Novel Architectures in Cavitand Chemistry: Shaping Molecular Inner Space

DISSERTATION

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By

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Abstract

As long as chemists have marveled at the specificity of interactions in enzymes, nucleic acids, and other biological motifs that contain an inner cavity, there has been much desire to construct molecules that mimic these in function. Inspired by work performed by Charles J. Pederson on crown ethers, Donald J. Cram conducted seminal research into the construction and the host-guest interactions of a number of molecular architectures, specifically with his work on carcerands and hemicarcerands. Since Cram’s early work, the field of cavitand chemistry has taken off, providing endless examples in architecture capable of enclosing the space around a guest molecule. Some common examples of artificial hosts are cryptophanes, cucurbit[n]urils, and calixaranes. Function and application vary as much as structure, and range from stabilizing reactive intermediates and probing fundamental questions in physical organic chemistry, to drug delivery and chiral separations. Meanwhile, in the Badjić Group, the development of cavitands functionalized with dynamic apertures, or gates, has allowed us to probe fundamental questions in the kinetics of encapsulation. These studies, however, have relied upon a single C$_{3v}$ symmetric host. As a result, the group has taken on the challenge of constructing new architectures giving consideration toward the inner space geometry to allow for installation of “gate” moieties onto these architectures. My research efforts have focused on the development of these new molecular architectures, with applications towards molecular recognition. Three journeys will be described, about how the key
bicyclic core is transformed to give rise to differently shaped hosts. These synthetic methodologies allow for multi-gram syntheses of desired products and better potential control of their stereochemistry, all the while utilizing more environmentally friendly methodologies. Currently being explored is using these architectures for different possible applications, including studying recognition phenomena, and perhaps building chiroptical sensors capable of reporting on the presence of minute quantities of chiral substances in the environment.
Dedication

Snoopy
Acknowledgments

I thank everyone I have come across along my journey to this point. In some way you helped me realize something that transformed me into who I am today. Perhaps the subtlest affects have the greatest impact. Thank you.
Vita

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Publications


Hermann, K., Nakhla, M., Gallucci, J., Dalkilic, E., Dastan, A., & Badjić, J. D. (2013). A
Molecular Claw: A Dynamic Cavitand Host. Angewandte Chemie International Edition,
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**Fields of Study**

Major Field: Chemistry
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Chapter 1: Shaping Molecular Inner Space


1.1 Introduction

Since the first artificial hosts emerged years ago, chemists have been fascinated by the characteristics and in exploring the utility of compounds with an enforced cavity.\(^1\) Currently, it is recognized that cavitands trap guest molecules that are complementary in shape, size and electronic attributes to their concave interior.\(^2\) In addition, the formation of such host–guest complexes, often driven by desolvation,\(^3\) play a critical role in complexation events.\(^4\) In his seminal paper about cavitand hosts,\(^5\) D. J. Cram discussed the prospect of using these concave structures for promoting chemical reactions,\(^6\) stabilizing reactive intermediates,\(^7\) or controlling the rates of encapsulation and release.\(^8\) So in 1985, the UCLA group first reported the synthesis of the D\(_{4h}\) symmetric host 1.1 (Figure 1A). They had successfully synthesized a host with a sizable enforced interior,
Figure 1: Chemical structures of carcerands 1.1 (A) and 1.2 (B). Three solvent molecules (red) were trapped in the cavity of 1.2 during its preparation.

although the host was found to be poorly soluble in many solvents due to a lack of solubilizing side-chains. Several years later, a more soluble carcerand 1.2 was prepared, and with $^1$H-NMR spectroscopy was shown to contain a solvent molecule (DMSO, DMA, or DMF) residing in its cavity.$^9$

Interestingly, [1.2•DMSO] possessed a long lifetime with the entrapped DMSO molecule unable to depart from its inner space at 150°C for 24 h!$^9$ It was deduced that DMSO was permanently trapped in the cavity of 1.2, and its departure necessitated a cleavage of covalent bonds (>90 kcal mol$^{-1}$). To reduce the high activation energy of the complexation/decomplexation of carcerands, Cram and co-workers next designed the hemicarcerands (Figure 2).$^{10}$ Molecular capsule 1.3 (R = CH$_2$CH$_2$C$_6$H$_5$, Figure 2) was
composed with three methylenedioxy bridging units connecting its northern and southern cups.\textsuperscript{11} With one methylenedioxy group missing in hemicarcerand 1.3, the side portal was big enough to permit decomplexation ($E_a > 20$ kcal mol$^{-1}$) of several guests (DMSO, DMA, DMF).\textsuperscript{12} The activation energy of the process was large, given the small affinity of guests for populating the host. Cram coined the term “constrictive binding”\textsuperscript{13} to describe an apparent “physical barrier” corresponding to the guest departure.

Figure 2: Dioxacyclooctadiene rings in hemicarcerand 1.3 ($R = \text{CH}_2\text{CH}_2\text{Ph}$) undergo chair-to-boat conformational changes. Two methylenedioxy bridges (brown) alter the position to create a sizeable portal for more facile trafficking of guests (DMF is shown).
This term derives from the Latin word *constrictus* meaning to “narrow a passage.” Later, Houk and co-workers were first to contemplate that conformational changes occurring within hemicarcerands ought to be considered in understanding the trafficking of molecules.\(^{14}\) In particular, a chair-to-boat interconversion of one dioxacyclooctadiene ring within the carcerand/hemicarcerand was computed to require a considerable activation energy\( (> 12 \text{ kcal mol}^{-1}) \). The opening of the two methylenedioxy gates\( (> 20 \text{ kcal mol}^{-1}, \text{Figure 2}) \) was then proposed to promote the access/departure of guests residing in the inner space of the hemicarcerand.\(^{15}\) If the host’s dioxacyclooctadiene rings solely assume the chair conformation, the activation barrier for guest departure becomes insurmountable at experimentally accessible temperatures.\(^{16}\) Almost two decades after Houk’s original proposal, the process of gating appears to be important for the operation\(^{17}\) of various dynamic hosts. In addition, gating could be used in developing supramolecular systems capable of controlling the outcome of chemical reactions\(^{18}\) or the delivery and trafficking of useful molecules.\(^{19}\)

### 1.2 Gated Molecular Baskets

In line with this premise, molecular basket \(1.4\) (Figure 3, \(R=\text{CH}_3\)) was designed and first prepared in the Badjić laboratory eight years ago.\(^{20}\) The key reaction for the preparation of this dynamic host was the tris-annulation of a racemic norbornene compound using a transition metal catalyst, either Cu(I) or Pd(0) (Figure 3A).\(^{21}\) In particular, De Lucchi *et. al.* previously developed useful cyclotrimerization protocols.\(^{22}\) The reaction gives a
mixture of syn/anti diastereomeric products (Figure 3A) for which the undesired anti compound usually dominates. The syn isomer, molecular basket 1.4 (Figure 3B/C), is a C$_{3v}$ symmetric compound with a flat aromatic base fused to three bicyclo[2.2.1]heptane rings to form a curved unit. Three phthalimides extend this semi-rigid structure into a bowl-shaped cavitand (Figure 3C). Importantly, the pyridine-based gates are capped with an amide functional group, and in non-competitive organic solvents form a seam of N–H---N intramolecular hydrogen bonds (Figure 3B), giving rise to a dynamic molecular inner space. Over the last eight years, a number of studies have probed the effects of gate’s opening and closing on binding. This control was used to modify the time a guest resides in the cavity, and to probe the elucidation of the mechanism for the encapsulation process. While results have yielded research that met the challenges above, we still look back to an initial concept presented in the chapter: Cavitands trap guest molecules that are complementary in shape, size and electronic attributes to their concave interior. This was also apparent in molecular basket 1.4.
Figure 3: (A) The tris-annulation of stannylated norbornenes is promoted with either Cu(I) or Pd(0) catalysts, to give a mixture of syn and anti cyclotrimers. (B) Chemical structure of gated molecular baskets (1.4, R=CH₃) with three intramolecular N–H---N hydrogen bonds. (C) ORTEP representation of the solid-state structure of a gated basket; note that a molecule of CHCl₃ resides in the cavity of this host having three phenyl gates at the rim.
1.3 The Shape of Molecular Inner Space

From its center outward, the basket’s shape is defined by the curvature in the bicyclic unit. In the case of molecular basket 1.4, the [2.2.1] bicyclic unit gives rise to a highly symmetrical $C_{3v}$ cavitand structure (Figure 3). Since the cavitand shape is defined by the bicyclic unit (Figure 4), and complimentary shape is of critical importance in host-guest interactions, it would make sense to extend the library of hosts to allow for selective interactions with a variety of differently shaped and sized guests. If thinking about fusing two aromatic rings to possible bicyclic units (Figures 4 – 7), two of the three carbon bridges composing the bicyclic skeleton must have at least two carbons. If there is not at least two carbons, the aromatics cannot be fused to the two bridges, due to the significant bridgehead strain.26 The largest of the three carbon bridges must also not be too large (i.e. the largest carbon bridge must be 3 or less to induce rigid enough curvature, based on MM calculations in Spartan 06'). In fact, it seems likely that only a few units may be used in place of the [2.2.1] bicyclic core utilized in molecular basket 1.4, namely the [2.2.2] and [3.2.1], which in addition to a more complex polycyclic framework, will be the topics of this work.
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Figure 4: Thirteen small bicyclic units, ranging from the smallest, [1.1.0], to the sizable [3.3.3]. No box indicates that a dibenzo-fused product is either not possible (due to bridgehead strain) or would be too flexible (bottom right, based on MMs). The blue boxes indicate units that have previously been fused to two aromatics and are explored further in this work.

### 1.4 Previous Explorations in Dibenzo-Fused Bicyclic Skeletons

It has been observed that diaromatic-fused bicyclic skeletons exhibit many kinds of molecular recognition properties, in addition to those outlined for molecular basket 1.4. Using Figure 4 as a reference, and going from left to right and top-to-bottom, the first bicyclic skeleton that we encounter on our journey is the [3.3.1] framework.
1.4.1 The [3.3.1] Skeleton – Kagan’s Ether and Tröger’s Base

Many examples of dibenzobicyclo[3.3.1]nonane derivatives have found their way into the literature, probably the most notable being in the study of molecules named Kagan’s Ether 1.5 (Figure 5) and Tröger’s Base.27,28 While not a hydrocarbon-based derivative, Kagan’s Ether is a dibenzo-fused [3.3.1] bicyclic skeleton with an oxygen atom in place of the methylene bridge (Figure 5). One orientation of the dibenzo fused [3.3.1] framework in Kagan’s Ether 1.5 gives rise to a secondary structure that is fairly rigid along the x and y axes, yet able to bend along the z-axis, giving rise to tweezer-like behavior (Figure 5). Additionally, the second possible way of constructing the same skeleton gives rise to a $C_s$ symmetric compound 1.6 (Figure 5), but this compound has not previously been synthesized and does not hint at promise as an artificial host due (MMs, Spartan). Additional derivation to the core structure is more commonly referred to as a molecular cleft.29 Extensive work undertaken by Hermata et. al., as well as other groups have shown the utility of these compounds for the purpose of molecular recognition, in particular for the recognition of chiral molecules.30 The drawback of this type of host, however, may be the lack of a “tripodal binding mode,” which has been shown to be critical within the inner space of enzymes active sites.31 In line with the premise, the enantiodiscrimination of many derivatives with this $C_2$ host skeleton have been shown to be modest.32 The same modesty with respect to recognition with Tröger’s Base has been observed,33 and applications have fallen short of initial expectations.28 This idea will be expanded on in our discussion of chiral inner space in Chapter 4.
Figure 5: (A) On the left is Kagan’s ether 1.5, an extensively studied system because of its inherent $C_2$ chirality. To the right is 1.6, the $C_1$ variant of Kagan’s ether, which has not previously been synthesized, and is much more rigid than 1.5. (B) Shows three snapshots (MMs, Chem3D) corresponding to different conformations of 1.5. Due to the motion along only one axis in the substrate, it became referred to as a molecular tweezer.
1.4.2 The [2.2.1] Skeleton – Unexpected Motivations

Probably even more extensively explored than the [3.3.1] framework, a diaromatic-fused [2.2.1] bicyclic skeleton has been a remarkably common motif found throughout supramolecular chemistry. It has found application as molecular clips,\textsuperscript{34} but also in optical sensors and in the binding of ions,\textsuperscript{35} in addition to molecular basket 1.4 described in previous sections. A different use of a complex [2.2.1] bicyclic skeleton was described in the original synthesis of dodecahedrane.\textsuperscript{36} The early steps in the process\textsuperscript{37} (Figure 6) give rise to molecule 1.8 containing two of these [2.2.1] bicyclic skeletons fused together, and its conversion into a host with a unique topology is explored further in Chapter 2.

![Figure 6](image.png)

Figure 6: Shows the first two steps in the original synthesis of dodecahedrane. Firstly, a reductive dimerization of cyclopentadiene take place to afford compound 1.7, followed by a subsequent double Diels-Alder with DMAD to afford compound 1.8, a key intermediate in the construction of a new cavitand host with a unique topology discussed in Chapter 2.
1.4.3 The [2.2.2] Skeleton – New Directions

Like the [2.2.1] skeleton, the [2.2.2] skeleton has been explored so extensively in the literature that practical discussion of different motifs becomes impossible within the context of this piece. However, a few notable examples are the triptycene derivatives and interesting “crab-like” molecules formed via a series of [2.2.2] bicyclic frameworks. The diaromatic substituted [2.2.2] skeleton is common, but probably in part because of the instability observed in barrelene and its fused-derivatives.

Figure 7: Shows the facile conversion of dibenzobarrelene 1.9 into compound 1.10, via Wagner-Meerwein rearrangements induced by an ionic addition of bromine across the double bond of the bicyclic core.

There is a natural propensity for the conversion of the [2.2.2] skeleton shown in Figure 7 into the [3.2.1] core due to the lesser ring strain in the latter. Once a third aromatic ring is fused to the bicyclic framework, however, and as in the triptycene derivatives, the framework becomes stable. This change in preference is because rearrangement to a [3.2.1] skeleton would require an aryl group to be fused to the bridgehead, something that is energetically unfavorable. So perhaps by encircling the space of dibenzobarrelene 1.9 such as that created by molecular basket 1.4 (Figure 3), a new cavitand element may be
constructed, and in fact this inspiration is based off of a previous study\textsuperscript{42} by Hart \textit{et. al.}. The diaromatic-fused [2.2.2] skeleton is the motif found on 9,10-bridged anthracene derivatives, such as dibenzobarrelene \textbf{1.9} (Figure 7), and our attempts to construct a new cavitand element based off of this previous work will be discussed in Chapter 3.

\textbf{1.4.4 The [3.2.1] Skeleton – Giving Rise to a Chiral Inner Space}

The [3.2.1] skeleton is probably the most common bicyclic core, especially in natural products such as the tri- and tetracyclic sesqui- and diterpenes,\textsuperscript{43} and probably in part because of it facile transformation from dibenzobarrelene \textbf{1.9} (Figure 7) and derivatives. However it does not seem to be a motif that is commonly found within host-guest chemistry. It is argued that this is because the core is quite compact and does not contain any type of cavity element as discussed in the previous section. Additionally, unlike the [2.2.1] and similar to the [3.3.1] framework, the core is flexible along more than a single axis (MMs, Spartan, Figure 5). It is hypothesized again that by encircling space (Figure 3), a new cavitand element may emerge, giving rise to a new type of chiral inner space due to this translocation along more than one axis and is the topic of Chapter 4.

\textbf{1.4.5 Larger Skeletons}

Based on MM observations made using Spartan, the larger skeletons ([3.2.2], [3.3.2], and [3.3.3]) give rise to highly flexible structures due to the larger carbon bridges. Therefore, they will not be discussed at the present, but could certainly prove to be useful in the future.
1.5 Conclusions

Cavitands trap guest molecules that are complementary in shape, size and electronic attributes to their concave interior. By making use of different bicyclic skeletons and encircling the space such as that for molecular basket 1.4, this work will go on to describe the synthesis and initial functions of three novel host molecules, each with their own unique inner shape space. This will allow for eventual applications to be developed that match specific sized and shaped guests, including studying recognition phenomena, and perhaps building chirooptical sensors capable of reporting on the presence of minute quantities of chiral substances in the environment (Chapter 4).
Chapter 2: A Molecular Claw: A Dynamic Cavitand Host


2.1 Introduction

The design, synthesis, and study of concave molecules with enforced cavities\(^\text{44}\) have revealed benefits of molecular encapsulation in the last four decades.\(^1\) Cavitands can be used to promote chemical reactions,\(^\text{45}\) stabilize reactive intermediates,\(^\text{46}\) investigate new forms of stereoisomerism,\(^\text{47}\) detect important analytes\(^\text{48}\) and even resolve the solid-state structure of compounds of interest.\(^\text{49}\) The strategy for obtaining a synthetic host consists of employing methods of computational chemistry to design a desired receptor followed by experimental optimization of its synthesis including kinetic/thermodynamic templation,\(^\text{50}\) self-assembly\(^\text{51}\) or transition-metal catalyzed macrocyclization.\(^\text{22}\) Despite many advances, creating a supramolecular receptor/catalyst remains a challenging task requiring time-consuming optimization of both the synthesis and operation. Furthermore, placing functional groups on the inner side of a cavitand’s concave surface is difficult but essential for improving its function.\(^\text{52}\) Indeed, self-assembled cages with functionalized
inner faces have been investigated, while covalent hosts with such topology remain elusive. The folding of oligomers into three-dimensional globular or rod-like structures presents an elegant solution to the problem, yet there remains uncertainty about the nature of the chemical information embedded in functional oligomers to ensure folding into desired secondary/tertiary structure. Herein, we describe a synthetic method for obtaining internally functionalized and dynamic cavitands of type 2.1–2.3 (Figure 8). These hosts are modular, comprising intriguing electronic characteristics, unique topology and remarkable mode of action: there could be interest in using these type of molecules as “claws” for selectively “grabbing” small chemical analytes and reporting on their presence.

### 2.2 Synthesis of Hosts 2.1\textsubscript{syn} and 2.2\textsubscript{syn}

The synthesis of C\textsubscript{3v} symmetric 2.1\textsubscript{syn} and 2.2\textsubscript{syn} was completed following the convergent strategy described in Figure 8A.\textsuperscript{37} In particular, we investigated the condensation of transient hexaaminobenzene 2.4 and diketones 2.5\textsubscript{a-c} (Figure 8C). Although hexaaminobenzene 2.4\textsuperscript{55} decomposes under ambient conditions, this compound can be generated\textsuperscript{56} in situ and used in the synthesis of various derivatives of 1,4,5,8,9,12-hexaazatriphenylene (HAT).\textsuperscript{57} Furthermore, Paquette and co-workers employed diacid 2.7 in the synthesis of curved hydrocarbons dodecahedrane\textsuperscript{36} and C\textsubscript{16}-hexaquinalene.\textsuperscript{58} This molecule can now be prepared on large scale by a domino Diels–Alder reaction of 9,10-dihydrofulvalene and dimethyl acetylenedicarboxylate (DMAD, Figure 8A).

Importantly, compound 2.7 can be converted into 2.5\textsubscript{a-c}, which is unstable and undergoes decomposition at room temperature. In the Schiff base condensation of 2.4 and 2.5\textsubscript{a-c},
Figure 8: A) The preparation of \( C_{3v} \) symmetric 2.1_{syn}–2.2_{syn} can be completed on a large scale using simple starting materials and a convergent synthetic strategy. B) Energy-minimized structure of 2.1_{syn} (MMFFs, Spartan) and van der Waals surface of this molecule showing its cavity (\( V = 123 \text{ Å}^3 \)). C) The condensation of hexaaminobenzene 2.4 (in \( \text{CH}_3\text{OH/CH}_2\text{O} \)) and diketones 2.5_{a-c} (in \( \text{CH}_2\text{Cl}_2 \)) gives syn and anti diastereomers of 2.1–2.3 in different ratios (yields are of isolated products).
combined in an approximate 1:3 stoichiometric ratio and at low temperature, we observed the formation of both syn and anti diastereomers of $2.1 - 2.3$ isolated in overall 7–55 % yield (Figure 8C); note that the yield was estimated since the unstable reactants ought to be generated in situ. The proportion of diastereomers was, in these reactions, expected to correlate with solvent polarity$^{59}$ and the size of appended alkyl groups in $2.5_{a-c}$. That is to say, more polar solvents ought to facilitate the formation of the compact $2.1_{syn} - 2.3_{syn}$ stereoisomers, as assisted by the hydrophobic effect,$^{59}$ while more sizeable alkyl groups in $2.5_{a-c}$ should favor the formation of $2.1_{anti} - 2.3_{anti}$ stereoisomers, as a result of the steric strain. In line with such reasoning, the greatest quantity of desired syn compound formed in the case of $2.2_{syn}$ in CH$_3$OH/H$_2$O = 8:2 (Figure 8C). We deduce that the propyl chains in $2.5_b$ are long enough to permit favorable desolvation of the syn transition state and at the same time short enough to avoid adverse interactions, that is, van der Waals strain in the course of forming $2.2_{syn}$ versus $2.2_{anti}$. When the reaction was run with neat CH$_3$OH, we only isolated trace quantities of $2.2_{syn}$, suggesting the important role of the hydrophobic effect in controlling the outcome of the condensation.

2.3 Spectral Properties of Hosts

The $^1$H NMR spectrum of $2.2_{syn}$ (400 MHz, 298 K) in CD$_2$Cl$_2$ revealed a set of signals corresponding to a $C_{3v}$ symmetric molecule (Figure 9A); with the assistance of $^1$H–$^1$H COSY/NOESY spectroscopic methods, we assigned all of the proton resonance signals (Figure 29 — Figure 30). After placing host $2.2_{syn}$ in C$_2$D$_2$Cl$_4$, the signal corresponding to CH$_3$ group underwent a considerable upfield shift ($\Delta d = 0.39$ ppm, Figure 9A).
In addition, the resonances of \( \text{CH}_2^A (\Delta d = +0.28 \text{ ppm}) \), \( \text{CH}_2^B (\Delta d = 0.15 \text{ ppm}) \), \( \text{He} (\Delta d = +0.18 \text{ ppm}) \), and \( \text{H}_c (\Delta d = 0.03 \text{ ppm}) \) protons altered as well. To account for the observation, we first realized that changing the nature of bulk solvent caused the perturbation of protons adjacent to the aromatic “floor”. While the polarity of dichloromethane \( (\varepsilon = 9.1) \) and tetrachloroethane \( (\varepsilon = 8.4) \) is comparable, the size difference between these two solvents is considerable. Presumably, smaller molecules of \( \text{CD}_2\text{Cl}_2 \) \( (61 \text{ Å}^3, \text{Spartan}) \) could fill the pocket in \( 2.2_{\text{syn}} \) \( (190 \text{ Å}^3) \) and push the propyl chains to extend out and adopt anti conformation (Figure 9B/C). On the contrary, sizeable \( \text{C}_2\text{D}_2\text{Cl}_4 \) \( (108 \text{ Å}^3, \text{Spartan}) \) could not effectively solvate the interior of \( 2.2_{\text{syn}} \) to drive the propyl chains to assume the less stable gauche conformation and thereby coil into the host’s cavity (Figure 9B/C). In line with the mechanistic scenario, \( \text{CH}_3 \) and \( \text{CH}_2^B \) groups pivot about the cavitand to reside on top of the central HAT ring in the shielded region of the magnetic field (Figure 9A/B, \( \text{C}_2\text{D}_2\text{Cl}_4 \)) or further away from the HAT aromatic to experience reduced anisotropic effects (Figure 9A/B, \( \text{CD}_2\text{Cl}_2 \)).
Figure 9: A) $^1$H NMR spectra (400 MHz, 298.0 K) of 2.2$_{\text{syn}}$ in C$_2$D$_2$Cl$_4$ (top) and CD$_2$Cl$_2$ (bottom). B) Side and top views of energy-minimized structures of 2.2$_{\text{syn}}$ (MMFFs, Spartan) with propyl chains assuming anti (green) and gauche (black) conformation about C$_1$–C$_2$ sigma bond. (C) Newman projections of anti/gauche conformers of 2.2$_{\text{syn}}$ in dynamic equilibrium.

Finally, each CH$_2^A$ group at the rim is the pivoting point about which the alkyl chain revolves: the position of the CH$_2^A$ protons alters to face the inner (CD$_2$Cl$_2$, Figure 9A) or outer side (C$_2$D$_2$Cl$_4$, Figure 9A) of the host’s cavity (Figure 9B), which is reflected in the chemical shift of these protons (Figure 9A); note that similar spectroscopic changes accompanied compound 2.1$_{\text{syn}}$ (Figure 31) upon the same alteration of solvents. The revolution of the alkyl groups within 2.2$_{\text{syn}}$ must be fast on the NMR time scale to average the observed proton resonance signals (Figure 9). In fact, the folded state of 2.2$_{\text{syn}}$ is C$_3$ symmetric with gauche alkyl chains forming right ($P$) or left-handed ($M$)
stereoisomers and therefore including diastereotopic CH\textsubscript{2}\textsuperscript{A}/CH\textsubscript{2}\textsuperscript{B} protons (Figure 9B).\textsuperscript{61}

Variable-temperature NMR study of 2.2\textsubscript{syn} in both C\textsubscript{2}D\textsubscript{2}Cl\textsubscript{4} (298–248 K, Figure 32) and CD\textsubscript{2}Cl\textsubscript{2} (298–177 K, Figure 33) did not show any decoalescence but a consistent shift of the alkyl resonance signals: in particular, triplet corresponding to CH\textsubscript{3} moved upfield at higher temperatures. Apparently, a low activation barrier must be characterizing the folded/unfolded dynamic equilibrium (Figure 9C) with the folded state of 2.2\textsubscript{syn} being preferred at higher temperatures. We reason that the formation of folded 2.2\textsubscript{syn} in both solvents is accompanied by a release of solvent molecules (ΔS\textsuperscript{‡} > 0) for which the equilibrium free energy is more favorable (ΔG\textsuperscript{‡} < 0) at higher temperatures.

2.4 Molecular Recognition

Since the solvation of the inner space of 2.2\textsubscript{syn} is a form of molecular recognition\textsuperscript{62} we decided to titrate CH\textsubscript{2}Cl\textsubscript{2} to this host in noncompeting C\textsubscript{2}D\textsubscript{2}Cl\textsubscript{4} and quantify the interaction. As larger quantities of the guest could not saturate 2.2\textsubscript{syn} (Figure 34), we tested more sizeable CHCl\textsubscript{3} (75 Å\textsuperscript{3}) and CCl\textsubscript{4} (89 Å\textsuperscript{3}, Figure 35). The binding affinity improved, but it was still difficult to quantify the interaction with \textsuperscript{1}H NMR spectroscopy. Ultimately, we completed an incremental addition of CBr\textsubscript{4} (108 Å\textsuperscript{3}, Figure 10B) to 2.2\textsubscript{syn}: the nonlinear least-square fitting of the experimental data to a 1:1 stoichiometric model (R\textsuperscript{2} = 0.99, Figure 10B) gave an association constant of K\textsubscript{a} = 1.74 ± 0.02 M\textsuperscript{-1}.\textsuperscript{63}
Figure 10: A) Energy-minimized structure of folded and unfolded (MMFFs, Spartan) forms of 2.2\text{syn} trapping CBr₄ guest. B) \textsuperscript{1}H NMR spectra (400 MHz, 298.0 K) of 2.2\text{syn} (1.0 mM) in C₂D₂Cl₄ obtained upon incremental addition of CBr₄ (0–1.1 mM) and the nonlinear least-square analysis of the \textsuperscript{1}H NMR chemical shifts of CH₃ (ppm) in 2.1\text{syn} (1.0 mM, red) and 2.2\text{syn} (1.0 mM, black) as a function of CBr₄ concentration (M). A 1:1 stoichiometric model gave association constants Kₐ (M\textsuperscript{-1}) at 298.0 K.
Evidently, the formation of the 1:1 complex was accompanied with downfield shift of CH$_3$ (Figure 10B) resonances, which is in line with the “opening” of the host to accept the guest (Figure 10A). We reasoned that the small binding energy ($\Delta G^\ddagger$) for the formation of [2.2$_{\text{syn}}$•CBr$_4$] is, in part, due to relatively stable ground state of the folded host having its cavity already populated with three alkyl chains. In fact, the affinity of 2.1$_{\text{syn}}$ toward complementary CBr$_4$ was somewhat greater with $K_a = 3.73 \pm 0.02$ M$^{-1}$ ($R^2 = 0.99$, Figure 10B): it costs less energy to displace shorter ethyl groups from the interior of 2.1$_{\text{syn}}$ than the longer propyl groups in 2.2$_{\text{syn}}$. Furthermore, it could be argued that less polarizable and shorter ethyl groups form less favorable contacts with the HAT “floor”, note that changing the nature of bulk solvent might improve the stability of the host–guest complex.

2.5 Conclusions

Novel hosts of type 2.1$_{\text{syn}}$–2.2$_{\text{syn}}$ comprise a unique topology and also employ an intriguing mode of action in trapping guests. Importantly, the organic framework of these compounds can be modified to give functional molecules and materials with tunable electrochemical or optical characteristics. In particular, we are investigating the functionalization of the inner amides as well as an extension of the outer olefins for optimizing the recognition characteristics of molecular claws.
Chapter 3: Toward Dual Cavity Baskets: The Functionalization of Heptiptycene Derivatives


3.1 Introduction

About four decades ago, Huebner and co-workers reported on the preparation and solid-state structure of heptiptycene 3.1 (Figure 11). This $D_{3h}$-symmetric cavitand is formally a derivative of triptycene with two enforced cavities sharing a benzene “floor”. The host–guest characteristics of heptiptycene have not been studied, although this open-cavity hydrocarbon might exhibit modest (if any) affinity toward the entrapment of properly sized/shaped guests. We reason that encircling the space of 3.1 (Figure 11) shall permit for trapping useful analytes, promoting supramolecular catalysis or studying gated molecular encapsulation. A synthetic method for obtaining
functional derivatives of 3.1 (Figure 11) was not currently available, thereby preventing the corresponding recognition/reactivity studies. Indeed, a series of fascinating double-cavity cages with intriguing photophysical characteristics were built from truxene derivatives.\textsuperscript{71} Due to their optical properties,\textsuperscript{72} these compounds could be used as chemosensors or for building organic electronic devices.\textsuperscript{73} This chapter discusses the functionalization of this intriguing host molecule, to produce a dodecamethylester derivative, 3.2. Further functionalization yielded hosts 3.3\textsubscript{a-c}, which resemble the gated molecular basket discussed in Chapter 1.

\textbf{3.2 The Original Synthesis of Heptiptycene}

In the original synthesis of heptiptycene 3.1, the cyclotrimerization of 11-chloro-9,10-dihydro-9,10-ethenoanthracene 3.4 (Figure 11) was promoted by \textit{n}-BuLi to give this compound in an approximately 20\% yield.\textsuperscript{66} In fact, Hart and co-workers showed\textsuperscript{74} that a strong base (\textit{n}BuLi) abstracts the vinylic proton in 3.4 to give carbanion 3.5 that is persistent at low temperatures (\textdegree{}78\textdegree{}C). At high temperatures (>25\textdegree{}C), however, this carbanion eliminates LiCl to give rise to the transient bicycloalkyne intermediate 3.6 (Figure 1). In a series of somewhat related experiments, Gassman and co-workers presented compelling evidence for the existence of norbornyne intermediates.\textsuperscript{75}
Figure 11: Original synthesis of heptiptycene 3.1 started with compound 3.4. The formation of reactive intermediates 3.5–3.8 was validated with a series of trapping experiments.
Furthermore, as shown in Figure 11, compound 3.6 reacts with 3.5 to give nucleophilic compound 3.7, which subsequently traps another bicycloalkyne 3.6. Finally, trimer 3.8 undergoes a thermal electrocyclic (6π) ring-closure followed by LiCl elimination to give heptiptyocene 3.1. Alternatively, Komatsu and co-workers have shown that the lithiation of 2,3-dibromobicyclo[2.2.2]oct-2-ene could give a trimeric dibromoalkene, which yields the desired cyclotrimer after a reductive cyclization. The yield of lithium-based cyclotrimerizations could indeed be improved with the addition of Cu(I) salts, although the necessity of using a strong base as well as the occurrence of nucleophilic intermediates limit the scope of this methodology. In other words, with the carbanion-mediated approach, one could prepare a narrow range of heptiptycenes in a relatively low yield.

3.3 Synthesis of Host and Methodology Studies

To address the quandary about the annulation of bicyclic cyclotrimers, De Lucchi and co-workers as well as others have shown that the cyclotrimerization of bicyclic vinyl halides can be promoted with Cu(I), Cu(II), or Pd(0) transition-metal complexes. In these procedures, mild reaction conditions enabled the preparation of a variety of cyclotrimers in good to excellent yields. In line with such findings, we reasoned that the synthesis of functionalized heptiptycenes could be accomplished following literature protocols and set to out examine the hypothesis. In order to create bicyclic vinyl halides of types 3.11 and 3.12 (Figure 12) and subsequently examine their cyclotrimerization, we attempted the cycloaddition of bis(trimethylsilyl)-acetylene (BTMSA) to tetramethylanthracene-2,3,6,7-tetracarboxylate (at reflux in CH₃OH/H₂O = 1:1). Interestingly, the reaction gave no desired cycloadduct in spite of the matching electronic characteristics of
the reactants. In another synthetic route, we began with tetramethylidene compound 3.9 (Figure 12), which could be prepared in gram quantities following published procedures. In the Diels–Alder reaction of dimethyl acetylenedicarboxylate (DMAD) and 3.9, followed by oxidation of the cycloadduct with chloranil (tetrachloro-p-benzoquinone), we obtained tetraester 3.10 in an overall 83% yield. This compound was efficiently brominated, using a low concentration of Br2 (presumably, via radical addition), to give the vicinal dibromo product; moreover, such reaction conditions were necessary to circumvent Wagner–Meerwein rearrangements occurring with the ionic addition of Br2 to bicyclic compounds of type 3.10.

Figure 12: Synthesis of Compounds 3.11 and 3.12 and Their Reaction with Pd(OAc)2 under the (b) Heck and (c) Griggs Coupling Conditions

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After dehydrobromination (DBU), we obtained the bromo-olefin **3.11** and subsequently attempted stannylation under standard reaction conditions (Figure 12A); note that bromostannylated alkenes are known to undergo cyclotrimerization reactions. Interestingly, the reduction of **3.11** into **3.10** took place with no formation of the desired compound (Figure 12). To avoid complications encountered in the stannylation, we investigated the cyclotrimerization of dibromoalkene **3.12** by following the methodology developed by Grigg (Figure 12B). Under these conditions, we observed the oligomerization process (1H NMR spectroscopy) at both higher (30−100 mM) and lower (10 mM) concentrations of the dibromoalkene reactant **3.12** (Figure 12B). Subsequently, we decided to probe the cyclotrimerization of **3.11** using optimized Heck type conditions (Figure 12C). In this case, the conversion of **3.11** (10−30 mM) into oligomers (1H NMR spectroscopy) appeared as the principal reaction pathway (Figure 12); in this case, we also observed (1H NMR spectroscopy) the formation of only trace quantities of the desired cyclized **3.2**. Since the Heck-type coupling of bromoalkene **3.11** failed to give the desired cyclotrimer **3.2**, we were intrigued to discover if dibromoalkene **3.12** could form **3.2** under similar experimental conditions (Figure 13). In fact, Dyker reported that aryl diiodides dissolved in DMF and in the presence of Pd(OAc)$_2$/K$_2$CO$_3$/n-Bu$_4$NBr undergo palladium-catalyzed annulation to give Ullmann-type products. The homocoupling of vinyl halides is less common but nonetheless known to produce dienes in satisfactory yields. Markedly, compound **3.12** cyclotrimerized into the desired **3.2** (77% yield, Table 3.1) when promoted by Pd(OAc)$_2$ (10%) in dioxane and in the presence of K$_2$CO$_3$, Ph$_3$P, n-Bu$_4$NBr, and 4Å molecular sieves.
Figure 13: (Top) $^1$H NMR spectra (500 MHz, CDCl3) of compounds 3.12 and 3.2 at 298.0 K. (Right) Homocoupling of 3.12 is promoted by Pd(OAc)$_2$ to give the dodecamethyl ester derivative of heptiptycene, 3.2; energy-minimized structure of compound 2.2 (Spartan, MMFFs) is shown on the right. (Bottom) Principal signal in ESI-MS spectra of 3.2 corresponds to the [M + Na]$^+$ cation, with consistent theoretical and experimental distributions of isotopes.
The $^1$H NMR spectrum of $D_{3h}$-symmetric 3.2 (Figure 13) has three signals and is akin to the one corresponding to monomeric 3.12. In particular, $^1$H NMR resonance of the bridgehead H_b proton in 3.2 is shifted further downfield ($\Delta \delta = 0.7$ ppm, Figure 13) via, presumably, magnetic deshielding of this proton by the central benzene ring (Figure 13). Furthermore, the isotope distribution of the sodiated parent ion [M + Na]$^+$ in the electrospray ionization mass spectrum of 3.2 concurs with the atomic composition of this molecule (Figure 13).

Table 1: Varying the Concentration of 3.12 Affects the Outcome of Its Cyclotrimerization with Pd(OAc)$_2$ (10 mol %) in Anhydrous Dioxane at 100°C (All reactions contained 20 mol % PPh$_3$, 10 molar equivalents of K$_2$CO$_3$, 2 molar equivalents of $n$-Bu$_4$NBr, and pulverized 4 Å molecular sieves).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration of 3.12 (mM)</th>
<th>Yield of 3.2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dioxane</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Dioxane</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane</td>
<td>15</td>
<td>36</td>
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<td>4</td>
<td>Dioxane</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>5</td>
<td>Oligomers</td>
</tr>
</tbody>
</table>
Interestingly, varying the concentration of dibromoalkene $3.2$ altered the course of the cyclotrimerization$^91$ at lower ($<10$ mM) or higher ($>15$ mM) concentration of the reactant, the yield would drop considerably (Table 3.1); the reaction was experimentally examined with up to $\sim 100$ mg of the starting material. The nature of the solvent appears to have an effect on the catalytic cycle$^92$ with more polar acetonitrile/DMF inhibiting the formation of dual-cavity $3.2$ (Table 3.1). Finally, the PPh$_3$, K$_2$CO$_3$, and $n$-Bu$_4$NBr reagents were all necessary for an effective homocoupling of $3.12$ (Table 3.2): by altering or completely removing one reactant at a time, the reaction’s outcome changed, giving rise to oligomers and/or undesired products (Table 3.2). A functionalization of $3.12$ esters in heptiptycene $3.2$ (Figure 13) would give an intriguing multivalent receptor comprising two juxtaposed cavities (Figure 14). Importantly, each of the 12 reactions must, in a linear synthesis, be high yielding to give useful quantities of the product. Alternatively, we set to probe a convergent strategy for obtaining dual-cavity baskets of type $3.3_{a-c}$ (Figure 14). First, we converted compound $3.12$ into bis-imides $3.13_{a-c}$ carrying the desired functional groups at the periphery. Then, we completed the homocoupling of the dibromoalkenes with Pd(OAc)$_2$ to obtain $3.3_{a-c}$ in $27-47\%$ yield.
Evidently, the cyclotrimerization procedure could be used for obtaining various derivatives of heptiptycene: one can place aliphatic (R = CH₂CH₂CH₃, 3.3a), benzylic (R = CH₂C₆H₅, 3.3b) or aromatic (R = C₆H₅, 3.3c) groups at the rim of the fused southern and northern cavitands (Figure 14). With proper functional groups at the rim of the dual-cavity baskets (Figure 14), one could turn these multivalent compounds into chemosensors or catalysts.⁹³
Table 2: Cyclotrimerization of 3.12 (10 mM) in Anhydrous Dioxane at 100 °C with 10 mol% Pd(OAc)₂. All reactions used 20 mol % ligand, 10 molar equivalents of base, 2 molar equivalents of the quaternary ammonium salt, and pulverized 4 Å molecular sieves.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>Molecular Sieves</th>
<th>Quaternary Salt</th>
<th>Product-Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃</td>
<td>Et₃N</td>
<td>4Å</td>
<td>n-Bu₄NBr</td>
<td>Oligomers</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃</td>
<td>Pyridine</td>
<td>4Å</td>
<td>n-Bu₄NBr</td>
<td>Oligomers</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃</td>
<td>K₂CO₃</td>
<td>4Å</td>
<td>n-Bu₄NBr</td>
<td>3.2 (77)</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>K₂CO₃</td>
<td>4Å</td>
<td>n-Bu₄NBr</td>
<td>3.10 (95)</td>
</tr>
<tr>
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<td>PPh₃</td>
<td>K₂CO₃</td>
<td>4Å</td>
<td>n-Me₄NBr</td>
<td>3.10 (95)</td>
</tr>
<tr>
<td>6</td>
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<td>No Reaction</td>
</tr>
<tr>
<td>7</td>
<td>PPh₃</td>
<td>K₂CO₃</td>
<td>4Å</td>
<td>n-Bu₄NBr</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

3.4 Spectral Properties of Host

Accordingly, understanding the absorption as well as emission characteristics of dual cavitands is important for assessing a potential application in the area of sensor design. Compounds 3.14, 3.15, and 3.3ₕ contain an increasing number of phthalimide chromophores (from one to six, Figure 15), which in two baskets are embedded within the bicyclic framework. The UV–vis spectrum of the model compound 3.14 showed an electronic transition at 220 nm (ε = 56000 M⁻¹ cm⁻¹, Figure 15) that is presumed to be of
Figure 15: UV−vis and emission spectra ($\lambda_{ex} = 220$ nm, CH$_3$CN) of compounds 3.14 (black box), 3.15 (red box), and 3.3b (blue box) were obtained at 298.0 K; for the emission measurements, each sample was 0.1 μM. Computed (B3LYP/SV(P)) electronic transitions of 3.14 (top right) and 3.3b (bottom right) along with difference density plots corresponding to transitions at 219 and 242 nm, respectively; note that the red contours represent the depletion of electron density from the ground state, while the green contours represent the accumulation of electron density in the excited state. Computational analysis was provided by the Hadad group.
The π → π* character, in addition to a less prominent band at 237 nm ($\varepsilon = 12800 \text{ M}^{-1} \text{ cm}^{-1}$, Figure 15). Interestingly, the π → π* transition at 220 nm becomes red-shifted in $C_{3v}$-symmetric basket 3.15 ($\Delta\lambda = 7.0 \text{ nm}$, Figure 15) and even more red-shifted in $D_{3h}$-symmetric 3.3b ($\Delta\lambda = 21.0 \text{ nm}$, Figure 15); thus, there ought to be a conjugative interaction between the chromophores, despite their formal “isolation” with saturated carbon atoms. Moreover, the intensities of the π → π* transitions at $\lambda_{\text{max}}$ (ε3.15:ε3.16:ε3.3b = 1:3:2:18, Figure 15) increases with the number of phthalimide units (1:3:6, Figure 15): the proportion of the extinction coefficients exceeds the number of phthalimides. To obtain more insight into the photophysical characteristics of these compounds, we computed the electronic spectra of 3.14 and 3.3b using time-dependent density functional theory (B3LYP/SV(P)). In particular, model compound 3.14 was found to exhibit an electronic transition of π → π* character at 219 nm, consistent with the experimental data (Figure 15). Furthermore, the computed UV–vis spectrum of 3.3b shows a pronounced vertical excitation at 242 nm (Figure 15), corroborating the observed red shift of the π → π* transition. In fact, the electron density difference plot of 3.3b (Figure 15) indicates a delocalization of the electron density of the corresponding transition contributing to the observed π → π* shift. N-Alkylphthalimides exhibit a rather weak emission characterized with a low quantum yield ($\Phi \sim 10^{-3}$). Upon excitation at 220 nm, the emission intensity from dual-cavity basket 3.3b appeared 4 times greater than in 3.15 and 12 times greater than in the model compound, 3.14 (Figure 15).
3.5 Conclusions

Apparently, embedding a phthalimide chromophore within a rigid bicyclic framework of dual-cavity 3.3b improves the efficiency of the fluorescence emission, which could potentially be used for signaling the presence of various analytes. In conclusion, palladium acetate promotes the homocoupling of dibromoalkenes into a variety of functional heptiptycenes. The cyclotrimerization procedure complements those already available in the literature and will be of interest for the preparation of multivalent dual-cavity hosts that could, perhaps, report on the presence of small guest molecules in organic and aqueous media\textsuperscript{97} or promote chemical reactions inside the confined environments.\textsuperscript{98}
Chapter 4: Towards Chiral Inner Space


4.1 Introduction

The resolution of chiral drugs and drug intermediates via fractional crystallization of diastereomeric salts represents a form of molecular recognition, allowing the production of enantiopure pharmaceuticals. In line with the methodology, M. Newman and coworkers completed the separation of racemic (P/M)–hexahelicenes using a chiral derivative of fluorenone. Allegedly, the aromatic fluorenone forms a charged-transfer complex with inherently chiral hexahelicenes so that numerous π–π interactions trigger the aggregation and thereby precipitation of the less-soluble diastereomer. Furthermore, Cram and coworkers developed a semi-empirical approach, "the tripodal binding model",
for predicting the complexation aptitude of $C_2/D_2$ symmetric 1,1'-binapthyl corands toward racemic amino acids.\textsuperscript{1} In this vein, the classical three-point interaction model\textsuperscript{104} or other variants\textsuperscript{105} are employed to explain diastereoselectivity of drug-receptor interactions as well as inclusion complexations.\textsuperscript{106} Hosts with an enforced cavity – cavitands are capable of resolving chiral compounds\textsuperscript{107} yet the experimental outcome of such recognition events is difficult to rationalize.\textsuperscript{108} As many naturally occurring molecules, drugs, metabolites, chemical weapons and commodity chemicals lack the rotation-reflection axis of symmetry there exists a need to expand the scope of artificial chiral hosts\textsuperscript{109} to selectively capture these substances\textsuperscript{110} on the basis of their size, shape and electronic structure as well as learn more about rules that govern the process of stereoselective recognition.\textsuperscript{111} Chiral receptors could thus serve as counterparts to naturally occurring enzymes and antibodies for rapidly and accurately reporting on the presence of stereoisomeric substances in environment\textsuperscript{112} and promoting their transformation.\textsuperscript{113} In this vein, this chapter delineates an effective macrocyclization strategy that can be used for the rapid preparation of hosts containing a $C_3$ axis of symmetry. In particular, we have used methods of experimental and computational chemistry for investigating the formation of cup-shaped 4.1\textsubscript{syn} possessing a twisted framework and chiral inner space (Figure 16). We then expanded the scope of our preliminary investigations by: (a) optimizing a procedure for obtaining functionalized and twisted baskets with either right- ($P$) or ($M$) sense of twist (Figure 21) and (b) preparatively resolving such racemic host into pure enantiomers (Figure 22).
These easily accessible hosts are $C_3$ symmetric, possessing: (a) six esters at the rim for additional functionalization, (b) unique chiroptical characteristics, (c) photochemically sensitizing sidewalls for promoting photochirogenesis$^{114}$ as well as having (d) deep and twisted inner space for discriminating chiral guests (Figure 27)$^{115}$.

4.2 Synthesis of the Novel [3.2.1] Fused Central Core

In the presence of Lewis- or Brønsted acids, indene 4.2 undergoes a cationic polymerization to give polyindenes (Figure 17A)$^{116}$. The propagation step of this addition includes the formation of the indanyl cation$^{117}$, which enables the chain growth. In light of this mechanism, we reasoned that in the presence of an acid, indene derivative 4.3 should undergo a cationic polymerization in competition with a Friedel–Crafts annulation to give dibenzobicyclo[3.2.1]octadiene 4.4$^{118}$ (Figure 17B); the hypothesis was based on earlier studies of electrophilic ring closures (cyclialkylations) of aryl-substituted compounds$^{119}$. Interestingly, we found that compound 4.3 (1.0 mM, CH$_2$Cl$_2$), in the presence of methanesulfonic acid (CH$_3$SO$_3$H, 50.0 mM) would give 4.4 in a low yield (Table 3), with the polymerization reaction dominating the conversion of starting material.
Figure 16: Top: Energy-minimized structure (B3LYP/6-31G*) of basket $4.1_{\text{syn}}$ and its $^1$H NMR spectrum (400 MHz, CDCl$_3$). Bottom: Energy-minimized structure (B3LYP/6-31G*) of compound $4.1_{\text{anti}}$ and its $^1$H NMR spectrum (400 MHz, CDCl$_3$).
Figure 17: A) In the presence of acid, indene (4.2, R = H) undergoes a cationic polymerization to give polymeric products. B) In the presence of CH$_3$SO$_3$H, compound 4.3 gives dibenzobicyclo[3.2.1]octadiene 4.4 in a 10–77 % yield (Table 3).

We then turned our attention to trivalent 4.5$^{a/b}$, which via a series of three of these cyclialkylation reactions could give cup-shaped 4.1$^{syn}$ (Figure 18). First, we synthesized 4.5$^{a/b}$ by completing the coupling of compound 4.6 with indene (Figure 4.3). Although the separation of diastereomeric 4.5$^{a}$ and 4.5$^{b}$ was an arduous task, $^1$H NMR spectroscopic measurements suggested that two species ($C_3$ symmetric 4.5$^{a}$ and $C_1$ symmetric 4.5$^{b}$) formed in an approximate 1:5 ratio (Figure 36). Indeed, the result of an HPLC separation corroborated this proportion of the 4.5$^{a}$/4.5$^{b}$ stereoisomers (Figure 37). We tested various acids for catalyzing the conversion of 4.5$^{a/b}$ into 4.1$^{syn/anti}$ in CH$_2$Cl$_2$ and at 298.0 K. Markedly, triflic (CF$_3$SO$_3$H, pKa = -14) and methanesulfonic acids (CH$_3$SO$_3$H, pKa = -2.6) promoted the reaction, giving the desired cyclotrimer as a mixture of syn/anti diastereomers in a 1:5 ratio and a 47% overall yield (Table 3).
Table 3: The annulation of compound 4.3 (1.0 mM) into 4.4 and of 4.5a/b into 4.1_{syn/anti} was promoted with CH₃SO₃H (50.0 mM), as determined after HPLC separation.\textsuperscript{[a]}

Substrate was added via syringe pump over 2h.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>Temperature (K)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3</td>
<td>CH₂Cl₂</td>
<td>298.0</td>
<td>10</td>
</tr>
<tr>
<td>4.3</td>
<td>ClCH₂CH₂Cl</td>
<td>344.0</td>
<td>62</td>
</tr>
<tr>
<td>4.3</td>
<td>ClCH₂CH₂Cl</td>
<td>344.0</td>
<td>77\textsuperscript{[a]}</td>
</tr>
<tr>
<td>4.5a/b</td>
<td>CH₂Cl₂</td>
<td>298.0</td>
<td>47</td>
</tr>
<tr>
<td>4.5a/b</td>
<td>CH₂Cl₂</td>
<td>344.0</td>
<td>57</td>
</tr>
<tr>
<td>4.5a/b</td>
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<td>344.0</td>
<td>75</td>
</tr>
<tr>
<td>4.5a/b</td>
<td>ClCH₂CH₂Cl</td>
<td>344.0</td>
<td>85\textsuperscript{[a]}</td>
</tr>
</tbody>
</table>
Figure 18: (Left) $C_3$ symmetric $4.1_{\text{syn}}$ has a screw-shaped structure with either a right \((M)-4.1_{\text{syn}}\) or left-handed \((P)-4.1_{\text{syn}}\) sense of twist. (Right) HPLC chromatogram of $4.1_{\text{syn}}$ (hexane/isopropanol = 93:7, Chiracel OD-H) shows two signals corresponding to a racemic mixture of \((M/P)-4.1_{\text{syn}}\) baskets. (Right) The synthesis of $4.5_{a/b}$ and an electron-pushing mechanism to describe the first cyclialkylation with $4.5_{a/b}$ transforming into $4.1_{\text{syn/anti}}$. 
The cationic polymerization of 4.5a/b (Figure 17B) is a bimolecular process with, perhaps, a negative entropy of activation characterizing the chain extension. In line with this premise, we increased the reaction’s temperature to assist the intramolecular annulation at the expense of the intermolecular polymerization. Indeed, the overall yield of 4.1syn/anti (Table 3) improved in refluxing CH2Cl2 (57 %), and the yield increased to 75% with the higher boiling ClCH2CH2Cl. In fact, when the cyclialkylation of 4.5a/b was completed with a slow addition of the substrate (using a syringe pump), the yield of desired 4.1syn/anti increased to 85% (Table 3). Compounds 4.1syn and 4.1anti were separated by column chromatography (SiO2, hexanes/acetone = 10:1).

4.3 Mechanistic Considerations to the Cyclialkylation

The full assignment of the 1H NMR resonances (Figure 4.1) was accomplished with the assistance of 1H-1H COSY and NOESY correlations (Figure 38 - Figure 41). Importantly, C3 symmetric 4.1syn comprises three [3.2.1] bicyclic rings twisted in the same direction so that the molecule is helical with either a right (P) or left-handed (M) sense of twist (Figure 18A). Indeed, the HPLC chromatogram of 4.1syn revealed two peaks corresponding to a racemic mixture of (R6/S6)-4.1syn basket. To investigate the mechanism of the macrocyclization of 4.5a/b, we used methods of both experimental and computational chemistry (Figures 4.4 and 4.5). First, the electron-pushing formalism suggests that the formation of the indanyl cation intermediate is followed by an
intramolecular Friedel–Crafts reaction to close the seven-membered ring (Figure 18); the process is then repeated twice to give $4.1_{\text{syn/anti}}$. If the proton transfer(s) governs the rate law of the reaction (Figure 19), then general-acid catalysis (A-SE$_2$ type mechanism) takes place.$^{120}$ Alternatively, if the formation of the σ complex is rate-limiting, then a specific-acid (A1 type, Figure 19) mechanism operates. We monitored the depletion of reactant 4.5$_{a/b}$ with time to find that the reaction is first order in this compound (Figure 19).

Additionally, we found that the reaction is of a higher order in methanesulfonic acid: note that the excessive amounts of acid (10–80 equivalents) were used to imply pseudo-first order conditions. Higher rate order in acid has been previously observed in electrophilic additions,$^{121}$ occurring in nonpolar solvents and thereby suggesting the involvement of multiple CH$_3$SO$_3$H molecules in the protonation. In fact, the rate law pertaining to the cyclization of monomeric 4.3 (Figure 17) was also found to be higher order in acid ($v=k_{\text{obs}}[4.3][\text{CF}_3\text{SO}_3\text{H}]^2$, Figure 42). Furthermore, we observed the formation of the two reactive intermediates during the conversion of 4.5$_{a/b}$ into 4.1$_{\text{syn/anti}}$ (Figure 43), which is in line with the sequential nature of this transformation (Figure 19). Since the experimental rate law ($v=k_{\text{obs}}[4.5_{a/b}][\text{CF}_3\text{SO}_3\text{H}]^n$, $n = 2$ or 3) could be fit to both general and specific-acid mechanistic scenarios, we examined the addition of CD$_3$SO$_3$D to 4.5$_{a/b}$.

In particular, we hypothesized that a pre-equilibrium step would cause for deuterium atoms to be incorporated into the reactant upon the initiation of the reaction. In line with that discerning the complete role of the acid in promoting the formation of 4.1$_{\text{syn/anti}}$ would necessitate additional experimentation. Along with the kinetic measurements, we
Figure 19: Top: A potential energy diagram for the conversion of 4.5a/b into 4.1syn/anti with CH₃SO₃H (HA). Bottom: The change in the concentration of 4.5a/b (1.0 mM) with CH₃SO₃H (10–80 mM) was monitored by HPLC (334 K, ClCH₂CH₂Cl). The data was analyzed by a nonlinear least-square analysis (SigmaPlot 12.0) and fitted to a first-order kinetic model to give kobs (R² > 0.99). When pseudo-first-order coefficients kobs were plotted against the concentration of CH₃SO₃H, a second (R² > 0.96) or third-order dependence (R² > 0.97, see the fitted line) on the reactant was apparent. The calculated thermodynamic ΔG values (in kcal mol⁻¹) were computed at the TPSSh/6-311 + G**/B3LYP/6-31G* level of theory. Computational analysis was provided by the Hadad group.
this premise, we found no deuterium atoms (\(^1\)H NMR spectra, Figure 44) in \(4.5_{a/b}\) after ~40% completion of the reaction. Moreover, we found a primary kinetic isotope effect of \(k_H/k_D = 2.2\) (Figure 45) suggesting that the proton transfer step(s) are rate limiting;\(^{122}\) note utilized a computational approach with density functional theory,\(^{123}\) and optimized various geometries of \(4.5_{a/b}, I_1, I_2,\) and \(4.1_{syn/anti}\) at the B3LYP/6-31G* level of theory and then completed a single-point energy calculation at the TPSSh/6-311 +G** level of theory (Figure 19). We noted that there is a considerable difference in the thermodynamic stability of these constitutional isomers. In brief, the conversion of \(4.5_{a/b} \rightarrow I_1 \rightarrow I_2 \rightarrow 4.1_{syn/anti}\) follows a “downhill” trajectory in which the stability of the product is 17.2 kcal mol\(^{-1}\) (\(\Delta G_{298}\), Figure 19) greater than that of the reactant. The two diastereomeric products \(4.1_{syn}\) and \(4.1_{anti}\), however, were calculated to have a comparable energy content (\(\Delta G_{298}^{syn/anti} = -0.8\) kcal mol\(^{-1}\)). Importantly, a mixture of diastereomeric \(4.5_{a/b}\) (~1:5) was found under all reaction conditions give \(4.1_{syn/anti}\) in the same ~1:5 ratio (Figure 18). In line with the computational results, we deduced that the reaction is under kinetic control, with two reaction pathways occurring simultaneously (Figure 18): the \(RRR/SSS\) stereoisomer (compound \(4.5_a\)) converts into \(4.1_{syn}\) basket whereas the other \(RRS/SSR\) stereoisomer (compound \(4.5_b\)) turns into \(4.1_{anti}\).
Figure 20: A) The occurrence of the Wagner–Meerwein shifts was probed with the conversion of a $4.5_{a/b}$-d$_6$ substrate into $4.1_{3syn/anti}$-d$_6$ (Figure 46). B) The macrocyclization of the indanyl cation of $4.3$ was found (TPSSh/6-311+G**//B3LYP/6-31G*) to have a low activation barrier ($\Delta G = 9.9$ kcal mol$^{-1}$) relative to possible hydride migrations. Computational analysis was provided by the Hadad group.
In line with such a proposition, we treated 4.1\text{syn/anti} with CH₃SO₃H (50.0 mM) to find no change in the quantity or the proportion of the two compounds after a prolonged period of time (24h). Furthermore, the intermediate indanyl cation could be a subject of rapid hydride-shifts (Figure 20A), which may cause the “crossover” between two parallel reaction pathways. First, we completed the annulation of tris-indene 4.5\text{a/b-d6} (with isotopes installed at C₁ and C₄, Figure 20A) to find product 4.1\text{syn/anti-d6} carrying deuterium atoms at the original sites (Figure 46). Evidently, the Wagner–Meerwein rearrangements (Figure 20A) were not occurring in the reaction. This experimental observation is also in agreement with computational results (TPSSh/6-311 + G**//B3LYP/6- 31G*, Figure 20B) showing a considerable activation barrier of 21.2 kcal mol⁻¹ for the 1,2-hydride shift. The suprafacial 1,4-sigmatropic shift of hydride (Figure 20B) was found to be even more energy-demanding (ΔG²⁹⁸K = 53.8 kcal mol⁻¹). In fact, the conversion of the indanyl cation into the σ complex appears to be the lowest energy pathway (ΔG²⁹⁸K = 9.9 kcal mol⁻¹, Figure 20B) available to this high-energy intermediate. Rapid access to concave compounds is critical for obtaining useful quantities of hosts capable of trapping smaller molecules, for application in the area of sensing and catalysis.¹²⁴ The preceding section described an effective cyclialkylation reaction that one can use for obtaining cavitands with a chiral inner space. The stage is now set for exploring the scope and characteristics of these concave hosts.
4.4 Reaction Methodology and Resolution of Twisted Baskets

With a new method in hand to generate a complex chiral host in two steps utilizing indene derivatives in a convergent strategy, we then turned our attention to installing functionalities onto the periphery for the purpose of additional functionalization and the resolution of the enantiomers. To obtain the extended chiral cavity as seen in basket (M/P)-4.7_syn (Figure 21), we started with commercially available 5-indanol and converted it into compound **4.8** (Figure 22),\textsuperscript{125} following known procedures (Figure 28).\textsuperscript{126} The free-radical bromination of indane derivative **4.8** followed by, allegedly, E\textsubscript{1} elimination of the bromoalkane intermediate gave indene **4.9**. Compound **4.9** was then deprotonated with a strong base (n-BuLi) at low temperature, acting as a nucleophile in promoting SN\textsubscript{2}-like substitution of the three iodine groups in compound **4.10**. When equimolar quantities of the reactants were used, the reaction gave two diastereomeric products **4.11\textsubscript{a/b}** (Figure 22) in the ratio of 1:5. The cyclialkylation of such diastereomeric mixture of **4.11\textsubscript{a/b}** was then catalyzed with methanesulfonic acid to give (M/P)-4.7\textsubscript{syn} and (M/P)-4.7\textsubscript{anti} in the ratio of 1:5 (Figure 22). On the basis the earlier sections, we reason that this transformation is also under kinetic control, with homochiral **4.11\textsubscript{a}** giving a racemic mixture of (M/P)-4.7\textsubscript{syn} and heterochiral **4.11\textsubscript{b}** transforming into (M/P)-4.7\textsubscript{anti}.\textsuperscript{127,128}
Figure 21: (A) Energy-minimized structures of twisted baskets \((P)− 4.7_{syn}\) and \((M)− 4.7_{syn}\) and their corresponding chemical structures; note that each host has six stereogenic centers of the same kind \(R\) or \(S\). (B) A view of the van der Waals surface (Chimera) of twisted basket \((P)− 4.7_{syn}\) (left) with sidewalls having right-handed helicity and six ester groups at its rim (right).
Figure 22: The synthesis of twisted basket \((M/P)-4.7_{\text{syn\-anti}}\) can be completed in several steps and an overall 42\% yield.

In order to obtain more of cup-shaped \((M/P)-4.7_{\text{syn}}\), one clearly needs to govern the stereoselectivity of the conversion of 4.9 into 4.11\textsubscript{a/b}, thereby increasing the formation of the homochiral 4.11\textsubscript{a} (Figure 22). Toward this goal, we investigated the coupling of indene derivatives 4.9, 4.12, 4.13. (Figure 23) with the triiodo 4.10 under identical
experimental conditions. Importantly, compound 4.9 (pKa < 18) is believed to be the most acidic in the series, while the acidities of 4.13 (pKa = 18 - 20) and 4.12 (pKa = 20) are somewhat lower; note that we estimated pKa of 4.13 from ¹H NMR spectroscopic studies (Figure 47). More basic and therefore more nucleophilic indenes (Figure 23) gave rise to greater quantities of the homochiral 4.11a. Presumably, stronger nucleophiles promote faster nucleophilic substitutions with two diastereomeric products forming in a ratio close to the statistical one (3:1).

Figure 23: Three indene derivatives 4.9, 4.12, 4.13 were reacted with 4.10 to give a diastereomeric mixtures of products in different ratio. Reactions were run with 3 equivalents of the indene derivative. aThis reaction utilized 6 molar equivalents.
Figure 24: The chromatographic separation (SiO₂, hexanes : diethyl ether = 2:1) of 4.15ₚ and 4.15ₘ, obtained via Titanium(IV) promoted trans-esterification of (M/P)-4.7ₚₚ, is facile with each compound showing a separate band on a thin-layer chromatographic plate. Additional spectroscopic analysis of each chromatographic fraction is in line with the top band corresponding to 4.15ₘ while the bottom one to 4.15ₚ.
In accord with this logic, we used a greater excess of compound 4.9 with respect to electrophilic 4.10 to increase the reaction's rate (Figure 23). Under the reaction's conditions we were indeed able to generate more of desired 4.11a with six molar equivalents of the nucleophile being optimal for completing the substitution. To resolve the racemic (M/P)-4.7syn, we decided to investigate the transesterification128 of (M/P)-4.7syn with (1R,2S,5R)-(−)-menthol in the presence of a titanium(IV) catalyst 4.14 (Figure 24).129 To ensure complete transformation of the hexaester reactant into sterically hindered 4.15p and 4.15m, with six menthol moieties at the rim, we used menthol as solvent and run the reaction at an elevated temperature (180 ºC) for a prolonged period of time.130 Importantly, the chromatographic separation of diastereomeric 4.15p/4.15m was facile with each compound having a distinct Rf value (Rf = 0.37 and 0.50, Figure 24). 1H NMR spectra (400 MHz, CDCl3) of isolated 4.15p and 4.15m (Figure 25A) revealed a single set of resonances corresponding to, in each case, a C3 symmetric compound; note that there was no decoalescence of 1H NMR signals at lower temperatures (Figure 48).

First, we examined the 1H NMR spectrum of model compound 4.16 (Figure 25A) and assigned all of its hydrogen nuclei with the assistance of its 1H−1H COSY NMR spectrum (Figure 49) and the 1H NMR spectroscopic data for (1R, 2S, 5R)-(−)-menthol. Next, we recorded 1H−1H COSY NMR spectra of 4.15p/4.15m (Figure 50 -Figure 51) and assigned the resonances to proton nuclei in these dendrimer-like molecules (Figure 25). A correlation between the 1H NMR spectra of C2 symmetric...
Figure 25: (A) $^1$H NMR spectra (400 MHz, CDCl₃) of model compound 4.16 (top) and twisted baskets 4.15ₘ (middle) and 4.15ₚ (bottom). (B) Chemical structures of 4.16 and 4.15ₚ with selected protons labeled from Hₐ to Hₙ. (C) Energy-minimized (MMFFs, Monte-Carlo conformational search; 1000 steps) structures of 4.15ₘ and 4.15ₚ, representing the most abundant conformers (> 95%) obtained in the calculation; note that C–H---π centroid distances are shown: hydrogen atoms are removed for clarity.
4.16 and C3 symmetric 4.15p/4.15m is obvious, although there is an upfield shift of two doublets corresponding to Hα/β nuclei and a multiplet corresponding to adjacent Hm proton (Figure 25A/B). To address the observation, we completed a Monte Carlo conformational search (MMFFs force field, Spartan) of 4.15p/4.15m with the calculation suggesting a conformational distribution being predominantly populated (>95% on the basis of the Boltzmann distribution at 298 K) with structures closely resembling those shown in Figure 25C. Thus the 4.15p diastereomer places one of its isopropyl groups in the cavity of the cup-shaped and twisted framework with Hα/Hβ and Hm nuclei residing in the shielding region of the surrounding naphthalene rings. On the contrary, 4.15m stereoisomer positions an isopropyl group at top of the cavity (Figure 25C) with Hα/Hβ and Hm nuclei being less diamagnetically shielded with the basket’s aromatics. The results of the conformational analysis, therefore, suggest that the middle 1H NMR spectrum in Figure 25A corresponds to 4.15m (Rf = 0.50, Figure 24) while the bottom one correlates with 4.15p (Rf = 0.37, Figure 24)!

4.5 Optical Properties of the Diastereomeric Hosts

To additionally probe the absolute configuration of compounds 4.15p/4.15m, encompassing right- and left-handed "cups" (Figure 21), we used the exciton chirality method (Exciton Coupled Circular Dichroism spectroscopy, ECCD).131 In this regard, three naphthalene chromophores132 that constitute the "sides" of twisted baskets
4.15_p/4.15_m are embedded in the bicyclic and chiral framework, formally belonging to the second chiral sphere.\textsuperscript{133} Upon the absorption of light at about 220 nm (naphthalene’s $^1B_b$ transition in the Platt's notation), each of the juxtaposed naphthalenes should in

4.15_p/4.15_m develop a strong electric dipole transition moment positioned along the long axis of the aromatic ring (Figure 26). In line with the ECCD, there should be an exciton coupling of the $^1B_b$ transition dipole moments of the three degenerate chromophores to give rise to a bisignate spectrum whose rotational strengths and sign are a function of the interchromophoric distance (d) and orientation ($\Omega$). In particular, the sign of the couplet is based on the semiempirical exciton chirality rule which states: the negative chirality (the longer wavelength component has $\Delta \varepsilon < 0$) is obtained when the chromophores are positioned in space so that a counterclockwise rotation of the front electric dipole moment by an acute angle brings it onto the exciton axis in the back.\textsuperscript{134} Indeed, CD spectra of diastereomeric baskets 4.15_p/4.15_m (Figure 26) showed the expected ECCD couplets centered at 242 nm ($\pi$ to $\pi^*$ transition, Figure 26) with two diastereomeric baskets having the opposite rotational strengths. Specifically, the positive Cotton effect (CE) at 234 nm ($\Delta \varepsilon_1 = 284$ M$^{-1}$ cm$^{-1}$, blue spectrum in Figure 26) followed by a negative CE at 251 nm ($\Delta \varepsilon_2 = -252$ M$^{-1}$ cm$^{-1}$, blue spectrum in Figure 26) and therefore the negative sign of exciton chirality is consistent with the position of exciton axis in 4.15_p (Figure 4.11). As this spectrum corresponds to the basket isolated as the first chromatographic fraction ($R_f = 0.37$, Figure 22), the CD assignment corroborates the absolute chirality obtained from the $^1$H NMR spectroscopic measurements (Figure 23)!
Figure 26: Electronic absorption (UV-Vis, top left) and circular dichroism (CD, bottom left) spectra of 4.15ₚ (blue, 2.5 μM), 4.15ₘ (red, 2.5 μM) and 4.16 (black, 5.0 μM) in hexanes at 298 K. Energy-minimized structure of model compound 4.16 (MMFFs, Spartan) with the projected ¹Bₖ transition dipole moment along the naphthalene chromophore (top right). The negative exciton chirality characterizes twisted basket 4.15ₚ since its three naphthalene chromophores (only two are shown) are positioned in space so that a counterclockwise rotation of the front electric dipole moment (blue) by an acute angle brings it onto the exciton axis in the back (bottom right).
Furthermore, the large A (|Δε1| + |Δε2|) value of 535 indicates a through-space interaction of the naphthalene chromophores in 4.15p with a contribution from all three ECCD couplets135 thereby following the pairwise additivity principle. Notably, model compound 4.16 exhibits a featureless CD spectrum (black spectrum in Figure 26) with low rotational strengths at all wavelengths. Two menthol units are, in the absence of the bicyclic chiral framework, exerting a negligible symmetry-breaking perturbation of the electronic states of 4.16. At last, the emission spectra of diastereomeric 4.15p/4.15m are comparable (λex = 280 nm, Figure 27).

Figure 27: (A) Emission spectra of 4.15p (blue, 250 nM), 4.15m (red, 250 nM) and 4.16 (black, 500 nM) in hexanes at 298 K were obtained upon excitation of each compound at 280 nm. (B) Twisted baskets possess unique chiroptical (see Figure 26) and emission characteristics for reporting on the presence of minute quantities of important chiral substances in environment.
Importantly, the signal intensities were for the baskets (I = 282 a.u. at λ<sub>em</sub> = 363 nm, Figure 27) found to be seventy times stronger than for the model compound 4.16 (I = 4 a.u. at λ<sub>em</sub> = 363 nm, Figure 27A). Given that the absorption extinction coefficients (ε, Figure 26) at 280 nm are three times greater for baskets than for the model compound, we reason based on experiments performed in Chapter 3 that the naphthalene chromophores ought to have a greater fluorescence quantum yield, within the rigid framework of 4.15<sub>p</sub>/4.15<sub>m</sub>

4.6 Conclusions

The preceding chapter describes a convenient convergent synthetic strategy to construct an almost entirely chiral inner space as seen in 4.1<sub>syn</sub>. The facile separation of 4.15<sub>p</sub> and 4.15<sub>m</sub> will allow for exploration into many possible applications, including studying recognition phenomena, and perhaps building chiroptical sensors capable of reporting on the presence of minute quantities of chiral substances in the environment.136
5.1 General Procedures

All chemicals were purchased from commercial sources, and used as received unless stated otherwise. All solvents were dried prior to use according to standard literature protocols. Chromatography purifications were performed using silica gel 60 (Sorbent technologies 40-75 µm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed on silica-gel plate w/UV254 (200 µm). Chromatograms were visualized by UV-light. $^1$H and $^{13}$C NMR spectra were recorded, at 400 MHz and 100 MHz respectively, on a Bruker DRX-400 spectrometer. They were referenced using the solvent residual signal as internal standard. Samples were prepared using CDCl$_3$ and CD$_2$Cl$_2$ from Cambridge Isotope Laboratories. The chemical shift values are expressed as δ values and the coupling constants values (J) are in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad. High resolution electrospray ionization mass (HRMS-ESI) spectra were recorded on a Bruker Micro-TOF ESI instrument using a sodium formate solution as an internal standard.
5.2 Synthetic Procedures

5.2.1 Chapter 1 Synthetic Procedures

All compounds in Chapter 1 have previously been reported according to the literature described within. In particular, molecular basket 1.4 can be prepared according to the following literature protocol: Maslak, V., Yan, Z., Xia, S., Gallucci, J., Hadad, C. M., & Badjić, J. D. (2006). Design, Synthesis, and Conformational Dynamics of a Gated Molecular Basket. *Journal of the American Chemical Society*, 128(17), 5887–5894.

5.2.2 Chapter 2 Synthetic Procedures

Compounds 2.1–2.3: The balloon of hydrogen gas was removed from the reaction flask (see the preparation of 2.4) and the solvent evaporated by blowing argon gas over the reaction mixture. Following, degassed CH₃OH/H₂O = 4/1 (90.0 mL) solution was added and the flask kept under an atmosphere of argon. The solution of 2.4 (205 mg, 1.2 mmol) was cooled to -78°C and transferred to a CH₂Cl₂ solution of 2.5a (c.a. 1000 mg, 3.4 mmol; note that on the basis of multiple runs, we estimated 65% yield in the formation of 2.5a) using a cannula and positive pressure of argon. The reaction mixture was allowed to warm to room temperature and was stirred for 4 days. Note that right upon the addition of compound 2.4 to 2.5a-c the solution turned purple/red while at room temperature the color changed to red/brown. The solvent was removed under reduced pressure and the crude product re-dissolved in CH₂Cl₂ (50 mL) and washed with saturated NaHCO₃ (50 mL). The aqueous phase was extracted with CH₂Cl₂ (2 x 50 mL) while the combined organic phase was dried with Na₂SO₄ and the liquid removed under reduced pressure. The crude product was purified by column chromatography (SiO₂, EtOAc:hexanes:2-propanol:Et₃N = 100:10:1:0.5) to give 2.1anti (54 mg, 5%) as a yellow solid. Compound 2.1syn was
isolated by filtering the crude product (from column chromatography, Rf = 0.3) through a
pad of silica using EtOAc:hexanes:2-propanol:Et3N = 100:20:0.5:0.5 mobile phase to
wash off the impurities. The desired product 2.1syn was removed from the stationary
phase with CH2Cl2:CH3OH:Et3N = 5:1:0.1 and isolated as a crude yellow solid (17 mg,
1.6 %).

**Compound 2.1syn**: 1H NMR (400 MHz, CD2Cl2): 6.14 (t, J = 1.9 Hz, 6H), 4.43 (d, J = 2.6
Hz, 6H), 3.85 (dd, J = 4.7, 2.1 Hz, 6H), 3.56 (dd, J = 6.0, 2.7 Hz, 3H), 3.27 (dd, J = 6.2,
2.9 Hz, 3H), 3.09 (q, J = 7.1 Hz, 6H), 0.54 (t, J = 7.1 Hz, 9H). 13C NMR (100 MHz,
CD2Cl2): 172.69, 159.89, 141.03, 131.25, 65.57, 65.45, 63.33, 63.06, 62.77, 33.66, 13.28.
HR-MS (ESI): calculated (M+Na)+ = 932.2916, found: 932.2906.

**Compound 2.1anti**: 1H NMR (400 MHz, CD2Cl2): 6.11 (s, 6H), 4.43 (d, J = 3.5 Hz, 6H),
3.83 (s, 6H), 3.57 (s, 3H), 3.27 (s, 3H), 3.02 (m, 6H), 0.56-0.48 (m, 9H). 13C NMR (100
MHz, CD2Cl2): 172.84, 172.80, 172.61, 159.87, 159.82, 159.76, 141.02, 140.96, 131.32,
131.23, 131.17, 65.81, 65.73, 65.60, 65.58, 65.50, 63.34, 63.27, 63.22, 62.81, 62.78,
62.75, 62.61, 33.70, 33.60, 13.42, 13.29. Note that some of the 13C signals are missing,
and we suspect that their overlap may contribute to the observation. HR-MS (ESI):
calculated (M+Na)+ = 932.2916, found: 932.2909.

**Compound 2.2syn**: This compound was isolated in 14 % yield as a pale yellow solid. 1H
NMR (400 MHz, CD2Cl2): 6.15 (t, J = 1.9 Hz, 1H), 4.43 (d, J = 2.6 Hz, 1H), 3.86 (dd, J =
4.6, 2.1 Hz, 1H), 3.59 (d, J = 2.5 Hz, 1H), 3.28 (dd, J = 6.1, 3.0 Hz, 1H), 3.04 (t, J = 6.9
Hz, 1H), 1.14 – 0.98 (m, 1H), 0.29 (t, J = 7.4 Hz, 1H). 13C NMR (100 MHz, CDCl3):
172.02, 160.03, 140.64, 131.06, 64.93, 64.86, 63.04, 62.98, 62.50, 39.94, 20.82, 10.33.
HR-MS (ESI): calculated (M+Na)+ = 974.3385, found: 974.3419.
Compound 2.2\textsubscript{anti}: this compound was isolated in 21 % yield as a yellow solid. \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}): 6.12 (s, 6H), 4.44 (m, 6H), 3.84 (s, 6H), 3.58 (s, 3H), 3.28 – 3.26 (m, 3H), 2.97 (m, 6H), 1.00 (m, 6H), 0.26 (m, 9H). \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}): 173.13, 172.91, 159.94, 159.87, 159.84, 131.44, 131.37, 131.34, 131.32, 65.81, 65.70, 65.57, 65.56, 65.45, 63.40, 63.34, 63.28, 62.89, 62.85, 62.82, 40.30, 40.23, 21.15, 10.62, 10.07, 8.10. Note that some of the \textsuperscript{13}C signals are missing, and we suspect that their overlap may contribute to the observation. HR-MS (ESI): calculated (M+Na\textsuperscript{+}) = 974.3385, found: 974.3396.

Compound 2.3\textsubscript{anti}: this compound was isolated in 55 % yield as a yellow solid. \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}): 6.13 (t, J = 3.7 Hz, 6H), 4.46 (dd, J = 5.1, 2.5 Hz, 6H), 3.86 (dd, J = 4.2, 2.3 Hz, 6H), 3.62 – 3.57 (m, 3H), 3.31 – 3.26 (m, 3H), 3.02 (t, J = 6.9 Hz, 6H), 1.05 – 0.96 (m, 6H), 0.96 – 0.87 (m, 3H), 0.63 (dd, J = 15.1, 7.5 Hz, 6H), 0.59 – 0.50 (m, 3H), 0.32 (t, J = 7.3 Hz, 6H), 0.23 (t, J = 7.3 Hz, 3H). \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}): 173.08, 173.05, 172.84, 159.97, 159.87, 159.86, 141.05, 131.41, 131.33, 131.28, 65.87, 65.67, 65.61, 65.53, 65.41, 63.41, 63.29, 63.25, 62.93, 62.89, 62.85, 62.79, 62.57, 38.49, 38.39, 29.93, 29.89, 19.59, 19.54, 13.30, 13.26. Note that some of the \textsuperscript{13}C signals are missing, and we suspect that their overlap may contribute to the observation. HR-MS (ESI): calculated (M+Na\textsuperscript{+}) = 1016.3855, found: 1016.3834.

Compound 2.4: To a 100 mL round bottom flask, we placed 315 mg of 2.6 (TATB, 1.2 mmol), 117 mg of Pd/C catalyst into 22 mL of EtOAc; The solution was stirred vigorously and the flask evacuated and flushed with argon. Hydrogen gas was introduced into the reaction flask via balloon. The reaction was heated with oil bath to 75 °C for 5 h until all of the TATB reactant had dissolved and the solution became colorless, which
indicated complete reduction of the reactant and the formation of desired 2.4 (205 mg, with an assumption that the yield is quantitative). Note that the synthesis of unstable hexaaminobenzene 2.4 was run in parallel with the preparation of 2.5a–c to obtain hosts 2.1–2.3, as described below.

Compounds 2.5a–c: In a 500 mL round bottom flask, 9.98 g of compound 2.8a (41.0 mmol) was dissolved in 410 mL of anhydrous THF. To this solution, we added 6.5 mL of 1.0 % OsO₄ in t-BuOH (0.5 mol %) and 9.60 g of methylmorpholine-N-oxide in water (50%, 41.0 mmol). The reaction was left to stir at room temperature for two days. Following, 1.0 g of sodium dithionite was added to the mixture. The mixture was stirred for another hour and then filtered to remove all solids. The crude product was purified by column chromatography (SiO₂, EtOAc/hexanes = 3:1) to give 3.76 g of 2.8a-diol (27 %, 10.9 mmol) as a white solid.

2.8a-diol: ¹H NMR (400 MHz, CDCl₃): 5.90 (t, J = 2.0 Hz, 1H), 4.05 (d, J = 2.0 Hz, 1H), 3.42 (q, J = 7.2 Hz, 1H), 3.36 (dd, J = 4.7, 2.0 Hz, 1H), 3.15 (s, 1H), 3.02 (d, J = 2.6 Hz, 1H), 2.98 (dd, J = 6.3, 2.9 Hz, 1H), 2.78 (dd, J = 5.9, 2.7 Hz, 1H), 1.03 (t, J = 7.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): 174.41, 129.89, 129.77, 69.63, 65.58, 64.08, 60.54, 59.66, 46.59, 33.52, 13.84. HR-MS (ESI): calculated (M+Na)⁺ = 310.1050, found: 310.1058.

2.8b-diol: This compound was obtained in 41% yield as a white fluffy solid. ¹H NMR (400 MHz, CDCl₃): 5.91 (t, J = 1.9 Hz, 2H), 4.06 (s, 2H), 3.39 – 3.32 (m, 4H), 3.03 (d, J = 2.5 Hz, 2H), 2.98 (dd, J = 6.2, 2.9 Hz, 1H), 2.78 (dd, J = 5.8, 2.7 Hz, 1H), 1.52 – 1.38 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): 174.59, 130.05, 69.70,
65.58, 64.10, 60.59, 59.66, 46.56, 40.18, 21.46, 11.16. HRMS (ESI): calculated (M+Na)+ = 324.1206, found: 324.1198.

**2.8c-diol**: This compound was obtained in 43% yield as a white fluffy solid. $^1$H NMR (400 MHz, CDCl$_3$): 5.91 (t, J = 1.9 Hz, 1H), 4.06 (s, 1H), 3.41 – 3.34 (m, 1H), 3.02 (d, J = 2.5 Hz, 1H), 2.98 (dd, J = 6.3, 2.9 Hz, 1H), 2.94 (s, 1H), 2.77 (dd, J = 5.9, 2.7 Hz, 1H), 1.47 – 1.33 (m, 1H), 1.23 (dq, J = 14.5, 7.3 Hz, 1H), 0.89 (t, J = 7.3 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): 174.52, 130.02, 69.71, 65.56, 64.09, 60.57, 59.64, 46.55, 38.37, 30.29, 19.89, 13.58. HR-MS (ESI): calculated (M+Na)+ = 338.1363, found: 338.1351.

To a 250 mL round bottom flask and under an atmosphere of argon, we added 30 mL of dry CH$_2$Cl$_2$ and 0.85 mL of dry dimethyl sulfoxide (11.9 mmol). The solution was cooled to -78°C and stirred for 10 min upon which 1.6 mL of trifluoroacetic anhydride (11.7 mmol) was added and the solution was left to stir for another 15 min. After, 1.56 g of 2.8a-diol (5.4 mmol) was dissolved in 60 mL of dry CH$_2$Cl$_2$, the solution was degassed and added to the reaction mixture over 15 min. The reaction was left to stir for 2.5 h at -78°C. Following, 4.55 mL of dry Et$_3$N (32.0 mmol) was added and the mixture was left to stir for another 3 h, during which the solution turned bright yellow indicating the formation of desired diketone 2.5a. The reaction mixture was adjusted to -65 °C for 15 min and then brought back to -78°C; please note that diketones 2.5a-c were not possible to characterize because of their rapid decomposition under ambient conditions.

**Compound 2.7** was prepared following an already reported procedure: JACS, 1984. 106 (21), 6453-6454.

**Compounds 2.8a-c**: In a 250 mL round bottom flask, 12.0 grams of 2.7 (49.0 mmol) was suspended in 125 mL of dry toluene and cooled to 0 °C. Following, trifluoroacetic
anhydride (25.0 mL, 163.8 mmol) was added dropwise. The reaction mixture was stirred as it turned dark brown with all solid residues dissolved. The reaction was allowed to warm up to room temperature and then left to stir for another 24 h. The solvent and residual trifluoroacetic anhydride was removed under reduced pressure. The crude product was not purified, but directly used in the next step. A solution containing 100 mL toluene, 10 mL anhydrous pyridine and 2.2-4.7 mL of ethyl/propyl/butyl amine (48 mmol) was prepared and added to the flask containing crude anhydride from the prior step. The mixture was refluxed for three days at 110°C. The solvent was then removed under reduced pressure and the crude product filtered through a thick pad of SiO₂ (EtOAc/hexanes = 2:1). Upon removal of the solvent, we obtained compounds 2.8a−c as a yellow solid in 82−85 % yield.

**Compound 2.8a:** 1H NMR (400 MHz, CDCl₃): 5.99 (t, J = 1.9 Hz, 4H), 3.44 (dd, J = 4.2, 2.2 Hz, 4H), 3.38 (q, J = 7.2 Hz, 2H), 2.90 – 2.83 (m, 2H), 0.99 (t, J = 7.2 Hz, 3H). 13C NMR (100 MHz, CDCl₃): 175.07, 132.04, 66.77, 64.35, 62.10, 33.32, 13.85. HR−MS (ESI): calculated (M+Na)+ = 276.0995, found: 276.0996.

**Compound 2.8b:** 1H NMR (400 MHz, CDCl₃): 6.00 (t, J = 1.9 Hz, 4H), 3.45 (dd, J = 4.2, 2.2 Hz, 4H), 3.37 – 3.29 (m, 2H), 2.92 – 2.81 (m, 2H), 1.50 – 1.36 (m, 2H), 0.79 (t, J = 7.5 Hz, 3H). 13C NMR (100 MHz, CDCl₃): 175.33, 132.15, 66.81, 64.37, 62.15, 40.00, 21.36, 11.04. HR−MS (ESI): calculated (M+Na)+ = 290.1151, found: 290.1151.

**Compound 2.8c:** 1H NMR (400 MHz, CDCl₃): 6.01 (t, J = 1.9 Hz, 4H), 3.45 (dd, J = 4.2, 2.2 Hz, 4H), 3.36 (t, J = 7.2 Hz, 2H), 2.93 – 2.83 (m, 2H), 1.45 – 1.32 (m, 2H), 1.21 (dq, J = 14.5, 7.3 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H). 13C NMR (100 MHz, CDCl₃): 175.31,
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Compound 3.2: Compound 3.12 (25 mg, 0.054 mmol) was dissolved in 5.4 mL of anhydrous dioxane and the solution stirred under an atmosphere of nitrogen. To this, a solid “catalytic mixture” was added all at once (10 mol % of Pd(OAc)$_2$, 20 mol % of PPh$_3$, 2 molar equivalents of $n$-Bu$_4$NBr, 10 molar equiv of K$_2$CO$_3$, and 4 Å molecular sieves in the same amount as ammonium salt) and the solution brought to reflux at 100°C for 48 h. The reaction mixture was quenched with diluted HCl (2.5 mL) and then extracted with ethyl acetate (3 × 5 mL). The organic layer was dried over sodium sulfate, the solvent was removed in vacuum, and the crude product was purified by silica chromatography (dichloromethane/methanol = 10:1) to yield 18.0 mg (77%) of dual-cavity 3.2 as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): 7.74 (12H, s), 5.98 (6H, s), 3.85 (36H, s). $^{13}$C NMR (400 MHz, CDCl$_3$): 167.6, 146.3, 134.9, 130.3, 124.6, 52.8, 49.5. HR−MS (ESI): calculated (M+Na)$^+$ = 304.1361, found: 304.1367.

Compounds 3.3a−c: were prepared following the procedure for obtaining compound 3.2 in 43, 47, and 27% yield, respectively.

Compound 3.3a: $^1$H NMR (400 MHz, CDCl$_3$): 7.91 (12H, s), 6.19 (6H, s), 3.57 (12H, t, J = 7.2 Hz), 1.55 (12H, m), 0.85 (18H, t, J = 7.2 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): 167.6, 149.1, 135.0, 131.5, 119.0, 50.8, 39.8, 22.0, 11.2. HR−MS (ESI): calculated (M+Na)$^+$ = 1295.4161, found 1295.4138.
**Compound 3.3b**: ¹H NMR (400 MHz, CDCl₃): 7.87 (12H, s), 7.3−7.1 (30H, m), 6.18 (6H, s), 4.74 (12H, s). ¹³C NMR (100 MHz, CDCl₃): 167.2, 149.2, 136.3, 134.8, 131.4, 128.7, 128.5, 127.9, 119.2, 50.7, 46.2. HR−MS (ESI): calculated (M+Na)⁺ = 1584.4200, found 1584.4209.

**Compound 3.3c**: ¹H NMR (400 MHz, CDCl₃): 8.07 (12H, s), 7.20−7.50 (15H, m), 6.59 (6H, s). The low solubility of 3.3c in a range of solvents prevented us from obtaining a satisfactory ¹³C NMR spectrum. HR−MS (ESI): calculated (M+Na)⁺ = 1500.3271, found 1500.3255.


**Compound 3.10**: Compound 3.9 (263 mg, 1.7 mmol) was dissolved in 15 mL of anhydrous toluene and under an atmosphere of N₂ at 298 K. Freshly distilled DMAD (425 mL, 3.4 mmol) was added all at once, and the reaction mixture was heated 50°C for 6 h. Then, p-chloranil (2.3 g, 9.5 mmol) was added in portions, after which the reaction mixture was brought to reflux for 24 h. After a complete oxidation of the reactant (¹H NMR spectroscopy), the solvent was removed under a reduced pressure. The crude product was purified by column chromatography (SiO₂, hexanes/ethyl acetate = 1:1) to yield 652 mg (83%) of 3.10 as a light yellow solid. ¹H NMR (400 MHz, CDCl₃): 7.60 (4H, s), 6.97 (2H, m), 5.27 (2H, m), 3.84 (12H, s). ¹³C NMR (100 MHz, CDCl₃): 168.0, 148.3, 138.6, 129.3, 123.8, 52.8, 50.8. HR−MS (ESI): calculated (M+Na)⁺ = 459.1056, found 459.1059.
**Compound 3.11:** Compound 3.10 (50 mg, 0.11 mmol) was dissolved in 5.8 mL of benzene (Note: the concentration of the reactant must be kept below 0.025 M). A solution of bromine (0.13 mmol) in 1 mL of benzene was then slowly added to the reaction mixture over ~5 min. The reaction was allowed to stir for an additional 15 min, followed by removal of the solvent under reduced pressure to yield 61 mg (0.10 mmol, 99%) of the dibromoalkane as a reddish-brown oil. This compound (61 mg, 0.10 mmol) was dissolved in 2 mL of anhydrous DMF followed by the addition of 1,8-diazabicycloundecene (37.4 mL, 0.25 mmol) and heating at 80 °C for 20 min. The reaction mixture was cooled to room temperature and diluted with 15 mL of ethyl acetate, and the organic layer was washed with aqueous 5% HCl (5 × 10 mL). Upon removal of the residual water (Na2SO4) and filtration (SiO2), the filtrate was condensed in vacuo to give 44 mg (91%) of 3.11 as a white crystalline solid. 1H NMR (400 MHz, CDCl3): 7.71 (2H, s), 7.63 (2H, s), 7.02 (1H, dd; J = 6.4 Hz, J = 2 Hz), 5.26−5.24 (2H, m), 3.88 (6H, s) 3.88 (6H, s). 13C NMR (100 MHz, CDCl3): 167.6, 167.5, 162.7, 146.7, 146.6, 135.9, 131.4, 130.1, 129.4, 124.0, 123.7, 59.5, 52.7, 51.9. HR−MS (ESI): calculated (M+Na)+ = 537.0161, found 537.0164.

**Compound 3.12:** This molecule was prepared in 88% overall yield following the protocol described for obtaining 3.11. Note that in the bromination of 3.11, the concentration of this compound ought to be kept at 0.01 M or lower in order to avoid rearrangements at room temperature. 1H NMR (400 MHz, CDCl3): 7.71 (4H, s), 5.36 (2H, s), 3.88 (12H, s). 13C NMR (100 MHz, CDCl3): 145.4, 130.4, 129.1, 124.1, 77.5, 77.4, 77.2, 76.8, 60.3, 52.9, 52.9. HR−MS (ESI): calculated (M+Na)+ = 614.9246, found 614.9239.
**Compounds 3.13a-c:** Compound 3.12 (80 mg, 0.134 mmol) was dissolved in 2 mL of anhydrous THF. An aqueous solution (2 mL) of lithium hydroxide (221 mg, 5.387 mmol) was added to the reaction mixture. The reaction was kept at 80°C for 2 h and then cooled to room temperature. The solvent was evaporated followed by the addition of aqueous HCl (5%). The solution was subsequently extracted with ethyl acetate containing 5% methanol (5 × 30 mL), and the organic layer was evaporated to yield 66 mg (0.124 mmol, 93%) of tetraacid [(9s,10s)-11,12-dibromo-9,10-dihydro-9,10-ethenoanthracene-2,3,6,7-tetracarboxylic acid] product as white crystalline needles. $^1$H NMR (400 MHz, DMSO-d$_6$): 14.0−12.5 (4H, br), 7.82 (4H, s), 5.90 (2H, s). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 168.0, 145.2, 145.1, 129.7, 58.2. HR−MS (ESI): calculated (M+Li)$^+$ = 544.8882, found: 544.8888. Tetraacid (66 mg, 0.124 mmol) was dissolved in 5 mL of anhydrous THF followed by the addition of 175 mL (260 mg, 1.240 mmol) of trifluoroacetic anhydride. After 30 min, the solvent was removed in vacuum to give bis-anhydride as a yellow solid in 92% yield (57 mg, 0.114 mmol). $^1$H NMR (DMSO-d$_6$): 8.01 (4H, s), 6.03 (2H, s). The product was used without further purification as any characterization proved difficult due to its hydrolytic instability. To a solution of bis-anhydride (15 mg, 0.029 mmol) in anhydrous DMSO (0.6 mL), propylamine (3.4 mg, 0.058 mmol) was added, and the mixture was stirred for 10 min at room temperature. Pyridine (0.1 mL) was then added and the reaction temperature increased to 120°C for 2 h. The solvent was removed in vacuum and ethyl acetate (2 mL) added, which upon sonication gave desired 3.13a as a white solid (18.3 mg, 89%).

**Compound 3.13a:** $^1$H NMR (400 MHz, CDCl$_3$): 7.83 (4H, s), 5.54 (2H, s), 3.61 (4H, t, $J = 7.2$ Hz), 1.63 (4H, br.), 0.91 (6H, t, $J = 7.2$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): 167.9,
Compounds 3.13b and 3.13c were obtained (71 and 81% yield, respectively) following the preparative procedure for obtaining 3.13a.

**Compound 3.13b**: $^1$H NMR (400 MHz, CDCl$_3$): 7.82 (4H, s), 7.4–7.2 (10H, m), 5.53 (2H, s), 4.80 (4H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): 167.4, 148.7, 136.3, 132.0, 128.8, 128.6, 128.0, 118.8, 100.1, 61.4, 41.9. HR−MS (ESI): calculated (M+Na)$^+$ = 702.9667, found 702.9612.

**Compound 3.13c**: $^1$H NMR (400 MHz, CDCl$_3$): 7.98 (4H, s), 7.53–7.38 (10H, m), 5.63 (2H, s). $^{13}$C NMR (100 MHz, CDCl$_3$): 166.7, 149.0, 131.6, 131.1, 129.3, 129.2, 128.4, 126.5, 119.2, 61.5. HR−MS (ESI): calculated (M+Na)$^+$ = 674.9354, found 614.9345.


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Compounds 4.1_{syn/anti}: Methanesulfonic acid (6.8 mmol, 442 mL) was added to a flame-dried flask containing anhydrous 1,2-dichloroethane (136 mL), and the mixture was brought to reflux. Compound 4.5_{a/b} (656 mg, 1.42 mmol) was dissolved in anhydrous 1,2-dichloroethane (6 mL) and then added to the reaction mixture with a syringe pump over 2 h. After complete addition of the substrate, the reaction was allowed to reflux for an additional 2 h. The reaction mixture was then extracted three times with 50 mL of saturated sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent removed in vacuo. The crude product was purified by column chromatography (SiO₂, hexanes/acetone = 10:1) to yield 89.1 mg of 4.1_{syn} (14 %) and 467.2 mg of 4.1_{anti} (71 %).

Compound 4.1_{syn}: ¹H NMR (400 MHz, CDCl₃): 7.24 (3 H, d), 7.02–6.93 (6 H, m), 6.90–6.84 (3 H, m), 4.14 (3 H, d, J = 4.8 Hz), 3.52 (3 H, m), 3.41 (3 H, dd, J = 16.8 Hz, 4.8 Hz), 2.81 (3 H, d, J = 16.8 Hz), 2.52–2.43 (3 H, m), 2.01 (3 H, d, J = 10.4 Hz); ¹³C NMR (100 MHz, CDCl₃): 149.6, 146.65, 139.69, 126.92, 126.54, 122.91, 121.57, 41.00, 40.92, 40.25, 33.58. HR−MS (ESI): calculated (M+Na)⁺ = 485.2240, found 485.2250.

Compound 4.1_{anti}: ¹H NMR (400 MHz, CDCl₃): 7.37–7.20 (3 H, m), 7.18–6.94 (9 H, m), 4.13 (1 H, d, J = 4.8 Hz), 4.09 (1 H, d, J = 4.8 Hz), 4.06 (1 H, d, J = 4.8 Hz), 3.57–3.48 (3 H, m), 3.40–3.24 (3 H, m), 3.00–2.76 (3 H, m), 2.49–2.32 (3 H, m) and 1.98–1.86 (3 H, m); ¹³C NMR (100 MHz, CDCl₃): 150.46, 150.26, 150.04, 146.80, 146.77, 146.51, 139.78, 139.72, 139.46, 126.73, 126.69, 126.64, 126.61, 126.57 (2C), 126.54, 126.34, 126.34, 123.25, 123.10 (2C), 121.44, 121.28, 121.12, 40.90, 40.81, 40.78, 40.77, 40.46,
40.32 (two signals), 40.28, 34.92, 33.74, 33.46, 33.41. HR-MS (ESI): calculated (M+Na)^+ = 485.2245, found: 485.2221.

**Compound 4.2:** Technical grade indene (90%) was used and was purchased from Sigma-Aldrich.

**Compound 4.3:** Compound 4.2 (0.394 mL, 3.0 mmol, 90%) was added to a flame-dried flask containing 15 mL of anhydrous THF. The vessel was placed under nitrogen and cooled to -78°C, after which n-BuLi (1.6 M: 1.875 mL, 3.0 mmol) was added dropwise and the solution stirred at -78°C for 15 minutes. Benzyl chloride (0.345 mL, 3.0 mmol) was then added dropwise at -78°C and the mixture stirred for an additional 90 minutes. The reaction was subsequently quenched with 10 mL of water (at -78°C) followed with the addition of 15 mL of hexanes. The organic layer was extracted with water (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and then condensed in vacuo to yield a clear viscous oil. The crude oil was purified by column chromatography (SiO₂, hexanes:CH₂Cl₂ = 6:1) to yield 272.3 mg (44%) of compound 4.3 as a clear viscous oil.

^1H NMR (400 MHz, CDCl₃): 7.41-7.33 (3H, m), 7.32-7.12 (9H, m), 7.08-6.97 (3H, m), 6.86-6.77 (3H, m), 6.46-6.34 (3H, m), 3.76-3.64 (3H, m), 3.15-3.00 (3H, m), 2.83-2.70 (3H, m). ^13C NMR (CDCl₃): 147.07, 144.41, 140.04, 139.08, 130.97, 127.99, 126.69, 124.62, 123.34, 121.14, 51.88, and 37.83. The spectroscopic data is in agreement with that previously reported for compound 4.3 (see J. Organomet. Chem. 2000, 616, 112).

**Compound 4.4:** Methanesulfonic acid (142uL, 2.2mmol) was added to a flame-dried flask containing anhydrous 1,2-dichloroethane (42.0 mL) and the solvent was brought to reflux. Compound 4.3 (90.8mg, 0.440mmol) was dissolved in 2 mL anhydrous 1,2-dichloroethane and added to the flask using a syringe pump over 2 hours. After complete
addition, the reaction mixture was kept under reflux for another 2 hours. The flask was allowed to cool to room temperature and the solvent transferred to a separatory funnel, upon which it was extracted with aqueous sodium bicarbonate solution (3 x 20 mL). The organic layer was dried with sodium sulfate and condensed in vacuo. The crude product was purified by chromatography (SiO₂, hexanes:CH₂Cl₂ = 4:1) to yield 69.9 mg (77%) of compound 4.4 as a clear viscous oil. ¹H NMR (400 MHz, CDCl₃): 7.30 (d, 7.2 Hz, 1H), 7.20-7.00 (m, 6H), 6.95 (d, 7.2 Hz, 1H), 3.91 (d, 4.8 Hz, 1H), 3.56-3.47 (m, 1H), 3.27 (dd, 16.8 Hz, 4.8 HZ, 1H), 2.77 (d, 16.8 Hz, 1H), 2.61-2.53 (m, 1H), 2.16 (d, 10.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): 150.57, 145.65, 143.44, 133.80, 130.43, 126.82, 126.77, 126.69, 125.74, 125.72, 123.38, 121.61, 47.10, 41.20, 40.52, 34.42.

Spectroscopic Data is in agreement with that previously reported synthesis of compound 4.4 (See JACS. 1965, 87, 2870).

Compound 4.5a/b: Indene (0.654mL, 5.0mmol, 90%) was added to a flame-dried flask containing 50 mL of anhydrous THF. The vessel was placed under an atmosphere of nitrogen and cooled to -78°C. 1.6 M n-BuLi (3.125 mL, 5.0 mmol) was subsequently added dropwise and the mixture stirred for an additional 15 minutes. A solution of 4.6 (596mg, 1.67 mmol) in 5 mL of anhydrous THF was then added dropwise and the mixture stirred for an additional 15 minutes. The reaction was quenched with 25 mL of water (at -78°C) followed by the addition of 25 mL of hexanes. The organic layer was extracted with water (2 x 25 mL), dried over anhydrous sodium sulfate and the solvent removed in vacuo to yield a green viscous oil. The crude oil was purified by column chromatography (SiO₂, hexane:CH₂Cl₂ = 5:1) to give 494.5mg (64%) of compound 4.5a/b as a bright green viscous oil. ¹H-NMR (400 MHz, CDCl₃): 7.41-7.33 (3H, m), 7.32-7.12
(9H, m), 7.08-6.97 (3H, m), 6.86-6.77 (3H, m), 6.46-6.34 (3H, m), 3.76-3.64 (3H, m), 3.15-3.00 (3H, m), 2.83-2.70 (3H, m); $^{13}$C-NMR (100 MHz, CDCl$_3$): 147.25, 147.20, 144.59, 144.57, 140.22, 140.20, 139.24, 131.15, 131.12, 128.16, 128.06, 128.02, 126.86, 124.80, 123.52, 123.47, 121.31, 52.09, 52.05, 38.01. HRMS (ESI): calculated (M+Na)$^+$ = 485.2260, found: 485.2240.

**Compound 4.6:** N-bromosuccinimide (11.747 g, 66.6 mmol) and mesitylene (2.783 mL, 20.0 mmol) were added to 150 mL of benzene in a 250 mL round-bottom flask. Azobisisobutyronitrile (AIBN, 821 mg, 5.0 mmol) was added and the reaction was brought to reflux for 10 hours. The reaction was removed from heat and filtered through a pad of silica. The solvent was then evaporated in vacuo and the remaining solid recrystallized (hexanes:dichloromethane = 1:1) to give 4.57 g of 1,3,5-tris(bromomethyl)benzene (79%) as bright white needles. $^1$H-NMR: (400 MHz, CDCl$_3$): 7.35 (3H, s) and 4.46 (6H, m). $^{13}$C NMR: (100 MHz, CDCl$_3$): 139.43, 129.93, and 32.51. HRMS (ESI): calculated (M+Na)$^+$ = 520.7731, found: 520.7718.

**Compound 4.7:** Methanesulfonic acid (13.6 mmol, 8.8 mL) was added to a flame-dried flask containing anhydrous 1,2-dichloroethane (88 mL), and the mixture was brought to reflux. Compound 4.11$^{ab}$ (656 mg, 0.81 mmol) was dissolved in anhydrous 1,2-dichloroethane (6 mL) and then added to the reaction mixture with a syringe pump over 2 h. After complete addition of the substrate, the reaction was allowed to reflux for an additional 24 h. Anhydrous methanol (40 mL) was added and the reaction refluxed an additional 2 hours. The reaction mixture was then poured into an ice bath containing a saturated sodium bicarbonate solution so that the pH > 7. The organic layer was extracted and washed with water (2 x 75 mL), dried over sodium sulfate and the solvent removed in
vacuo. The crude product was purified by column chromatography (SiO$_2$, hexanes/acetone = 10:1) to yield 89.1 mg of $4.7_{\text{syn}}$ (14 %) and 467.2 mg of $4.7_{\text{anti}}$ (71 %).

Figure 28: Shows the synthetic scheme for Compounds 4.8-4.9.

**Compound 4.8:** To a stirred solution of Compound 5.2 (9.71 g, 28.7 mmol) in 150 mL of anhydrous CH$_3$CN, dimethyl furan-3,4-dicarboxylate (5.29 g, 28.7 mmol) and cesium fluoride (13.1 g, 86.1 mmol) were added. The reaction was put under argon and stirred for 24 hours, checking the $^{1}$H NMR for completion. Upon complete conversion, the reaction is filtered through a pad of neutral alumina, washing with acetonitrile (1 x 100 mL), then condensed to yield the intermediate product as a slowly crystallizing solid, which was used without further purification. $^{1}$H NMR (400 MHz, CDCl$_3$): 7.28 (s, 2H), 5.90 (s, 2H), 3.80 (s, 6H), 2.83 (t, J = 7.4 Hz, 4H), 2.09 (pd, J = 7.7, 2.1 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): 163.30, 151.80, 145.05, 142.35, 118.45, 85.14, 52.65, 32.82, 25.91. HRMS (ESI): calculated (M+Na)$^+$ = 323.0842, found: 323.0880. Following, TiCl$_4$ (12.0 mL, 105 mmol) was slowly added to 180 mL of anhydrous THF at 0°C, followed by the addition of NEt$_3$ (6.0 mL, 45.0 mmol) and LiAlH$_4$ (2.30 g, 60.0 mmol) under
argon. The mixture was refluxed for 30 min and then allowed to cool to room temperature. A solution of the intermediate product in 20 mL of anhydrous THF was added. The mixture was stirred for 2h at room temperature and was poured onto ice, then 1M HCl was added. The resulting mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate, filtered, and condensed in vacuo. The crude product was purified further by column chromatography (2:1 hexanes:ethyl acetate) to yield 6.89 g of Compound 4.8 as white crystalline solid (85% over two steps). $^1$H NMR (400 MHz, CDCl$_3$): 8.14 (s, 2H), 7.69 (s, 2H), 3.94 (s, 6H), 3.06 (t, $J = 7.3$ Hz, 4H), 2.15 (p, $J = 7.4$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): 168.81, 147.11, 133.29, 130.05, 127.78, 123.31, 52.91, 33.06, 26.30. HRMS (ESI): calculated (M+Na)$^+$ = 307.0934, found: 307.0941.

**Compound 4.9:** Compound 4.8 (6.89 g, 24.2 mmol) was dissolved in 100 mL of benzene, followed by the addition of N-Bromosuccinimide (4.31 g, 24.2 mmol) and AIBN (198 mg, 1.21 mmol). The reaction was brought to reflux for 2 hours then cooled to room temperature. The solvent was condensed in vacuo and the crude mixture was re-dissolved in 100 mL toluene, and brought to reflux overnight. The $^1$H NMR was checked in the morning to determine conversion and the reaction typically required 36 – 48 hours for complete conversion. The reaction was subsequently removed from heat and cooled to room temperature, diluted with 100 mL of toluene, and extracted with water (3 x 100 mL). The organic was then dried over anhydrous sodium sulfate, condensed in vacuo, and purified by column chromatography (2:1 hexanes: ethyl acetate) to yield 5.26 g of Compound 4.9 as a white crystalline solid (77% over two steps). $^1$H NMR (400 MHz, CDCl$_3$): 8.27 (s, 1H), 8.25 (s, 1H), 7.96 (s, 1H), 7.86 (s, 1H), 7.04-7.01 (m, 1H), 6.79-6.76 (m, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.61-3.59 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$):
Compound 4.10: Compound 4.6 (4.57 g, 15.8 mmol) was suspended in 100 mL of acetone (dried over 4Å molecular sieves) in a 250 mL round-bottom flask, and to the suspension sodium iodide (8.29 g, 55.3 mmol) was added and brought to reflux for two hours. The reaction was then cooled to room temperature, followed by filtration through neutral alumina. The solvent was condensed and the crude solid was recrystallized from benzene to yield 3.975 g of Compound 4.10 (87%) as long yellow needles. \(^1\)H-NMR: (400 MHz, CDCl₃): 7.25 (3H, s) and 4.37 (6H, m). \(^{13}\)C NMR: (100 MHz, CDCl₃): 140.90, 128.92, and 4.23. HRMS (ESI): calculated (M+Na)\(^+\) = 520.7731, found: 520.7718.

Compound 4.11\(_{ab}\): Compound 4.9 (1.41 g, 5.0 mmol) was added to a flame-dried flask containing 50 mL of anhydrous THF and 5 mL of freshly dried and distilled HMPA. The vessel was placed under an atmosphere of argon and cooled to -78°C. 2.33 M n-BuLi (2.15 mL, 5.0 mmol) was added drop wise and the mixture allowed to stir for an additional 5 minutes. A solution of compound 4.10 (416 mg, 0.85 mmol) in 10 mL of anhydrous THF was then added drop wise and the mixture stirred for an additional 10 minutes. The reaction was quenched with 25 mL of water (at -78°C) followed by the addition of 25 mL of ethyl acetate. The organic layer was extracted with 1 M HCl (2 x 25 mL), washed with water (1 x 25mL) and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo to yield an orange viscous oil. This crude oil was purified by column chromatography (1:1 hexanes:ethyl acetate) to give 685 mg (0.81
mmol, 89%) of Compound 4.11a/b (~4:1 ratio of diastereomers) as a deep orange solidifying oil.

**Compound 4.12:** Indene (98%) was purchased and was used as is from Sigma-Aldrich.

**Compound 4.13:** Freshly cracked 1,3-cyclopentadiene (1.00 g, 16.1 mmol) was added drop wise to excess sodium hydride (1.05 g, 43.7 mmol) suspended in 100 mL of THF at 25 °C. The gray suspension was cooled to 0°C while α,α,α'-tribromo-o-xylene137 (2.16 g, 6.29 mmol) dissolved in 100 mL of THF was slowly added, keeping the temperature at 0°C. The reaction mixture turned green over several minutes at 0°C, the cooling bath was removed, and the reaction mixture slowly turned purple as the reaction warmed. The reaction was allowed to stir for an additional 3 days, checking for conversion by NMR. The reaction was quenched by the slow addition of water (25 mL) at 0°C, followed by extraction with 1M HCl (1 x 100 mL) and then water (3 x 100 mL). The organic layer was dried over anhydrous sodium sulfate, and condensed in vacuo to yield a crude mixture that was purified by column chromatography (10:1 hexanes:ethyl acetate). This purification yielded 120 mg of benzo[f]indene as a white crystalline solid (12%). 1H NMR (400 MHz, CDCl3): 7.99 – 7.69 (m, 4H), 7.48 – 7.37 (m, 2H), 7.03 – 6.96 (m, 1H), 6.65 (dt, J = 5.6, 2.1 Hz, 1H), 3.55 (td, J = 2.1, 1.2 Hz, 2H). 13C NMR (100 MHz, CDCl3): 141.53, 135.78, 132.97, 132.07, 131.87, 127.92, 127.78, 125.08, 124.78, 122.09, 118.54, 77.21, 38.21.

**Compound 4.14:** See first part of the preparation of Compounds 4.15m/p.

**Compound 4.15m/p:** Firstly, the titanium catalyst was prepared prior to reaction. Titanium isopropoxide (0.10 mL, 0.338 mmol) was added to a flame-dried 10 mL round-bottom flask, followed by the addition of menthol (0.423 g, 2.704 mmol). The flask was heated
to 60°C under reduced pressure on a rotary evaporator for 1 hour to remove any residual isopropanol. The resulting slowly crystallizing oil may be stored under inert atmosphere and used as needed. When prepared, the syn isomer (11mg, 0.011 mmol) was added to the flask and equipped with a stir bar and placed under an argon atmosphere. The reaction was heated to 180°C in an aluminum mantle for 72 hours, followed by cooling to room temperature. To this, 10 mL of ethyl acetate is added and 1 mL of water. The reaction is filtered and the resulting solution is condensed in vacuo. The viscous oil is then heated to 150°C under reduced pressure (1 torr) on a Kugelrohr apparatus to remove excess menthol. The resulting crude solid product is purified by column chromatography (2:1 hexanes:diethyl ether) to yield 9 mg of the top spot (4.15m) and 9 mg of the bottom spot (4.15p) for a total combined yield of 81%.

**Compound 4.15m** ($R_f=0.50$): See Figure 103

**Compound 4.15p** ($R_f=0.37$): See Figure 104
References


58. Guest release and capture by hemicarcerands introduces the phenomenon of constrictive binding. *Journal of the American Chemical Society, 113*(20), 7717–7727.


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Appendix A: Supplementary Information

A.1 Supplementary Information for Chapter 2

Figure 29: $^1$H-$^1$H COSY NMR (400 MHz) spectrum of compound $2.2_{\text{syn}}$ in CD$_2$Cl$_2$ (298.0 K).

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Figure 30: $^1$H-$^1$H NOESY NMR (400 MHz) spectrum of compound $2.2_{\text{syn}}$ in CD$_2$Cl$_2$ (298.0 K, $d_1=2.5s$, $d_8=0.7s$).
Figure 31: $^1\text{H}$ NMR spectra of compound 2.1$_{\text{syn}}$ in C$_2$D$_2$Cl$_4$ (top) and CD$_2$Cl$_2$ (bottom) at 298.0 K.
Figure 32: Variable temperature $^1$H NMR spectra of compound $2.2_{syn}$ dissolved in C$_2$D$_2$Cl$_4$. 
Figure 33: Variable temperature $^1$H NMR spectra of compound 2.2$_{syn}$ dissolved in CD$_2$Cl$_2$. 
Figure 34: $^1$H NMR spectra (400 MHz, 298.0 K) of 2.2$_{syn}$ (0.53 mM) in C$_2$D$_2$Cl$_4$ obtained upon incremental addition of CH$_2$Cl$_2$ (up to 6000 molar equivalents).
Figure 35: $^1$H NMR spectra (400 MHz, 298.0 K) of $\text{2.2}_{\text{syn}}$ (1.05 mM) in C$_2$D$_2$Cl$_4$ obtained upon incremental addition of CCl$_4$ (up to 2800 molar equivalents).
A.2 Supplementary Information for Chapter 4

Figure 36: A region of the $^1$H NMR spectrum (400 MHz, CDCl$_3$) of compound 4.5$_{a/b}$ showing three signals (6.945-7.015 ppm) corresponding to the central aromatic protons in C$_3$ symmetric 4.5$_a$ (the middle signal) and C$_1$ symmetric 4.5$_b$ (the outer signals). The integration ratio of the two sets of signals is $\sim$1:5.
Figure 37: HPLC chromatogram of 4.5_{a/b}, showing four signals corresponding to its four stereoisomers: 4.5_a (RRR/SSS) and 4.5_b (RRS/SSR) in an approximate ratio of 1:5.
Figure 38: $^1$H-$^1$H COSY NMR spectrum of compound 4.1$_\text{syn}$ (400 MHz, CDCl$_3$).
Figure 39: $^1$H-$^1$H NOESY NMR spectrum of compound 4.1$_{syn}$ (400 MHz, CDCl$_3$). Note the NOE effect seen between H$_{fg}$ and H$_j$ due to the proximity of the atoms in the cup-shaped basket.
Figure 40: $^1$H-$^1$H COSY NMR spectrum of compound 4.1$_{anti}$ (400 MHz, CDCl$_3$).
Figure 41: $^1$H-$^1$H NOESY NMR spectrum of compound 4.1_{anti} (400 MHz, CDCl$_3$).
Figure 42: The change in the concentration of 4.3 (1.2 mM) with CH$_3$SO$_3$H (30-80 mM, ClCH$_2$CH$_2$Cl, 344.0 K) was monitored by HPLC. The data was analyzed by a nonlinear least-square analysis (SigmaPlot 12.0) and fitted to a first-order kinetic model to give k$_{obs}$ ($R^2 > 0.99$). When pseudo first order coefficients k$_{obs}$ were plotted against the concentration of CH$_3$SO$_3$H, a second order relationship emerged ($R^2 > 0.99$).
Figure 43: HPLC Chromatograph of the conversion of 4.5a/b in the presence of 0.05M CH$_3$SO$_3$H into 4.1$_{\text{syn/anti}}$. The presence of two intermediates is obvious with their concentrations increasing early then becoming depleted as the conversion in 4.1$_{\text{syn/anti}}$ approaches completion.
Figure 44: $^1$H NMR spectrum of compound $4.5_{a/b}$ (400MHz, CDCl$_3$). The compound was re-isolated two minutes upon the initiation of its reaction with 0.05M CD$_3$SO$_3$D (ClCH$_2$CH$_2$Cl, 344.0 K); note the presence of some intermediates and products. Two signals around 6.3-6.4 ppm correspond to HC=CH indanyl protons in $4.5_{a/b}$ with an unaltered intensity.
Figure 45: The change in the concentration of \(4.5_{ab}\) in the presence of 0.05M CH\(_3\)SO\(_3\)H (triangles) or CD\(_3\)SO\(_3\)D (squares). \(k_{obs}(CH_3SO_3H) = 0.012\), \(k_{obs}(CD_3SO_3D) = 0.0055\).
Figure 46: $^1$H NMR spectra (400MHz, CDCl$_3$) of compounds 4.1$_{\text{syn-d6}}$ (top) and 4.1$_{\text{syn}}$ (bottom).
Figure 47: Shows the results of a methyl iodide quenching experiment that contained a 1:1 mixture of compounds 4.12 and 4.13, and 1 equivalent of nBuLi in THF. The remaining indene was evaporated.
Figure 48: Shows the VT-NMR of $4.15\_p$ (400MHz, CD$_2$Cl$_2$)
Figure 49: $^1$H-$^1$H COSY of Compound 4.16 (400MHz, CD$_2$Cl$_2$)
Figure 50: $^1$H-$^1$H COSY of Compound 4.15\textsubscript{m} (400MHz, CD$_2$Cl$_2$)
Figure 51: $^1$H-$^1$H COSY of Compound 4.15$_p$ (400MHz, CD$_2$Cl$_2$)
Appendix B: NMR Spectra of New Compounds
Figure 52: $^1$H NMR spectrum of compound $2.1_{syn}$ (400MHz, CD$_2$Cl$_2$).
Figure 53: $^{13}$C NMR spectrum of compound 2,1$\text{syn}$ (100MHz, CD$_2$Cl$_2$).
Figure 54: $^1$H NMR spectrum of compound 2.1$_{\text{anti}}$ (400MHz, CD$_2$Cl$_2$).
Figure 55: $^{13}$C NMR spectrum of compound 2.1$_{\text{anti}}$ (100MHz, CD$_2$Cl$_2$).
Figure 56: 1H NMR spectrum of compound 2.2syn (400 MHz, CD2Cl2).
Figure 57: $^{13}$C NMR spectrum of compound $2.2_{syn}$ (100MHz, CD$_2$Cl$_2$).
Figure 58: $^1$H NMR spectrum of compound 2.2_{anti} (400MHz, CD$_2$Cl$_2$).
Figure 59: $^{13}$C NMR spectrum of compound 2.2$^{anti}$ (100MHz, CD$_2$Cl$_2$).
Figure 60: $^1$H NMR spectrum of compound $2,3_{\text{anti}}$ (400MHz, CD$_2$Cl$_2$).
Figure 61: $^{13}$C NMR spectrum of compound 2.3anti (100MHz, CD$_2$Cl$_2$).
Figure 62: $^1$H NMR spectrum of compound $2.8a$ (400MHz, CDCl$_3$).
Figure 63: $^{13}$C NMR spectrum of compound 2.8a (100MHz, CDCl$_3$).
Figure 64: $^1$H NMR spectrum of compound $2.8_b$ (400MHz, CDCl$_3$).
Figure 65: $^{13}$C NMR spectrum of compound 2.8a (100MHz, CDCl$_3$).
Figure 66: $^1$H NMR spectrum of compound $2.8_c$ (400MHz, CDCl$_3$).
Figure 67: $^{13}$C NMR spectrum of compound 2.8c (100MHz, CDCl$_3$).
Figure 68: $^1$H NMR spectrum of compound 3.2 (400MHz, CDCl$_3$).
Figure 69: $^{13}$C NMR spectrum of compound 3.2 (100MHz, CDCl$_3$).
Figure 70: \(^1\text{H NMR spectrum of compound } 3.3_a\) (400MHz, CDCl\(_3\)).
Figure 71: $^{13}$C NMR spectrum of compound 3.3a (100MHz, CDCl$_3$).
Figure 72: $^1$H NMR spectrum of compound 3.3b (400MHz, CDCl$_3$).
Figure 73: $^{13}$C NMR spectrum of compound 3.3b (100MHz, CDCl$_3$).
Figure 74: $^1$H NMR spectrum of compound $3.3_c$ (400MHz, CDCl$_3$).
Figure 75: $^1$H NMR spectrum of compound 3.10 (400MHz, CDCl$_3$).
Figure 76: $^{13}$C NMR spectrum of compound 3.10 (100MHz, CDCl$_3$).
Figure 77: $^1$H NMR spectrum of compound 3.11 (400MHz, CDCl$_3$).
Figure 78: $^{13}$C NMR spectrum of compound 3.11 (100MHz, CDCl$_3$).
Figure 79: $^1$H NMR spectrum of compound 3.12 (400MHz, CDCl$_3$).
Figure 80: $^{13}$C NMR spectrum of compound 3.12 (100MHz, CDCl$_3$).
Figure 81: $^1$H NMR spectrum of compound $3.13_a$ (400MHz, CDCl$_3$).
Figure 82: $^{13}$C NMR spectrum of compound 3.13$_a$ (100MHz, CDCl$_3$).
Figure 83: $^1$H NMR spectrum of compound 3.13b (400MHz, CDCl$_3$).
Figure 84: $^{13}$C NMR spectrum of compound $3.13_b$ (100MHz, CDCl$_3$).
Figure 85: $^1$H NMR spectrum of compound 3.13c (400MHz, CDCl$_3$).
Figure 86: $^{13}$C NMR spectrum of compound 3.13c (100MHz, CDCl$_3$).
Figure 87: $^1$H NMR spectrum of compound 4.1$_{\text{syn}}$ (bottom) and 4.1$_{\text{syn-d}}$ (400MHz, CDCl$_3$).
Figure 88: $^{13}$C NMR spectrum of compound $4.1_{syn}$ (100MHz, CDCl$_3$).
Figure 89: $^1$H NMR spectrum of compound $4.1_{\text{anti}}$ (bottom) and $4.1_{\text{anti-d}_6}$ (top) (400MHz, CDCl$_3$).
Figure 90: $^{13}$C NMR spectrum of compound 4.1$_{anti}$ (100MHz, CDCl$_3$).
Figure 91: $^1\text{H}$ NMR spectrum of compound $4.1_{\text{anti}}$ (bottom) and $4.1_{\text{anti-d6}}$ (top) (400MHz, CDCl$_3$).
Figure 92: $^{13}$C NMR spectrum of compound 4.1$_{anti}$ (100MHz, CDCl$_3$).
Figure 93: $^1$H NMR spectrum of compound 4.6 (400MHz, CDCl$_3$).
Figure 94: $^{13}$C NMR spectrum of compound 4.6 (100MHz, CDCl$_3$).
Figure 95: $^1$H NMR spectrum of compound 4.7$_{syn}$ (400MHz, CDCl$_3$).
Figure 96: $^{13}$C NMR spectrum of compound 4.7$_{\text{syn}}$ (100MHz, CDCl$_3$).
Figure 97: $^1$H NMR spectrum of compound 4.8 (400MHz, CDCl$_3$).
Figure 98: $^{13}$C NMR spectrum of compound 4.8 (100MHz, CDCl$_3$).
Figure 99: $^1$H NMR spectrum of compound 4.9 (400MHz, CDCl₃).
Figure 100: $^{13}$C NMR spectrum of compound 4.9 (100MHz, CDCl$_3$).
Figure 101: $^1$H NMR spectrum of compound 4.10 (400MHz, CDCl$_3$).
Figure 102: $^{13}$C NMR spectrum of compound 4.10 (100MHz, CDCl$_3$).
Figure 103: $^1$H NMR spectrum of compound 4.15$_m$ (400MHz, CDCl$_3$).
Figure 104: $^1$H NMR spectrum of compound 4.15_p (400MHz, CDCl$_3$).