Preparation of *N*-(*p*-Tolyl)azacalix[*n*](2,6)pyridines Constructed of Various Numbers of the Recurring Unit

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Abstract: Synthetic routes for *N*-(*p*-tolyl)-substituted azacalix[*n*](2,6)pyridines via Cu- and Pd-catalyzed aryl amination reactions have been elaborated, and the macrocycles constructed of various numbers (n = 3–8, and 10) of a *N*-(*p*-tolyl)aminopyridine recurring unit have been isolated. A cyclic trimer **1** was obtained in good yield. Molecular structures of some macrocycles and a Cu(I) complex of **1** were determined by X-ray crystallography.

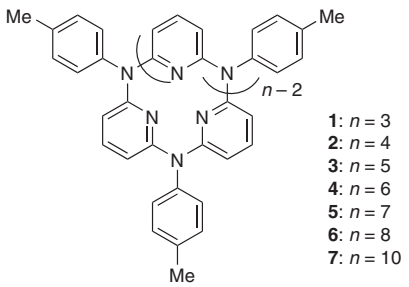
Key words: macrocycles, aminations, pyridines, copper, palladium, complexes

Oligo-α-aminopyridines have recently attracted much attention because they have multidentate coordination sites with significant flexibility that afford unique oligonuclear metal complexes.[1] Cyclization of the oligomers will change their coordination behavior and structural feature of the complexes because of restricted flexibility of the macrocycles. However, reported examples of such macrocyclic ligands have been limited.[2]

We previously reported the preparation of *N*-methyl-substituted azacalix[*n*](2,6)pyridines (n = 4 and 6) by the Pd-catalyzed aryl amination of 2,6-dibromopyridine with 2,6-bis(methylamino)pyridine.[2a] They acted as macrocyclic ligands and afforded a zinc complex. However, the previous process was effective to provide only the macrocycles constructed of even-numbered recurring units. In order to achieve selective metal ion inclusion, preparation of such macrocycles constructed of various numbers of the recurring unit is considered to be important. In parallel with this, substitution of the bridging amino group in the macrocycles will also be of interest. Introduction of bulky substituents such as aromatic groups, instead of the methyl group, at the bridging amino groups is expected to modify the cyclization reaction to give the macrocycles with various ring sizes, which will exhibit interesting inclusion behavior.

This situation prompted us to expand the chemistry of azacalix[*n*](2,6)pyridines to *N*-(*p*-tolyl)-substituted derivatives, and we found that adoption of new cyclization conditions gave the macrocycles with various numbers of the recurring unit. Especially, a cyclic trimer **1** (n = 3) was obtained in good yield. We here report the preparation of the new macrocycles (n = 3–8, and 10, **1**–**7**), and molecular structures of **1**, **2** (n = 4), **4** (n = 6, cf. Scheme 1). The complexation of **1** toward Cu(I) is also presented.

The trimer **1** was prepared by the Cu-catalyzed aryl amination[3] of *N*,*N*-bis[2-(6-bromopyridy)]-*p*-toluidine[4] (**8**) with 2,6-bis(*p*-tolylamino)pyridine[5] (**9**);[6] see the top equation in Scheme 2. The reaction was carried out under dilute conditions to minimize formation of linear oligomers, and provided **1** in 73% yield.[6] A similar reaction under 10 times higher concentrated conditions afforded **1** in a moderate yield (35%). On the other hand, the cyclization reaction of 2,6-dibromopyridine with **9** shown by the middle equation in Scheme 2 provided even-numbered macrocycles; a cyclic tetramer **2** was a main product (yield: **2**, 24%, **4**, 12%, **6**, 1%, **7**, trace).[7] The Cu-catalyzed cyclization of 2-bromo-6-(*p*-tolylamino)pyridine[8] (**10**, see bottom equation in Scheme 2) also afforded **1** (44%). Although other macrocycles (n = 4–8) were detected by HPLC and FAB-mass spectroscopy, they could not be isolated due to the coexistence of linear oligomers formed in the reaction. When a Pd catalyst was used for the aryl amination of **10**,[9] the produced macrocycles (n = 3–8) were isolated in good total yields (yield: **1**, 38%, **2**, 31%, **3**, 6%, **4**, 7%, **5**, 2%, **6**, trace).[10]



Scheme 1

Formation of the macrocycles was confirmed by FAB-mass and NMR spectroscopy. In the ^{1}H NMR spectra of **1** and **2**, sharp signals with aromatic AB_2 and AB spin patterns were observed at room temperature. They were assigned to the aromatic protons in pyridine units and the *p*-tolyl substituent, respectively. These signals were broadened at –50 °C, suggesting conformational flexibility of the macrocycles in the solution at room temperature. As for **4**, a split of the aromatic AB_2 pattern was observed at –50 °C. Intramolecular hydrogen bonding interaction between the pyridine units seems to bring about unequivalency for the pyridine units at –50 °C.

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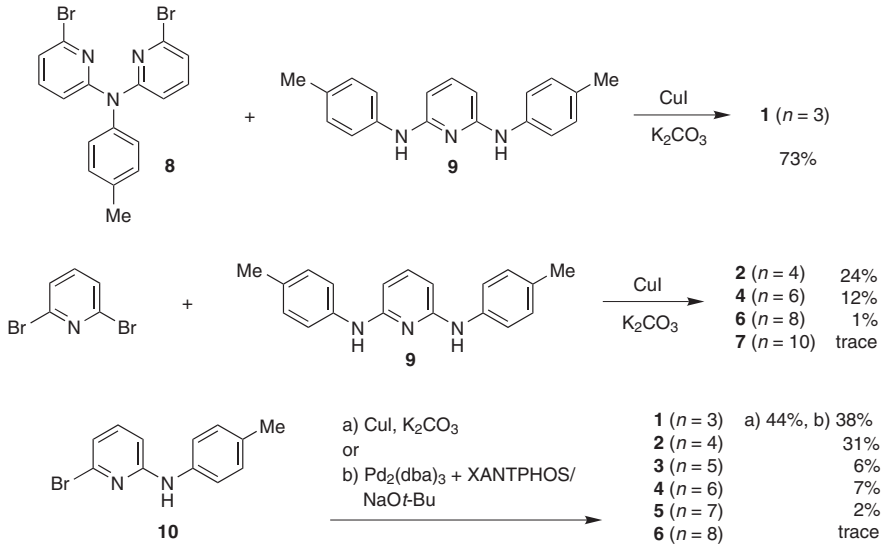

Scheme 2

The molecular structures of **1**, **2** and **4** were determined by X-ray crystallography (Figure 1).[11] Compound **1** adopts a triangular shape with approximate C_S symmetry, and one pyridine ring orients in a direction opposite to other two pyridine rings due to electrostatic repulsion between the pyridine nitrogens (N_{py}'s). The crystal packing suggests that the conformation of **1** is stabilized via intermolecular hydrogen bonds between N_{py}'s and aromatic protons of the *p*-tolyl substituents. The ORTEP drawing of **2** [Figure 1(b)] indicates that **2** adopts a saddle shape with an 1,3-alternating conformation, and the two of the opposed pyridine rings are in almost face-to-face arrangement with a twist angle of 28.3(4)° (C7–C6–C20–C19). The *p*-tolyl substituents are also oriented in opposite directions alternately. Compound **4** adopts a triangular shape and each pyridine ring alternately inclines upward and downward to the macrocyclic plane [Figure 1(c)] due to the electrostatic repulsion between the N_{py}'s and bridging amino groups in the cavity.

Pyridine-containing macrocycles form complexes with Cu(I) ion, and the Cu(I) ion usually assumes a tetrahedral geometry.[12] The reaction of **1** with CuI also yielded a Cu(I) complex **11**,[13] and the molecular structure of the complex was determined by X-ray crystallography (Figure 2).[14] The ORTEP drawing of **11** shows that the conformation of **1** is similar to that of free **1** and the Cu(I) ion is coordinated to two of the N_{py}'s and to an iodo ligand in a distorted trigonal-planar arrangement. The Cu–N_{py} bond lengths [2.053(9)–2.063(6) Å] are somewhat longer and the N_{py}–Cu–N_{py} bond angle [84.2(3)°] is smaller than those observed for the three-coordinated Cu(I) complexes with di-2-pyridylamine.[15] The unbound N_{py} (N1) is found at a distance of 2.42 Å from Cu(I). The ^{1}H NMR spectrum of **11** also supports that there are two magnetically unequivalent pyridine units (2:1) in CD_3CN at room temperature.[13] The stiff conformation of **1** seems to be due to the presence of the bulky *p*-tolyl substituent.

As described above, new heterocalixarenes constituted of various numbers of aminopyridine unit, *N*-(*p*-tolyl)azacalix[*n*](2,6)pyridines (*n* = 3–8, and 10), have been prepared by the Cu- and Pd-catalyzed aryl amination reactions, and **1** (*n* = 3) was obtained in good yield. The reaction of **1** with CuI afforded a unique Cu(I) complex. The larger macrocycles have many *N*-donor sites in the cavity, which will allow the molecules to include other metal ions and organic molecules. The macrocycles are thus expected to serve as host molecules and building blocks for the construction of molecular architectures and coordination polymers.

Acknowledgment

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(4) Compound **8**: A mixture of 2,6-dibromopyridine (3.53 g, 15 mmol) and *p*-toluidine (535 mg, 5 mmol) was dissolved in toluene (50 mL). Sodium-*t*-butoxide (1.44 g, 15 mmol), tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] (230 mg, 0.25 mmol), and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (XANTPHOS) (290 mg, 0.50 mmol) were added to the solution. The reaction mixture was stirred at 80 °C for 18 h under nitrogen. After cooling to r.t., the mixture was quenched by the addition of an aq solution of EDTA-2K (ca. 100 mL), and the product was extracted with $CHCl_3$.

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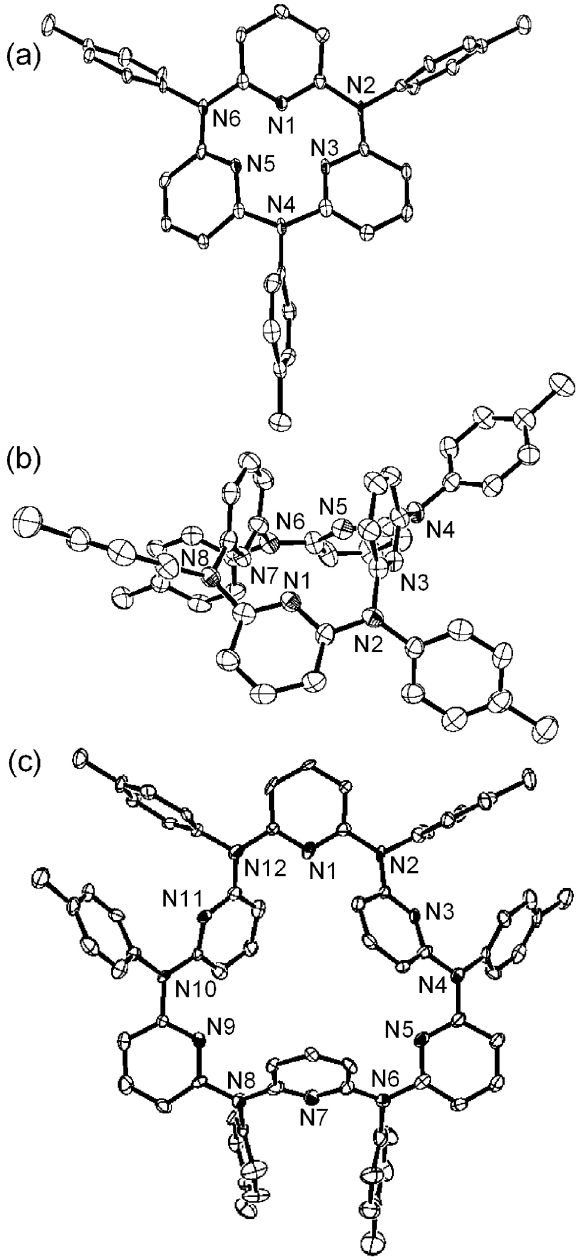

Figure 1 X-ray crystal structures of (a) **1**, (b) **2**, and (c) **4** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and solvent molecules are omitted for simplicity.

The crude product was purified by column chromatography on silica gel (1.62 g, 78% yield). FAB-MS: *m/z* = 420 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (t, *J* = 7.8 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.07 (d, *J* = 7.3 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 2.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 141.0, 139.5, 136.9, 130.8, 128.1, 122.9, 122.0, 114.9, 21.5.

(5) Preparation of compound **9** was carried out in analogy with ref.[4] using 2,6-diaminopyridine and 4-bromotoluene (58% yield). FAB-MS: *m/z* = 290 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 8.1 Hz, 1 H), 7.21 (d, *J* = 8.3 Hz, 4 H), 7.12 (d, *J* = 8.3 Hz, 4 H), 6.25 (s, 2 H), 6.24 (d, *J* = 7.8 Hz, 2 H), 2.33 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 139.2, 138.0, 132.2, 129.7, 121.0, 98.1, 20.8.

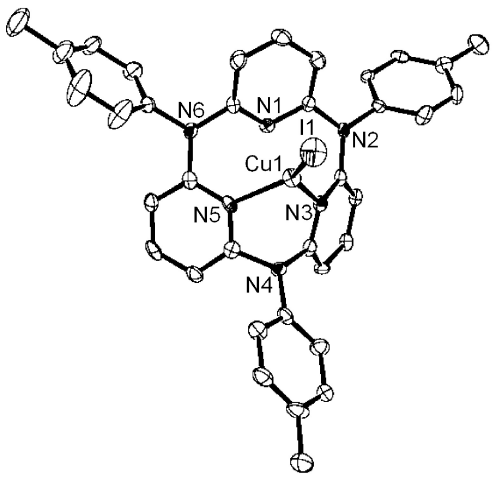

Figure 2 X-ray crystal structure of **11** with thermal ellipsoids drawn at the 50% probability level. Hydrogen atoms and a solvent molecule are omitted for simplicity.

(6) Macrocycle **1** (*n* = 3): A mixture of **8** (105 mg, 0.25 mmol) and **9** (72 mg, 0.25 mmol) was dissolved in nitrobenzene (50 mL). CuI (70 mg, 0.37 mmol) and anhyd K_2CO_3 (138 mg, 1.0 mmol) were added to the solution. The reaction mixture was stirred at 190 °C for 6 d under nitrogen. After the reaction, the solvent was removed by vacuum distillation. The remaining mixture was washed with an aq solution of EDTA-2K (ca. 100 mL) and extracted with $CHCl_3$. The organic fraction was concentrated, and the crude product was purified by column chromatography on aminopropylated silica gel (100 mg, 73% yield). FAB-MS: *m/z* = 547 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.4 Hz, 6 H), 7.27 (d, *J* = 8.4 Hz, 6 H), 7.16 (t, *J* = 8.2 Hz, 3 H), 6.06 (d, *J* = 8.0 Hz, 6 H), 2.41 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 146.8, 137.4, 137.0, 130.7, 129.1, 106.9, 21.2.

(7) Preparation of macrocycles **2**, **4**, **6**, and **7** was carried out in analogy with ref.[6] using 2,6-dibromopyridine and **9** (yield: **2**, 24%; **4**, 12%; **6**, 1%; **7**, trace).
Macrocycle **2** (*n* = 4): FAB-MS: *m/z* = 729 [M + H]$^+$, 365 [M + 2 H]$^{2+}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.8 Hz, 4 H), 7.13 (d, *J* = 8.3 Hz, 8 H), 7.05 (d, *J* = 8.1 Hz, 8 H), 6.48 (d, *J* = 7.8 Hz, 8 H), 2.30 (s, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 142.2, 138.1, 134.2, 129.6, 126.3, 111.1, 21.0.
Macrocycle **4** (*n* = 6): FAB-MS: *m/z* 1093 [M + H]$^+$, 547 [M + 2 H]$^{2+}$. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 7.26 (t, *J* = 8.0 Hz, 6 H), 6.96 (d, *J* = 8.3 Hz, 12 H), 6.91 (d, *J* = 8.5 Hz, 12 H), 6.40 (d, *J* = 7.8 Hz, 12 H), 2.32 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 142.3, 137.8, 134.4, 129.4, 128.2, 109.2, 21.1.
Macrocycle **6** (*n* = 8): FAB-MS: *m/z* = 1457 [M + H]$^+$, 729 [M + 2 H]$^{2+}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.1 Hz, 16 H), 6.98 (t, *J* = 8.2 Hz, 8 H), 6.88 (d, *J* = 7.8 Hz, 16 H), 6.28 (d, *J* = 7.8 Hz, 16 H), 2.32 (s, 24 H).
Macrocycle **7** (*n* = 10): FAB-MS: *m/z* = 1821 [M + H]$^+$, 911 [M + 2 H]$^{2+}$. ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C): δ = 7.00–6.90 (m, 30 H), 6.85 (d, *J* = 8.1 Hz, 20 H), 6.31 (d, *J* = 8.1 Hz, 20 H), 2.29 (s, 30 H).

(8) Preparation of compound **10** was carried out in analogy with ref.[4] using 2,6-dibromopyridine and *p*-toluidine (58% yield). FAB-MS: *m/z* = 263 [M + H]$^+$. ^{1}H NMR (400 MHz, acetone-d_6): δ = 8.30 (s, 1 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 7.40 (dd,

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J = 8.3, 8.3 Hz, 1 H), 7.11 (d, J = 8.1 Hz, 2 H), 6.86 (dd, J = 7.5, 0.6 Hz, 1 H), 6.77 (dd, J = 8.3, 0.7 Hz, 1 H), 2.27 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 140.2, 139.6, 136.6, 133.9, 129.9, 121.8, 117.6, 105.3, 20.8.

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(10) Compound **10** (658 mg, 2.5 mmol) was dissolved in toluene (500 mL). NaO*t*-Bu (360 mg, 3.75 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), and XANTPHOS (115 mg, 0.2 mmol) were added to the solution. The reaction mixture was stirred at 80 °C for 5 d under nitrogen. Purification of the product was carried out in analogy with ref.[6] (yield: **1**, 38%; **2**, 31%; **3**, 6%; **4**, 7%; **5**, 2%; **6**, trace).
Macrocycle **3** (n = 5): FAB-MS: m/z = 911 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, J = 8.0 Hz, 5 H), 7.01 (d, J = 9.0 Hz, 10 H), 6.98 (d, J = 8.8 Hz, 10 H), 6.38 (d, J = 7.8 Hz, 10 H), 2.31 (s, 15 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 142.1, 137.7, 134.2, 129.4, 127.3, 110.5, 21.1.
Macrocycle **5** (n = 7): FAB-MS: m/z = 1275 [M + H]$^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (t, J = 8.1 Hz, 7 H), 6.96 (d, J = 8.1 Hz, 14 H), 6.89 (d, J = 8.3 Hz, 14 H), 6.41 (d, J = 8.1 Hz, 14 H), 2.30 (s, 21 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 141.6, 137.5, 134.0, 129.1, 127.5, 108.8, 20.8.

(11) Crystallographic data for **1**: $C_{36}H_{30}N_6$, M = 546.67, monoclinic, $P2_1/a$, a = 11.225 (7), b = 21.541 (13), c = 12.989 (9) Å, β = 113.747 (8)°, V = 2874.8 (32) Å^3, Z = 4, D_{calcd} = 1.263 g cm^{-3}, μ(MoKα) = 0.77 cm^{-1}, T = 113 K, F(000) = 1152, 42080 reflections measured, 6688 unique, 3778 observed [$I > 3\sigma(I)$], 379 variables, R_1 = 0.037, R_w = 0.048, GOF = 0.929.
Crystallographic data for **2**: $C_{48}H_{40}N_8$, M = 728.90, triclinic, P1bar, a = 11.111 (9), b = 12.354 (7), c = 14.633 (9) Å, α = 71.37 (3), β = 89.86 (4)°, γ = 82.48 (4)°, V = 1885.4 (22) Å^3, Z = 2, D_{calcd} = 1.284 g cm^{-3}, μ(MoKα) = 0.78 cm^{-1}, T = 113 K, F(000) = 768, 28672 reflections measured, 8100 unique, 5582 observed [$I > 1\sigma(I)$], 505 variables, R_1 = 0.090, R_w = 0.131, GOF = 0.930.
Crystallographic data for **4**•2$CHCl_3$: $C_{74}H_{62}N_{12}Cl_6$, M = 1332.10, triclinic, P1bar, a = 13.283 (8), b = 14.980 (7), c = 19.459 (13) Å, α = 70.21 (3), β = 81.90 (3)°, γ = 67.21 (3)°, V = 3358.8 (34) Å^3, Z = 2, D_{calcd} = 1.317 g cm^{-3}, μ(MoKα) = 3.09 cm^{-1}, T = 113 K, F(000) = 1384, 49428 reflections measured, 14202 unique, 8401 observed [$I > 2\sigma(I)$], 829 variables, R_1 = 0.132, R_w = 0.171, GOF = 1.058.[16]

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(13) Cu(I) complex **11**: An MeCN solution (1 mL) of CuI (19 mg, 0.1 mmol) was added to an MeCN solution (1 mL) of **1** (54 mg, 0.1 mmol). The mixture was allowed to stir at r.t. for 30 min. An addition of Et_2O (about 1 mL) afforded a yellow precipitate. The precipitate was filtered and washed with Et_2O (21 mg, 56% yield). A single crystal was obtained by slow diffusion of hexane into a CH_2Cl_2 solution of the product. ^{1}H NMR (400 MHz, CD_3CN): δ = 7.60–7.20 (m, 15 H), 6.52 (d, J = 8.3 Hz, 2 H), 6.00 (d, J = 8.4 Hz, 4 H), 2.49 (s, 6 H), 2.39 (s, 3 H).

(14) Crystallographic data for **11**•CH_2Cl_2: $C_{37}H_{32}CuCl_2IN_6$, M = 822.06, triclinic, P1bar, a = 10.253 (5), b = 11.726 (7), c = 16.545 (9) Å, α = 82.68 (3), β = 74.12 (3)°, γ = 66.16 (2)°, V = 1749.5 (17) Å^3, Z = 2, D_{calcd} = 1.560 g cm^{-3}, μ(MoKα) = 16.95 cm^{-1}, T = 113 K, F(000) = 824, 25354 reflections measured, 7399 unique, 4688 observed [$I > 2\sigma(I)$], 456 variables, R_1 = 0.072, R_w = 0.086, GOF = 0.881.[16]

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(16) Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre; publication numbers CCDC 253651 (**1**), 241558 (**2**), 241559 (**4**), and 253652 (**11**).

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