Chirality Induction through the Reversible Catenation of Coordination Rings**

Akiko Hori, Akihiko Akasaka, Kumar Biradha, Shigeru Sakamoto, Kentaro Yamaguchi, and Makoto Fujita*

Although oligo(*m*-phenylene)s and their isostructural compounds containing heteroatoms often adopt helical conformations spontaneously,[1] formation of their double-helical assembly requires interstrand noncovalent interactions such as metal coordination[2,3] or complementary hydrogen bonding.[4] Pentakis(*m*-phenylene) can be one of the smallest units of choice for forming double-helical assemblies, as predicted by calculation ($\Delta H = -36.2$ kcal mol^{-1}).[5] However, nonfunctionalized oligo(*m*-phenylene)s have never favored double-helical stacking because of the high entropic cost of this process (Figure 1a). If the ligand motif is preorganized into a

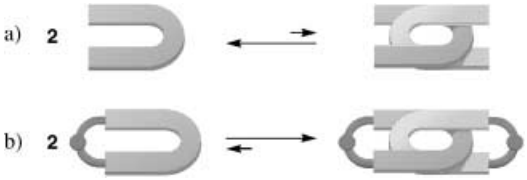

Figure 1. Schematic representation showing double helical stacking of a) open and b) metal-linked pentakis(*m*-phenylene) strands.

cyclic form by metal coordination, the entropy cost will be significantly reduced and the metal-linked cyclic oligo(*m*-phenylene) strands can assemble into a metal-linked catenane[6] through double-helical stacking of the nonfunctionalized organic strands (Figure 1b). This idea prompted us to design a pentakis(*m*-phenylene) compound **1** that contains pyridine units at both ends of the strand. Here we show that a coordination ring derived from ligand **1** is reversibly catenated through efficient aromatic stacking (Scheme 1). The catenated structure is characterized by the helical chirality and by the ancillary chiral unit on the metal ion. Molecular chirality is observed by circular dichroism only if the coordinated rings are catenated.

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The monomer ring **3** was obtained by treating the ligand **1** with the metal unit **2** in DMF. Typically, **1a** and **2a** were combined in DMF at 60 °C. The formation of **3a** as a single product was confirmed by NMR spectroscopy (Figure 2a) and cold spray ionization mass spectrometry (CSI-MS).[7] The proton NMR spectrum of **3a** in [D_7]DMF showed nine signals in the aromatic region. Major ion peaks in the CSI-MS spectrum were assigned as $[(M-(NO_3)_n)+(\mathrm{dmf})_m]^{n+}$ ($m = 0$–2, $n = 1$–2). The crystal structure was solved for the analogous Pt^{II} ring **3a′** which was prepared in a similar way and recrystallized from DMF/MeOH (Figure 3).[8] The macrocyclic framework of **3a′** was achiral.

In aqueous conditions, the monomer ring **3a** equilibrated with another compound. This new product was assigned as catenane **4a** based on NMR and CSI-MS, analogous to previous work on "molecular magic rings".[9–11] Thus, the equilibrium between **3a** and **4a** was shifted toward **4a** with the increase of D_2O in the solvent (Figure 2b–f). In 2:1 D_2O/[D_7]DMF, **4a** was quantitatively formed because of an enhanced hydrophobic effect which drives the catenation. The NMR spectrum of **4a** was qualitatively the same as that of **3a**, but featured the outstanding upfield shifts of the signals arising from the central aromatic protons, caused by interstrand contact between the two component rings. The CSI-MS spectrum of **4a** in an H_2O/DMF 2:1 solvent showed prominent peaks for $[(M-(NO_3)_n)+(\mathrm{dmf})_m]^{n+}$: for example, m/z 510 $[(M-(NO_3)_4)+(\mathrm{dmf})_4]^{4+}$, 653 $[(M-(NO_3)_3)+(\mathrm{dmf})_2]^{3+}$, 937 $[M-(NO_3)_2]^{2+}$, 1936 $[M-NO_3]^{+}$. Compound **4a** was precipitated from solution as a colorless powder in 90% yield by adding a large amount of water. The elemental analysis was consistent with the formula of **4a**·6 H_2O.

The ratio of **3a** and **4a** also depended on the concentration of the species. In 1:1 D_2O/[D_7]DMF, the ratios **3a**:**4a** were 1:2.5 at 1 mM, 1:11 at 20 mM, and 1:16 at 50 mM. An exchange spectroscopy (EXSY) spectrum indicated clear correlations between the corresponding protons of **3a** and **4a**, which shows rapid equilibration between **3a** and **4a** on the EXSY timescale (300 ms).[12] When the non-fluorinated ligand **1b** was employed, a mixture of monomer ring **3b** and catenane **4b** was formed similarly, in which the equilibrium was largely in favor of the monomer ring formation: for example, under the same conditions (10 mM, D_2O/[D_7]DMF 1:1), ratios **3a**:**4a** and **3b**:**4b** were 15:85 and 90:10, respectively. Because catenane **4b** was less soluble than **4a** in aqueous media, **4b** was not formed exclusively under any conditions.

The crystal structure was obtained of **4a***,[13] which is an alkoxy derivative of **4a** (Figure 4). As expected, efficient aromatic contacts are observed between two rings, which keeps the two ionic Pd^{II} centers as far apart as possible (Pd···Pd′ 18 Å). The mean planes of the two rings, defined by the centers of alkoxy-attached phenylene groups and a Pd cation in each ring, are associated with a cross angle of 64°. The two aromatic ligands efficiently interact with each other with interatomic distances of 2.9–3.5 Å. As a result, two aromatic strands are double-helicated, giving molecular chirality to the resulting catenated assembly.[14,15]

We expected that the molecular chirality induced by the catenation could be observed if a chiral ancillary ligand were placed on the component ring. Thus, (*R*,*R*)-1,2-diaminocyclo-

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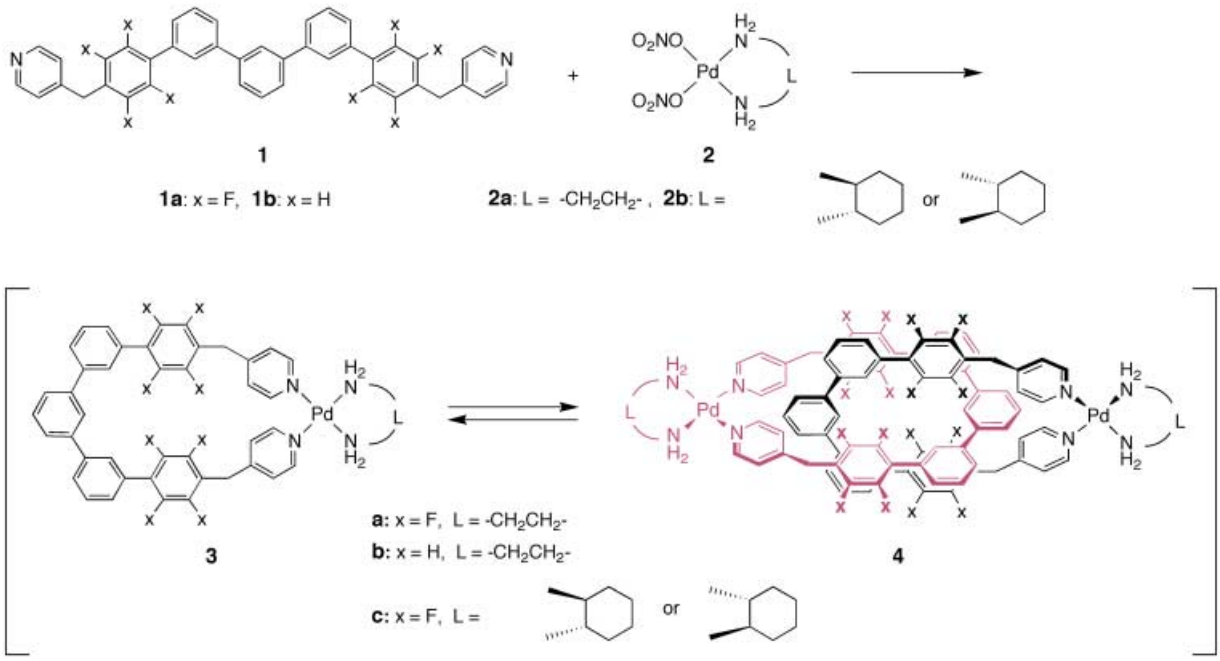

Scheme 1. Self-assembly of double helical [2]catenanes and the component rings.

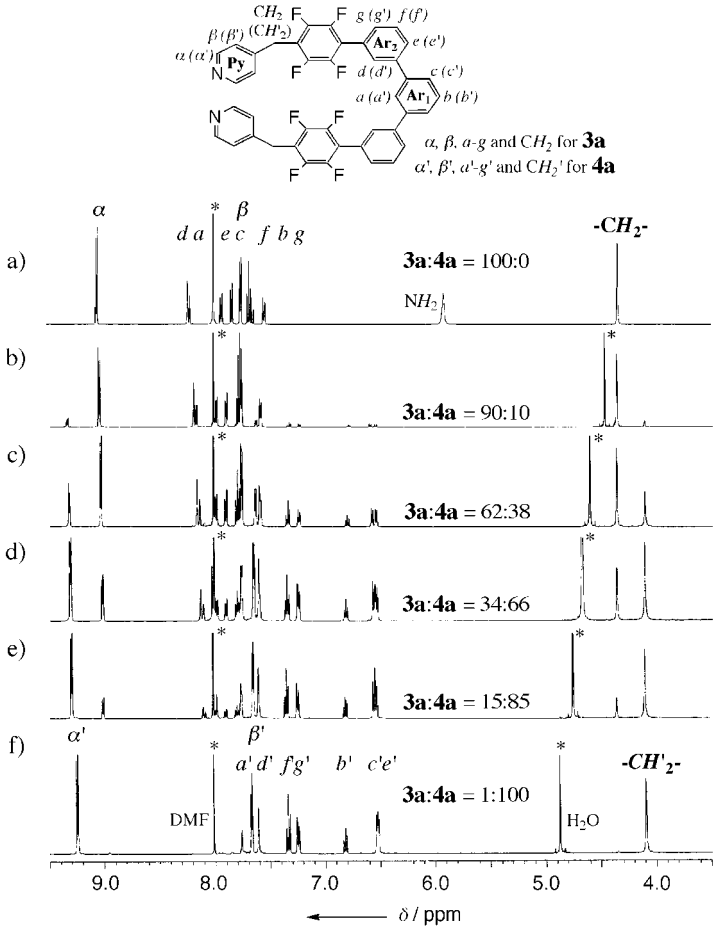

Figure 2. Equilibrium between **3a** and **4a**, monitored by ^{1}H NMR spectroscopy (aromatic region, 500 MHz, 25 °C, 10 mM, DMF formyl proton at $\delta = 8.05$ as an internal standard). Spectra were obtained by treating **1a** with **2a** for 30 min at 60 °C in a) [D$_7$]DMF; b) D$_2$O/[D$_7$]DMF 1:3; c) D$_2$O/[D$_7$]DMF 1:2; d) D$_2$O/[D$_7$]DMF 2:3; e) D$_2$O/[D$_7$]DMF 1:1, and f) D$_2$O/[D$_7$]DMF 2:1 solution. Asterisk (*): solvent.

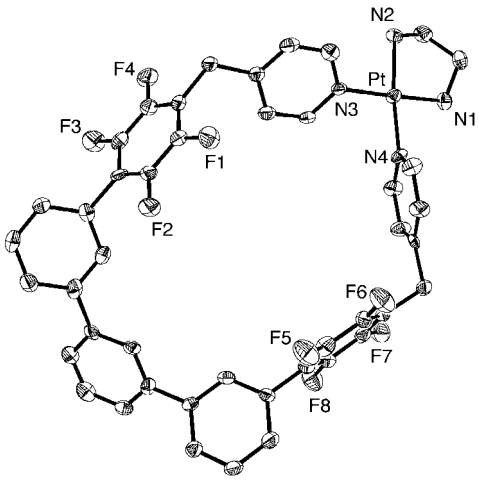

Figure 3. The ORTEP diagram of the crystal structure of **3a**′ showing 40 % probability thermal ellipsoids.

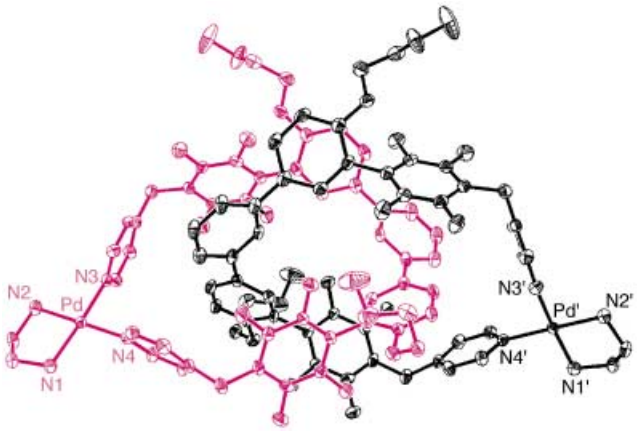

Figure 4. The ORTEP diagram of the crystal structure of **4a*** showing 40 % probability thermal ellipsoids.

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hexane was substituted onto the Pd^{II} center. The chiral Pd^{II} unit (*R*,*R*)-**2b** was treated with ligand **1a** to afford the monomer ring (*R*,*R*)-**3c** and the catenane (*R*,*R*,*R*,*R*)-**4c** in organic and aqueous media, respectively. The crystal structure of (*R*,*R*)-**3c** again displayed the planar conformation of the central -$(C_6H_4)_3$- site, despite the presence of a chiral ligand on the Pd^{II} center.[16] In CD (circular dichroism) spectroscopy, both (*R*,*R*)-**2b** and (*R*,*R*)-**3c** were almost silent. These results showed that the chiral ligand on the Pd^{II} center induced no chirality in the macrocycle framework of (*R*,*R*)-**3c** in solution, which is in good accordance with the X-ray result. In striking contrast, (*R*,*R*,*R*,*R*)-**4c** showed clear induced circular dichroism (ICD) (Figure 5a).[17] As the chiral auxiliary on the Pd^{II} ion is silent to CD spectroscopy, the observed ICD is ascribed to the chiral orientation of two aromatic strands, which is probably double-helical stacking, as suggested by the X-ray analysis. The clear temperature dependence of the ICD also supported the chiral aromatic stacking which should be less obvious at high temperature (Figure 5b).[18]

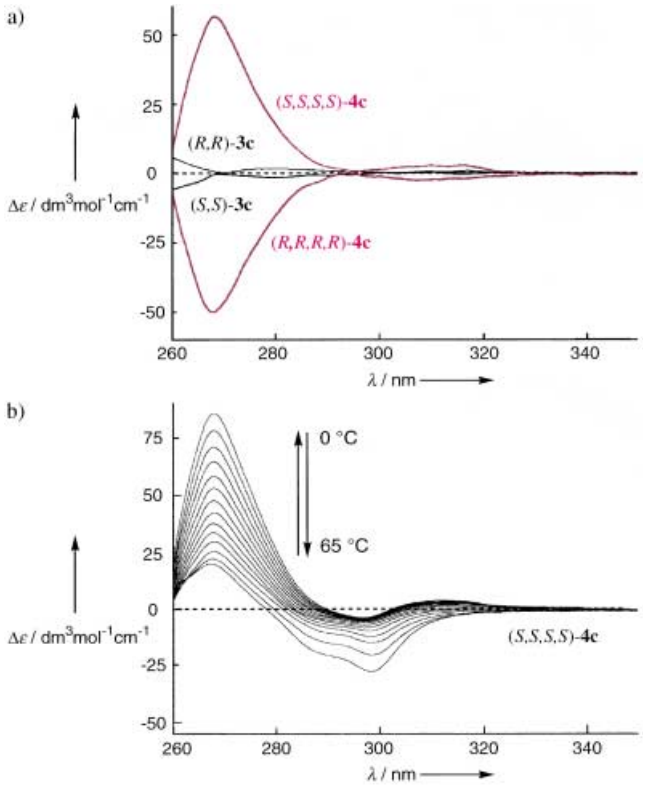

Figure 5. a) CD spectra of **3c** and **4c**; b) temperature dependent ICD of (*S*,*S*,*S*,*S*)-**4c**. $\Delta\varepsilon$: molar circular dichroism.

Experimental Section

Syntheses and physical properties of ligands **1a**, **1b**, and **1a*** (methoxy-ethoxy substituted derivative of **1a**) are summarized in the Supporting Information.

Self-assembly of **3a** and **4a**. **3a:** To a solution of **1a** (9.9 mg, 0.010 mmol) in DMF (1 mL), **2a** (2.9 mg, 0.010 mmol) was added and the mixture was stirred for 15 min at 60 °C to obtain a colorless solution. The monomer ring **3a** was isolated as pale yellow crystals by adding a large amount of diethyl ether to the reaction solution. Yield 80%; m.p. 200 °C dec.; ^{1}H NMR (500 MHz, [D$_7$]DMF, reference TMS, 25 °C): $\delta = 9.59$ (d, $J =$ 6.5 Hz, 4H; PyH_α), 8.76 (s, 2H; ArH_d), 8.74 (s, 1H; ArH_a), 8.46 (d, $J =$ 8.2 Hz, 2H; ArH_e), 8.37 (d, $J = 7.8$ Hz, 2H; ArH_c), 8.28 (d, $J = 6.5$ Hz, 4H; PyH_β), 8.21 (t, $J = 7.8$ Hz, 2H; ArH_f), 8.18 (t, $J = 7.8$ Hz, 1H; ArH_b), 8.07 (d, $J = 8.2$ Hz, 2H; ArH_g), 4.87 (s, 4H; -CH_2-), 3.46 ppm (brs, 8H; *H*-ethylene diamine); ^{13}C NMR (125 MHz, [D$_7$]DMF, reference $CDCl_3$, 25 °C): $\delta =$ 153.0 (CH_α), 152.0 (*C*q), 145.5 (d, $J = 248$ Hz, *C*F$_i$), 144.2 (d, $J = 248$ Hz, *C*F$_j$), 141.6 (*C*q), 141.0 (*C*q), 130.5 (CH_f), 130.1 (CH_g), 130.0 (CH_b), 129.2 (CH_d), 128.7 (CH_e), 128.2 (*C*q), 127.4 (CH_β), 127.1 (CH_c), 126.0 (CH_a), 120.4 (t, $J = 16.9$ Hz, *C*F$_h$), 116.6 (t, $J = 18.3$ Hz, *C*F$_k$), 47.9 (en), 28.0 ppm (CH_2); ^{19}F NMR (300 MHz, [D$_7$]DMF, CF_3COOH): $\delta = -66.02$ (m, 4F, Ar*F*), -66.20 ppm (m, 4F, Ar*F*); IR (KBr) $\tilde{\nu} =$ 1664, 1615, 1480, 1280, 1332, 1174, 998, 788 cm^{-1}; CSI-MS *m*/*z*: 509.9 $[(M-(NO_3)_2)+(dmf)_2]^{2+}$, 546.4 $[(M-(NO_3)_2)+(dmf)_3]^{2+}$, 936.1 $[M-NO_3]^+$; elemental analysis: calcd for $C_{44}H_{32}N_6F_8PdO_6\cdot 3.5H_2O$ (%): C 49.75, H 3.70, N 7.91; found: C 49.80, H 3.89, N 7.92. Similarly, **3c** was obtained by the reaction of **1a** with **2b** in DMF.

4a: Water (0.8 mL) was added dropwise to a DMF (0.4 mL) solution of **1a** (9.9 mg, 0.010 mmol) and **2a** (2.9 mg, 0.010 mmol), and the mixture was stirred for 1 h at 60 °C. Catenane **4a** was isolated as a white powder by adding a large amount of water to the reaction solution. Yield 90%; m.p. 200 °C dec.; ^{1}H NMR (500 MHz, D_2O/[D$_7$]DMF (2:1), TMS): $\delta = 9.25$ (d, $J = 6.5$ Hz, 8H; PyH_α), 7.81 (s, 2H; ArH_a), 7.71 (d, $J = 6.5$ Hz, 8H; PyH_β), 7.64 (s, 4H; ArH_d), 7.44 (t, $J = 8.0$ Hz $J = 7.5$ Hz, 4H; ArH_f), 7.35 (d, $J =$ 7.5 Hz, 4H; ArH_g), 6.85 (d, $J = 8.0$ Hz $J = 7.5$ Hz, 2H; ArH_b), 6.63 (d, $J =$ 8.0 Hz, 4H; ArH_c), 6.62 (d, $J = 8.0$ Hz, 4H; ArH_e), 4.16 (s, 8H; -CH_2-), 3.03 ppm (brs, *H*-en); ^{13}C NMR (125 MHz, D_2O/[D$_7$]DMF (2:1), $CDCl_3$): $\delta = 152.1$ (CH_α), 152.0 (*C*q), 144.7 (dd, $J = 249$ Hz, *C*F$_i$), 143.0 (dd, $J =$ 249 Hz, *C*F$_j$), 138.7 (*C*q), 138.6 (*C*q), 129.5 (CH_g), 129.4 (CH_b and CH_f), 128.2 (CH_β), 127.2 (*C*q), 126.6 (CH_e), 126.1 (CH_d), 125.0 (CH_c), 123.0 (CH_a), 118.3 (*C*F$_h$), 115.3 (d, $J = 18.6$ Hz, *C*F$_k$), 47.0 (en), 27.6 ppm (CH_2); ^{19}F NMR (300 MHz, D_2O/[D$_7$]DMF (2:1), CF_3COOH): $\delta = -66.00$ (brs, 4F, Ar*F*), -66.46 ppm (brs, 4F, Ar*F*); IR (KBr) $\tilde{\nu}$ 1625, 1601, 1480, 1375, 997, 788 cm^{-1}; CSI-MS *m*/*z* 510.4 $[(M-(NO_3)_4)+(dmf)_4]^{4+}$, 653.2 $[(M-(NO_3)_3)+(dmf)_2]^{3+}$, 936.2 $[M-(NO_3)_2]^{2+}$, 1936.3 $[M-NO_3]^+$; elemental analysis: calcd for $C_{88}H_{64}N_{12}F_{16}Pd_2O_{12}\cdot 6H_2O$ (%): C 50.18, H 3.64, N 7.98; found: C 50.34, H 3.65, N 7.91. Similarly, **4c** was obtained by the reaction of **1a** with **2b** in a 1:2 DMF/H_2O solution.

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[8] Crystal data for **3a**'·2H_2O ($C_{44}H_{36}F_8N_6O_8Pt$, $M_W = 1123.88$):[19] triclinic, $P\bar{1}$, $a = 9.603(2)$, $b = 13.484(3)$, $c = 17.828(4)$ Å, $\alpha = 88.621(5)$, $\beta =$ 82.884(6), $\gamma = 70.382(4)°$, $V = 2157.3(9)$ Å^3, $T = 193$ K, $Z = 2$, $R =$ 0.0679, $R_W = 0.1445$, GOF = 0.931.

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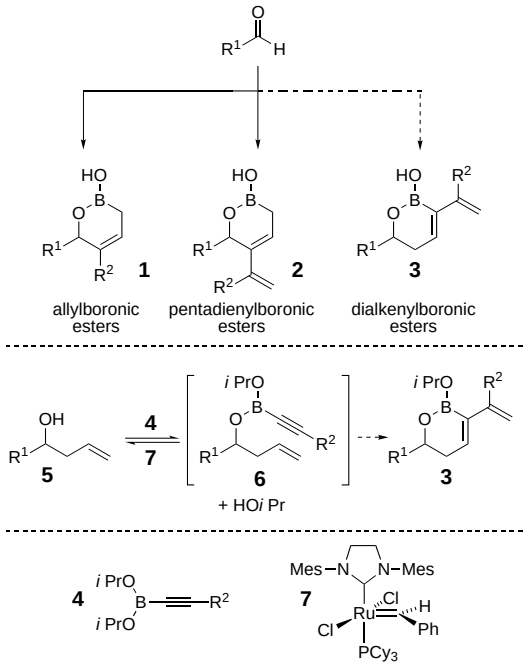
[13] Crystal data for **4a***·6 H_2O ($C_{100}H_{100}F_{16}N_{12}O_{26}Pd_2$, $M_W = 2402.72$):[19] orthorhombic, *Pbcn*, $a = 37.176(3)$, $b = 15.2673(11)$, $c = 18.2484(13)$ Å, $V = 10357.5(13)$ Å^3, $T = 193$ K, $Z = 4$, $R = 0.0526$, $R_W = 0.1364$, GOF = 0.929. Catenane **4a*** was obtained by the reaction of an alkoxy-attached derivative ligand **1a*** with **2a** in D_2O.
[14] Very similar orientations were observed in optimized structures which follow annealing by molecular dynamics simulations. Thus, the chiral orientation is considered to be unaffected by crystal-packing effects.
[15] The chiral orientation was not observed by NMR spectroscopy, which indicates that two enantiomeric *P* and *M* forms rapidly interconvert in solution.
[16] A single crystal of (*R*,*R*)-**3c** was obtained by slow diffusion of diethyl ether into the DMF/MeOH solution. Crystal data for **3c**·1.5 dmf·0.5 MeOH ($C_{53}H_{50.5}F_8N_{7.5}O_8Pd$, $M_W = 1178.91$):[19] triclinic, *P*1, $a = 11.6595(14)$, $b = 12.0387(14)$, $c = 20.209(2)$ Å, $\alpha = 82.508(2)$, $\beta = 83.352(2)$, $\gamma = 68.841(2)°$, $V = 2615.5(5)$ Å^3, $T = 193$ K, $Z = 2$, $R = 0.0883$, $R_W = 0.2154$, GOF = 1.560.
[17] CD spectra of monomer ring (*R*,*R*)-**3c** and [2]catenane (*R*,*R*,*R*,*R*)-**4c** were measured in DMF (0.125 mM) and D_2O/[D_7]DMF 2:1 (0.056 mM), respectively, at 25.0 °C.
[18] The optical purity of the catenane has been not determined.
[19] CCDC-189501 (**3c**·1.5 dmf·0.5 MeOH), CCDC-189502 (**3a′**·2 H_2O), and CCDC-189503 (**4a***·6 H_2O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

An Alkynylboronic Ester Annulation: Development of Synthetic Methods for Application to Diversity-Oriented Organic Synthesis**

Glenn C. Micalizio and Stuart L. Schreiber*

Dedicated to Professor William R. Roush

Diversity-oriented synthesis aims to prepare complex and diverse small molecules efficiently. These molecules can be used to explore biology—our goal is to be able to do so in a systematic way.[1] Whereas complex molecules can be synthesized efficiently using coupled complexity-generating reactions,[2] the goal of developing diversity-generating pathways yielding products with a high degree of skeletal diversity has not yet been realized. The development of synthetic pathways incorporating branch points holds promise as an effective route to skeletal diversity.[1] One such pathway, which diverges from common starting materials, aims to exploit the diverse reactivity of alkyl-, allyl-, pentadienyl-, alkenyl- and dialkenylboronic acids (Scheme 1).[3] This approach should enable the branching architecture of diversity-oriented synthesis pathways by using the diverse reactivity associated with these classes of reagents.[4]



Scheme 1. Development of branching reaction pathways for diversity-oriented organic synthesis; proposed alkynyl-boronic ester annulation. Mes = 2,4,6-trimethylphenyl, Cy = cyclohexyl.

Previously we reported annulation reactions of allylboronic esters with allylic and propargylic alcohols that stereospecifically provide allylboronic acids **1** and pentadienylboronic acids **2**.[3] Here we report new annulation reactions of electron-deficient alkynylboronic esters with homoallylic alcohols that provide functionalized dialkenylboronic acids **3**. In addition, we demonstrate oxidation and allene-forming hydroxyalkylation reactions of the resulting cyclic alkenyl boronic acids that further illustrate diversity-generating, branching reaction pathways.

Based on our earlier work on the allylboronic ester annulation,[3] we anticipated that the transesterification of an alkynylboronic ester **4** and a homoallylic alcohol **5** would afford a transient, mixed organoboronic ester **6** (Scheme 1), which could be trapped using ring-closing ene-yne metathesis to afford cyclic dialkenylboronic esters **3**. As expected, treatment of the homoallylic alcohol **8** with the *n*-propyl-substituted alkynylboronic ester **9** [5] and the Grubbs catalyst **7**[6] in benzene at 65 °C afforded the cyclic dialkenylboronic acid **12** in 69 % yield (Table 1, entry 1). The annulation

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