

# **Synthesis and Analysis of Multipyridyl Ligands for Multipoint Photodimerization**

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by

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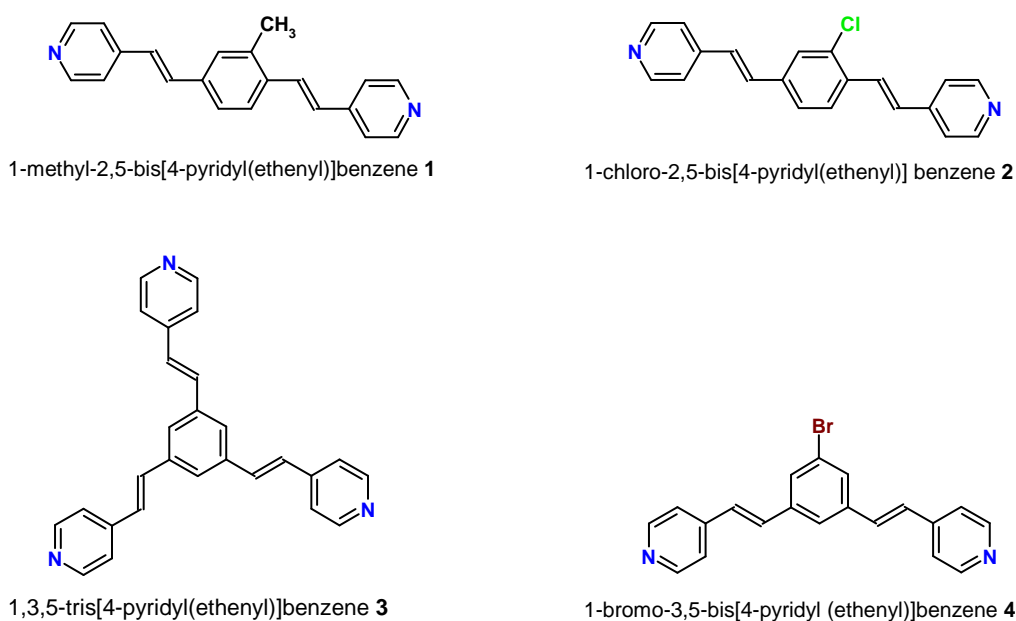
## 1. Abstract

Multifunctional and multidentate ligands are essential starting materials in the design of metal organic frameworks that can exhibit structural and functional diversity. The ultimate goal of this work is to synthesize chiral polydentate pyridyl ligands through template directed solid state photoreactions. Specifically, this work explored the synthesis of 1-methyl-2,5-bis[4-pyridyl(ethenyl)]benzene, 1-chloro-2,5-bis[4-pyridyl(ethenyl)]benzene, 1,3,5-tris[4-pyridyl(ethenyl)]benzene, and 1-bromo-3,5-bis[4-pyridyl(ethenyl)]benzene **1-4** using traditional synthetic methods and microwave assisted reactions. The results from the two methods are compared and the advantages of microwave assisted chemistry are discussed in the context of Heck coupling reactions. Furthermore, crystal structural analysis of some of the precursor pyridyl ligands and their complexation with templating resorcinol derivatives are discussed.

## 2. Scope and Background

The goal of this project is to create the foundation for chiral metal organic frameworks (MOFs) through the synthesis and characterization of novel multipyridyl ligands. Specifically, this work focuses on the synthesis of dipyridyl ligands that differ from each other only in functionality, a methyl, a chloro, or a bromo group. These three groups have nearly similar size, and the pyridyl ligands that contain these groups can be used in the preparation of supramolecular solid solutions (Section 2.7) for reactions in the solid state. The work also explores microwave irradiation as an alternative to traditional synthetic methods; the advantages of microwaves in the syntheses of asymmetric ligand

intermediates and products are addressed in Section 2.2. The desirability of these new ligands and the potential structural insight we can get from their solid state structures is addressed in Section 2.1. This section provides an overview of new asymmetric multipyridyl ligands, microwave assisted organic synthesis, cocrystallization, noncovalent interactions, polymorphism, template driven solid state synthesis, solid solutions, MOFs, and previous work relevant to the current research.

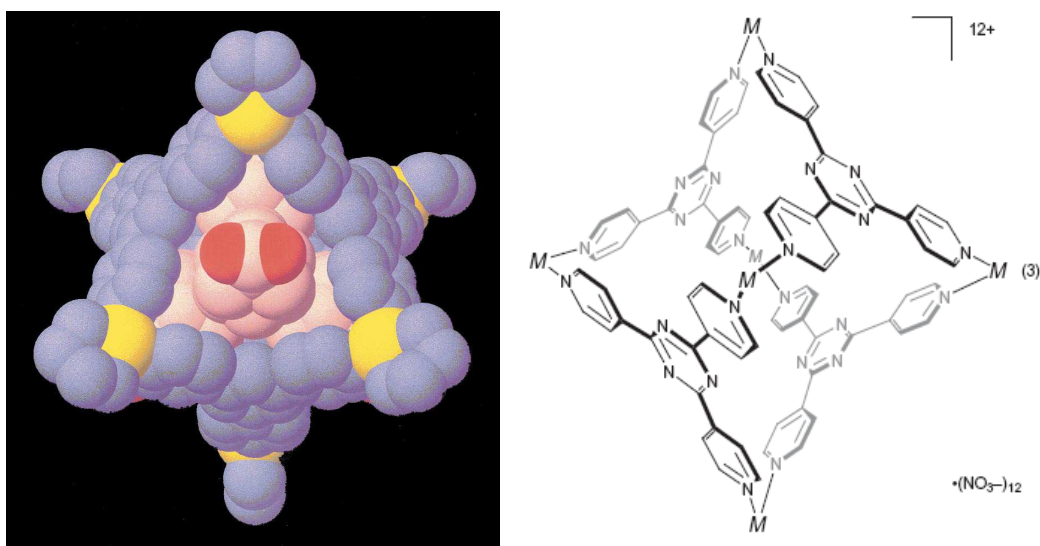


**Figure 1.** Molecular structures and names of target ligands **1-4**. Notice the asymmetry in the structures of ligands **1** and **2**.

## 2.1 New Asymmetric Multipyridyl Ligands

Multipyridyl ligands are desirable starting points for many applications. The nitrogen atom in a pyridyl group can participate in many different intermolecular interactions that range from hydrogen bonding with weak and strong donors to coordination bonding with a variety of metal ions. The ligands synthesized in this work have appropriate geometries

for cocrystallization with linear templates; these cocrystals can provide favorable conditions to induce intermolecular photoreactions in the solid state. Much work in coordination chemistry and MOFs is carried out with symmetric aza-ligands<sup>1</sup>; the asymmetric multipyridyl ligands (AMLs) designed in this work provide further advantage in that they offer dissimilar coordination points. As precursors for polydentate ligands, AMLs are important starting materials in the preparation of porous MOFs that present unique chiral cages within which enantio- and diastereoselective syntheses can be carried out.

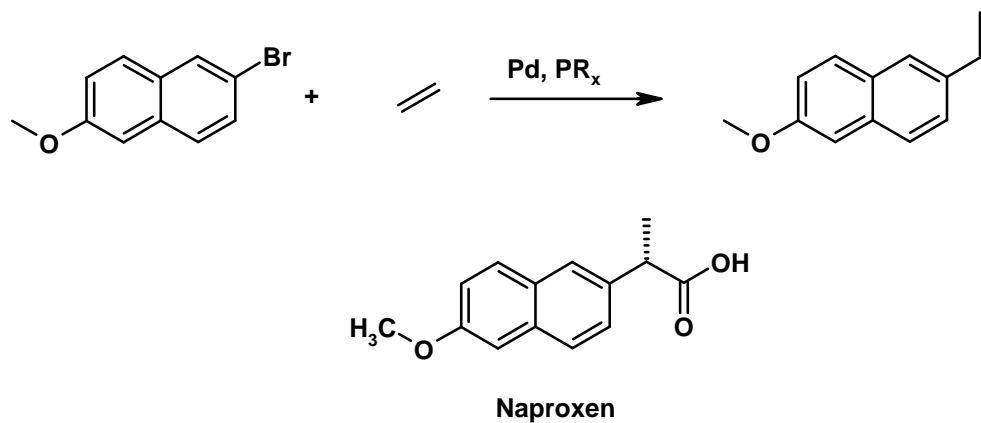


**Figure 2.** Example of a multipyridyl ligand used in the synthesis of a discrete coordination capsule. The pictures are taken from reference 1.

## 2.2 Microwave Assisted Organic Synthesis

Microwave assisted organic synthesis (MAOS) provides a means for improving yield while simultaneously reducing reaction times for many organic synthetic processes. The ability to reach higher temperatures and pressures than conventional heating opens the window to many possibilities including organic reactions in aqueous solutions. The benefits of MAOS range from reducing reaction times to creating environmentally benign

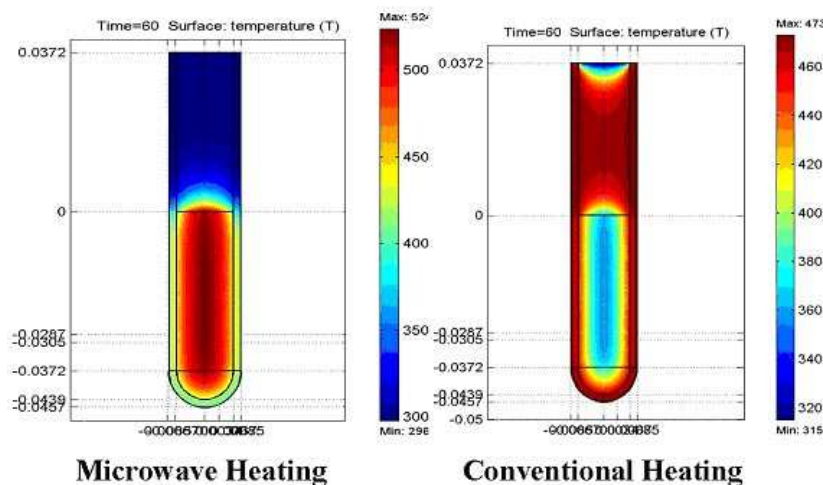
processes. In this work, we are specifically interested in the reduction of reaction times with the Heck coupling reaction. Typical reaction criteria for Heck couplings require heating in a mantle, oil bath, or sand bath at 110 °C for a time of 24-72 hours. It has been shown that the same Heck coupling reactions carried out in the presence of microwave radiation can be completed within one hour and at elevated temperatures.<sup>2</sup>



**Figure 3.** Heck coupling of ethylene with 2-bromo-6-methoxynaphthalene involved in the synthesis of Naproxen, a nonsteroidal anti-inflammatory drug.

Microwave irradiation produces an oscillating electric field of various frequencies. Molecular dipoles are susceptible to this oscillating electric field and attempt to align with it; this aligning largely depends on the microwave frequency. If the frequency is too high, the molecules can never align, but if the frequency is too low they can align perfectly with the oscillations and hence show no change in dielectric loss. In the ideal case, the frequency is just right (e.g., 2.45 GHz frequency used in microwave ovens) for the molecules to follow closely the path of oscillation, but do not quite align.<sup>2</sup> The last option is favorable for microwave heating because it induces random collisions and dipole polarization. All of these effects together provide a suitable atmosphere for

localized superheating to occur. Because of these internal hotspots, there are many benefits compared to the use of conventional heating methods, such as a hot plate or an oil bath. Classical heating relies on convection, which is directly related to the thermal conductivity of every material between the initial heat source and the solution being heated. A typical heat path for a reaction might require conduction through the surface of a hot plate, through a glass wall, through an oil bath, through a second glass wall, and eventually into the solution. One of the problems with this path is that glass has a very low thermal conductivity ( $k \cong 1 \text{ W/mK}$  at  $20 \text{ }^\circ\text{C}$ ) (for comparison, copper metal has a  $k \cong 400 \text{ W/mK}$  at  $20 \text{ }^\circ\text{C}$ ). Not only does the poor conductivity of the glass lengthen the time taken to transfer heat from source to solution, it also hampers the attainment of thermal equilibrium between the source and reaction media. Conversely, because of the internal hotspots that are formed through microwave irradiation, the solution heating occurs inside out, which results in a more volumetric and even distribution of temperature and to a higher overall heating.

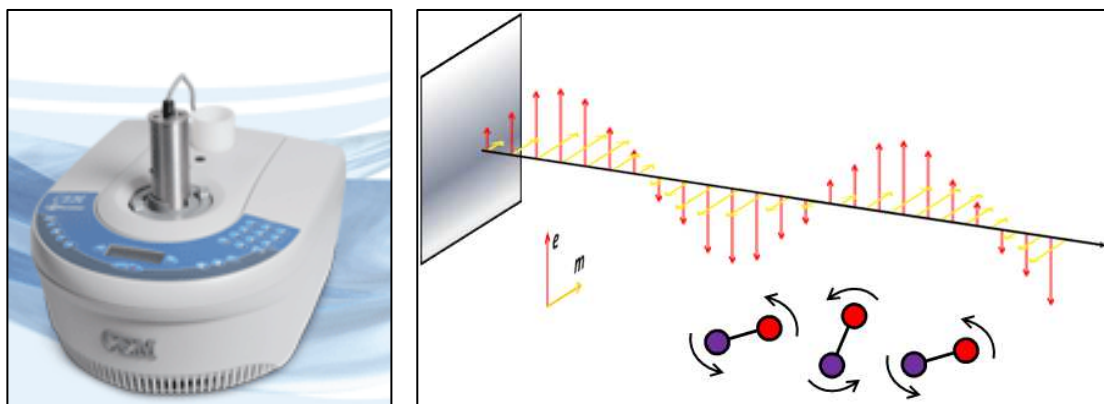


**Figure 5.** Comparison of heating profiles simulated under microwave irradiation and conventional heating. Notice the global, inside-out heating in the microwave field and gradual, outside-in heating in convection methods.<sup>2</sup>

**Table 1.** Loss tangent ( $\tan \delta$ ) values of some solvents at 2.45 GHz and 20 °C).<sup>2</sup>

Solvent	$\tan \delta$	Solvent	$\tan \delta$
Ethylene glycol	1.350	DMF	0.161
Ethanol	0.941	Water	0.123
DMSO	0.825	Chloroform	0.091
Methanol	0.659	Acetonitrile	0.062
Nitrobenzene	0.589	Acetone	0.054
2-butanol	0.447	Toluene	0.040
Acetic acid	0.174	Hexane	0.020

For this volumetric heating to be possible, microwave susceptible molecules need to be present in the reaction medium to be affected by the applied radiation. Polar solvents, such as ethanol or water, are susceptible to microwave radiation and hence solutions made from these solvents are rapidly heated in microwave ovens. It has also been shown that the addition of metals to the solution can lead to rapid overall heating. Molecular susceptibility to microwave irradiation is dependent on the dielectric properties of the compound, the loss tangent,  $\tan \delta$ . The loss tangent is a measure of the ability of a molecule to convert electromagnetic energy into heat at a given frequency and temperature; it is related to the dielectric loss,  $\epsilon''$ , and a dielectric constant,  $\epsilon'$ , which pertains to the polarizability of a molecule in an electric field. These are related by the quotient  $\tan \delta = \epsilon''/\epsilon'$ .<sup>2</sup>

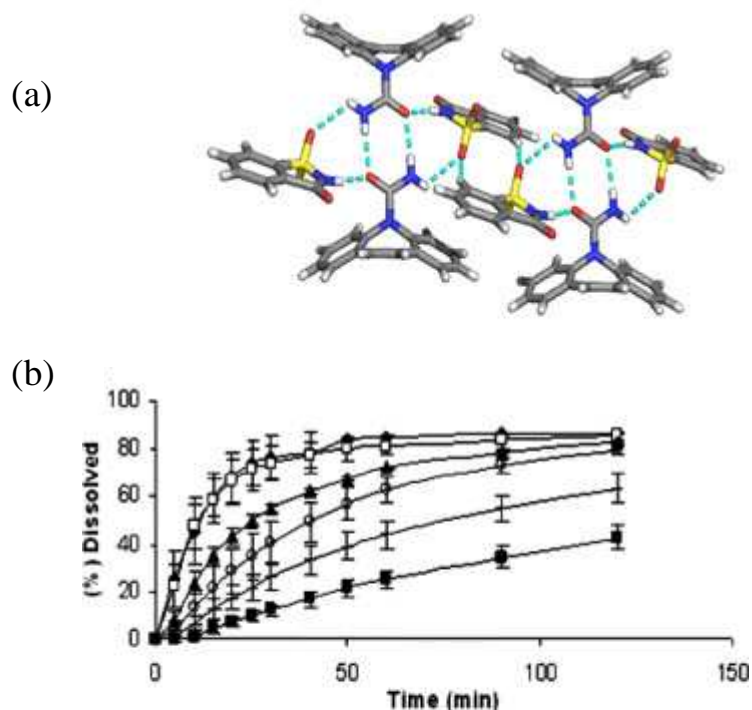


**Figure 4.** CEM Discover Labmate (left) is used in the MAOS reported in this work. The diagram on the right shows the schematic description of dipole polarization in liquid media.

### 2.3 Cocrystallization

Cocrystallization is the process of crystallizing two or more different organic compounds in stoichiometric ratio into one crystal lattice. Cocrystals have the advantage that they have components that are present in a stoichiometric ratio and organized into a definite supramolecular structure. The formation of cocrystals typically depends on the ability of the components to accommodate each other through strong, directional noncovalent interactions, such as hydrogen bonding between hydroxyl groups and nitrogen atoms. Intermolecular interactions govern crystal packing and influence mutual orientation of molecules; understanding and controlling crystal packing is therefore critical to synthetic solid state photochemistry. Crystal packing can be directly controlled by preparing cocrystals in which different components are designed to be at appropriate separations and orientations for achieving targeted solid state photoreactions.

Another benefit of using cocrystals is their direct effect on material properties. Cocrystals have been re-emerging as new forms of drug materials with designed structures and improved properties (e.g. solubility). In pharmaceutical solid drugs, solubility plays one of the most important roles in drug delivery; many drugs on the market exhibit low aqueous solubility and must be administered in higher doses to achieve a physiological response. Higher doses equal higher costs, greater pollution, and unnecessary waste of compounds; therefore, it is beneficial to alter the material properties of the drug to improve solubility. In drugs such as carbamazepine, it has been shown that the addition of saccharin as a cocrystal effectively increases the aqueous solubility of the parent drug (Figure 6).



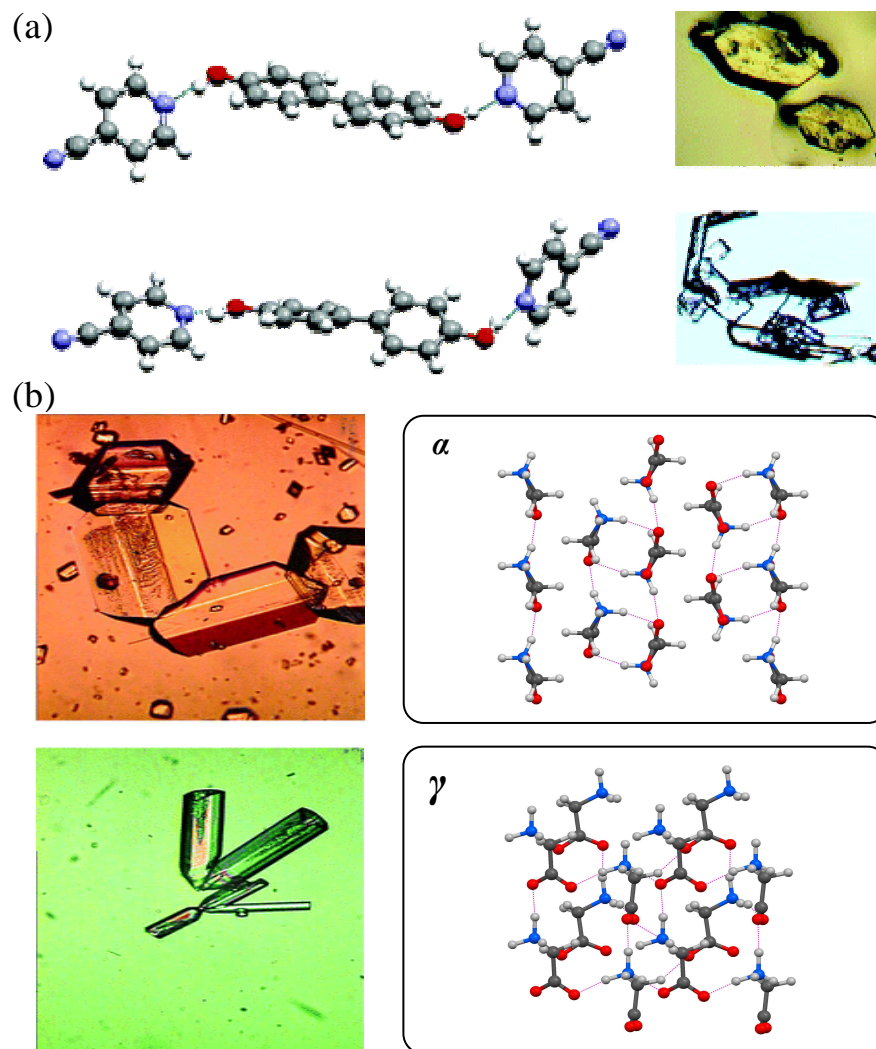
**Figure 6.** Some recent examples of cocrystals formed from active pharmaceutical ingredients. (a) carbamazepine:saccharin; (b) Mean dissolution profiles ( $n = 3$ , ~355 mg of co-crystal corresponding to 200 mg of pure drug used for all sieved fractions) of various sizes of carbamazepine:saccharin in SGF at 37 °C.<sup>3</sup>

## 2.4 Noncovalent Interactions

Noncovalent bonding refers to a class of intermolecular interactions that rely on electrostatic and polarization induced interactions between atoms instead of the direct sharing of electron pairs. These can be divided into five types of interactions: ionic bonds, hydrophobic interactions, hydrogen bonds, van der Waals forces, and dipole-dipole bonds. In this work we are interested primarily in hydrogen bonding. Hydrogen bonds are typically denoted as  $X-H\cdots Y$ ; they can further be classified into strong ( $O-H\cdots O$ ,  $N-H\cdots O$ ), moderate ( $N-H\cdots N$ ), and weak hydrogen bonds ( $C-H\cdots O$ ,  $C-H\cdots N$ ,  $C-H\cdots \pi$ ). This work involves the synthesis and structural analysis of multipyridyl ligands; it therefore allows us to gain better structural insight into the role of  $C-H\cdots N$  hydrogen bonds that are investigated to a lesser extent than  $C-H\cdots O$  hydrogen bonds.

## 2.5 Polymorphism

Polymorphism is the ability of a compound to exist in more than one crystal structure. There are two major types of polymorphism: packing and conformational. Packing polymorphism refers to molecules that pack in different mutual arrangements depending on the conditions in which the crystals are formed. Conformational polymorphism refers to molecules that exist in different conformers in various crystals. Polymorphs exhibit different material properties such as solubility, density, and melting point. For this reason, polymorphs are important in many situations where material properties restrict chemical functionality. Pharmaceutical companies spend much time and effort in the discovery of polymorphism because different polymorphs of a drug can be patented separately.

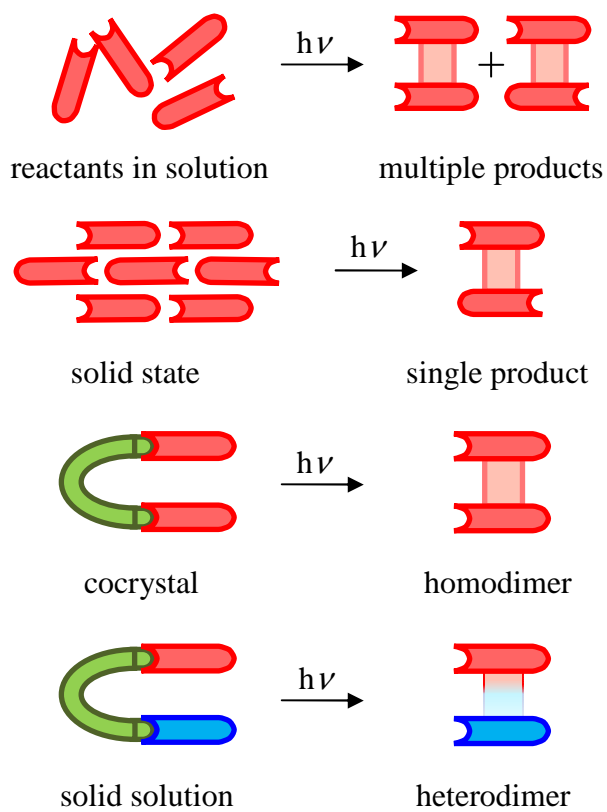


**Figure 7.** (a) The cocrystal of 4-cyanopyridine and 4,4'-biphenol exhibits conformational polymorphism.<sup>4</sup> (b) The  $\alpha$  and  $\gamma$  forms of glycine exhibit packing polymorphism.

## 2.6 Template Driven Solid State Synthesis

Template driven solid state organic synthesis is a concept in which linear templates are used to align  $\pi$ -systems of multiple molecules for solid state photoreactions. These small molecular templates assemble (through hydrogen bonding or other noncovalent interactions) chromophores at distances suitable to induce photo-transformations.

Reactions in the solid state allow targets to be synthesized that often may not be approachable through solution mediated synthesis. In addition, solid state synthesis is considered “green” as it does not utilize any harmful solvents.



**Figure 8.** Photodimerization in the liquid and solid states, and in templated solids. Random orientations of molecules in the liquid lead to multiple products; fewer products form in single component solids *if* the  $\pi$ -systems are in proximity. Greater control over product stereochemistry can be achieved by selecting appropriate templates as shown at the bottom.

## 2.7 Solid Solutions

A solid solution consists of molecular components in a non-stoichiometric ratio. The components in a solid solution are randomly distributed even though they adopt a definite

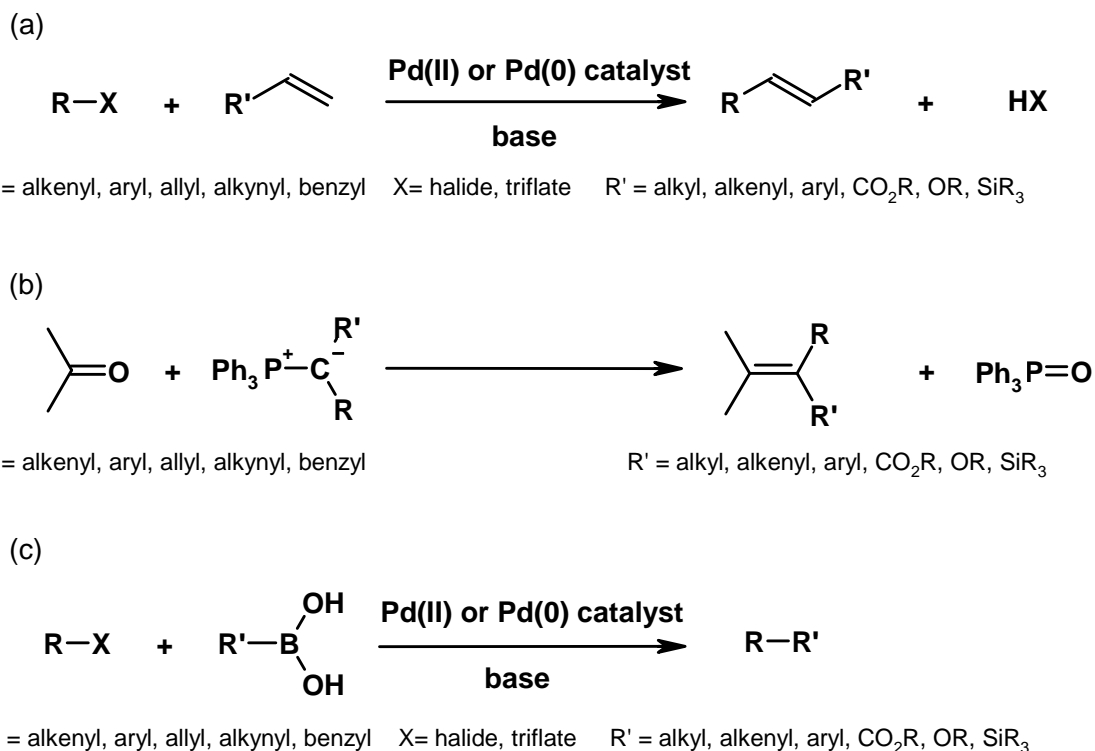
overall structure. In general, solid solutions are formed by components having similar shapes and sizes; therefore, it is difficult to create solid solutions of any arbitrary compound. Solid solutions are often compared to the more common material that metal ions form via the same process, alloys. These “organic alloys”, as they are sometimes called, provide a platform for control of material properties without altering the chemical properties through gradual modification of component ratio.

## **2.8 Metal Organic Frameworks**

MOFs are materials made from the coordination of metal ions or clusters to organic molecules to form one-, two-, and three-dimensional networks. Often, these MOFs are porous and used in applications such as gas separation, purification, and storage, catalysis and sensors. Chiral MOFs have the additional advantage of providing molecular level dissymmetric cages in which entantio- and diastereoselective separations and catalytic transformations can occur.

## **2.9 Previous Work**

The addition of carbon-carbon bonds to a molecule in minimal step reactions can be achieved by established reactions such as Heck coupling, Wittig reaction, and Suzuki coupling.



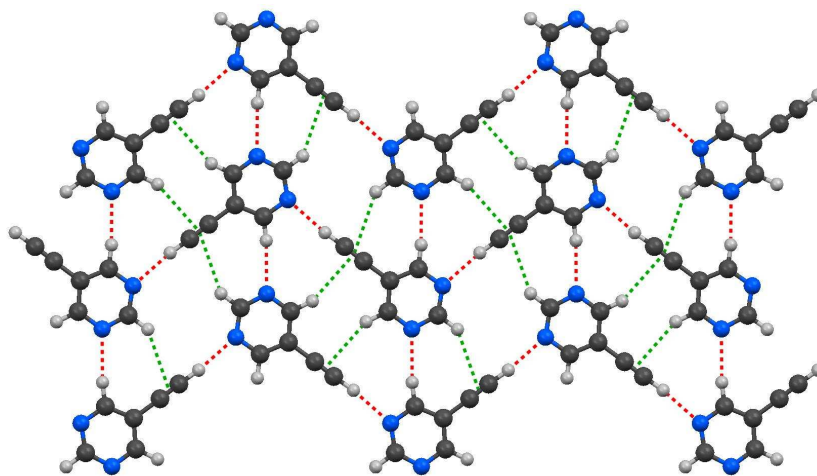
**Figure 9.** General transformation for (a) Heck reaction, (b) Wittig reaction, and (c) Suzuki reaction.

The general transformation of the Heck coupling reaction (Figure 9a) shows that double bond retention is possible in an easy one step process. Another benefit of this reaction is that it is stereoselective to produce *trans* double bonds. This reaction has been an attractive approach to the synthesis of multipyridyl ligands due to its stereoselectivity and better yields than related reactions (i.e. Wittig).<sup>5</sup> The disadvantages of this reaction are that it requires expensive palladium catalysts, high temperatures, and prolonged reaction times. Many of these problems can be solved through the use of microwave irradiation as a heating source for the reaction.

The Heck coupling reaction has been extensively explored in MAOS. In the early 90s, knowledge was spreading of microwaves benefits in assisting organic reactions. Many

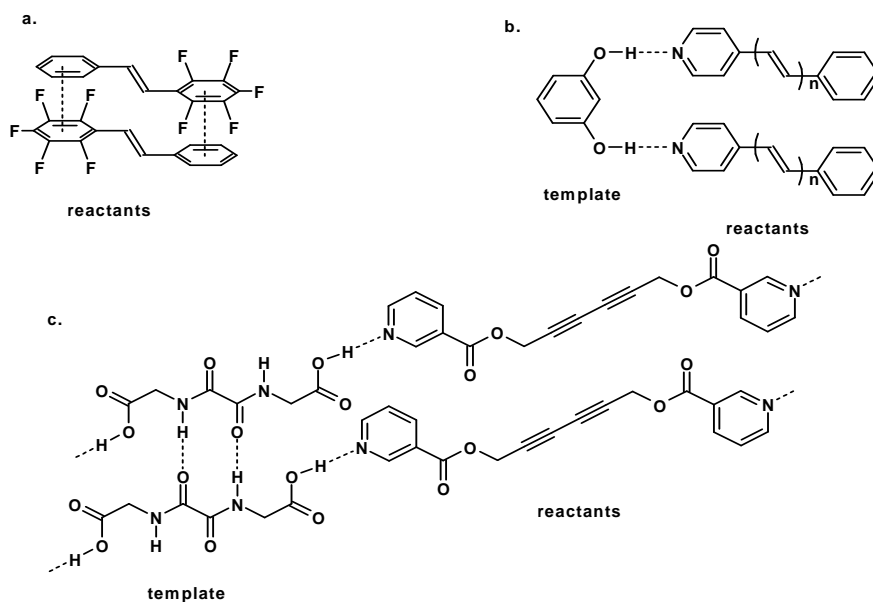
became interested in pursuing Heck reactions in microwaves due to the decreased reaction times that were potentially attainable. The exploration of Heck couplings in microwaves led to many optimized MAOS processes; these new methods reduced reaction times from many hours or days down to as short as four minutes.<sup>2</sup>

Of all of the weak hydrogen bond varieties, C–H···N interactions are studied the least. Previously, a number of compounds that contain both C–H donors and N acceptors were investigated experimentally to determine their role in crystal structure.<sup>6</sup> Of these structures, it has been determined that the C–H···N bonds determine structure over the other interactions present (e.g. C–H··· $\pi$ ) and that the strength of the interaction is directly related to that of the C–H acidity. Our work continues to show that the C–H···N interactions are the dominating force in controlling the solid state structures of the ligands reported in this work.



**Figure 10.** Crystal structure of ethynylpyrimidine showing important C–H···N interactions.<sup>7</sup>

Another way that has been used to control crystal packing is the use of templates to orient molecules through hydrogen bonds (e.g. O–H···N),  $\pi$ – $\pi$ , acid-base, and other interactions. Typically the intention of these templates is to allow chromophores to come into close-proximity to undergo photochemical reactions. Templating can be achieved in three different ways, self-templating, molecular templating, and supramolecular templating (Figure 11). Self-templating is evident in pentafluoro[2-phenyl(ethenyl)]benzene where the  $\pi$ – $\pi$  interactions of the Ph and F<sub>5</sub>-Ph rings bring the double bond into photoreactive proximity.<sup>8</sup> Molecular templating is the concept that one template molecule contains the necessary code required to bring reactive compounds to appropriate distance and orientation. Supramolecular templating is a larger form of molecular templating in that multiple molecules must assemble to form the necessary code required to bring reactive centers into photoreactive proximity.



**Figure 11.** Some examples of known templates and interactions: (a) Self-templating phenyl-perfluorophenyl  $\pi$ -stacking interactions. (b) Molecular template resorcinol and pyridyl-ended olefins ( $n= 1, 2, 3\dots$ ). (c) Supramolecular templating of oxalamide derivative of glycine with a bis-pyridyl substituted diacetylene.<sup>9</sup>

### 3. Experimental

This section describes the methods and materials used in the research of this project. NMR spectra were obtained using a Brücker 400 MHz spectrometer. <sup>1</sup>H-NMR spectra were reported in ppm relative to proton chemical shift of TMS. IR spectra were obtained using a Brücker Vertex 70 spectrometer.

#### 3.1 Materials

All solvents were obtained from Pharmco and used without further purification, with the exception of triethylamine, which was dried over molecular sieves before use. 1,3,5-Tribromobenzene, 2,5-dibromotoluene, 1-chloro-2,5-dibromobenzene, palladium acetate, tri-*o*-tolylphosphine (TOTP), and 4-vinylpyridine were all obtained from Alfa Aesar and TCI Chemicals, and used without further purification.

#### 3.2 Conventional Synthesis of Ligands

1-methyl-2,5-bis[4-pyridyl(ethenyl)]benzene **1**, 1-chloro-2,5-bis[4-pyridyl(ethenyl)]benzene **2**, 1,3,5-tris[4-pyridyl(ethenyl)]benzene **3**, and 1-bromo-3,5-bis[4-pyridyl(ethenyl)]benzene **4** were all prepared by following the same procedure.

In a pressure vessel, palladium acetate (10.2 mg), 4-vinylpyridine (0.96 mL), tri-*o*-tolylphosphine (27.2 mg), 2,5-dibromotoluene (0.61 mL), and dry triethylamine (2.2 mL)

were added and purged with nitrogen before sealing. The vessel was heated in an oil-bath to 110 °C for 72 hours. The resulting brown-yellow solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL), dried over MgSO<sub>4</sub>, the resulting clear yellow liquid was evaporated to dryness. The yellow powder was sonicated for 20 min in ether and compound **1** (0.85 g) was concentrated *in vacuo* as a mixture with triethylammonium bromide.

In a pressure vessel, palladium acetate (10.3 mg), 4-vinylpyridine (0.96 mL), tri-*o*-tolylphosphine (27.4 mg), 1-chloro-2,5-dibromobenzene (1.203 g), and dry triethylamine (2.22 mL) were added and purged with nitrogen before sealing. The vessel was heated in an oil-bath to 110 °C for 72 hours. The resulting brown-yellow solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL), dried over MgSO<sub>4</sub>, the resulting clear yellow liquid was evaporated to a brown oil. The brown oil was sonicated for 20 min in ether and a yellow powder compound **2** (0.93 g) was concentrated *in vacuo* as a mixture with triethylammonium bromide.

In a pressure vessel, palladium acetate (10.2 mg), 4-vinylpyridine (2.80 mL), tri-*o*-tolylphosphine (20.7 mg), 1,3,5-tribromobenzene (2.25 g), and dry triethylamine (3.57 mL) were added and purged with nitrogen before sealing. The vessel was heated in an oil-bath to 110 °C for 72 hours. The resulting brown-red solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL), dried over MgSO<sub>4</sub>, the resulting clear brown liquid was evaporated to dryness. The brown powder

was sonicated for 20 min in ether and compounds **3** and **4** (1.83 g) were concentrated *in vacuo* as a mixture with triethylammonium bromide.

### 3.3 Microwave Synthesis of Ligands

1-methyl-2,5-bis[4-pyridyl(ethenyl)]benzene **1**, 1-chloro-2,5-bis[4-pyridyl(ethenyl)]benzene **2**, 1,3,5-tris[4-pyridyl(ethenyl)]benzene **3**, and 1-bromo-3,5-bis[4-pyridyl(ethenyl)]benzene **4** were all prepared by the same methods in a CEM Discover Labmate microwave.

In a pressure sealable microwave vial, palladium acetate (10.2 mg), 4-vinylpyridine (0.96 mL), tri-*o*-tolylphosphine (27.2 mg), 2,5-dibromotoluene (0.61 mL), and dry triethylamine (2.2 mL) were added and the vial was sealed. The vessel was heated in the microwave to 175 °C at 90 psi for 60 minutes. The resulting brown-yellow solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL), dried over MgSO<sub>4</sub>, the resulting clear yellow liquid was evaporated to dryness. The yellow powder was sonicated for 20 min in ether and compound **1** (1.2 g) was concentrated *in vacuo* as a mixture of product with triethylammonium bromide.

In a pressure sealable microwave vial, palladium acetate (10.3 mg), 4-vinylpyridine (0.96 mL), tri-*o*-tolylphosphine (27.4 mg), 1-chloro-2,5-dibromobenzene (1.203 g), and dry triethylamine (2.22 mL) were added and the vial was sealed. The vessel was heated in the microwave to 175 °C at 90 psi for 60 minutes. The resulting brown-yellow solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL),

dried over MgSO<sub>4</sub>, the resulting clear yellow liquid was evaporated to a brown oil. The brown oil was sonicated for 20 min in ether and a yellow powder compound **2** (1.14 g) was concentrated *in vacuo* in as a mixture of product and triethylammonium bromide.

In a pressure sealable microwave vial, palladium acetate (10.2 mg), 4-vinylpyridine (2.80 mL), tri-*o*-tolylphosphine (20.7 mg), 1,3,5-tribromobenzene (2.25 g), and dry triethylamine (3.57 mL) were added and the vial was sealed. The vessel was heated in the microwave to 175 °C at 90 psi for 60 minutes. The resulting brown-red solid was dissolved in dichloromethane (200 mL) washed and extracted with water (3×300 mL), dried over MgSO<sub>4</sub>, the resulting clear brown liquid was evaporated to dryness. The brown powder was sonicated for 20 min in ether and **3** and **4** (2.1 g) were concentrated *in vacuo* as a mixture of products with triethylammonium bromide.

### 3.4 Crystallization

Compounds **2** and **3** were dissolved in hot solvent (acetone, dichloromethane, or nitromethane) and quickly filtered through a cotton plug to remove triethylammonium bromide. The solutions were added to 20 mL vials and allowed to slowly evaporate until crystals were formed. Compounds **2** and **4** were isolated as crystals through mechanical separation. The competition in the mixture of **3** and **4** allowed only **4** to crystallize.

Compound **1** was dissolved in hot solvent (acetone, dichloromethane, or nitromethane) and quickly filtered through a cotton plug to remove triethylammonium bromide. The

solution was added to a 20 mL vial and allowed to slowly evaporate. No crystals of **1** were obtained to date.

### **3.5 X-Ray Crystallography**

Single crystal X-ray data were collected on a Brücker Kappa APEX II diffractometer using MoK $_{\alpha}$  ( $\lambda = .71073 \text{ \AA}$ ) radiation. The crystal structures of **2** and **4** were studied at 100K and 298K. A single crystal of each compound was mounted on goniometer heads using kapton loops, centered in the X-ray beam, and subjected to data collection in  $\omega$  and  $\phi$  scan methods. Cell constants were calculated using reflections obtained from a preliminary data collection. The data were integrated using SAINT and corrected for absorption using empirical methods by the program SADABS. Structure solution was accomplished with the aid of SHELXS and refinement was conducted using SHELXL programs incorporated in the SHEXLTL suite. After anisotropic refinement of non-hydrogen atoms, hydrogen atoms bonded to sp<sup>2</sup> hybridized carbon atoms were placed in idealized positions and allowed to ride on the atom to which they are attached. A summary of the data collection parameters is given in Table 2.

**Table 2.** Crystal Data and Structure Refinement for **2** and **4**

Compound	<b>2</b>	<b>2'</b>	<b>4</b>	<b>4'</b>
Formula	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> Cl	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> Cl	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> Br	C <sub>20</sub> H <sub>15</sub> N <sub>2</sub> Br
Formula weight	318.82	318.82	363.27	363.27
T, K	100	100	298	100
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic
Space group	<i>P</i> 2 <sub>1</sub> / <i>n</i>	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>C</i> 2/ <i>c</i>	<i>P</i> 2 <sub>1</sub> / <i>n</i>
<i>a</i> , Å	19.3758	8.0538	11.2103	10.8262
<i>b</i> , Å	4.7747	22.4291	13.741	13.6308
<i>c</i> , Å	35.5309	8.7333	11.8292	11.691
$\beta$ , deg.	100.471	96.001	116.138	114.385
Z	8	4	4	4
<i>V</i> , Å <sup>3</sup>	3232.35	1568.93	1635.83	1571.33
Crystal dimensions, mm	.04×.18×.36	.08×.27×.60	.06×.10×.30	.07×.09×.11
Density, g/cm <sup>3</sup>	1.456	1.35	1.471	1.566
Observed reflections	2468	3253	1099	2974
Independent reflections	3382	3894	1673	3912
<i>R</i> <sub>int</sub>	0.030	0.027	0.027	0.050
<i>R</i> <sub>1</sub>	0.072	0.057	0.078	0.087
w <i>R</i> <sub>2</sub>	0.234	0.237	0.214	0.235

## 4. Results and Discussion

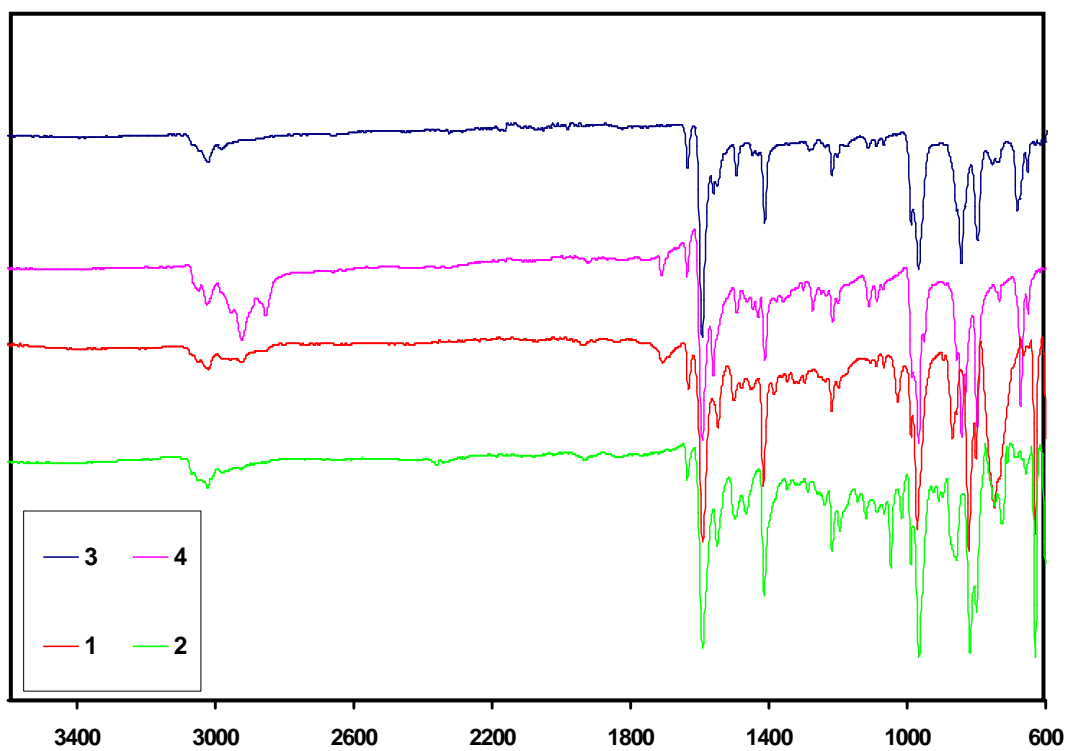
### 4.1 Synthesis and Characterization

The optimization of the conditions for MAOS of compounds **1–4** was not achieved due to time constraints. This however was beneficial, in the synthesis of **3**, partial reaction of the 1,3,5-tribromobenzene resulted in the collecting of compound **4**. The identity and purity of compounds **1**, **2**, and **4** have been established by <sup>1</sup>H NMR spectra, IR spectra, single

crystal x-ray diffraction, and DSC. All products were attainable through both conventional heating and microwave heating techniques. After one reaction via oil bath of each compound, only MAOS were used.

#### 4.1.1 Infrared Spectra

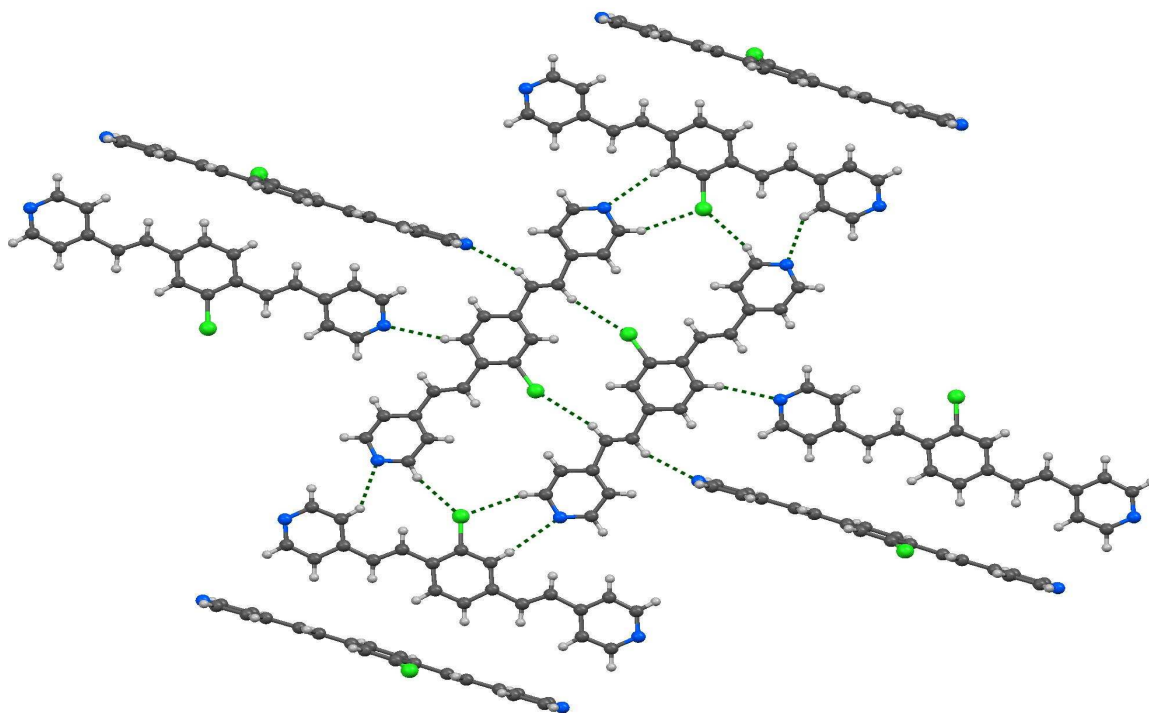
Due to the extreme similarity of compounds **1–4**, differences in IR spectra are very minimal. The IR spectra exhibit subtle differences in the fingerprint region relating to the substitution of the central benzene ring.



**Figure 12.** IR spectra of compounds **1-4**. Note the similarities in all regions.

### 4.1.2 X-Ray Crystallography

Despite numerous experiments, our attempts to grow the crystals of **1** and **3** suitable for X-ray diffraction analysis were unsuccessful. Large and good quality crystals of compounds **2** and **4** have been grown from slow evaporation of acetone (**2'**, **4**, and **4'**), dichloromethane (**2**), and nitromethane (**4** and **4'**).

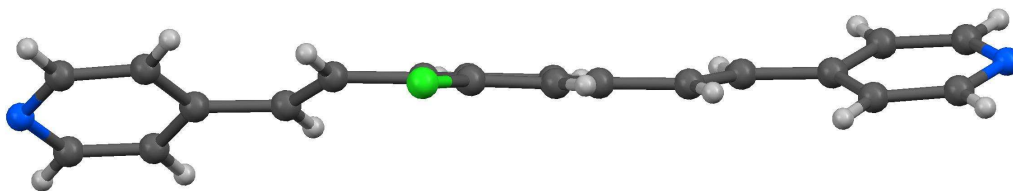


**Figure 13.** Crystal structure of compound **2** belonging to the space group  $P2_1/n$ . The pair of symmetry related molecules in the center (chloro-to-chloro facing) are surrounded by 4 pairs of symmetry related molecules (back-to-back facing).

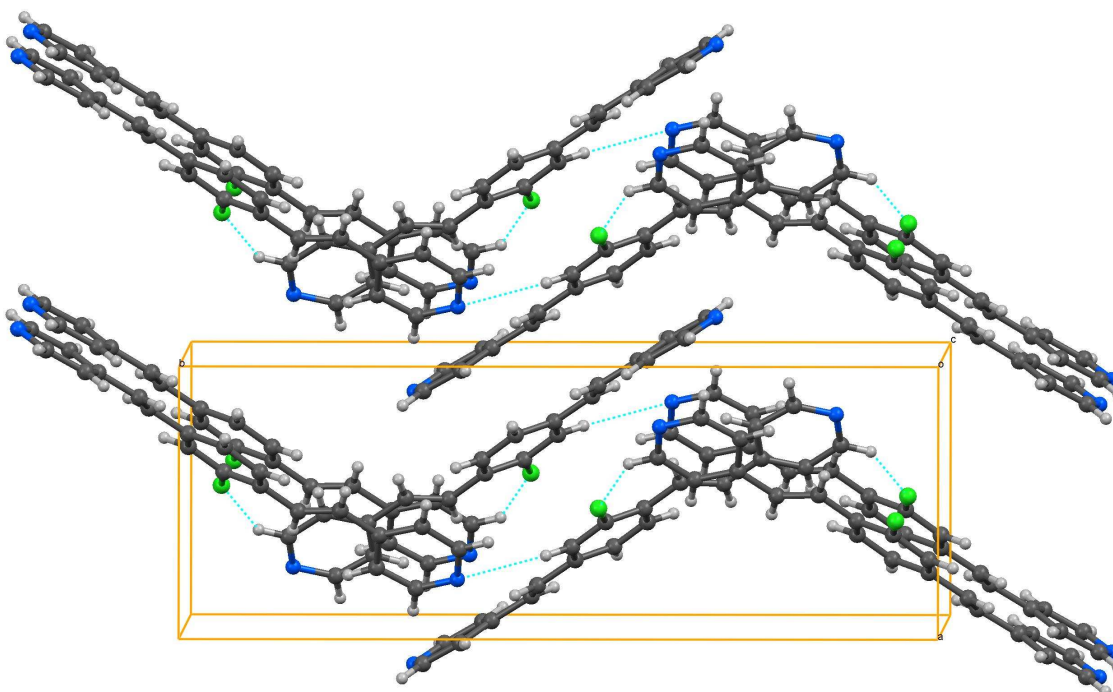
X-ray analysis of a needle shaped crystal of **2** (obtained from dichloromethane) reveals that it belongs to the monoclinic space group  $P2_1/n$  with two symmetry independent molecules in the unit cell. In one of the molecules, the pyridyl rings, ethenyl groups, and benzene ring are all co-planar. In the other molecule, the pyridyl rings are twisted out of

plane. In the crystal structure of **2** (Figure 13) molecules that are *not* related by symmetry are connected to each other by short intermolecular C–H···N interactions. Molecules that *are* related by symmetry, however, are primarily associated with each other by  $\pi$ - $\pi$  stacking or herringbone interactions. Reasonably short C–H···Cl interactions can be seen between symmetry related and symmetry independent molecules.

(a)



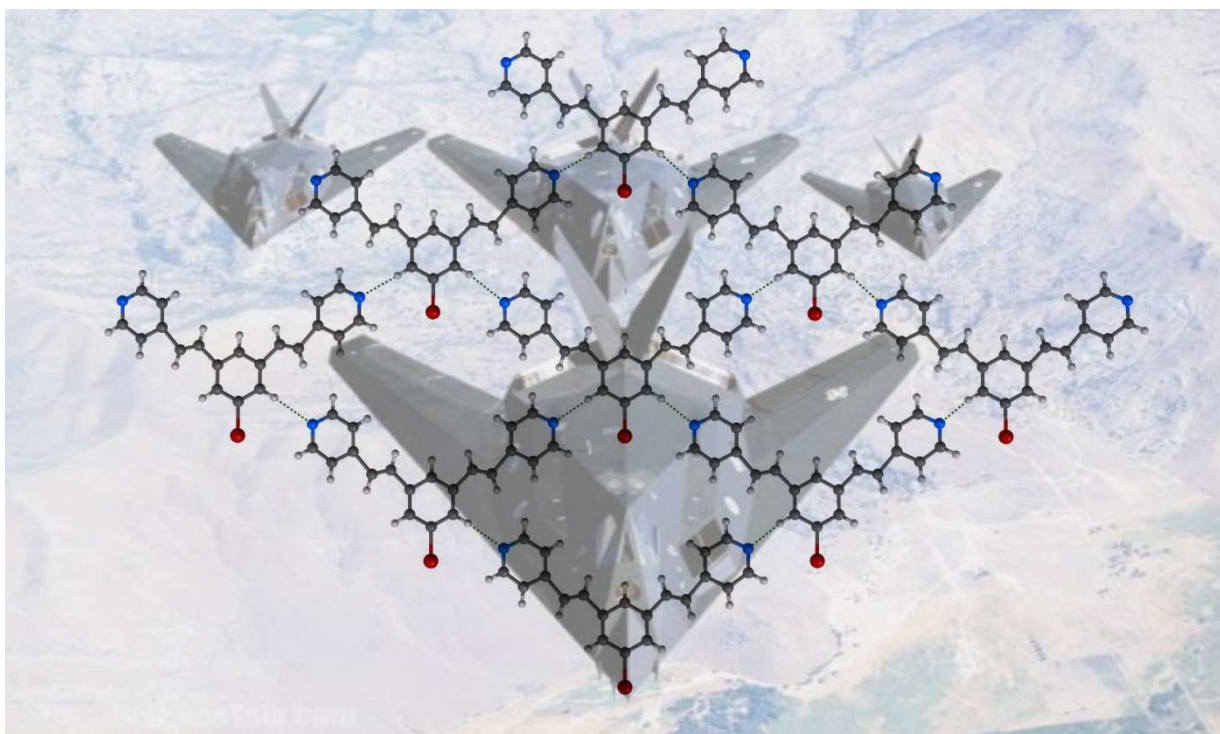
(b)



**Figure 14.** The structure of compound **2'** belonging to the space group  $P2_1/c$ . (a) Note that the pyridyl rings are twisted to a greater extent when compared to those shown in Figure 13. (b) Overall crystal packing of **2'** showing the zig-zag pattern containing alternating dovetailed molecules.

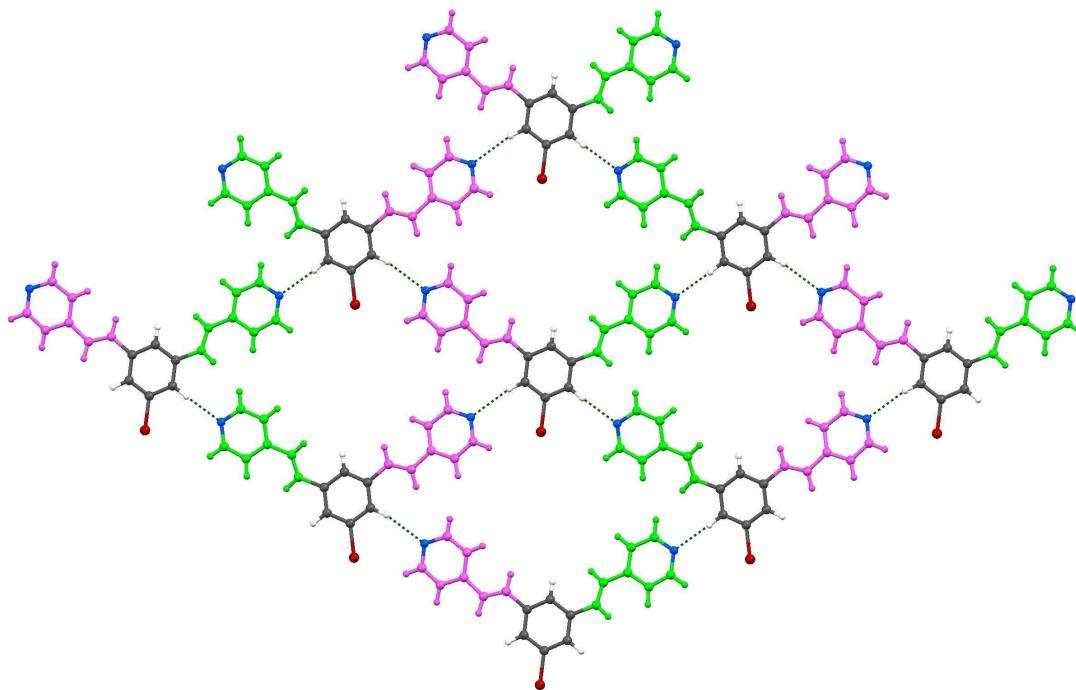
In a separate crystallization experiment, crystals of compound **2** grew as parallelepipeds from acetone. Noting the differences in morphology from the previous experiment, we have analyzed the structure of these crystals. Surprisingly, these crystals labeled **2'** belong to the monoclinic space group  $P2_1/c$ . Unlike in **2**, there is only one molecule in the asymmetric unit (Figure 14a), and this molecule shows severe torsions between peripheral and central rings (22.4 and 34.0 °). The overall structure of **2'** may be viewed as close- packing long, flat, and flexible strips (Figure 14b). At one end of the strip, the aromatic rings are dovetailed into each other, while at the other end they are juxtaposed making edge-to-edge contacts. This arrangement leads to a two-dimensional zig-zag layer parallel to  $bc$ -plane; further association of these layers along the  $a$ -axis results in a three-dimensionally close-packed structure.

It is unclear why compound **2** crystallizes as two separate polymorphic structures. It is wellknown that awkward shaped molecules with high aspect ratio are often difficult to crystallize. It seems possible that compound **2** tries to overcome these problems in one polymorph by having two symmetry independent molecules and in the other by a severely twisted conformation.



**Figure 15.** Compound **4** belonging to the  $C2/c$  space group produces planar 2D sheets with all the nitrogen atoms participating in C–H···N interactions, much like a flight pattern of F-117 bombers.

X-ray analysis of compound **4** (obtained from nitromethane) reveals that it belongs to the monoclinic space group  $C2/c$  at room temperature. The molecules are bisected by a two-fold axis rendering the two pendant pyridyl groups symmetrically equivalent. The pyridyl and central rings are all essentially coplanar and pack two-dimensionally to form sheets of unidirectional arrowheads. Within these sheets, each nitrogen atom participates in C–H···N interactions with hydrogen atoms *ortho* to the bromo group of a neighboring molecule (Figure 15). The inter-sheet stacking is predominantly governed by  $\pi$ – $\pi$  and C–H···Br interactions.



**Figure 16.** Crystal structure of compound **4'** belonging to the space group  $P2_1/n$ . Compare with Figure 15 to notice the overall similarity in the packing pattern. Contrast with Figure 15 to notice the differences between the two pyridyl rings (colored violet and green) and the contortion of the central benzene ring.

Having analyzed compound **4** at room temperature, we decided to cool the same crystal down to 100K and perform X-ray analysis. This cooling revealed that compound **4** adopted the monoclinic space group  $P2_1/n$  at lower temperature; this new structure is labeled as **4'**. The change in structure is a result of one of the ethenyl groups flipping in what appears to be a cascading motion along the  $a$ -axis (Figure 16). The structural analysis of **4** and **4'** revealed the disorder around the double bonds in both cases; however, in the low temperature there is also disorder around the bromo group due to a distortion of the central benzene ring. Consideration of these observations led us to believe that the disorder in the ethenyl groups is dynamic and thus **4** and **4'** can be considered as conformational polymorphs.

### **4.1.3 Cocrystallization of Ligands with Resorcinol Templates**

Attempted cocrystallizations of compound **3** with resorcinol, 4,6-dichlororesorcinol, 4-chlororesorcinol, orcinol, and methyl dihydroxybenzoate all proved to be unsuccessful at this point in time. We suspect that the difficulties in the crystallization of pure compound **3** by itself (possibly due to a salt impurity) are directly related to our failed cocrystallization attempts. Due to the time constraints of this project we have not been able to attempt cocrystallization with any of the other ligands.

## **5. Conclusions**

This work resulted in the synthesis and characterization of multiple poly-aza-ligands. The microwave assisted synthesis of these compounds enabled days of saved time and saved resources. The conditions for the generic Heck reaction involving vinylpyridines and halogenated benzenes could not be fully optimized due to restricted access to a synthetic microwave oven. We prepared three new structures through our synthesis; two of those structures exhibit both conformational and packing polymorphism. We intend to pursue cocrystallization of these asymmetric ligands with resorcinol templates, and to photodimerize the ethenyl groups of the ligands to create a new polydentate chiral ligands, and prepare chiral MOFs from these ligands through coordination and hydrogen bonding schemes. We plan to extend our synthetic accomplishments to other larger brominated compounds such as dibromoporphyrin and subsequently create MOFs of extreme three-dimensional character and porosity.

## 6. References

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