SUPPORTING INFORMATION

Insertion of benzyne into the Pd–C bond. Synthesis of unnatural amino acid derivatives by sequential insertion of benzyne and CO: 2,2'-functionalized biaryls containing alkylamino and carboxymethyl substituents. Isolation of stable carbopalladated-benzyne intermediates

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Experimental Section

General Procedures. Melting points were determined on a Reicher apparatus and are uncorrected. Elemental analyses were carried out with a Carlo Erba 1106 microanalyzer. Exact masses were recorded on an AUTOSPEC 5000 VG mass spectrometer. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer with Nujol mulls between polyethylene sheets. NMR spectra were recorded on a Brucker Avance 300 or 400 spectrometer, at room temperature. Chemical shifts were referenced to TMS (^{1}H, ^{13}C{^{1}H}) or H_3PO_4 (^{31}P{^{1}H}). NMR assignments were performed with the help of APT, HMQC and HMBC techniques. Chart 1 shows the atom numbering used for NMR assignments.

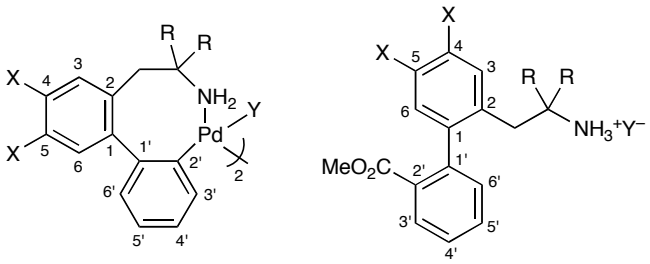

Chart 1. Numbering Scheme

Synthesis of [Pd(*C*,*N*-C$_6$H$_4${(C$_6$H$_4$CH$_2$CMe$_2$NH$_2$-2)-2'})(μ-Cl)]$_2$ (1a). A solution of 2-(trimethylsylil)phenyl trifluoromethanesulphonate (370 μL, 1.52 mmol) in dry CH_3CN (10 mL) was added dropwise to a suspension of palladacycle **A** (250 mg, 0.431 mmol) and CsF (300 mg, 1.975 mmol) in dry CH_3CN (10 mL) under N_2 atmosphere. The mixture was stirred for 48 h and filtered though a plug of Celite. The solvent from the orange filtrate was

removed, and CH_2Cl_2 (40 mL) was added. The solution was washed with H_2O (2 x 15 mL) to remove inorganic salts, and the combined organic layers were dried over $MgSO_4$. The suspension was filtered, the pale orange filtrate was concentrated to ca. 1 mL, and Et_2O (15 mL) was added. The resulting suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford the complex **1a** as a pale yellow solid. Yield: 200 mg, 0.273 mmol, 63%. Mp: 192 ºC. Anal. Calcd for $C_{32}H_{36}Cl_2N_2Pd_2$ (732.397): C, 52.48; H, 4.95; N, 3.82. Found: C, 52.09; H, 5.25; N, 3.86. IR (cm^{-1}): ν(NH) 3282 (m), 3117 (m). ^{1}H NMR (400.91 MHz, DMSO-d_6): δ 1.26 (s, 3 H, Me, CMe_2), 1.29 (s, 3 H, Me, CMe_2), 2.24 (br d, 1 H, CH_2Ar, $^2J_{HH}$ = 14.0 Hz), 2.44 (br d partially obscured by the resonance of DMSO, 1 H, CH_2Ar, $^2J_{HH}$ = 14.4 Hz), 3.63 (br d, 1 H, NH_2, $^2J_{HH}$ = 11.2 Hz), 3.84 (br d, 1 H, NH_2, $^2J_{HH}$ = 10.4 Hz), 6.83 (dd, 1 H, H6', $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 2.0 Hz), 7.02 (m, 2 H, H3' + H4'), 7.13 (m, 1 H, H6), 7.28–7.35 (m, 4 H, H3 + H4 + H5 + H5'). ^{13}C{^{1}H} NMR (100.81 MHz, DMSO-d_6): δ 28.0 (s, Me, CMe_2), 33.4 (s, Me, CMe_2), 44.0 (s, CH_2Ar), 55.7 (s, *C*Me_2), 123.9 (s, CH, C3'), 125.9 (s, CH, C5), 126.1 (s, CH, C4'), 126.3 (s, CH, C4), 127.0 (s, CH, C6'), 128.8 (s, CH, C6), 132.2 (s, CH, C3), 133.9 (s, CH, C5'), 136.3 (s, C2), 145.8 (s, C1), 146.1 (s, C1'), 150.3 (s, C2').

Synthesis of [Pd(*C*,*N*-C_6H_4{$(C_6H_2CH_2CH_2NH_2$-2,$(OMe)_2$-4,5)-2'}$)(\mu$-Br)$]_2$ (1b). A solution of 2-(trimethylsylil)phenyl trifluoromethanesulphonate (298 μL, 1.227 mmol) in dry CH_3CN (20 mL) was added dropwise to a suspension of palladacycle **B** (300 mg, 0.409 mmol) and CsF (186 mg, 1.227 mmol) in dry CH_3CN (10 mL) under N_2 atmosphere. The mixture was stirred for 48 h, the solvent was removed, CH_2Cl_2 (30 mL) was added, and the suspension was filtered through a plug or $MgSO_4$. The filtrate was washed with H_2O (3 x 10 mL), the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was removed to ca. 2 mL, and Et_2O (30 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford a first crop of complex **1b** as a dark orange solid (280 mg). The filtrate was concentrated to ca. 2 mL, and *n*-pentane (20 mL) was added. The suspension was filtered, and the solid was washed with *n*-pentane (2 x 5 mL) and air-dried to give a second crop of complex **1b** as a dark orange solid (24 mg). Yield: 304 mg, 0.343 mmol, 84%. Mp: 182 °C. Anal. Calcd for $C_{32}H_{36}Br_2N_2O_4Pd_2$ (885.297): C, 43.41; H, 4.10; N, 3.16. Found: C, 43.29; H, 4.06; N, 3.16. IR (cm^{-1}): ν(NH) 3306 w, 3249 m. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 2.00 (m, 1 H, CH_2Ar), 2.59 (br dd, 1 H, CH_2Ar, $^2J_{HH}$ = 14.6, $^3J_{HH}$

= 4.7 Hz), 2.88 (m, 1 H, CH_2N), 3.01–3.08 (m, 1 H, CH_2N), 3.71 (s, 3 H, MeO), 3.73–3.78 (m, partially obscured by the MeO signal, 1 H, NH_2), 3.79 (s, 3 H, MeO), 3.73 4.05 (br d, 1 H, NH_2, $^2J_{HH}$ = 9.5 Hz), 6.67 (s, 1 H, H6), 6.91 (br dd, H6', $^2J_{HH}$ = 6.5, $^3J_{HH}$ = 1.9 Hz), 6.95 (s, 1 H, H3), 6.97–7.04 (m, 2 H, H4' + H5'), 7.27 (br dd, H3', $^2J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 1.8 Hz). $^{13}C\{^1H\}$ NMR (100.81 MHz, DMSO-d_6): δ 32.9 (s, CH_2Ar), 47.2 (s, CH_2N), 55.5 (s, MeO), 55.7 (s, MeO), 112.4 (s, CH, C6), 113.5 (s, CH, C3), 123.9 (s, CH, C5'), 126.3 (s, CH, C4'), 127.2 (s, CH, C6'), 131.9 (s, C2), 133.7 (s, CH, C3'), 137.1 (s, C1), 145.9 (s, C1'), 146.4 (s, C5), 148.0 (s, C4). The ^{13}C NMR resonance corresponding to the C2' was not observed.

Although the elemental analysis of complex **1b** agrees with the proposed structure, its ^1H NMR spectra shows a small impurity (ca. 95:5, according to resonances corresponding to the OMe groups), which cannot be removed by fractional crystallization or chromatography tecniques. Nevertheless, crude **1b** can be used as starting material to prepare **2b** and **3b**.

Synthesis of [Pd(*C*,*N*-C_6H_4{$(C_6H_4CH_2CMe_2NH_2$-2)-2'})Cl(4-pic)] (2a). 4-Picoline (30 μL, 0.308 mmol) was added to a suspension of complex **1a** (100 mg, 0.137 mmol) in CH_2Cl_2 (10 mL). The resulting pale yellow solution was stirred for 20 min, concentrated to ca. 2 mL, and Et_2O (25 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to afford complex **2a** as pale yellow solid. Yield: 120 mg, 0.261 mmol, 95%. Mp: 181 ºC. Anal. Calcd for $C_{22}H_{25}ClN_2Pd$ (459.327): C, 57.53; H, 5.47; N, 6.10. Found: C, 57.35; H, 5.81; N, 6.14. IR (cm^{-1}): ν(NH) 3293 (m), 3188 (m), 3114 (m); ν(C=N) 1616 (m). ^1H NMR (400.91 MHz): δ 1.33 (s, 3 H, Me, CMe_2), 1.62 (s, 3 H, Me, CMe_2), 2.23 (s, 3 H, Me, pic), 2.29 (br d, 1 H, NH_2, $^2J_{HH}$ = 10.0 Hz), 2.34 (d, 1 H, CH_2Ar, $^2J_{HH}$ = 14.4 Hz), 2.53 (dd, 1 H, CH_2Ar, $^2J_{HH}$ = 13.5, $^4J_{HH}$ = 1.2 Hz), 3.20 (br d, 1 H, NH_2, $^2J_{HH}$ = 10.0 Hz), 6.86–6.89 (m, 3 H, H2' + *m*-H of pic), 6.93 (d, 1 H, H5, $^3J_{HH}$ = 7.2 Hz) 6.97 (td, 1 H, H3', $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.02 (td, 1 H, H4', $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.25 (m, partially obscured by the resonance of traces of $CHCl_3$ present in the deuterated solvent, 1 H, H4), 7.34–7.37 (m, 2 H, H2 + H3) 7.44 (dd, 1 H, H5', $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2 Hz), 8.14 (br d, 2 H, *o*-H pic, $^3J_{HH}$ = 6.4 Hz). $^{13}C\{^1H\}$ NMR (75.45 MHz): δ 20.9 (s, Me, pic), 28.0 (s, Me, CMe_2), 35.1 (s, Me, CMe_2), 44.7 (s, CH_2Ar), 56.1 (s, CMe_2), 123.7 (s, CH, C3'), 125.1 (s, *m*-CH, pic), 126.1 (s, CH, C4), 126.3 (s, CH, C4'), 126.5 (s, CH, C3), 126.9 (s, CH, C2'), 128.6 (s, CH, C5), 132.4 (s, CH, C2), 133.3 (s, CH, C5'), 135.9 (s, C1), 146.4 (s, C6), 147.2 (s, C1'), 148.9 (s, *p*-C, pic), 150.9 (s, C6'), 151.5 (s, *o*-CH, pic). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of *n*-pentane into a solution of **2a** in $CHCl_3$.

Synthesis of [Pd (*C*,*N*-C_6H_4{$(C_6H_2CH_2CH_2NH_2$-2,$(OMe)_2$-4,5)-2'}$)Br(PPh_3)$] (2b). PPh_3 (59 mg, 0.225 mmol) was added to a solution of complex **1b** (100 mg, 0.113 mmol) in CH_2Cl_2 (25 mL), and the resulting solution was stirred for 30 min. The mixture was filtered through a plug of Celite, the filtrate was concentrated to ca. 2 mL, and Et_2O (30 mL) was added. The suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and air-dried to give a first crop of complex **2b** as a yellow solid (86 mg). The filtrate was concentrated to ca. 2 mL, and *n*-pentane was added. The suspension was filtered, and the solid was washed with *n*-pentane (2 x 5 mL) and air-dried to give a second crop of complex **2b** as a yellow solid (25 mg). Yield: 111 mg, 0.157 mmol, 70%. An analytically pure sample of complex **2b** was obtained by recrystallization from CH_2Cl_2/Et_2O. Mp: 151 °C. Anal. Calcd for $C_{34}H_{33}BrNO_2PPd$ (704.926): C, 57.93; H, 4.72; N, 1.99. Found: C, 57.90; H, 4.55; N, 1.94. IR (cm^{-1}): ν(NH) 3304 m, 3243 w. ^{1}H NMR (300.1 MHz): δ 1.56 (br s, H_2O), 2.12 (m, 1 H, CH_2Ar), 2.21–2.34 (m, partially obscured by the CH_2Ar signal, 1 H, NH_2), 2.70 (br dd, 1 H, CH_2Ar, $^2J_{HH}$ = 15.0, $^3J_{HH}$ = 5.4 Hz), 3.28–3.35 (m, partially obscured by the MeO signal, 1 H, CH_2N), 3.38 (s, 3 H, MeO), 3.45–3.52 (m, partially obscured by the MeO signal, 1 H, CH_2N), 3.53–3.61 (m, 1 H, NH_2), 4.03 (s, 3 H, MeO), 5.72 (s, 1 H, H6), 6.74–6.87 (m, 2 H, H4' + H5' + H6'), 6.90 (s, 1 H, H3), 7.08–7.23 (m, 13 H, 6H *o*-H + 6 H *m*-H of PPh_3 and 1 H of H3'), 7.27–7.40 (m, 3 H, *p*-H, PPh_3). $^{13}C\{^1H\}$ NMR (75.45 MHz): δ 33.4 (s, CH_2Ar), 46.5 (s, CH_2N), 55.6 (s, MeO), 56.1 (s, MeO), 111,7 (s, CH, C6), 112.6 (s, CH, C3), 123.3 (s, CH, C5'), 126.6 (s, CH, C4'), 127.8 (d, *m*-CH, PPh_3, $^3J_{CP}$ = 10.7 Hz), 128.2 (s, C6'), 130.0 (d, *p*-CH, PPh_3, $^4J_{CP}$ = 2.6 Hz), 131.3 (d, *i*-C, PPh_3, $^1J_{CP}$ = 49.8 Hz), 131.4 (s, C2), 134.5 (d, *o*-CH, PPh_3, $^2J_{CP}$ = 11.6 Hz), 134.5 (d, CH, C3', $^3J_{CP}$ = 4.8 Hz), 138.7 (s, C1), 146.1 (s, C1'), 146.9 (s, C5), 148.4 (s, C4), 155.0 (s, C2'). ^{31}P NMR (121.5 MHz): 29.3 (s). Single crystals of **2b**·CH_2Cl_2 suitable for an X-ray diffraction study were obtained by slow diffusion of Et_2O into a solution of **2b** in $CHCl_3$.

Synthesis of 2-(2-amino-2,2-dimethylethyl)-2'-carboxymethyl-[1,1'-biphenyl] hydrochloride (3a). In a Carius tube, CO was bubbled through a suspension of complex **1a** (100 mg, 0.137 mmol) in MeOH (15 mL) for 3 min. The pressure of CO was increased to 1 atm and the reaction mixture was stirred for 12 h. Decomposition to palladium black was observed. The suspension was filtered through a plug of Celite, and the solvent from the colorless filtrate was removed to dryness. The residue was dissolved in CH_2Cl_2 (1 mL), and *n*-

pentane (25 mL) was added. The resulting suspension was filtered, and the solid was washed with *n*-pentane (2 x 5 mL) and air-dried to afford compound **3a** as a colorless solid. Yield: 64 mg, 0.200 mmol, 73%. Mp: 78 ºC. IR (cm^{-1}): ν(NH) 3391 (br); ν(CO) = 1727 (vs). ^{1}H NMR (400.91 MHz): δ 1.12 (s, 3 H, Me, CMe_2), 1.26 (s, 3 H, Me, CMe_2), 2.78 (d, 1 H, CH_2Ar, $^2J_{HH}$ = 14.0 Hz), 3.21 (d, 1 H, CH_2Ar, $^2J_{HH}$ = 14.0 Hz), 3.62 (s, 3 H, OMe), 7.09 (m, 1 H, H5) 7.26–7.30 (m, 3 H, H2' + H3 + H4), 7.39 (m, 1 H, H2), 7.45 (t, 1 H, H4', $^3J_{HH}$ = 7.6 Hz), 7.57 (t, 1 H, H3', $^3J_{HH}$ = 7.6 Hz), 7.95 (d, 1 H, H5', $^3J_{HH}$ = 7.6 Hz), 8.16 (br s, 3 H, NH_3). $^{13}C\{^1H\}$ NMR (100.81 MHz): δ 25.3 (s, Me, CMe_2), 26.1 (s, Me, CMe_2), 42.3 (s, CH_2Ar), 52.2 (s, OMe), 56.1 (s, *C*Me_2), 127.0 (s, CH, C4), 127.6 (s, CH, C4'), 127.8 (s, CH, C3), 130.2 (s, CH, C5), 130.45 (s, C6'), 130.48 (s, CH, C5'), 131.7 (s, CH, C2), 131.8 (s, CH, C3'), 131.9 (s, CH, C2'), 132.2 (s, C1), 141.8 (s, C1'), 141.9 (s, C6), 168.2 (s, CO). ESI-HRMS: exact mass calcd for $C_{18}H_{22}NO_2$ 284.16505 $[(M - Cl)^+]$; found 284.1657; Δ = 0.0006.

Synthesis of 2-(2-aminoethyl)-4,5-dimethoxy-2'-carboxymethyl-[1,1'-biphenyl] hydrobromide (3b). In a Carius tube, CO was bubbled through a suspension of complex **1b** (80 mg, 0.09 mmol) in MeOH (25 mL) for 3 min. The pressure of CO was increased to 1 atm and the reaction mixture was stirred for 16 h. Decomposition to palladium black was observed. The resulting suspension was filtered through a plug of Celite, and the solvent from the filtrate was removed to dryness. The residue was vigorously stirred in Et_2O (30 mL), the suspension was filtered, and the solid was washed with Et_2O (2 x 5 mL) and dried under N_2 atmosphere to afford compound **3b** as a colorless solid. Yield: 43 mg, 0.109 mmol, 61%. Mp: 55 °C. Λ_M (Ω^{-1} cm^2 mol^{-1}) = 1.66 (6.00 x 10^{-4} M). IR (cm^{-1}): ν(NH) 3395 br m; ν(CO) 1725 s. ^{1}H NMR (300.1 MHz): δ 2.55–2.72 (m, 1 H, CH_2N), 3.07–3.21 (m, 3 H, 1 H of CH_2N + 2 H of CH_2Ar), 3.76 (s, 3 H, MeO), 3.78 (s, 3 H, MeO), 4.00 (s, 3 H, MeO), 6.44 (s, 1 H, H6), 7.15 (s, 1 H, H3), 7.30 (br d, 1 H, H6', $^3J_{HH}$ = 7.8 Hz), 7.45 ("t", 1 H, H4', $^3J_{HH}$ = 7.2 Hz), 7.56 ("t", 1 H, H5', $^3J_{HH}$ = 7.8 Hz), 7.62 (br s, 3 H, NH_3), 7.86 (br d, 1 H, H3', $^3J_{HH}$ = 7.5 Hz). $^{13}C\{^1H\}$ NMR (75.45 MHz): δ 30.1 (s, CH_2Ar), 38.7 (s, CH_2N), 53.0 s, CO_2*Me*), 56.0 (s, MeO), 56.3 (s, MeO), 112.6 (s, CH, C6), 114.4 (s, CH, C3), 124.1 (s, C2), 127.8 (s, C4'), 130.2 (s, C3'), 130.7 (s, C6'), 130.8 (s, C2'), 132.0 (s, C5'), 132.9 (s, C1), 141.2 (s, C1'), 148.0 (s, C5), 148.6 (s, C4), 169.5 (s, CO). EI-HRMS: exact mass calcd for $C_{18}H_{22}NO_4$ 316.1543 $[(M - Br)^+]$; found 316.1549; Δ = 0.0006.

Single-Crystal X-ray Structure Determinations. Relevant crystallographic data and details of the refinements for the structures of compounds **2a** and **2b**·CH_2Cl_2 are summarized in Table 1. Data Collection: Crystals suitable for X-ray diffraction were mounted in inert oil on a glass fiber and transferred to a Bruker SMART APEX diffractometer. Data were recorded at 100(2)K using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and *ω*-scan mode. Multiscan absorption corrections were applied. Solution and Refinements: Crystal structures were solved by direct method and all nonhydrogen atoms refined anisotropically on F^2 using the program SHELXL-97.[1] Hydrogen atoms were refined as follows: NH_2, free with SADI; methyl, rigid group; all others, riding.

[1] Sheldrick, G. M. SHELX-97; University of Göttingen, Göttingen, Germany, 1997.

Table 1. Crystal Data and Structure Refinement Details for Complexes **2a** and **2b**·CH_2Cl_2.

	2a	**2b**·CH_2Cl_2
formula	$C_{22}H_{25}ClN_2Pd$	$C_{35}H_{35}BrCl_2NO_2PPd$
fw	459.29	789.82
temp (K)	100(2)	100(2)
cryst habit	colorless block	colorless lath
cryst size (mm)	0.27 x 0.10 x 0.06	0.25 x 0.10 x 0.03
cryst syst	triclinic	triclinic
space group	$P\ \bar{1}$	$P\ \bar{1}$
a (Å)	9.2021(7)	8.8675(7)
b (Å)	10.3321(7)	13.5117(11)
c (Å)	11.8365(9)	15.0521(12)
α (deg)	73.850(2)	68.116(2)
β (deg)	78.692(2)	79.424(2)
γ (deg)	65.084(2)	75.791(2)
V (Å^3)	976.33(12)	1613.8(2)
Z	2	2
ρ_{calcd} (Mg m^{-3})	1.562	1.625
μ(Mo, Kα) (mm^{-1})	1.095	2.062
F(000)	468	796
θ range (deg)	1.80–28.60	1.66–28.71
no. rflns collected	11 858	19 839
no. indep rflns	4558	7568
R_{int}	0.0182	0.0202
max, min transmsn	0.937, 0.799	0.941, 0.829
no. of restraints/params	1/246	1/398
goodness of fit on F^2	1.094	1.035
R1 ($I > 2\sigma(I)$)	0.0220	0.0289
wR2 (all rflns)	0.0536	0.0727
largest diff peak, hole (e Å^{-3})	0.506, –0.458	0.767, –0.615

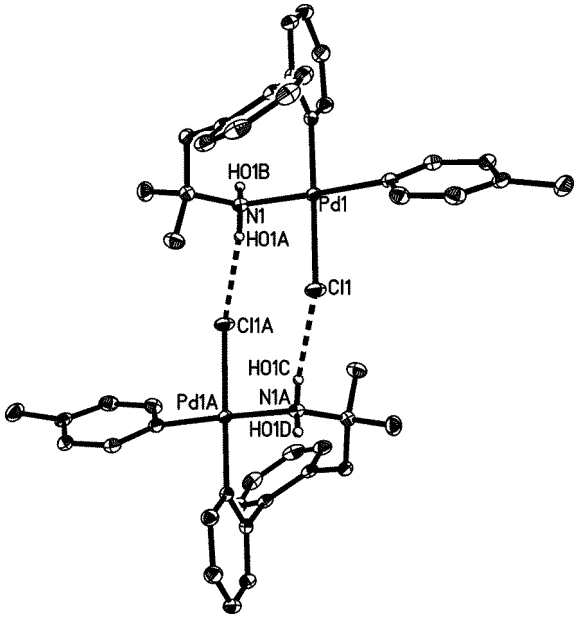

Figure 1. X-ray packing view of complex **2a** (50% probability) showing the dimers formed through N(1)–H(01A)···Cl(1A) hydrogen bond interactions. Symmetry operator: (A) 1–*x*, –*y*, 2–*z*.

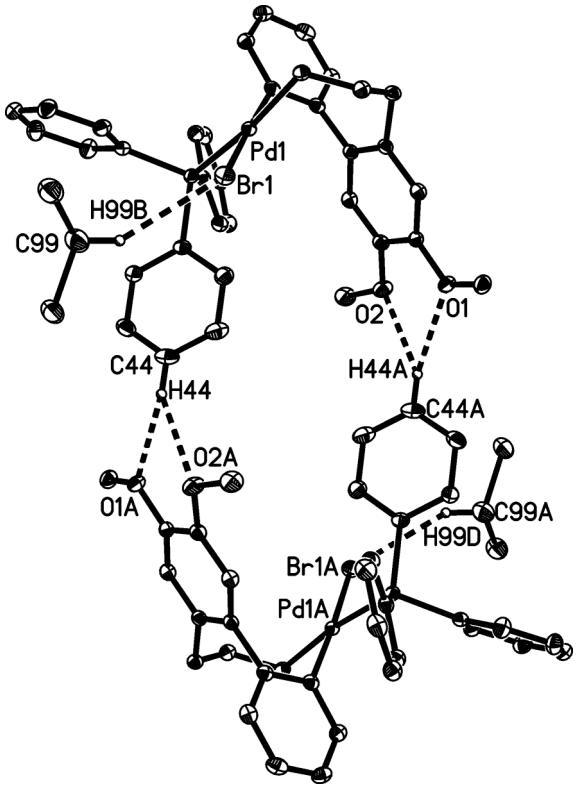

Figure 2. X-ray packing view of complex **2b·CH_2Cl_2** (50% probability) showing the dimers formed through C(44)–H(44)···O(1A) and C(44)–H(44)···O(2A) hydrogen bond interactions. Symmetry operator: (A) 2–*x*, –*y*, 1–*z*. The C(99)–H(99B)··Br(1) hydrogen interaction with the solvent is also shown.