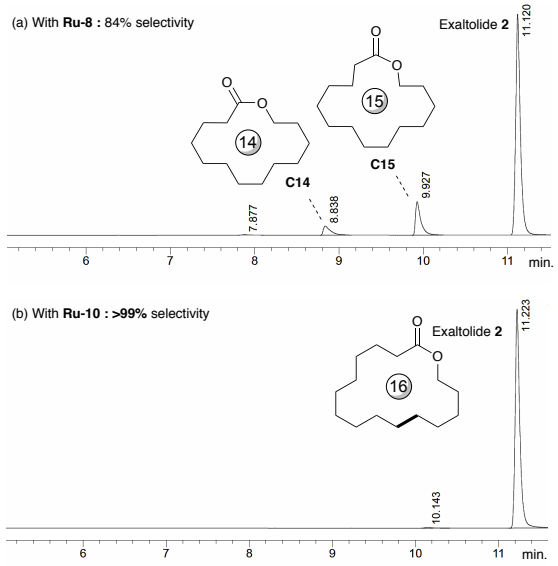
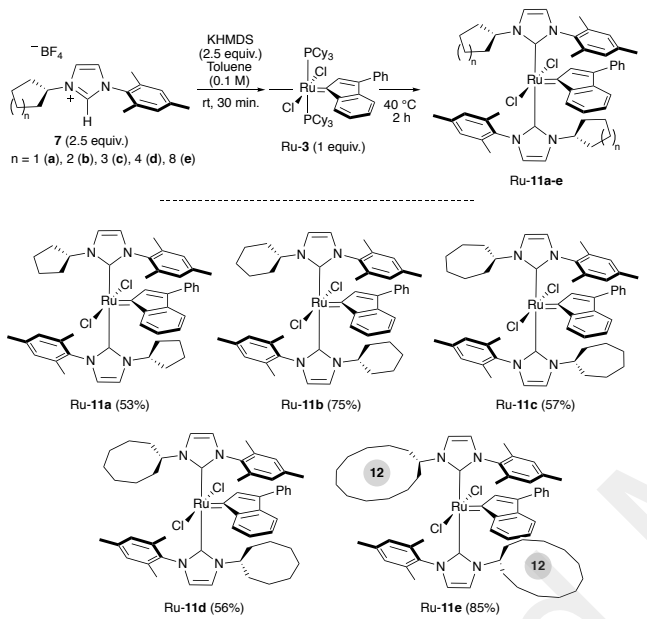


Figure 4. Selectivity of the macrocyclic RCM of **5** determined by GC analysis: chromatograms of the SiO_2 purified exaltolide **2** obtained with catalyst Ru-**8** (a) and with catalyst Ru-**10** (b).

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Gratifyingly, we found that the indenylidene-based complex Ru-**10**[23] bearing an unsymmetrical unsaturated (U_2) cyclopentyl-IMes NHC ligand was able to afford the desired 16-membered macrocycle with a remarkable >99% purity (Figure 4, chromatogram (b)). However, this complex appeared quite unstable under the reaction conditions as a poor 31% yield was observed (entry 10). Encouraged by this promising result, we decided to develop more robust complexes towards thermic conditions required for macrocyclic-RCM transformations. Indeed, as previously reported by our group, Ru-**10** showed a lower thermic stability than SIMes-based parent complexes Ru-**2** and Ru-**4**.[24]



Scheme 1. Synthesis of (cycloalkyl-IMes)$_2$RuCl$_2$(3-phenylindenylid-1-ene) complexes Ru-**11a-e**

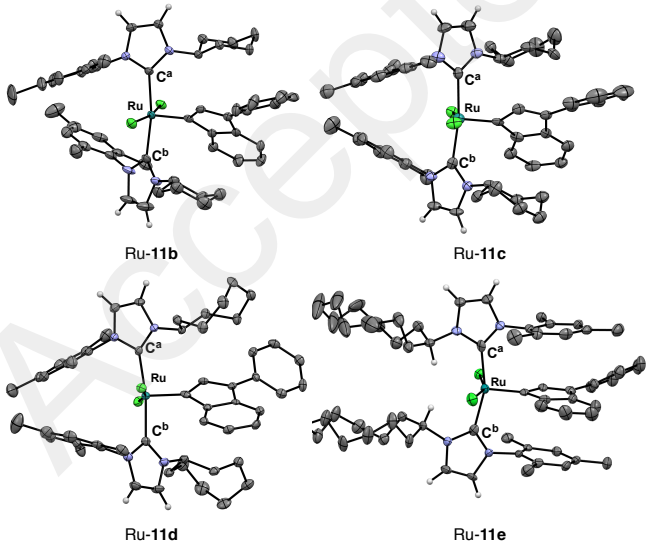
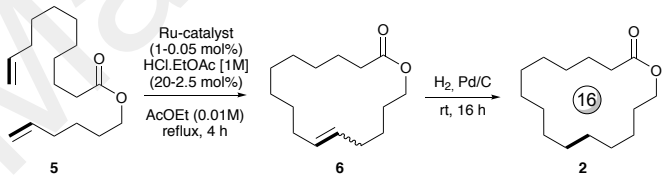


Figure 5. Solide-state structure of Ru-indenylidene complexes **Ru-11b-e** from single crystal X-ray diffraction. Hydrogen atoms have been omitted for clarity (N in blue, C in grey, Cl in green and Ru in pink).

To tackle this, we focused our attention on Ru-complexes bearing two diaminocarbene units. Indeed, as previously reported by several research groups[25] and more recently by our group,[26] bisNHC arylidene complexes have proved to be highly stable at elevated temperature. Therefore, we decided to replace the PCy_3 ligand by an additional U_2-NHC unit. As depicted in Scheme 1, thanks to our recently reported highly modular and straightforward multicomponent synthesis of unsymmetrical NHC precursors **7**,[27] a set of five (cycloalkyl-IMes)$_2$RuCl$_2$(3-phenylindenylid-1-ene) complexes Ru-**11a-e** were easily prepared from the commercially available bis-phosphine Ru-complex Ru-**3** (M1). By employing an excess of imidazolium salt **7** in presence of potassium hexamethyldisilazane (KHMDS), pre-catalysts Ru-**11a-e** were isolated in moderate to good yields (53-85%). Structures of complexes Ru-**11b-e** were confirmed by single crystal X-ray diffraction studies, revealing some important structural information (Figure 5, see the ESI for details).[28] Unfortunately, all attempts to crystallise cyclopentyl-IMes Ru-**11a** have failed. Having complexes Ru-**11a-e** in hands, their catalytic behaviours were evaluated in the macrocyclic-RCM of **5** under aforementioned standard conditions (Table 2).

Table 2. Screening of Ru-indenylidene complexes Ru-**11a-e** in the macrocyclic RCM of hex-5-enyl undec-10-enoate **5** leading to Exaltolide **2** after hydrogenation[a]



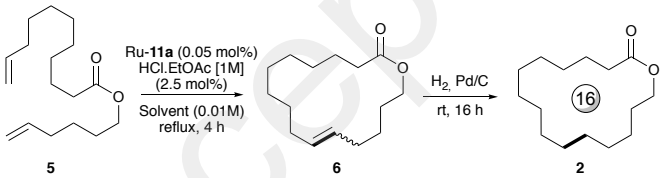
Entry	Catalyst (mol%)	HCl.EtOAc [1M] (mol%)	**6** GC yield[c,d]/yield[e] (%)	**2** Yield(%)[f]	Selectivity (%)[g]
1[b]	Ru-**11a** (1)	-	<5	Nd[h]	Nd[h]
2	Ru-**11a** (1)	-	8	Nd[h]	Nd[h]
3	Ru-**11a** (1)	20	88/80	99	>99
4	Ru-**11a** (1)	10	90/76	99	>99
5	Ru-**11a** (0.1)	5	88/76	99	>99
6	Ru-**11a** (0.05)	2.5	90/78	99	>99
7[i]	Ru-**11a** (0.05)	2.5	76/67	99	>99
8	Ru-**11b** (1)	2.5	95/72	99	>99
9[j]	Ru-**11c** (1)	2.5	93/73	99	>99
10[j]	Ru-**11d** (1)	2.5	90/70	99	>99
11	Ru-**11e** (1)	2.5	93/73	99	>99

[a] Conditions: (1) Ru-catalyst (1 to 0.05 mol%), EtOAc (0.01 M), HCl.EtOAc (1M) (20 to 2.5 mol%), reflux (oil bath set at 110°C), 4 h. (2) H_2 (1 atm), Pd/C (2.5 mol %), rt, 16 h. [b] Metathesis reaction performed at 70°C (oil bath set at 80°C) for a duration of 29 h. 8/2 [c] Determined by GC analysis with tetradecane as standard. [d] E/Z selectivity: 8/2 for entries 3,5-7; 7/3 for entries 4,8,10-11; 6/4 for entry 9 (determined by GC). [e] Isolated yields after SiO_2 purification. [f] Determined by GC analysis of **2** (see ESI for details). [h] Not determined. [i] Concentration at 0.02 M. [j] Time of reaction is 1 h.

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Despite an increasing thermal stability in comparison with its analogue Ru-**10**[23] (14 days *vs* 5 hours at 60 °C, see ESI for details), bis(cyclopentylIMes) complex Ru-**11a** was inefficient in macrocyclisation at either 70 °C or refluxed condition (entries 1 and 2, <8% conv.). This lack of reactivity could be explained by the strong binding of the NHC to the metal, which drastically reduces the pre-catalyst initiation rate.[25,26] Recently, Grubbs and Bertrand described an acidic-mediated protonolysis of the ruthenium-carbene bond to activate bis-carbenic metathesis catalysts.[29] This prompted us to study the lability of the cyclopentylIMes ligand in presence of a Brönsted acid during the RCM. Pleasantly, by adding 20 mol% of 1M HCl/EtOAc solution, catalyst Ru-**11a** yielded the expected metathesis macrocycle **6** in relatively good isolated yield (80%, entry 3). After hydrogenation, Exaltolide **2** was then isolated in quantitative yield and >99% purity. Similar good results were obtained by diminishing the amount of acid down to 10 mol% (entry 4). At lower catalyst loadings (0.1 and 0.05 mol%) in presence of 5 to 2.5 mol% of HCl, the catalytic system remained quite efficient as exaltolide **2** was formed in 76 and 78% yield respectively and >99% purity (entries 5-6). Interestingly, at higher concentration (0.02M), the yield of RCM product **6** was only slightly altered, leading to **2** in 67% isolated yield but the purity remained >99% (entry 9). With the optimized conditions in hands, complexes Ru-**11b-e** bearing different cycloalkyl-*N* substituents were also screened, revealing no significant differences in catalytic efficiency (entries 8-11). Nonetheless, complex Ru-**11c** and Ru-**11d** bearing respectively a cycloheptyl and cyclooctyl fragment were able to complete the reaction within 1 h instead of 4 h (entries 10-11). At last, to complete our study, we next screened other green solvents such as Me-THF, diethylcarbonate (DEC) or isopropanol (Table 3).[30] The RCM conducted in Me-THF afforded the desired exaltolide **2** in 73 % isolated yield and >99% purity (entry 1). In DEC, our catalyst Ru-**11a** appeared quite inefficient, yielding **2** in extremely low 7% yield but without any traces of by-products (entry 2).

Table 3. Screening of various green solvents for the macrocyclic RCM of hex-5-enyl undec-10-enoate **5** catalysed by Ru-**11a** complex[a]



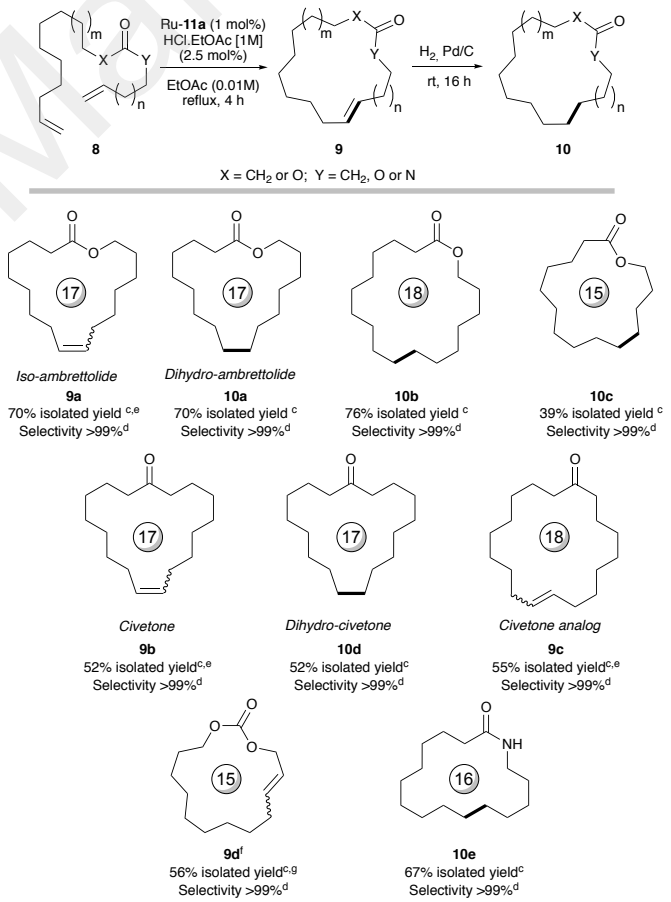
Entry	Solvent	**6** GC yield[b,c]/yield[d] (%)	**2** Yield (%)[d]	Selectivity (%)[e]
1	EtOAc	90/78	99	>99
2	Me-THF	91/73	99	>99
3	$(EtO)_2CO$	13/7	99	>99
4	*i*-PrOH	26/20	99	76

[a] Conditions: (1) Ru-**11a** (0.05 mol%), solvent (0.01 M), HCl.EtOAc (1M) (2.5 mol%), reflux (oil bath set at 110°C), 4 h. (2) H_2 (1 atm), Pd/C (2.5 mol %), rt, 16 h. [b] Determined by GC analysis with tetradecane as standard. [c] E/Z selectivity: 8/2 (determined by GC). [d] Isolated yields after SiO_2 purification. [e] Determined by GC analysis of **2** (see ESI for details).

In alcoholic solvent, the formation of hydrido-Ru species was predominant as **2** was isolated in low 20% yield with a selectivity dropping drastically to 76%.

We then decided to extend the scope of macrocyclic RCM by involving the more promising complex Ru-**11a** in optimized conditions (EtOAc, 0.01M, reflux, 2.5 mol% of 1M HCl/EtOAc solution). We started with the synthesis of ambrettolide derivatives **9a** and **10a**, two attractive artificial fragrances featuring a seventeen-membered macrolactone, which are considered as an alternative musk resource (Scheme 2).[31] With a catalyst loading of 1 mol%,[32] the metathesis cyclised product **9a** was isolated in good 70% yield without any traces of ring-contraction by-products (>99% purity). The following hydrogenation of the double-bound afforded the corresponding dihydro-ambrettolide **10a**[33] in quantitative yield (>99% purity). While similar yield and purity were observed in the formation of the eighteen-membered macrolactone **10b**[34] (76% and >99% resp.), catalyst Ru-**11a** appeared less efficient in the RCM leading to the fifteen-membered lactone **10c**[35] in poor 39% yield but the purity remained excellent.

Scheme 2. Scope of macrocyclic RCM of dienic substrates **8** catalysed by Ru-**11a** complex leading to the corresponding macrocyclic metathesis product **9**[a] or related hydrogenated macrocycle **10**[b]



[a] Conditions: Ru-**11a** (1 mol%), AcOEt (0.01 M), 1M HCl.EtOAc (2.5 mol%), reflux, 4 h. [b] Conditions: H_2 (1 atm), Pd/C (2.5 mol %), rt, 16 h. [c] Isolated yields after SiO_2 purification. [d] Determined by GC analysis (see ESI for details). [e] *E/Z* ratio: 7/3. [f] 2 mol% of catalyst were used (overnight). [g] *E/Z* ratio: 9/1

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This lack of reactivity could be attributed to conformational constraints that disfavour the cyclisation.[36] The formation of macrocyclic ketones was next studied. The well-known and highly desirable civetone and dihydro-civetone fragrances[37] **9b** and **10d** were isolated in pure form with moderate 52% yields.[38] A similar moderate 55% yield was observed with the civetone analog **9c**[39] featuring an eighteen-membered ring. Finally, our methodology was also successful in the formation of macrocyclic carbonate **9d**[40] and macrolactam **10e**[41] which were isolated with 56 and 67% yields respectively in >99% purity.

Conclusions

To conclude, we developed a set of new ruthenium-indenylidene complexes bearing two unsymmetrical unsaturated NHC ligands with a *N*-cycloalkyl moiety. These low-cost catalysts[42] proved to be highly selective in the macrocyclic ring-closing metathesis reactions performed in ethylacetate solvent at low dilution (0.01M) *without the requirement of benzoquinone derivatives to prevent the isomerisation side reactions*. This unprecedented environmentally friendly catalytic process enabled the synthesis of various macrocyclic odorant molecules, which were achieved with a remarkable >99% purity and good isolated yields (up to 78%). As the isomerization of terminal olefins remains a major obstacle to numerous industrial applications of olefin metathesis, this highly selective technology pave the way to a prosperous future.

Conflicts of interest

There are no conflicts to declare.

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