


# [3+3] Cyclocondensation of Disubstituted Biphenyl Dialdehydes: Access to Inherently Luminescent and Optically Active Hexa-substituted C<sub>3</sub>-Symmetric and Asymmetric Trianglimine Macrocycles

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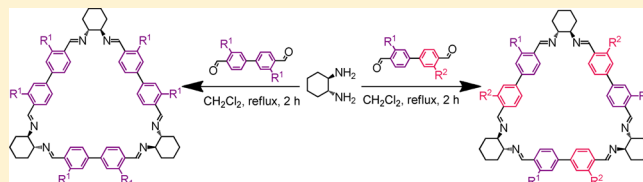
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## Supporting Information

**ABSTRACT:** A general synthetic route to inherently luminescent and optically active 6-fold substituted C<sub>3</sub>-symmetric and asymmetric biphenyl-based trianglimines has been developed. The synthesis of these hexa-substituted triangular macrocycles takes advantage of a convenient method for the synthesis of symmetrically and asymmetrically difunctionalized biphenyl dialdehydes through a convergent two-step aromatic nucleophilic substitution-one-pot Suzuki-coupling reaction protocol. A modular [3+3] diamine-dialdehyde cyclocondensation reaction between both the symmetrically and asymmetrically difunctionalized-4,4'-biphenyldialdehydes with enantiomerically pure (1*R*,2*R*)-1,2-diaminocyclohexane was employed to construct the hexa-substituted triangular macrocycles. B97-D/6-311G(2d,p) density functional theory determined structures and X-ray crystallographic analysis reveal that the six substituents appended to the biphenyl legs of the trianglimine macrocycles adopt an alternating conformation not unlike the 1,3,5-alternate conformation observed for calix[6]arenes. Reduction of the imine bonds using NaBH<sub>4</sub> afforded the corresponding 6-fold substituted trianglimine without the need to alkylate the amine nitrogen atoms which could hinder their later use as metal coordination sites and without having to introduce asymmetric carbons.



## ■ INTRODUCTION

Trianglimine macrocycles have attracted the interest of supramolecular chemists for more than a decade.<sup>1</sup> On account of their highly symmetric structure, and easily tunable cavity size; trianglimines are ideal candidates for building larger stacked and cage-like superstructures<sup>2</sup> with potential applications in molecular recognition. By employing a highly modular [3+3] imine cyclocondensation synthetic approach,<sup>1a</sup> the size of the cavity,<sup>3</sup> the incorporated functional groups,<sup>4</sup> and the electronic properties<sup>5</sup> of trianglimines can be controlled. Moreover, as a result of their chirality, trianglimines have been employed as chiral probes for anion recognition in ion-trap ESI-MS,<sup>6</sup> chiral solvating and shift reagents for NMR spectra,<sup>7</sup> and as chiral ligands for various metal catalysts,<sup>8</sup> such as Cu<sup>9</sup> and Zn.<sup>10</sup> Furthermore, mechanically interlocked trianglimine- $\beta$ -cyclodextrin-[2]-catenanes have also been reported,<sup>11</sup> providing evidence that the trianglimine macrocycle can play a role in constructing more sophisticated molecular architectures.

However, the trianglimine macrocycle as a scaffold upon which to build increasingly complex functional molecular structures and superstructures, has not yet reached its full potential. The prevailing obstacle limiting the utility of

trianglimine chemistry is the lack of synthetic strategies to obtain highly substituted trianglimine macrocycles. With regards to biphenyl-based trianglimines, which are particularly attractive structures owing to their large cavity size<sup>4</sup>, reports of synthetic strategies for obtaining various symmetrically and asymmetrically functionalized biphenyl dialdehyde precursors are much needed but unfortunately sparse. As a result, the ability to precisely tailor the physical and chemical properties of biphenyl-based trianglimines by way of covalent modification is limited. Herein, we report for the first time, a convergent synthetic protocol for the preparation of inherently luminescent symmetrically and asymmetrically hexa-substituted trianglimine macrocycles.

## ■ RESULTS AND DISCUSSION

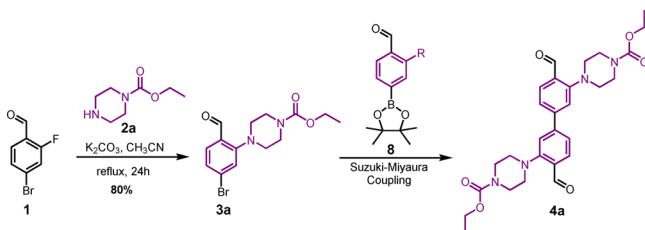
Although a variety of synthetic pathways to trianglimine macrocycles have been developed<sup>12,4</sup> since they were first reported<sup>1a</sup> by Gawroński and co-workers, only a single protocol for the synthesis of trisubstituted trianglimines has been described.<sup>13</sup> Unfortunately, a modified pathway based on this

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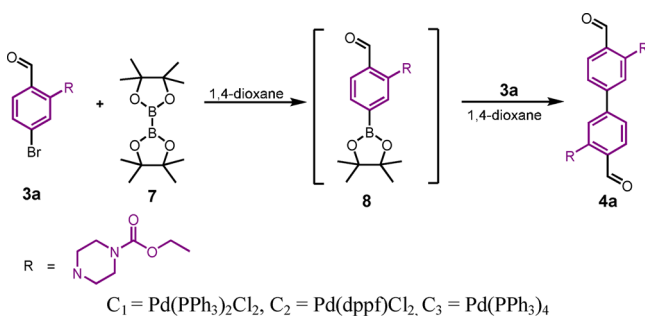
previous work, which was designed to proceed through the nucleophilic aromatic substitution of a 3-fluoro-3'-substituted-[1,1'-biphenyl]-4,4'-dicarbaldehyde, was not successful in affording disubstituted biphenyl dialdehydes. We then turned our attention to intermediate **3a** (Scheme 1) which could be

Scheme 1. Route to Disubstituted Biphenyl Dialdehyde



synthesized in high yield through the nucleophilic aromatic substitution of 4-bromo-2-fluorobenzaldehyde **1** with ethyl piperazine-1-carboxylate **2a**. It was envisioned that intermediate **3a** could then be converted to the corresponding boronic ester **8** and subsequently subjected to a Suzuki-Miyaura coupling (Scheme 1, Table 1) to efficiently synthesize the disubstituted

Table 1. Optimization of the One-Pot Suzuki-Miyaura Conditions<sup>a</sup>

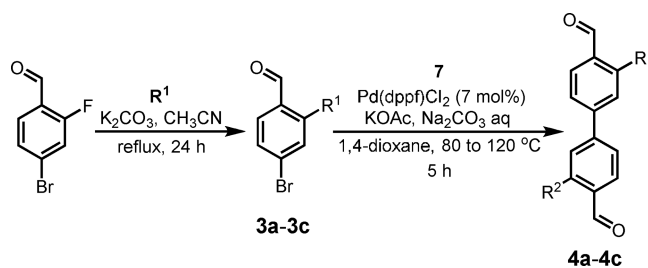


entry	catalyst	base	T(°C)	product <sup>b</sup>
1	C <sub>1</sub>	KOAc	80	<b>8</b>
2	C <sub>1</sub> +C <sub>2</sub>	KOAc	80	<b>8</b>
3	C <sub>1</sub> + C <sub>2</sub> +C <sub>3</sub>	KOAc	80	<b>8</b>
4	C <sub>1</sub> + C <sub>2</sub> +C <sub>3</sub>	KOAc, Na <sub>2</sub> CO <sub>3</sub> aqueous	80 to 120	<b>4a</b> (70%)
5	C <sub>1</sub> +C <sub>3</sub>	KOAc, Na <sub>2</sub> CO <sub>3</sub> aqueous	80 to 120	<b>4a</b> (40%)
6	C <sub>2</sub>	KOAc, Na <sub>2</sub> CO <sub>3</sub> aqueous	80 to 120	<b>4a</b> (86%)

<sup>a</sup>Reaction condition: **3a** (1 mmol), bis(pinacolato)diboron (1.2 mmol), catalyst (7%), KOAc (1.5 mmol), 1,4-dioxane (5 mL), 80 °C, and 3 h; and then Na<sub>2</sub>CO<sub>3</sub> (2 mmol) in 1 mL H<sub>2</sub>O, **3a** (1 mmol), 120 °C, and 2 h. <sup>b</sup>Product: **8** was detected through TLC; **4a** was obtained through chromatography.

biphenyl dialdehyde **4a**. Attempts to synthesize the boronic ester **8** through the borylation of **3a** yielded a product which was found to be unstable on silica gel. Consequently, a more efficacious one-pot Suzuki-Miyaura coupling approach (Table 1) was adopted and optimized which effectively removed the need to isolate and purify **8**. Following the simple addition of a second equivalent of bromide **3a**, the reaction was monitored by thin layer chromatography until all starting material was consumed. Following this strategy, the desired disubstituted biphenyl dialdehydes were obtained in good yield (Table 1, Entry 4). Screening of the palladium catalysts revealed that Pd(dppf)Cl<sub>2</sub> was the best catalyst for the one-pot dialdehyde coupling. Under these optimized conditions, the symmetric

Table 2. Optimized Synthesis of Disubstituted Biphenyl Dialdehydes

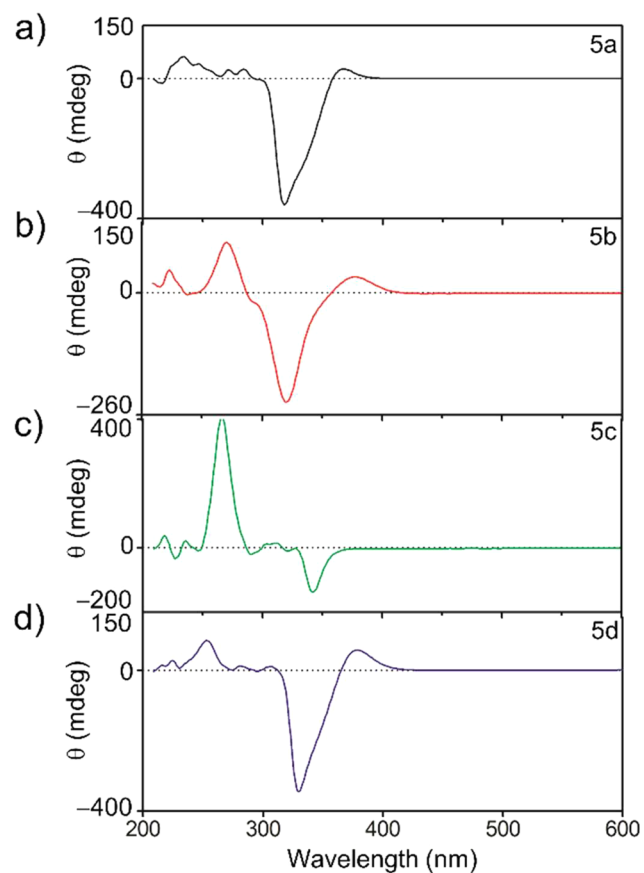
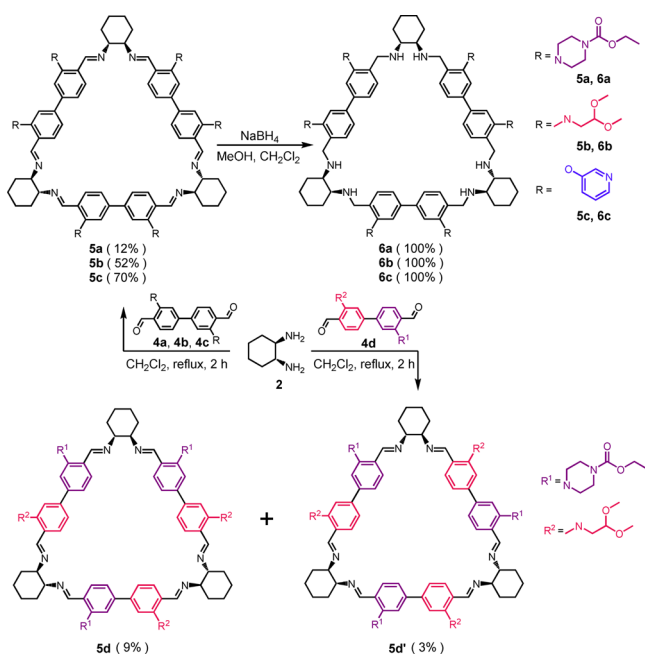


Entry	R <sup>1</sup>	R <sup>2</sup>	Yield for <b>3</b>	Yield for <b>4</b>
1			<b>3a</b> (80%)	<b>4a</b> (87%)
2			<b>3b</b> (91%)	<b>4b</b> (84%)
3			<b>3c</b> (51%)	<b>4c</b> (70%)
4			<b>3a</b> (80%) <b>3b</b> (91%)	<b>4d</b> (84%)

disubstituted biphenyl dialdehydes **4a**, **4b**, and **4c** were synthesized in good yields (Table 2, Entry 1, 2, and 3). As a testament to the usefulness of the one-pot Suzuki-Miyaura coupling approach, the asymmetrically disubstituted dialdehyde **4d** was also prepared in high yield (Table 2, Entry 4), providing the opportunity to construct various asymmetrically disubstituted biphenyl dialdehyde building blocks.

The synthesis of the 6-fold substituted trianglimine macrocycles proceeds through a modular [3+3] diamine-dialdehyde cyclocondensation reaction.<sup>1a</sup> The C<sub>3</sub>-symmetric trianglimines **5a**, **5b**, and **5c** were easily obtained from the reactions of disubstituted diphenyl dialdehydes **4a**, **4b**, and **4c** with (1R, 2R)-1,2-diaminocyclohexane **2** (Scheme 2, top left) in CH<sub>2</sub>Cl<sub>2</sub> at reflux for 2 h. Typically, imine bonds are only stable under anhydrous conditions as they can readily hydrolyze back to the amine and carbonyl precursors. A commonly reported method<sup>14</sup> to circumvent the hydrolysis of trianglimine macrocycles is to reduce the imine bonds in order to generate the more stable trianglimine macrocycle. Therefore, to demonstrate further the usefulness of our protocol, we subjected the trianglimines to hydride reduction. Reduction of the trianglimines **5a**, **5b**, and **5c** using NaBH<sub>4</sub> in a mixture of MeOH and CH<sub>2</sub>Cl<sub>2</sub> led to the formation of hexa-substituted trianglimines **6a**, **6b**, and **6c** in excellent yield and for which no further purification was required (Scheme 2, top right).

Furthermore, we were able to also construct the asymmetric hexa-substituted trianglimine **5d** in a one-pot reaction from the asymmetrically difunctionalized dialdehyde **4d**. The incorporation of the asymmetric dialdehyde building block **4d** into the trianglimine macrocyclic structure leads to two regioisomeric macrocycles, **5d** and **5d'**. Of the two regioisomeric macrocycles, only the asymmetric trianglimine **5d** could be isolated via silica gel chromatography and obtained in 9% yield. However, it was determined by <sup>1</sup>H NMR spectroscopy that the ratio of **5d** to **5d'** is close to 3:1, which is the expected statistical distribution for the random dynamic assembly of the trianglimine components. Therefore, the yield of **5d** was inferred to be roughly 3%.

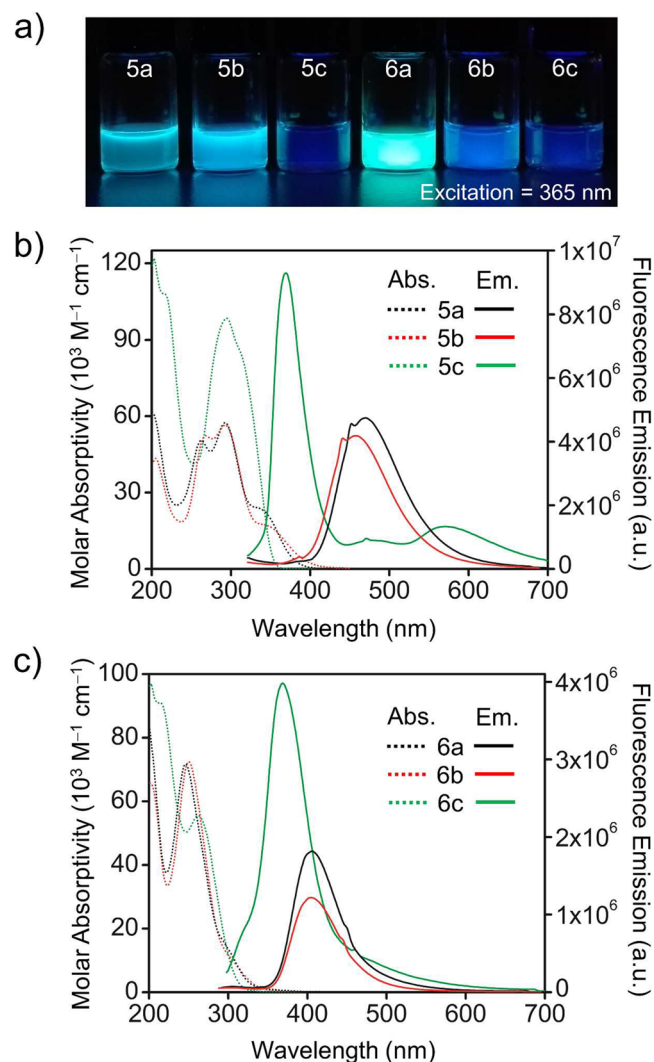
Scheme 2. Synthesis of Hexa-Substituted C<sub>3</sub>-Symmetric and Asymmetric Biphenyl-based Trianglimines

**Figure 1.** (a) Stacked CD spectra of a  $1 \times 10^{-3}$  M solution of **5a** in  $\text{CH}_3\text{CN}$ , (b) of **5b** in  $\text{CH}_3\text{CN}$ , (c) of **5c** in ethanol, and (d) of **5d** in  $\text{CH}_3\text{CN}$ .

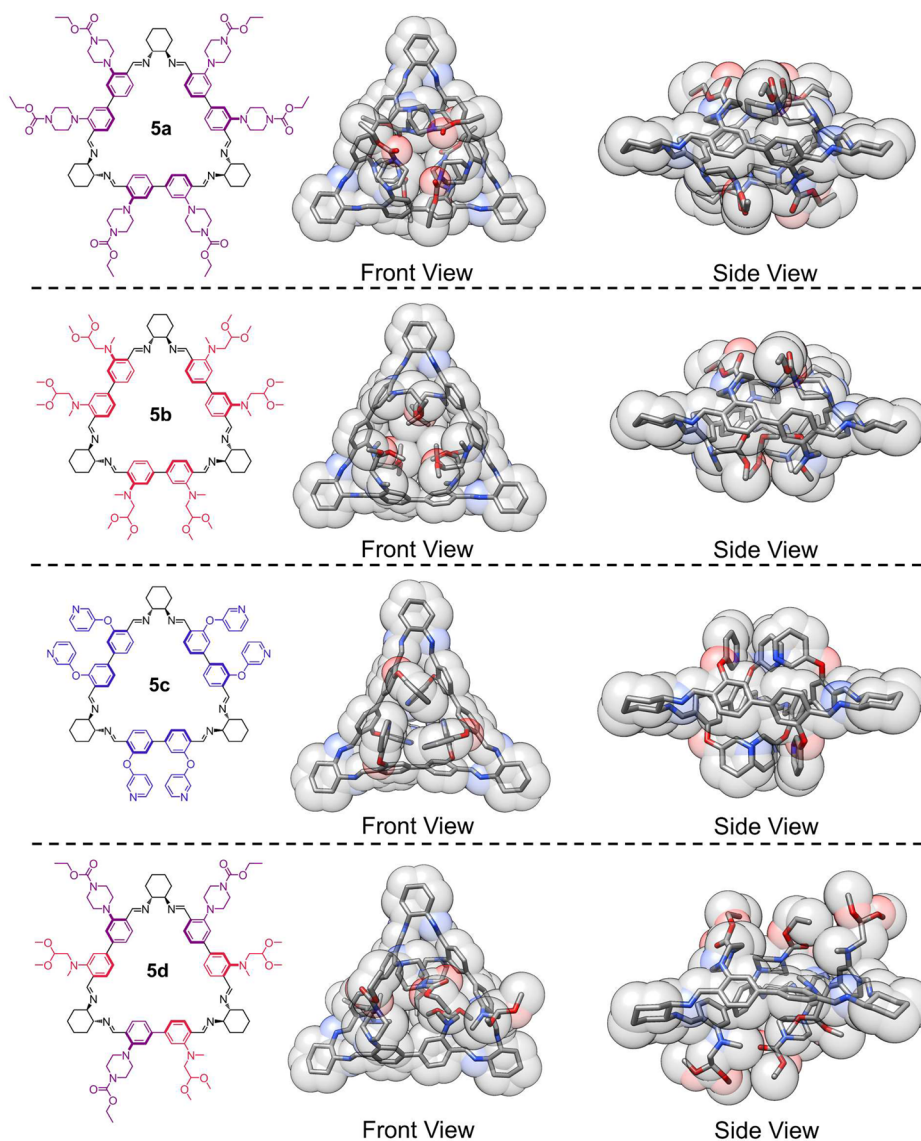
The chiral nature of the trianglimine macrocycles was unambiguously confirmed by circular dichroism (CD) spectroscopy as shown in Figure 1. In accordance with the chirality

of (1*R*,2*R*)-1,2-diaminocyclohexane, which imparts its optical activity onto the macrocyclic trianglimines, the CD spectra (Figure 1a, b, and d) of the all-*R* trianglimines **5a**, **5b**, and **5d** are characterized by a strong negative Cotton effect with a zero intercept at around 318, 311, and 320 nm, respectively. The observed Cotton effects are generated by exciton coupling of the allowed transitions of the neighboring diimine. The strong positive Cotton effect around 257 nm for all-*R* **5c** (Figure 1c) is most likely due to solvent effects.<sup>15</sup>

Upon irradiation with 365 nm light, macrocyclic trianglimines **5a**, **5b**, **5c**, and trianglimines **6a**, **6b**, **6c** were found to exhibit strong fluorescence (Figure 2a). To further characterize the photophysical properties of the triangular macrocycles, UV-vis absorption and steady-state fluorescence spectroscopy measurements were carried out (Figure 2b and c). Fluorescence emission ( $\lambda_{\text{Em}}$ ) bands with maxima centered at 470, 458, and 369 nm were recorded (Figure 2b) for trianglimines **5a** and **5b** in  $\text{CH}_3\text{CN}$ , and **5c** in ethanol, after excitation ( $\lambda_{\text{Exc}}$ ) at 252, 263,



**Figure 2.** (a) Photograph of vials containing solutions of **5a–c** and **6a–c** upon irradiation with 365 nm light. (b) Overlaid UV-vis absorption and fluorescence emission spectra of solutions ( $1 \times 10^{-5}$  M and  $1 \times 10^{-7}$  M respectively) of **5a** and **5b** in  $\text{CH}_3\text{CN}$  and **5c** in ethanol. (c) Overlaid UV-vis absorption and fluorescence emission spectra of solutions ( $1 \times 10^{-5}$  M and  $1 \times 10^{-7}$  M respectively) of **6a** and **6b** in  $\text{CH}_3\text{CN}$  and **6c** in ethanol.



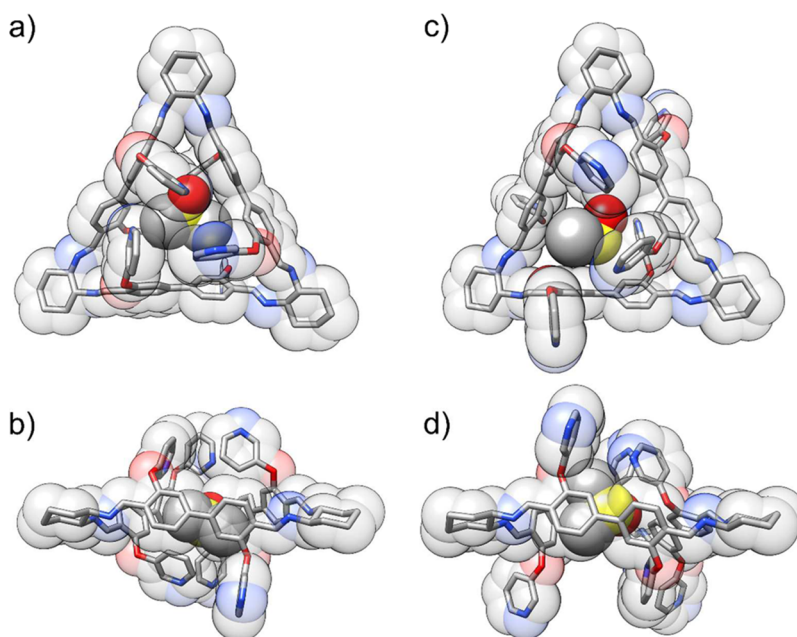
**Figure 3.** Structural formulas and the front and side views of the mixed stick and space filling representations of the B97-D/6-311G(2d,p) optimized structures of trianglimine macrocycles **5a–5d**. Hydrogens have been omitted for clarity.

and 232 nm, respectively. On account of the 6-fold reduction of the imine bonds of trianglimines **5a–c**, which effectively reduces the extent of conjugation in trianglimines **6a–c**, both the UV–vis absorption and fluorescence emission bands for **6a–b** (Figure 2c) are hypsochromically shifted from those observed for **5a–b**. Fluorescence emission ( $\lambda_{Em}$ ) bands with maxima centered at 406, 405, and 369 nm were recorded (Figure 2c) for trianglimines **6a** and **6b** in  $\text{CH}_3\text{CN}$ , and **6c** in ethanol, after excitation ( $\lambda_{Exc}$ ) at 245, 250, and 235 nm, respectively. Sizeable changes in Stokes' shifts were observed for the trianglimines **5a–b** upon reduction to trianglimines **6a–b**. A change in the Stokes' shift of 57 nm was recorded (218 to 161 nm) for **5a** upon reduction to **6a** and of 40 nm (195 to 155 nm) for **5b** upon reduction to **6b**. Only a minor change in the Stokes' shift of 3 nm (137 to 134 nm) was observed<sup>15</sup> for **5c** upon reduction to **6c**.

The molecular structures and geometries of the new trianglimine and trianglimine macrocycles were assigned and fully characterized by using various 2D NMR techniques. For example, the 2D ROESY NMR spectrum of macrocycles **5a–b** showed through space interactions between the protons  $\text{H}_C-$

$\text{H}_D$ ,  $\text{H}_D-\text{H}_I$ ,  $\text{H}_D-\text{H}_H$ ,  $\text{H}_I-\text{H}_H$ ,  $\text{H}_J-\text{H}_K$ ,  $\text{H}_H-\text{H}_K$ ,  $\text{H}_E-\text{H}_F$ ,  $\text{H}_G-\text{H}_E$ , and  $\text{H}_E-\text{H}_D$  (see SI). The through space interactions between  $\text{H}_G$  and  $\text{H}_F$  clearly indicates that the conformation of the six substituents were arranged in an alternating fashion along the triangular structural framework. The presence of these interactions were further supported by subsequent molecular modeling calculations (Figure 3). The structures of the trianglimine macrocycles were optimized at the B97-D<sup>16</sup>/6-311G(2d,p)<sup>17</sup> level of theory. While the alternating substituent conformation in these trianglimines is not unlike the 1,3,5-alternate conformation of calix[6]arenes,<sup>18</sup> the energy barrier for the “through the annulus” ring inversion of their aromatic units is most likely sufficiently low enough to permit conformational switching at room temperature.

Single crystals suitable for X-ray crystallographic analysis were grown from a saturated solution of **5c** in DMSO. The solid-state crystal structure (Figure 4) of **5c** was found to be in agreement with our energy minimized molecular modeling calculations and confirmed that macrocycle **5c** adopts a 1,3,5-alternate-like conformation. The six alternating pyridine substituents of **5c** form a cage-like structure above and below



**Figure 4.** Mixed stick and space filling representations of the solid-state crystal structure of **5c** from the top view (a and c) and the side-on view (b and d), illustrating each of the two trianglimine macrocycles of **5c** which comprise the unit cell. Hydrogen atoms have been omitted for clarity.

the plane of the triangular structural framework (Figure 4b and d) where a single molecule of DMSO (Connolly solvent excluded volume = 66.14 Å<sup>3</sup>) is sterically trapped within the cavity. The interaction energy between DMSO and **5c**, obtained at the  $\omega$ B97<sup>19</sup>/Def2-TZVP<sup>20</sup>//B97-D/6-311G(2d,p) level of theory, is −22.9 kcal/mol (i.e., exothermic). Interestingly, the deformation energy from the optimized structure depicted in Figure 3 (**5c**) to the conformation adopted within the solid-state host–guest superstructure depicted in Figure 4 was computed to be +8.5 kcal/mol at the same level of theory. The calculated host–guest configuration shows a hydrogen bond interaction between DMSO and **5c**, as also supported by the electron density rearrangement upon interaction (see SI, Figure S66). In particular, one sees electron depletion (purple regions, Figure S66) around the hydrogen atom involved in the H-bond, and electron accumulation (green regions) around the nitrogen lone pairs, typical of electronic density rearrangement observed in the formation of H-bonds.<sup>21</sup> It is also worth noting that the X-ray crystal structural unit cell for **5c** is in fact a  $\pi$ -stacked superstructure comprised of two unsymmetrical molecules of **5c** (Figure 4a,b and c,d).

## CONCLUSION

In conclusion, a general route to 6-fold substituted C<sub>3</sub>-symmetric and asymmetric biphenyl-based trianglimines has been developed. Access to this class of luminescent and optically active hexa-substituted triangular macrocycles capitalizes on a convenient method for the synthesis of symmetrically and asymmetrically difunctionalized biphenyl dialdehydes. This route to highly derivatized biphenyl-based trianglimines/trianglimines, enables the incorporation of a wide variety of functional groups into the triangular structural framework. Moreover, these structures can be synthesized without having to introduce additional asymmetric carbons<sup>22</sup> or the need for alkylating the amine nitrogen atoms<sup>23</sup> which could otherwise potentially hinder their later use as metal coordination sites.

The use of hexa-substituted trianglimines derived from this methodology as components in constructing larger extended structures and/or superstructures is currently under investigation in our laboratory. We believe this work will increase the attractiveness for such macrocycles in designing increasingly complex host–guest functional materials with the added benefit of also being inherently luminescent and optically active.

## EXPERIMENTAL SECTION

**Materials and General Methods.** Starting materials, reagents, and solvents were purchased as reagent grade and used without further purification. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 400 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm and calibrated relative to the residual signal of the solvent. The peak patterns are defined as follows: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; dd, doublet of doublets, and td, triplet of doublets. The coupling constants J, are reported in Hertz (Hz). Flash column chromatography was performed over silica gel (200–300 mesh or 300–400 mesh) using a mixture of *n*-hexane and ethyl acetate (EtOAc) as the eluent. TLC plates (Silica gel GF254) were visualized by exposure to ultraviolet light. High-resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectrometer. Melting points were determined with a melting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 °C in vacuum. Compounds **3a** and **3b** were prepared according to literature.<sup>13</sup> Single crystals suitable for X-ray crystallographic analysis were selected and their X-ray diffraction intensity data was collected on a rotating anode diffractometer equipped with a hybrid photon counting detector, using graphite-monochromated Mo K $\alpha$  radiation ( $\lambda$  = 0.71073 Å) at  $T$  = 113 K. UV–vis absorption spectra, fluorescence spectra, infrared absorption spectra, and circular dichroism spectra were measured on the relevant instruments.

**Synthetic Procedures.** *Ethyl 4-(5-Bromo-2-formylphenyl)piperazine-1-carboxylate (3a)*. K<sub>2</sub>CO<sub>3</sub> (8.2 g, 60

mmol) and ethyl *N*-piperazinecarboxylate (4.4 mL, 30 mmol) were added to a stirred solution of 4-bromo-2-fluorobenzaldehyde (4.04 g, 20 mmol) in acetonitrile. The mixture was heated at 100 °C for 40 h. The reaction mixture was then cooled to r.t. and the solvent was removed under vacuum. Water was added to the crude product and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:9 to 3:7) as eluent to provide the desired product as a white yellow solid (5.28 g, 87%). *R*<sub>f</sub> = 0.18 (EtOAc/*n*-hexane = 1:5). mp: 95–96 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 3.05 (t, *J* = 4.8 Hz, 4H), 3.68 (t, *J* = 4.8 Hz, 4H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.23 (d, *J* = 1.6 Hz, 1H), 7.26–7.31 (m, 1H), 7.67 (d, *J* = 8.3 Hz, 1H), 10.24 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 14.8, 43.8, 53.6, 61.8, 122.8, 126.4, 127.5, 130.1, 132.0, 155.5, 155.8, 190.0. IR (KBr): 2856 (w), 1684 (s), 1581(m), 1249 (m), 1191 (w), 988 (w), 937 (w), 821 (w) cm<sup>-1</sup>. The <sup>1</sup>H and <sup>13</sup>C spectra were in accordance with the literature.<sup>13</sup>

**4-Bromo-2-((2, 2-dimethoxyethyl)(methyl) amino) Benzaldehyde (3b).** K<sub>2</sub>CO<sub>3</sub> (8.2 g, 60 mmol) and methylaminoacetaldehyde dimethyl acetal (2.5 mL, 20 mmol) were added to a stirred solution of 4-bromo-2-fluorobenzaldehyde (4.0 g, 20 mmol) in acetonitrile. The mixture was heated at 100 °C for 40 h. The reaction mixture was then cooled to r.t. and the solvent was removed under vacuum. Water was added to the crude product and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:20 to 1:10) as the eluent to provide the desired product as a yellow liquid (5.48g, 91%). *R*<sub>f</sub> = 0.28 (EtOAc/*n*-hexane = 1:5). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 2.97 (s, 3H), 3.29 (d, *J* = 5.4 Hz, 2H), 3.30 (s, 6H), 4.56 (t, *J* = 5.3 Hz, 1H), 7.16 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.26 (s, 1H), 7.60 (d, *J* = 8 Hz, 1H), 10.18 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 43.0, 53.8, 59.2, 102.4, 123.0, 124.8, 126.7, 129.7, 132.1, 156.1, 190.4. IR (KBr): 2833 (w), 1683 (s), 1583 (s), 1190 (m), 1121 (s), 1074 (s), 960 (m), 843 (s) cm<sup>-1</sup>. The <sup>1</sup>H and <sup>13</sup>C spectra were in accordance with the literature.<sup>13</sup>

**4-Bromo-2-(pyridin-3-yloxy) Benzaldehyde (3c).** K<sub>2</sub>CO<sub>3</sub> (1.22 g, 8.9 mmol) and 3-hydroxypyridine (0.5 g, 5.4 mmol) were added to a stirred solution of 4-bromo-2-fluorobenzaldehyde (1.0 g, 4.9 mmol) in dimethylformamide. The mixture was heated at 90 °C for 12 h. The reaction mixture was then cooled to r.t. and the solvent was removed under vacuum. Water was added to the crude product and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:5 to 1:3) as the eluent to provide the desired product as a yellow solid. (0.7 g, 51%). *R*<sub>f</sub> = 0.16 (EtOAc/*n*-hexane = 1:5). mp: 82 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 7.00 (d, *J* = 1.7 Hz, 1H), 7.33–7.45 (m, 3H), 7.81 (d, *J* = 8.3 Hz, 1H), 8.49 (d, *J* = 2.6 Hz, 1H), 8.51 (dd, *J* = 4.5, 1.5 Hz, 1H), 10.44 (d, *J* = 0.7 Hz, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 121.1, 124.8, 125.6, 127.0, 127.6, 130.2, 130.5, 142.2, 146.4, 152.3, 159.5, 187.9. IR (KBr): 2860 (w), 1688 (s), 1587 (s), 1472 (s), 1424 (s), 1388 (s), 1231 (s), 1201 (s), 833 (m), cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd for C<sub>12</sub>H<sub>8</sub>NO<sub>2</sub>Br: 277.9811; found: 277.9810 [M+H]<sup>+</sup>.

**Diethyl-4,4'-(4,4'-diformyl-[1,1'-biphenyl]-3,3'-diyl)bis(piperazine-1-carboxylate) (4a).** 3a (3.4 g, 10 mmol) and bis(pinacolato)diboron (3.0 g, 12 mmol) were dissolved in 50 mL 1,4-dioxane. Argon was then bubbled through the mixture in order to degas the solution for 20 min. Then Pd(dppf)Cl<sub>2</sub> (570 mg, 0.78 mmol) and KOAc (1.47 g, 15 mmol) were added to the mixture. The mixture was stirred at 80 °C until compound 3a was no longer detected by TLC (EtOAc/*n*-hexane = 1:5). Na<sub>2</sub>CO<sub>3</sub> (2.12 g, 20 mmol) and 3a (3.4 g, 10 mmol) were added to the mixture and the solution was heated at 120 °C for 2 h. The solvent was removed under vacuum. Water was added to the crude product and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:5 to 1:1) as the eluent to provide the desired product as a yellow solid (4.5 g, 86%). *R*<sub>f</sub> = 0.40 (EtOAc/*n*-hexane = 1:1). mp: 180–181 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 1.28 (t, *J* = 7.1 Hz, 6H), 3.12 (t, *J* = 4.4 Hz, 8H), 3.1 (t, *J* = 4.4 Hz, 8H), 4.17 (q, *J* = 7.1 Hz, 4H), 7.25 (d, *J* = 1.3 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H), 10.35 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 14.8, 43.9, 53.8, 61.7, 118.2, 122.2, 128.4, 131.3, 146.7, 155.55, 155.64, 190.5. IR (KBr): 1700 (s), 1596 (s), 1432 (s), 1244 (s), 1122 (m), 989 (w), 922 (w), 828 (w) cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd for C<sub>28</sub>H<sub>34</sub>N<sub>4</sub>O<sub>6</sub>: 545.2371; found: 545.2378 [M+Na]<sup>+</sup>.

**3,3'-Bis((2, 2-dimethoxyethyl)(methyl) amino)-[1, 1'-biphenyl]-4,4'-dicarbaldehyde (4b).** 3b (3.00 g, 10 mmol) and bis(pinacolato)diboron (3.00 g, 12 mmol) were dissolved in 50 mL 1,4-dioxane. Argon was bubbled through the mixture in order to degas the solution for 20 min. Then Pd(dppf)Cl<sub>2</sub> (570 mg, 0.78 mmol) and KOAc (1.47 g, 15 mmol) were added to the mixture. The mixture was stirred at 80 °C until compound 3b was no longer detected by TLC (EtOAc/*n*-hexane = 1:5). Na<sub>2</sub>CO<sub>3</sub> (2.12 g, 20 mmol) and 3b (3.4 g, 10 mmol) were added to the mixture and the solution was heated at 120 °C for 2 h. The solvent was then removed under vacuum. Water was added to the crude product and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:5 to 1:1) as the eluent to provide the desired product as a yellow solid (4.3 g, 81%). *R*<sub>f</sub> = 0.33 (EtOAc/*n*-hexane = 1:5). mp: 80–82 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 3.05 (s, 6H), 3.33 (s, 12H), 3.36 (d, *J* = 5.2 Hz, 4H), 4.61 (t, *J* = 5.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.32 (s, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 10.31 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 43.6, 53.8, 59.2, 102.7, 118.8, 120.8, 127.8, 131.2, 146.5, 155.9, 191.0. IR (KBr): 2839 (w), 1688 (s), 1598 (s), 1548 (m), 1482 (m), 1418 (m), 1082 (m), 842 (w), 821 (w) cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>: 467.2153; found: 467.2157 [M+Na]<sup>+</sup>.

**3-(Pyridin-3-ylmethyl)-3'-(pyridin-3-yloxy)-[1,1'-biphenyl]-4,4'-dicarbaldehyde (4c).** 3c (200 mg, 0.72 mmol) and bis(pinacolato)diboron (219 mg, 0.86 mmol) were dissolved in 4 mL dimethylformamide. Argon was bubbled through the mixture in order to degas the solution for 20 min. Then Pd(dppf)Cl<sub>2</sub> (40 mg, 0.05 mmol) and KOAc (106 mg, 1.1 mmol) were added to the mixture. The mixture was stirred at 80 °C until compound 3c was no longer detected by TLC (20% EtOAc in *n*-hexane). Na<sub>2</sub>CO<sub>3</sub> (116 mg, 1.1 mmol) and 3c (3.0 g, 10 mmol) were added to the mixture and the solution

was heated at 120 °C for 2 h. Then the solvent was removed under vacuum. Water was added to the crude product and the aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:3 to 2:1) as the eluent to provide the desired product as a white solid (200 mg, 70%). *R*<sub>f</sub> = 0.15 (EtOAc/*n*-hexane = 1:1). mp: 181–182 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 7.00 (s, 2H), 7.32–7.42 (m, 6H), 8.01 (d, *J* = 8.1 Hz, 2H), 8.48 (s, 4H), 10.48 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 117.2, 123.2, 124.6, 126.3, 126.9, 129.9, 141.7, 145.9, 146.6, 153.0, 159.3, 188.1. IR (KBr): 1686 (s), 1603 (s), 1554 (s), 1473 (s), 1425 (s), 1390 (s), 1226 (s), 825 (s) cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd for C<sub>24</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub>: 397.1188; found: 397.1183 [M+H]<sup>+</sup>.

**Ethyl-4-(3'-((2,2-dimethoxyethyl)(methyl) amino)-4,4'-diformyl-[1,1'-biphenyl]-3-yl) piperazine-1-carboxylate (4d).** **3a** (3.40 g, 10 mmol) and bis(pinacolato)diboron (2.79 g, 11 mmol) were dissolved in 50 mL 1,4-dioxane. Argon was bubbled through the mixture in order to degas the solution for 20 min. Then Pd(dppf)Cl<sub>2</sub> (570 mg, 0.78 mmol) and KOAc (1.47 g, 15 mmol) were added to the mixture. The mixture was stirred at 80 °C until compound **3a** was no longer detected by TLC (20% EtOAc in *n*-hexane). Na<sub>2</sub>CO<sub>3</sub> (2.12 g, 20 mmol) and **3b** (3.0 g, 10 mmol) were added to the mixture and the solution was heated at 120 °C for 2 h. Then the solvent was removed under vacuum. Water was added to the crude product and the aqueous was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried with Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum. The residue was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane (from 1:5 to 1:1) as the eluent to provide the desired product as a yellow liquid (4.25 g, 88%). *R*<sub>f</sub> = 0.40 (EtOAc/*n*-hexane = 1:5). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 1.26 (td, *J* = 0.9, 7.1 Hz, 3H), 3.03 (s, 3H), 3.10 (s, 4H), 3.30 (d, *J* = 1.0 Hz, 6H), 3.34 (d, *J* = 5.1 Hz, 2H), 3.69 (s, 4H), 4.14 (tt, *J* = 3.5, 7.1 Hz, 2H), 4.60 (t, *J* = 5.1 Hz, 1H), 7.21–7.25 (m, 2H), 7.29 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 1.1, 8.0 Hz, 1H), 7.87 (dd, *J* = 1.1, 8.0 Hz, 1H), 10.28 (s, 1H), 10.33 (s, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 14.7, 24.9, 43.4, 43.8, 53.7, 59.1, 61.6, 102.5, 118.1, 118.7, 120.7, 122.1, 127.7, 128.2, 131.1, 131.2, 146.1, 147.0, 155.48, 155.54, 155.9, 190.5, 190.9. IR (KBr): 2833 (w), 1683 (s), 1596 (s), 1430 (m), 1396 (m), 1288 (m), 1123 (m), 832 (m) cm<sup>-1</sup>. HRMS (ESI): *m/z* calcd for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>6</sub>: 506.2262; found: 506.2264 [M+Na]<sup>+</sup>.

**Trianglimine (5a).** (1*R*,2*R*)-1, 2-Diaminocyclohexane (360 mg, 3.15 mmol) in anhydrous dichloromethane (25 mL) was added to a solution of **4a** (1100 mg, 2.1 mmol) in 25 mL of anhydrous dichloromethane. The mixture was stirred at 50 °C for 2 h. The solvent was then removed under vacuum. The crude mixture was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane/trimethylamine (from 3:7:0.5 to 4:6:0.5) as the eluent to provide the desired product as a yellow solid (200 mg, 16%). *R*<sub>f</sub> = 0.33 (EtOAc/*n*-hexane/trimethylamine = 10:10:1). mp: 203–204 °C. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz, 25 °C): δ = 1.17 (t, *J* = 7.1 Hz, 4H), 1.41–1.53 (m, 6H), 1.70–2.14 (m, 18H), 2.20–2.70 (m, 24H), 3.20–3.80 (m, 30H), 4.05–4.25 (m, 12H), 6.99 (s, 6H), 7.24 (d, *J* = 8.1 Hz, 6H), 8.27 (d, *J* = 8.0 Hz, 6H), 8.77 (s, 6H). <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz, 25 °C): δ = 15.0, 25.0, 33.4, 44.2, 52.2, 53.6, 61.4, 76.3, 119.1, 122.4, 128.6, 129.5, 144.2, 153.6, 155.2, 157.7. IR (KBr): 2926 (m), 1701 (s), 1598 (m), 1430

(m), 1243 (s), 1118 (m), 1081 (m), 803 (s) cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>102</sub>H<sub>132</sub>N<sub>18</sub>O<sub>12</sub>: 902.0226; found 902.0233 [M+2H]<sup>2+</sup>.

**Trianglimine (5b).** (1*R*,2*R*)-1, 2-Diaminocyclohexane (155 mg, 1.36 mmol) in anhydrous dichloromethane (10 mL) was added to a solution of **4b** (500 mg, 1.2 mmol) in 10 mL anhydrous dichloromethane. The mixture was stirred at 50 °C for 2 h. The solvent was then removed under vacuum. The crude mixture was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane/trimethylamine (3:7:0.5 to 6:4:1) as the eluent to provide the desired product as a yellow solid (310 mg, 52%). *R*<sub>f</sub> = 0.23 (EtOAc/*n*-hexane/trimethylamine = 10:10:1). mp: 101–102 °C. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz, 25 °C): δ = 1.42 (t, *J* = 9.4 Hz, 6H), 1.64–2.13 (m, 18H), 2.60 (s, 18H), 2.92–3.26 (m, 48H), 3.69–3.77 (m, 6H), 4.47 (t, *J* = 4.5 Hz, 6H), 7.18–7.28 (m, 12H), 8.33 (d, *J* = 8.0 Hz, 6H), 9.03 (s, 6H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz, 25 °C): δ = 25.1, 33.7, 44.0, 53.0, 53.1, 58.5, 75.9, 103.0, 119.5, 121.7, 129.2, 130.3, 143.2, 154.1, 158.4. IR (KBr): 2926 (m), 1633 (w), 1599 (w), 1453 (w), 1392 (w), 1261 (s), 1099 (s), 1026 (s), 804 (s) cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>90</sub>H<sub>126</sub>N<sub>12</sub>O<sub>12</sub>: 523.3279; found 523.3279 [M+3H]<sup>3+</sup>.

**Trianglimine (5c).** (1*R*,2*R*)-1, 2-Diaminocyclohexane (1.26 g, 9.0 mmol) in anhydrous dichloromethane (75 mL) was added to a solution of **4c** (2.45 g, 6.0 mmol) in 75 mL of anhydrous dichloromethane. The mixture was stirred at 50 °C for 2 h. The solvent was then removed under vacuum. The crude mixture was purified by recrystallization from dichloromethane and cyclohexane to provide the desired product as a white solid (2.0 g, 70%). *R*<sub>f</sub> = 0.17 (EtOAc/*n*-hexane/trimethylamine = 2:1:1). mp: 205 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz, 25 °C): δ = 1.41 (s, 6H), 1.70–1.85 (m, 18H), 3.25–3.35 (m, 6H), 7.00–7.09 (m, 18H), 7.12 (d, *J* = 8.3 Hz, 6H), 7.82 (d, *J* = 8.2 Hz, 6H), 8.10 (d, *J* = 4.3 Hz, 6H), 8.19 (d, *J* = 2.1 Hz, 6H), 8.44 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz, 25 °C): δ = 24.4, 32.6, 74.4, 117.9, 123.3, 124.2, 124.7, 127.4, 128.4, 140.6, 142.9, 144.4, 154.2, 155.40, 155.43. IR (KBr): 2927 (w), 2854 (w), 1638 (w), 1476 (w), 1423 (w), 1390 (w), 1229 (s), 821 (w) cm<sup>-1</sup>. HRMS (ESI) *m/z* calcd for C<sub>90</sub>H<sub>78</sub>N<sub>12</sub>O<sub>6</sub>: 475.2128; found 475.2132 [M+3H]<sup>3+</sup>.

**Trianglimine (5d).** (1*R*,2*R*)-1, 2-Diaminocyclohexane (360 mg, 3.15 mmol) in anhydrous dichloromethane (25 mL) was added to a solution of **4d** (1000 mg, 2.07 mmol) in 25 mL of anhydrous dichloromethane. The mixture was stirred at 50 °C for 4 h. The solvent was then removed under vacuum. The crude mixture was purified by column chromatography on silica gel (200–300 mesh) using gradient EtOAc/*n*-hexane/trimethylamine (from 3:7:0.5 to 4:6:0.5) as the eluent to provide the desired product as a yellow solid (100 mg, 9%). *R*<sub>f</sub> = 0.12 (EtOAc/*n*-hexane/trimethylamine = 3:7:0.5). mp: 198 °C. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz, 25 °C): δ = 1.11–1.21 (m, 9H), 1.35–1.50 (m, 6H), 1.62–1.80 (s, 6H), 1.82–2.42 (m, 24H), 2.65 (s, 1H), 2.79 (s, 1H), 2.88 (s, 1H), 3.06–3.90 (m, 42H), 4.12–4.28 (m, 6H), 4.50 (t, *J* = 5.2 Hz, 1H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.59 (t, *J* = 5.2 Hz, 1H), 6.65 (d, *J* = 5.8 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 2H), 7.19 (s, 2H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.69 (s, 1H), 8.17–8.28 (m, 3H), 8.32–8.42 (m, 3H), 8.61 (s, 1H), 8.65 (s, 1H), 8.79 (s, 1H), 9.07 (s, 2H), 9.17 (s, 1H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>, 100 MHz, 25 °C): δ = 14.96, 15.00, 25.0, 25.1, 33.1, 33.5, 33.7, 33.78, 33.83, 43.6, 43.7, 44.2, 44.3, 52.8, 53.0, 53.06, 53.10, 53.16, 53.24, 58.8, 59.0, 59.3, 61.3, 61.4, 61.5, 75.6, 75.9, 76.0, 76.27, 76.31, 76.5, 103.2, 103.3, 103.4, 118.7, 119.1, 120.0, 121.1, 121.7, 121.9,

122.1, 122.2, 122.3, 122.4, 128.6, 128.7, 128.9, 129.1, 129.3, 129.4, 129.7, 130.4, 130.6, 143.0, 143.3, 143.4, 143.9, 144.3, 144.5, 153.0, 153.2, 153.3, 153.9, 154.4, 154.8, 155.2, 155.26, 155.31, 157.7, 157.99, 158.04, 158.4. mp: 198 °C. IR (KBr): 2928 (m), 1701 (s), 1633 (m), 1432 (m), 1390 (m), 1243 (m), 1123 (m), 937 (m), 825 (m)  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{96}\text{H}_{129}\text{N}_{15}\text{O}_{12}$ : 843.5062; found 843.5062  $[\text{M}+2\text{H}]^{2+}$ .

**Trianglamine (6a).**  $\text{NaBH}_4$  (14 mg, 0.39 mmol) was added to a solution of trianglamine **5a** (100 mg, 0.055 mmol) in the mixture of  $\text{CH}_2\text{Cl}_2$  and MeOH (10 mL). The mixture was stirred at r.t. for 2 h. The solvent was then removed under vacuum. Water was added to the crude product and the aqueous was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum to give the pure product as a white solid (100 mg, 100%). mp: 155 °C.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz, 25 °C): 1.05 (t,  $J = 7.1$  Hz, 24H), 1.15–1.30 (m, 6H), 1.71 (d,  $J = 7.2$  Hz, 6H), 1.99 (s, 6H), 2.20–2.35 (d,  $J = 8.5$  Hz, 12H), 2.81 (td,  $J = 11.5, 6.1$  Hz, 24H), 3.34–3.71 (m, 30H), 4.01–4.18 (m, 18H), 7.29 (s, 6H), 7.34 (d,  $J = 7.9$  Hz, 6H), 7.44 (d,  $J = 7.9$  Hz, 6H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 100 MHz, 25 °C):  $\delta = 14.9, 25.6, 31.9, 44.6, 47.3, 52.8, 61.3, 62.4, 119.4, 123.3, 131.1, 135.2, 141.6, 152.4, 155.4$ . IR (KBr): 2927 (m), 1701 (s), 1603 (w), 1431 (s), 1386 (m), 1244 (s), 1219 (m), 1122 (m), 990 (w)  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{102}\text{H}_{144}\text{N}_{18}\text{O}_{12}$ : 605.7154; found 605.7152  $[\text{M}+3\text{H}]^{3+}$ .

**Trianglamine (6b).**  $\text{NaBH}_4$  (17 mg, 0.44 mmol) was added to a solution of trianglamine **5b** (100 mg, 0.063 mmol) in the mixture of  $\text{CH}_2\text{Cl}_2$  and MeOH (10 mL). The mixture was stirred at r.t. for 2 h. The solvent was then removed under vacuum. Water was added to the crude product and the aqueous was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum to give the pure product as a white solid (100 mg, 100%). mp: 51 °C.  $^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 400 MHz, 25 °C): 1.10–1.30 (m, 12H), 1.70 (d,  $J = 6.4$  Hz, 6H), 2.25 (s, 6H), 2.34 (d,  $J = 11.0$  Hz, 6H), 2.44 (d,  $J = 7.6$  Hz, 6H), 2.73 (s, 18H), 3.11 (s, 36H), 3.33–3.19 (m, 12H), 3.87 (d,  $J = 12.6$  Hz, 6H), 4.24 (d,  $J = 12.8$  Hz, 6H), 4.54 (t,  $J = 5.1$  Hz, 6H), 7.35 (d,  $J = 7.8$  Hz, 6H), 7.52 (s, 6H), 7.60 (d,  $J = 7.8$  Hz, 6H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 100 MHz, 25 °C):  $\delta = 25.7, 31.8, 43.9, 47.2, 52.78, 52.81, 58.3, 62.1, 103.0, 120.3, 122.9, 130.9, 135.8, 141.2, 152.7$ . IR (KBr): 2928 (s), 1603 (w), 1555 (w), 1450 (s), 1124 (s), 1071 (s), 971 (m), 816 (m)  $\text{cm}^{-1}$ . HRMS (ESI)  $m/z$  calcd for  $\text{C}_{90}\text{H}_{138}\text{N}_{12}\text{O}_{12}$ : 527.3592; found 527.3592  $[\text{M}+3\text{H}]^{3+}$ .

**Trianglamine (6c).**  $\text{NaBH}_4$  (9 mg, 0.24 mmol) was added to a solution of trianglamine **5c** (50 mg, 0.035 mmol) in the mixture of  $\text{CH}_2\text{Cl}_2$  and MeOH (8 mL). The mixture was stirred at r.t. for 2 h. The solvent was then removed under vacuum. Water was added to the crude product and the aqueous was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$  and evaporated under vacuum to give the pure product as a white solid (50 mg, 100%). mp: 99 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, 25 °C): 0.96 (d,  $J = 7.8$  Hz, 6H), 1.18 (t,  $J = 9.9$  Hz, 6H), 1.69 (d,  $J = 7.8$  Hz, 6H), 2.00 (s, 6H), 2.14 (d,  $J = 12.4$  Hz, 6H), 2.19–2.24 (m, 6H), 3.65 (d,  $J = 13.5$  Hz, 6H), 3.93 (d,  $J = 13.5$  Hz, 6H), 7.06 (d,  $J = 1.6$  Hz, 6H), 7.13–7.15 (m, 12H), 7.35 (dd,  $J = 7.9, 1.6$  Hz, 6H), 7.52 (d,  $J = 7.9$  Hz, 1H), 8.25–8.28 (m, 6H), 8.34 (t,  $J = 1.4$  Hz, 6H).  $^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 100 MHz, 25 °C):  $\delta = 25.0, 31.4, 45.2, 61.1, 117.9, 123.3, 124.16, 124.23, 130.9, 131.9, 140.5, 140.6, 144.1, 154.1, 154.2$ . IR (KBr): 3428 (s), 2925 (m), 2853 (w), 1614 (w), 1556 (w), 1475 (m), 1423 (m), 1387 (w), 1225 (s), 1102

(w), 1120 (w), 882 (w), 803 (w), 731 (w), 705 (w)  $\text{cm}^{-1}$ ; IR (KBr): 3428 (s), 2925 (m), 1475 (s), 1387 (w), 1226 (s), 1102 (m), 803 (m), 705 (m)  $\text{cm}^{-1}$ ; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{90}\text{H}_{90}\text{N}_{12}\text{O}_6$ : 479.2447; found 479.2445  $[\text{M}+3\text{H}]^{3+}$ .

**Computational Details.** The structural and energetic analysis of the molecular systems described in this study were carried out using both the Gaussian09<sup>24</sup> and GAMESS 2014R1 software.<sup>25</sup> Geometries were optimized with the former software in both gas and solution phase with DFT<sup>26</sup> at the B97-D<sup>16</sup>/6-311G(2d,p)<sup>17</sup> level of theory. Full geometry optimizations were performed in their corresponding symmetry point group representations,  $D_3$  for **5a**, **5b**, and **5c** and  $C_3$  for **5d**. An ultra fine integration grid of 99 radial shells and 590 angular points per shell was selected. Stationary points were determined when the maximum gradient convergence tolerance and the root-mean-square gradient were below 0.00045 hartree/Bohr and 0.00030 hartree/Bohr, respectively. Effects of solvent employed the C-PCM method in combination with the Klamt radii.<sup>27</sup> For more accurate energetics, the interaction energy between **5c** and the encapsulated DMSO molecule was computed at the  $\omega\text{B97}^{19}/\text{Def2-TZVP}^{20}/\text{B97-D}/6-311\text{G}(2\text{d,p})$  level of theory, using the GAMESS 2014R1 open source software. A larger number of radial points in the Euler-MacLaurin quadrature and a finer Lebedev grid<sup>28</sup> than the army-grade grid were used ( $n_{\text{rad}} = 155$  and  $n_{\text{leb}} = 1202$ , respectively). The SCF density convergence criterion was lowered to  $2.5 \times 10^{-07}$  and the integral cutoff was lowered to  $10^{-11}$ . The rationale for using the hybrid long-range corrected  $\omega\text{B97}$  functional resulted from an exhaustive performance study on a broad set of noncovalent interacting systems.

In the discussions of the electronic rearrangement upon complexation, the total electronic density change caused by the interaction between host and guest is considered and is defined as

$$\Delta\rho = \rho_{\text{comp}} - \rho_{\text{host}} - \rho_{\text{guest}} \quad (1)$$

where  $\rho_{\text{comp}}$  is the electronic density of the host–guest complex and  $\rho_{\text{host}}$  and  $\rho_{\text{guest}}$  are the electron densities of the subunits forming the host–guest complex in exactly the configuration adopted in the relaxed host–guest complex. Within this definition, a positive value indicates electron accumulation and a negative value indicates electron deletion.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02868.

$^1\text{H}$ ,  $^{13}\text{C}$ , HMQC, HSQC, HMBC, ROESY NMR and mass spectra for all new substrates and products (PDF) Single crystal X-ray diffraction data for compound **5c** (CIF)

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### Notes

The authors declare no competing financial interest.



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## REFERENCES

- (1) (a) Gawroński, J.; Kolbon, H.; Kwit, M.; Katrusiak, A. *J. Org. Chem.* **2000**, *65*, 5768–5773. (b) Kwit, M.; Skowronek, P.; Kolbon, H.; Gawroński, J. *Chirality* **2005**, *17*, S93–S100. (c) Srimurugan, S.; Suresh, P.; Babu, B.; Pati, H. N. *Mini-Rev. Org. Chem.* **2008**, *5*, 228–242. (d) Alfonso, I. *Curr. Org. Synth.* **2010**, *7*, 1–23.
- (2) Kuhnert, N.; Burzlaff, N.; Patel, C.; Lopez-Periago, A. *Org. Biomol. Chem.* **2005**, *3*, 1911–1921.
- (3) (a) Kuhnert, N.; Rossignolo, G. M.; Lopez-Periago, A. *Org. Biomol. Chem.* **2003**, *1*, 1157–1170. (b) Akine, S.; Hashimoto, D.; Saiki, T.; Nabeshima, T. *Tetrahedron Lett.* **2004**, *45*, 4225–4227. (c) Kuhnert, N.; Patel, C.; Jami, F. *Tetrahedron Lett.* **2005**, *46*, 7575–7579. (d) Kuhnert, N.; Lopez-Periago, A.; Rossignolo, G. M. *Org. Biomol. Chem.* **2005**, *3*, 524–537.
- (4) Korupoju, S. R.; Mangayarkarasi, N.; Ameerunisha, S.; Valente, E. J.; Zacharias, P. S. *J. Chem. Soc., Dalton Trans.* **2000**, 2845–2852.
- (5) Kuhnert, N.; Marsh, D.; Nicolau, D. C. *Tetrahedron: Asymmetry* **2007**, *18*, 1648–1654.
- (6) (a) Gualandi, A.; Grilli, S.; Savoia, D.; Kwit, M.; Gawroński, J. *Org. Biomol. Chem.* **2011**, *9*, 4234–4241. (b) Tanaka, K.; Fukuda, N.; Fujiwara, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2657–2661.
- (7) (a) Fitzsimmons, P. M.; Jackels, S. C. *Inorg. Chim. Acta* **1996**, *246*, 301–310. (b) Li, Z.; Jablonski, C. *Chem. Commun.* **1999**, *16*, 1531–1532. (c) Kim, G.-J.; Park, D.-W.; Tak, Y.-S. *Catal. Lett.* **2000**, *65*, 127–133. (d) Gregoliński, J.; Lisowski, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6122–6126. (e) Gregoliński, J.; Ślepokura, K.; Lisowski, J. *Inorg. Chem.* **2007**, *46*, 7923–7934. (f) Kwit, M.; Zabicka, B.; Gawronski, J. *Dalton Trans.* **2009**, *32*, 6783–6789.
- (8) Tanaka, K.; Hachiken, S. *Tetrahedron Lett.* **2008**, *49*, 2533–2536.
- (9) (a) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2795–2800. (b) Gao, J.; Martell, A. E. *Org. Biomol. Chem.* **2003**, *1*, 2801–2806. (c) Gao, J.; Zingaro, R. A.; Reibenspies, J. H.; Martell, A. E. *Org. Lett.* **2004**, *6*, 2453–2455. (d) Gajewy, J.; Kwit, M.; Gawroński, J. *Adv. Synth. Catal.* **2009**, *351*, 1055–1063. (e) Gajewy, J.; Gawronski, J.; Kwit, M. *Org. Biomol. Chem.* **2011**, *9*, 3863–3870. (f) Gajewy, J.; Gawronski, J.; Kwit, M. *Monatsh. Chem.* **2012**, *143*, 1045–1054.
- (10) (a) Gallant, A. J.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5307–5310. (b) Ma, C.; Lo, A.; Abdolmaleki, A.; MacLachlan, M. J. *Org. Lett.* **2004**, *6*, 3841–3844. (c) Gallant, A. J.; Patrick, B. O.; MacLachlan, M. J. *J. Org. Chem.* **2004**, *69*, 8739–8744. (d) Ma, C. T. L.; MacLachlan, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 4178–4182. (e) Gallant, A. J.; Hui, J. K. -H.; Zahariev, F. E.; Wang, Y. A.; MacLachlan, M. J. *J. Org. Chem.* **2005**, *70*, 7936–7946. (f) Gallant, A. J.; Yun, M.; Sauer, M.; Yeung, C. S.; MacLachlan, M. J. *Org. Lett.* **2005**, *7*, 4827–4830. (g) Hui, J. K. -H.; MacLachlan, M. J. *Chem. Commun.* **2006**, 2480–2482. (h) Gallant, A. J.; Chong, J. H.; MacLachlan, M. J. *Inorg. Chem.* **2006**, *45*, 5248–5250.
- (11) Kuhnert, N.; Tang, B. *Tetrahedron Lett.* **2006**, *47*, 2985–2988.
- (12) (a) Srimurugan, S.; Viswanathan, B.; Varadarajan, T. K.; Varghese, B. *Tetrahedron Lett.* **2005**, *46*, 3151–3155. (b) Srimurugan, S.; Suresh, P.; Pati, H. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **2007**, *59*, 383–388. (c) López-Periago, A. M.; García-González, C. A.; Domingo, C. *Chem. Commun.* **2010**, *46*, 4315–4317.
- (13) Nour, H. F.; Matei, M. F.; Bassil, B. S.; Kortz, U.; Kuhnert, N. *Org. Biomol. Chem.* **2011**, *9*, 3258–3271.
- (14) Kuhnert, N.; Lopez-Periago, A. M. *Tetrahedron Lett.* **2002**, *43*, 3329–3332.
- (15) Due to poor solubility of macrocycles **5c** and **6c** in CH<sub>3</sub>CN, spectra for these compounds were measured in ethanol.
- (16) Grimme, S. *J. Comput. Chem.* **2006**, *27*, 1787–1799.
- (17) (a) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639–5648. (b) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650–654.
- (18) Ménand, M.; Leroy, A.; Marrot, J.; Luhmer, M.; Jabin, I. *Angew. Chem., Int. Ed.* **2009**, *48*, 5509–5512.
- (19) Chai, J.-D.; Head-Gordon, M. *J. Chem. Phys.* **2008**, *128*, 084106–084106–15.
- (20) Weigend, F.; Ahlrichs, R. *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–32305.
- (21) (a) Neugebauer, J.; Scheffler, M. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1992**, *46*, 16067–16080. (b) Hu, X. L.; Michaelides, A. *Surf. Sci.* **2008**, *602*, 960–974.
- (22) Savoia, D.; Gualandi, A.; Stoeckli-Evans, H. *Org. Biomol. Chem.* **2010**, *8*, 3992–3996.
- (23) (a) Padmaja, M.; Periasamy, M. *Tetrahedron: Asymmetry* **2004**, *15*, 2437–2441. (b) Kuhnert, N.; Göbel, D.; Thiele, C.; Renault, B.; Tang, B. *Tetrahedron Lett.* **2006**, *47*, 6915–6918.
- (24) Frisch, M. J., et al., *Gaussian09*; Gaussian Inc.: Wallingford, 2009.
- (25) Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, M.; Nguyen, K. A.; Su, S.; Windus, T. L.; Elbert, S. T.; et al. *J. Comput. Chem.* **1993**, *14*, 1347–1363.
- (26) (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864–B871. (b) Kohn, W.; Sham, L. *Phys. Rev.* **1965**, *140*, A1133–A1138.
- (27) (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, *2*, 799–805. (b) Baldrige, K. K.; Klamt, A. *J. Chem. Phys.* **1997**, *106*, 6622–6633.
- (28) Lebedev, V. I.; Laikov, D. N. *Dokl. Math.* **1999**, *59*, 477–481.