

Synthesis of Ligands for Potential Application in Selective Heteroleptic Cage Assembly Projects

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Degree Project in Organometallic Chemistry, 2024
Department of Chemistry
Lund University
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MSc, 30 hp



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Popular Science Summary

One of the major advances in organometallic chemistry is the construction of cages made of metal nucleus linked to each other throughout organic molecules. These structures receive the name of metal-organic cages, or MOCs, and show promising applications in fields like drug delivery, chemical catalysis and gas storage. Nowadays, researchers are trying to create cages with more than one type of organic molecules to increase the number of functionalities that one MOC can do at the same time. These are called heteroleptic MOCs, and they are not as easy to prepare as combining metals and organic molecules, doing so would result in unpredictable mixtures of different components and shapes. Instead, an incredible amount of work and scientists are required to strategize the synthesis of a single heteroleptic MOC. This work aims to prepare a set of four organic molecules, meanwhile registering their unique structural features, that could be used in a more simple and convenient way to build an heteroleptic MOC. Unfortunately, just one of these was successfully prepared due to matters of time and failed experimental attempts.

Abstract

Recent research in organo-metallic cages composites (MOCs); discrete, self-assembled coordination compounds; has highlighted their significant potential in host-guest chemistry and catalysis. New studies focus on synthesizing multifunctional MOCs by combining more than one ligand. However, due to the unpredictable nature of coordination-driven self-assembly, intricate strategies were imperative to obtain a single cage rather than statistical mixtures of homoleptic and heteroleptic MOCs. These well-designed strategies demand the expertise from multiple scientific areas, making them unfeasible for small research groups. The objective of this work was to synthesize and fully characterize ligands with potential to be used in an organic chemistry inspired protecting group approach to construct a heteroleptic MOC by employing blocker ligands. A library of four bidentate, linear and nitrogen donor ligands (G1, G2, G3 and G4) was developed for that purpose. All the intermediates and G2 were successfully synthesized and identified via NMR spectroscopy; nevertheless, HRMS, HPLC, EA and IR spectra remains to be recorded on those compounds. On the other hand, G2 and G4 were not attempted due to time restrictions, and G3 could not be isolated from the crude while performing the quenching procedure. The low yields obtained in those synthetical procedures pointed out the necessity of further optimization, particularly in reaction conditions, purification techniques and quenching procedures.

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1 List of abbreviations

CNMR	Carbon Nuclear Magnetic Ressonance
DCM	Dichloromethane
DCVC	Dry Column Vacuum Chromatography
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
EA	Elemental Analysis
HNMR	Proton Nuclear Magnetic Ressonance
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
R _f	Retardation factor
TMSA	Trimethylsilylacetylene
TMS	Tetramethylsilane
THF	Tetrahydrofurane
TLC	Thin-layer chromatography

2 Introduction

In 1893, Alfred Werner described for the first time the structure of an octahedral transition metal complex and proposed a method to deduct the coordination number and oxidation state of complexes. Before his studies, organometallic chemists were puzzled by the observations of transition metal compounds surrounding themselves of multiple neutral species even after electroneutrality principles were already satisfied by counterions (e.g. $\text{CoCl}_3 \cdot 6\text{NH}_3$). [1] This phenomenon exposed that transition metals preferred specific geometrical distributions of ligands, which led to further studies and development of new procedures to integrate multiple kind of ligands into coordination species. All that foundational understanding culminated into two new branches of modern coordination chemistry, metal-organic frameworks (MOFs) and supramolecular coordination complexes (SCCs) like metal-organic cages (MOCs).

MOFs are infinite 1D, 2D, or 3D structures generated from metal centres bonded to organic ligands. [2] These ligands must have more than one anchoring point, which must also be separated inside the structure. If the ligand contains multiple binding sites too close to each other, a single metal ion might occupy all of them generating what it is called a chelate. As network growth depends on the capacity of the ligand to interconnect metal centres, therefore the formation of chelates can inhibit the process. For instance, a 2,2'-bipyridine would potentially generate chelates rather than polymeric structures, while 4,4'-bipyridine would be more likely to generate a MOF (Figure 1).

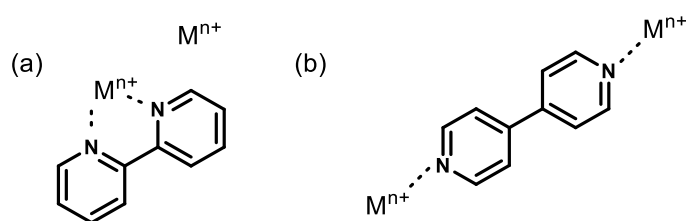


Figure 1. Chelating effect of 2,2'- bipyridine versus 4,4'-bipyridine.

The most common method to prepare MOFs is via coordination-driven self-assembly, in which ligands and metal precursors are combined in solution to form, through metal-ligand interactions, the most thermodynamically stable coordination compound. Many materials synthesized using this method, have shown incredible potential in optics, sensors, gas absorption and separation, gas storage, catalysis and drug delivery, due to their usual high porosity and surface area. [3] The aforementioned high porosity arises from small cavities located within the macrostructure, where no bonds or molecules can be found. These cavities,

which are called pores, are surrounded by functionalized ligands (hosts) that attract chemical species (guests) through non-covalent interactions. Hosts can perform two different actions on a guest: storing it or facilitating its transformation acting as a catalyst (Figure 2).

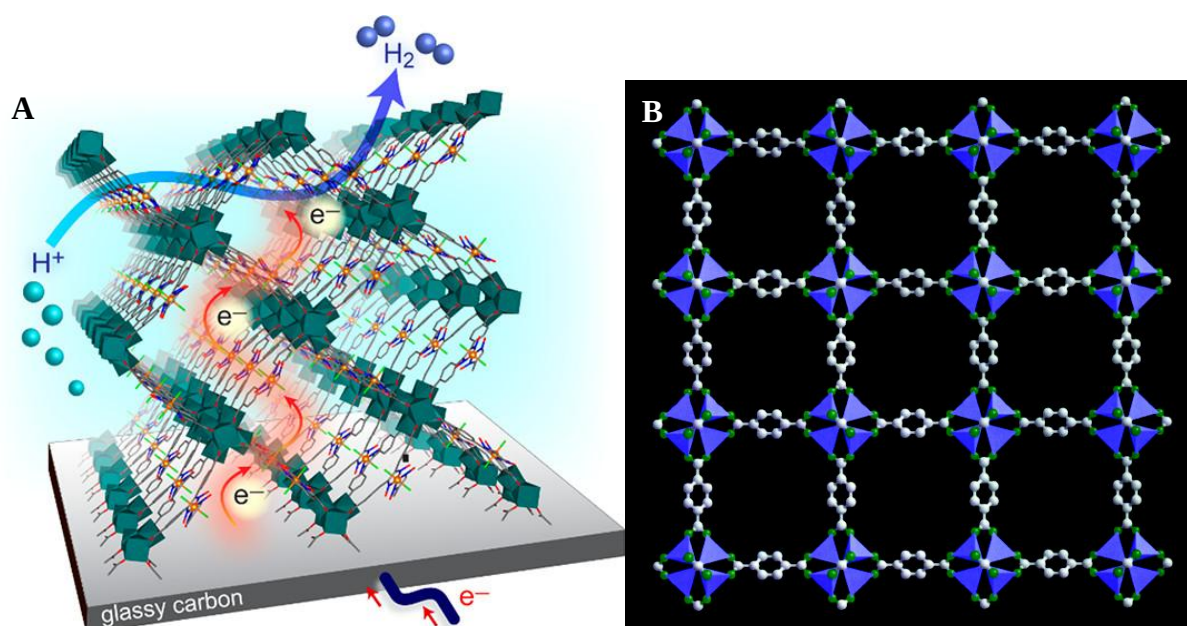


Figure 2. Examples of host-guest interaction systems: (A) Structural model of UU-100, a 3D MOF used as a molecular hydrogen evolution catalyst and (B) Layer of MOF-5 framework, a 3D MOF used to storage hydrogen gas; image (A) extracted from Roy, S., et al., *Electrocatalytic Hydrogen Evolution from a Cobaloxime-Based Metal–Organic Framework Thin Film*. *Journal of the American Chemical Society*, 2019. 141(40): p. 15942-15950. Image (B) extracted from Li, H., et al., *Design and synthesis of an exceptionally stable and highly porous metal-organic framework*. *Nature*, 1999. 402(6759): p. 276-279.

Despite of the growing interest on this field, it has been reported that MOFs capabilities can be diminished by poor accessibility of internal pores (Figure 3). Furthermore, their usually high molar mass may result in insoluble coordination compounds which are difficult to elucidate using solution-based analytical methods like NMR spectroscopy.[4-6]

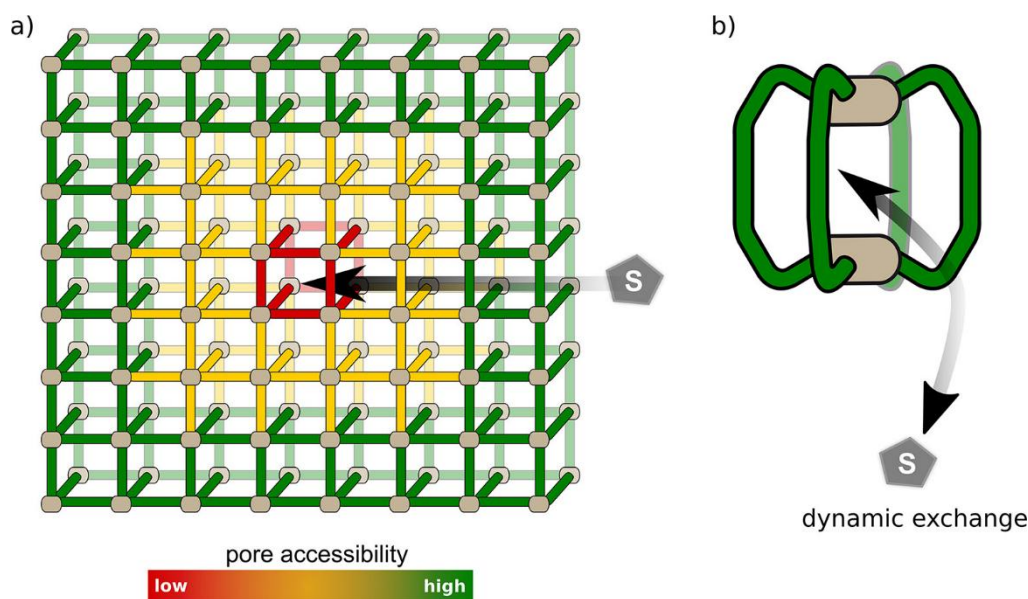


Figure 3. Pore accessibility in MOFs (a) versus pore accessibility in MOCs (b) composites; image extracted from Pullen, S. and G.H. Clever, *Mixed-Ligand Metal–Organic Frameworks and Heteroleptic Coordination Cages as Multifunctional Scaffolds—A Comparison*. *Accounts of Chemical Research*, 2018. 51(12): p. 3052-3064.

On the other hand, SCCs are discrete structures prepared by using the same coordination-driven self-assembly, but employing blocker ligands to inhibit polymerization. This kind of ligands bind strongly to the coordination positions that are not intended for geometrical connectivity, while simultaneously stabilizing the coordination compound through electronic donation. For these purposes, ligands with strong sigma donor capability, and in some cases high backdonation, are commonly used as blockers. Pioneering works by Fujita et al.[7, 8], Stang et al.[9, 10], Newkome et al.[11], Nitsche et al.[12, 13], among others, laid the fundamental principles of building metal-organic compounds. These efforts culminated in the development of various geometrical structures like metal-organic macrocycles (MOMs) and metal-organic cages (MOCs). Among both, MOCs showed the best variety of shapes and easier to control pore sizes.

The common metal-ligand coordination bond used in both MOFs and MOCs, is the cause of their similarities in composition, topology and potential applications. However, since MOCs are simpler structures than MOFs, issues related to solubility or poor internal pore accessibility do not arise (Figure 3). This makes MOCs a perfect candidate to start experimenting with, while MOFs a future material in which to apply the knowledge developed to construct advanced materials or systems with new or increased functionalities.

The coordination-driven self-assembly of MOCs has been a thoroughly investigated research topic during the last decades. A lot of structural data in the form of NMR spectra and single

crystal X-ray diffraction has been recorded of multiple geometrical cages. And even showing their high applicability, there are some limitations compared to biological supramolecular structures like proteins. While proteins contained several linking sites in the same structure to perform multiple tasks simultaneously, MOCs could only do one action. Inspired by nature, some researchers envisioned the idea of incorporating more than one type of ligand on MOCs to replicate protein multifunctionality. From it, a new classification of MOCs arose. The structures assembled with one kind of ligand were then called homoleptic while the structures assembled with two types of ligands, or more were called heteroleptic. Most of the heteroleptic MOCs synthesized by now contained two different ligands due to the highly unpredictable overall structure. Indeed, it was observed that when introducing a transition metal precursor into a solution of bis-monodentate ligands, only three outcomes could be obtained: both ligands form its own homoleptic cages (narcissistic assembly), a randomized mixture of heteroleptic cages forms (statistical mixture) or the desired heteroleptic cage forms (integrative self-sorting). To achieve an integrative self-sorting process, it is usually required a rational design of the ligands that are used.[14, 15] Various strategies have been developed in recent years to rationally design ligands with specific structures that promote the formation of a single heteroleptic cage (Figure 4).

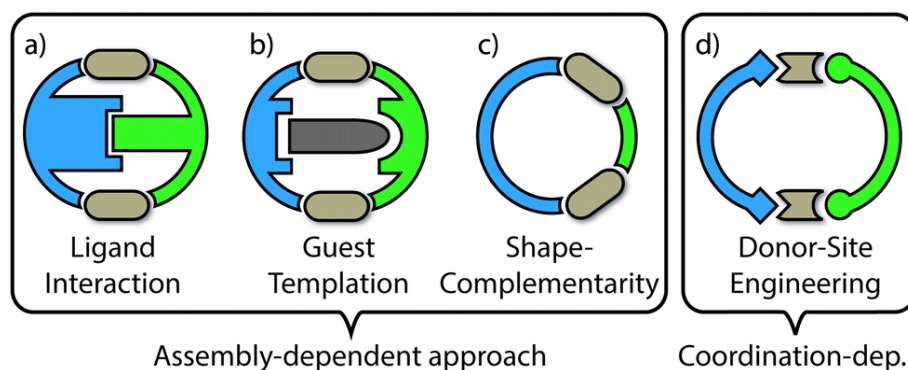


Figure 4. Strategic ways of integrative self-assembly of heteroleptic cages: (a) Stabilizing interactions between the ligands hold the cage. (b) The same as (a), however through an intermediary molecule. (c) Different shaped ligands generate a structurally stable cage. (d) A specific combination of donors leads to a stable cage; (a) and (b) usually sacrifice the cavity and with it any guest-host application; From (a) to (c) the stabilization comes from the overall structure, while in (d) the stabilization is provided by the immediate environment of the metal centres; image extracted from Bloch, W.M. and G.H. Clever, *Integrative self-sorting of coordination cages based on 'naked' metal ions. Chemical Communications*, 2017. 53(61): p. 8506-8516.

One strategy that was thought was the use of template molecules that could bond with non-covalent forces to both ligands during the cage formation. In 2000, Fujita et al. mixed a cis-protected Pd(II) with two different tridentate ligands and found that the assembly proportions of homoleptic and heteroleptic cages were governed by the template molecule added.[16] They tried later a similar procedure using Pt(II), tris(pyridine)triazine, pyrazine, and triphenylene as

molecular template, and observed that the addition of larger aromatic templates resulted in bigger structures; in that case, an heteroleptic prism.[17] In more recent years, Yoshizawa et al. showed the incredible potential of fullerene (C_{60}) as a molecular template (Figure 5). First, two homoleptic cages were built using derivative ligands of anthracene with phenylene or naphthalene backbones. While the pores of the larger cage were able to retain C_{70} and a C_{60} derivative, the smaller cage did not have the appropriate dimensions. When these homoleptic cages were mixed without guests or molecular templates, statistical heteroleptic cage mixtures would generate. Despite of that, reorganization would occur when C_{60} was added, favouring one heteroleptic cage structure. As a molecular template, C_{60} showed a strong stabilization due to strong interactions with the ligands.[18] Guest templating can be a valuable technique to generate a single structure; however, it occupies the cavity making the resulting cage difficult to liberate without perturbing the assembly.

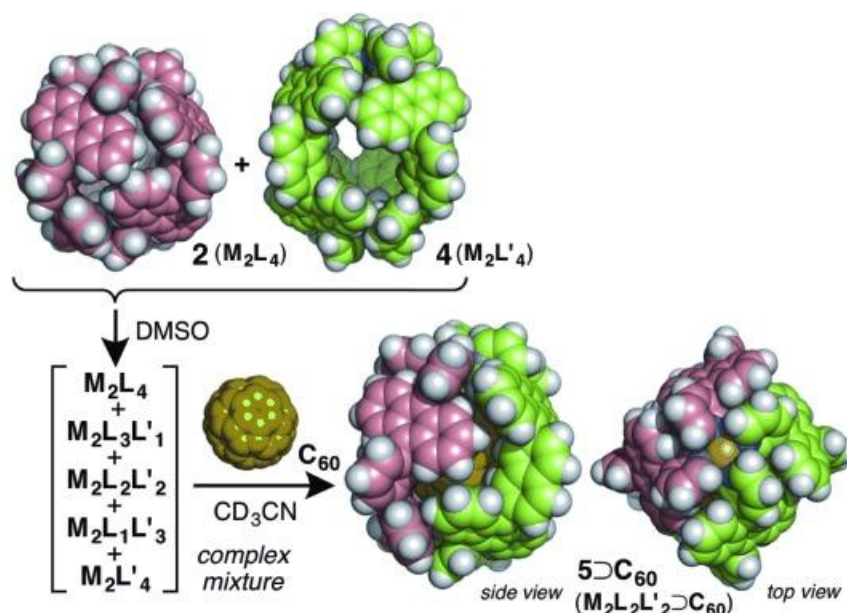


Figure 5. Fullerene used as a molecular template for heteroleptic cage assembly; image adapted from Yamashina, M., et al., Anisotropic Expansion of an M_2L_4 Coordination Capsule: Host Capability and Frame Rearrangement. *Chemistry – A European Journal*, 2015. 21(11): p. 4200-4204.

In 2011, Hooley et al. developed a second strategy while investigating how steric bulk in bis(pyridine) ligands could affect the formation of heteroleptic cages. They designed three derivative ligands with increasing sizes of central functional groups and mixed them with their unfunctionalized derivative. By adding these ligands to Pd(II), Hooley et al. observed the formation homoleptic cages (narcissistic assembly) in less bulky ligands, and the formation of heteroleptic cage mixtures when adding more bulky ligands. Due to steric constraints, only one highly bulky ligand could be fitted in the structure, resulting in three unfunctionalized ligands and one functionalized ligand per cage (Figure 6). However, the use of sterically demanding

central motifs implied filling the cavities that were meant to be used in guest-host interactions.[19] In a seemingly unrelated study, Crowley et al. tuned tripyridine ligands sterically and electronically to prepare a more stable homoleptic cage towards nucleophilic attack of the metal. Adding amino groups to the 2- and 3- positions of the pyridyls did not only increase the donor properties while protecting the Pd(II) from nucleophiles as it was expected, but it also favoured the formation of heteroleptic cages of 1:1 tunned and non-tunned tripyridyl ligands due to hydrogen interactions between the amines and the alpha hydrogens of the unsubstituted ligands (Figure 7).[20, 21]

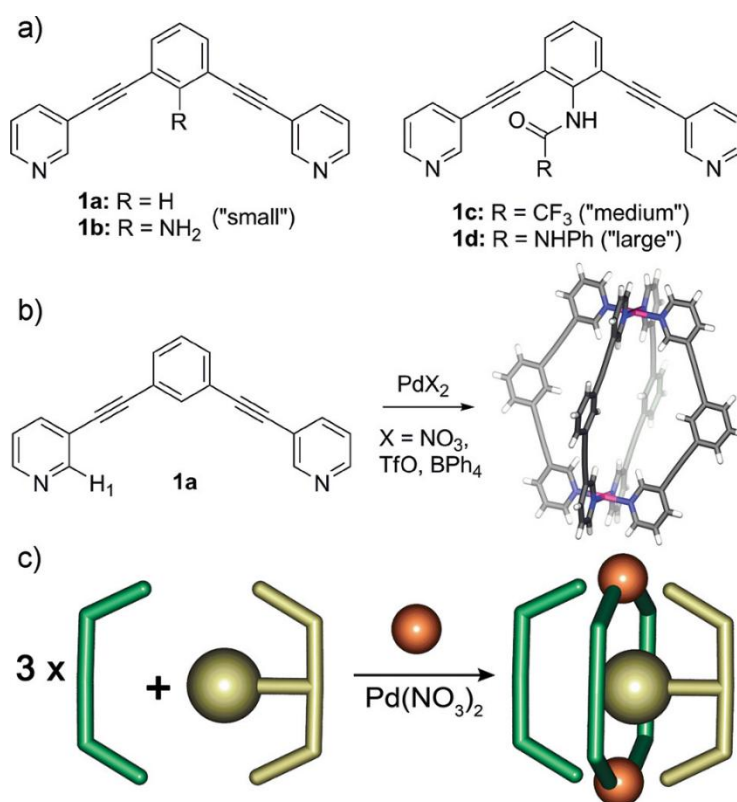


Figure 6. (a) Library of ligands used in Hooley et al. steric bulk study. (b) Homoleptic cage generated without adding any of the bulky derivative ligands. (c) Endohedral bulk strategy to form heteroleptic cages; image extracted from Johnson, A.M. and R.J. Hooley, *Steric Effects Control Self-Sorting in Self-Assembled Clusters. Inorganic Chemistry*, 2011. 50(11): p. 4671-4673.

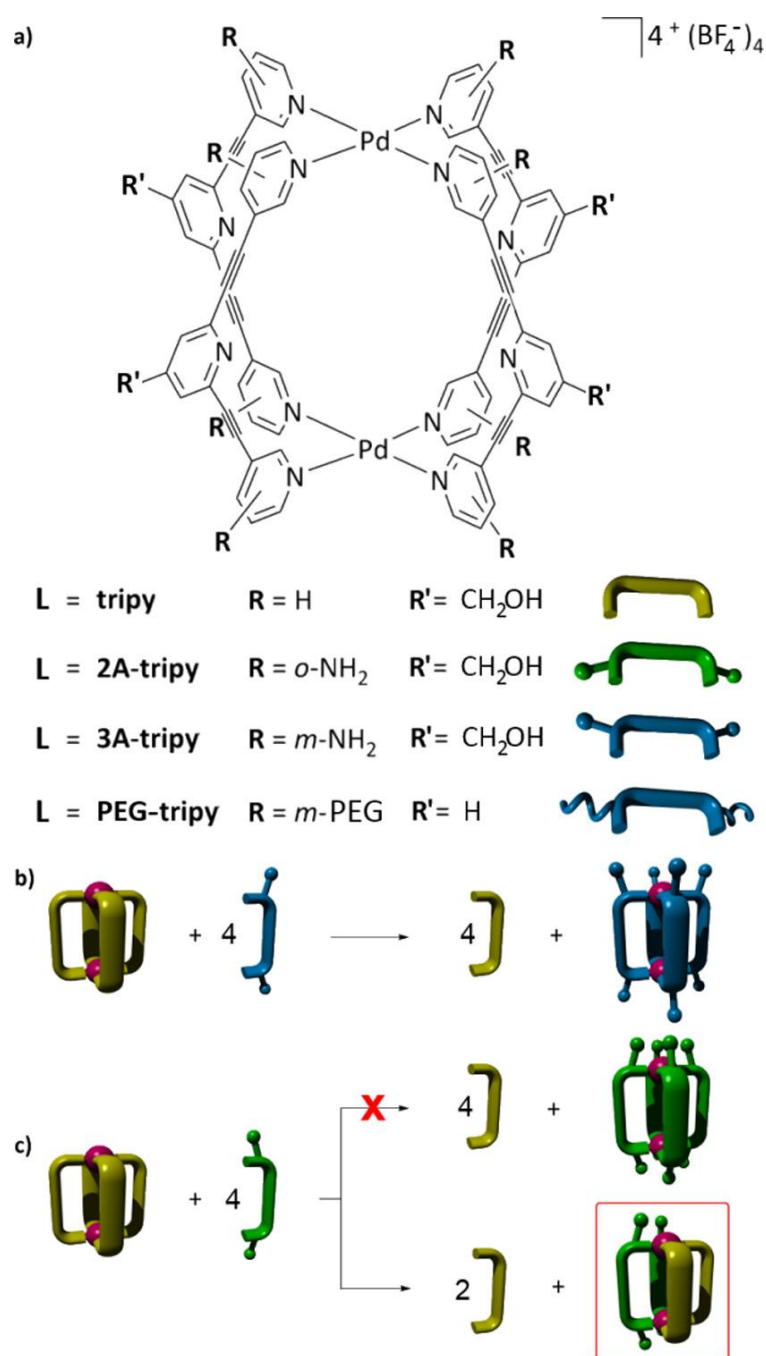


Figure 7. (a) Schematic structure of the Pd(II) cage designed by Crowley et al. and all the ligands synthesized. (b) Exchange of underived ligands due to their lower sigma donation effect compared to the amino substituted ligands. Substituents strategically located in meta to neglect steric effects. (c) Stabilization of a 1:1 heteroleptic cage assembly through hydrogen bonding between the amines of the ortho substituted ligand and the alpha hydrogens of the underived ligand; image extracted from Preston, D., et al., Controlled Formation of Heteroleptic $[\text{Pd}_2(\text{L}_a)_2(\text{L}_b)_2]^{4+}$ Cages. *Journal of the American Chemical Society*, 2016. 138(33): p. 10578-10585.

The third strategy emerged as a combined effort from several organometallic research groups. Li and Zhou's work involved building homoleptic cages of units of dicarboxylic acid ligands and Co(II) in paddlewheel structures. Longer dicarboxylate ligand were added to the homoleptic structure resulting in a singular heteroleptic cage.[22] Kitagawa et al. got similar results by directly mixing 5-(tert-butyl)isophthalic acid and azobenzene-3,3'-dicarboxylic acid

in a Cu(II) solution.[23] Fujita et al. explored different ligand combination by mixing a small bis(pyridyl)benzene with a large bis(pyridylethynylphenyl)benzene ligand and Pd(II) in a 1:1:1 proportion, which led to the formation of a heteroleptic cuboctahedra complex. These findings suggested that stable heteroleptic structures could be achieved by employing a combination of ligands with different spatial arrangements.[24] Clever et al. ultimately developed the strategy of “shape-complimentary ligands” by designing ligands with “complementary geometry”, which are ligands with linking points closer to each other, and ligands with linking points more far away to each other (Figure 8).[25] It is suggested that the stabilization occurs from the coordination units adjusting their geometries and bond angles to the intrinsic shape of the organometallic complex (ex. Square planar), thereby promoting a better overlap between d metal orbitals and ligand orbitals.

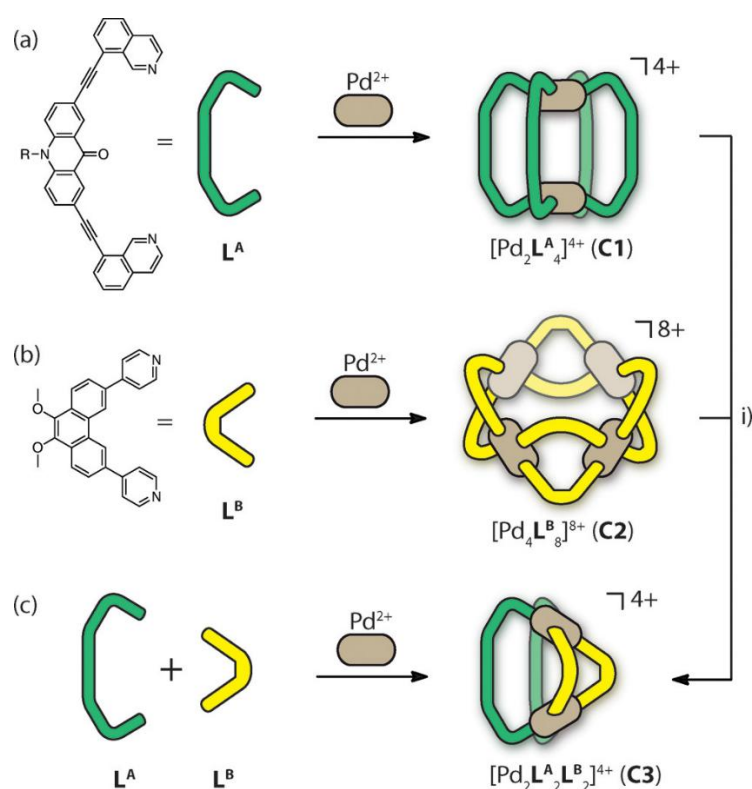


Figure 8. (a) and (b) depict distorted structures around the metal centre compared to the commonly observed square planar Pd(II). (c) When both ligands are combined, the structure adopts a geometry that enhances better the overlap between metal d orbitals and ligand orbitals, stabilizing the overall cage. This structure is indeed the typical square planar; image extracted from Bloch, W.M., et al., *Geometric Complementarity in Assembly and Guest Recognition of a Bent Heteroleptic cis-[Pd₂L^A₂L^B₂]* Coordination Cage. *Journal of the American Chemical Society*, 2016. 138(41): p. 13750-13755.

Stang et al. introduced another methodology by making use of charge separation as a driving force. Diverse multicomponent supramolecular prisms were obtained upon combining dicarboxylate and different pyridyl donors with cis-Pt(PEt₃)₂(OTf)₂ (Figure 9). The stabilization observed was attributed to the minimization of electrostatic repulsion by preventing two

negatively or positively partial charges from connecting through a metal centre.[26] Another novel donor-site engineering method was exposed by Fujita et al. in 2005 with an heteroleptic $M_6L_3L'_2$ prism prepared from a mixture of tris(pyridine)triazine, bilutidinyl and cis protected Pd(II) precursors (Figure 10). The sterically demanding groups near the linking nitrogen of the latter ligand rendered its homoleptic assembly highly unstable. As the combined stabilization energy of the two possible homoleptic cages did not surpass the one provided by a mixed cage, it was possible to generate a single heteroleptic cage.[27]

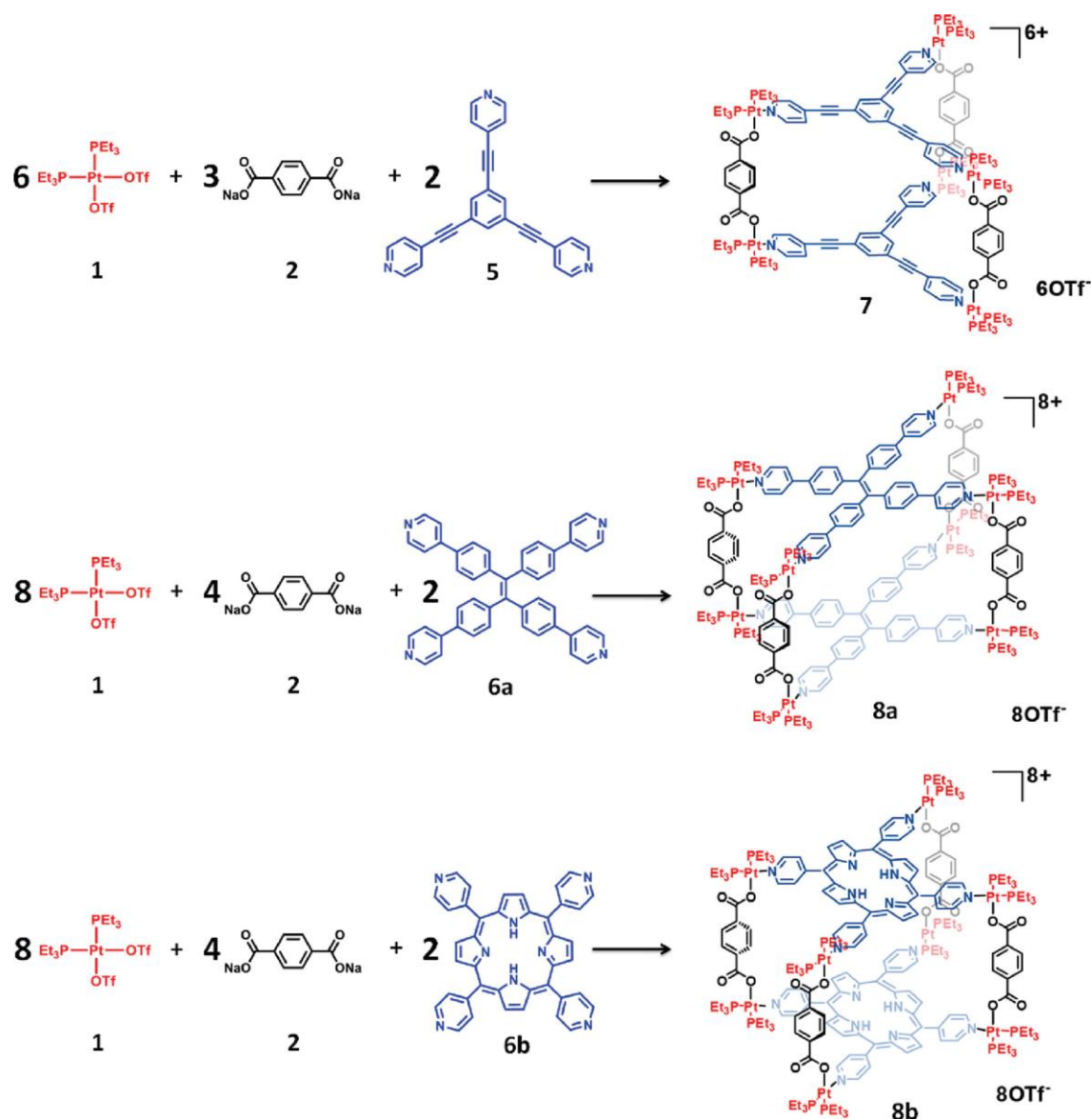


Figure 9. Multiple heteroleptic cages prepared from combinations of dicarboxylate ligands, different pyridyl donors and $Pt(PEt_3)_2(OTf)_2$ using the charge separation approach; image extracted from Zheng, Y.-R., et al., A Facile Approach toward Multicomponent Supramolecular Structures: Selective Self-Assembly via Charge Separation. *Journal of the American Chemical Society*, 2010. 132(47): p. 16873-16882.

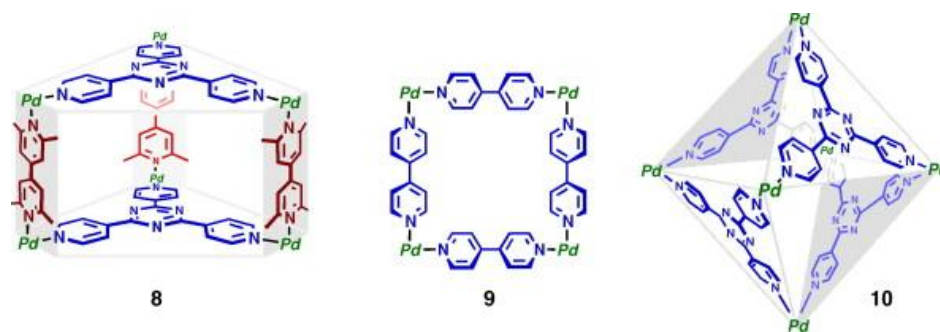


Figure 10. Outcomes of applying ligands with different steric constraints around the metal centres: in (9) and (10) both ligands form its homoleptic cage as no impeding substituents are located near the donor nitrogen. However, when methyls are added to those positions, is formed an heteroleptic cage which is more stable than a mixture of the steric constrained and the non-substituted tridentate donor homoleptic cages; image adapted from Yoshizawa, M., et al., Side chain-directed complementary cis-coordination of two pyridines on Pd(II): Selective multicomponent assembly of square-, rectangular-, and trigonal prism-shaped molecules. *Journal of Organometallic Chemistry*, 2005. 690(23): p. 5383-5388.

Rationally designing the ligands using the aforementioned methods requires extensive multidisciplinary research teams, and even in that situation, favourable results are not guaranteed by computational models or meticulously designed structures. This problem highlights the necessity of developing an easier, more accessible and convenient path to strategize the preparation of heteroleptic MOCs. Drawing the inspiration from protecting groups in organic chemistry, we have adopted a similar approach to synthesize heteroleptic MOCs using ligand blockers. To build our heteroleptic cage, it was used as a reference the cubic homoleptic cage designed by Thomas et al. in 1998, which proves that it is possible to generate a stable MOC structure binding Ru to pyridine motif ligands while blocking the other positions of the metal with a 1,4,7-Trithiacyclononane thia-crown ether.[28] For this purpose, four bidentate ligands with linear and rigid structure are designed. Two pyridines on the sides of the structure are used as linkers, due to their strong sigma donation interaction and their low hindrance, while a modifiable unit is positioned at the centre of the structure to provide a versatile platform for future modification. The structure with triple bonds presents greater flexibility than the other ligands, being it a fail-safe piece in case of developing excessive tension in the synthesized heteroleptic cage.

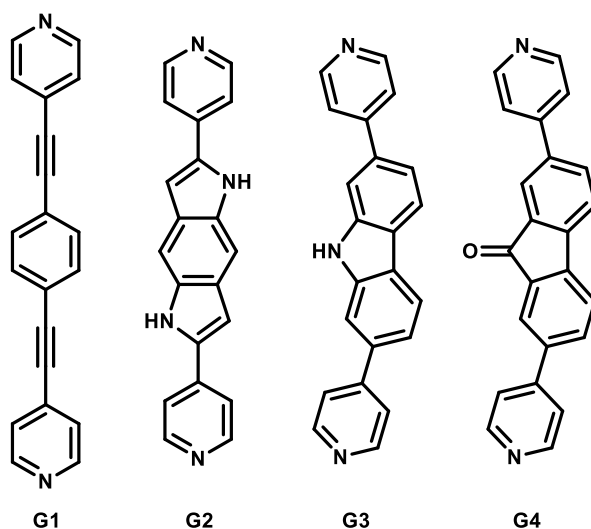


Figure 11. Library of ligands with potential application in selective heteroleptic cage assembly.

Nevertheless, this work focuses primarily on the synthesis of these ligands, which hold potential application to selectively form an heteroleptic MOC, and their full characterization during the process.

3 Project outline

This work presented will be part of a broader, and highly ambitious project to selectively assemble a heteroleptic cage. To support this overall goal, multiple organic ligands with potential applicability will be synthesized and fully characterized via NMR spectroscopy, HRMS spectroscopy, IR spectroscopy, EA, HPLC chromatography, R_f values, melting points and visual aspects. The aims of this thesis are to synthesize all the intermediates and ligands, and to fully characterize them using the above-mentioned analytical techniques. Meanwhile, the procedures used will be improved, multiple new organometallic reactions will be learnt and performed, and Schlenk inert techniques will be used and mastered as long-term objectives.

4 Results and discussions

As part of this work, multiple synthetic routes were designed or adapted to prepare a collection of ligands (Figure 10) with potential use in the previously suggested protecting group strategy. The initial approach was employing the slightly flexible G1 and the rigid G2 ligand to build a minimally tensioned cage. However, due to various failed attempts at synthesizing G2, other similarly rigid structures were proposed; those were G3 and G4 ligands. Most intermediates and products obtained were cleared from impurities via Dry Column Vacuum Chromatography (DCVC), an improved technique created by Pedersen *et al.* based on the older dry-column flash chromatography developed by Harwood *et al.*[29, 30] The use of DCVC promised better resolving power, higher scales of purification, cost-effective materials and less time-consuming procedures compared to the original technique or a conventional flash column. Specific details of preparation, setup, necessary materials and other information can be found in Pedersen *et al.* article and Tortzen descriptive short guide.[29, 31]

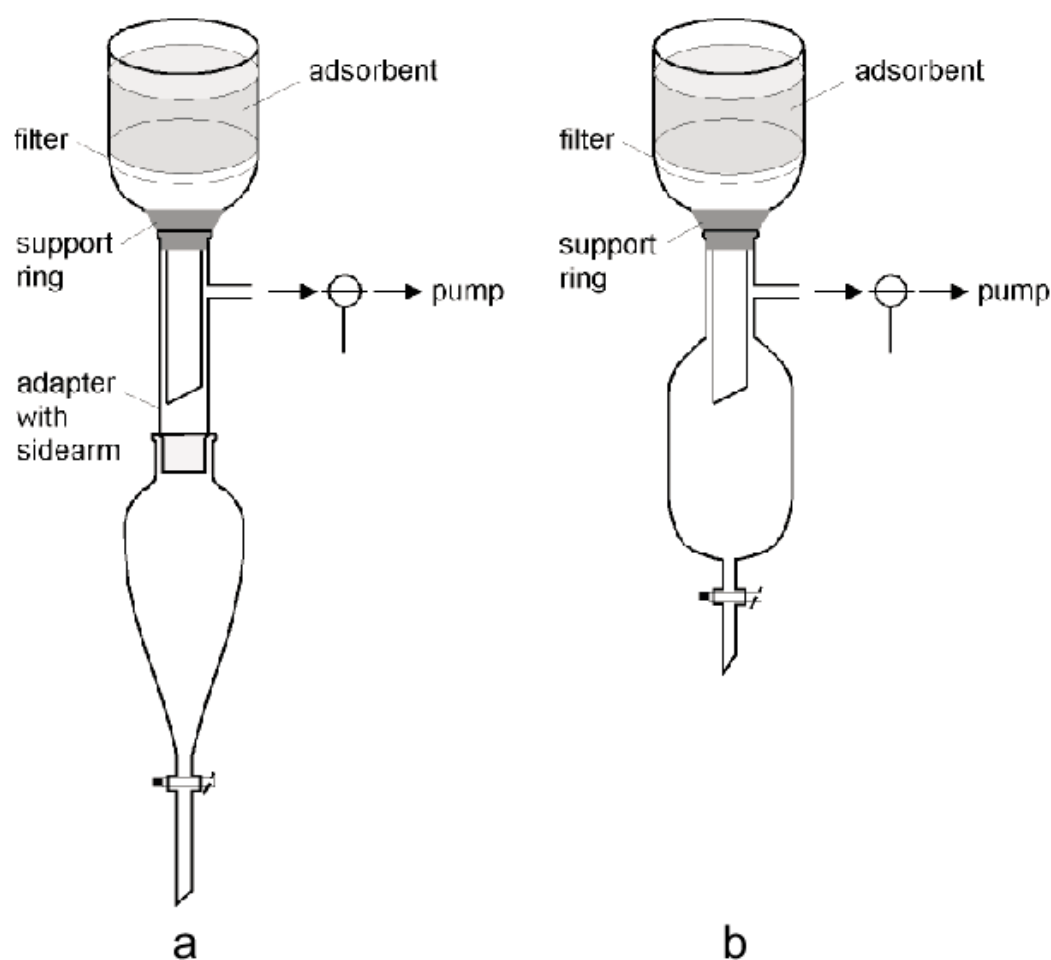
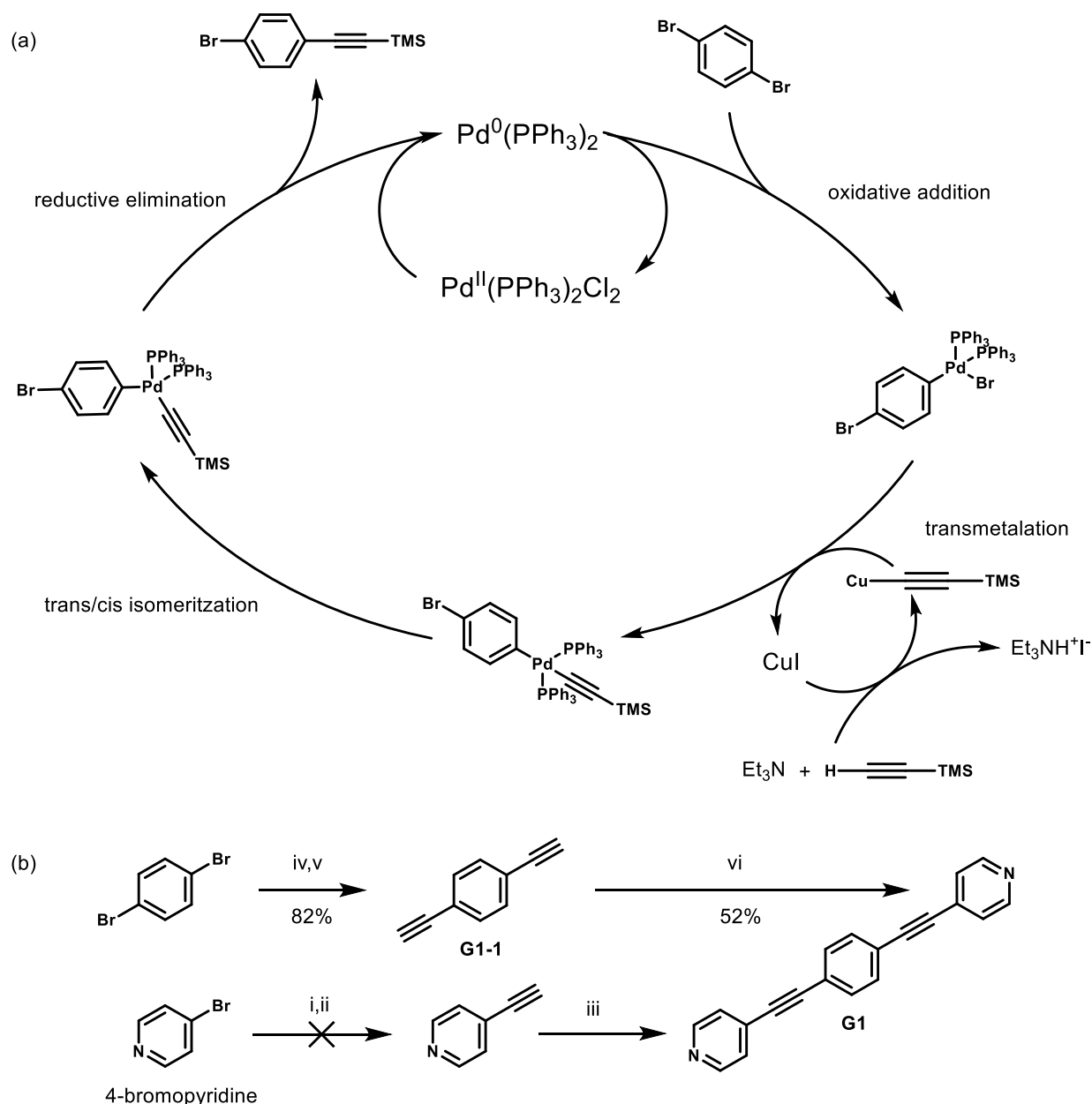


Figure 12. Setup to perform a DCVC using more readily available glassware (a) versus a more specified one for the task (b). To purify the compounds of this work it was used (a); image extracted from Pedersen, D.S. and C. Rosenbohm, *Dry Column Vacuum Chromatography*. *Synthesis*, 2001. 2001(16): p. 2431-2434.

The synthesis of G1 was first attempted as a three-step reaction involving a cross coupling of 4-bromopyridine with TMSA using a Sonogashira reaction, then a removal of the TMS protecting groups with TBAF, and finally a cross coupling of the obtained 2-pyridinylethyne with p-dibromobenzene again through a Sonogashira reaction. Unfortunately, the last step could not be reached, as the 2-pyridinylethyne intermediate was highly volatile, being drag with the solvent when evaporated under reduced pressure. Then, a literature procedure employing inverted reactive motifs of the coupled molecules was found. The number of steps was the same, and the authors of the article claimed high yields of reaction. This new approach started with the coupling of the p-dibromobenzene to TMS using a Sonogashira reaction. Then, the TMS protecting group was removed with TBAF, and the intermediate G1-1 was cross coupled with 4-bromopyridine via another Sonogashira reaction. It was observed that in this case, the deprotected intermediate (G1-1) was not highly volatile. Moreover, the number of steps could not be further reduced, as the TMS protecting group ensures that the terminal proton of the triple bonds in the intermediate do not enter the catalytic cycle generating polymerized byproducts. After multiple trials testing different experimental conditions and reagent amounts, the yields were increased from 10% to 52% in the last reaction. However, it was unfeasible to reach the yields of 95% in each reaction step as it was claimed in the literature protocol. The significant difference was attributed to possible loss of product in the unavoidable emulsions formed in the liquid-liquid extraction due to remaining traces of catalyst and the highly hydroscopic activity of the 4-bromopyridine used in the last reaction step.

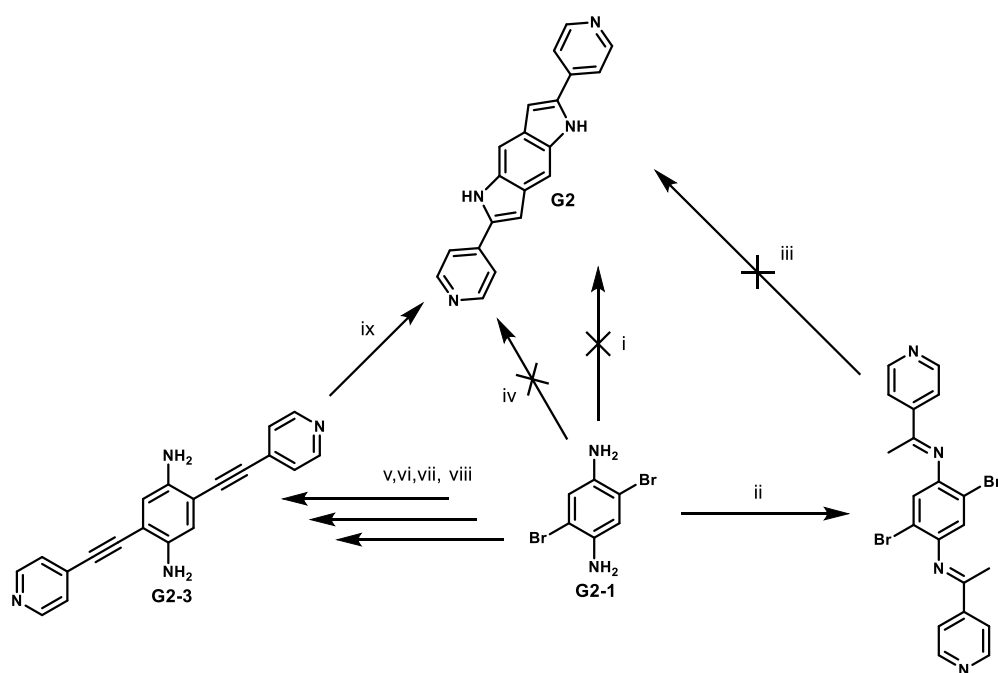


Scheme 1. (a) Illustrative mechanism of the first Sonogashira Coupling cycle towards **G1** synthesis. (b) Multiple attempted synthetic routes for **G1** ligand: i) TMSA (2.0 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (2.5 mol%), CuI (3.0 mol%), 2:1 triethylamine/THF, 60°C, 16h; ii) TBAF (2.5 equiv), THF, 0°C to rt, 1h; iii) Not specified as it was not attempted; iv) TMSA (2.3 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (2.5 mol%), CuI (2.5 mol%), triethylamine, 80°C, 16h; v) TBAF (2.5 equiv), THF, 0°C to rt, 1h; vi) 4-bromopyridine (3.0 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.2 equiv), CuI (0.1 equiv), 1:1 triethylamine/THF, 60°C, 16h.

All the intermediates and the **G1** product synthesized were analysed via HNMR to confirm their structures, check purity, and evaluate the completeness of reaction. Special attention was given to the number of peaks in the aromatic region ($\delta \sim 6.5\text{--}8.5$ ppm) and the presence of a terminal alkyne proton peak ($\delta \sim 2.5\text{--}3.5$ ppm), which should only appear in **G1-1** spectrum. After verifying the compounds, **G1-1** and **G1** crudes were subjected to purification using DCVC to further analyse via CNMR and HSQC. The protected intermediate with TMS group could not be purified and subsequently further analysed due to the high sensitivity of TMS to even slightly

acidic mediums as the one provided in silica gel. All relevant spectra can be found in *appendix A*.

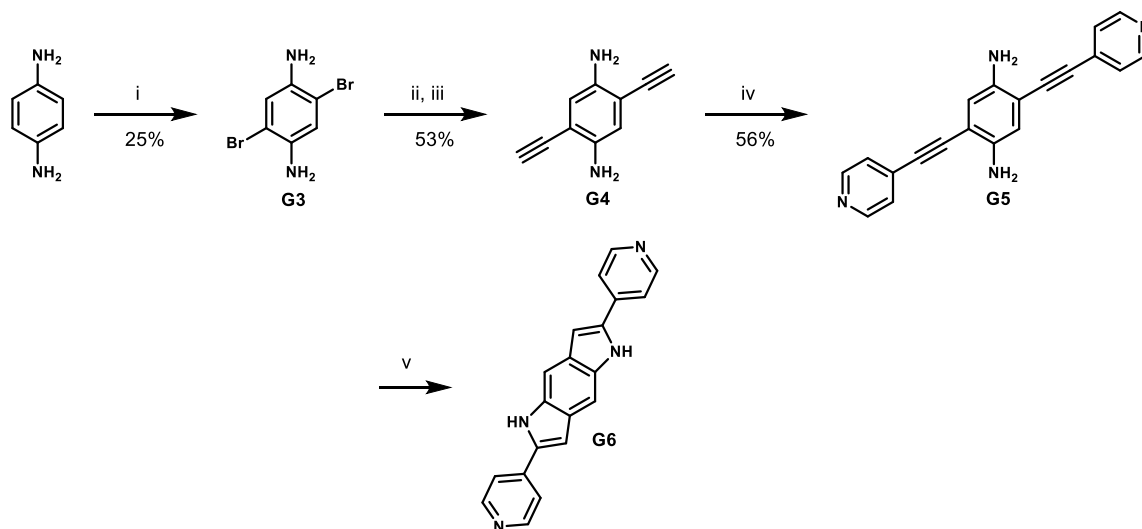
For the second ligand, various synthesizing approaches were attempted, as no previous literature could be found on G2 ligand. The most logical to use Fisher indol synthesis, was not successful to prepare G2. Then, a strategical imine was designed and successfully obtained to afterwards be cyclated using a simple nucleophilic substitution reaction. However, the latter step did not succeed, as partial or non-cyclation at all occurred. After both failures, a Mercks indol synthesis was attempted, but again, it was unsuccessful. Then, an alternative methodology was proposed undergoing a Larock indole synthesis, nonetheless, it was not finally attempted due to the difficulties of removing the TMS protecting group on the positions it would have been anchored. Ultimately, it was used an analogue synthetical path to the one used for the first synthesized ligand, G1.



Scheme 2. Schematic overview of the multiple attempts proposed to synthesize **G2** ligand. i) 4-acetylpyridine (3.0 equiv.), $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mol%), 1,4-Diazabicyclo[2.2.2]octane (6.0 equiv.), DMF, 85°C, 6-12h; ii) 4-acetylpyridine (2.0 equiv.), HCl conc. (3.6 equiv.), 80°C, 72h; iii) LDA used as base. Conditions unknown; iv) 4-acetylpyridine (2.0 equiv.), potassium *tert*-butoxide (3.0 equiv.), bathophenanthroline, THF, 40°C, 16h; v-ix) See conditions in Scheme 3.

To prepare the starting material used for G2 synthetical route, a dibromination of a *p*-phenyldiamine was required. However, being it a radical reaction, the yields obtained were remarkably variable. Interestingly, it was found that the higher yields were achieved when a certain addition rate of bromine was employed. Despite of that, it was not possible to surpass

yields higher than 25% on this step. Subsequent steps resulted in moderately low yields of reaction. It is still unclear what might cause the significantly reduced yields in the first Sonogashira coupling in comparison to the analogous of the G1 synthetical route, however it might be related to steric hindrance effects of the amino groups.



Scheme 3. Schematic synthesis of **G2** ligand. i) Br_2 (2.0 equiv), AcOH , 80°C , 3.5 h. ii) TMSA (2.6 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (1.0 mol%), CuI (4.0 mol%), PPh_3 (4.0 mol%), triethylamine, 80°C , 24 h. iii) TBAF (2.5 equiv), THF , 0°C to rt, 1 h. iv) 4-bromopyridine (3.0 equiv), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.2 equiv), CuI (0.1 equiv), 1:1 triethylamine/ THF , 60°C , 16 h.

Once more, all the compounds synthesized were analysed through HNMR to verify the compound, purity and completeness of the reaction. Given the structural analogy of the intermediates of G1 and G2 ligands, the same regions of the proton NMR spectra were examined. Additionally, it was explored the aromatic amine region ($\delta \sim 3.5\text{--}6.0$ ppm). To be able to see the amine protons of the structures, it was used a deuterated solvent does not participate in proton-deuterium exchange, DMSO. In all the structures it would be expected to show a singlet peak due to the highly symmetrical intermediates and ligand. All compound crudes were purified through DCVC and further analysed through CNMR and HSCQ. For the same reasons as explained in G1 synthesis, the protected with TMS compound could not be cleared from impurities as the process would also remove the protecting groups. All relevant spectra can be found in *appendix A*.

Moreover, the HNMR spectrum of G2-1 crude revealed three distinct peaks in the aromatic amine proton region, and one extra peak in the aromatic proton region. To further investigate this matter, a sample of the main impurity isolated from the DCVC column was analysed through HNMR. Interestingly, the spectrum exhibited a doublet in the aromatic amino region, which meant that the byproduct did not have two symmetrical amino groups. After considering

this fact, and the overall ortho/para directing effect of the amino groups on the aromatic cyclic compound, it was determined that the impurity was the 2,6-dibromobenzene-1,4-diamine. The summing ortho/para director effect of the amino groups favoured equally all positions; however, two halides in the same side of the aromatic cycle would be too much sterically hindered and therefore unstable (Figure 12).

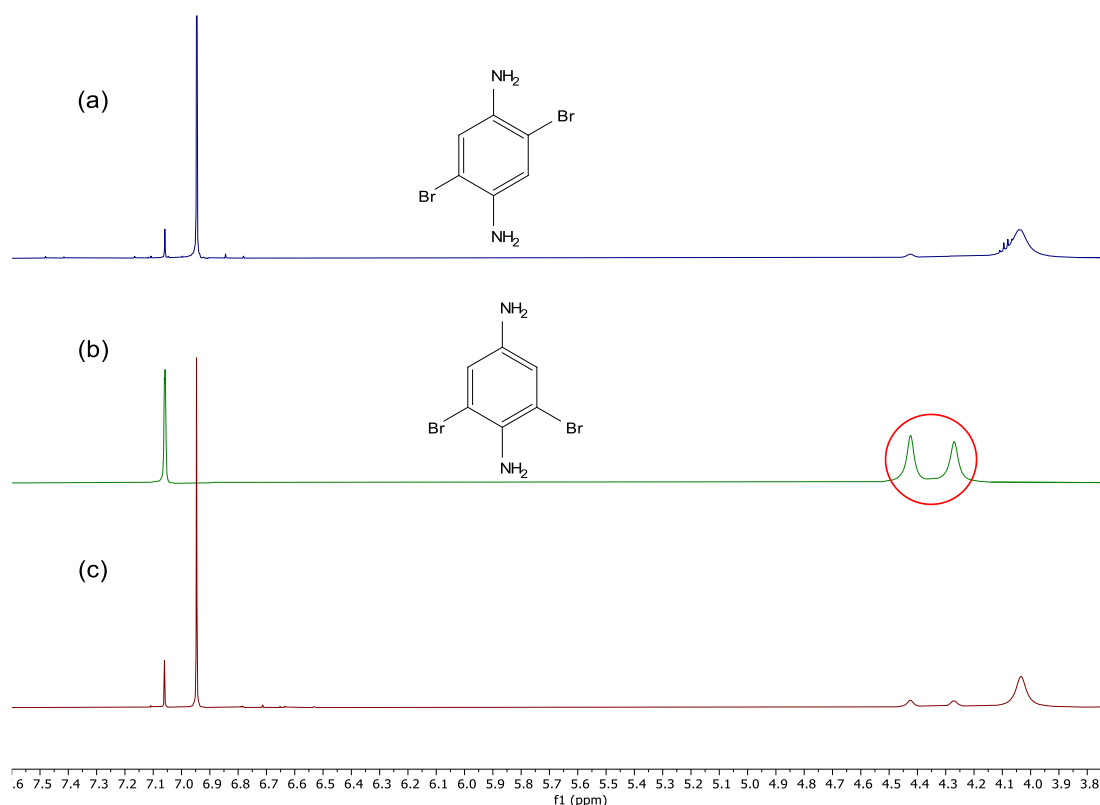
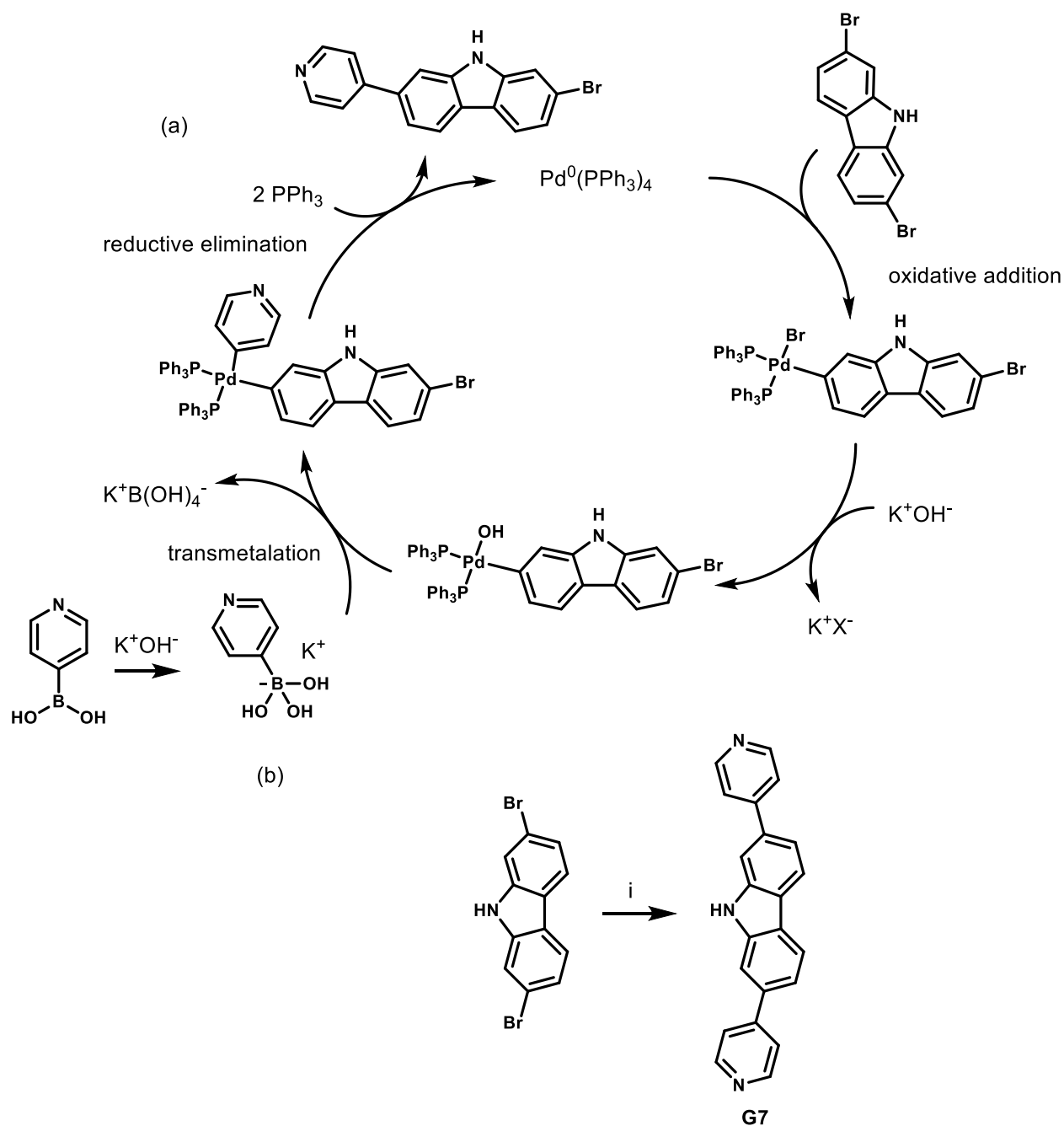


Figure 13. (a) ¹H NMR spectrum of the intermediate G3 with slight impurities of 2,6-dibromobenzene-1,4-diamine. (b) ¹H NMR spectrum of the 2,6-dibromobenzene-1,4-diamine isolated from the bromination reaction crude. (c) ¹H NMR of the crude of the bromination reaction.

Although this compound encountered might not entirely explain the obtained yields of reaction, it is one step further to reach a general overview of what could be optimized in the bromination reaction.

The third ligand (G3) was synthesized following the same compounds and procedures used in a previous literature found. The protocol consisted of a one-step Suzuki coupling reaction between 2,7-dibromo-9H-carbazole and 4-pyridinylboronic. As the catalyst used was commercially bought a long time ago, the double amount of catalyst was used to ensure good results.



Scheme 4. (a) First Suzuki cross-coupling reaction general mechanism. (b) Schematic synthesis of ligand G7. i) 4-pyridinylboronic acid (4.4 equiv), $\text{Pd}(\text{PPh}_3)_4$ (2.5 mol%), K_2CO_3 (4.4 equiv), 1:4 $\text{H}_2\text{O}/\text{DMF}$, 95°C , 16 h.

The ligand was analysed through HNMR, which made evident that a removal of impurities was required. The crude was purified through DCVC and the compound obtained analysed via HNMR, CNMR and HSQC. However, the spectra did not resemble the structure of G3, nor had the according number of peaks. It was determined that the compound isolated was the 4-pyridinylboronic acid, as the number of peaks was correct when disregarding the acidic protons, due to possible interchange with the deuterated solvent. All relevant spectra can be found in *appendix A*.

Upon reviewing the outcome spectra from the synthesis of G3, it was concluded that the ligand may have been retained somewhere during the quenching. This would explain why the starting reagent, nor the final product are visible in the HNMR spectrum.

Lastly, the ligand G4 was not attempted due to time constraints. However, it was proposed as an analogous Suzuki coupling reaction to the one used in G3 synthesis, however, employing 2,7-dibromo-9H-fluoren-9-one as the starting material (Scheme 4). The procedure and compounds required are also specified in the same literature resource used for G3 synthesis.

5 Conclusions

Even though the scopes for this project were too ambitious to be accomplished in the due time frame, it was feasible to synthesize all the intermediates and one of the ligands proposed. Also, all the purified compounds were successfully elucidated through NMR spectroscopy; however, due to time limitations, it was not possible to perform the *full characterization* of the compounds obtained. Despite of that, this project provided multiple valuable learning opportunities, as learning state of the art inert Schleck line techniques, DCVC purification methods, safety procedures when working with dangerous reagents as bromine, and clean ways of transferring intermediates or products into more adequate vessels for each purpose. Moreover, it served to enhance essential skills as teamwork, effective organization of daily and weekly tasks and managing responsibilities.

6 Future directions

In future research, it would be convenient to redo and repurify all the compounds in a much cleaner way with the objective of designing much optimal purifying columns with detailed indications and record much cleaner “ready for publication” NMRs. It would be also necessary to record an HMRS, IR, EA and HPLC spectrum to finally achieve “full characterization” of all the compounds. The same applies to the ligands that were attempted to synthesize and the ones that were not possible to synthesize during the time frame of the current project.

It would be also interesting to do further research on the bromination reaction to identify which parameters should be modified to achieve better yields of reaction. Also, it would be required to optimize with more detail the protocols used to synthesize the ligands to achieve higher yields of reaction.

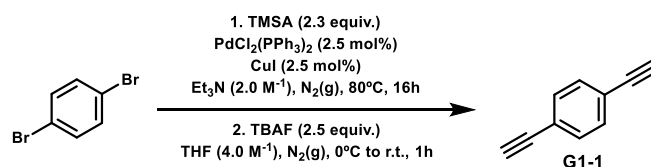
7 Experimental Procedures

7.1 General procedures

All the reagents and catalysts used on the syntheses were commercially bought and used without further manipulation, unless otherwise indicated. Every solvent used in the experiments was purchased in analytical grade and only degassed if the reaction required to be performed under inert conditions. Exceptionally, already degassed and dry THF was collected from a sodium and benzophenone distil system under nitrogen atmosphere, and triethylamine was always added directly from a sealed commercial bottle capped with a septum. All the organometallic reactions were executed in inert conditions by means of a Schlenk line, Schlenk flasks, Schlenk techniques and nitrogen gas. TLCs were prepared using aluminium plates of silica gel 60 F254 and seen under a UV-lamp of 254 and 365 nm wavelength. To clear impurities, *dry vacuum chromatography columns* were used instead of traditional *flash chromatography columns*. The required material to purify compounds was a chromatography column with vacuum connection and a porous disk, circular filter paper, celite and *silica gel 60 (0.015-0.040 mm)* acquired from Merck. The mixtures of solvents used in the DCVC columns had a total volume of 100 mL and were split into two fractions of 50 mL each. The NMR spectra were recorded in a Bruker Avance II spectrometer at room temperature and 500 or 126 MHz. Melting points were registered in an Gallenkamp GU-SM8 apparatus. Relative volumes of solvents are expressed in “mL of solvent/mmol of starting material” (M^{-1}).

7.2 Syntheses

1,4-diethynylbenzene (G1)



Scheme 5. Synthesis of 1,4-diethynylbenzene via Sonogashira reaction and deprotection with TBAF.

1,4-dibromobenzene (1.001 g, 4.2 mmol, 1 equiv.), PdCl₂(PPh₃)₂ (75 mg, 0.1 mmol, 2.5 mol%) and CuI (21 mg, 0.1 mmol, 2.5 mol%) were added to a Schlenk flask under a nitrogen atmosphere. The flask was flushed, and the mixture of solids were dissolved in triethylamine (8.5 mL, 2.0 M⁻¹). The temperature was then increased to 80 °C. Following, TMSA (1.35 mL,

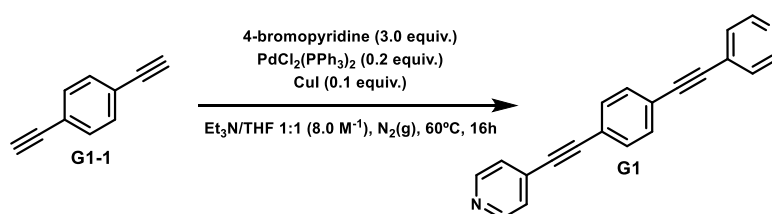
9.7 mmol, 2.3 equiv.) was added dropwise while mixing vigorously to achieve a black/brown solution. After all night stirring, the reaction mixture was cooled down to room temperature and quenched with water (15 mL, 3.0 M⁻¹). Once approximately 20 min had passed, the catalysts were excluded via suction filtration with celite (1 cm packing), and the retained solids were washed with 50 mL diethyl ether. An extraction with diethyl ether (3 x 20 mL) and brine (10 mL) was performed, and the organic extracts were dried with MgSO₄. The ether extracts were passed via suction filtration through neutral/basic alumina, and the solvent was evaporated under reduced pressure to obtain 1.301 g of nearly pure 1,4-bis((trimethylsilyl)ethynyl)benzene.

The 1,4-bis((trimethylsilyl)ethynyl)benzene (1.301 g, 4.8 mmol, 1 equiv.) was added to a round bottom flask and dissolved in THF (20 mL, 4.0 M⁻¹). The flask was then capped with a septum, nitrogenated and settled in an ice water bath. Once the solution was cooled down to 0°C, TBAF (12 mL, 12 mmol, 2.5 equiv.) was added slowly while mixing vigorously the solution. After completing the addition, the flask was removed from the ice water bath and left stirring for 1h. The reacting mixture was quenched with water and 20 min later the THF was removed under reduced pressure. An extraction with DCM (3 x 40 mL) and brine (20 mL) was performed, and the resulting organic extracts were dried with MgSO₄ and filtered via suction filtration through silica gel (4 cm packing). The solids retained were cleaned with DCM, and the solvent was removed under reduced pressure to result in 441 mg **G1-1** (82%).

¹H NMR (500 MHz, DMSO) δ (ppm) 7.49 (s, 4H), 4.37 (s, 2H). ¹³C NMR (126 MHz, DMSO) δ (ppm) 132.33, 122.56, 83.29, 83.27, 83.21.

Aspect = Pale pink; Rf value (1:1 DCM/heptane) = 0.71; mp = 94-98 °C

1,4-bis(pyridin-4-ylethynyl)benzene (**G1**)



Scheme 6. Synthesis of 1,4-bis(pyridin-4-ylethynyl)benzene via Sonogashira reaction.

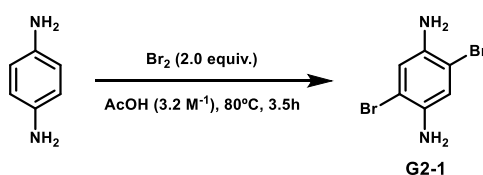
4-bromopyridine (2.405 g, 12.4 mmol, 3.0 equiv.) grinded in a mortar and pestle, PdCl₂(PPh₃)₂ (579 mg, 0.8 mmol, 0.2 equiv.) and CuI (78 mg, 0.4 mmol, 0.1 equiv.) were added to a Schlenk flask under a nitrogen atmosphere and flushed afterwards. Then, **G1-1** (520 mg, 4.1 mmol, 1 equiv.) was transferred to the Schlenk flask dissolved in anhydrous THF (16 mL, 4.0 M⁻¹). The whole mix was sonicated before adding the triethylamine (16 mL, 4.0 M⁻¹) and leaving the

pitch-black solution stirring at 60°C overnight. After completion, the reaction was quenched with water (40 mL, 9.0 M⁻¹) and after 20 min the inactive catalysts were removed via suction filtration with celite (1 cm packing). The solids retained were rinsed with a mix of ethylacetate and THF (50 mL + 15 mL), and the THF was evaporated under reduced pressure. Extractions with mixtures of ethylacetate and ammonia chloride (3 x 30 mL + 15 mL) were performed, and the organic extracts were dried with MgSO₄ to be evaporated under reduced pressure resulting in a pale yellow solid. The solid obtained was purified through DCVC progressing from 0% to 100% in increases of 25% ethylacetate/chloroform, followed by 0% to 5% in increases of 1% methanol/ethylacetate to yield 610 mg **G1** (52%).

¹H NMR (500 MHz, CDCl₃) δ (ppm) 8.65 (m, 4H), 7.58 (s, 4H), 7.41 (m, 4H). ¹³C NMR (126 MHz, CDCl₃) δ (ppm) 149.80, 131.85, 130.94, 125.42, 122.79, 93.08, 88.73.

Aspect = Yellow; R_f value (ethylacetate) = 0.34; mp = 184-189 °C

2,5-dibromobenzene-1,4-diamine (**G2-1**)



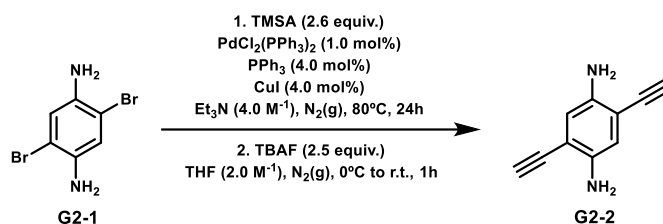
Scheme 7. Synthesis of 2,5-dibromobenzene-1,4-diamine through bromination.

p-phenyldiamine (1.000 g, 9.25 mmol, 1 equiv.) was dissolved in glacial acetic acid (20 mL, 2.2 M⁻¹) in a round bottom flask before adding a solution of Br₂ (0.94 mL, 18.5 mmol, 2.0 equiv.) in glacial acetic acid (10 mL, 1.0 M⁻¹) at a drop frequency of 130 bpms with the assistance of a pressure equalizing addition funnel. The black solution obtained was heated up to 80°C and left stirring for 3.5 hours. The resulting grey solution was cooled down for a few minutes in an ice water bath and then filtered via suction filtering. The acidic aqueous phase was discarded, and the solid was cleansed thoroughly with water. The aqueous purple solution was then basified to pH ≥ 7 using a 2.0 M NaOH stock solution and the precipitate was collected with suction filtering. The black precipitate obtained was dried overnight under vacuum in the suction filter. The next day, the crystals were dissolved in acetone and transferred in a round bottom flask to evaporate under reduced pressure. After purifying through DCVC progressing from 5% to 50% in increases of 5% ethylacetate/heptane, 616 mg pure **G2-1** was obtained (25%).

¹H NMR (500 MHz, DMSO) δ (ppm) 6.92 (s, 2H), 4.64 (s, 4H). ¹³C NMR (126 MHz, DMSO) δ (ppm) 137.88, 118.94, 108.69.

Aspect = Coffee; *R*_f value (DCM) = 0.38; mp = 178-182 °C

2,5-diethynylbenzene-1,4-diamine (G2-2)



Scheme 8. Synthesis of 2,5-diethynylbenzene-1,4-diamine via Sonogashira reaction and deprotection with TBAF.

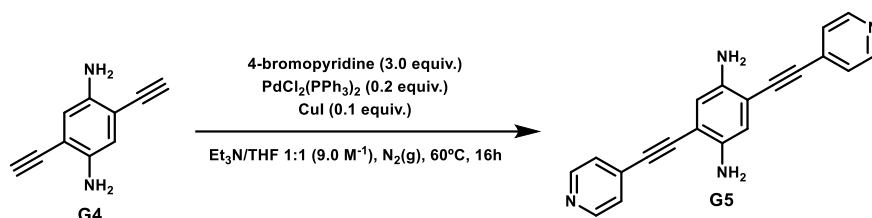
PdCl₂(PPh₃)₂ (103 mg, 0.1 mmol, 1.0 mol%), CuI (112 mg, 0.6 mmol, 4.0 mol%) and triphenylphosphine (155 mg, 0.6 mmol, 4.0 mol%) were added to a Schlenk flask under a nitrogen atmosphere. The flask was flushed and impure **G2-1** (3.895 g, 14.6 mmol, 1 equiv.) was added solved in triethylamine (60 mL, 4.0 M⁻¹). The temperature was increased to 80°C prior to adding TMSA (5.3 mL, 38 mmol, 2.6 equiv.) dropwise while vigorously stirring. The drops retained their shape for a few seconds before homogenizing in the mixture. After 24 hours, the reacting mixture was quenched with water (70 mL, 4.6 M⁻¹), and left resting for 20 min. The catalysts were extracted via suction filtration through celite (1 cm packing) and washed with DCM (50 mL). The organic phase was extracted with DCM (3 x 20 mL) and dried with MgSO₄. The extracts were passed through neutral/basic alumina via suction filtration, and the solvent was completely removed under reduced pressure to obtain 4.303 g of the protected intermediate, 2,5-bis((trimethylsilyl)ethynyl)benzene-1,4-diamine.

The 2,5-bis((trimethylsilyl)ethynyl)benzene-1,4-diamine (4.303 g, 14.3 mmol, 1 equiv.) was added to a round bottom flask and dissolved in THF (30 mL, 2.0 M⁻¹). The flask was then capped with a septum, nitrogenated and settled in an ice water bath. Once the solution was cooled down to 0°C, TBAF (36 mL, 36 mmol, 2.5 equiv.) was added slowly while mixing vigorously the solution. After completing the addition, the flask was removed from the ice water bath and left stirring for 1h. The reacting mixture was quenched with water and 20 min later the THF was removed under reduced pressure. An extraction with DCM (3 x 40 mL) and brine (30 mL) was performed, and the resulting organic extracts were dried with MgSO₄, and the solvent was removed under reduced pressure. The orange oil obtained was purified through DCVC progressing from 92.5% to 100% in increases of 2.5% chloroform/heptane, followed by 0% to 5% in increases of 1% ethylacetate/chloroform to yield 1,210 g **G2-2** (53%).

¹H NMR (500 MHz, DMSO) δ (ppm) 6.64 (s, 2H), 4.64 (s, 4H, broad), 4.37 (s, 2H). **¹³C NMR** (126 MHz, DMSO) δ (ppm) 140.97, 117.51, 108.58, 86.25, 86.23, 81.36.

Aspect = Red; *R_f* value (1:1 ethylacetate/heptane) = 0.5; *mp* = undetermined

2,5-bis(pyridin-4-ylethynyl)benzene-1,4-diamine (G2-3)



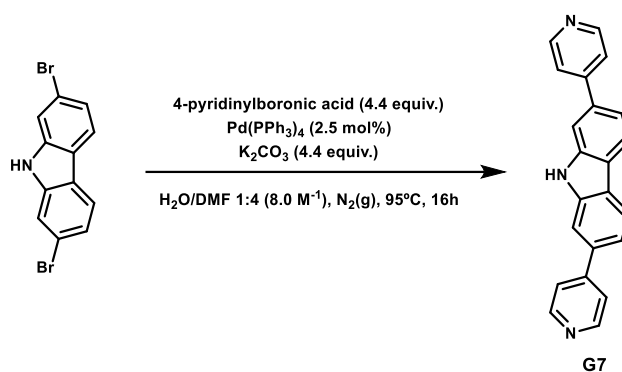
Scheme 9. Synthesis of 2,5-bis(pyridin-4-ylethynyl)benzene-1,4-diamine via Sonogashira reaction.

4-bromopyridine (650 mg, 3.3 mmol, 3.0 equiv.) grinded in a mortar and pestle, PdCl₂(PPh₃)₂ (157 mg, 0.2 mmol, 0.2 equiv.) and CuI (21 mg, 0.1 mmol, 0.1 equiv.) were added to a Schlenk flask under a nitrogen atmosphere and flushed afterwards. Then, **G2-2** (174 mg, 1.1 mmol, 1 equiv.) was transferred to the Schlenk flask dissolved in anhydrous THF (5 mL, 4.5 M⁻¹). The whole mix was sonicated before adding the triethylamine (5 mL, 4.5 M⁻¹) and leaving the pitch-black solution stirring at 60°C overnight. After completion, the reacting mixture was quenched with water (12 mL, 10.5 M⁻¹) and left resting for 20 min. The catalysts were removed via suction filtration through celite (1 cm packing) and washed with THF and MeOH (50 mL + 50 mL). The solvents were removed by evaporating under pressure before extracting with a mixture of ethylacetate and ammonium chloride (3 x 30 mL + 10 mL). After drying with MgSO₄, the solvents were evaporated under reduced pressure and the deep brown solid was purified through DCVC progressing from 0% to 100% in increases of 50% ethylacetate/chloroform, followed by 0% to 7% in increases of 1% methanol/ethylacetate to yield 725 mg **G2-3** (56%).

¹H NMR (500 MHz, DMSO) δ (ppm) 8.61 (m, 4H), 7.58 (m, 4H), 6.78 (s, 2H), 4.99 (s, 4H). **¹³C NMR** (126 MHz, DMSO) δ (ppm) 150.18, 141.39, 130.94, 125.62, 117.43, 108.81, 92.82, 91.90.

Aspect = Deep brown; *R_f* value (5% methanol/ethylacetate) = 0.21; *mp* = undetermined

2,7-di(pyridin-4-yl)-9H-carbazole (G3)



Scheme 10. Synthesis of 2,7-di(pyridin-4-yl)-9H-carbazole via Suzuki reaction.

2,7-Dibromo-9H-carbazole (1.004 mg, 3.1 mmol, 1 equiv.), 4-pyridinylboronic acid (1.660 g, 13.5 mmol, 4.4 equiv.), K₂CO₃ (1.864 g, 13.5 mmol, 4.4 equiv.) and Pd(PPh₃)₄ (92.4 mg, 0.08 mmol) were added to a Schlenk flask under nitrogen atmosphere, and flushed. A mixture of degassed 1:4 water and DMF (25 mL, 8.0 M⁻¹) was added to the flask and the temperature was increased to 95°C. After stirring at this temperature overnight, the mixture was allowed to cool down and water (30 mL, 10 M⁻¹) was added to quench the reaction. The mixture was then extracted with DCM (3 x 50 mL) and cleansed with brine (100 mL). After drying the with MgSO₄, the pale-yellow solid obtained is purified through DCVC progressing from 0% to 100% in increases of 50% ethylacetate/chloroform, followed by 5% to 30% in increases of 5% methanol/ethylacetate to yield 123 mg of **unknown** substance. *It is brought to readers attention that the data exposed below corresponds to the only isolated compound, which is the **unknown** substance, and not the actual ligand. This is done to facilitate the discussion of results in the corresponding section of this report: results and discussion pàg. 25-26.*

¹H NMR (500 MHz, CHDCl₃) δ (ppm) 8.77 (d, 2H), 7.56 (m, 2H). ¹³C NMR (126 MHz, CHDCl₃) δ (ppm) 150.63, 145.46, 121.34.

Aspect = White; R_f value (ethylacetate) = 0.13; mp = 112 – 115°C

8 References

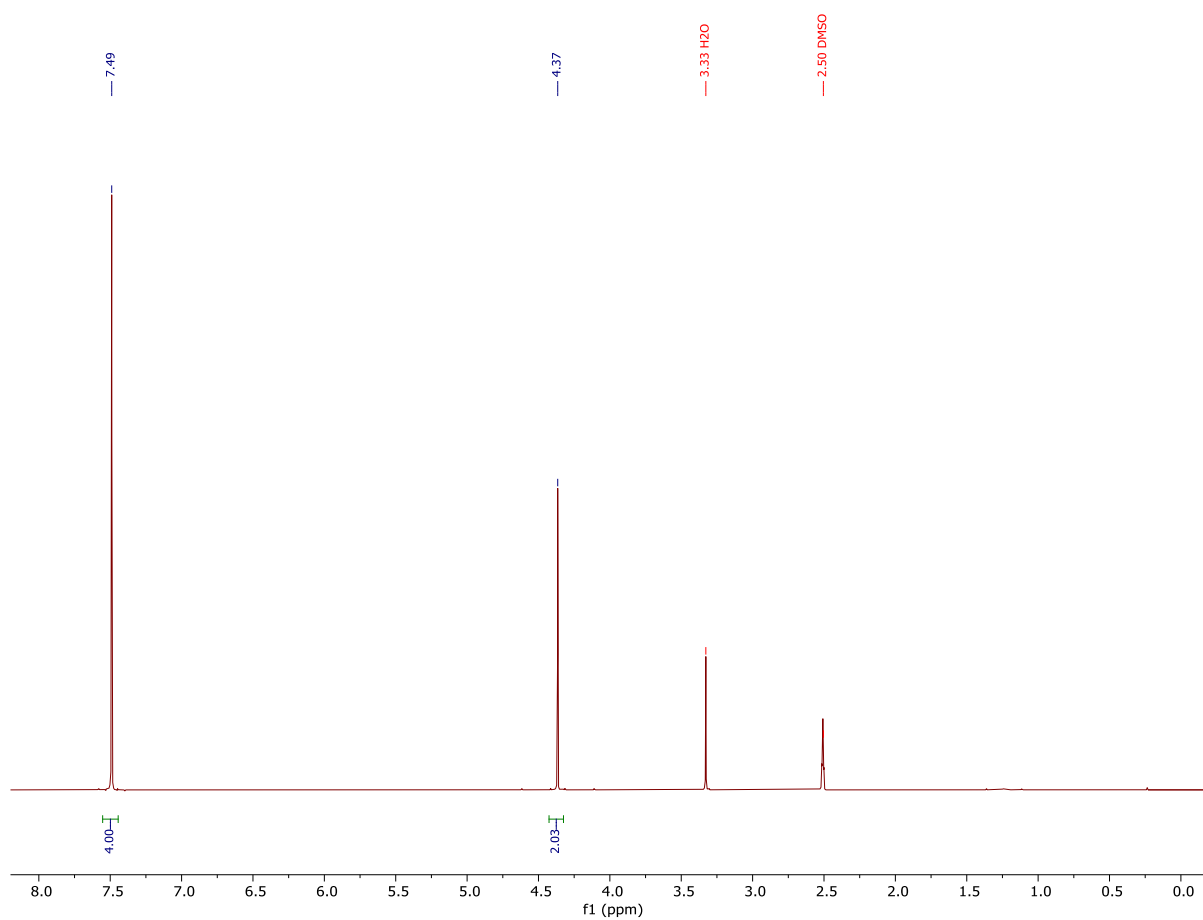
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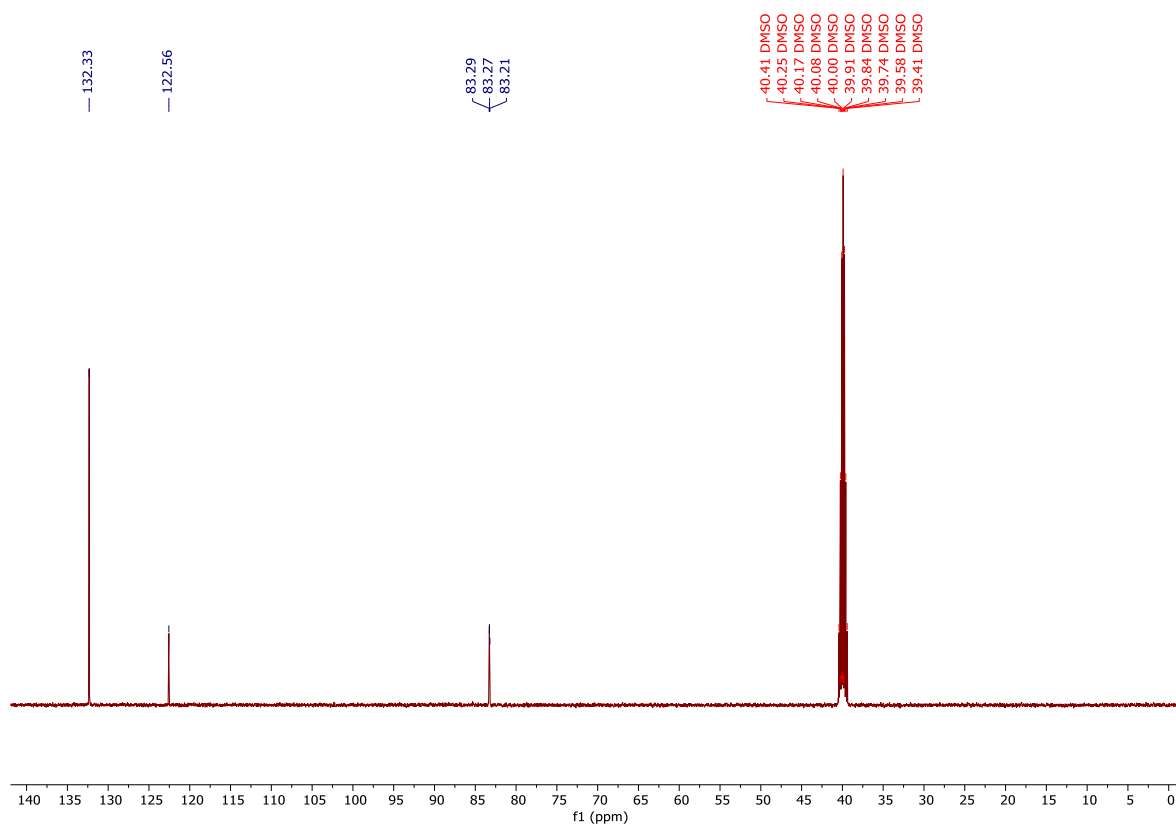
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Appendix A

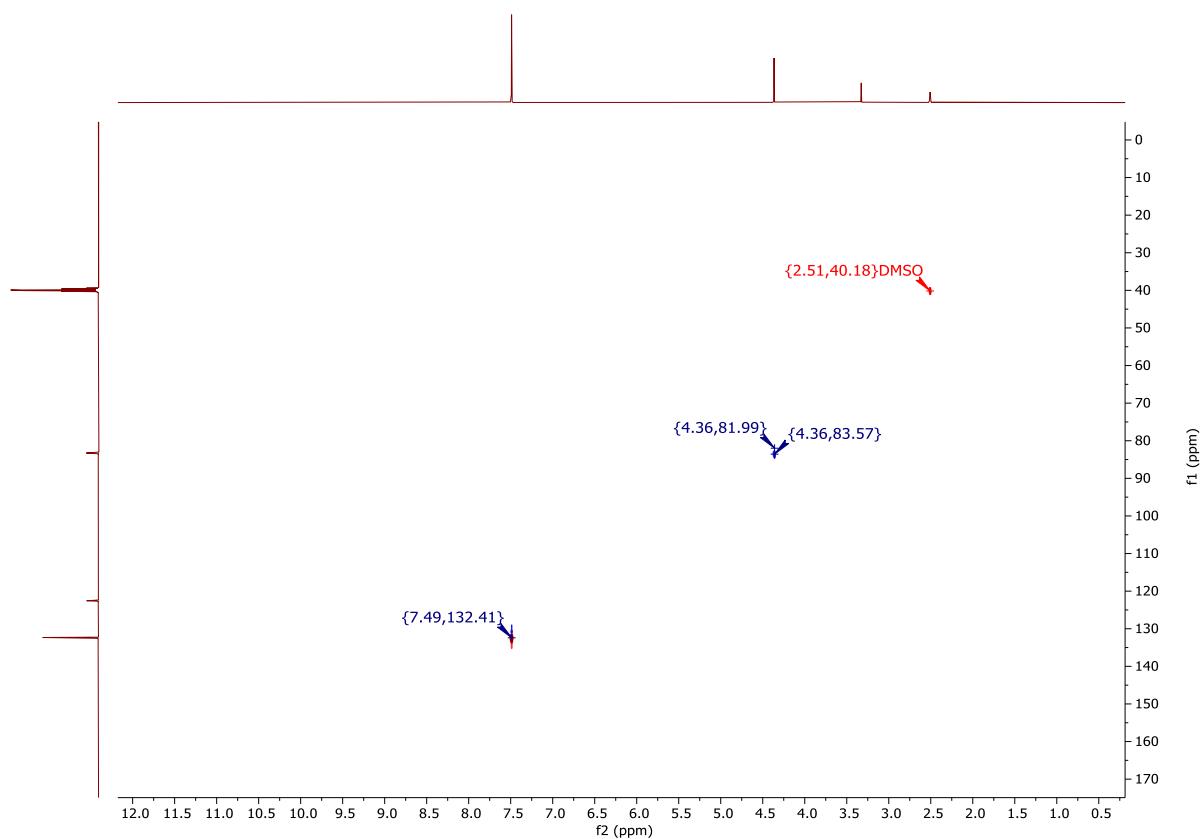
NMR Spectra



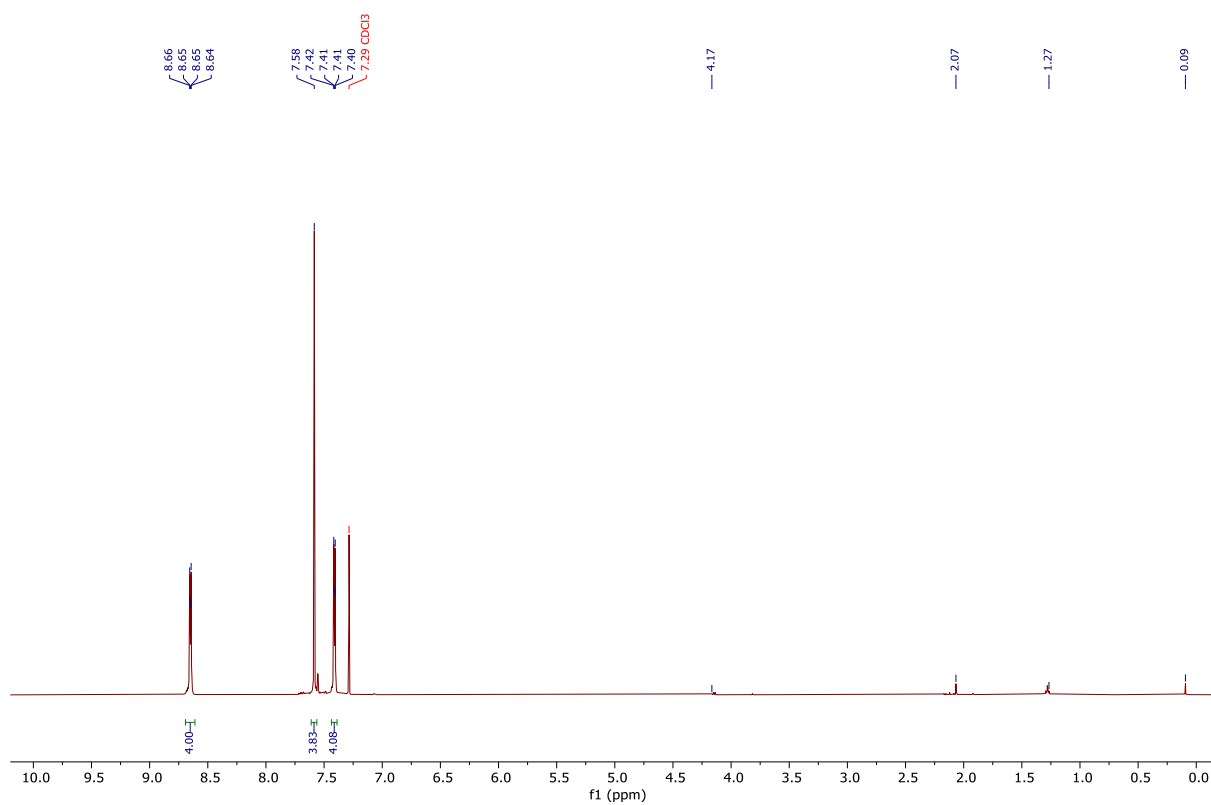
Spectra 1. *¹H*NMR spectrum of 1,4-diethynylbenzene (G1-1) in DMSO.



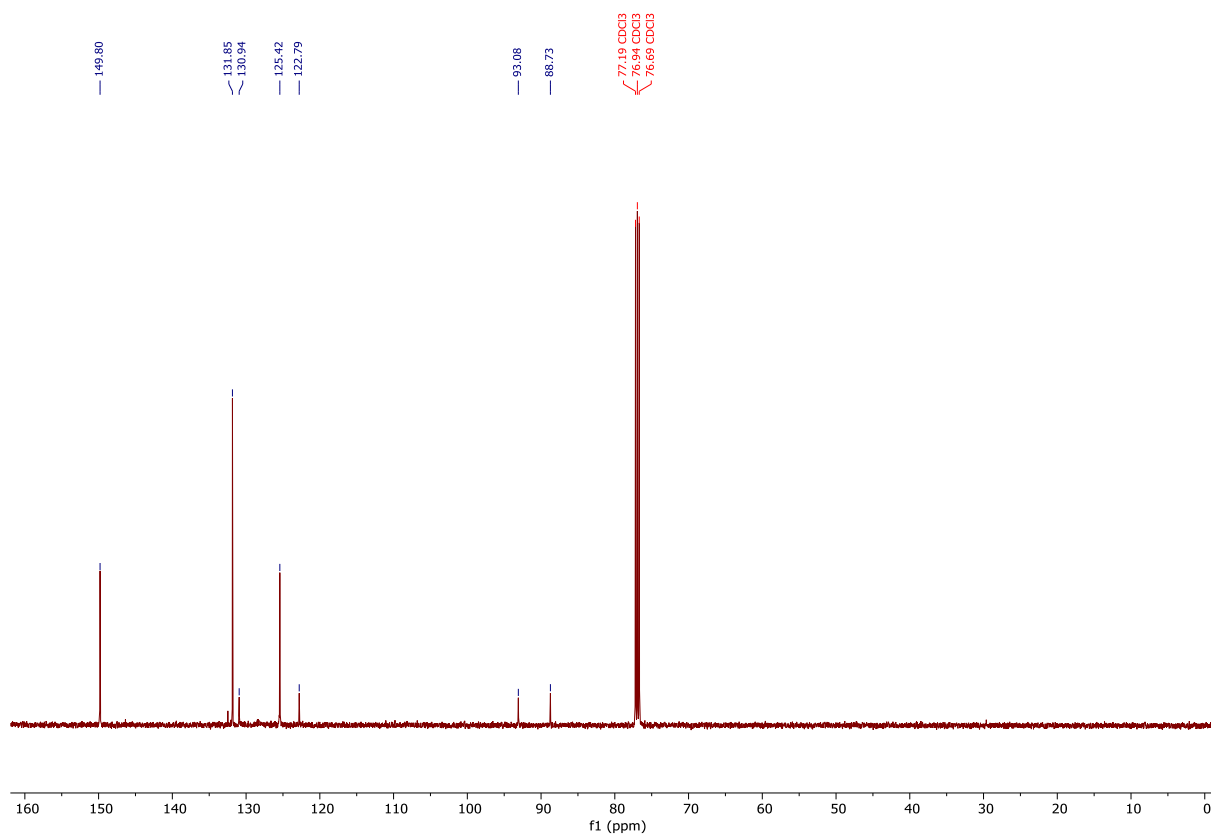
Spectra 2. *¹³C*NMR spectrum of 1,4-diethynylbenzene (G1-1) in DMSO.



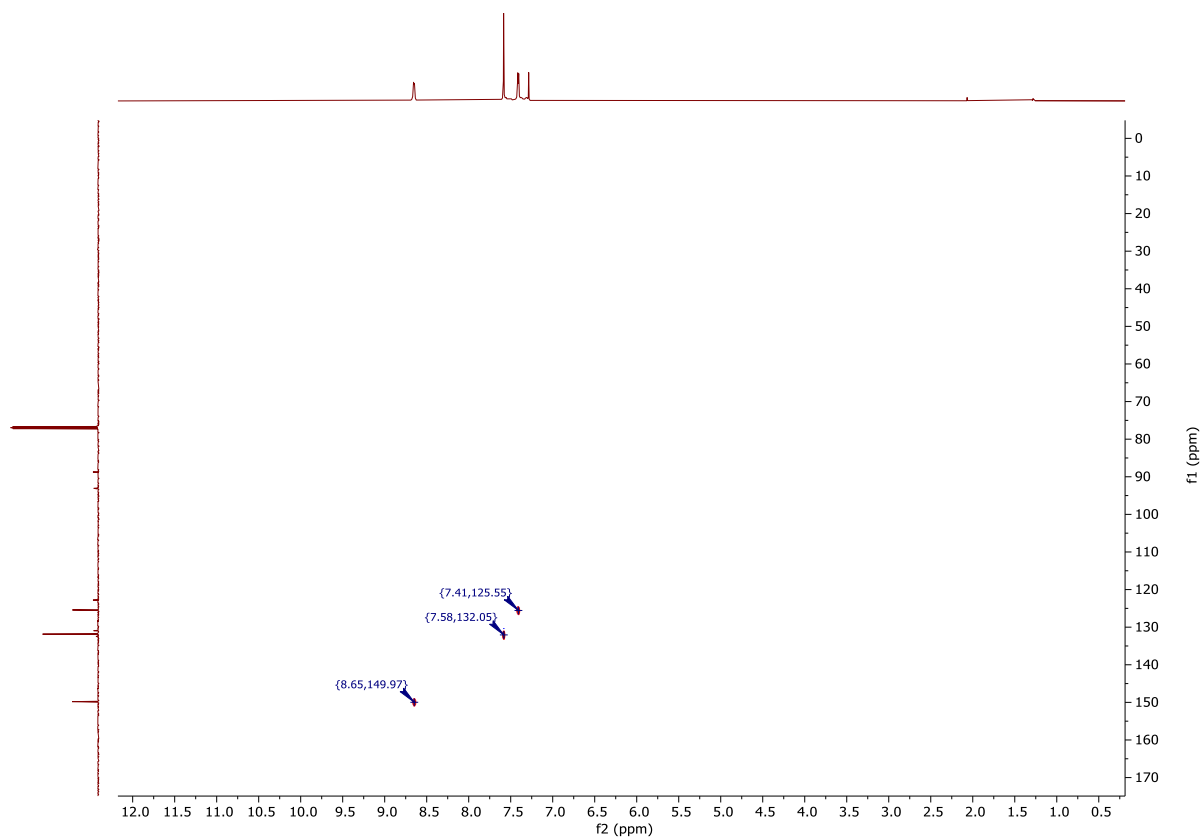
Spectra 3. HSQC spectrum of 1,4-diethynylbenzene (G1-1) in DMSO.



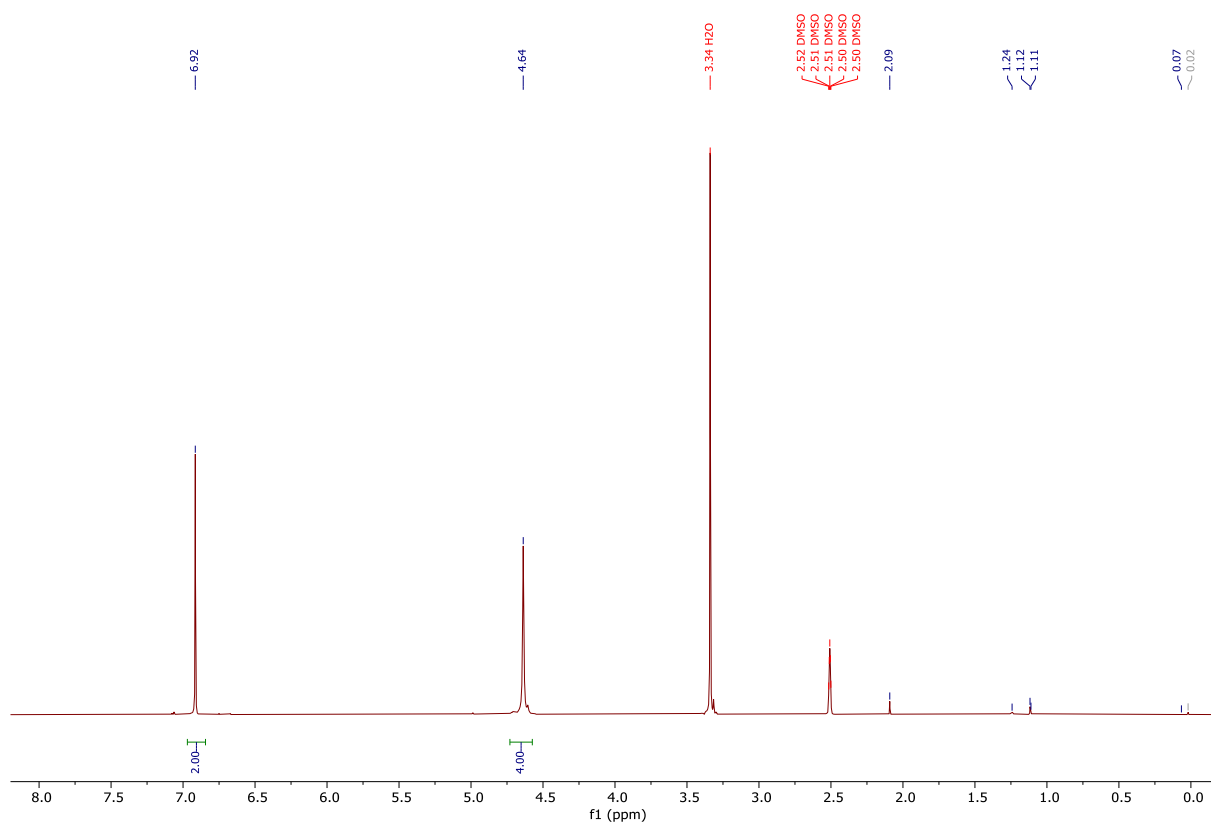
Spectra 4. HNMR spectrum of 1,4-bis(pyridin-4-ylethynyl)benzene (G1) in chloroform.



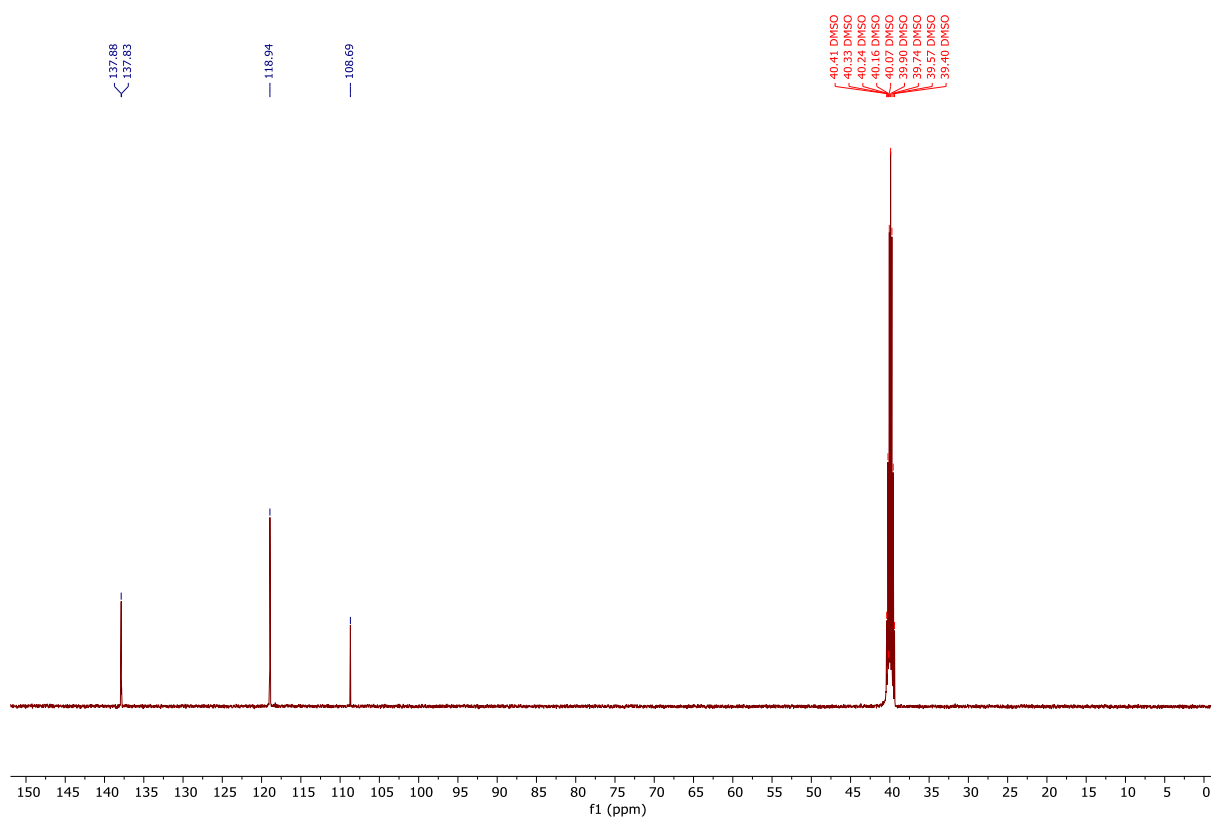
Spectra 5. *CNMR spectrum of 1,4-bis(pyridin-4-ylethynyl)benzene (G1) in chloroform.*



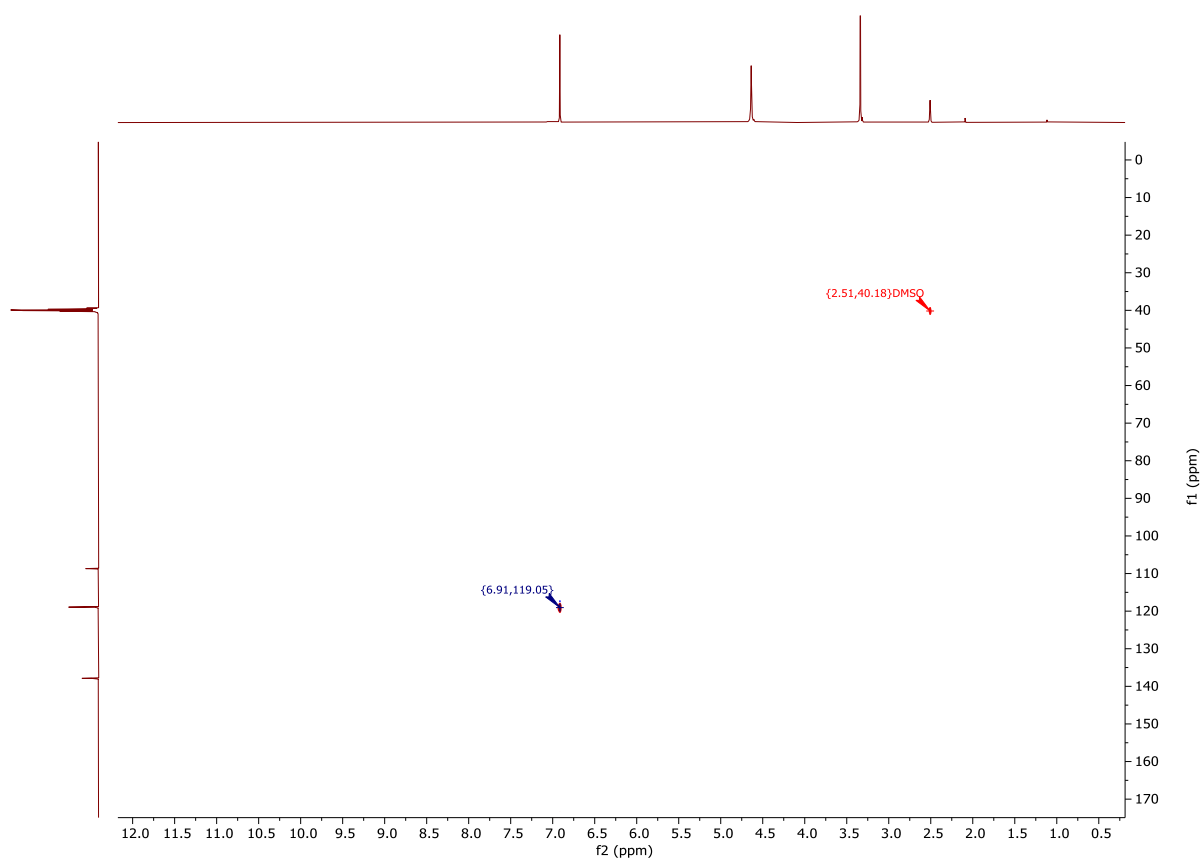
Spectra 6. *HSQC spectrum of 1,4-bis(pyridin-4-ylethynyl)benzene (G1) in chloroform.*



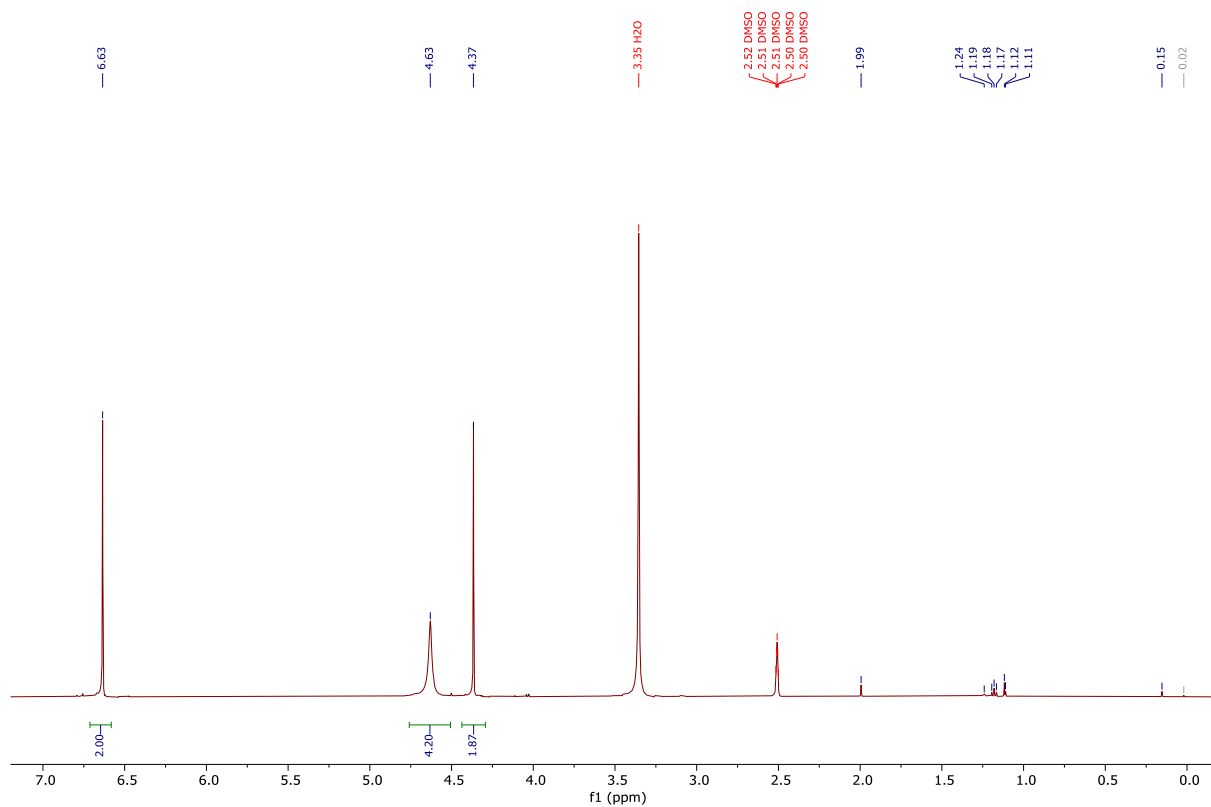
Spectra 7. ¹H NMR spectrum of 2,5-dibromobenzene-1,4-diamine (G2-1) in DMSO.



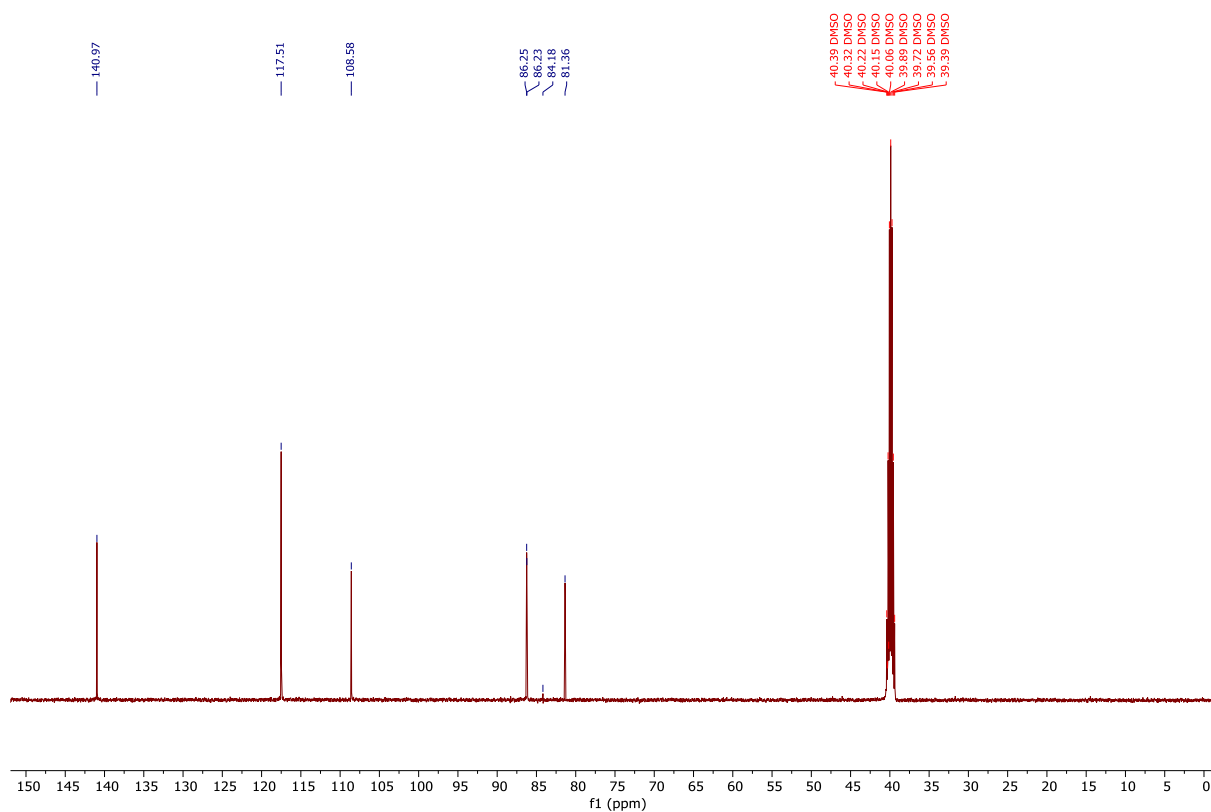
Spectra 8. ¹³C NMR spectrum of 2,5-dibromobenzene-1,4-diamine (G2-1) in DMSO.



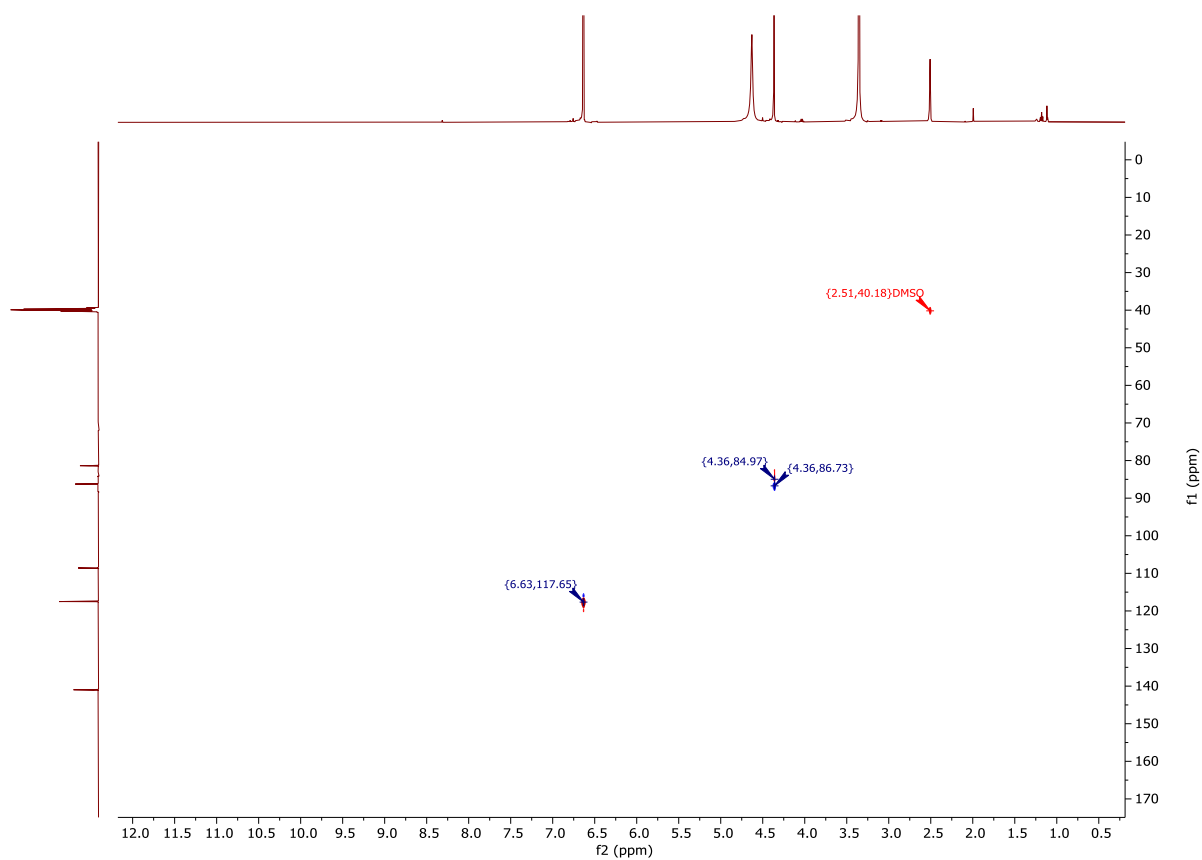
Spectra 9. HSQC spectrum of 2,5-dibromobenzene-1,4-diamine (G2-1) in DMSO.



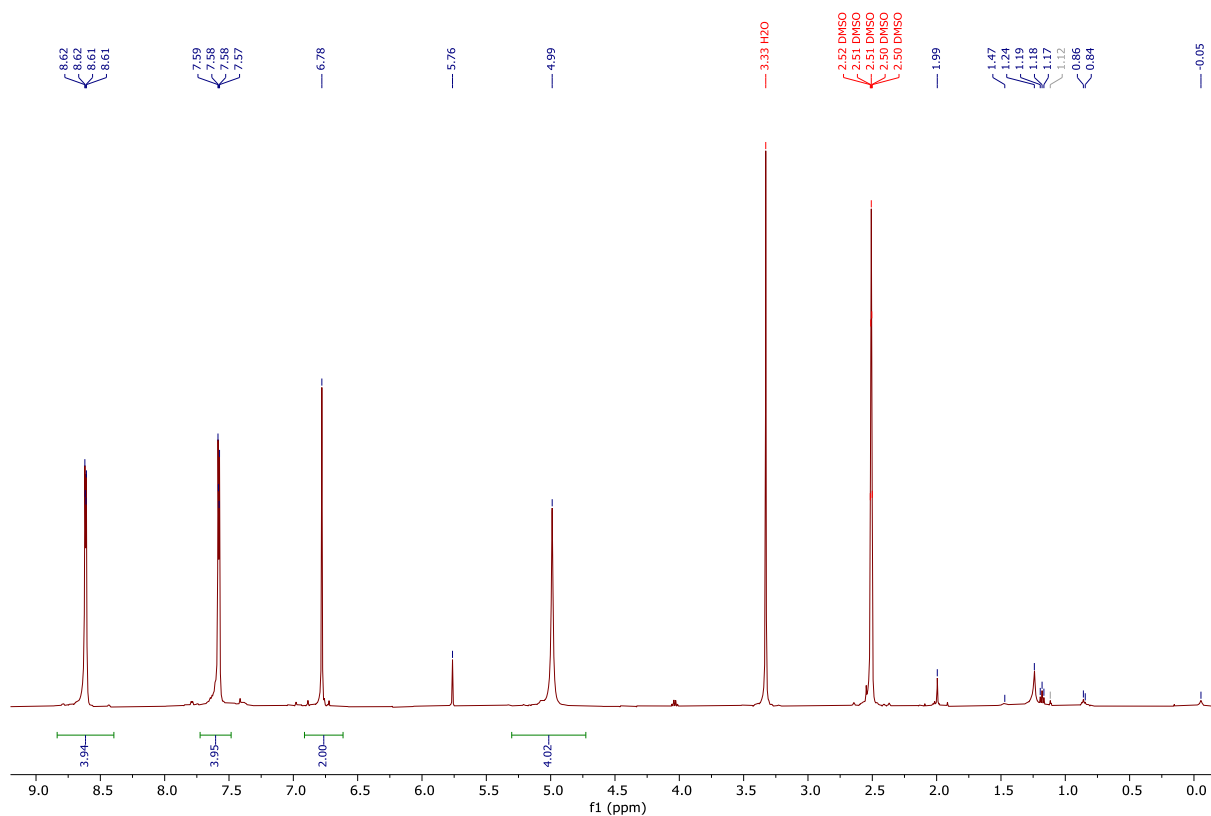
Spectra 10. HNMR spectrum of 2,5-diethynylbenzene-1,4-diamine (G2-2) in DMSO.



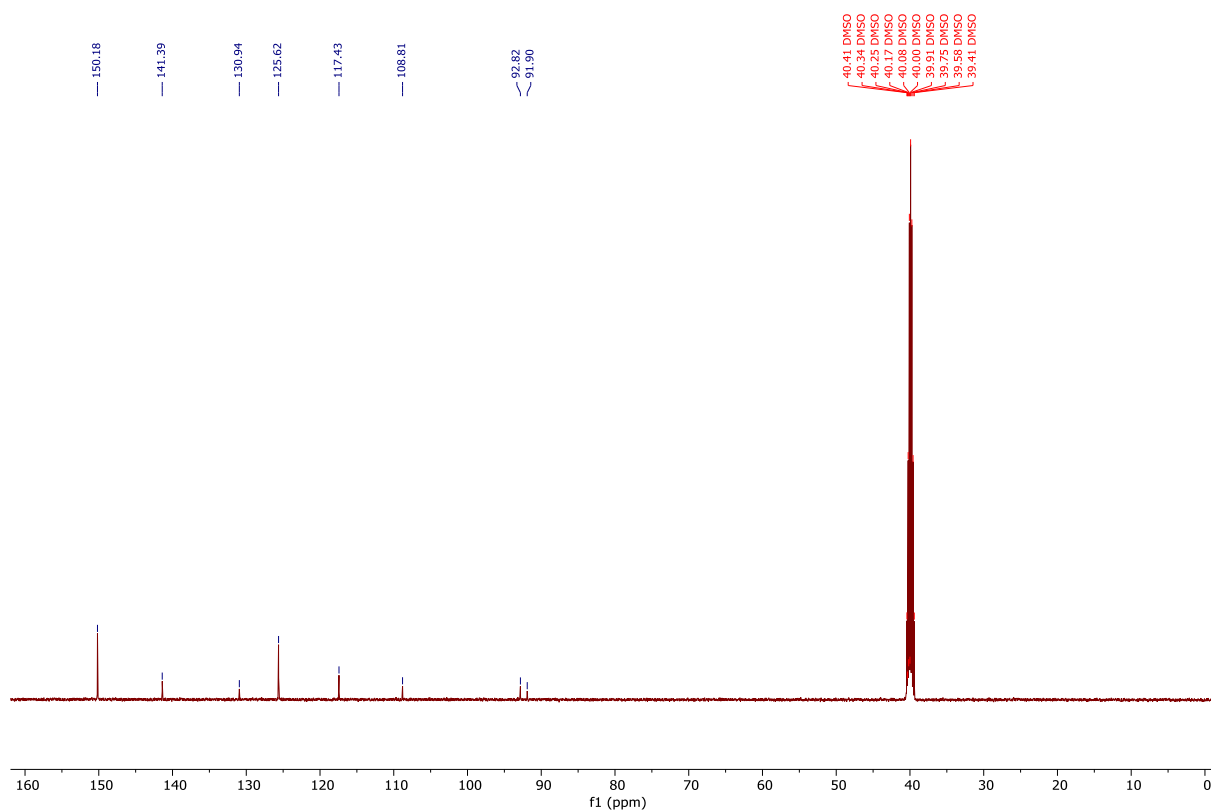
Spectra 11. CNMR spectrum of 2,5-diethynylbenzene-1,4-diamine (G2-2) in DMSO.



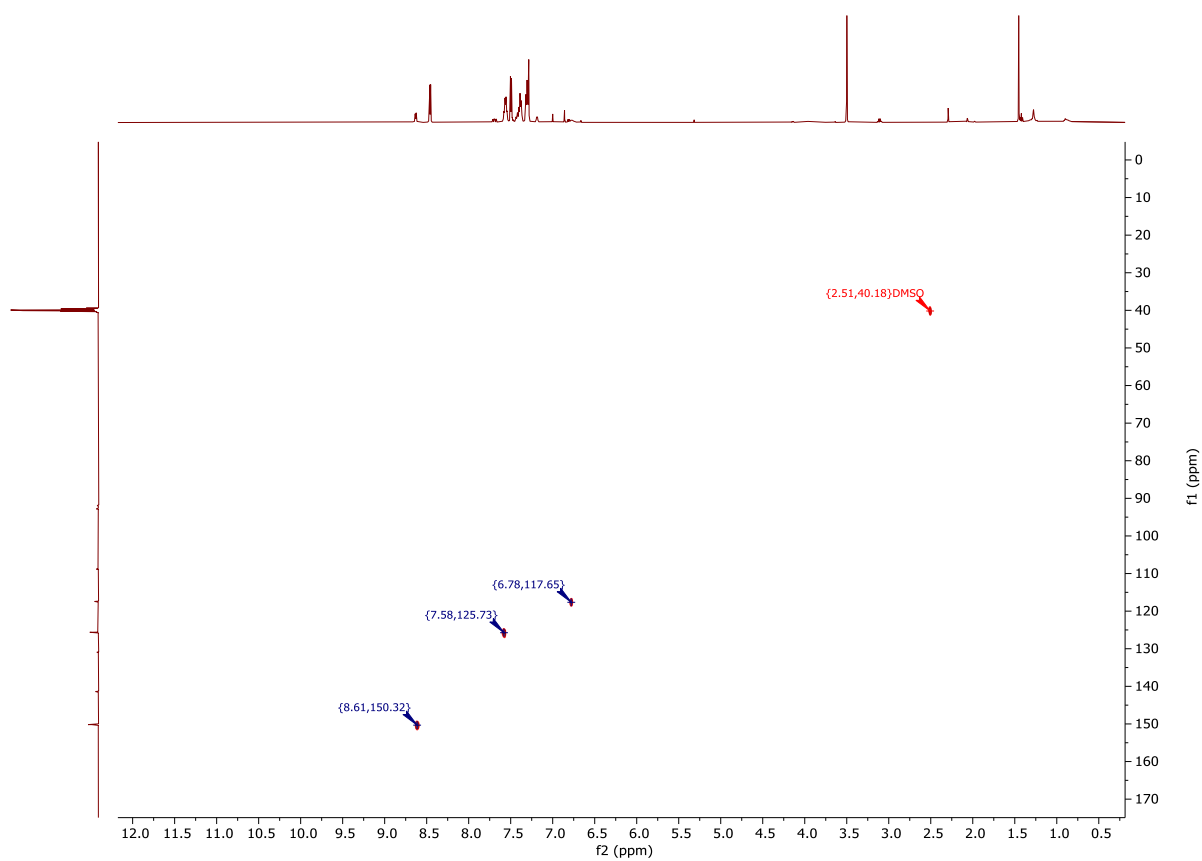
Spectra 12. HSQC spectrum of 2,5-diethynylbenzene-1,4-diamine (G2-2) in DMSO.



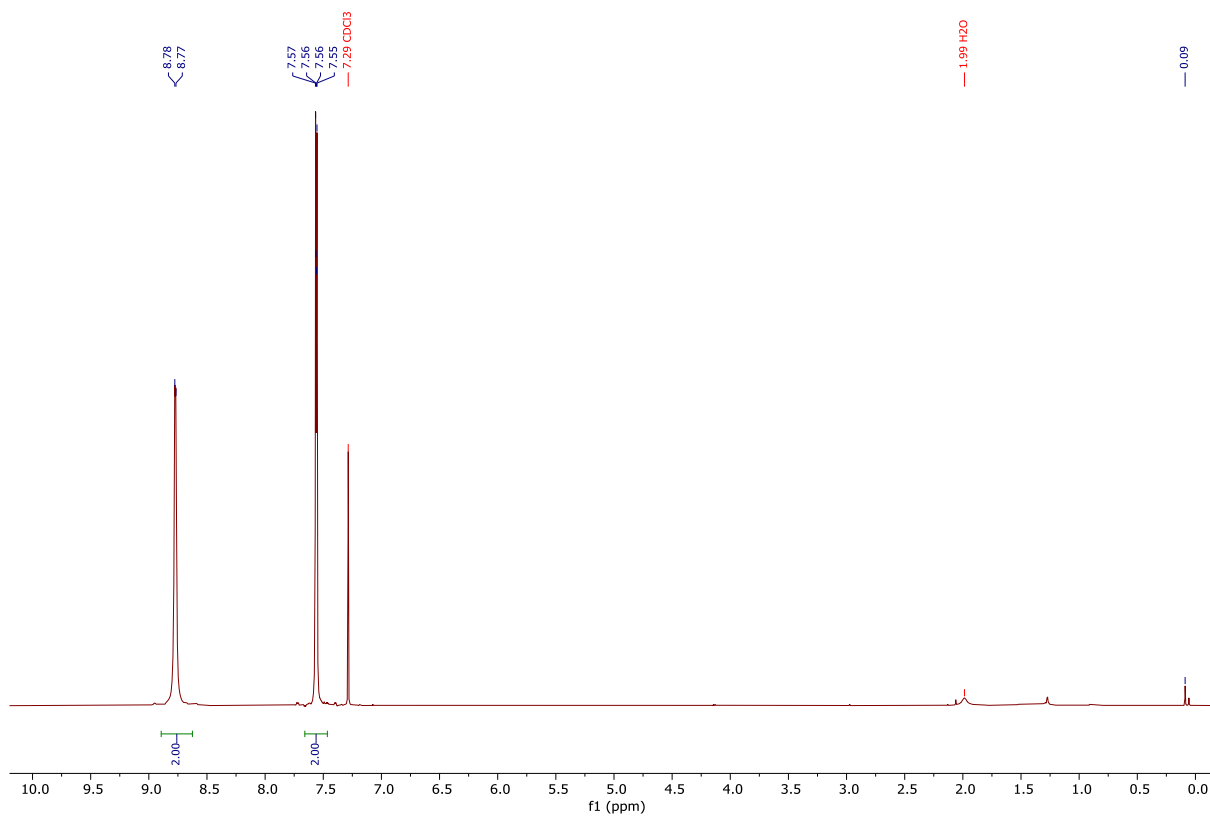
Spectra 13. *¹H*NMR spectrum of 2,5-bis(pyridin-4-ylethynyl)benzene-1,4-diamine (G2-3)



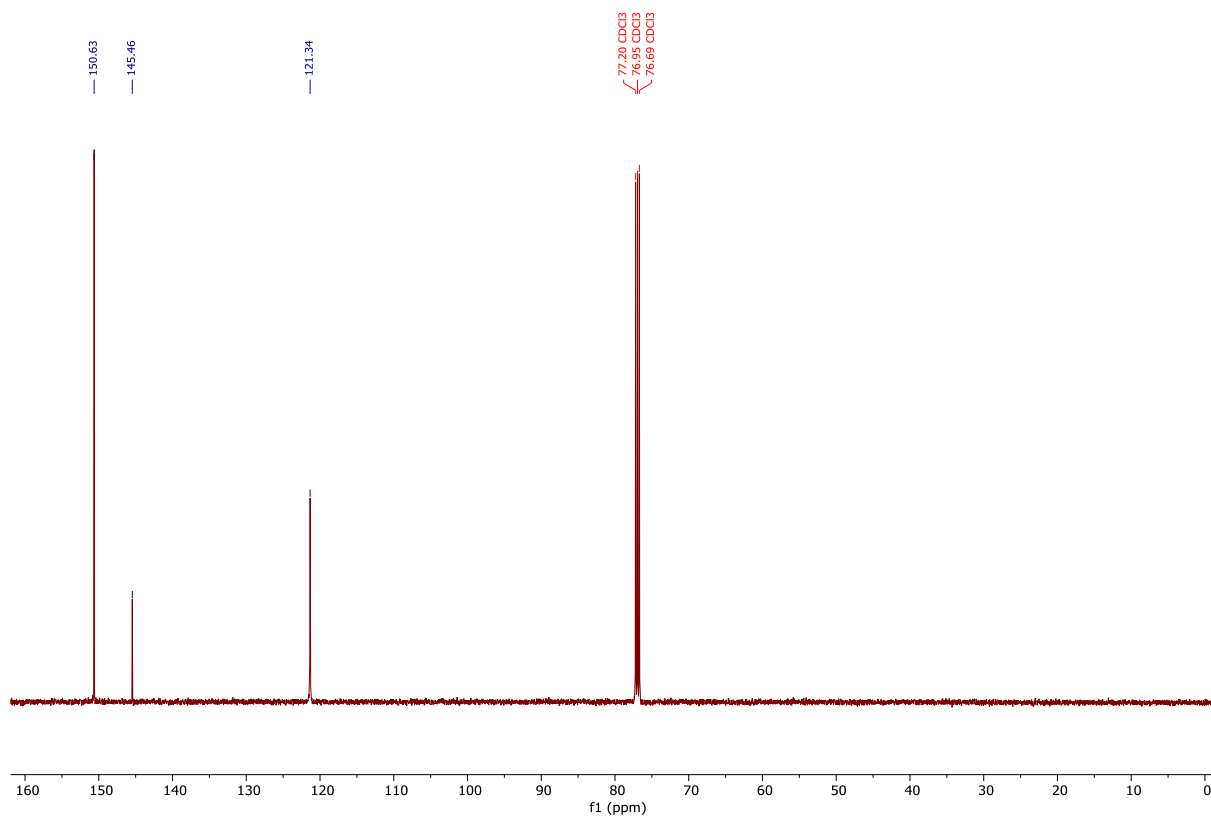
Spectra 14. *¹³C*NMR spectrum of 2,5-bis(pyridin-4-ylethynyl)benzene-1,4-diamine (G2-3)



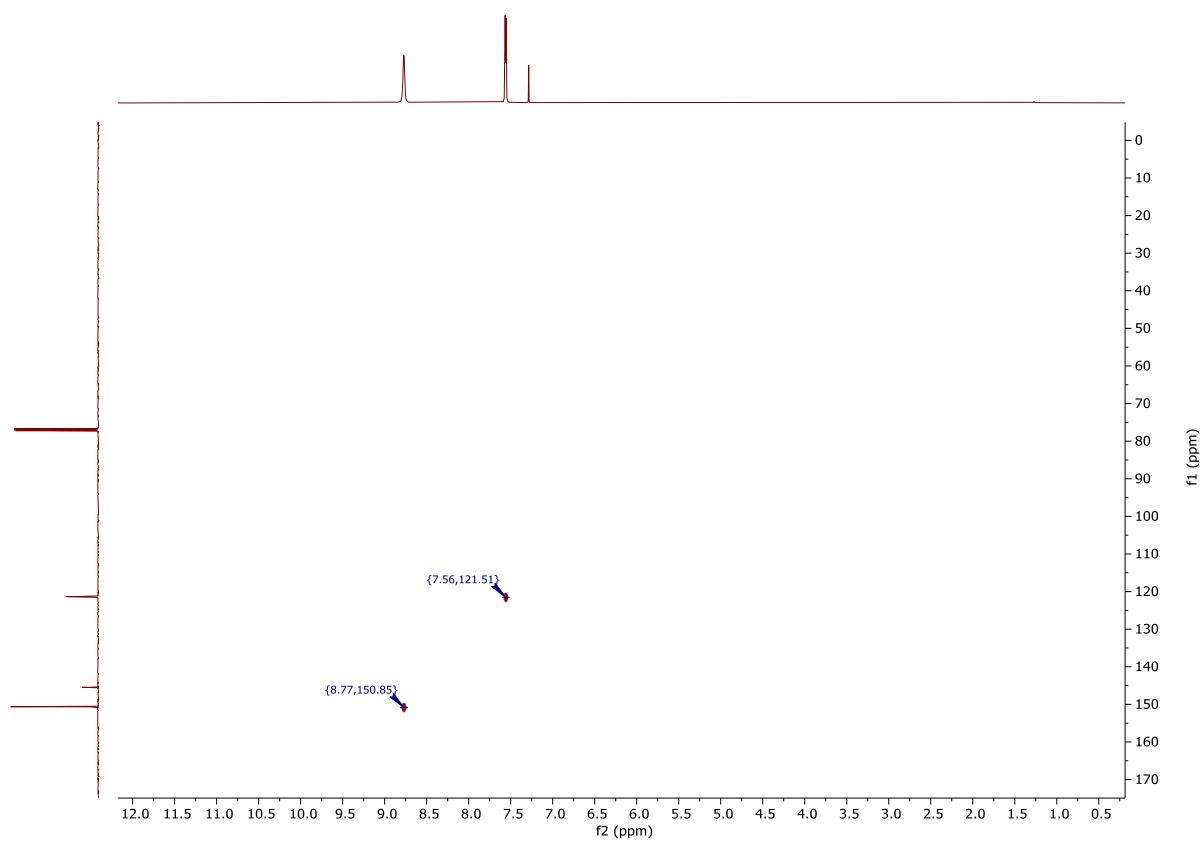
Spectra 15. HSQC spectrum of 2,5-bis(pyridin-4-ylethynyl)benzene-1,4-diamine (G2-3)



Spectra 16. HNMR spectrum of the impurity found in 2,7-di(pyridin-4-yl)-9H-carbazole synthesis in chloroform.



Spectra 17. CNMR spectrum of the impurity found in 2,7-di(pyridin-4-yl)-9H-carbazole synthesis in chloroform.



Spectra 18. HSQC spectrum of the impurity found in 2,7-di(pyridin-4-yl)-9H-carbazole synthesis in chloroform.