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Reaction Intermediates

First Detection of a Ruthenium–Carbene–Resorc[4]arene Complex During the Progress of a Metathesis Reaction

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Abstract: For the first time we describe the detection of a ruthenium-carbene-resorc[4]arene complex produced, as a key intermediate, during an olefin metathesis reaction carried out on a resorc[4]arene bicyclic olefin with [Ru(=CHPh)$Cl_2(PCy_3)_2$] Grubbs first-generation (G_1ST) catalyst. The complex was identified by using high-resolution (600 MHz) ^{1}H, ^{31}P NMR and DOSY spectroscopy, in a non-invasive fashion. The singlet at δ = 19.98 ppm (^{1}H NMR), attributed to the alkylidene proton in the G_1ST catalyst and that at δ = 53.37 ppm (^{31}P NMR), attributed to the phosphorus atom coordinated with the metal, were selected as probes for a kinetic analysis. The intensity of these signals decreased at the expense of the singlets at 19.26 (^{1}H NMR) and 52.68 ppm (^{31}P NMR), diagnostic for the formation of the ruthenium-carbene-resorc[4]arene complex **3a**[Ru]. The resorc[4]arene activated olefin proved to behave as a key propagating species leading to oligomers according to a ROMP pathway.

Introduction

The metathesis reaction catalyzed by well-defined homogeneous transition-metal complexes has become a staple technique for the synthesis of complex natural products and synthetic compounds.[1–4] In particular, ruthenium-based catalysts[5] have been extensively used in organic and polymer chemistry because of their high reactivity towards olefin substrates in the presence of the most common functional groups.[6,7] The elucidation of the mechanism of metathesis reaction catalyzed by Grubbs catalysts has been the subject of intense experimental[8–14] and theoretical[15–18] investigations. In the specific case of olefin metathesis, it has been proposed that carbenes and metallocyclobutanes are the key intermediates of the reaction.[19] The first step to clarify the mechanism of the metathesis reaction has been the direct identification of the two ruthenium complexes mentioned above by NMR spectroscopy. In 1992, Grubbs reported the first NMR spectroscopic evidence of a carbene intermediate produced during the reaction of a strained olefin with a well-defined Ru^{II} complex.[20] Such carbene species proved capable of polymerizing norbornene in protic media through a ring-opening metathesis polymerization (ROMP) pathway. Later, the selectivity and reactivity in ring-opening metathesis (ROM) reactions was investigated by another research group based on ^{1}H and ^{31}P NMR studies of the ruthenium alkylidenes formed during the reaction of cyclobutene-containing substrates.[21–23] The utility and limitations of ^{1}H NMR methods for monitoring the progress of ring-closing metathesis (RCM) reactions were also examined.[24]

The first observation and characterization by NMR spectroscopy of the ruthenacyclobutane intermediate was made during the reaction of ethylene with 14-electron ruthenium catalysts at low temperature.[25] As an extension of their work, the same authors demonstrated the formation of ruthenacyclobutane and ruthenium carbene intermediates in RCM reactions,[26] and provided a direct spectroscopic characterization of them. Recently, we submitted undecenyl resorc[4]arene macrocycles in both the *chair*[27] and *cone*[28] conformation to olefin metathesis reaction, with the aim of synthesizing macrocyclic compounds capable of behaving as preorganized hosts for the supramolecular recognition of appropriate molecular guests. Both stereoisomers proved to be suitable substrates to yield cyclic alkenes by both intra- and intermolecular metathesis. In particular, the reaction performed on the *chair* stereoisomer **1a** led mainly to the formation of the resorc[4]arene bicyclic olefin **2a**, along with the dimer **3a** (Scheme 1). The latter proved to develop from two molecules of **2a** reacting together through a ring-opening cross-metathesis (ROM-CM) sequence, according to a hypothesized mechanism.[27]

The key role played by resorc[4]arene bicyclic olefin **2a** as a monomeric building block for the construction of more complex architectures prompted us to investigate in more detail the mechanism of the ROM-CM sequence of reactions. Typically, ROM-CM reactions are most successful when using highly

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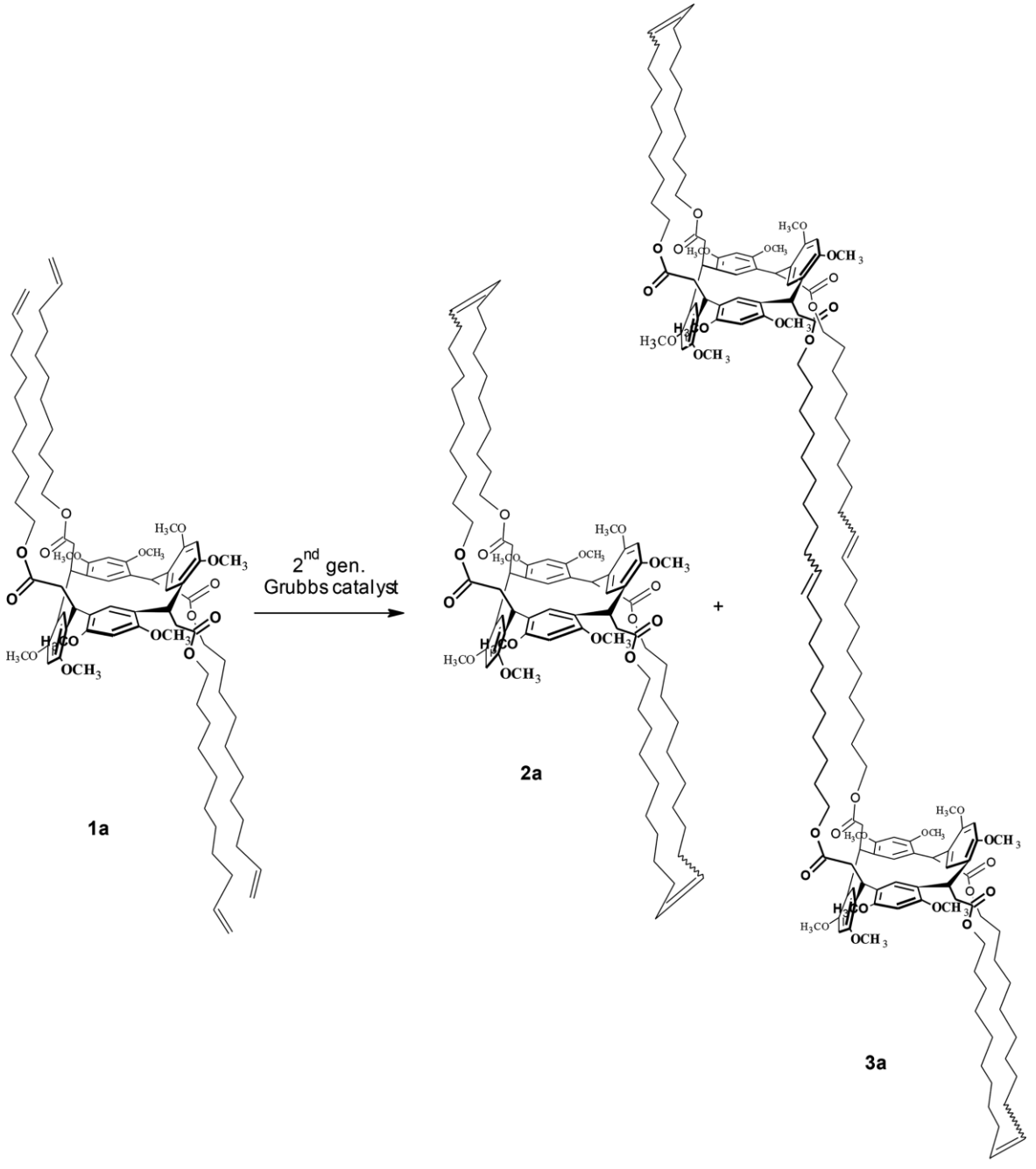


Scheme 1. Olefin metathesis reaction of undecenyl resorc[4]arene **1a**.

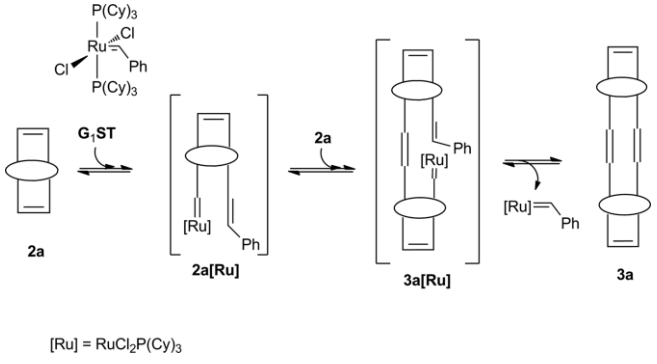
strained substrates that show a good propensity to undergo a ring opening, which is the initial step then followed by CM. In the presence of reactive metal carbenes, also unstrained olefins proved to be suitable substrates for ROM-CM reactions,[29,30] by effecting ring-expansion reactions leading to a variety of macrocycles the ring sizes of which can be modulated by using appropriate cyclic olefins.[31]

We report here for the first time the detection of a ruthenium-carbene-resorc[4]arene complex produced during a metathesis reaction of a resorc[4]arene bicyclic olefin with the Grubbs first-generation (G_1ST) catalyst.

Results and Discussion

In a previous work,[27] we showed that undecenyl resorc[4]arene **1a** (in the *chair* conformation), due to the relatively simple arrangement of its chains, may give different metathesis products upon exposure to Grubbs catalysts. Under optimized reaction conditions, two major products were isolated; namely, bicyclic alkene **2a** (46 %) and dimer **3a** (5 %) (Scheme 1). The synthesis of compound **2a** occurs by two almost contemporary RCM reactions, driven by the elimination of two molecules of ethylene,

which proved to be a powerful driving force for intra- and intermolecular metathesis.[32] Furthermore, we clearly demonstrated that dimer **3a** is formed by reaction of two molecules of **2a** (Scheme 2) by submitting **2a** to the same reaction conditions (namely, time, temperature and catalyst) as those used for the starting terminal olefin **1a**. Accordingly, the mechanism was interpreted as involving two steps: (1) the ring-opening metathesis (ROM) of **2a**, and (2) the concerted double cross-metathesis (CM) between the ruthenium-carbene-resorc[4]arene complex **2a**[Ru] and a second molecule of **2a**, passing through the carbene complex **3a**[Ru].



Scheme 2. Proposed mechanism for the dimerization of resorc[4]arene bicyclic olefin **2a**.

In the current study, we have monitored the formation of such ruthenium-carbene-resorc[4]arene complexes by high-resolution (600 MHz) ^{1}H and ^{31}P NMR spectroscopy, to gain a detailed picture of the mechanism involved. To this end, resorc[4]arene bicyclic olefin **2a** was allowed to react with the metathesis catalyst directly in the NMR tube, using a suitable deuterated solvent.

The first problem we faced was the choice of suitable catalyst generation: Grubbs and co-workers proposed a general mechanism for ruthenium-catalyzed olefin metathesis in which dissociation of an organophosphine ligand is a critical step in forming a 14-electron ruthenacarbene intermediate, which reacts with the olefin to generate a four-coordinate intermediate.[5] We needed a catalyst that had a reduced catalytic activity towards our substrate so that we could monitor the reaction step by step. It is widely accepted that there exists an inverse relationship between organophosphine dissociation (i.e., catalyst production) and catalytic activity for the two Grubbs catalyst generations: in the bis-phosphine systems (namely, first-generation catalysts, G_1ST), the 14-electron intermediate is formed faster than in the second-generation catalysts (G_2ND), but they show a much lower catalytic activity. The different rates of catalyst production in G_1ST and G_2ND precatalysts have been quantitatively attributed to the different energy barriers for the rotation of the carbene, which also plays a key role in the olefin binding step.[33] We therefore decided to use G_1ST as the catalyst for the metathesis reaction of resorc[4]arene bicyclic olefin **2a**, because we expected a scenario in which the inactive rotamer would be favored.

A first experiment was performed by using a 1:1 ratio of resorc[4]arene bicyclic olefin **2a** to G_1ST, in $CDCl_3$. The ^{1}H NMR spectrum of the G_1ST catalyst shows a sharp singlet centered at δ = 19.98 ppm (see Figure S1 of the Supporting Information), which can be ascribed to the alkylidene proton. The corresponding ^{31}P NMR spectrum shows the expected signal at δ = 53.37 ppm.

With regard to the kinetic analysis, the ^{1}H NMR spectrum of the freshly prepared reaction mixture shows two well-separated signals centered at δ = 19.98 and 19.26 ppm (Figure S2 of the Supporting Information), due to the native form of the catalyst and the supposed intermediate ruthenium complex **3a**[Ru], respectively. In the 1D TOCSY spectrum, the signal centered at δ = 19.26 ppm gave scalar correlations to the methylene protons directly bound to the oxygen of the resorc[4]arene bridges (Figure 1). In addition, a correlation with a signal at δ = 2.75 ppm is detected, which is attributed to the allylic methylene protons. These results indicate that a ruthenium species containing phosphorus ligands has been linked to the resorc[4]arene core.

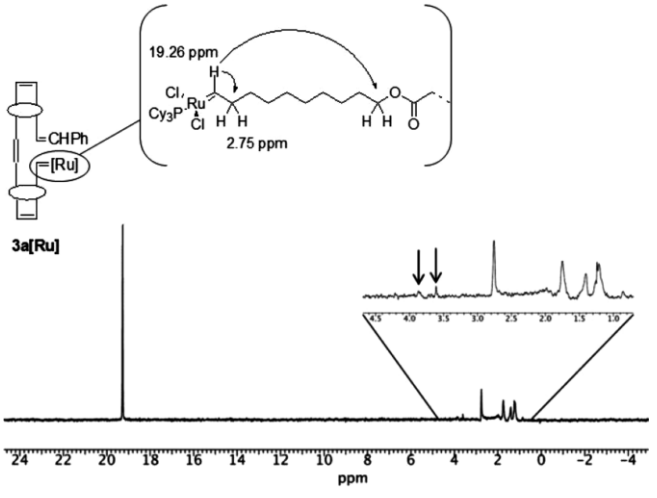


Figure 1. 1D TOCSY (600 MHz, $CDCl_3$, 25 °C, mixing time 150 ms) spectrum of the proton at δ = 19.26 ppm; the arrows indicate the methylene protons bound to the oxygen atom of the resorc[4]arene.

In the ^{31}P NMR spectrum of the mixture, two distinct resonances at δ = 53.37 and 52.68 ppm are detected, the integrated areas of which are in agreement with those detected in the ^{1}H NMR spectrum for the two signals centered at δ = 19.98 ppm and 19.26 ppm, respectively (see Figure S2 of the Supporting Information).

The increase of the ^{1}H resonance at δ = 19.26 ppm during the reacting time is followed by a congruent increase of signals (partially superimposed to the aromatic resorc[4]arene signals), and centered at δ = 6.35 and 6.20 ppm. They were attributed to the two protons of the –HC=CHPh system installed on the resorc[4]arene, as clearly demonstrated by the reciprocal scalar correlation and the dipole–dipole interactions detected between such protons and the phenyl (*ortho* protons) resonance at δ = 7.31 ppm in the 2D ROESY spectrum (Figure S3 of the

Supporting Information). These olefin resonances are *J*-coupled to the allylic methylene protons at δ = 2.17 ppm (CH_2 at δ = 33.0 ppm, gHSQC). Their connection to the resorc[4]arene core unit was confirmed by TOCSY correlations produced by the signal centered at δ = 2.17 ppm and the methylene protons directly bound to the oxygen of the resorc[4]arene pendants (Figure S4 of the Supporting Information).

In the double bonds region ranging from 5.45 to 5.20 ppm, a new resonance at δ = 5.38 ppm appears, which is not present in the ^{1}H NMR spectrum of **2a** (Figure 2a). Moreover, the signals in this spectral region have an integrated area that is less than that generated by the methine protons on the resorc[4]arene bridges (δ = 5.02 ppm). Interestingly, the lack of integrated area to achieve a 1 to 1 ratio (as in **2a**) between these two regions (olefin/methine bridge protons) is correlated to the integrated area of olefin protons at δ = 6.35 ppm and 6.20 ppm bound to the phenyl moiety. Such new kinds of double bond signals (δ = 5.38 ppm and 6.35/6.20 ppm) are formed during the reaction at the expense of the internal vinyl protons of the resorc[4]-arene core (δ = 5.31 ppm and 5.33 ppm, Figure 2b–c).

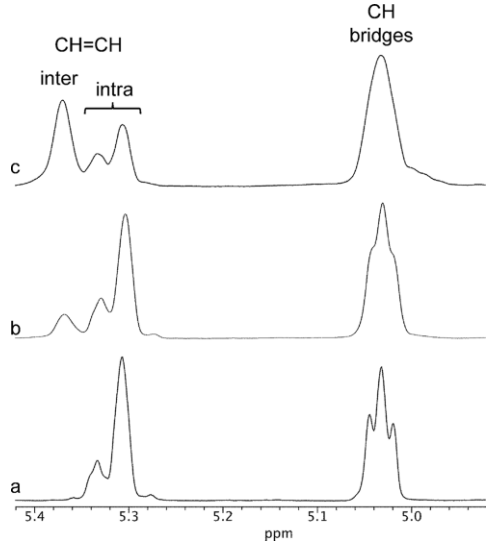


Figure 2. Expansion of the 5.45–4.70 ppm region in the ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C) spectra of **2a** (a), freshly prepared 1:1 resorc[4]arene **2a**/G_1ST reaction mixture (b) and after 6.5 h reaction time (c).

The proton(s) resonating at δ = 5.38 ppm gave a ^{1}H-^{13}C correlation at δ = 130.3 ppm, which is typical of olefin protons; in the 1D TOCSY experiment, correlations are detected with the allylic methylene at δ = 1.93 ppm (δ = 36.3 ppm in the ^{13}C NMR spectrum) to methylene protons directly bound to the oxygens of the resorc[4]arene pendants (Figure S5 of the Supporting Information). This new signal corresponds to the internal double bond formed during an intermolecular reaction leading to dimer or trimer aggregates.

We found that the species linked to the metal (both the catalyst and the Ru-resorc[4]arene complexes) were subjected to degradation: in the ^{1}H NMR spectrum recorded after 22 h from the beginning of the reaction, the singlets at δ = 19.98 and 19.26 ppm disappeared, as well as the corresponding ^{31}P NMR resonances (namely, 53.37 and 52.68 ppm), and several new phosphorus signals were detected (see Figure S6 of the Supporting Information). After degradation, an average diffusion coefficient of 1.7×10^{-10} m^2 s^{-1} was measured in the DOSY map (see Figure S7 of the Supporting Information), to be compared to the value of 4.5×10^{-10} m^2 s^{-1} measured for the starting resorc[4]arene olefin **2a**. This value confirmed the formation of dimer-to-trimer aggregates.

The experimental conditions reported thus far allowed us to carry out a qualitative characterization of the ruthenium-carbene-resorc[4]arene **3a**[Ru] complex, but the instability of the G_1ST catalyst in $CDCl_3$ prevented a quantitative characterization of the reaction outcome. Therefore, we performed several experiments in different solvents and C_6D_6 was selected as the optimum for the greater stability of the G_1ST catalyst.[7]

Quantitative Characterization of the Reaction Outcome

The metathesis reaction of resorc[4]arene bicyclic olefin **2a** was carried out in benzene under static conditions. Two different ratios were selected, involving an excess of olefin substrate relative to the catalyst (namely, **2a**/G_1ST, 4:1) or the reverse (**2a**/G_1ST, 1:4). Extensive purifications of the reaction mixtures by silica gel column chromatography (DCM/ethyl acetate mixtures as eluents) led to the isolation among the reaction products of some pure compounds and some partially enriched mixtures. Under both conditions, unreacted starting **2a** was recovered (35–40 %) along with oligomeric products, which were not isolated.

The reaction carried out in a 4:1 ratio (**2a**/G_1ST) led to the isolation, beside the known dimer **3a** (6 %), of a new compound **4a** (2 % yield, Figure 3); whereas the opposite conditions (namely, 1:4 ratio **2a**/G_1ST) again yielded product **4a** (12.5 %) and also a new compound **5a** (6 %), and two enriched mixtures named **I** and **II** (see below). The characterization of both pure and enriched mixture products allowed us to develop an accurate NMR analytical protocol for direct analysis of the crude reaction in a non-invasive fashion.

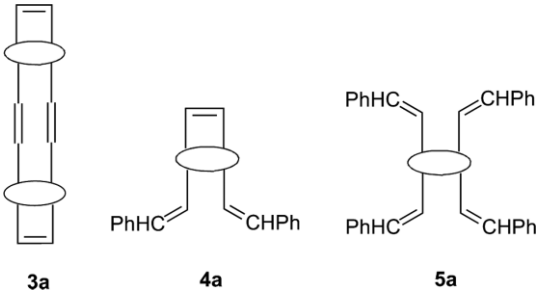


Figure 3. Schematic representation of the products isolated in the metathesis reaction of **2a** in benzene with G_1ST catalyst (**2a**/G_1ST, 4:1 and 1:4 ratio). For the chemical structures of compounds **3a**–**5a**, see Figure S8 of the Supporting Information.

Compounds **4a** and **5a** proved to be monomers on the basis of their diffusion coefficients ($D = 3.6 \times 10^{-10}$ m^2 s^{-1} and 3.8×10^{-10} m^2 s^{-1}, respectively), which were quite similar to that measured for the starting olefin **2a** ($D = 4.0 \times 10^{-10}$ m^2 s^{-1} in

C_6D_6). For compound **3a**, a value of 2.6×10^{-10} m^2 s^{-1} was obtained, corresponding to a dimeric assembly.

Compound **4a** (for the structure, see Figure 4) shows a loss of the symmetry typical of **2a**, as well highlighted by inspection of the signals due to the resorc[4]arene core protons, the methine bridge protons, and the O- and C=C-bound methylene protons (Figure 4a–b). Two typical olefin signals centered at δ = 6.38 ppm and 6.14 ppm and their integrated areas pointed out the presence of two CH=CHPh groups inserted on the resorc[4]arene skeleton. Furthermore, only one of the two intramolecular bridges initially present in **2a** was detected (5.37 and 5.45 ppm). Notably, the aromatic protons of the A/A′ rings, which are not involved in the formation of the intramolecular double bond between two side chains, are little affected, producing signals at 6.30 (H11/H23) and 6.85 (H25/H27) ppm. A strong perturbation was detected, instead, for the corresponding protons of the B/B′ rings. In particular, the signal for the H5/H17 protons centered at δ = 6.08 ppm in the parent **2a** (Figure 4a) is split into two signals (1:1 ratio) at 6.07 (for H5) and 6.15 (for H17) ppm. In fact, proton H5 is in the same environment as in **2a**, whereas H17 is surrounded by the two phenyl-bearing chains (see structure in Figure 4). The loss of symmetry for **4a** was confirmed by inspection of the methylene protons directly bound to the oxygen, which showed the original triplet (at δ = 4.02 ppm), together with two strongly differentiated diastereotopic signals at δ = 4.11 and 4.03 ppm (δ = 64.3 ppm in the ^{13}C NMR spectrum). The quartet at δ = 2.12 ppm was diagnostic for the allylic methylene protons directly bound to the CH=CHPh terminal portion. The full NMR characterization of compound **4a** is given in the Experimental Section.

Compound **5a** showed the original symmetry featured by the starting bicyclic olefin **2a**, and the following patterns (Figure 4c): the lack of the signals for intramolecular double bonds; the aromatic protons H5/H17 of the B/B′ rings at the same chemical shift as observed for **4a**; a 2:1 olefin/methine bridge protons ratio, which suggests the presence of four open chains ending with CH=CHPh groups (Figure 3). The methylene protons directly bound to the oxygen and to the CH=CHPh moiety have the same spectral pattern found in **4a** (Figure 4b–c).

Compound **3a**, which was already isolated in a previous work,[27] was identified from the signal at δ = 5.53 ppm (δ = 130.4 ppm in the ^{13}C NMR spectrum), which confirmed the presence of an intermolecular double bond (Figure 4d). No CH=CHPh moieties, such as those in **4a** or **5a** were detected. All the signals were in agreement with the structure already described.[27]

Purification of the crude mixture obtained from the reaction carried out in a 1:4 ratio (**2a**/G_1ST) gave, beside compound **5a**, two additional reaction mixtures named **I** and **II**. To get a picture of the plausible structures of such mixtures, we used the following two parameters (see Table 1): (1) the ratio between the integrated NMR areas of intermolecular double bonds (δ = 5.52 ppm) and olefin protons at δ = 6.39 ppm (namely, inter/CH=CHPh ratio); (2) the ratio between the intermolecular (δ = 5.52 ppm) and intramolecular (δ = 5.45 ppm and 5.37 ppm) double bonds (namely, inter/intra ratio). The combination of such parameters, which yielded the average number of CH=CHPh, intermolecular and intramolecular CH=CH groups, al-

Table 1. Ratios between the integrated NMR areas of the different types of double bonds expected for **2a**, **3a**, **6a**–**8a** and NMR experimental values found in mixtures **I** and **II** and in the reaction mixture with a 4:1 (**2a**/G_1ST) ratio.

Double bonds	**2a**	**3a**	**6a**	**7a**	**8a**	**I**	**II**	**2a**/G_1ST = 4:1
inter/CH=CHPh	0:0	2:0	1:2	1:1	1:4	1:1.8	1:1.1	1.7:1
inter/intra	0:2	1:1	1:2	2:1	1:1	1.5:1	3.2:1	1:3.6

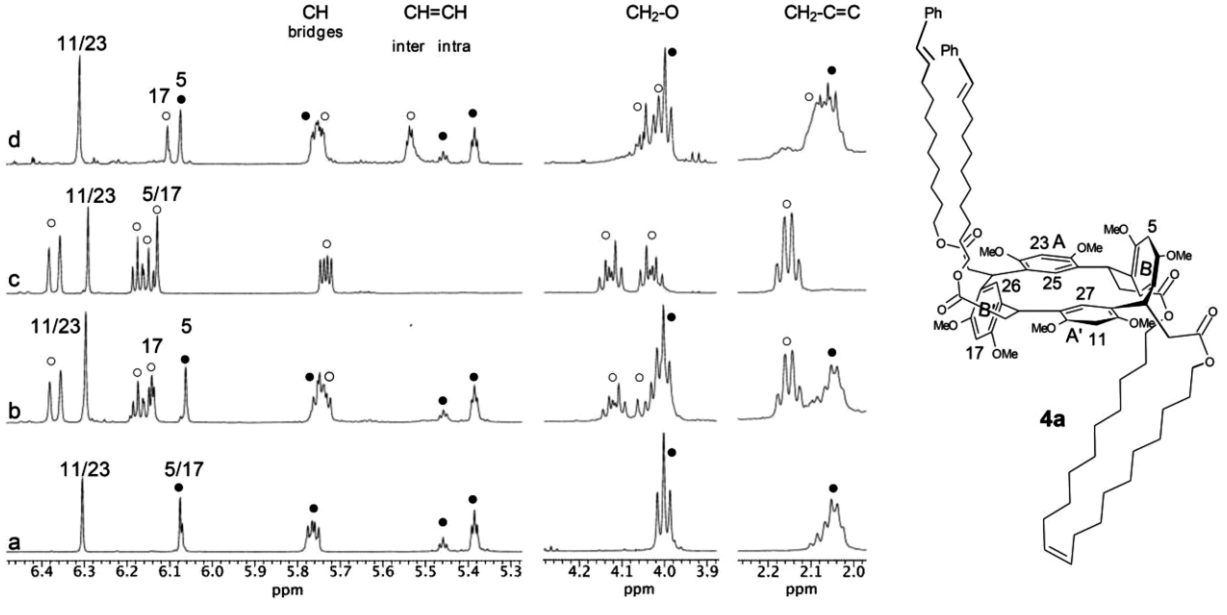


Figure 4. ^{1}H NMR (600 MHz, C_6D_6, 25 °C) spectra of compounds **2a** (a), **4a** (b), **5a** (c), and **3a** (d). (filled circles) Signals arising from the B ring and its chains; (open circles) Signals arising from the B′ ring and its chains.

lowed the identification of three plausible dimers (namely, **6a**–**8a**), the schematic structures of which are given in Figure 5. The average diffusion coefficient measured on the methine bridge protons of mixture **I** was 2.2×10^{-10} m^2 s^{-1}, which suggests the prevalence of dimers in the mixture. In fact, the ratio between the integrated areas of the aromatic protons at δ = 6.08 ppm, due to H5 proton of B ring included between intramolecularly bound chains, and the aromatic protons H11/H23 of the A/A′ rings at δ = 6.32 ppm was 1:4. For mixture **II**, an average diffusion coefficient of 1.5×10^{-10} m^2 s^{-1} was obtained, which suggests the presence of trimeric architectures built in a similar way to those in **6a**–**8a**.

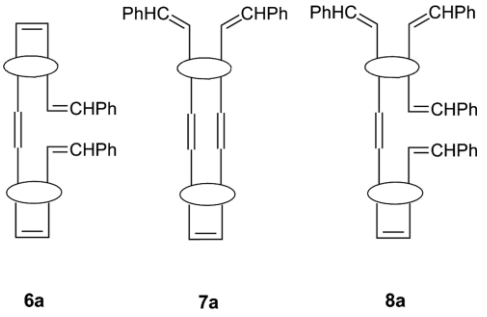
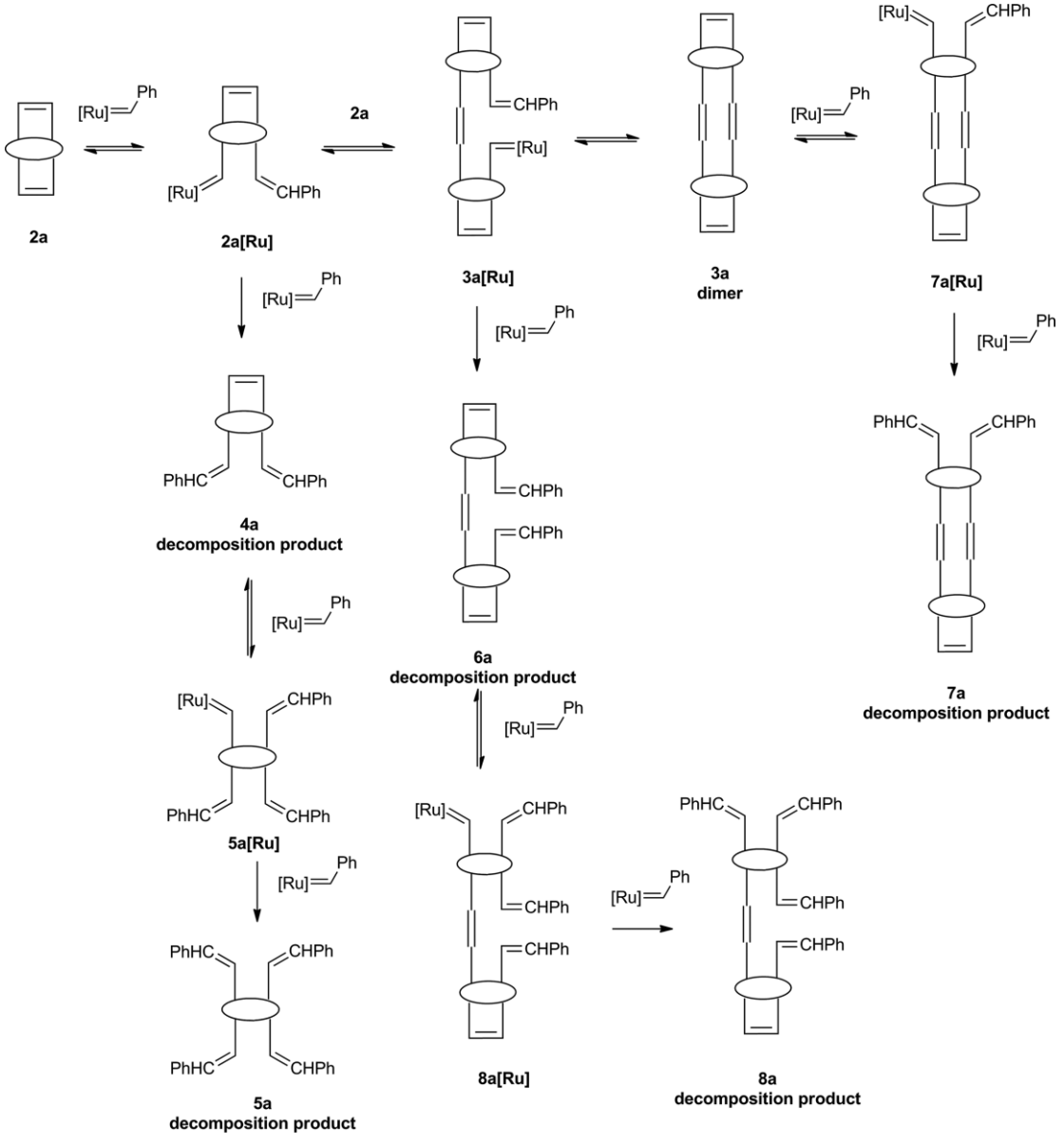


Figure 5. Schematic representation of the plausible dimers formed in the metathesis reaction of **2a** in benzene with G_1ST catalyst (**2a**/G_1ST = 1:4 ratio).

The isolation of compounds **4a** and **5a** from the reaction mixture has been taken as an indirect proof of the formation of the ruthenium-carbene-resorc[4]arene complex **2a**[Ru] (Scheme 2), the first complex to be formed by ROM of the starting olefin **2a**, which rapidly evolves into **3a**[Ru], by reaction with a second molecule. Indeed, when a fourfold excess of the resorc[4]arene olefin **2a** was used, the ruthenium-carbene-resorc[4]arene complex **2a**[Ru] leads mainly to the self-metathesis



Scheme 3. General pathway for the decomposition of ruthenium-carbene-resorc[4]arene **2a**[Ru] and **3a**[Ru] complexes.

product **3a** through a double CM with a second molecule of **2a** (see Scheme 3). When a fourfold excess of catalyst was used, instead, the two carbene complexes **2a**[Ru] and **3a**[Ru] underwent a decomposition pathway typical of the G_1ST catalyst itself,[34] as outlined in Scheme 3.

As a final refinement of our analytical NMR protocol, we wanted to reproduce the same metathesis reaction carried out in benzene in the NMR tube, and selected, as probe reaction conditions, the 4:1 (**2a**/G_1ST) ratio.

The reaction proceeds with an increase in the amount of the species featuring an intermolecular double bond (see Table S1 of the Supporting Information), but the inter/CH=CHPh ratio was in favor of species such as **3a** and **7a** (namely, 2:0 and 1:1, respectively, see Table 1). The decomposition of the catalyst was assessed to occur after 23 h of reaction time, based on the complete disappearance of the ^{1}H NMR signals at δ = 20.60 ppm and 19.80 ppm. As a consequence, the intra/inter ratio proved to be >1 (see Table 1), indicating a high percentage of the starting olefin **2a**. Accordingly, the diffusion coefficient, measured on the intermolecular double bond (δ = 5.52 ppm), remains almost constant at 2.5×10^{-10} m^2 s^{-1}, which is consistent with a dimeric structure, but the diffusion coefficient, measured on the protons of the resorc[4]arene bridges is higher (D = 3.8×10^{-10} m^2 s^{-1}), in agreement with a high percentage of unreacted monomer. Moreover, an intermediate diffusion coefficient (D = 3.0×10^{-10} m^2 s^{-1}), measured on the CH=CHPh double bond, indicates the presence of monomer and dimer species containing CH=CHPh moieties.

These results proved to be in good agreement with those previously described for the reaction carried out under the same experimental conditions after work-up and purification.

Conclusions

We detected for the first time the formation of a ruthenium-carbene-resorc[4]arene complex during the metathesis reaction of resorc[4]arene olefin **2a** with G_1ST catalyst in $CDCl_3$. The NMR analytical protocol we developed proved capable of yielding both qualitative and quantitative information. In the first case, we were able to identify the complex **3a**[Ru] as a key intermediate in the ROM-CM sequence of reactions, giving us definitive proof of the previously hypothesized mechanism.[27] As a further feedback of the pathway, we performed a quantitative analysis with benzene in place of $CDCl_3$, because of the poor stability of the catalyst in the latter solvent. The reaction allowed the isolation of decomposition products of the ruthenium-carbene-resorc[4]arene complex **2a**[Ru] such as compound **4a**, which, because of the presence of still reactive alkene functions, proved to behave as propagating alkylidene species, leading to further decomposition products.

We also demonstrated that, beside highly strained and unstrained olefins,[29–31] macrocycles themselves could be appropriate substrates for "macrocyclization" reactions, according to a ROM-CM mechanism, and the size of the macrocycles can be modulated by using appropriate substrate/catalyst ratios. Such structures would have the advantage of sharing supramolecular properties (e.g., molecular recognition of appropriate guests, propensity to self-assembly) with the intrinsic ability to yield suitable materials for biomedical applications (namely, drug delivery, tissue engineering, and regenerative medicine).

Experimental Section

General Information: All manipulations were performed by using a combination of glovebox and high-vacuum, under a nitrogen atmosphere. HPLC grade solvents were dried and degassed by using standard procedures. First-generation Grubbs catalyst was purchased from Sigma Aldrich, together with QuadraSil AP silica gel and deuterated chloroform ($CDCl_3$, containing silver wire as stabilizer). Deuterated benzene (C_6D_6) was purchased from Deutero GmbH. Both solvents were employed without further purification.

Metathesis Reaction in the NMR Tube: Resorc[4]arene bicyclic olefin **2a** (20 mg, 0.014 mmol) was dissolved in $CDCl_3$ (0.35 mL) in a glovebox under a nitrogen atmosphere, and the solution was transferred into an NMR tube by using a syringe. A solution of G_1ST [Ru(=CHPh)Cl_2(PCy_3)$_2$] catalyst (12 mg, 0.014 mmol) in $CDCl_3$ (0.35 mL) was then introduced, and the progress of the reaction was monitored by ^{1}H NMR, ^{31}P NMR, and DOSY spectroscopy.

Metathesis Reaction in Benzene (2a/G_1ST = 4:1): Resorc[4]arene bicyclic olefin **2a** (120 mg, 0.087 mmol) was dissolved in benzene (1.5 mL). The solution was exposed to a solution of the G_1ST [Ru(=CHPh)Cl_2(PCy_3)$_2$] catalyst (18 mg, 0.0218 mmol) in benzene (1.5 mL), previously prepared in the glovebox, to reach a 3×10^{-2} M substrate concentration. After stirring for 4 d at room temperature under a nitrogen atmosphere, the reaction mixture was heated to 50 °C for 6 h. After cooling to room temperature, QuadraSil AP metal scavenger (aminopropyl silica gel, 6 g) was added and the mixture was stirred overnight. After filtration and evaporation, the residue was suspended in DCM and purified by silica gel column chromatography to give compounds **4a** (2.7 mg, 2 %, with DCM/ethyl acetate, 97:3), **2a** (48.2 mg, 40 %, with DCM/ethyl acetate, 97:3), and **3a** (7.3 mg, 6 %, with DCM/ethyl acetate, 95:5).

The reaction was also reproduced in an NMR tube by using C_6D_6 as the solvent and monitored over time by ^{1}H NMR, ^{31}P NMR and DOSY spectroscopy.

Metathesis Reaction in Benzene (2a/G_1ST = 1:4): Resorc[4]arene bicyclic olefin **2a** (100 mg, 0.072 mmol) was dissolved in benzene (1.2 mL) and exposed to a solution of G_1ST [Ru(=CHPh)Cl_2(PCy_3)$_2$] catalyst (237 mg, 0.288 mmol) in benzene (1.2 mL), previously prepared in a glovebox, to reach a 3×10^{-2} M substrate concentration. After stirring for 4 d at room temperature under a nitrogen atmosphere, the reaction mixture was heated at 50 °C for 6 h. After cooling to room temperature, QuadraSil AP metal scavenger (aminopropyl silica gel, 6 g) was added and the mixture was stirred overnight. After filtration and evaporation, the residue was suspended in DCM and purified by silica gel column chromatography to give compounds **5a** (7.7 mg, 6 %, with DCM/ethyl acetate, 97:3), **4a** (14.2 mg, 12.5 %, with DCM/ethyl acetate, 97:3), **2a** (35 mg, 35 %, with DCM/ethyl acetate, 97:3) and two enriched mixtures products named **I** and **II** (with DCM/ethyl acetate, 90:10).

NMR Characterization (solvent: C_6D_6) of Metathesis Reaction Products 2a–5a: The NMR spectroscopic data are referred to the numbering schemes reported in Figure S8 of the Supporting Information.

Compound 2a: Resorc[4]arene bicyclic olefin **2a** was synthesized as described previously.[27] White powder; mp 191.4–190.4 °C. ^{1}H NMR (600 MHz, C_6D_6, 10 mM, 25 °C): δ = 7.45 (s, 2 H, H26/H28), 6.87 (s, 2 H, H25/H27), 6.31 (s, 2 H, H11/H23), 6.08 (s, 2 H, H5/H17), 5.76 (dd, $J_{CH\text{-}29}$ = 10.1, $J_{CH\text{-}29'}$ = 5.7 Hz, 4 H, H2/H8/H14/H20), 5.45 (t, ^3J = 5.1 Hz, 0.96 H, CH=CH *cis*), 5.38 (t, ^3J = 3.8 Hz, 3.04 H, CH=CH *trans*), 4.01 (t, ^3J = 7.1 Hz, 8 H, O-CH_2), 3.52 (s, 12 H, OMe10′/OMe12′/OMe22′/OMe24′), 3.21 (s, 12 H, OMe4′/OMe6′/OMe16′/OMe18′), 3.13 (dd, $J_{29'\text{-}29}$ = 15.4, $J_{29'\text{-}CH}$ = 5.7 Hz, 4 H, H29′), 3.06 (dd, $J_{29\text{-}29'}$ = 15.4, $J_{29\text{-}CH}$ = 10.1 Hz, 4 H, H29), 2.04 (m, 8 H, CH_2-C=C), 1.54–1.00 (m, 56 H, lateral chains) ppm. ^{13}C NMR (150 MHz, C_6D_6, 10 mM, 25 °C): δ = 171.9 (CO), 157.2 (C4/C6/C16/C18), 156.1 (C10/C12/C22/C24), 131.1 (C=C *cis*), 130.4 (C=C *trans*), 128.3 (C3/C7/C15/C19), 127.0 (C25/C27), 126.2 (C26/C28), 122.6 (C1/C9/C13/C21), 97.0 (C5/C17), 95.6 (C11/C23), 64.4 (O-CH_2), 55.4 (C10′/C12′/C22′/C24′), 55.3 (C4′/C6′/C16′/C18′), 40.1 (C29), 33.6 (C2/C8/C14/C20), 32.5 (CH_2 allylic), 30.2–26.3 (CH_2, lateral chains) ppm.

Compound 3a: Dimer **3a** was synthesized as described previously.[27] White powder; mp 167.4–166.4 °C. ^{1}H NMR (600 MHz, C_6D_6, 25 °C): δ = 7.44 (s, 4 H, H26/H28), 6.86 (s, 4 H, H25/H27), 6.32 (s, 4 H, H11/H23), 6.11 (s, 2 H, H17), 6.08 (s, 2 H, H5), 5.75 (dd, $J_{CH\text{-}29}$ = 6.2, $J_{CH\text{-}29'}$ = 2.4 Hz, 4 H, H2/H8/H14/H20), 5.73 (dd, $J_{CH\text{-}29}$ = 5.5, $J_{CH\text{-}29'}$ = 2.4 Hz, 4 H, H2/H8/H14/H20), 5.53 (m, 4 H, CH=CH inter), 5.45 (t, ^3J = 5.1 Hz, 1.08 H, CH=CH *cis*), 5.37 (t, ^3J = 3.7 Hz, 2.92 H, CH=CH *trans*), 4.05 (m, 8 H, O-CH_2 of B′ rings), 4.01 (m, 8 H, O-CH_2 of B rings), 3.53 (s, 12 H, OMe10′/OMe24′ or OMe12′/OMe22′), 3.52 (s, 12 H, OMe10′/OMe24′ or OMe12′/OMe22′), 3.23 (s, 12 H, OMe16′/OMe18′), 3.21 (s, 12 H, OMe4′/OMe6′), 3.13–2.99 (m, 16 H, H29/29′ of B and B′), 2.07 (m, 8 H, CH_2-C=C inter) 2.04 (m, 8 H, CH_2-C=C intra), 1.84–0.70 (m, 112 H, lateral chains) ppm. ^{13}C NMR (150 MHz, C_6D_6, 25 °C): δ = 171.9 (CO), 171.8 (CO), 157.2 (C4/C6 or C16/C18), 157.1 (C4/C6 or C16/C18), 156.1 (C10/C24 or C12/C22), 156.0 (C10/C24 or C12/C22), 131.0 (C=C *trans*), 130.6 (C=C intermolecular), 130.7 (C=C *cis*), 126.2 (C26/C28), 127.0 (C25/C27), 122.6 (C3/C7 or C15/C19), 122.5 (C3/C7 or C15/C19), 96.9 (C5/C17), 95.6 (C11/C23), 64.3 (O-CH_2), 55.3 (C10′/C12′/C22′/C24′), 55.2 (C4′/C6′/C16′/C18′), 40.1 (C29), 33.1 (CH_2 allylic), 32.4 (CH_2 allylic), 40.3–19.9 (CH_2, lateral chains) ppm.

Compound 4a: Yellow oil. ^{1}H NMR (600 MHz, C_6D_6, 25 °C): δ = 7.43 and 7.42 (s, 2 H, H26/H28), 7.29 (dd, $J_{o\text{-}m}$ = 8.0 Hz, 4 H, Ho), 7.15 (t, $J_{m\text{-}o}$ =, $J_{m\text{-}p}$ = 8.0 Hz, 4 H, Hm), 7.06 (t, $J_{p\text{-}m}$ = 8.0 Hz, 2 H, Hp), 6.85 (s, 2 H, H25/H27), 6.38 (d, $J_{CH\text{-}CH}$ = 15.9 Hz, 2 H, C=CH-Ph), 6.30 (s, 2 H, H11/H23), 6.17 (dt, $^2J_{CH\text{-}CH}$ = 15.9, ^3J = 6.7 Hz, 2 H, -CH=C-Ph), 6.15 (s, 1 H, H17), 6.06 (s, 1 H, H5), 5.75 (m, 2 H, H2/H8), 5.74 (m, 2 H, H14/H20), 5.45 (t, ^3J = 5.2 Hz, 0.54 H, CH=CH *cis*), 5.37 (t, ^3J = 3.7 Hz, 1.46 H, CH=CH *trans*), 4.11 (dt, ^2J = 10.7, ^3J = 6.9 Hz, 2 H, O-C*H*H), 4.04 (dt, ^2J = 10.7, ^3J = 6.4 Hz, 2 H, O-CH*H*), 4.02 (t, ^3J = 7.1 Hz, 4 H, O-CH_2), 3.52 (s, 6 H, OMe10′/OMe24′ or OMe12′/OMe22′), 3.50 (s, 6 H, OMe10′/OMe24′ or OMe12′/OMe22′), 3.26 (s, 6 H, OMe16′/OMe18′), 3.20 (s, 6 H, OMe4′/OMe6′), 3.17 (dd, ^2J = 15.7, ^3J = 5.3 Hz, 2 H, H29 of B′ ring), 3.13 (dd, ^2J = 15.3, ^3J = 6.1 Hz, 4 H, H29′ of B ring), 3.08 (dd, ^2J = 15.3, ^3J = 3.6 Hz, 2 H, H29 of B ring), 3.04 (dd, ^2J = 15.7, ^3J = 5.0 Hz, 2 H, H29′ of B′ ring), 2.12 (q, ^3J = 7.6 Hz, 2 H, CH-C=C), 2.04 (q, ^3J = 6.1 Hz, 2 H, CH-C=C), 1.54–0.84 (m, 56 H, lateral chains) ppm. ^{13}C NMR (150 MHz, C_6D_6, 25 °C): δ = 171.9 (CO), 171.8 (CO), 157.2 (C4/C16, C6/C20), 156.1 (C10/C24, C12/C22), 138.4 (Ar quaternary), 131.1 (C=C-Ph, C=C *cis*), 130.5 (C=C-Ph), 130.4 (C=C *trans*), 127.0 (C25/C27, Cp), 126.5 (Cm), 126.3 (Co), 126.2 (C1/C13, C9/C21, C26/C28), 122.7 (C3/C15, C7/C19), 96.9 (C5, C17), 95.6 (C11/C23), 64.4 (O-CH_2), 64.3 (O-CH_2), 55.4 (C10′/C24′, C12′/C22′), 55.3 (C4′/C6′, C16′/C18′), 40.2 (C29), 39.8 (C29), 33.6 (C2/C8/C14/C20), 33.5 (CH_2 allylic), 32.6 (CH_2 allylic), 37.7–23.0 (CH_2 lateral chains) ppm. HRMS (ESI-FT-ICR) *m/z* calcd for $C_{98}H_{132}O_{16}Na$ [*M* + Na]$^+$ 1587.94076 (monoisotopic mass); found 1587.94248.

Compound 5a: White oil. ^{1}H NMR (600 MHz, C_6D_6, 25 °C): δ = 7.37 (s, 2 H, H26/H28), 7.25 (dd, $J_{o\text{-}m}$ = 8.0, $J_{o\text{-}p}$ = 1.2 Hz, 8 H, Ho), 7.11 (t, $J_{m\text{-}o}$ = $J_{m\text{-}p}$ = 8.0 Hz, 8 H, Hm), 7.01 (tt, $J_{p\text{-}m}$ = 8.0, $J_{p\text{-}o}$ = 1.2 Hz, 4 H, Hp), 6.79 (s, 2 H, H25/H27), 6.34 (d, $J_{CH\text{-}CH}$ = 15.7 Hz, 4 H, C=CH-Ph), 6.26 (s, 2 H, H11/H23), 6.13 (dt, $J_{CH\text{-}CH}$ = 15.7, $J_{CH\text{-}CH2}$ = 6.9 Hz, 4 H, -CH=C-Ph), 6.10 (s, 2 H, H5/H17), 5.69 (dd, $J_{CH\text{-}29}$ = 5.5, $J_{CH\text{-}29'}$ = 10.4 Hz, 4 H, H2/H8/H14/H20), 4.08 (dt, ^2J = 10.5, $J_{CH2\text{-}CH2}$ = 6.8 Hz, 4 H, O-CH_2), 4.00 (dt, ^2J = 10.5, $J_{CH2\text{-}CH2}$ = 6.8 Hz, 4 H, O-CH_2), 3.47 (s, 12 H, H10′/H22′, H12′/H24′), 3.21 (s, 12 H, H4′/16′, H6′/H18′), 3.13 (dd, $J_{29\text{-}29'}$ = 15.8, $J_{29\text{-}CH}$ = 5.5 Hz, 4 H, H29), 3.04 (dd, $J_{29'\text{-}29}$ = 15.8, $J_{29'\text{-}CH}$ = 10.4 Hz, 4 H, H29′), 2.08 (q, $J_{CH\text{-}CH}$ = $J_{CH\text{-}CH2}$ = 7.10 Hz, 8 H, CH_2-C=C), 1.50–0.8 (m, 56 H) ppm. ^{13}C NMR (150 MHz, C_6D_6, 25 °C): δ = 171.5 (CO), 156.8 (C4/C16, C6/C20), 155.7 (C10/C22, C12/C24), 138.0 (Ar quaternary), 130.7 (C=C-Ph), 130.1 (C=C-Ph), 126.7 (C25/C27, Cp), 126.0 (Co), 125.8 (C1/C13, C9/C21, C26/C28, Cm), 122.3 (C3/C15, C7/C19), 96.5 (C5/C17), 95.3 (C11/C23), 64.0 (O-CH_2), 55.0 (C4′/C16′, C6′/C18′, C10′/C22′, C12′/C24′), 39.5 (C29), 33.2 (C2/C8/C14/C20), 33.1 (C allylic), 37.2–22.9 (lateral chains) ppm. HRMS (ESI-FT-ICR) *m/z* calcd for $C_{112}H_{144}O_{16}Na$ [*M* + Na]$^+$ 1768.03466 (monoisotopic mass); found 1768.03373 ± 7.02 10^{-4} (mean value of seven experiments).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{31}P NMR spectra of the reaction mixtures of resorc[4]arene **2a** with G_1ST catalyst; 2D ROESY map of the metathesis reaction mixture; DOSY maps of resorc[4]arene bicyclic olefin **2a**. ESI-HRMS and NMR spectra of compounds **4a** and **5a**; 1D TOCSY spectra are also included.

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Keywords: Metathesis · Ruthenium · Carbene ligands · NMR spectroscopy · Reaction mechanisms · Grubbs catalyst

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