New Synthetic Approach to a [1.1.6] Metapara Cyclophane Derivative *via* Suzuki–Miyaura Cross-Coupling and Ring-Closing Metathesis[#]

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Abstract: The synthesis of a [1.1.6] metapara cyclophane derivative, 1,5(1,4),3(1,3)-tribenzenacycloundecaphan-8-ene-6,11-dione, has been achieved *via* the Suzuki–Miyaura cross-coupling of α,α′-dibromo-*m*-xylene with an arylboronic acid derivative followed by an allylation and ring-closing metathesis reaction sequence.

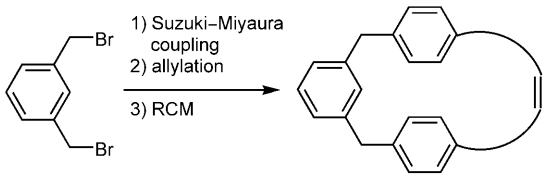
Keywords: cyclophanes; olefin metathesis; palladium; ruthenium; Suzuki–Miyaura cross-coupling

Cyclophanes, under investigation since the 1950s, are useful model systems for studying through-space interactions.[1] Over the years, several strategies have been developed for their synthesis. These compounds have found many applications in supramolecular chemistry. For example, they provide an intricate source for a variety of host molecules.[2] For these reasons, there is still a need to develop new and simple strategies. Herein, we report a simple and straightforward synthetic strategy for a [1.1.6] metapara cyclophane derivative, 1,5(1,4),3(1,3)-tribenzenacycloundecaphan-8-ene-6,11-dione, using the Suzuki–Miyaura (SM) cross-coupling reaction and the ring-closing metathesis (RCM) as key steps. The strategy adopted in our study is shown in Scheme 1.

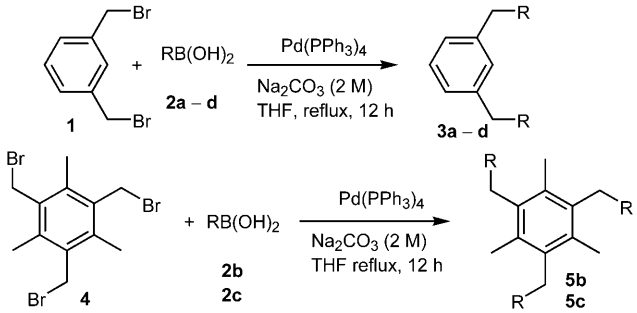
The palladium-catalyzed SM cross-coupling reaction is one of the most powerful methods for the construction of carbon-carbon bonds.[3] The non-toxic nature of the boronic acids offers several practical advantages as compared to the other cross-coupling partners. The majority of the SM cross-coupling reactions described so far have been associated with the coupling of aryl halides with an aryl boronic acid. However, benzyl bromides as SM coupling partners have been relatively less explored.[4]

To test the feasibility of the first step in our strategy, various functionalized boronic acids were coupled with the bis-armed benzyl bromide **1** (Scheme 2). In this regard, we found that **1** reacts with various boronic acids in presence of the palladium catalyst [$Pd(PPh_3)_4$] to generate the required cross-coupling products in good yield (Table 1).[5] This methodology has also been extended to tris-armed benzyl bromides such as **4** (Table 1). In view of the importance of C_3-symmetric molecules as useful core units for dendrimer design and for the synthesis of useful ligands, this methodology is likely to have an impact in these areas.

To prepare the target cyclophane derivative **9**, compound **3b** was allylated by using allyl bromide in the presence of indium (Scheme 3). Having the diallyl de-



Scheme 1.



Scheme 2. The reaction was conducted using a boronic acid (1.5 equivalents for each bromine atom in the substrate) and $Pd(PPh_3)_4$ (6–10 mol %) as catalyst.

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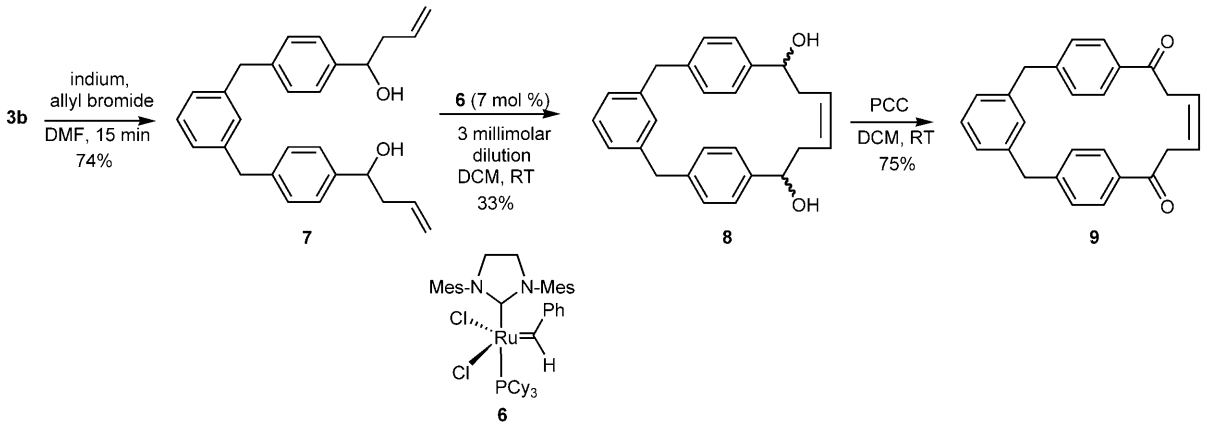
Table 1. Suzuki–Miyaura cross-coupling reaction of **1** and **4** with various functionalized boronic acids

Entry	Starting bromide	**2**	**3**	**5**	R	Yield[a] [%] of **3**	Yield[a] [%] of **5**
i	**1**	**a**	**a**	–	*p*-OMePh	32	
ii	**1**	**b**	**b**	–	*p*-CHOPh	80	
iii	**1**	**c**	**c**	–	*p*-CNPh	84[b]	
iv	**1**	**d**	**d**	–	*p*-AcPh	71[b]	
v	**4**	**b**	–	**b**	*p*-CHOPh		70
vi	**4**	**c**	–	**c**	*p*-CNPh		82

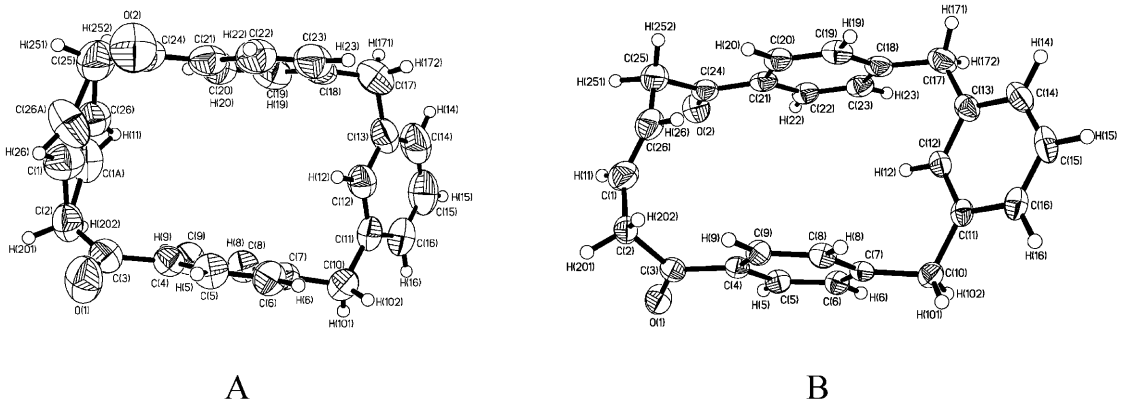
[a] Yields of isolated products.
[b] Purification was carried out by repeated crystallizations after column chromatography.

rivative in hand, compound **7** was subjected to RCM by using Grubbs' catalyst[6] [$RuCl_2(PCy_3)_2$(=CHPh)], giving a complex mixture of products. However, the 2nd generation catalyst [$Ru(H_2IMes)(PCy_3)Cl_2$(=CHPh)] (**6**) delivered the cyclophane derivative **8** as a mixture of diastereomers (2:1) in 33% yield.[7] The lower yield could be accounted for by the formation of various oligomeric side-products in the macrocyclization reaction as reported earlier.[6] Subsequently, oxidation of the above mixture gave cyclophane **9**, which was confirmed on the basis of X-ray crystallographic data (Figure 1). Close inspection of the ORTEP diagram of **9** reveals that, in the solid state arrangement, the ethylene bridge is disordered with an averaged population of 70:30 (Figure 1A), perhaps due to the availability of void space. Such a disorder is known for ethylene bridges as seen in *trans*-β-nitrostyrene which in fact accounts for unusual photochemical reaction product.[8] Furthermore, this disorder is dynamic in nature as the crystals cooled to 133 K did not show any disorder, as shown in Figure 1B. Thus, this macrocyclic compound could be a potential target for charge-density studies in addition to host-guest complex experiments.

In summary, we have developed a new synthetic approach for the synthesis of a [1.1.6] metapara cyclophane derivative *via* the SM cross-coupling reaction of α,α′-dibromo-*m*-xylene with arylboronic acid **3b** followed by allylation and RCM reactions.[9]



Scheme 3.



A B

Figure 1. Crystal structure of compound **9**: **A:** crystal arrangement at room temperature; **B:** crystal arrangement at 133 K.

Experimental Section

General Remarks

Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulphate as a binder). Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light. Flash chromatography was performed using Acme's silica gel (100–200 mesh). Petroleum ether refers to fraction having boiling point 60–80 °C. Yields refer to the chromatographically isolated yield. 1st and 2nd generation Grubbs' catalysts were purchased from Strem Chemicals, Inc. and Fluka, respectively. All the commercial grade reagents were used without further purification. Infrared spectra were recorded on a Nicolet 400 FT IR spectrometer in $KBr/CHCl_3/CCl_4$ and the absorptions are reported in cm^{-1}. ^1H NMR spectra were determined on a Bruker 300 MHz spectrometer as $CDCl_3$ solutions. Coupling constants (*J* values) are given in hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from internal reference tetramethylsilane.

General Procedure for Coupling of Arylboronic Acids with α,α′-Dibromo-*m*-xylene (1)

A mixture of α,α′-dibromo-*m*-xylene 1 (1 equiv.), arylboronic acid (3 equivs.), $Pd(PPh_3)_4$ (6–10 mol %), Na_2CO_3 (4 equivs.) 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. The combined organic layer was washed with water, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated and the crude product was charged on a silica gel column. Elution of the column with EtOAc/petroleum ether gave the desired cross-coupling product.

RCM of 1,3-Bis-[4-(1-hydroxybut-3-enyl)-benzyl]-benzene (7) using 2nd Generation Grubbs' Catalyst

A solution of compound **7** (90 mg, 0.23 mmol) in dry, degassed DCM (60 mL) was added over a period of 1 h through an addition funnel to a solution of Grubbs' catalyst **6** (13 mg, 7 mol %) in dry, degassed DCM (10 mL). The reaction mixture was stirred at room temperature for 24 h and concentrated. The crude product was purified by silica gel column chromatography. Elution of the column with 20% EtOAc/petroleum ether gave the compound **8** as a mixture of diastereomers as a white crystalline solid; yield: 28 mg (33%).

Spectral Data

3a: mp 73 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 6H), 3.88 (s, 4H), 6.82 (d, 4H, *J* = 8.8 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 7.01 (s, 1H), 7.08 (d, 4H, *J* = 8.8 Hz), 7.18 (t, 1H, *J* = 7.3 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 41, 55.3, 113.9, 126.6, 128.6, 129.5, 129.9, 133.4, 141.7, 158.0; HR-MS (EI): *m/z* = 318.1612, calcd. for $C_{22}H_{22}O_2$: 318.1619.

3b: colourless oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.02 (s, 4H), 7.01 (s, 1H), 7.04 (d, 2H, *J* = 7.5 Hz), 7.25 (t, 1H, *J* = 7.5 Hz) 7.33 (d, 4H, *J* = 8 Hz), 7.8 (d, 4H, *J* = 8.2 Hz), 9.97 (s, 2H); ^{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; HR-MS (QTOF): *m/z* = 337.1208, calcd. for $C_{22}H_{18}O_2Na$ (M + Na): 337.1204.

3c: mp 114–115 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.0 (s, 4H), 6.97 (s, 1H), 7.02 (d, 2H, *J* = 7.3 Hz), 7.23–7.27 (m, 5H), 7.57 (d, 4H, *J* = 8 Hz); HR-MS (QTOF): *m/z* = 309.1398, calcd. for $C_{22}H_{17}N_2$ (M + H): 309.1392.

3d: mp 81 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 6H), 3.99 (s, 4H), 7.01 (s, 1H), 7.02 (d, 2H, *J* = 7.9 Hz), 7.20–7.26 (m, 5H), 7.87 (d, 4H, *J* = 8.5 Hz); HR-MS (QTOF): *m/z* = 365.1515, calcd. for $C_{24}H_{22}O_2Na$ (M + Na): 365.1517.

5b: mp 198 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 9H), 4.24 (s, 6H), 7.20 (d, 6H, *J* = 8.1 Hz), 7.79 (d, 6H, *J* = 8.1 Hz), 9.97 (s, 3H); ^{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; HR-MS (QTOF): *m/z* = 475.2296, calcd. for $C_{33}H_{31}O_3$ (M + H): 475.2273.

5c: mp 232 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 9H), 4.2 (s, 6H), 7.12 (d, 6H, *J* = 8.1 Hz), 7.56 (d, 6H, *J* = 8.1 Hz); ^{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; HRMS (QTOF): *m/z* = 466.2262, calcd. for $C_{33}H_{28}N_3$ (M + H): 466.2283.

7: mp 60–61 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.04 (d, 2H, *J* = 4.4 Hz), 2.47–2.53 (m, 4H), 3.93 (s, 4H), 4.71 (t, 2H, *J* = 6.2 Hz), 5.12–5.2 (m, 4H), 5.74–5.88 (m, 2H), 7.0–7.02 (m, 3H), 7.13–7.22 (m, 5H), 7.27 (d, 4H, *J* = 8.1 Hz); ^{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; HR-MS (EI): *m/z* = 421.2139, calcd. for $C_{28}H_{30}O_2Na$ (M + Na): 421.2143.

8: mp 222–223 °C. The spectroscopic data given below are for the major isomer. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.74 (d, 2H, *J* = 4 Hz), 2.50–2.55 (m, 4H), 3.89 (s, 4H), 4.67–4.71 (m, 2H), 5.10 (t, 2H, *J* = 3.7 Hz), 6.33 (s, 1H), 6.97 (d, 4H, *J* = 8.4 Hz), 7.07 (d, 4H, *J* = 8.1 Hz), 7.14 (d, 2H, *J* = 8.4 Hz), 7.26 (t, 1H, *J* = 7.5 Hz); HR-MS (QTOF): *m/z* = 393.1823, calcd. for $C_{26}H_{26}O_2Na$ (M + Na): 393.1831.

9: mp 174 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.61 (dd, 4H, *J* = 3.6, 1.5 Hz), 3.91 (s, 4H), 5.75 (tt, 2H, *J* = 3.6, 1.5 Hz), 6.01(s, 1H), 6.99 (d, 4H, *J* = 8.4 Hz), 7.14 (d, 2H, *J* = 7.7 Hz), 7.26 (t, 1H, *J* = 7.5 Hz); 7.7 (d, 4H, *J* = 8.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 41.2, 43.9, 126.4, 128.1, 128.3, 129, 129.6, 133.5, 140.8, 146.2, 197.1; HR-MS (EI): *m/z* = 366.1620, calcd. for $C_{26}H_{22}O_2$: 366.1620.

X-Ray Crystallographic Study of 1,5(1,4),3(1,3)-Tribenzenacycloundecaphan-8-ene-6,11-dione (9)

Crystal data for disordered structure (A): $C_{26}H_{22}O_2$, *M* = 366.44, monoclinic, space group $P2_1/n$, *a* = 11.868(2), *b* = 5.781(1), *c* = 28.980(4) Å, β = 97.62(3)°, *V* = 1970.7(4) Å^3, *T* = 293(2) K, *Z* = 4, μ(Mo-K_α) = 0.077 mm^{-1}, 8132 reflections measured, 2841 unique (R_{int} = 0.0406), observed with $I > 2\sigma(I)$ which were used in all refinements. R_1 = 0.038, wR_2 = 0.073 for the observed data, CCDC 233847.

Crystal data for ordered structure (B): $C_{26}H_{22}O_2$, *M* = 366.44, monoclinic, space group $P2_1/n$, *a* = 11.828(2), *b* = 5.742 (1), *c* = 28.555(6) Å, β = 97.47(1)°, *V* = 1922.9(6) Å^3,

$T = 133(2)$ K, $Z = 4$, μ(Mo-K_α) = 0.079 mm^{-1}, 7868 reflections measured, 2774 unique ($R_{int} = 0.0229$), observed with $I > 2\sigma(I)$ which were used in all refinements. $R_1 = 0.041$, $wR_2 = 0.103$ for the observed data, CCDC 233846.

Acknowledgements

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References and Notes

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