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Hydrogen-Bond-Driven Controlled Molecular Marriage in Covalent Cages

Koushik Acharyya and Partha Sarathi Mukherjee*[a]

Abstract: A supramolecular approach that uses hydrogen-bonding interaction as a driving force to accomplish exceptional self-sorting in the formation of imine-based covalent organic cages is discussed. Utilizing the dynamic covalent chemistry approach from three geometrically similar dialdehydes (**A**, **B**, and **D**) and the flexible triamine tris(2-aminoethyl)amine (**X**), three new [3+2] self-assembled nanoscopic organic cages have been synthesized and fully characterized by various techniques. When a complex mixture of the dialdehydes and triamine **X** was subjected to reaction, it was found that only dialdehyde **B** (which has OH groups for H-bonding) reacted to form the corresponding cage $\mathbf{B_3X_2}$ selectively. Surprisingly, the same reaction in the absence of aldehyde **B** yielded a mixture of products. Theoretical and experimental investigations are in complete agreement that the presence of the hydroxyl moiety adjacent to the aldehyde functionality in **B** is responsible for the selective formation of cage $\mathbf{B_3X_2}$ from a complex reaction mixture. This spectacular selection was further analyzed by transforming a nonpreferred (non-hydroxy) cage into a preferred (hydroxy) cage $\mathbf{B_3X_2}$ by treating the former with aldehyde **B**. The role of the H-bond in partner selection in a mixture of two dialdehydes and two amines has also been established. Moreover, an example of unconventional imine bond metathesis in organic cage-to-cage transformation is reported.

Introduction

Nature has demonstrated the magical artifices of making multifunctional complex architectures with sheer selectivity and utmost delicacy over millions of years. One such artifice is self-sorting,[1] which is spontaneous association through mutual recognition of complementary building units into a well-defined ordered architecture, within a random reaction mixture. In the biological regime this "order out of chaos" process is a well-established synthetic protocol.[2] Formation of the DNA double helix through hydrogen bonding is one of the prototypes of biological self-sorting. To understand such a complex biological phenomenon in a better way, immense efforts have been made in the last few decades to construct numerous artificial elegant architectures. Noncovalent interactions, especially metal–ligand coordination-driven self-recognition,[3] hydrogen bonding,[4] charge–charge interaction,[5] and so forth, have been employed for this purpose by Lehn, Stang, Schmittel, and others. On the contrary, hitherto self-sorted systems utilizing covalent bonding have not been well studied.[6] Dynamic covalent bonding has recently been coupled with metal–ligand coordination to construct self-sorted metallacycles and cages.[7]

In the last two decades, with profound advancement of dynamic covalent chemistry,[8] several sophisticated purely covalent cages[9] have been synthesized. Such three-dimensional (3D) cages have earned a substantial appreciation in recent times from the scientific community owing to their potential applications in sensing,[10] catalysis,[11] gas storage,[12] and separation.[13] However, from the perspective of their synthetic methodology, the self-sorting protocol has been overlooked.

The dynamic covalent bond, namely the imine bond, allows the removal of errors during formation, which leads to a thermodynamically most stable combination in the majority of cases.[8a] Does this dynamic nature of the imine bond allow self-sorting in 3D organic cage formation? Indeed it does. In our recent publication,[14] we were successfully able to show how the dynamic nature of the imine bond maneuvered the efficient formation of 3D self-sorted architectures. Additionally, we also showed an example of a cage-to-cage transformation, depending on the preference for a partner over another in a complex reaction mixture. Therein, our main focus was to look into the self-sorting behavior of two randomly selected aldehydes, irrespective of their geometrical background. After having such unusual self-sorting behavior in the formation of purely covalent cages from randomly chosen components, the question that we asked is whether chemists can direct/control such self-sorting. If so, what strategy can help chemists to control the outcome?

It is a well-accepted fact that most of the self-sorting systems operate on the basis of difference in geometric shapes/

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sizes and electronic properties of the competing components. Thus, increasing similarity makes the situation more complicated. To overcome this difficulty and to achieve an effective self-sorting system, it is necessary to incorporate a structural element that can modulate the reactivity of the reaction site. This will aid in discriminating the reacting components, much like in biological systems. In this regard, we turned our attention towards a noncovalent interaction, particularly hydrogen bonding. As already known, the H-bond plays a pivotal role in the formation of several unprecedented abiological architectures.[15] Herein, we report our investigation on the role of intramolecular H-bonding in selective synthesis of a 3D organic cage from a complex reaction mixture of four dialdehydes and one triamine, in which the dialdehydes have similar geometrical features. Furthermore, we also present our effort to achieve exquisite control over a self-sorting process operating between two dialdehydes and two triamines solely guided by H-bonding to construct two selective cages out of myriad possibilities. Moreover, we report unconventional imine bond metathesis in transforming one set of cages to another set of cages, and intramolecular H-bond-directed organic cage-to-cage transformation. To the best of our knowledge, this represents the first example of systematic control of self-sorting in 3D organic cage formation utilizing a secondary interaction such as H-bonding as a driving force.

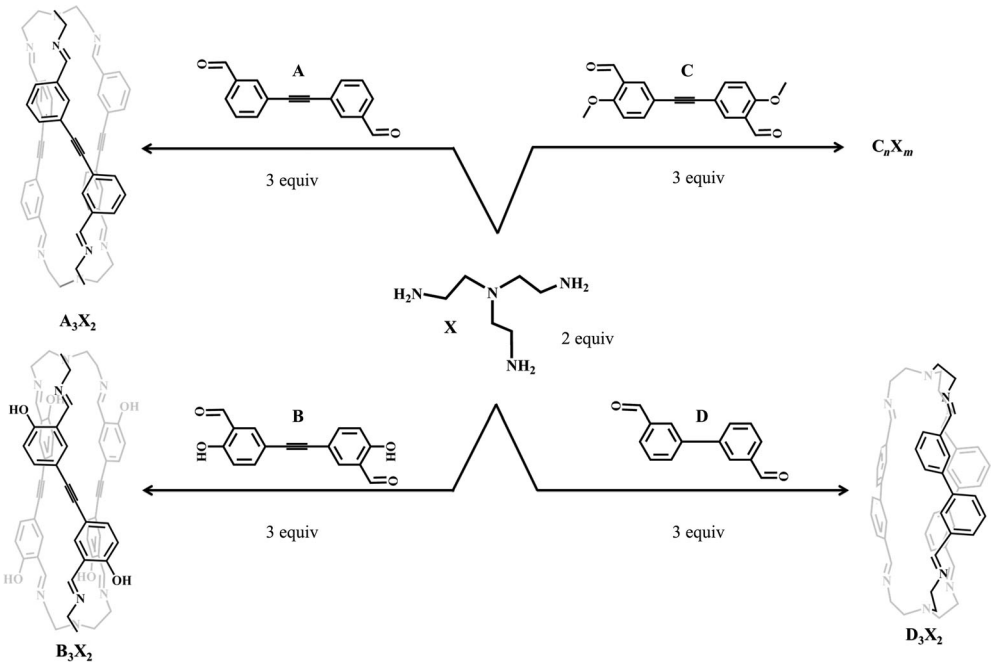
Results and Discussion

Dialdehydes **A**, **B**, **C**, and **D** were selected for the present study (Scheme 1). Among them, **B** is furnished with a hydroxyl moiety adjacent to the aldehyde functionality. It is well documented in the literature that a hydroxyl group adjacent (*ortho* position) to an aldehyde/imine functionality is capable of forming a stable six-membered ring through $H^{OH}\cdots O^{CHO}/H^{OH}\cdots N^{CHN}$ intramolecular hydrogen bonding.[16,17] We envisioned that such supramolecular interaction can manipulate the fate of a reaction in which competing components are present. Before performing competitive experiments, all of the dialdehydes were allowed to react separately with the triamine tris(2-aminoethyl)amine (**X**) in chloroform at room temperature under dilute conditions. The purity and formation of all the newly synthesized compounds were fully verified on the basis of ^1H and ^{13}C NMR, ^1H–^1H COSY, HMQC, FTIR, ESI-HRMS, and single-crystal X-ray diffraction analyses. These experimental results unambiguously affirmed the formation of [3+2] imine-based cages except in the case of **C**, for which we encountered the formation of insoluble oligomeric or polymeric material. This could be attributed to the steric bulk arising due to the presence of a methoxy group adjacent to the aldehyde functionality, which restricts it to preorganize during the reaction and thus leads to the formation of undesired oligomeric or polymeric species.

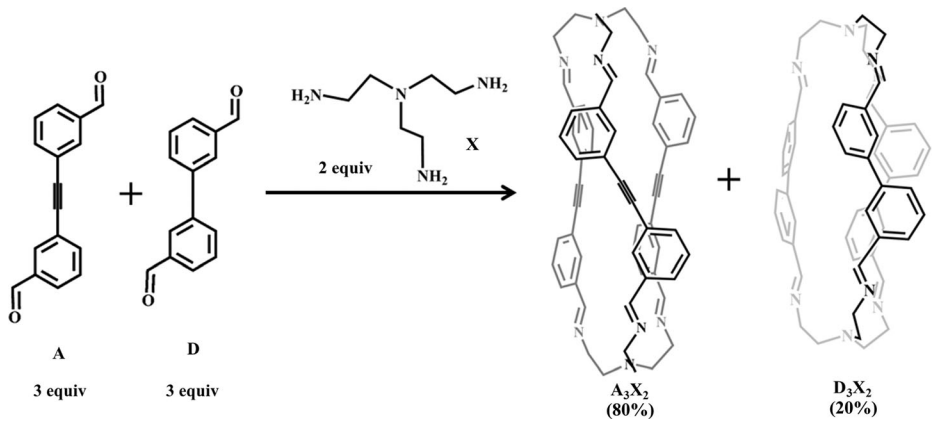
After successful synthesis of the three cages ($\mathbf{A_3X_2}$, $\mathbf{B_3X_2}$, and $\mathbf{D_3X_2}$), our main objective was to investigate the selective formation of one of them in a competitive reaction environment. In this context, a mixture of dialdehydes **A** and **D** was subjected to reaction with triamine **X** in a 3:3:2 molar ratio (amine **X** was taken at a little less than 2 equiv) at room temperature in chloroform for 48 h. From the experimental outcome it was ascertained that although triamine **X** displayed a preference to form a cage with aldehyde **A**, it also reacted with aldehyde **D** to form the corresponding cage $\mathbf{D_3X_2}$ (Scheme 2).

^1H NMR tracking (Figure 1) of the reaction in $CDCl_3$ revealed that at the initial stage both the products $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$ were formed in almost equal amount. This is suggested by the integration of the characteristic proton NMR signals at $\delta = 5.60$ and 5.99 ppm, respectively. But with further progress of the reaction, $\mathbf{D_3X_2}$ was gradually converted into $\mathbf{A_3X_2}$ and finally reached equilibrium within approximately 116 h (after that there was no change in the product composition). From the integration of the proton NMR signals it was estimated that the equilibrium product mixture contains 80% of $\mathbf{A_3X_2}$ and 20% of $\mathbf{D_3X_2}$.

Quite surprisingly a different picture emerged when, in a separate set of experiments, a mixture of dialdehydes **B** and **D** was treated with triamine **X**. In this case no peak corresponding to $\mathbf{D_3X_2}$ was observed rather than cage $\mathbf{B_3X_2}$. The same story iterated when aldehyde **B** was treated



Scheme 1. Schematic representation of the formation of [3+2] self-assembled organic cages $\mathbf{A_3X_2}$, $\mathbf{B_3X_2}$, $\mathbf{D_3X_2}$, and polymeric/oligomeric $\mathbf{C_nX_m}$.



Scheme 2. Formation of a mixture of cages $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$ from a reaction mixture of two dialdehydes (**A**, **D**) and amine **X** (3:3:2).

assigned to the aldehyde functionality of **B** at $\delta = 9.90$ ppm decreased selectively over time, and the appearance of a new proton NMR signal corresponding to cage $\mathbf{B_3X_2}$ at $\delta = 7.04$ ppm within 12 h (after that there was no change in product composition) clearly supports the fact. This selective formation of cage $\mathbf{B_3X_2}$ from a reaction mixture of four aldehydes and an amine can be considered as a 1^5-fold (2+3) incomplete self-sorting according to the classification of Mahata and Schmittel,[3o] as only one type of discrete cage ($\mathbf{B_3X_2}$) was formed from a five-component reaction mixture (four dialdehydes and one triamine) in which two components (**B** and **X**) were used and the other three components (**A**, **C**, and **D**) remained unreacted.

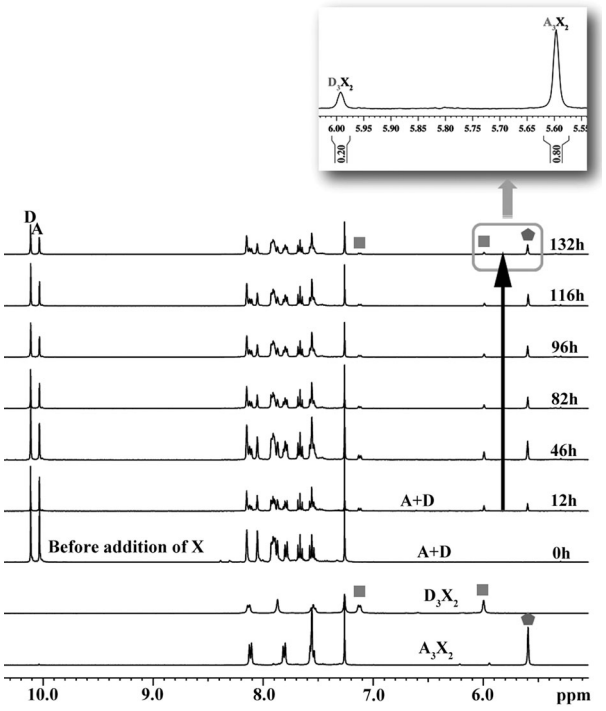


Figure 1. Time-dependent ^{1}H NMR spectra recorded in $CDCl_3$ during the formation of cages $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$ from a reaction mixture of dialdehydes **A** and **D** and triamine **X** (3:3:2). The spectra of pure cages are also shown for comparison.

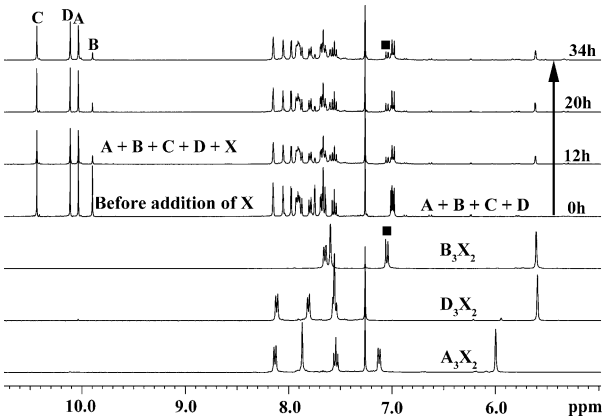
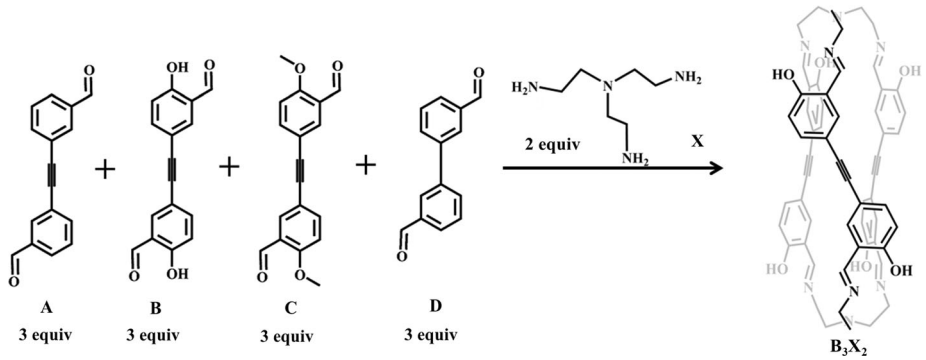


Figure 2. Time-dependent ^{1}H NMR spectra recorded in $CDCl_3$ during selective formation of cage $\mathbf{B_3X_2}$ from a reaction mixture of aldehydes **A**–**D** and amine **X** (3:3:3 3:2), with spectra of all three possible cages for comparison.

with amine **X** in the presence of aldehyde **A** or **C**. In a final set of experiments, a $CDCl_3$ solution containing all four dialdehydes **A**–**D** was subjected to reaction with triamine **X** in a 3:3:3:3:2 molar ratio (amine **X** was taken at a little less than 2 equiv). ^{1}H NMR analysis of the reaction indicated that triamine **X** again selectively picked up dialdehyde **B** as a preferred partner, though other aldehydes were present in equal amount in the mixture (Scheme 3). As shown in the spectrum (Figure 2), there is no evidence of formation of any other possible products ($\mathbf{A_3X_2}$, $\mathbf{D_3X_2}$, or oligomeric species corresponding to aldehyde **C**). Under the experimental conditions, the signal

Selective formation of hydroxyl-based aldehyde-containing cage $\mathbf{B_3X_2}$ from a complex reaction mixture encouraged us to address the question: can a cage of non-hydroxy aldehyde after formation be converted to $\mathbf{B_3X_2}$? Thus, we performed an experiment to check the possibility of transforming a nonpreferred (non-hydroxy) cage into a preferred (hydroxy) cage. In this context cage $\mathbf{D_3X_2}$ was selected and its possibility of transforming into cage $\mathbf{B_3X_2}$ was investigated.

First of all a solution containing dialdehyde **D** and triamine **X** was stirred in $CDCl_3$ for 24 h at room temperature to synthesize cage $\mathbf{D_3X_2}$. ^{1}H NMR spectra of the resulting reaction mixture after 24 h clearly suggested the formation of the desired cage with the presence of a very small amount of unreacted dialdehyde **D**. The requisite amount of dialdehyde **B** was added to this reaction mixture and the solution was stirred at room temperature. The progress of the reaction was checked periodically by ^{1}H NMR spectroscopy. Although the transforma-



Scheme 3. Exclusive formation of cage $\mathbf{B_3X_2}$ from a reaction mixture of four dialdehydes (**A**–**D**) and triamine **X** (3:3:3:3:2).

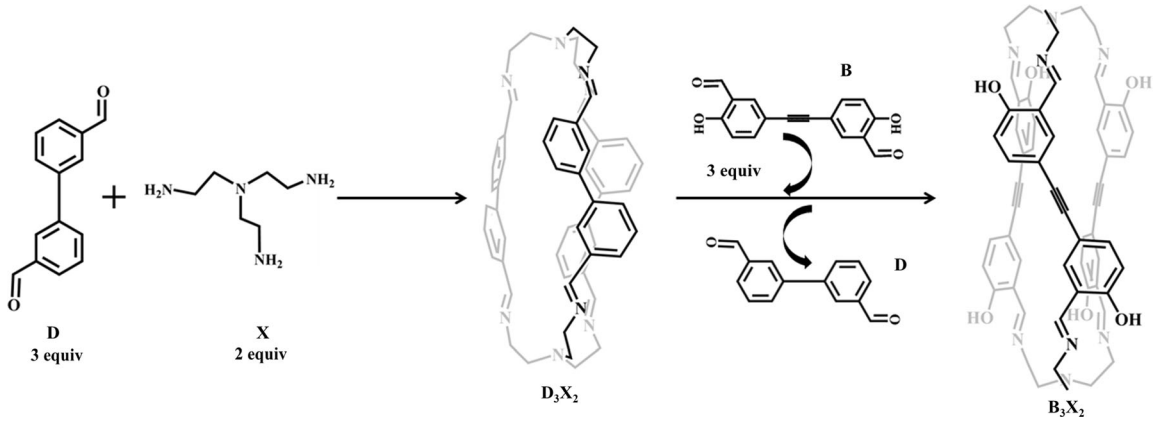
tion was very slow, cage $\mathbf{D_3X_2}$ gradually converted into cage $\mathbf{B_3X_2}$ and released dialdehyde **D** (Scheme 4). As depicted in the spectra (Figure S38 in the Supporting Information), characteristic proton NMR signals assigned to cage $\mathbf{D_3X_2}$ and dialdehyde **B** diminish with the appearance of signals corresponding to cage $\mathbf{B_3X_2}$ and dialdehyde **D**.

Kinetic and thermodynamic background of H-bonding assistance in self-sorting

A self-sorting process is generally governed by either kinetics or thermodynamics. When the outcome of the process is determined by reaction rates of product formation then it is kinetically controlled, whereas if the penultimate stability of the resulting assembly makes a difference then it is thermodynamically controlled. To understand kinetic factors associated with the self-sorting, the rate constant of individual cage formation needs to be calculated. Unfortunately complications arose due to the formation of several uncharacterized intermediates during the reaction, which precluded us from such calculation. To gain a brief overview of this subject, individual cage formation was monitored separately in $CDCl_3$ at room temperature for a certain period of time and the yield of the desired cage after that time was calculated. A solution of triamine **X** was mixed with a solution of dialdehyde (**A**, **B**, or **D**) and immediately the ^{1}H NMR spectrum of the reaction mixture was recorded. NMR spectra indicated that within approximately 6 min after mixing the reactants **B** and **X**, aldehyde was substantially consumed unlike the other cases. Letting the reaction proceed without stirring or shaking for another 80 min and checking the spectra afterwards suggested ≈80% formation of cage $\mathbf{B_3X_2}$ (Figure S42 in the Supporting Information), whereas during the same time lag yields of cages $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$ reached only ≈28 and ≈17%, respectively (Figures S40 and S44 in the Supporting Information).

From the yields of the products it is quite clear that dialdehyde **B** has the fastest reaction kinetics towards triamine **X** among the competing partners. Hence, cage $\mathbf{B_3X_2}$ is kinetically most favorable. The extremely fast reaction rate associated with aldehyde **B** is consistent with the role of H-bonding in the higher reactivity of salicylaldehyde over benzaldehyde reported in the literature.[17a] As stated earlier, the *O*-hydroxyl moiety can form a strong noncovalent interaction with the adjacent aldehyde group, which makes it more nucleophilic towards amine.

To examine thermodynamic control, gas-phase DFT (B3LYP, 6-31G) calculations were executed to estimate roughly the heat of reaction of individual cage formation (see Figure 3). All the reacting components and products were optimized and the energy differences between the products and the reactants were calculated. Theoretical results are summarized in Table 1. It is clearly evident that entropy plays a vital role in the cage formation process, as the enthalpy of reaction is positive. Interestingly, cage $\mathbf{B_3X_2}$ formation required the least energy (6.33 kcal mol^{-1}), which suggests that it is thermodynamically the most stable product. The very high enthalpy of reaction



Scheme 4. Formation of nonpreferred cage $\mathbf{D_3X_2}$ and its transformation to preferred cage $\mathbf{B_3X_2}$ upon treatment with aldehyde **B** driven by intramolecular H-bonding.

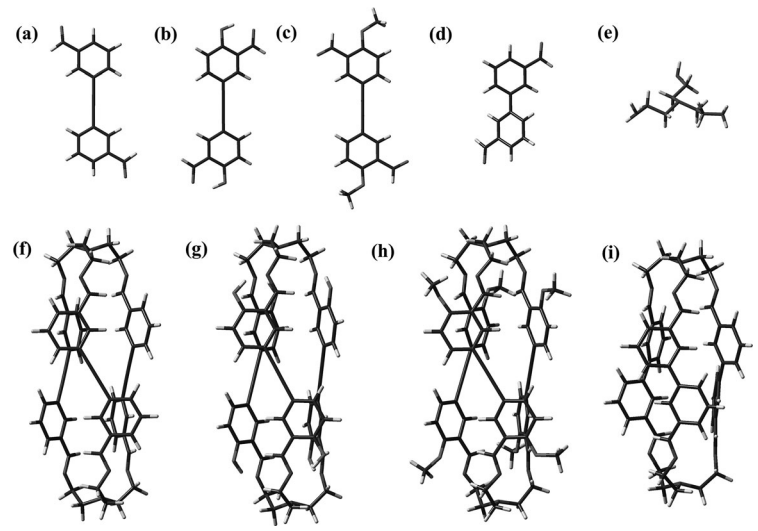


Figure 3. DFT (B3LYP, 6-31G) optimized structures of dialdehydes a) **A**, b) **B**, c) **C**, and d) **D**, e) amine **X**, and cages f) $\mathbf{A_3X_2}$, g) $\mathbf{B_3X_2}$, h) $\mathbf{C_3X_2}$, and i) $\mathbf{D_3X_2}$.

Table 1. Calculated reaction enthalpies of formation of cages.

Entry	Reaction	Calculated reaction enthalpy (ΔH_g) [kcal mol^{-1}]
1	$3\mathbf{A}+2\mathbf{X}\rightarrow\mathbf{A_3X_2}+6H_2O$	30.65
2	$3\mathbf{B}+2\mathbf{X}\rightarrow\mathbf{B_3X_2}+6H_2O$	6.33
3	$3\mathbf{C}+2\mathbf{X}\rightarrow\mathbf{C_3X_2}+6H_2O$	65.54
4	$3\mathbf{D}+2\mathbf{X}\rightarrow\mathbf{D_3X_2}+6H_2O$	32.51

(65.54 kcal mol^{-1}) associated with cage $\mathbf{C_3X_2}$ justified why formation of this cage was not feasible. These experimental and theoretical results strongly recommend that the selectivity is not guided solely by kinetics or thermodynamics; indeed, it is the outcome of both. So, intramolecular H-bonding is playing a dual role here: it increases the reactivity of the aldehyde functionality, which is manifested in higher reaction kinetics or kinetic stability, as well as providing higher thermodynamic stability to the final assembly (cage $\mathbf{B_3X_2}$).

With the above results in hand we were quite excited to test another set of reactions in which triamine **X** was present in the amount needed for the formation of all possible cages. A first set of experiments was carried out between two aldehydes (**A**, **B**) and amine **X** in 3:3:4 molar ratio. ^{1}H NMR spectra (Figure S34 in the Supporting Information) recorded in $CDCl_3$ with time indicated formation of the desired two cages ($\mathbf{A_3X_2}$ and $\mathbf{B_3X_2}$), but a considerable amount of dialdehyde **A** remained unreacted along with the formation of uncharacterized products. A similar scenario was observed when triamine **X** was treated with a mixture of dialdehydes **A**, **B**, and **D** in 6:3:3:3 molar ratio. In this case, though ^{1}H NMR spectra (Figure S35 in the Supporting Information) indicated the formation of the desired three cages ($\mathbf{A_3X_2}$, $\mathbf{B_3X_2}$, and $\mathbf{D_3X_2}$), for further assessment we employed ESI-MS analysis. Mass spectrometric analysis (Figure S36 in the Supporting Information) revealed the formation of three cages along with the hetero cages $\mathbf{A_2BX_2}$ and $\mathbf{AB_2X_2}$ as byproducts. From the kinetic point of view it could easily be rationalized that reaction rates follow the order $\mathbf{B_3X_2} > \mathbf{AB_2X_2} > \mathbf{A_2BX_2} > \mathbf{A_3X_2} > \mathbf{D_3X_2}$. This means that the higher affinity of triamine **X** for dialdehyde **B** leads to the fast formation of cages $\mathbf{B_3X_2}$, $\mathbf{AB_2X_2}$, and $\mathbf{A_2BX_2}$, which in turn regulates the reaction equilibrium of the two parallel reactions (formation of cages $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$) and does not allow completion of the reaction.

The above results suggest that the presence of the hydroxyl moiety makes a commanding difference between dialdehyde **B** and the rest of the dialdehydes. Motivated by this fact, the next question that we asked was: what would be the consequence of a reaction in which two aldehydes (one of which has a hydroxyl group neighboring the aldehyde functionality) and two triamines are present in a mixture when both the aldehydes have a preference for the same amine? In such circumstances, can the aldehyde bearing a hydrogen-bonding motif regulate the fate of the competing dialdehyde? To address these questions a set of experiments was carried out in which aldehydes **E** and **F** were selected for study and their behavior towards amines **X** and **Y** was investigated.

In a recent report, we have shown that dialdehyde **E** preferentially reacts with triamine **X** to form cage $\mathbf{E_3X_2}$ and this affinity did not alter even in a complex reaction mixture.[14] Dialdehyde **F** was employed for the present study as it fulfills the necessary two criteria: 1) the presence of a hydroxyl group adjacent to the aldehyde functionality and 2) preferential reaction with triamine **X** in a mixture of triamines **X** and **Y**. A mixture of dialdehydes **E** and **F** in chloroform was allowed to react with triamines **X** and **Y** in a 3:3:2:2 molar ratio at room temperature for 48 h. After completion of the reaction, the solvent was completely removed and the composition of the as-obtained solid mass was examined by ^{1}H NMR spectroscopy in $CDCl_3$. The NMR spectra of the reaction mixture and all the possible cages ($\mathbf{E_3X_2}$, $\mathbf{E_3Y_2}$, $\mathbf{F_3X_2}$, and $\mathbf{F_3Y_2}$) along with the starting aldehydes are assembled in Figure 4.

Analysis of these spectra pointed out several facts: dialdehyde **F** was fully consumed during the course of the reaction whereas some amount of dialdehyde **E** remained unreacted. Most interestingly, spectra of the reaction mixture revealed the formation of cages $\mathbf{F_3X_2}$ and $\mathbf{E_3Y_2}$, though the formation of cage $\mathbf{E_3X_2}$ was expected from earlier experience (Scheme 5).

This result demonstrates that fast and stable formation of cage $\mathbf{F_3X_2}$ forced dialdehyde **E** to react with triamine **Y** (which is not a preferred choice) to form nonpreferred cage $\mathbf{E_3Y_2}$, though in the absence of dialdehyde **F** the same reaction yielded exclusively $\mathbf{E_3X_2}$. This result reflects that H-bonding may play a crucial role in forcing an aldehyde to bind with its nonpreferred partner.

Partner exchange by imine bond metathesis

Exchange of Schiff bases, popularly known as imine metathesis, has been a subject of interest to synthetic chemists for a long time. According to the mechanism proposed by Ingold

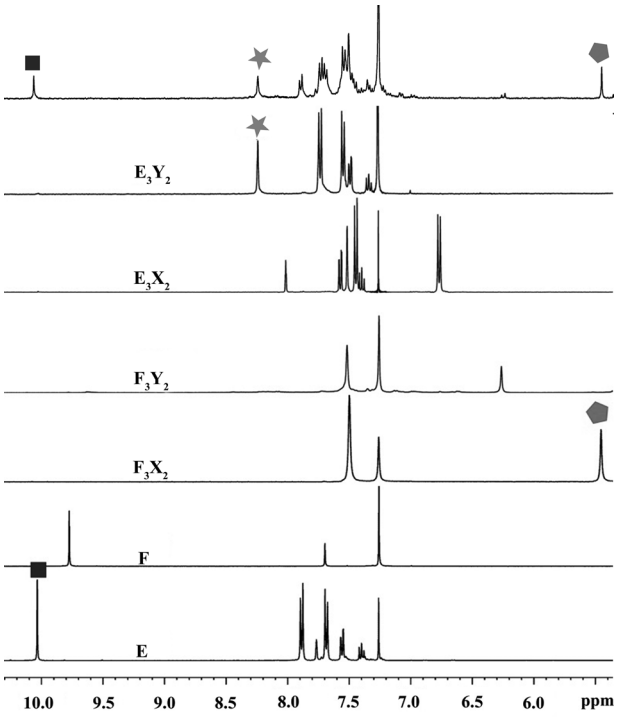
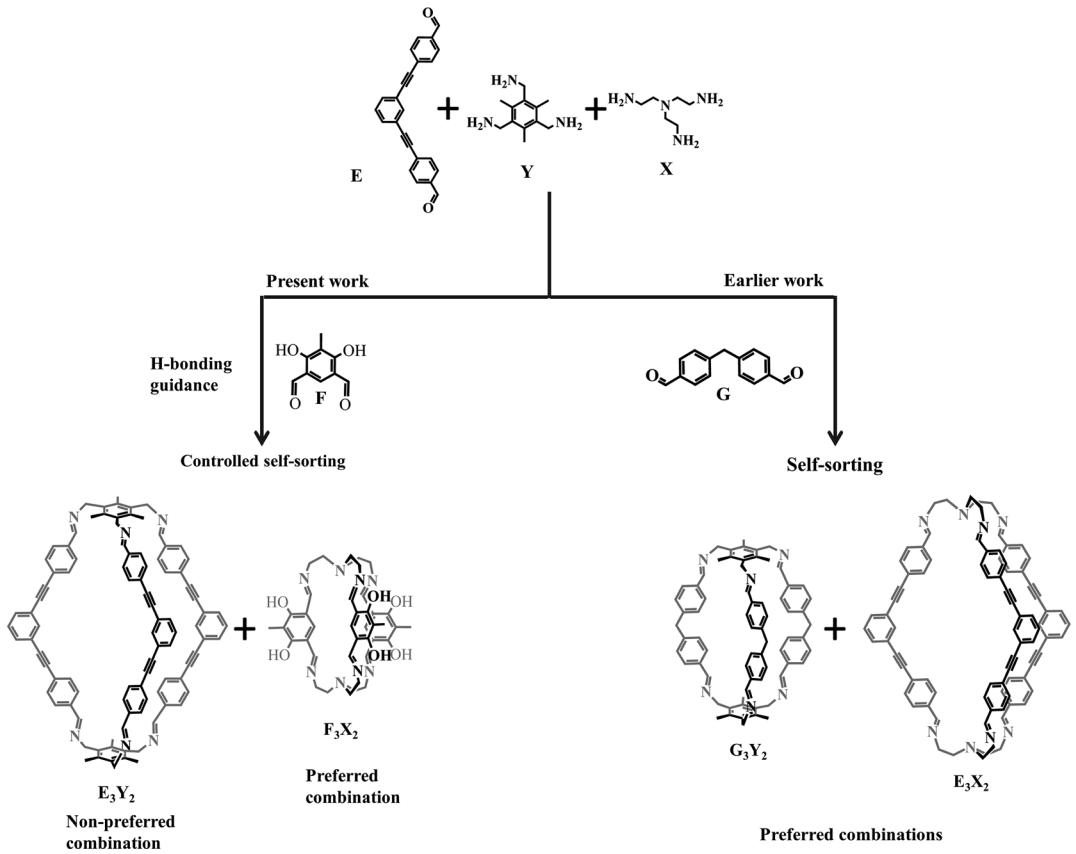
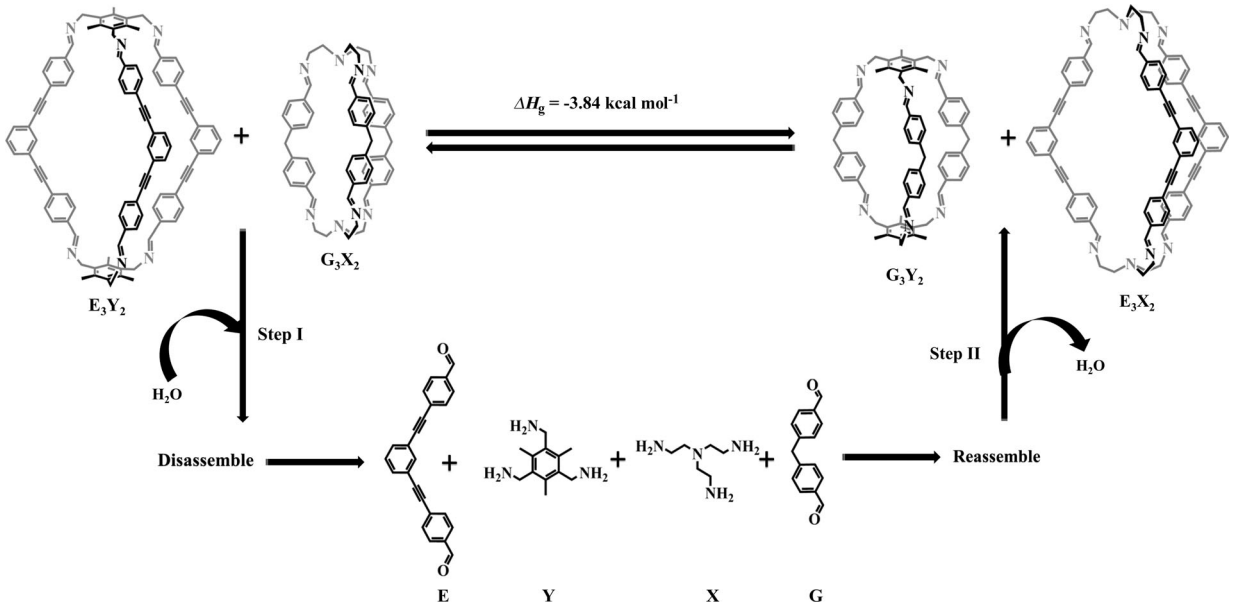


Figure 4. ^{1}H NMR spectra of the self-sorting experiment recorded in $CDCl_3$ after 48 h along with the spectra of all possible cages and reacting components involved for comparison.

and Piggott[18] in the early 20th century, it proceeds through a symmetry-forbidden [2+2] cycloaddition reaction via the formation of a concerted 1,3-diazetidine intermediate. A few decades later Messmer[19] showed that catalyst is required for the progress of the reaction as it goes through an ionic intermediate. So the next question that comes to mind is: would such imine exchange be possible in covalent cages? If so, then how? To reach this goal, we have revisited our recent work,[14] and two previously synthesized non-self-sorted cages ($\mathbf{E_3Y_2}$ and $\mathbf{G_3X_2}$) have been selected. A solution containing cages $\mathbf{E_3Y_2}$ and $\mathbf{G_3X_2}$ in $CDCl_3$ was stirred at room temperature without adding any catalyst (Scheme 6) and the progress of the reaction was monitored by ^{1}H NMR spectroscopy (Figure S36 in the Supporting Information). Investigation throughout the reaction progress suggested slow exchange of partners and the formation of the desired two cages ($\mathbf{E_3X_2}$ and $\mathbf{G_3Y_2}$), but unexpectedly we also observed peaks assigned to aldehydes **F** and **G**. This experimental outcome opposes the conventional imine exchange pathway and rather we anticipated that it follows a two-step process: disassembly into aldehydes and amines followed by reassembly by the process of self-sorting. We believe that dissolved water in $CDCl_3$ is responsible for the transformation. Theoretical calculation (DFT, B3LYP, 6-31G) predicts that thermodynamically this process is possible, as it gains -3.84 kcal mol^{-1} extra stability.



Scheme 5. Self-sorting (molecular marriage) of a complex mixture (**E**, **G**, **Y**, and **X**) and change in partner choice (controlled self-sorting) controlled by dialdehyde **F** due to H-bonding.



Scheme 6. Imine bond metathesis in organic cage-to-cage transformation.

X-ray crystal structures

Colorless rodlike crystals suitable for X-ray diffraction of the cage $\mathbf{A_3X_2}$ were grown by slow cooling of a hot ethanolic solution to room temperature. Cage $\mathbf{A_3X_2}$ crystallized in the monoclinic crystal system with space group *C*2/*c*. Three crystallographically independent cage molecules along with several ethanol molecules were found to exist in the asymmetric unit. Yellow block-shaped single crystals of the cage $\mathbf{B_3X_2}$ were grown in the same way from hot CH_3CN solution. This compound crystallized in the monoclinic crystal system with space group *P*21/*c*. An asymmetric unit was found to have one cage molecule along with one water molecule and two acetonitrile molecules. Cage $\mathbf{D_3X_2}$ crystallized in the orthorhombic crystal system with *Pccn* space group. Colorless block-shaped single crystals were grown by slow evaporation of an acetonitrile solution. An asymmetric unit comprised two crystallographically independent cage molecules and three water molecules. Interestingly, these two cage molecules have different spatial arrangements (conformations). One conformation can easily be transformed into another by twisting the molecule around the axis passing through the apical nitrogen atoms as shown in Figure 5.

Observations of broad ^{1}H NMR signals at room temperature corresponding to $-CH_2$ protons in the case of cages $\mathbf{A_3X_2}$ and $\mathbf{D_3X_2}$ indicate the higher conformational flexibility relative to cage $\mathbf{B_3X_2}$ (sharp $-CH_2$ proton signals). However, the expected sharp signals due to the $-CH_2$ protons were found in the NMR spectrum at very low temperature due to restricted flexibility (Figures S31 and S33 in the Supporting Information).

Solid-state structural examination elucidates that in all cases three molecules of aldehyde reacted with two molecules of amine to form [3+2] self-assembled cages in which imine bonds are, as expected, in the preferred *trans* conformation with C=N bond lengths in the range of 1.26–1.28 Å (see Figure 6). Aldehyde groups adopted an antiparallel alignment with respect to each other during the formation of the desired cages. In the case of cage $\mathbf{B_3X_2}$, strong intramolecular H···N hydrogen bonds are found to occur between imine nitrogen and the hydroxyl groups. This fact is reinforced by the O–N distances between hydroxyl groups and the imine nitrogen atoms, which are in the range of 2.52–2.58 Å. The distance between two central nitrogen atoms of amine **X** in cages $\mathbf{A_3X_2}$ and $\mathbf{B_3X_2}$ is $\approx$17 Å whereas, due to lack of ethynyl functionality in aldehyde **D**, cage $\mathbf{D_3X_2}$ is slightly smaller in size with a distance of $\approx$14 Å. Some of the selected bond lengths and angles are listed in the Supporting Information (Table S1).

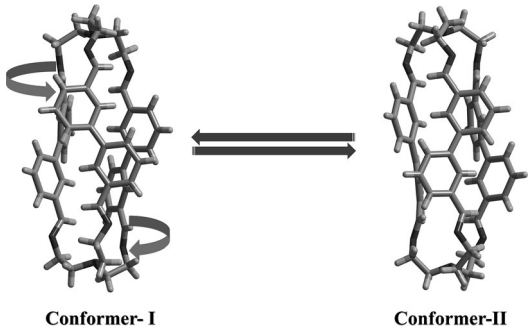


Figure 5. Two conformers of cage $\mathbf{D_3X_2}$ present in the asymmetric unit.

Conclusion

We have successfully shown that intramolecular H-bonding can play a decisive role in selective formation of an imine-based organic cage out of several equally probable possibilities from a mixture in which competitors (dialdehydes) are geometrically identical. Both theoretical and experimental studies support the fact that it provides extra stability to the final as-

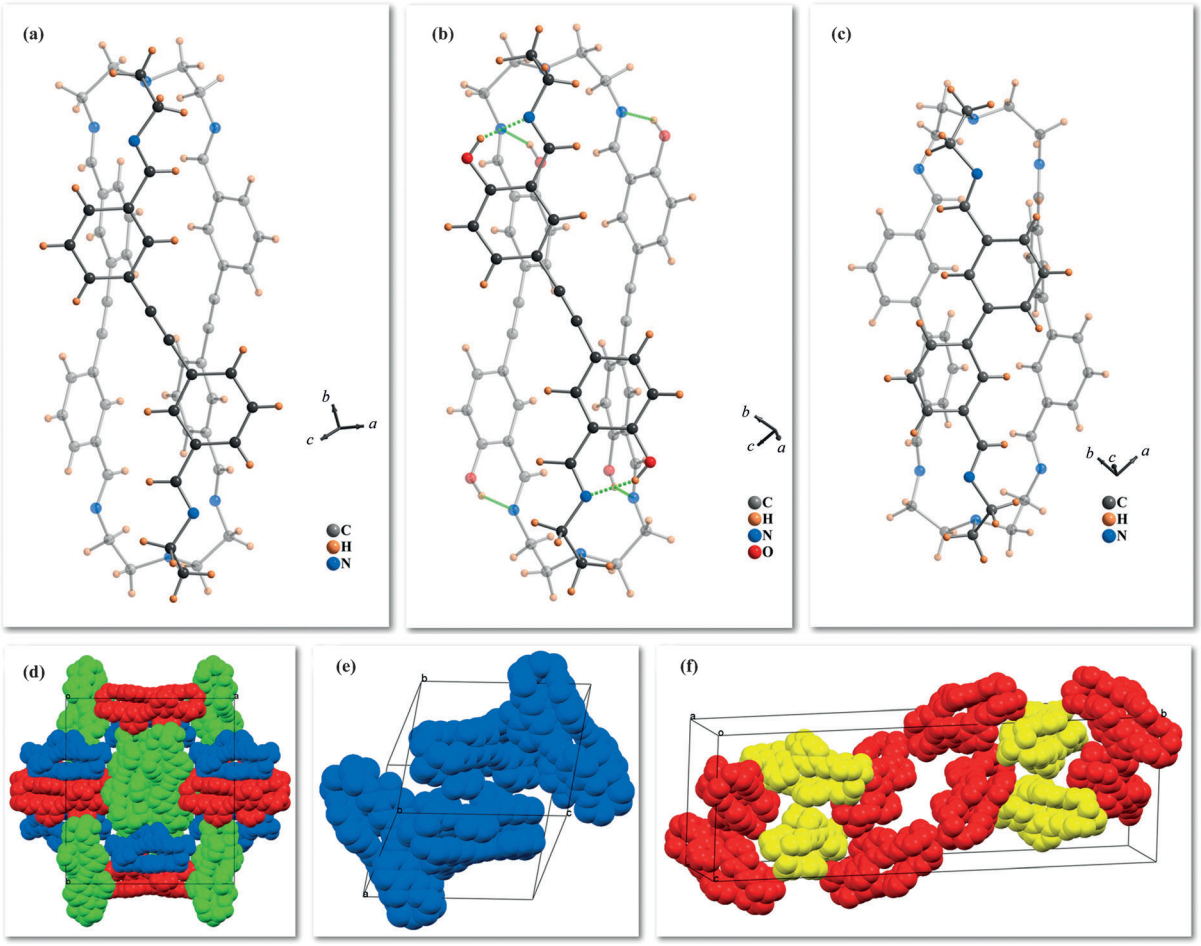


Figure 6. Ball-and-stick diagrams of the single-crystal X-ray structures of the cages a) $\mathbf{A_3X_2}$, b) $\mathbf{B_3X_2}$ with intramolecular H-bonding indicated by green dotted lines, and c) $\mathbf{D_3X_2}$. d–f) Packing of the cages in the unit cell. Solvent molecules and hydrogen atoms are omitted for clarity.

sembly by means of kinetics as well as thermodynamics. This concept of intramolecular H-bonding-guided selectivity has been usefully exploited to achieve quite remarkable control over a self-sorting process operational between two dialdehydes and two triamines to synthesize selectively two specific combinations. Moreover, H-bonding has been used as a driving force for the first time for covalent cage-to-cage transformation and partner exchange in a mixture of cages. Furthermore, the dynamic nature of the imine bond has been used for a fruitful purpose to reach the goal of exchange of partners through unconventional imine bond metathesis. Experimental results in our case ruled out the conventional concerted imine exchange pathway, rather they pointed to a two-step process: disassembly of the cages into starting aldehydes and amines followed by self-sorting into preferred combinations.

Experimental Section

Materials and methods

All chemicals and solvents were purchased from commercially available sources and were used without further purification. 1,3,5-Tris(aminomethyl)-2,4,6-trimethylbenzene (**Y**)[20] and aldehyde **F**[21] were synthesized according to the reported procedures. Aldehydes **A**, **B**, and **D** were synthesized according to modified synthesis procedures.[22] Triethylamine was dried over sodium prior to use for synthesis. ^{1}H and ^{13}C NMR, 2D ^{1}H–^{1}H COSY, and ^{13}C–^{1}H HMQC spectra for the characterization of the products were recorded on a Bruker 400 MHz spectrometer. In ^{1}H NMR spectra chemical shift (δ) values are reported in ppm relative to TMS ($\delta = 0.00$ ppm) as an internal standard in $CDCl_3$. A Bruker ALPHA FTIR spectrometer was used for recording IR spectra. High-resolution mass spectra were recorded on a Q-TOF instrument by electrospray ionization (ESI).

Synthesis of aldehyde A

In a 100 mL flame-dried double-neck round-bottomed flask, 3-ethynylbenzaldehyde (200 mg, 1.54×10^{-3} mol), 3-bromobenzaldehyde (570 mg, 3.08×10^{-3} mol), $Pd(PPh_3)_2Cl_2$ (50 mg, 7.04×10^{-5} mol), CuI (10 mg, 5.26×10^{-5} mol), and PPh_3 (10 mg, 3.82×10^{-5} mol) were dissolved in triethylamine (30 mL). The reaction mixture was then stirred under a nitrogen atmosphere at 75 °C for 24 h. After completion of the reaction, the solvent was completely removed. The resulting solid mass was purified by silica gel column chromatography in hexane/dichloromethane (1:3) to give a pale yellow solid. Yield of isolated product: 152 mg (42%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.56$ (dd, 2H), 7.79 (d, 2H), 7.88 (d, 2H), 8.06 (s, 2H), 10.04 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 89.8$, 124.4, 129.7, 129.9, 133.5, 137.0, 137.6, 191.9 ppm; FTIR: $\tilde{\nu} = 1692$ cm^{-1} (C=O).

Synthesis of aldehyde B

In a 100 mL flame-dried double-neck round-bottomed flask, 5-ethynylsalicylaldehyde (400 mg, 2.74×10^{-3} mol), 5-bromosalicylaldehyde (830 mg, 4.13×10^{-3} mol), $Pd(PPh_3)_2Cl_2$ (100 mg, 1.40×10^{-4} mol), CuI (20 mg, 1.05×10^{-4} mol), and PPh_3 (20 mg, 7.63×10^{-5} mol) were dissolved in triethylamine (50 mL). The reaction mixture was then stirred under a nitrogen atmosphere at 80 °C for 36 h. The solvent was completely removed after the completion of the reaction and the resulting solid mass was purified by silica gel column chromatography in hexane/dichloromethane (1:3) to isolate the pale yellow solid. Yield of isolated product: 255 mg (35%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.00$ (d, 2H), 7.66 (dd, 2H), 7.75 (d, 2H), 9.90 (s, 2H), 11.14 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 87.5, 115.3, 118.7, 121.0, 137.2, 140.1, 161.9, 196.4 ppm; FTIR: $\tilde{\nu}=$ 1686 cm^{-1} (C=O).

Synthesis of aldehyde C

In a 100 mL flame-dried double-neck round-bottomed flask, 5-ethynyl-2-methoxybenzaldehyde (320 mg, 2.00×10^{-3} mol), 5-bromo-2-methoxybenzaldehyde (650 mg, 3.00×10^{-3} mol), $Pd(PPh_3)_2Cl_2$ (70 mg, 9.85×10^{-5} mmol), CuI (15 mg, 7.8×10^{-5} mol), and PPh_3 (15 mg, 5.72×10^{-5} mol) were dissolved in triethylamine (40 mL). The reaction mixture was then stirred under a nitrogen atmosphere at 80 °C for 48 h. The solid product was isolated after removal of the solvent and the product was purified by silica gel column chromatography in dichloromethane to isolate pure product as a yellow powder. Yield of isolated product: 224 mg (38%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=3.96$ (s, 3H), 6.98 (d, 2H), 7.68 (dd, 2H), 7.97 (d, 2H), 10.44 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.3$, 88.1, 112.4, 116.2, 125.2, 132.3, 139.1, 161.9, 189.4 ppm; FTIR: $\tilde{\nu}=$ 1675 cm^{-1} (C=O); ESI-HRMS ($CHCl_3/CH_3CN$, 1:3): *m/z*: calcd for $[M+H]^+$: 295.0925; found: 295.0958; calcd for $[M+Na]^+$: 317.0789; found: 317.0815.

Synthesis of aldehyde D

In a 100 mL flame-dried double-neck round-bottomed flask, 3-bromobenzaldehyde (740 mg, 4.00×10^{-3} mol) and 3-formylphenylboronic acid (900 mg, 6.00×10^{-3} mol) were taken in THF (50 mL) and an aqueous solution (20 mL) of K_2CO_3 (1 g, 7.25×10^{-3} mol) was added. The resulting solution mixture was stirred under a nitrogen atmosphere at room temperature for 10 min followed by addition of $Pd(PPh_3)_4$ (100 mg, 8.65×10^{-5} mol) and heating to 80 °C for 48 h. After completion of the reaction THF was completely removed and the aqueous part was extracted with dichloromethane (50 mL×3). The organic part was dried over sodium sulfate and the solvent was completely removed to obtain a pale yellow solid. The resulting solid mass was purified by silica gel column chromatography in dichloromethane to give a white powder. Yield of isolated product: 824 mg (98%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=7.67$ (t, 2H), 7.91 (m, 2H), 8.16 (t, 2H), 10.11 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=128.4$, 129.9, 130.2, 133.4, 137.5, 141.1, 192.5 ppm; FTIR: 1687 cm^{-1} (C=O).

Synthesis of cage A_3X_2

In an 8 mL glass vial, a chloroform solution (4 mL) of amine **X** (2.9 mg, 1.98×10^{-5} mol) was added slowly to a stirred solution of aldehyde **A** (7 mg, 2.99×10^{-5} mol) in chloroform (3 mL). The resulting solution mixture was stirred at room temperature for an additional 24 h. After completion of the reaction, the solvent was completely removed and the obtained white solid mass was washed with ethanol to remove unreacted starting materials. Yield of isolated product: 7.5 mg (85%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=2.83$ (br, 6H), 3.37–3.69 (br, 6H), 5.60 (s, 6H), 7.54 (m, 12H), 7.80 (d, 6H), 8.11 ppm (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.6$, 60.4, 90.1, 124.9, 125.4, 129.0, 133.7, 134.2, 137.0, 161.1 ppm; FTIR: $\tilde{\nu}=$ 1649 cm^{-1} (C=N); ESI-HRMS ($CHCl_3/CH_3CN$, 1:3): *m/z*: calcd for $[M+H]^+$: 887.4505; found: 887.4654.

Synthesis of cage B_3X_2

In an 8 mL glass vial, a chloroform solution (4 mL) of amine **X** (2.9 mg, 1.98×10^{-5} mol) was added dropwise slowly to a stirred solution of aldehyde **B** (7.9 mg, 2.99×10^{-5} mol) in chloroform (3 mL). The resulting solution mixture was stirred at room temperature for an additional 24 h. After completion of the reaction, the solvent was reduced in volume and a yellow solid product was precipitated out by adding *n*-pentane. Yield of isolated product: 7.9 mg (80%). ^{1}H NMR: ($CDCl_3$, 400 MHz) $\delta=2.79$ (t, 6H), 2.92 (t, 6H), 3.22 (t, 6H), 3.79 (t, 6H), 5.60 (s, 6H), 7.04 (d, 6H), 7.60 (s, 6H), 7.65 (dd, 6H), 14.49 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.4$, 58.4, 88.0, 115.4, 117.9, 118.6, 134.5, 136.0, 161.8, 166.1 ppm; FTIR: $\tilde{\nu}=$ 1631 cm^{-1} (C=N); ESI-HRMS ($CHCl_3/CH_3CN$, 1:3): *m/z*: calcd for $[M+H]^+$: 983.4199; found: 983.4363.

Synthesis of cage D_3X_2

In an 8 mL glass vial, amine **X** (2.9 mg, 1.98×10^{-5} mol) was dissolved in acetonitrile (4 mL). This solution was added dropwise to a stirred solution of aldehyde **D** (6.3 mg, 3.00×10^{-5} mol) in acetonitrile (3 mL). The resulting solution mixture was stirred at room temperature for an additional 24 h. After completion of the reaction, the solvent was completely removed followed by addition of a few drops of ethanol and then the product was precipitated out by adding *n*-pentane. Yield of isolated product: 6.4 mg (78%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=2.87$ (br, 12H), 3.71 (br, 12H), 5.99 (s, 6H), 7.12 (d, 6H), 7.54 (t, 6H), 7.87 (s, 6H), 8.13 ppm (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=56.3$, 60.5, 125.0, 128.2, 128.8, 130.7, 137.6, 140.1, 162.1 ppm; FTIR: $\tilde{\nu}=1644$ cm^{-1} (C=N); ESI-HRMS (CH_3CN): *m/z*: calcd for $[M+H]^+$: 815.4505; found: 815.4648.

Synthesis of cage F_3X_2

In an 8 mL glass vial, a chloroform solution (4 mL) of amine **X** (2.9 mg, 1.98×10^{-5} mol) was added dropwise slowly to a stirred solution of aldehyde **F** (5.4 mg, 2.99×10^{-5} mol) in chloroform (3 mL). The resulting solution mixture was stirred at room temperature for an additional 24 h. After completion of the reaction, the solvent was completely removed and the obtained yellow solid mass was washed with ethanol to remove unreacted starting materials. Yield of isolated product: 6.6 mg (91%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=$ 2.14 (s, 9H), 2.71 (t, 6H), 2.86 (s, 6H), 3.23 (t, 6H), 3.72 (s, 6H), 5.46 (s, 3H), 7.50 (s, 6H), 15.18 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=7.8$, 55.8, 56.2, 111.3, 113.1, 136.0, 166.2, 167.8 ppm; FTIR: $\tilde{\nu}=$ 1633 cm^{-1} (C=N); ESI-HRMS ($CHCl_3/CH_3CN$, 1:1): *m/z*: calcd for $[M+H]^+$: 725.3730; found: 725.3860.

Synthesis of cage F_3Y_2

In an 8 mL glass vial, amine **Y** (4.1 mg, 2.00×10^{-5} mol) was dissolved in chloroform (4 mL). This solution was added dropwise to a stirred solution of aldehyde **F** (5.4 mg, 3.00×10^{-5} mol) in chloroform (3 mL). Pure solid product was isolated after removing the solvent on completion of the reaction followed by washing with acetonitrile. Yield of isolated product: 4.2 mg (58%). ^{1}H NMR

($CDCl_3$, 400 MHz): $\delta = 2.11$ (s, 18H), 2.18 (s, 9H), 5.01 (s, 12H), 6.27 (s, 3H), 7.52 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.7$, 16.6, 30.1, 53.3, 111.8, 113.2, 130.5, 132.5, 139.6, 160.8, 164.4 ppm; FTIR $\tilde{\nu} = 1618\ cm^{-1}$ (C=N); ESI-HRMS ($CHCl_3/CH_3CN$, 1:1): *m/z*: calcd for $[M+H]^+$: 847.4138; found: 847.4215.

Self-sorting experiment (3A + 3D + 2X)

A solution of amine **X** (0.8 mg, 5.47×10^{-6} mol) in $CDCl_3$ (0.5 mL) was added to a $CDCl_3$ solution (0.5 mL) containing aldehyde **A** (2.3 mg, 9.82×10^{-6} mol) and aldehyde **D** (2.1 mg, 9.82×10^{-6} mol) in a 4 mL glass vial. The resulting solution mixture was stirred at room temperature and transferred into an NMR tube periodically for ^1H NMR monitoring of the reaction progress.

Self-sorting experiment (3A + 3B + 3C + 3D + 2X)

A solution of amine **X** (0.8 mg, 5.47×10^{-6} mol) in $CDCl_3$ (0.5 mL) was added to a $CDCl_3$ solution (0.5 mL) containing aldehydes **A** (2.3 mg, 9.82×10^{-6} mol), **B** (2.7 mg, 9.82×10^{-6} mol), **C** (2.9 mg, 9.82×10^{-6} mol), and **D** (2.1 mg, 9.82×10^{-6} mol) in a 4 mL glass vial. The resulting solution mixture was stirred at room temperature and transferred into an NMR tube periodically for ^1H NMR monitoring of the reaction progress.

Self-sorting experiment (3B + 3D + 4X)

In a 4 mL glass vial, aldehyde **B** (1.3 mg, 4.88×10^{-6} mol) and aldehyde **D** (1.0 mg, 4.88×10^{-6} mol) were dissolved in $CDCl_3$ (1.0 mL). Then a $CDCl_3$ solution (0.5 mL) containing amine **X** (1.0 mg, 6.85×10^{-6} mol) was added slowly. The resulting solution mixture was stirred at room temperature and transferred into an NMR tube periodically for ^1H NMR monitoring of the reaction progress.

Self-sorting experiment (3A + 3B + 3D + 6X)

In a 4 mL glass vial, aldehyde **A** (1.1 mg, 4.88×10^{-6} mol), aldehyde **B** (1.3 mg, 4.88×10^{-6} mol), and aldehyde **D** (1.0 mg, 4.88×10^{-6} mol) were dissolved in $CDCl_3$ (1.0 mL). Then a $CDCl_3$ solution (1.0 mL) containing amine **X** (1.5 mg, 1.02×10^{-5} mol) was added slowly. The resulting solution mixture was stirred at room temperature and transferred into an NMR tube for ^1H NMR analysis. This process was repeated during the transformation.

Self-sorting experiment (3E + 3F + 2X + 2Y)

In a 20 mL glass vial, aldehyde **E** (2.7 mg, 1.50×10^{-5} mol) and aldehyde **F** (5.0 mg, 1.50×10^{-5} mol) were dissolved in chloroform (10 mL). Then a chloroform solution (8 mL) containing amine **X** (1.5 mg, 1.02×10^{-5} mol) and amine **Y** (2.1 mg, 1.02×10^{-5} mol) was added dropwise with stirring. The resulting solution mixture was stirred at room temperature for another 48 h. The solvent was completely removed and the composition of the solid mass was checked by ^1H NMR spectroscopy in $CDCl_3$.

Cage D_3X_2 to cage B_3X_2 transformation experiment

In a 4 mL glass vial, aldehyde **D** (2.1 mg, 9.82×10^{-6} mol) and amine **X** (1.0 mg, 6.85×10^{-6} mol) were stirred at room temperature in $CDCl_3$ (1 mL) for 24 h to synthesize cage $\mathbf{D_3X_2}$. After that time period, aldehyde **B** (2.7 mg, 1.01×10^{-5} mol) dissolved in $CDCl_3$ (0.5 mL) was added slowly to the reaction mixture and the resulting solution was stirred. Progress of the reaction was monitored by transferring an aliquot into an NMR tube and subsequently checking the ^1H NMR spectrum. This process was repeated throughout the transformation.

Imine metathesis experiment

In a 4 mL glass vial, cage $\mathbf{E_3Y_2}$ (1.9 mg, 2.3×10^{-6} mol) was mixed with cage $\mathbf{G_3X_2}$ (2.0 mg, 2.3×10^{-6} mol) in $CDCl_3$ (1 mL). Progress of the reaction was monitored by transferring an aliquot into an NMR tube and subsequently checking the ^1H NMR spectrum. This process was repeated throughout the transformation.

X-ray crystal data collection and structure solution

X-ray data of the cages $\mathbf{A_3X_2}$, $\mathbf{B_3X_2}$, and $\mathbf{D_3X_2}$ were collected on a Bruker SMART APEX CCD diffractometer equipped with a low-temperature device, using the SMART/SAINT software.[23] All the diffraction-quality crystals were mounted on a loop coated with traces of viscous oil. The intensity data of $\mathbf{A_3X_2}$ and $\mathbf{B_3X_2}$ were collected at 100(2) K, but at 110(2) K for $\mathbf{D_3X_2}$ by using graphite-monochromated $Mo_{K\alpha}$ radiation (0.7107 Å). The structures were solved by direct methods and refined by full-matrix least squares on F^2 by employing the SHELX-97[24] incorporated in WinGX.[25] Empirical absorption corrections were applied with SADABS.[26] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed by using the riding models and refined isotropically. Crystallographic data and refinement parameters are provided in Table 2.

Computational methodology

Full geometry optimizations were carried out using the Gaussian 09 package.[27] The hybrid B3LYP functional was used in all calculations as implemented in the Gaussian 09 package, by mixing the exact Hartree–Fock-type exchange with Becke's expression for the exchange functional[28] and that proposed by Lee–Yang–Parr for the correlation contribution.[29] The 6-31G basis set was used for all calculations. Frequency calculations carried out on the opti-

Table 2. Crystallographic data and refinement parameters for cages $\mathbf{A_3X_2}$, $\mathbf{B_3X_2}$, and $\mathbf{D_3X_2}$.

	$\mathbf{A_3X_2}$	$\mathbf{B_3X_2}$	$\mathbf{D_3X_2}$
empirical formula	$C_{129}H_{108}N_{16}O_4$	$C_{64}H_{54}N_{10}O_7$	$C_{54}H_{54}N_8O_2$
formula weight	1946.31	1075.17	847.05
T [K]	100(2)	100(2)	110(2)
crystal system	monoclinic	monoclinic	orthorhombic
space group	*C*2/*c*	$P2_1/c$	*Pccn*
a [Å]	34.3058(13)	17.861(6)	10.9552(4)
b [Å]	34.3058(13)	17.674(5)	63.0820(17)
c [Å]	20.9080(7)	19.284(6)	19.9511(4)
α [°]	90.000(0)	90.000(0)	90.000(0)
β [°]	116.853(2)	113.396(11)	90.000(0)
γ [°]	90.000(0)	90.000(0)	90.000(0)
V [Å^3]	21540.7(14)	5587(3)	13787.7(7)
Z	8	4	12
ρ_{calcd} [g cm^{-3}]	1.200	1.278	1.224
μ ($Mo_{K\alpha}$) [mm^{-1}]	0.074	0.085	0.076
λ [Å]	0.71073	0.71073	0.71073
F(000)	8160.0	2256.0	5400
collected reflns	171178	56400	89513
unique reflns	18873	9835	12116
goodness of fit (F^2)	1.174	0.893	1.028
R_1 [$I > 2\sigma(I)$][a]	0.0734	0.0778	0.0858
wR_2 [$I > 2\sigma(I)$][b]	0.2526	0.2314	0.2094

[a] $R_1 = \Sigma\big|\ |F_o| - |F_c|\ \big| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma\{w(F_o^2 - F_c^2)^2\}/\Sigma\{w(F_o^2)^2\}]^{1/2}$.

mized structures confirmed the absence of any imaginary frequencies. Change in entropy had an impact on the cage formation process. Release of water molecules was the main contributor to the entropy change, so the entropy changes have similar contributions in the overall process that are approximated.

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Keywords: aldehydes · cage compounds · hydrogen bonds · metathesis · self-sorting

[1] a) M. M. Safont-Sempere, G. Fernández, F. Würthner, *Chem. Rev.* **2011**, *111*, 5784 – 5814; b) M. L. Saha, M. Schmittel, *Org. Biomol. Chem.* **2012**, *10*, 4651 – 4684; c) K. Osowska, O. Š. Miljanić, *Synlett* **2011**, 1643 – 1648; d) K. Osowska, O. Š. Miljanić, *J. Am. Chem. Soc.* **2011**, *133*, 724 – 727; e) P. Mukhopadhyay, A. Wu, L. Isaacs, *J. Org. Chem.* **2004**, *69*, 6157 – 6164; f) Y. Rudzevich, V. Rudzevich, F. Klautzsch, C. A. Schalley, V. BÖhmer, *Angew. Chem.* **2009**, *121*, 3925 – 3929; *Angew. Chem. Int. Ed.* **2009**, *48*, 3867 – 3871; g) M. Schmittel, K. Mahata, *Chem. Commun.* **2010**, *46*, 4163 – 4165; h) A. Wu, L. Isaacs, *J. Am. Chem. Soc.* **2003**, *125*, 4831 – 4835; i) P. Mukhopadhyay, P. Y. Zavalij, L. Isaacs, *J. Am. Chem. Soc.* **2006**, *128*, 14093 – 14102.

[2] a) G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, *Angew. Chem.* **2007**, *119*, 2418 – 2445; *Angew. Chem. Int. Ed.* **2007**, *46*, 2366 – 2393; b) A. L. Lehninger, D. L. Nelson, M. M. Cox, *Lehninger Principles of Biochemistry*, 5th ed., W. H. Freeman, New York, **2008**; c) R. C. Weisenberg, *Science* **1972**, *177*, 1104 – 1105.

[3] a) R. Kramer, J.-M. Lehn, A. Marquisrigault, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5394 – 5398; b) J.-M. Lehn, *Science* **2002**, *295*, 2400 – 2403; c) Y.-R. Zheng, B. H. Northrop, H.-B. Yang, L. Zhao, P. J. Stang, *J. Org. Chem.* **2009**, *74*, 3554 – 3557; d) B. H. Northrop, Y.-R. Zheng, K.-W. Chi, P. J. Stang, *Acc. Chem. Res.* **2009**, *42*, 1554 – 1563; e) H.-B. Yang, K. Ghosh, B. H.Northrop, P. J. Stang, *Org. Lett.* **2007**, *9*, 1561 – 1564; f) L. Zhao, B. H. Northrop, Y. R. Zheng, H. B. Yang, H. J. Lee, Y. M. Lee, J. Y. Park, K.-W. Chi, P. J. Stang, *J. Org. Chem.* **2008**, *73*, 6580 – 6586; g) R. J. Sarma, J. R. Nitschke, *Angew. Chem.* **2008**, *120*, 383 – 386; *Angew. Chem. Int. Ed.* **2008**, *47*, 377 – 380; h) R. Chakrabarty, P. S. Mukherjee, P. J. Stang, *Chem. Rev.* **2011**, *111*, 6810 – 6918; i) D. Samanta, P. S. Mukherjee, *Chem. Commun.* **2013**, *49*, 4307 – 4309; j) K. Mahata, M. L. Saha, M. Schmittel, *J. Am. Chem. Soc.* **2010**, *132*, 15933 – 15935; k) T. Kamada, N. Aratani, T. Ikeda, N. Shibata, Y. Higuchi, A. Wakamiya, S. Yamaguchi, K. S. Kim, Z. S. Yoon, D. Kim, A. Osuka, *J. Am. Chem. Soc.* **2006**, *128*, 7670 – 7678; l) S. J. Lee, S.-H. Cho, K. L. Mulfort, D. M. Tiede, J. T. Hupp, S. T. Nguyen, *J. Am. Chem. Soc.* **2008**, *130*, 16828 – 16289; m) M. A. Masood, E. J. Enemark, T. D. P. Stack, *Angew. Chem.* **1998**, *110*, 973 – 977; *Angew. Chem. Int. Ed.* **1998**, *37*, 928 – 932; n) A. M. Johnson, R. J. Hooley, *Inorg. Chem.* **2011**, *50*, 4671 – 4673; o) K. Mahata, M. Schmittel, *J. Am. Chem. Soc.* **2009**, *131*, 16544 – 16554; p) S. Ghosh, P. S. Mukherjee, *Inorg. Chem.* **2009**, *48*, 2605 – 2613; q) A. K. Bar, G. Mostafa, P. S. Mukherjee, *Inorg. Chem.* **2010**, *49*, 7647 – 7649.

[4] a) K. A. Jolliffe, P. Timmerman, D. N. Reinhoudt, *Angew. Chem.* **1999**, *111*, 983 – 986; *Angew. Chem. Int. Ed.* **1999**, *38*, 933 – 936; b) P. S. Corbin, L. J. Lawless, Z. T. Li, Y. G. Ma, M. J. Witmer, S. C. Zimmerman, *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 5099 – 5104; c) Y. G. Ma, S. V. Kolotuchin, S. C. Zimmerman, *J. Am. Chem. Soc.* **2002**, *124*, 13757 – 13769; d) S. Ghosh, A. Wu, J. C. Fettinger, P. Y. Zavalij, L. Isaacs, *J. Org. Chem.* **2008**, *73*, 5915 – 5925; e) E. S. Barrett, T. J. Dale, J. Rebek, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 2344 – 2350; f) N. Tomimasu, A. Kanaya, Y. Takashima, H. Yamaguchi, A. Harada, *J. Am. Chem. Soc.* **2009**, *131*, 12339 – 12348; g) A. S. Singh, S.-S. Sun, *Chem. Commun.* **2012**, *48*, 7392 – 7394.

[5] a) W. Jiang, W. I. Linder, F. Klautzsch, C. A. Schalley, *Chem. Eur. J.* **2011**, *17*, 2344 – 2348; b) W. Jiang, H. D. F. Winkler, C. A. Schalley, *J. Am. Chem. Soc.* **2008**, *130*, 13852 – 1353; c) W. Jiang, D. Sattler, K. Rissanen, C. A. Schalley, *Org. Lett.* **2011**, *13*, 4502 – 4505; d) W. Jiang, A. Schäfer, P. C. Mohr, C. A. Schalley, *J. Am. Chem. Soc.* **2010**, *132*, 2309 – 2320; e) F. Wang, C. Han, C. He, Q. Zhou, J. Zhang, C. Wang, N. Li, F. Huang, *J. Am. Chem. Soc.* **2008**, *130*, 11254 – 11255; f) M. M. Safont-Sempere, P. Osswald, M. Stolte, M. Grüne, M. Renz, M. Kaupp, K. Radacki, H. Braunschweig, F. Würthner, *J. Am. Chem. Soc.* **2011**, *133*, 9580 – 9591; g) K. Tahara, T. Fujita, M. Sonoda, M. Shiro, Y. Tobe, *J. Am. Chem. Soc.* **2008**, *130*, 14339 – 14345.

[6] a) S. J. Rowan, D. G. Hamilton, P. A. Brady, J. K. M. Sanders, *J. Am. Chem. Soc.* **1997**, *119*, 2578 – 2579; b) J.-B. Lin, X.-N. Xu, X.-K. Jiang, Z.-T. Li, *J. Org. Chem.* **2008**, *73*, 9403 – 9410; c) J. Han, J. Pan, T. Lei, C. Liu, J. Pei, *Chem. Eur. J.* **2010**, *16*, 13850 – 13861.

[7] a) A. Granzhan, C. Schouwey, T. Riis-Johannessen, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2011**, *133*, 7106 – 7115; b) M. M. J. Smulders, A. Jiménez, J. R. Nitschke, *Angew. Chem.* **2012**, *124*, 6785 – 6789; *Angew. Chem. Int. Ed.* **2012**, *51*, 6681 – 6685.

[8] a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem.* **2002**, *114*, 938 – 993; *Angew. Chem. Int. Ed.* **2002**, *41*, 898 – 952; b) S. Ladame, *Org. Biomol. Chem.* **2008**, *6*, 219 – 216; c) *Dynamic Combinatorial Chemistry* (Eds.: J. N. H. Reek, S. Otto), Wiley-VCH, Weinheim, **2010**; d) R. A. R. Hunt, S. Otto, *Chem. Commun.* **2011**, *47*, 847 – 858; e) M. E. Belowich, J. F. Stoddart, *Chem. Soc. Rev.* **2012**, *41*, 2003 – 2024; f) J.-M. Lehn, *Chem. Eur. J.* **1999**, *5*, 2455 – 2463; g) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652 – 3711; h) F. B. L. Cougnon, J. K. M. Sanders, *Acc. Chem. Res.* **2012**, *45*, 2211 – 2221.

[9] a) M. L. C. Quan, D. J. Cram, *J. Am. Chem. Soc.* **1991**, *113*, 2754 – 1755; b) X. Liu, Y. Liu, G. Li, R. Warmuth, *Angew. Chem.* **2006**, *118*, 915 – 918; *Angew. Chem. Int. Ed.* **2006**, *45*, 901 – 904; c) D. Xu, R. Warmuth, *J. Am. Chem. Soc.* **2008**, *130*, 7520 – 7521; d) Y. Liu, X. Liu, R. Warmuth, *Chem. Eur. J.* **2007**, *13*, 8953 – 8959; e) N. Christinat, R. Scopelliti, K. Severin, *Angew. Chem.* **2008**, *120*, 1874 – 1878; *Angew. Chem. Int. Ed.* **2008**, *47*, 1848 – 1852; f) B. Içli, N. Christinat, J. Tönnemann, C. Schüttler, R. Scopelliti, K. Severin, *J. Am. Chem. Soc.* **2009**, *131*, 3154 – 3155; g) T. Hasell, X. Wu, J. T. A. Jones, J. Bacsa, A. Steiner, T. Mitra, A. Trewin, D. J. Adams, A. I. Cooper, *Nat. Chem.* **2010**, *2*, 750 – 755.

[10] a) M. Arunachalam, I. Ravikumar, P. Ghosh, *J. Org. Chem.* **2008**, *73*, 9144 – 9147; b) O. Francesconi, A. Ienco, G. Moneti, C. Nativi, S. Roelens, *Angew. Chem.* **2006**, *118*, 6845 – 6848; *Angew. Chem. Int. Ed.* **2006**, *45*, 6693 – 6696; c) R. Alberto, G. Bergamaschi, H. Braband, T. Fox, V. Amendola, *Angew. Chem.* **2012**, *124*, 9910 – 9914; *Angew. Chem. Int. Ed.* **2012**, *51*, 9772 – 19776; d) P. Mateus, R. Delgado, P. Branda ~o, V. Félix, *J. Org. Chem.* **2012**, *77*, 4611 – 4621.

[11] a) N. De Rycke, F. Couty, O. R. P. David, *Tetrahedron Lett.* **2012**, *53*, 462 – 466; b) O. Perraud, A. B. Sorokin, J.-P. Dutasta, A. Martinez, *Chem. Commun.* **2013**, *49*, 1288 – 1290.

[12] a) M. Mastalerz, W. Schneider, I. M. Oppel, O. Presly, *Angew. Chem.* **2011**, *123*, 1078 – 1083; *Angew. Chem. Int. Ed.* **2011**, *50*, 1046 – 1051; b) T. Tozawa, J. T. A. Jones, S. I. Swamy, S. Jiang, D. J. Adams, S. Shakespeare, R. Clowes, D. Bradshaw, T. Hasell, S. Y. Chong, C. Tang, S. Thompson, J. Parker, A. Trewin, J. Bacsa, A. M. Z. Slawin, A. Steiner, A. I. Cooper, *Nat. Mater.* **2009**, *8*, 973 – 978; c) T. Hasell, M. Schmidtmann, C. A. Stone, M. W. Smith, A. I. Cooper, *Chem. Commun.* **2012**, *48*, 4689 – 4691; d) M. W. Schneider, L. G. Lechnerb, M. Mastalerz, *J. Mater. Chem.* **2012**, *22*, 7113 – 7116.

[13] a) Y. Jin, B. A. Voss, A. Jin, H. Long, R. D. Noble, W. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6650 – 6658; b) T. Mitra, K. E. Jelfs, M. Schmidtman, A. Ahmed, S. Y. Chong, D. J. Adams, A. I. Cooper, *Nat. Chem.* **2013**, *5*, 276 – 281.

[14] K. Acharyya, S. Mukherjee, P. S. Mukherjee, *J. Am. Chem. Soc.* **2013**, *135*, 554 – 557.

[15] a) L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469 – 472; b) R. Ahmed, A. Papmeyer, D. M. D'Souza, D. A. Leigh, K. M. Mullen, M. Papmeyer, A. M. Z. Slawin, J. K. Y. Wong, J. D. Woollins, *J. Am. Chem. Soc.* **2011**, *133*, 12304 – 12310; c) D. Ajami, H. Dube, J. Rebek, Jr., *J. Am. Chem. Soc.* **2011**, *133*, 9689 – 9691; d) M. D. Tzirakis, N. Marion, W. B.

Schweizer, F. Diederich, *Chem. Commun.* **2013**, *49*, 7605 – 7607; e) A. R. Stefankiewicz, E. Tamanini, G. D. Pantoş, J. K. M. Sanders, *Angew. Chem.* **2011**, *123*, 5843 – 5846; *Angew. Chem. Int. Ed.* **2011**, *50*, 5725 – 5728; f) N. Ponnuswamy, G. D. Pantos, M. M. J. Smulders, J. K. M. Sanders, *J. Am. Chem. Soc.* **2012**, *134*, 566 – 573; g) R. P. Sijbesma, F. H. Beijer, L. Brunsveld, B. J. B. Folmer, J. Hirschberg, R. F. M. Lange, J. K. L. Lowe, E. W. Meijer, *Science* **1997**, *278*, 1601 – 1604; h) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647 – 1668.

[16] a) A. Kovács, A. Szabó, I. Hargittai, *Acc. Chem. Res.* **2002**, *35*, 887 – 894; b) G. Gilli, F. Bellucci, V. Ferretti, V. Bertolasi, *J. Am. Chem. Soc.* **1989**, *111*, 1023 – 1028; c) G. Chung, O. Kwon, Y. Kwon, *J. Phys. Chem. A* **1998**, *102*, 2381 – 2387; d) M. Čuma, S. Scheiner, T. Kar, *J. Am. Chem. Soc.* **1998**, *120*, 10497 – 10503; e) M. Palusiak, S. Simon, M. Sola', *J. Org. Chem.* **2009**, *74*, 2059 – 2066; f) M. Palusiak, S. Simon, M. Sola', *J. Org. Chem.* **2006**, *71*, 5241 – 5248.

[17] a) P. Kovaříček, J.-M. Lehn, *J. Am. Chem. Soc.* **2012**, *134*, 9446 – 9455; b) B. E. Leach, D. L. Leussing, *J. Am. Chem. Soc.* **1971**, *93*, 3377 – 3384; c) R. M. B. Singh, L. Main, *Aust. J. Chem.* **1983**, *36*, 2327 – 2332.

[18] C. K. Ingold, A. Piggott, *J. Chem. Soc. Trans.* **1922**, *121*, 2793 – 2804.

[19] G. Tóth, I. Pintér, A. Messmer, *Tetrahedron Lett.* **1974**, *15*, 735 – 738.

[20] A. K. Mishra, S. Verma, *Inorg. Chem.* **2010**, *49*, 3691 – 3693.

[21] S.-Q. Wu, Q.-W. Xie, G.-Y. An, X. Chen, C.-M. Liu, A.-L. Cui, H.-Z. Kou, *Dalton Trans.* **2013**, *42*, 4369 – 4372.

[22] a) A. Vidal-Ferran, Z. Clyde-Watson, N. Bampos, J. K. M. Sanders, *J. Org. Chem.* **1997**, *62*, 240 – 241; b) K.-L. Kuo, C.-C. Huang, Y.-C. Lin, *Dalton Trans.* **2008**, 3889 – 3898; c) E. F. Santos-Filho, J. C. Sousa, N. M. M. Bezerra, P. H. Menezes, R. A. Oliveira, *Tetrahedron Lett.* **2011**, *52*, 5288 – 5291.

[23] SMART/SAINT; Bruker AXS, Inc., Madison, WI, **2004**.

[24] G. M. Sheldrick, SHELX-97, Program for the Solution and Refinement of Crystal Structures; University of Gottingen: Gottingen, Germany, **1998**.

[25] L. J. Farrugia, WinGX: An Integrated System ofWindows Programs for the Solution, Refinement and Analysis for Single Crystal X-ray Diffraction Data, version 1.80.01; Department of Chemistry: University of Glasgow, **2003**. (L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837 – 838).

[26] G. M. Sheldrick, SADABS, Bruker Nonius Area Detector Scaling and Absorption Correction, version 2.05; University of Gottingen: Gottingen, Germany, **1999**.

[27] Gaussian 09 (Revision A.02), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.

[28] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098 – 3100.

[29] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785 – 789.

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