ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2015, **51**, 3804

Received 6th January 2015,
Accepted 27th January 2015

DOI: 10.1039/c5cc00087d

www.rsc.org/chemcomm

Diastereoselective synthesis of *O* symmetric heterometallic cubic cages†

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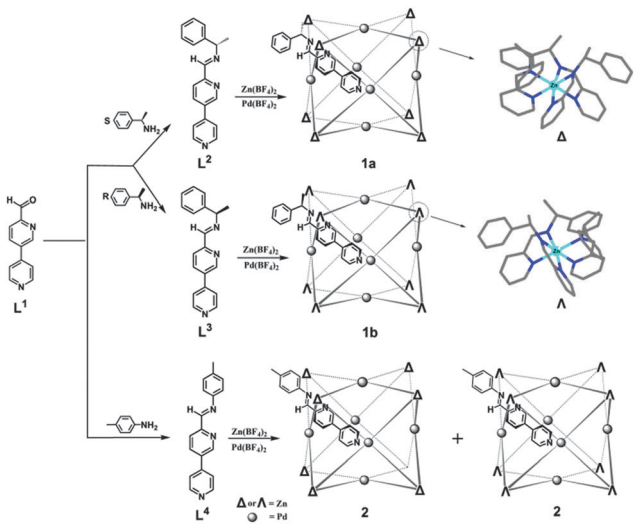
Enantiopure chiral cubic cages have been diastereoselectively synthesized for the first time. Chiral amines lead to the isolation of *O* symmetric homochiral cubic cages, while an achiral amine gives a racemic mixture. CD enhancement is observed as a result of configuration rigidity.

Coordination cage compounds are of special interest due to their well-defined structures, and potential applications such as catalysis, encapsulation of intermediates, and storage of labile substances.[1] Their formation is usually based on the self-assembly of metal centers and bridging ligands.[2] Chirality is an important issue with cage compounds, as asymmetric arrangement of ligands around a metal center or spatial twisting of ligands could generate supramolecular chirality.[3] The chiral environments enable guests to experience sensations of dissymmetry, facilitating chiral separation and/or stereoselective reactions.[4,5]

Chiral M_4L_n (n = 4 or 6) coordination tetrahedral cages are well studied.[5,6] In contrast, there is no report on homochiral M_8L_n (n = 6 or 12) cubes, which have eight chiral vertices leading to much more possible stereoisomers.[7] So far, all the structurally determined chiral cubic cages reported in the literature are racemic mixtures.[8,9] Li *et al.* reported a spontaneously resolved chiral homometallic cage, unfortunately the absolute structure is not reliable due to an unsatisfactory Flack parameter.[10] Therefore, definitive evidence has not been presented for resolving cubic cages or have they ever been diastereoselectively synthesized.

A cube has four C_3 and three C_4 axes, so the incorporation of C_3 moieties into C_4 units favors the formation of a coordination cubic cage. Previously we have reported a cubic cage assembled from C_3 metalloligands and C_4 symmetric palladium(II) ions.[9a] Nitschke *et al.* have prepared cubic cages by mixing C_4 symmetric tetrakis-amine, 2-formylpyridines and octahedral metals (C_3 symmetric).[9,11] However, these examples are not homochiral. For efficient chirality control, we choose to diastereoselectively synthesize cubic cages with chiral ligands. Herein, we report a facile approach to synthesize homochiral cubic cages with the combination of C_3 and C_4 components. We designed a ligand precursor $\mathbf{L^1}$ consisting of a formylpyridyl and a pyridyl group, which can react with chiral amines to form chiral ditopic ligands containing both bidentate pyridylimine and monodentate pyridine donors. Two enantiomeric chiral ligands are facilely synthesized, which are available for integrating C_3 octahedral metals and C_4 square planar metals in one entity (Scheme 1).

As shown in Scheme 1, the reaction between $\mathbf{L^1}$ and *S*-1-phenylethylamine, a chiral amine widely applied in controlling the absolute configuration,[6e,12] gave a chiral heterotopic ligand $\mathbf{L^2}$. Then $\mathbf{L^2}$ was used *in situ* to ligate zinc(II) and finally palladium(II) ions in a ratio of 24 : 8 : 6. This three-step synthesis afforded a cubic cage $[Zn_8Pd_6(\mathbf{L^2})_{24}(BF_4)_{28}]$ (**1a**) in high yield.



Scheme 1 Synthetic routes of the ligands and the cubic cages.

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† Electronic supplementary information (ESI) available: Synthesis, characterization details and X-ray crystallographic (CIF) data. CCDC 1036634 (**1a**), 1036635 (**1b**), 1036633 (**2**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc00087d

Crystalline **1a** was grown by diffusion of diethylether into an acetonitrile solution of **1a**, which was characterized by NMR, ESI-MS, IR and elemental analysis. Compound **1a** is insoluble in common solvents such as methanol and dichloromethane, but it is highly soluble in acetonitrile. The solution behavior of **1a** was studied in acetonitrile. The sharp and well resolvable ^{1}H (Fig. 1), ^{13}C NMR (Fig. S5, ESI†) signals of **1a** in CD_3CN revealed that the ligands were in an identical magnetically distinct environment, suggesting the cage's high symmetry. Compared with the free ligand, most of the signals were shifted indicating the coordination with metal ions. The full assignment was with the help of 2D COSY and NOESY spectra. In ^{1}H diffusion ordered spectroscopy (DOSY), all the proton signals of **1a** had the same diffusion coefficients, indicating that there was a single species in solution. According to the Stockes–Einstein equation,[13] the dynamic radius of the species was calculated to be about 16 Å, which implies the self-assembly of a large sized cage.[1e,14] The spectrum of the reaction mixture was similar to that prepared from the crystalline product, manifesting that the cage was formed in solution, not in the crystallization process.

Electrospray ionization mass spectrometry (ESI-MS) analysis further confirmed the formation of cage **1a**, as shown in Fig. 2. A series of multi-charge peaks with *m*/*z* values at 962.0, 1078.6, 1224.3, 1411.6 and 1661.4 could be assigned to molecular ions of **1a** from +10 to +6, respectively, which were derived from the loss of corresponding numbers of BF_4^- counterions. The assignment was verified by carefully matching the simulated data with experimental results. For example, the simulated isotopic patterns of $[\mathbf{1a}\text{-}9(BF_4)]^{9+}$ and $[\mathbf{1a}\text{-}8(BF_4)]^{8+}$ perfectly fit those experimental ones (Fig. 2b).

The cage structure was unambiguously revealed by single crystal X-ray structural analysis. **1a** crystallizes in a chiral cubic *P*432 space group. There is only one $\mathbf{L^2}$ ligand in the asymmetric unit with the pyridylimine moiety chelating a zinc(II) cation and terminal pyridine coordinated to a palladium(II) cation. Zn^{II} and Pd^{II} are located at crystallographically special positions. Cage **1a** comprises 6 Pd^{II}, 8 Zn^{II} and 24 $\mathbf{L^2}$ ligands (Fig. 3a). The eight vertices of the cube, each occupied by a C_3-symmetric Zn-tris(pyridylimine) unit with identical Δ chiral configuration, and the six square faces, each capped by a C_4-symmetric square-planar Pd^{II} coordinated to four pyridine units are observed. The arrangement style of the 24 ligands of **1a** with *O* symmetry is analogous to that of the 24 protein subunits in ferritin.[15] All cage molecules in crystal **1a** are of the same handedness. This fact clearly demonstrates the successful diastereoselective synthesis of a chiral cubic cage. The phenyl groups of the stereogenic centers of the imine form face to face π–π interactions with the pyridyl ring of adjacent ligands, with a centroid to centroid distance of 3.64 Å. The distance between two Pd^{II} of two opposite square faces is about 16.18 Å. The longest Zn···Zn distance from diagonal vertices across the cubic center is about 24.42 Å. The diameter of the cube is approximately 33 Å, in accordance with the dynamic radius obtained from DOSY experiments. By switching the amine to its enantiomer *R*-1-phenylethylamine in the preparation (Scheme 1), we obtained $[Zn_8Pd_6(\mathbf{L^3})_{24}(BF_4)_{28}]$ (**1b**). Structural determination confirmed that **1b** and **1a** are a pair of enantiomers (Fig. 3b). The Zn^{II} centers at the eight corners of the cube are in Λ configurations. The Flack factors of both crystals are 0.02(2) for **1a** and 0.035(17) for **1b**, which verify the absolute configuration and enantiopurity. The crystals studied are representative of the entire sample since they showed the same solution behaviors with the bulk sample. Thus the chirality of the cage is dictated by the chiral amine used. In a control experiment, achiral 4-toluidine was used in place of *S*-1-phenylethylamine. Following the synthetic procedure of **1a**, $[Zn_8Pd_6(\mathbf{L^4})_{24}(BF_4)_{28}]$ (**2**) was formed. A yellow block single crystal of **2** was applied in X-ray structural analysis. Compound **2** crystallizes in a centrosymmetric space group $P\bar{3}1c$, and it also has a cubic cage structure with 14 metal centers (Fig. 3d). Each individual cage is chiral with eight corners having either $\Delta\Delta\Delta\Delta\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda$ configurations. However, both enantiomers are present equally giving a racemic mixture in contrast to enantiopure **1a** and **1b**.‡

Eight counterions were enclosed inside each cage as observed in the X-ray crystal structure. The ^{19}F NMR signal of the BF_4^- ions in cage **1a** was shifted compared with free BF_4^- (Fig. S21, ESI†), suggesting rapid exchange of the anions with those inside the cage in solution. However the anion template effect for the cage formation was ruled out, because the same cage structure still formed with the use of counterions of different sizes and geometries (nitrate, trifluoromethanesulfonate, *etc.*) (Fig. S23, ESI†). We think that the binding angles between the donors of the ligand and the coordination preferences of the metals are crucial in the assembly of the cubic cages.

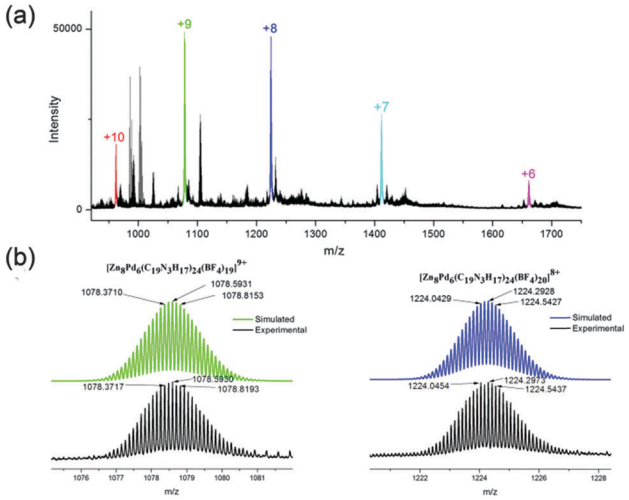

Fig. 2 (a) ESI-MS spectrum of **1a** in MeCN, molecular ion peaks with various multi-charges are shown in different colors. (b) The experimental (bottom trace) and simulated (top trace) isotopic patterns of the molecular ion peaks of $[Zn_8Pd_6(\mathbf{L^2})_{24}(BF_4)_{19}]^{9+}$ (left) and $[Zn_8Pd_6(\mathbf{L^2})_{24}(BF_4)_{20}]^{8+}$ (right).

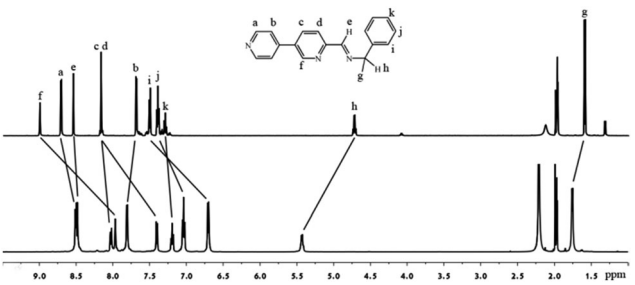

Fig. 1 ^{1}H NMR (500.2 MHz) spectra of the free ligand $\mathbf{L^2}$ (top) and **1a** (bottom) in CD_3CN.

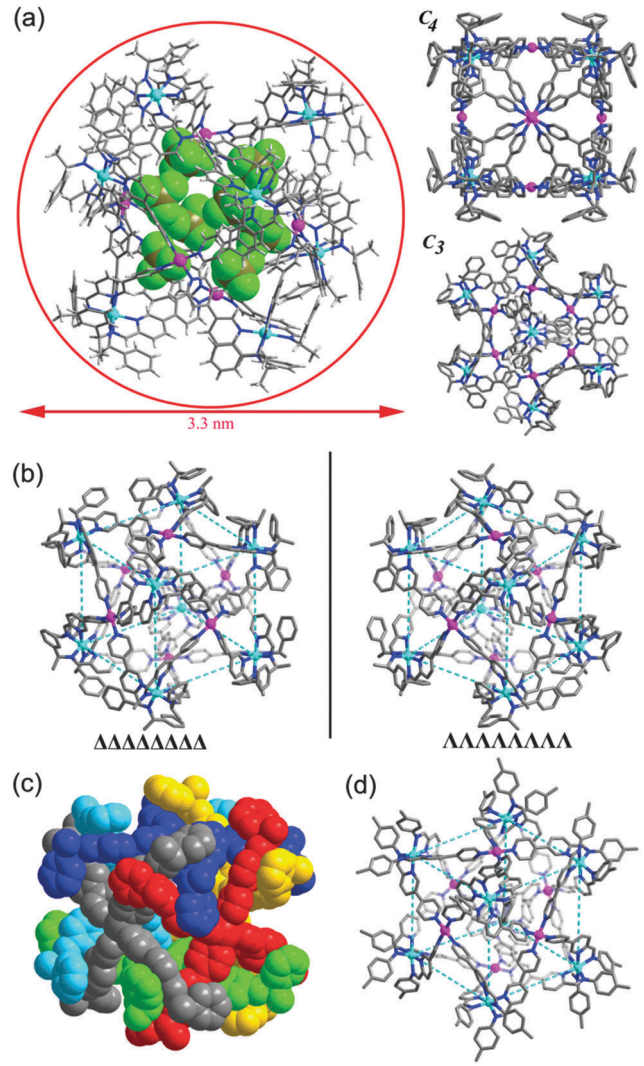

Fig. 3 X-ray crystal structures of the cubic cages: (a) **1a** with eight encapsulated tetrafluoroborate anions in space-filling mode, inset: view from one of the C_4 axes (top) and view from one of the C_3 axes (bottom); (b) $\Delta\Delta\Delta\Delta\Delta\Delta\Delta\Delta$-**1a** (left) and $\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda$-**1b** (right); (c) space-filling mode of **1a** with six faces in different colours; (d) $\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda\Lambda$-**2**. Hydrogen atoms and counter ions are omitted in the inset, (b), (c) and (d). Color legend: purple Pd; cyan Zn; green F; blue N; gray C; dark yellow B; white H.

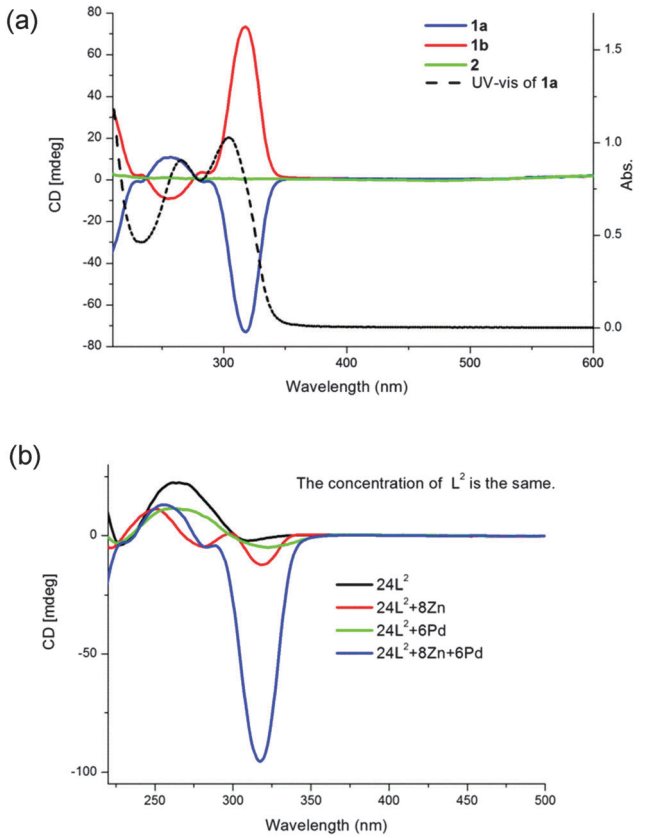

Fig. 4 (a) CD spectra of **1a** (blue line), **1b** (red line), **2** (green line) and the UV-vis spectrum of **2a** (black dashed line) in MeCN. (b) CD spectra of solutions containing: 24 equivalents of $\mathbf{L^2}$ (black); 24 equivalents of $\mathbf{L^2}$ and 8 equivalents of $Zn(BF_4)_2$ (red); 24 equivalents of $\mathbf{L^2}$ and 6 equivalents of $Pd(BF_4)_2$ (green); 24 equivalents of $\mathbf{L^2}$, 8 equivalents of $Zn(BF_4)_2$ and 6 equivalents of $Pd(BF_4)_2$ (blue). The concentration of $\mathbf{L^2}$ is the same (8.7×10^{-5} mol L^{-1}) in all these solutions.

Circular dichroism (CD) spectroscopy was applied to examine the optical properties of the cubic cages (Fig. 4a). **1a** and **1b** in acetonitrile showed perfect mirror image signals, whereas **2** in solution was CD silent. Several solutions of **1a** (or **1b**), each prepared from only one single crystal, have the same profile, in line with bulk samples. This evidence rules out the formation of conglomerates. The CD spectra confirm that **1a** and **1b** are enantiomers and optically active, but **2** is a racemic mixture as found in crystal structures. Absorption bands at around 237–350 nm of **1** was assigned to ligand centered π–π* transitions.[6e,16] Bisignate signals of the CD bands appear at this area, due to exciton coupling.[12b,16] The positive cotton effect at a longer wavelength associated with Δ configuration was in agreement with the chirality at Zn^{II} centers in the crystal structure of **1a** and *vice versa*, a negative cotton effect at a longer wavelength was observed in **1b**.

It is worth noting that the CD signals of **1a** were much more stronger than those of the same amount of free ligand $\mathbf{L^2}$. Simply mixing 24 equivalents of $\mathbf{L^2}$ with 8 equivalents of $Zn(BF_4)_2$ or 6 equivalents of $Pd(BF_4)_2$, respectively, did not improve the signals at all (Fig. 4b). The CD signals become intense only when the cage structure is formed. Such a CD enhancement is related to the fixed configuration after the cage structure is formed. Since **1a** and **1b** are the first examples of homochiral cubic cages, this is the first CD study of a chiral cubic cage structure integrating as much as eight chiral metal centers together.

No cage product **1a** or **1b** could be obtained starting from the racemic ligand indicating the lack of self-sorting of the chiral ligands. And once the cages formed, it is hard for them to exchange ligands. Adding large excess enantiomeric $\mathbf{L^2}$ into **1b** could not invert the characteristic CD signals at around 300–350 nm of the cage, which would invert if all $\mathbf{L^3}$ were exchanged to $\mathbf{L^2}$. Partially exchanging ligands with opposite handedness will lower the symmetry of the cages resulting in a change in the NMR spectrum. Signals of **1b** remained the same, which could be clearly distinguished from signals of free $\mathbf{L^2}$. And no obvious change has been observed in the NMR spectrum of a mixture of **1a** and **1b** after stirring overnight (Fig. S24–S26, ESI†).

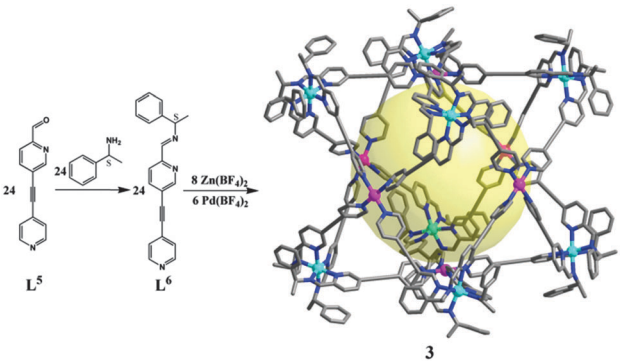

Fig. 5 Synthetic path of **3** with a longer precursor $\mathbf{L^5}$; the large void inside the cube is shown as a yellow ball. Hydrogen atoms and counterions are omitted for clarity. Color legend: purple Pd; cyan Zn; blue N; gray C.

The synthetic strategy can be applied in the preparation of a chiral cubic cage of larger size, with precursor ligand $\mathbf{L^5}$ having a longer backbone (Fig. 5). $\mathbf{L^5}$ was readily transformed into chiral $\mathbf{L^6}$ using *S*-1-phenylethylamine. A larger chiral cube $[Zn_8Pd_6(\mathbf{L^6})_{24}(BF_4)_{28}]$ (**3**) was also obtained similar to the case of **1a**. The formation of **3** has been confirmed by different NMR techniques. ^{1}H NMR of **3** is in a similar pattern to **1a**. And in comparison to **1a**, a smaller diffusion factor for **3** was determined from DOSY experiments, which is indicative of a larger sized **3**. Cage **3** also displays intense CD signals, much higher than the mixtures of $\mathbf{L^6}$ with $Zn(BF_4)_2$ or $Pd(BF_4)_2$, respectively (Fig. S27, ESI†). On the basis of the CD spectrum, **3** also has a *ΔΔΔΔΔΔΔΔ* configuration. Unfortunately, the crystals of **3** are too small for X-ray diffraction, and a molecular model of **3** is shown in Fig. 5 for reference.

In summary, we have successfully synthesized a series of new heterometallic chiral cubic cages by employing a heterotopic precursor ligand bearing a formyl group available for facile condensation with various amines. The structures and solution behavior of the cubic cages have been studied, and CD data confirm that homochiral cubic cages have been isolated. CD enhancement is observed with the formation of the cage structure. We demonstrate that a chiral amine is able to control the handedness of metal centers, leading to the diastereoselective formation of *O* symmetric cubic cages, *i.e.* the chirality of carbon centers of the chiral amine is transferred to the supramolecular entity. We are using this precursor ligand $\mathbf{L^1}$ to generate new ligands of different geometries and functionalities in the construction of various supramolecular coordination cages.

This work was supported by the 973 program (2014CB845603) and the National Natural Science Foundation of China (21125102, 21390390 and 21473139).

Notes and references

‡ (a) Crystal data for **1a:** $C_{456}H_{408}B_{28}F_{112}N_{72}Pd_6Zn_8$, $a = b = c = 25.9101(3)$ Å, $\alpha = \beta = \gamma = 90.00^\circ$, $V = 17394.3(3)$ Å^3, cubic space group *P*432, $Z = 1$, $T = 100(2)$ K, 15 768 reflections measured, 5506 unique ($R_{int} = 0.0661$), final $R_1 = 0.0763$, w$R_2 = 0.2291$ for 3516 observed reflections [$I > 2\sigma(I)$]. Flack factor = 0.02(2). (b) Crystal data for **1b:** $C_{456}H_{408}B_{28}F_{112}N_{72}Pd_6Zn_8$, $a = b = c = 25.9709(3)$ Å, $\alpha = \beta = \gamma = 90.00^\circ$, $V = 17517.1(4)$ Å^3, cubic space group *P*432, $Z = 1$, $T = 100(2)$ K, 16 722 reflections measured, 5830 unique ($R_{int} = 0.0920$), final $R_1 = 0.0736$, w$R_2 = 0.1931$ for 4406 observed reflections [$I > 2\sigma(I)$]. Flack factor = 0.035(17). (c) Crystal data for **2:** $C_{432}H_{360}B_{28}F_{112}N_{72}Pd_6Zn_8$, $a = b = 31.0248(10)$, $c = 42.9572(17)$ Å, $\alpha = \beta = 90.00^\circ$, $\gamma = 120.00^\circ$, $V = 35\,808(2)$ Å^3, trigonal space group $P\bar{3}1c$, $Z = 2$, $T = 100(2)$ K, 84 155 reflections measured, 22 914 unique ($R_{int} = 0.0541$), final $R_1 = 0.0986$, w$R_2 = 0.2846$ for 15 153 observed reflections [$I > 2\sigma(I)$].

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