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Rim-Functionalized Cryptophane-111 Derivatives via Heterocapping, and their Xenon Complexes[†]

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Akil I. Joseph,^{a,#} Gracia El-Ayle,^{a,#} Céline Boutin,^b Estelle Léonce,^b Patrick Berthault,^b and K. Travis Holman^{a*}Received 00th January 2014,
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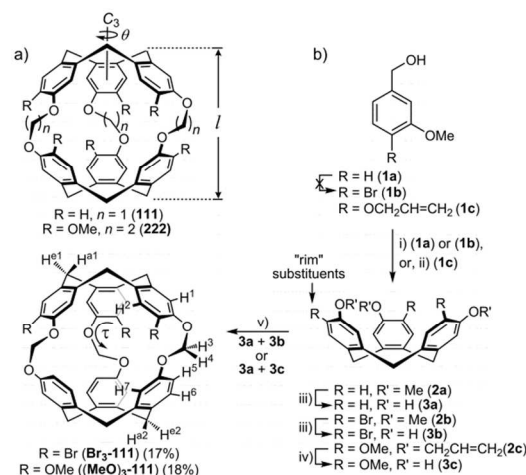
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Capping of cyclotriphenolene (3a) by the more available cyclotriguaiacylene (3c) or trisbromocyclotriphenolene (3b) gives the first rim-functionalized cryptophane-111 derivatives. Crystal structures of the xenon complexes reveal high cavity packing coefficients and unprecedentedly short Xe...C contacts.

Cryptophanes (Scheme 1) are cage-like container molecules constructed by the covalent linking of two concave cyclotribenzylenes (CTBs), most commonly by alkyldioxy linkers.¹ They typically possess electron rich hydrophobic cavities that strongly and selectively bind complementary small molecules, gases, cations,² or even anions.³ One of the most promising potential applications of cryptophanes is related to the smaller ones being the highest known affinity hosts for xenon, allowing development of as-low-as picomolar^{4,5} detection limit ¹²⁹Xe NMR based indirect sensors or imaging/contrast agents.⁶ To date, essentially all such sensors—e.g., pH, temperature, protein, nucleotide, peptide, and Zn²⁺ ion sensors, to name a few—are derived from the (±)-cryptophane-222 core (**222**; R = OMe, n = 2). The **222** core features ethylenedioxy linkers that provide a flexible cavity ranging from ~85–119 Å³ in volume (*V_c*)⁷ and methoxy or other⁸ substituents amenable to synthetic manipulation for the installment of water solubilizing and/or substrate binding sites for sensing applications. Although the parent **222** exhibits a high xenon binding constant in organic solvents (*K_a* ≈ 3000 M⁻¹ at 278 K in (CDCl₂)₂)⁹, the core **222** cavity appears to be somewhat large for xenon (*V_{Xe}* = 42 Å³), even in its most contracted conformation (*V_c* = 89 Å, for Xe@**222**). The smaller, also flexible, (±)-cryptophane-111 (**111**, R = H, n = 1, *V_c* ≈ 32–72 Å³), however, is thought to possibly be a better core platform for xenon, at least in terms of its xenon affinity. The room temperature xenon binding constant of **111** is more than three times that of **222** in organic solvents under similar conditions (*K_a* ≈ 10⁴ M⁻¹).¹⁰ The cage of the **111** core is also insusceptible to collapse.¹¹ To date, however, only a few derivatives of **111** have appeared, limited in part due to the low yield (6%) synthesis of the requisite cyclotriphenolene (CTP, Scheme 1a) precursor.^{12,13} Nonetheless, the first water soluble **111** derivative, namely the pentamethylcyclopentadienyl ruthenium functionalized salt [(Cp**Ru*)₆(**111**)]Cl₆,¹² was found to exhibit a high room temperature

xenon binding constant (*K_a* = 2.9(2) × 10⁴ M⁻¹ in D₂O, by ¹²⁹Xe NMR) comparable to the best water soluble **222** derivatives.^{8a} We report here the synthesis and xenon binding properties of two new rim-substituted cryptophane-111 derivatives achieved by a heterocapping synthetic approach that exploits the greater availability of methoxy or, ostensibly, bromine functionalized cyclotriphenols **3b** and **3c** (Scheme 1). The surprising crystal structures of their xenon complexes reveal extremely compact xenon complexes with unprecedentedly short Xe...C contacts.



Scheme 1. a) General cryptophane structure. b) Synthesis of rim-substituted cryptophane-111 derivatives (**(MeO)₃-111** and **Br₃-111**) by the heterocapping method. i) P₂O₅, Et₂O or CH₂Cl₂, reflux, ii) 60% HClO₄, iii) BBr₃, CH₂Cl₂, -78 °C, iv) 10% Pd/C, 1,4-dioxane, v) Cs₂CO₃, DMF, 80 °C, BrCH₂Cl. All chiral compounds are isolated as racemates.

All reported **111** derivatives to date^{12,13}—none of them rim-functionalized—were obtained by post-synthetic modification of **111**, which itself is best synthesized by the S_N2-mediated dimerization of two units of cyclotriphenolene **3a** using excess bromochloromethane (Scheme 1b, 46% optimized yield).¹⁴ Unfortunately, despite recent progress,¹⁵ the availability of **3a** remains limited by the low yield (6–14%) synthesis of its methylated cyclotriphenylene precursor (**2a**) from 3-methoxybenzylalcohol (**1a**). We reasoned that synthesis of rim-functionalized **111** derivatives might be achieved more directly

by the heterocapping of **3a** with a pre-functionalized cyclotriphenolene, such as trisbromocyclotriphenolene (**3b**) or cyclotriguaiacylene (**3c**). Considering that homodimeric **111**-core cryptophanes of **3b** or **3c** should, at best, occur only in low yield due to steric crowding at opposing CTB rims,¹⁶ the heterocapping approach could, in principal, alleviate up to half of the demand for precious **3a** while also directly providing functionalized **111** derivatives (**(MeO)₃-111** or **Br₃-111**). Like **222**, which is rim-functionalized with methoxy (or other) substituents, the new rim-functionalized **111** derivatives ought to be amenable to further modification. Moreover, trisphenol **3c** is readily available in many-gram quantities and trisphenol **3b** is obtained from **1b** in two steps in reasonable yield.¹⁷ Also, **3b** ought to be more accessible due to a somewhat recent report of the high yield, regioselective bromination of **1a** to give **1b**,¹⁸ removing two steps from the overall synthesis of **3b**.

We also hypothesized that the introduction of substituents (e.g., methoxy or bromo) on one of the inner rims of **111** might enhance the binding affinity of the cryptophane toward small gases due to: i) increased host-guest dispersion interactions resulting from the introduction of heavy atoms—and, particularly, polarizable atoms like Br—at the surface of the binding site; ii) the presence of a permanent dipole in the host, also thought to likely enhance host-guest dispersion interactions, and iii) the bulk of the rim substituents prohibiting the **111** core from achieving the most contracted, small-cavity-volume conformation. It was thought that inhibiting contracted conformations may effectively pre-organize the cryptophane toward the more expanded, xenon-accommodating conformations and counter possible entropic consequences of substrate binding.

Reaction of **3a** with excess **3b** or **3c** under conditions similar to those used for synthesis of **111**,¹⁴ was found to give the expected functionalized **111** derivatives (**(MeO)₃-111** or **Br₃-111**) in 18% and 17% yield based on **3a** (Scheme 1). The *anti*-stereochemistry of the products was confirmed by crystallography and there was no evidence for the presence of *syn* diastereomers in the products. Notably, as anticipated, only very small amounts of the homodimeric hexamethoxy- or hexabromo-**111** derivatives are observed. The latter (**Br₆-111**) remains as a minor impurity (<2%) in the **Br₃-111** product after purification. The results suggest that a heterocapping approach may also be successful if applied to a recent attempted synthesis of functionalized cryptophane-000 derivatives.¹⁶ Unfortunately, the proposed shorter approach to **3b** did not proceed as intended; the previous report¹⁸ of the regioselective bromination of **1a** to give the necessary **1b** was concluded to be erroneous, yielding instead the unproductive 2-bromo-5-methoxybenzyl alcohol regioisomer. **1b** was consequently synthesized from 3-hydroxybenzoic acid as reported in the literature.^{17,†}

Preliminary evidence for the binding of xenon by **(MeO)₃-111** and **Br₃-111** was obtained by room temperature ¹H and hyperpolarized (HP) ¹²⁹Xe NMR spectroscopy in CDCl₃ and nitrobenzene-*d*₅ (or CD₂Cl₂), respectively. The solvents are too large to enter the **111** cavity and essentially cannot compete with xenon. The degassed, xenon-free ¹H spectra (Fig. 2) are indicative of C₃ symmetric cryptophanes. After saturation of the solutions with xenon, the host resonances in the ¹H spectra of **(MeO)₃-111** and **Br₃-111** split into two signals. Under similar conditions, the HP ¹²⁹Xe spectra simultaneously show the appearance of resonances corresponding to Xe@**(MeO)₃-111** and Xe@**Br₃-111** (in CD₂Cl₂) at 39.3 and 80.7 ppm (Fig. S12-13), respectively. The data demonstrate, as expected, slow

exchange of the xenon between bound and free states on both spectral timescales, but time-averaged C₃-symmetry host conformations. The Xe@**(MeO)₃-111** resonance is significantly downfield from the Xe@**111** resonance (31.1 ppm)¹⁰ and that of a hexaphenolic Xe@**(OH)₆-111** derivative (31 ppm),^{13a} this may suggest there is less space available to xenon within this rim-functionalized **111** derivative. Preliminary data (not provided) also shows that guest in-out exchange is slower for **Br₃-111** and **(MeO)₃-111** than for **111**, reflecting the presence of substituents at the cavity windows. Though further study is needed to extract accurate binding constants, the *K_a* values are similar for both cryptophanes and are lower than expected (*K_a* < 100 M⁻¹, estimated). It is not yet known whether the lower xenon binding constants are due to entropic or enthalpic issues. In any case, xenon binding affinity is expected to increase considerably in aqueous solution should these hosts be further modified to provide water soluble derivatives.

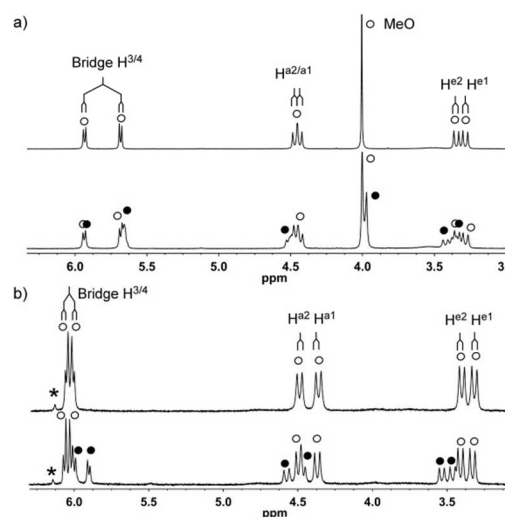


Figure 1. Selected portions of room temperature ¹H spectra before (top) and after (bottom) saturation of the solvent with xenon. a) **(MeO)₃-111** in CDCl₃, b) **Br₃-111** in nitrobenzene-*d*₅. Open and filled circles represent signals of the free and xenon-occupied hosts, respectively. *Represents the homodimeric hexabromo derivative (**Br₆-111**), found as an impurity (~2%).

Single crystals of **(MeO)₃-111**·1.5DCE, the corresponding xenon complex, 0.92Xe@**(MeO)₃-111**·1.5DCE, **(MeO)₃-111**·2/3NO₂Me, **Br₃-111**, and its xenon complex, 0.96Xe@**Br₃-111**, were grown at room temperature from 1,2-dichloroethane (DCE), NO₂Me, and NO₂C₆H₅, respectively, and were analysed by X-ray diffraction (Fig. 3).[†] Crystals of the xenon complexes were obtained from vessels pressurized with xenon (14 or 17 bar), ensuring nearly 100% xenon occupancy.

The conformation of **111** and its derivatives can be described by several structural parameters: the length of the cryptophane (*l*), defined by the CH₂ carbons of the CTB units, the relative twist angle between the CTB units (*θ*), and the torsion angles about the Ar-O bonds involving the methylenedioxy linkers (*τ*, defines in Scheme 1). The cryptophane cavity volume (*V_c*) can also be quantified and the reported crystal structures of 0.75H₂O@**111**·2CHCl₃ and metalated [(Cp**Ru*)₆(**111**)]₆·*x*NO₂Me serve as useful comparisons (Fig. 3 a,b).¹² In the former compound, **111** is found to have scavenged water from CHCl₃ solution and the cryptophane adopts a fully expanded conformation characterized by six *syn*periplanar conformations of the

ArOCH₂ connections ($\tau = 4(4)^\circ$), an 8.6 Å end-to-end length (l), a minimal twist angle ($\theta = 18(1)^\circ$) and a cavity volume (V_c) that measures 69 Å³. In contrast the conformation of the empty **111** core of [(Cp**Ru*)₆(**111**)][(CF₃SO₃)₆·*x*NO₂Me is seemingly as-contracted-as-possible ($l = 7.4$ Å), being highly twisted ($\theta = 61^\circ$) with all six ArOCH₂ connections in an *antiperiplanar* ($\tau = 177(2)^\circ$) arrangement and a minimized cavity volume ($V_c \approx 32$ Å³). In the absence of xenon, (MeO)₃-**111** and Br₃-**111** are also found to be empty in the solid state.[†] Both (MeO)₃-**111** and Br₃-**111** exhibit conformations in between the fully contracted and fully expanded forms exhibited by empty and water-occupied **111**. In short, though there is some cryptophane conformational disorder in (MeO)₃-**111**·1.5DCE, 2.35 of the three crystallographically unique cryptophanes observed in the two crystal structures of empty (MeO)₃-**111** have only three of their six ArOCH₂ connections (τ) residing in the *antiperiplanar* “closed” conformation (0.65/3 show four of the six connections in this conformation) whereas the remaining connections are all “gauche” (synclinal or anticlinal). Similarly, in the structure of empty Br₃-**111**, only two of the six ArOCH₂ connections (τ) are *antiperiplanar* while four are *gauche*. The net result of these linker conformations are less twisted (Fig. 3) cryptophane conformations and larger cavity volumes as compared to empty **111** core of [(Cp**Ru*)₆(**111**)]⁶⁺ ($V_c = 42$ and 46 Å³ for (MeO)₃-**111** and Br₃-**111**, respectively). The observation suggests that, as hypothesized, the steric bulk imposed by the rim substituents prevents the empty cryptophanes from contracting as much as is possible with **111**, and that the range of achievable conformations (and cavity volumes) is narrower for the rim-functionalized **111** derivatives. Further conformational details are available in the Supporting Information (Table S3, Fig. S14-19).

Surprisingly, the crystal structures of the xenon-occupied cryptophanes—0.92Xe@((MeO)₃-**111**)·1.5DCE and 0.96Xe@Br₃-**111**—are isostructural and nearly identical to their empty crystal forms, except that xenon is found within the cryptophane cavities at nearly 100% occupancy. The unit cell volume of 0.96Xe@Br₃-**111**, for instance, is only 24 Å³ greater than Br₃-**111**—almost completely attributable to the slight (5 Å³, 11%) expansion of the Br₃-**111** cavities—despite the introduction of 4×42 Å³ of atomic xenon. The xenon atom is centered within the Br₃-**111** cavity (Fig. S21) and the 36 closest heavy atoms to the xenon are the arene carbon atoms of the host. In fact, several of the Xe⋯C(arene) distances are the shortest ever measured for a complex of atomic xenon,¹⁹ ranging from 3.66–4.20 Å (avg. = 3.89(16) Å), with more than 15 contacts being shorter than the sum of the van der Waals radii (3.86 Å). The Xe⋯centroid(arene) distances average 3.63(4) Å, considerably shorter than that measured for the Xe⋯C₆H₆ complex in the gas phase (3.77 Å).²⁰ The result is clearly a very tightly enshrouded xenon atom; the packing coefficient (PC, V_{Xe}/V_c) of xenon within the Br₃-**111** cavity measures 0.82, extremely high for supramolecular complexes governed by dispersion forces (typically 0.55±0.09) and particularly so for gas complexes.²¹ Notably, this is the highest PC reported to date for any structurally characterized neutral guest@cryptophane complex.²² In comparison, the Xe@**111** complex exhibits a cavity volume of 70 Å³ (PC = 0.62) and significantly longer, likely more optimal, Xe⋯C(arene) contacts, with Xe⋯C(arene) distances averaging 4.01(9) Å (range: 3.86–4.20 Å) and Xe⋯centroid(arene) distances measuring 3.77(3) Å.²³ The xenon thermal parameters (at 100 K) are also noticeably larger for the Xe@**111** complex than for Xe@Br₃-**111**. Similarly, the xenon atoms of the Xe@**222**

complex is even less crowded, exhibiting longer Xe⋯C(arene) contacts and a packing coefficient of 0.47. Interestingly, single crystals of 0.96Xe@Br₃-**111** appear to be indefinitely stable under ambient conditions; over a period of months, no loss of xenon can be detected by X-ray diffraction, despite the otherwise volatile nature of the guest. We note that gas-encapsulating molecules such as these may have materials applications related to gas confinement or separations.²⁴

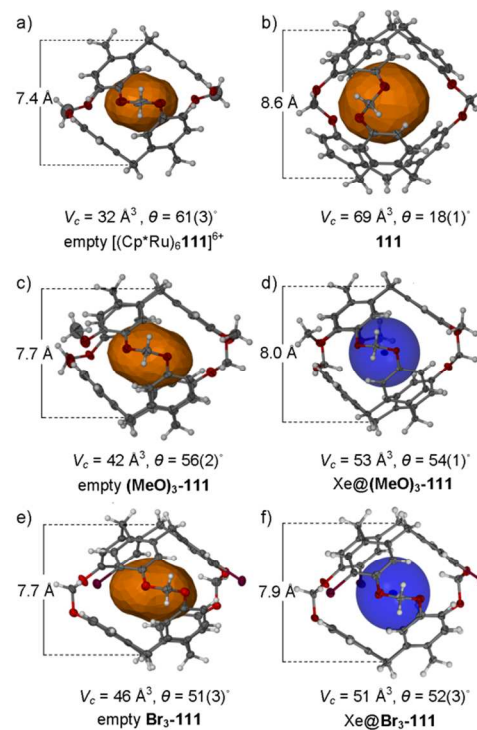


Figure 2. Thermal ellipsoid plots of a) the contracted **111** core of the reported empty [(Cp**Ru*)₆(**111**)]⁶⁺ cation,¹² b) the expanded **111** conformation from the reported structure of 0.75H₂O@**111**·2CHCl₃,¹² c) empty (MeO)₃-**111** from the crystal structure of (MeO)₃-**111**·1.5DCE, d) the Xe@((MeO)₃-**111**) complex from the crystal structure of Xe@((MeO)₃-**111**)·1.5DCE, e) empty Br₃-**111**, and f) Xe@Br₃-**111**. The twist angles, θ , and cavity volumes (V_c , depicted in orange) are provided. Only the major occupancy positions of disordered species are shown. Xenon is depicted as semi-transparent blue spheres.

Crystals of 0.92Xe@((MeO)₃-**111**)·1.5DCE are similarly isostructural to the empty crystal form (MeO)₃-**111**·1.5DCE, except that the (65:35) conformational disorder of the cryptophane observed in the empty structure is not present in 0.92Xe@((MeO)₃-**111**)·1.5DCE. Only the more open of the two conformers is observed (Fig. S14,20), yet, like Xe@Br₃-**111**, the xenon is centered and highly crowded within an intermediate cryptophane-111 core conformation (PC = 0.79, $V_c = 53$ Å³). Similarly also, close Xe⋯C(arene) intermolecular contacts are observed for the Xe@((MeO)₃-**111**) complex, ranging from 3.64–4.35 Å (avg. = 3.91(19) Å) and exhibiting Xe⋯centroid(arene) distances averaging 3.65(14) Å.

Conclusions

The first rim-functionalized derivatives of cryptophane-111 were synthesized by a heterocapping synthetic approach. As observed by crystallography and ¹H and ¹²⁹Xe NMR

spectroscopy, (MeO)₃-**111** and Br₃-**111** bind xenon in organic solvents, albeit more weakly than expected. The crystallographically characterized xenon complexes exhibit the shortest known Xe...C intermolecular contacts. At this time, we do not have a definitive explanation for the crowded xenon complexes. It is possible that crystal packing forces dictate that the complexes maintain somewhat contracted conformations. It is more likely, however, that the rim-positioned functional groups may prevent the cryptophanes from adopting the synperiplanar ArOCH₂ conformations (τ) characteristic of the most expanded **111** core conformation. Rim-functionalization thus appears to significantly limit the range of achievable conformations of the **111** core and suggests that such **111** derivatives may be better hosts than **111** for smaller gases such as N₂, O₂, etc.

Notes and references

^a Department of Chemistry, Georgetown University, Washington, D.C., USA, 20057. Fax: (+1) 202-687-6209. E-mail: kth7@georgetown.edu

^b CEA, IRAMIS, NIMBE, Laboratoire Structure et Dynamique par Résonance Magnétique, UMR CEA/CNRS 3299, 91191 Gif-sur-Yvette, France.

Both of these authors contributed equally to this work.

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- 1 T. Brotin and J. P. Dutasta, *Chem. Rev.*, 2009, **109**, 88-130.
- 2 T. Brotin, S. Goncalves, P. Berthault, D. Cavagnat and T. Buffeteau, *J. Phys. Chem. B*, 2013, **117**, 12593-12601.
- 3 R. M. Fairchild and K. T. Holman, *J. Am. Chem. Soc.*, 2005, **127**, 16364-16365.
- 4 a) M. M. Spence, S. M. Rubin, I. E. Dimitrov, E. J. Ruiz, D. E. Wemmer, A. Pines, S. Q. Yao, F. Tian and P. G. Schultz, *Proc. Natl. Acad. Sci.*, 2001, **98**, 10654-10657; b) L. Schroder, T. J. Lowery, C. Hilty, D. E. Wemmer and A. Pines, *Science*, 2006, **314**, 446-449.
- 5 a) Y. Bai, P. A. Hill and I. J. Dmochowski, *Anal. Chem.*, 2012, **84**, 9935-9941; b) K. K. Palaniappan, R. M. Ramirez, V. S. Bajaj, D. E. Wemmer, A. Pines and M. B. Francis, *Angew. Chem. Int. Ed.*, 2013, **52**, 4849-4853.
- 6 a) K. K. Palaniappan, M. B. Francis, A. Pines and D. E. Wemmer, *Isr. J. Chem.*, 2014, **54**, 104-112; b) L. Schröder, *Physica Medica*, 2013, **29**, 3-16; c) O. Taratula and I. J. Dmochowski, *Curr. Opin. Chem. Biol.*, 2010, **14**, 97-104; d) P. Berthault, G. Huber and H. Desvaux, *Prog. Nucl. Magn. Reson. Spectrosc.*, 2009, **55**, 35-60.
- 7 a) D. Cavagnat, T. Brotin, J.-L. Bruneel, J.-P. Dutasta, A. Thozet, M. Perrin and F. Guillaume, *J. Phys. Chem. B*, 2004, **108**, 5572-5581; b) O. Taratula, P. A. Hill, N. S. Khan, P. J. Carroll and I. J. Dmochowski, *Nature Comm.*, 2010, **1**, 148-154.
- 8 a) D. R. Jacobson, N. S. Khana, R. Collé, R. Fitzgerald, L. Laureano-Pérez, Y. Baia and I. J. Dmochowski, *Proc. Nat. Acad. Sci.*, 2011, **108**, 10969-10973; b) L. Delacour, N. Kotera, T. Traoré, S. Garcia-Argote, C. Puente, F. Leteurtre, E. Gravel, N. Tassali, C. Boutin, E. Léonce, Y. Boulard, P. Berthault and B. Rousseau, *Chem. Eur. J.*, 2013, **19**, 6089-6093.
- 9 K. Bartik, M. Luhmer, J.-P. Dutasta, A. Collet and J. Reisse, *J. Am. Chem. Soc.*, 1998, **120**, 784-791.
- 10 a) H. A. Fogarty, P. Berthault, T. Brotin, G. Huber, H. Desvaux and J. P. Dutasta, *J. Am. Chem. Soc.*, 2007, **129**, 10332-10333; b) K. E. Chaffee, H. A. Fogarty, T. Brotin, B. M. Goodson and J.-P. Dutasta, *J. Phys. Chem. A*, 2009, **113**, 13675-13684.
- 11 S. T. Mough, J. C. Goeltz and K. T. Holman *Angew. Chem. Int. Ed.*, 2004, **43**, 5631-5635.
- 12 R. M. Fairchild, A. I. Joseph, K. T. Holman, H. A. Fogarty, T. Brotin, J.-P. Dutasta, C. Boutin, G. Huber and P. Berthault, *J. Am. Chem. Soc.*, 2010, **132**, 15505-15507.
- 13 a) E. Dubost, J.-P. Dognon, B. Rousseau, G. Milanole, C. Dugave, Y. Boulard, E. Léonce, C. Boutin and P. Berthault, *Angew. Chem. Int. Ed.*, 2014, **53**, 9837-9840; b) E. Dubost, N. Kotera, S. Garcia-Argote, Y. Boulard, E. Léonce, C. Boutin, P. Berthault, C. Dugave and B. Rousseau, *Org. Lett.*, 2013, **15**, 2866-2868; c) T. Traoré, G. Clavé, L. Delacour, N. Kotera, P.-Y. Renard, A. Romieu, P. Berthault, C. Boutin, N. Tassali and B. Rousseau, *Chem. Commun.*, 2011, **47**, 9702-9704.
- 14 T. Traoré, L. Delacour, S. Garcia-Argote, P. Berthault, J.-C. Cintrat and B. Rousseau, *Org. Lett.*, 2010, **12**, 960-962.
- 15 a) T. Traoré, L. Delacour, N. Kotera, G. Merer, D.-A. Buisson, C. Dupont and B. Rousseau, *Org. Process Res. Dev.*, 2011, **15**, 435-437; b) M. A. Little, J. Donkin, J. Fisher, M. A. Halcrow, J. Loder and M. J. Hardie, *Angew. Chem. Int. Ed.*, 2012, **51**, 764-766.
- 16 M. A. Little, M. A. Halcrow and M. J. Hardie, *Chem. Commun.*, 2013, **49**, 1512-1514.
- 17 a) D. J. Cram, M. E. Tanner, S. J. Keipert and C. B. Knobler, *J. Am. Chem. Soc.*, 1991, **113**, 8909-8916; b) J. Canceill and A. Collet, *New J. Chem.*, 1986, **10**, 17-23.
- 18 A. Speicher, T. Backes and S. Grosse, *Tetrahedron*, 2005, **61**, 11692-11696.
- 19 Y. Miyahara, K. Abe and T. Inazu, *Angew. Chem. Int. Ed.*, 2002, **41**, 3020-3023.
- 20 T. Brupbacher, J. Makarewicz, A. Bauder, *J. Chem. Phys.*, 1994, **101**, 9736-9746.
- 21 S. Mecozzi and J. J. Rebek, *Chem. Eur. J.*, 1998, **4**, 1016-1022.
- 22 Though the CDCl₃@**222** complex was originally estimated (a) to have a PC of 0.89, our analysis of the crystal structures of the complex (b) reveal that the value is closer to 0.61. a) G. Laurent, D. Jean-Pierre and A. Collet, *Angew. Chem., Int. Ed.*, 1993, **32**, 1169-1171; b) D. Cavagnat, T. Brotin, J.-L. Bruneel, J.-P. Dutasta, A. Thozet, M. Perrin, F. Guillaume, *J. Phys. Chem. B*, 2004, **108**, 5572-5581.
- 23 A. I. Joseph, S. H. Lapidus, C. M. Kane and K. T. Holman, *Angew. Chem. Int. Ed.* 2014, in press.
- 24 L. Chen, P. S. Reiss, S. Y. Chong, et al. *Nat. Mat.*, 2014, **13**, 954-960.