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Suzuki–Miyaura Cross-Coupling and Ring-Closing Metathesis: A Strategic Combination for the Synthesis of Cyclophane Derivatives

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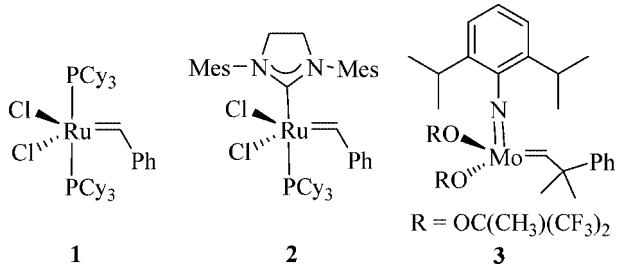
The synthesis of cyclophane derivatives through a sequence involving Suzuki–Miyaura cross-coupling between α,α′-dibromo-*m*-xylene and arylboronic acid derivatives, alkenylation and ring-closing metathesis has been achieved. One of the cyclophanes was obtained by tandem isomerization and metathesis. Significant magnetic anisotropic effects on the intra-annular hydrogen atoms were observed.

Introduction

Ruthenium-catalysed metathesis and palladium-catalysed cross-coupling reactions have recently made a profound impact on carbon–carbon bond formation in organic synthesis. In particular, with the advent of the commercially available and well defined metal carbene complexes[1] (Figure 1) of Grubbs (e.g., **1** and **2**) and Schrock (e.g., **3**), metathesis has attracted renewed interest and has been quickly accepted into the mainstream of organic synthesis.[2] These catalysts function under mild reaction conditions and exhibit a wide range of functional group tolerance, and these advances have opened up a completely new set of possibilities in organic synthesis. Of the various modes of olefin metathesis, the intramolecular version (i.e., ring-closing metathesis, RCM) has become more popular than other metathesis processes. RCM is a powerful tool for the construction of small (≥5 members), medium and large carbocyclic (or heterocyclic) ring systems starting from acyclic precursors.[3]

Similarly, of the various Pd-catalysed cross-coupling reactions, the Suzuki–Miyaura (SM) cross-coupling reaction is one of the most efficient methods for the construction of C–C bonds.[4] The preferred status of the SM cross-coupling reaction over other Pd-catalysed cross-coupling reactions is not coincidental: its key advantages are its mild reaction conditions and the commercial availability of diverse boronic acids, which are also environmentally safer than other organometallic reagents. In addition, the handling and removal of boron-containing by-products are easier than those associated with the use of other organometallic reagents, especially in large-scale syntheses. The combination of these two powerful tools should therefore open up new and short synthetic routes to various complex targets.



1 **2** **3**

Figure 1. Commonly used olefin metathesis catalysts.

A cyclophane is defined as a molecule containing a bridged aromatic ring and usually contains a molecular cavity of varied size. Cyclophanes, subjects of investigations since the 1950s, are useful model systems for studying through-space interactions,[6] have also found many applications in supramolecular chemistry, metal ion transport and catalysis, and represent intricate resources for a variety of host–guest interactions,[7] as a result of which there is a continuous need to develop new and simple strategies for their synthesis. Several such strategies have been developed over the years, but methods for the synthesis of cyclophanes based on the usage of metathesis, Suzuki–Miyaura (SM) cross-coupling or combinations of these two reactions are limited.

Very few groups have successfully employed metathesis as a key step for the synthesis of cyclophane derivatives,[8] application of SM cross-coupling for the synthesis of cyclophanes is less explored than that of metathesis,[9] whilst reports involving a combination of metathesis and SM coupling are rare in organic synthesis. Guan and co-workers were the first to use the combination of palladium-catalysed SM cross-coupling and RCM for the efficient synthesis of

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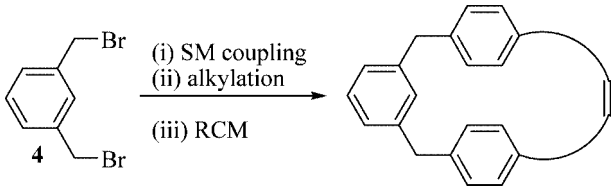
m-terphenyl-based cyclophane, with the aid of Grubbs' 2nd generation catalyst **2**.[10]

Here we report a simple and straightforward synthetic strategy for cyclophane derivatives using the SM cross-coupling reaction and RCM as key steps. The strategy adopted in our study is shown in Scheme 1. The preliminary results of this research were published elsewhere.[5]

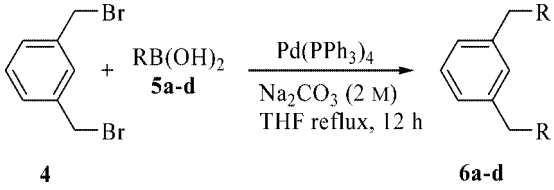


Scheme 1. Synthetic strategy for cyclophane synthesis.

Results and Discussion

In general, the majority of SM cross-coupling reactions described so far have been associated with the coupling of aryl halides with arylboronic acids. The use of benzyl bromides as SM coupling partners, however, is less well explored.[11]

To test the feasibility of the first step in our strategy, various functionalized boronic acids were coupled with the two-armed benzyl bromide **4** (Scheme 2). We found that **4** would react with various boronic acids in the presence of the palladium catalyst [$Pd(PPh_3)_4$] to generate the required cross-coupling products in good yields (Table 1).[12]



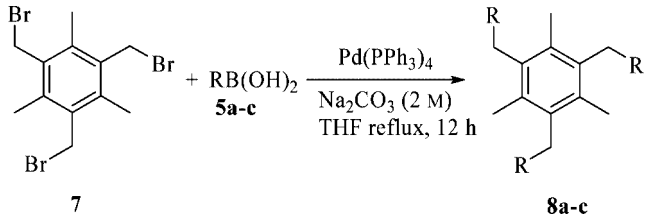
Scheme 2. The reaction was conducted with the boronic acid (1.5 equiv. for each bromine atom in the substrate), $Pd(PPh_3)_4$ (6–10 mol-%).

Table 1. Suzuki cross-coupling reactions between **4** and various functionalized boronic acids.

Entry	Boronic acids	R	Products	Yield[a] (%)
i	**5a**	*p*-OMePh	**6a**	32
ii	**5b**	*p*-CHOPh	**6b**	80
iii	**5c**	*p*-CNPh	**6c**	84[b]
iv	**5d**	*p*-AcPh	**6d**	71[b]

[a] Isolated yields. [b] Purification was carried out by repeated recrystallization after column chromatography.

This methodology was also extended to the three-armed benzyl bromide derivative **7** (Scheme 3, Table 2). Since C_3-symmetric molecules are valuable core units for dendrimer design and for the synthesis of useful ligands, this methodology is likely to find applications in these areas.



Scheme 3. The reaction was conducted with boronic acid (1.5 equiv. for each bromine atom in the substrate), $Pd(PPh_3)_4$ (10–15 mol-%).

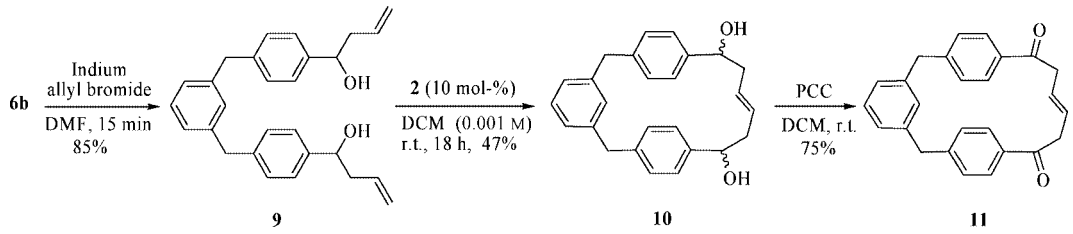
Table 2. Suzuki cross-coupling reactions between **7** and various functionalized boronic acids.

Entry	Boronic acids	R	Products	Yield[a] (%)
i	**5a**	*p*-OMePh	**8a**	61
ii	**5b**	*p*-CHOPh	**8b**	70
iii	**5c**	*p*-CNPh	**8c**	82

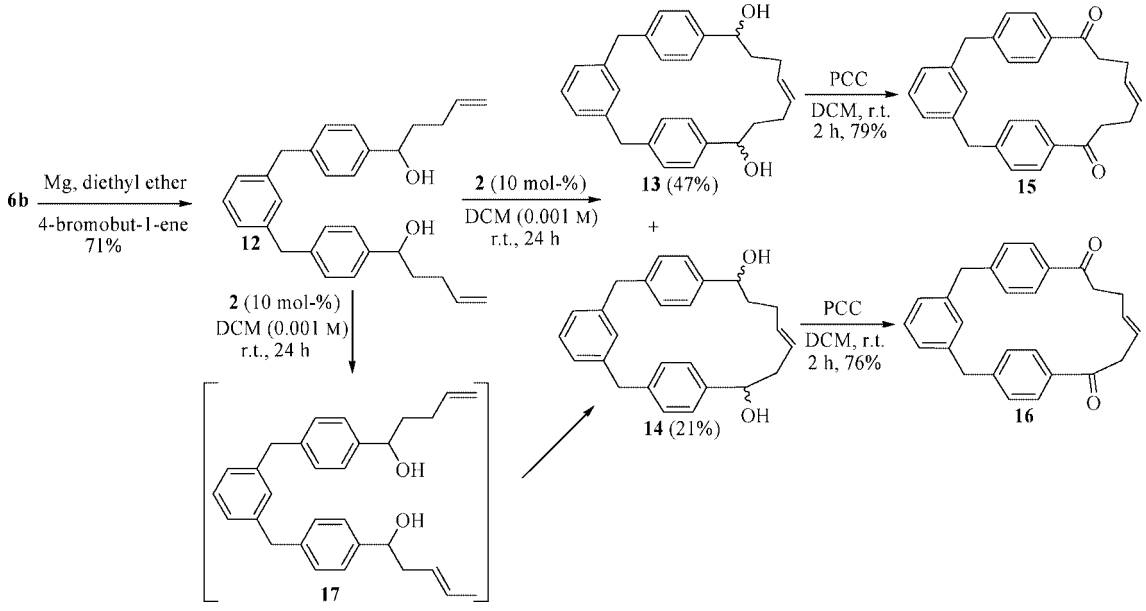
[a] Isolated yields.

In an attempted synthesis of the target cyclophane **11**, compound **6a** was allylated by treatment with allyl bromide in the presence of indium (Scheme 4)[13] and the diol **9** was then subjected to RCM in the presence of Grubbs' 1st generation catalyst **1**, giving a complex mixture of products. However, use of the 2nd generation catalyst **2** under high-dilution conditions (0.001 M) at room temp. delivered the cyclophane derivative **10** as a mixture of diastereomers (1:2; determined by ^{1}H NMR integration) in 47% yield.[14] The lower yield could be accounted for by the formation of various oligomeric side products during the macrocyclization reaction, as reported earlier.[2] The successful formation of **10** was indicated by its ^{1}H NMR spectroscopic data, whilst the molecular ion peak at *m*/*z* = 393 [M + Na] in the mass spectrum further confirmed the structure of the desired cyclophane derivative. Subsequent PCC oxidation of the above mixture gave cyclophane **11**, the structure of which, with the assigned *trans* geometry, was confirmed by X-ray crystallographic data.[5] The crystal structure of **11** reveals that in the solid state arrangement, the ethylene bridge is disordered with an averaged population of 70:30, perhaps due to the availability of void space. Further, this disorder is dynamic in nature, as the crystals did not show any disorder when cooled to 133 K.

To generalize the method, we turned our attention to the preparation of the higher analogues of **11** as depicted in Scheme 5. The RCM precursor **12** was prepared by Grignard treatment of **6b** with 4-bromobut-1-ene in 71% yield, and exposure of the diolefinic compound **12** to Grubbs' 2nd generation catalyst **2** in dichloromethane under high-dilution conditions (0.001 M) at room temp. resulted in the formation of the cyclophane derivative **13** (1:1.7; mixture of two diastereomers as determined from the ^{1}H NMR integration ratio) as the major product. The successful formation of **13** was indicated by its ^{1}H NMR spectroscopic data, and the structure of the desired cyclophane derivative **13** was further confirmed by the molecular ion peak at *m*/*z* = 421 [M + Na] in the mass spectrum. To our surprise, a



Scheme 4. Synthesis of **11** with RCM as a key step.



Scheme 5. Synthesis of higher analogues of **11**.

minor product was isolated along with the target product as a mixture of two diastereomers (1:2.2; determined from ^{1}H NMR integration ratio) in significant yield. The structure of this minor product was assigned as **14** and its unsymmetrical nature is supported by its ^{1}H NMR spectrum. The molecular ion peak at m/z = 407 [M + Na] in the mass spectrum further confirmed the assigned structure of compound **14**.

The unusual formation of compound **14** could be explained in terms of a tandem isomerization induced by the Grubbs' catalyst, followed by a RCM sequence through the intermediacy of **17** (Scheme 5).[15] Finally, oxidation of the mixture of diastereomers gave the cyclophanedione as a single compound. Treatment of diols **13** and **14** with PCC in dichloromethane at room temp. for 2 h thus gave the cyclophane derivatives **15** and **16**, respectively, each as a single isomer in modest yield. The formation of compounds **15** and **16** was confirmed by their IR and ^{1}H NMR spectroscopic data, and the exclusive *trans* geometry of the cyclophane derivative **16** was assigned through the observed coupling constant (J = 15.0 Hz) of the olefinic proton in its ^{1}H NMR spectrum. Finally, the structures of **15** and **16** were further confirmed by high-resolution mass spectral analysis.

Interestingly, significant magnetic anisotropic effects on the intra-annular aromatic hydrogens (H_i) were observed in all the cyclophane derivatives, as shown in Figure 2. The H_i protons in the open-chain analogues **9** and **12** absorb in the region of δ = 7.02 ppm, but in the cyclic forms (i.e., in the cyclophane derivatives **10**, **11** and **13**–**16**) the intra-annular

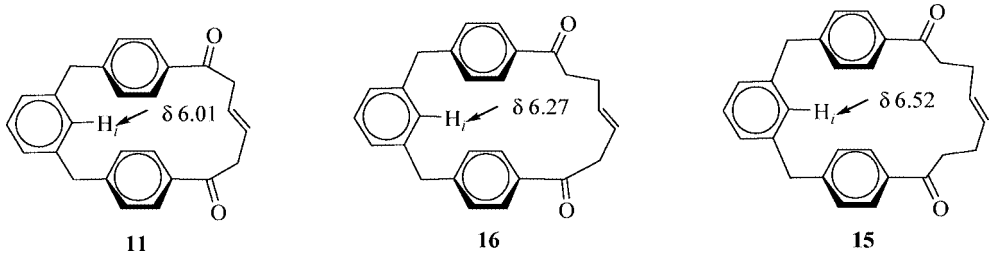


Figure 2. Magnetic anisotropic effects in various cyclophane derivatives.

hydrogen atoms (H_i) located between the planes of the two *para*-substituted benzene rings are found to be shifted moderately upfield. As the cavity size (or aliphatic chain length) in such phane systems decreased, the upfield shifts of H_i increased, due to the increase in shielding effects (Figure 2).

Conclusions

In summary, we have demonstrated a new approach for the synthesis of cyclophane derivatives through the use of a combination of SM cross-coupling and RCM as key steps. One of the cyclophane derivatives was obtained through a tandem isomerization and metathesis reaction. Significant magnetic anisotropic effects on the intra-annular hydrogen atoms were observed, so these macrocyclic compounds could be potential targets for charge density studies in addition to host–guest complex experiments.

Experimental Section

General Remarks: All reactions were monitored by thin layer chromatography (TLC) carried out on glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder). Visualization of the spots on TLC plates was achieved by exposure either to iodine vapour or to UV light. Flash chromatography was performed with Acme's silica gel (100–200 mesh). Petroleum ether refers to the fraction of boiling point 60–80 °C. All the commercial grade reagents were used without further purification. 1st and 2nd generation Grubbs' catalysts (**1** and **2**), α,α′-dibromo-*m*-xylene, 4-bromobut-1-ene and all the boronic acids used here were purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI USA). Magnesium, indium and allyl bromide (s. d. fine-Chem Ltd.) were used as received. $Pd(PPh_3)_4$ was prepared by the reported procedure.[16] Infrared spectra were recorded on a Nicolet Impact 400 FT-IR spectrometer in $KBr/CHCl_3/CCl_4$. ^1H NMR (300, 400 MHz) and ^{13}C NMR (75.4, 100.6 MHz) spectra were determined at room temperature on a Varian VXR 300 or an AX 400 mercury plus in $CDCl_3$ solutions. Coupling constants (*J* values) are given in Hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference. High-resolution mass spectra were determined on a Micromass Q-Tof spectrometer.

General Procedure for Coupling between Arylboronic Acids and α,α′-Dibromo-*m*-xylene (4): A mixture of α,α′-dibromo-*m*-xylene (**4**, 1 equiv.), the arylboronic acid (3 equiv.), $Pd(PPh_3)_4$ (6–10 mol-%) and Na_2CO_3 (4 equiv.) in water and THF (1:1) was heated at 80 °C. The reaction mixture was degassed with argon for 20 min prior to the addition of the catalyst. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with water and extracted with ethyl acetate, and the combined organic layer was washed with water and brine and dried with anhydrous $MgSO_4$. The solvent was evaporated and the crude product was loaded onto a silica gel column. Elution of the column with EtOAc/petroleum ether gave the desired cross-coupling product.

1,3-Bis(4-methoxybenzyl)benzene (6a): 4-Methoxyphenylboronic acid (50 mg, 0.33 mmol) and aqueous Na_2CO_3 (2 M solution, 4 equiv.) were added to a solution of **4** (26 mg, 0.1 mmol) in dimethoxyethane (3 mL), and the resulting reaction mixture was degassed with argon for 20 min. $Pd(PPh_3)_4$ (12 mg, 0.01 mmol, 10 mol-%) was then added, the reaction mixture was heated at reflux for 12 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with petroleum ether gave compound **6a** (10 mg, 32%) as a white solid. R_f = 0.5 (silica gel, EtOAc/petroleum ether 1:39); m.p. 73 °C (from hexane). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 6 H, 2×OCH_3), 3.88 (s, 4 H, 2×CH_2), 6.82 (d, *J* = 8.8 Hz, 4 H, ArH), 6.98 (d, *J* = 8.1 Hz, 2 H, ArH), 7.01 (s, 1 H, ArH), 7.08 (d, *J* = 8.8 Hz, 4 H, ArH), 7.18 (t, *J* = 7.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 41.0, 55.3, 113.9, 126.6, 128.6, 129.5, 129.9, 133.4, 141.7, 158.0 ppm. UV: $\lambda_{max}(CHCl_3)$/nm 279 (ε/dm^3 mol^{-1} cm^{-1} 3908). HRMS (EI): calcd. for $C_{22}H_{22}O_2$: 318.1619; found: 318.1612.

1,3-Bis(4-formylbenzyl)benzene (6b): 4-Formylphenylboronic acid (170 mg, 1.14 mmol) and aqueous Na_2CO_3 (2 M solution, 4 equiv.) were added to a solution of **4** (100 mg, 0.38 mmol) in THF, and the resulting reaction mixture was degassed with argon for 20 min. $Pd(PPh_3)_4$ (36 mg, 0.03 mmol, 8 mol-%) was then added, the reaction mixture was heated at reflux for 12 h and worked up as described in the General Procedure, and the crude product was purified by silica gel column chromatography. Elution of the column with EtOAc/petroleum ether (10%) gave compound **6b** as a colourless oil (95 mg, 80%). R_f = 0.38 (silica gel, EtOAc/petroleum ether 1:4). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.02 (s, 4 H, 2×CH_2), 7.01 (s, 1 H, ArH), 7.04 (d, *J* = 7.5 Hz, 2 H, ArH), 7.25 (t, *J* = 7.5 Hz, 1 H, ArH) 7.33 (d, *J* = 8 Hz, 4 H, ArH), 7.8 (d, *J* = 8.2 Hz, 4 H, ArH), 9.97 (s, 2 H, 2×CHO) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 42.1, 127.3, 129.2, 129.7, 129.8, 130.1, 134.9, 140.4, 148.3, 192.0 ppm. IR (neat): $\tilde{\nu}$ = 1699 (C=O) cm^{-1}. UV: $\lambda_{max}(CHCl_3)$/nm 265 (ε/dm^3 mol^{-1} cm^{-1} 17327). HRMS (Q-Tof): *m*/*z* calcd. for $C_{22}H_{18}O_2Na$ [M + Na]: 337.1204; found: 337.1208.

1,3-Bis(4-cyanobenzyl)benzene (6c): 4-Cyanophenylboronic acid (125 mg, 0.85 mmol) and aqueous Na_2CO_3 (2 M solution, 4 equiv.) were added to a solution of **4** (77 mg, 0.29 mmol) in THF, and the resulting reaction mixture was degassed with argon for 20 min. $Pd(PPh_3)_4$ (27 mg, 0.02 mmol, 8 mol-%) was then added, the reaction mixture was heated at reflux for 12 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with EtOAc/petroleum ether (15%) gave compound **6c** as a white solid (76 mg, 84%). R_f = 0.20 (silica gel, EtOAc/petroleum ether 1:4); m.p. 114–115 °C (from DCM/hexane 1:9). ^1H NMR (300 MHz, $CDCl_3$): δ = 4.0 (s, 4 H, 2×CH_2), 6.97 (s, 1 H, ArH), 7.02 (d, *J* = 7.3 Hz, 2 H, ArH), 7.23–7.27 (m, 5 H, ArH), 7.57 (d, *J* = 8 Hz, 4 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 41.9, 110.1, 119.0, 127.3, 129.2, 129.6, 132.4, 139.9, 146.5 ppm. UV: $\lambda_{max}(CHCl_3)$/nm 284 (ε/dm^3 mol^{-1} cm^{-1} 5621). HRMS (Q-Tof): *m*/*z* calcd. for $C_{22}H_{17}N_2$ [M + H]: 309.1392; found: 309.1398.

1,3-Bis(4-acetylbenzyl)benzene (6d): 4-Acetylphenylboronic acid (93 mg, 0.57 mmol) and aqueous Na_2CO_3 (2 M solution, 4 equiv.) were added to a solution of **4** (50 mg, 0.19 mmol) in THF, and the resulting reaction mixture was degassed for 20 min. $Pd(PPh_3)_4$ (21.8 mg, 10 mol-%) was then added, the reaction mixture was heated at reflux for 12 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with EtOAc/petroleum ether (25%) gave compound **6d** (46 mg, 71%). R_f = 0.4 (silica gel, EtOAc/petroleum ether 3:7); m.p. 81 °C (from DCM/hexane 1:9). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 6 H, 2×CH_3), 3.99 (s, 4 H, 2×CH_2), 7.01 (s, 1 H, ArH), 7.02 (d, *J* = 7.9 Hz, 2 H, ArH), 7.20–7.26 (m, 5 H, ArH), 7.87 (d, *J* = 8.5 Hz, 4 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 26.6, 41.9, 127.1, 128.7, 129.0, 129.1, 129.6, 135.3, 140.5, 146.7 ppm. IR (neat): $\tilde{\nu}$ = 1681 cm^{-1}

(C=O). UV: λ_{max}($CHCl_3$)/nm 274 (ε/dm^{3}mol^{-1}cm^{-1} 18273). HRMS (Q-Tof): *m*/*z* calcd. for $C_{24}H_{22}O_2Na$ [M + Na]: 365.1517; found: 365.1515.

1,3,5-Tris(4-methoxybenzyl)-2,4,6-trimethylbenzene (8a): 4-Methoxyphenylboronic acid (89 mg, 0.59 mmol) and aqueous Na_2CO_3 (1.5 mL, 2 M solution, 6 equiv.) were added to a solution of **7** (52 mg, 0.13 mmol) in THF, and the resulting reaction mixture was degassed for 20 min. $Pd(PPh_3)_4$ (22 mg, 0.02 mmol, 15 mol-%) was then added, the reaction mixture was heated at reflux for 24 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with EtOAc/petroleum ether (20%) gave compound **8a** (38 mg, 61%). R_f = 0.25 (silica gel, EtOAc/petroleum ether 1:3); m.p. 148 °C (from chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 9 H, 3×ArCH_3), 3.77 (s, 9 H, 3×OCH_3), 4.07 (s, 6 H, 3×ArCH_2), 6.79 (d, *J* = 9.0 Hz, 6 H, ArH), 6.95 (d, *J* = 8.7 Hz, 6 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 16.8, 35.4, 55.3, 113.9, 128.8, 132.4, 134.6, 135.2, 157.7 ppm. UV: λ_{max}($CHCl_3$)/nm 279 (ε/dm^{3}mol^{-1}cm^{-1} 6734). HRMS (Q-Tof): *m*/*z* calcd. for $C_{33}H_{36}O_3K$ (M + K): 519.2302; found: 519.2318.

1,3,5-Tris(4-formylbenzyl)-2,4,6-trimethylbenzene (8b): 4-Formylphenylboronic acid (155 mg, 1.03 mmol) and aqueous Na_2CO_3 (2 M solution, 6 equiv.) were added to a solution of **7** (104 mg, 0.26 mmol) in THF, and the resulting reaction mixture was degassed for 20 min. $Pd(PPh_3)_4$ (45 mg, 0.04 mmol, 15 mol-%) was then added, the reaction mixture was heated at reflux for 24 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with EtOAc/petroleum ether (20%) gave compound **8b** (87 mg, 70%). R_f = 0.25 (silica gel, EtOAc/petroleum ether 3:7); m.p. 198 °C (from chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 9 H, 3×CH_3), 4.24 (s, 6 H, 3×CH_2), 7.20 (d, *J* = 8.1 Hz, 6 H, ArH), 7.79 (d, *J* = 8.1 Hz, 6 H, ArH), 9.97 (s, 3 H, 3×CHO) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.1, 36.8, 128.6, 130.3, 134.5, 134.8, 135.3, 147.9, 192.1 ppm. IR (neat): $\tilde{\nu}$ = 1690 cm^{-1} (C=O). UV: λ_{max}($CHCl_3$)/nm 293 (ε/dm^{3}mol^{-1}cm^{-1} 13354). HRMS (Q-Tof): *m*/*z* calcd. for $C_{33}H_{31}O_3$ [M + H]: 475.2273; found: 475.2296.

1,3,5-Tris(4-cyanobenzyl)-2,4,6-trimethylbenzene (8c): 4-Cyanophenylboronic acid (75 mg, 0.51 mmol) and aqueous Na_2CO_3 (2 mL, 2 M solution) were added to a solution of **7** (51 mg, 0.13 mmol) in THF (15 mL), and the resulting reaction mixture was degassed for 20 min. $Pd(PPh_3)_4$ (22 mg, 0.02 mmol, 15 mol-%) was then added, the reaction mixture was heated at reflux for 24 h and worked up as described in the General Procedure, and the crude product was purified by column chromatography. Elution of the column with EtOAc/petroleum ether (20%) gave compound **8c** (49 mg, 82%) R_f = 0.19 (silica gel, EtOAc/petroleum ether 3:7); m.p. 232 °C (from chloroform). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 9 H, 3×CH_3), 4.2 (s, 6 H, 3×CH_2), 7.12 (d, *J* = 8.1 Hz, 6 H, ArH), 7.56 (d, *J* = 8.1 Hz, 6 H, ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.0, 36.6, 110.2, 119.0, 128.6, 132.5, 134.2, 135.4, 145.9 ppm. IR (neat): $\tilde{\nu}$ = 2227 cm^{-1} (C≡N). UV: λ_{max}($CHCl_3$)/nm 252 (ε/dm^{3}mol^{-1}cm^{-1} 13345). HRMS (Q-Tof): *m*/*z* calcd. for $C_{33}H_{28}N_3$ [M + H]: 466.2283; found: 466.2262.

1,3-Bis[4-(1-hydroxybut-3-enyl)benzyl]benzene (9): Allyl bromide (32 mg, 0.26 mmol) and indium metal (26 mg, 0.23 mmol) were added to a solution of **6b** (32 mg, 0.1 mmol) in DMF (2 mL), and the resulting reaction mixture was allowed to stir at room temp. After completion of the reaction (15 min, TLC monitoring) the reaction mixture was quenched with HCl (50%), diluted with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water and brine and dried with $MgSO_4$, the solvent was evaporated, and the crude product was loaded onto a silica gel column. Elution of the column with EtOAc/petroleum ether (20%) gave the desired product **9** (34 mg, 85%). R_f = 0.27 (silica gel, EtOAc/petroleum ether 1:4); m.p. 60–61 °C (from hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.04 (d, *J* = 4.4 Hz, 2 H, 2×OH), 2.47–2.53 (m, 4 H, 2×CH_2CH=CH_2), 3.93 (s, 4 H, 2×ArCH_2), 4.71 (t, *J* = 6.2 Hz, 2 H, 2×C*H*OH), 5.12–5.2 (m, 4 H, 2×CH_2CH=CH_2), 5.74–5.88 (m, 2 H, 2×CH_2C*H*=CH_2), 7.0–7.02 (m, 3 H, ArH), 7.13–7.22 (m, 5 H, ArH), 7.27 (d, *J* = 8.1 Hz, 4 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 41.6, 43.9, 73.2, 118.5, 126.0, 126.8, 128.6, 129.0, 129.6, 134.6, 140.5, 141.3, 141.7 ppm. IR (neat): $\tilde{\nu}$ = 3398 cm^{-1} (OH). UV: λ_{max}($CHCl_3$)/nm 265 (ε/dm^{3}mol^{-1}cm^{-1} 1956). HRMS (EI): *m*/*z* calcd. for $C_{28}H_{30}O_2Na$ [M + Na]: 421.2143; found: 421.2139.

1,3-Bis[4-(1-hydroxypent-4-enyl)benzyl]benzene (12): A small crystal of iodine was added to a suspension of magnesium (19 mg, 0.79 mmol) under argon in dry ether (3 mL). While the contents were stirred, 4-bromobut-1-ene (0.09 mL, 0.89 mmol, dissolved in 5 mL of dry ether) was added slowly. The iodine colour disappeared completely and the reaction mixture was then stirred at room temp. for 1 h. Compound **12** (80 mg, 0.25 mmol) in diethyl ether (5 mL) was then added slowly, the ice-cold temperature being maintained. The reaction mixture was then allowed to stir at room temp. for 24 h, quenched with saturated ammonium chloride, diluted with water (10 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water and brine and dried with $MgSO_4$, the solvent was evaporated, and the crude product was loaded onto a silica gel column. Elution of the column with EtOAc/petroleum ether (20%) gave compound **12** as a colourless liquid (77 mg, 71%). R_f = 0.36 (silica gel, EtOAc/petroleum ether 3:7). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.73–1.93 (m, 6 H, 2×OH, 2×C$H_2$$CH_2$CH=$CH_2$), 2.05–2.20 (m, 4 H, 2×CH_2CH=CH_2), 3.93 (s, 4 H, 2×ArCH_2), 4.67 (dd, *J* = 7.8, 5.6 Hz, 2 H, 2×C*H*OH), 4.98 (d, *J* = 10.4 Hz, 2 H, 2×CH=CH*H*), 5.04 (d, *J* = 16.8 Hz, 2 H, 2×CH=C*H*H), 5.79–5.89 (m, 2 H, 2×C*H*=CH_2), 7.01 (d, *J* = 6.4 Hz, 2 H, 2×ArH), 7.02 (s, 1 H, ArH), 7.17 (d, *J* = 8.4 Hz, 4 H, 4×ArH), 7.20 (t, *J* = 8.4 Hz, 1 H, ArH), 7.25 (d, *J* = 7.2 Hz, 4 H, 4×ArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.3, 38.2, 41.7, 74.0, 115.1, 126.2, 126.9, 128.8, 129.2, 129.8, 138.4, 140.7, 141.4, 142.5 ppm. IR (neat): $\tilde{\nu}$ = 3402 cm^{-1} (OH). UV: λ_{max}($CHCl_3$)/nm 265 (ε/dm^{3}mol^{-1}cm^{-1} 1975). HRMS (Q-Tof): *m*/*z* calcd. for $C_{30}H_{34}O_2Na$ [M + Na]: 449.2457; found: 449.2471.

RCM of 1,3-Bis[4-(1-hydroxybut-3-enyl)benzyl]benzene (9) in the Presence of 2nd Generation Grubbs' Catalyst 2: Grubbs' catalyst **2** (7 mg, 10 mol-%) was added to a solution of compound **9** (32 mg, 0.08 mmol) in dry degassed DCM (80 mL, 1 mmolar) and the solution was stirred for 18 h at room temp. The reaction mixture was then concentrated, and the crude product was purified on a silica gel column. Elution of the column with EtOAc/petroleum ether (20%) gave compound **10** as a white solid (14 mg, 47%) and as a mixture of diastereomers (1:2; determined from the ^{1}H NMR integration ratio of the protons attached to the chiral carbon atom). The spectroscopic data are for the major isomer: R_f = 0.23 (silica gel, EtOAc/petroleum ether 3:7); m.p. 222–223 °C (from methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, *J* = 4 Hz, 2 H, 2×OH), 2.50–2.55 (m, 4 H, 2×CH_2CH=CH), 3.89 (s, 4 H, 2×ArCH_2), 4.67–4.71 (m, 2 H, 2×ArC*H*OH), 5.10 (t, *J* = 3.7 Hz, 2 H, 2×CH_2C*H*=), 6.33 (s, 1 H, ArH), 6.97 (d, *J* = 8.4 Hz, 4 H, ArH), 7.07 (d, *J* = 8.1 Hz, 4 H, ArH), 7.14 (d, *J* = 8.4 Hz, 2 H, ArH), 7.26 (t, *J* = 7.5 Hz, 1 H, ArH) ppm. IR (neat): $\tilde{\nu}$ = 3392 cm^{-1} (OH). UV: λ_{max}($CHCl_3$)/nm 262 (ε/dm^{3}mol^{-1}cm^{-1} 1700). HRMS

(Q-Tof): *m*/*z* calcd. for $C_{26}H_{26}O_2Na$ [M + Na]: 393.1831; found: 393.1823.

RCM of 1,3-Bis[4-(1-hydroxypent-4-enyl)benzyl]benzene (12) in the Presence of 2nd Generation Grubbs' Catalyst 2: Grubbs' catalyst **2** (11 mg, 10 mol-%) was added to a solution of compound **12** (50 mg, 0.12 mmol) in dry degassed DCM (100 mL, 1.26 mmolar) and the solution was stirred for 24 h at room temp. The reaction mixture was then concentrated, and the crude product was purified on a silica gel column. Elution of the column with EtOAc/petroleum ether (40%) gave compound **13** as a white solid (22 mg, 47%) and as a mixture of diastereomers (1:1.7; determined from the ^{1}H NMR integration ratio of the protons attached to the chiral carbon atom). The spectroscopic data are for the major diastereomer of **13**: R_f = 0.4 (silica gel, EtOAc/petroleum ether 1:1); m.p. 213–214 °C (from methanol). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48–2.0 [m, 10 H, 2×CH(O*H*)CH_2CH_2C=], 3.90 (s, 4 H, 2×ArCH_2), 4.53–4.59 (m, 2 H, 2×C*H*OH), 5.34–5.38 (m, 2 H, 2×*H*C=), 6.69 (s, 1 H, ArH), 6.99–7.32 (m, 11 H, ArH) ppm. IR (neat): $\tilde{\nu}$ = 3401 cm^{-1} (OH). UV: λ_{max}($CHCl_3$)/nm 263 (ε/dm^3 mol^{-1} cm^{-1} 2588). HRMS (Q-Tof): *m*/*z* calcd. for $C_{28}H_{30}O_2Na$ [M + Na]: 421.2144; found: 421.2157.

Continued elution of the column with the same solvent system gave **14** as a white solid (10 mg, 21%) and as a mixture of diastereomers (1:2.2; determined from the ^{1}H NMR integration ratio of the protons attached to the chiral carbon atom). The spectroscopic data are for the major isomer of **14**: R_f = 0.35 (silica gel, EtOAc/petroleum ether 1:1); m.p. 218–220 °C (from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57–1.68 [m, 4 H, CH(OH)CH_2CH_2C= and 2×OH], 2.31–2.38 [m, 2 H, CH(OH)CH_2CH_2C=], 2.50–2.57 [m, 2 H, CH(OH)CH_2C=], 3.91 (s, 2 H, ArCH_2), 3.92 (s, 2 H, ArCH_2), 4.52–4.58 (m, 2 H, 2×C*H*OH), 5.27–5.30 (m, 2 H, C*H*=C*H*), 6.77 (s, 1 H, ArH), 6.99 (d, *J* = 8 Hz, 4 H, ArH), 7.04–7.07 (m, 4 H, ArH), 7.17 (d, *J* = 8 Hz, 2 H, ArH), 7.29 (t, *J* = 7.6 Hz, 1 H, ArH) ppm. IR (neat): $\tilde{\nu}$ = 3402 cm^{-1} (OH). UV: λ_{max}($CHCl_3$)/nm 263 (ε/dm^3 mol^{-1} cm^{-1} 2678). HRMS (Q-Tof): *m*/*z* calcd. for $C_{27}H_{28}O_2Na$ [M + Na]: 407.1987; found: 407.1979.

1,5(1,4),3(1,3)-Tribenzenacycloundecaphan-8-ene-6,11-dione (11): Compound **10** (12 mg, 0.03 mmol) in anhydrous DCM (3 mL) was added in one portion to a vigorously stirred suspension of PCC (15 mg, 0.07 mmol) in anhydrous DCM (10 mL). Stirring was continued at room temp. for 2 h. Anhydrous ether (50 mL) was added and decanted off, and the black residue was washed with further diethyl ether (3×10 mL). The combined ether extracts were concentrated, and the crude product was purified by silica gel column chromatography. Elution of the column with EtOAc/petroleum ether (10%) gave compound **11** (9 mg, 75%) as white, needle-like crystals. R_f = 0.77 (silica gel, EtOAc/petroleum ether 3:7); m.p. 174 °C (from DCM/hexane 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (dd, *J* = 3.6, 1.5 Hz, 4 H, 2×COCH_2), 3.91 (s, 4 H, 2×ArCH_2), 5.75 (tt, *J* = 3.6, 1.5 Hz, 2 H, 2×CH=), 6.01 (s, 1 H, Ar-H$_i$), 6.99 (d, *J* = 8.4 Hz, 4 H, ArH), 7.14 (d, *J* = 7.7 Hz, 2 H, ArH), 7.26 (t, *J* = 7.5 Hz, 1 H, ArH); 7.7 (d, *J* = 8.4 Hz, 4 H, ArH) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 41.2, 43.9, 126.4, 128.1, 128.3, 129.0, 129.6, 133.5, 140.8, 146.2, 197.1 ppm. IR (neat): $\tilde{\nu}$ = 1676 cm^{-1} (C=O). UV: λ_{max}($CHCl_3$)/nm 258 (ε/dm^3 mol^{-1} cm^{-1} 14479). HRMS (EI): calcd. for $C_{26}H_{22}O_2$: 366.1620; found: 366.1620.

1,5(1,4),3(1,3)-Tribenzenacyclotridecaphan-9-ene-6,13-dione (15): Compound **13** (9 mg, 0.02 mmol) in anhydrous DCM (3 mL) was added in one portion to a vigorously stirred suspension of PCC (13 mg, 0.06 mmol) in anhydrous DCM (3 mL). Stirring was continued at room temp. for 2 h. Anhydrous diethyl ether (25 mL) was added and decanted off, and the black residue was washed with further diethyl ether (3×5 mL). The combined ether extracts were concentrated, and the crude product was purified by silica gel column chromatography. Elution of the column with EtOAc/petroleum ether (10%) gave compound **15** (7 mg, 79%) as white, needle-like crystals. R_f = 0.35 (silica gel, EtOAc/petroleum ether 1:4); m.p. 159–160 °C (from DCM/hexane 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.33–2.40 (m, 4 H, 2×COCH_2CH_2), 2.85 (dd, *J* = 8.1, 7.1 Hz, 4 H, 2×COCH_2), 3.97 (s, 4 H, 2×ArCH_2), 5.55 (t, *J* = 4.8 Hz, 2 H, 2×CH_2C*H*=), 6.52 (s, 1 H, ArH), 7.08 (d, *J* = 8.4 Hz, 4 H, ArH), 7.17 (d, *J* = 6.9 Hz, 2 H, ArH), 7.29 (t, *J* = 7.5 Hz, 1 H, ArH), 7.73 (d, *J* = 8.4 Hz, 4 H, ArH) ppm. IR (neat): $\tilde{\nu}$ = 1679 cm^{-1} (C=O). UV: λ_{max}($CHCl_3$)/nm 255 (ε/dm^3 mol^{-1} cm^{-1} 5549). HRMS (Q-Tof): *m*/*z* calcd. for $C_{28}H_{27}O_2$ [M + H]: 395.2011; found: 395.2019.

1,5(1,4),3(1,3)-Tribenzenacyclododecaphan-8-ene-6,12-dione (16): Compound **14** (8 mg, 0.02 mmol) in anhydrous DCM (3 mL) was added in one portion to a vigorously stirred suspension of PCC (13 mg, 0.06 mmol) in anhydrous DCM (2 mL). Stirring was continued at room temp. for 2 h, anhydrous diethyl ether (25 mL) was added and decanted off, and the black residue was washed with further diethyl ether (3×5 mL). The combined ether extracts were concentrated, and the crude product was purified by silica gel column chromatography. Elution of the column with EtOAc/petroleum ether (10%) gave compound **16** (6 mg, 76%) as white, needle-like crystals. R_f = 0.34 (silica gel, EtOAc/petroleum ether 1:4); m.p. 165 °C (from DCM/hexane 1:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.53–2.59 (m, 2 H, COCH_2CH_2), 2.91–2.95 (m, 2 H, COCH_2CH_2), 3.48 (dd, *J* = 7.1, 1.2 Hz, 2 H, COCH_2C=), 3.92 (s, 2 H, ArCH_2), 3.96 (s, 2 H, ArCH_2), 5.37 (dtt, *J* = 15.3, 6.6, 1.5 Hz, 1 H, CH_2CH_2C*H*=), 5.67 (dtt, *J* = 15.6, 6.0, 1.5 Hz, 1 H, COCH_2C*H*=), 6.27 (s, 1 H, ArH), 6.96 (d, *J* = 8.7 Hz, 2 H, ArH), 7.08 (d, *J* = 8.4 Hz, 2 H, ArH), 7.12–7.20 (m, 2 H, ArH), 7.25–7.30 (m, 1 H, ArH), 7.63 (d, *J* = 8.4 Hz, 2 H, ArH), 7.72 (d, *J* = 8.1 Hz, 2 H, ArH) ppm. IR (neat): $\tilde{\nu}$ = 1676 cm^{-1} (C=O). UV: λ_{max}($CHCl_3$)/nm 255 (ε/dm^3 mol^{-1} cm^{-1} 13982). HRMS (Q-Tof): *m*/*z* calcd. for $C_{27}H_{24}O_2Na$ [M + Na]: 403.1674; found: 403.1676.

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[13] Yield varies from 74 to 85%.

[14] A similar yield was observed when the reaction was performed in presence of 7 mol-% catalyst in 0.001 M dilution, but a longer time (28 h) was necessary for the completion of the reaction. However, under low dilution conditions (0.003 M), the yield of **15** decreased to 33%.[5].

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