



New bonding motifs towards lanthanide-based metal-organic cages for PARASHIFT imaging

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Abstract

Magnetic resonance imaging (MRI) is a ubiquitous diagnostic technique in medicine that can produce images of most biological tissues in the body. Despite being such a powerful tool, MRI still sees challenges when it comes to background signals caused by the large amounts of fat and water in biological tissues. Paramagnetic shift (PARASHIFT) MRI utilises the paramagnetic nature of lanthanide ions which have many unpaired electrons, that shift neighbouring hydrogen environments on an MRI scan up or down chemical shift. To maximise the intensity of the shifted peaks, *tert*-butyl groups can be used, allowing for a clearer reading of your desired signal. Metal-organic cages are an interesting choice for PARASHIFT agents, as they are highly symmetrical. By leveraging the high order of symmetry, we can increase the integration of the *tert*-butyl group from 9 on one ligand to 108 in a metal organic cage. They also have the inherent voids that can hold other valuable molecules such as drugs, allowing for drug delivery to be monitored. In this work, we develop new bonding motifs that incorporate *tert*-butyl reporter group within triazole motifs to have a signal with high peak intensity to experience paramagnetic shifts, allowing for a range of cage linkers to be added through the use of alkyne-azine cycloadditions.

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Introduction

Metal Organic Cages

Concept

Metal-organic cages (MOCs) are discrete, three-dimensional (3D) supramolecular assemblies with a well-defined internal cavities allowing for host-guest chemistry.¹ MOCs are fundamentally built on the principles of coordination chemistry, where lone pair donors, called ligands, form a dative-covalent bond to a central metal ion, forming a coordination complex.² In the case of MOCs, there are multiple metal ions in its structure and often ligands will coordinate with two or more metal ions to form a cage structure.³ The amount of dative-covalent bonds a metal ion can have is called its coordination number, whereas the amount of coordinate bonds a ligand can make is known as the denticity of the ligand. For instance, a ligand that forms one bond to a metal ion is called monodentate, and two bidentate, and so on, typically denoted by the symbol κ .⁴ A ligand can be further categorised based on how many metal ions it can bond to at once, known as ligand bridging,⁵ for example, a ditopic ligand will datively bond to two metal centres, while a tritopic ligand will bond to three.⁶ The angle between two bridging ligands connected to a the same metal ion is called its coordination angle, α , and plays a role in determining the shape MOCs.⁷ Like mononuclear complexes, MOCs can form with mixed-ligand composition, giving rise to heteroleptic cages,⁸ while homoleptic cages feature one species of ligand.⁹

MOCs are similar to metal-organic frameworks (MOFs) as they are built from the same fundamental principles of coordination chemistry, forming large structures datively bonded structures, but unlike MOFs, cages are discrete, having a specific combination of ligands and metals within their structure.¹⁰ Cages take on specific topologies that allow them to maintain their cavities in solution and are often described geometrically by considering the metal ions as vectors of a 3D shape, often denoted in the format ' $(M_aL_b)^c$ ', where M is the metal ion, L is the ligand, a and b are integers, and c is the charge of the complex.¹¹

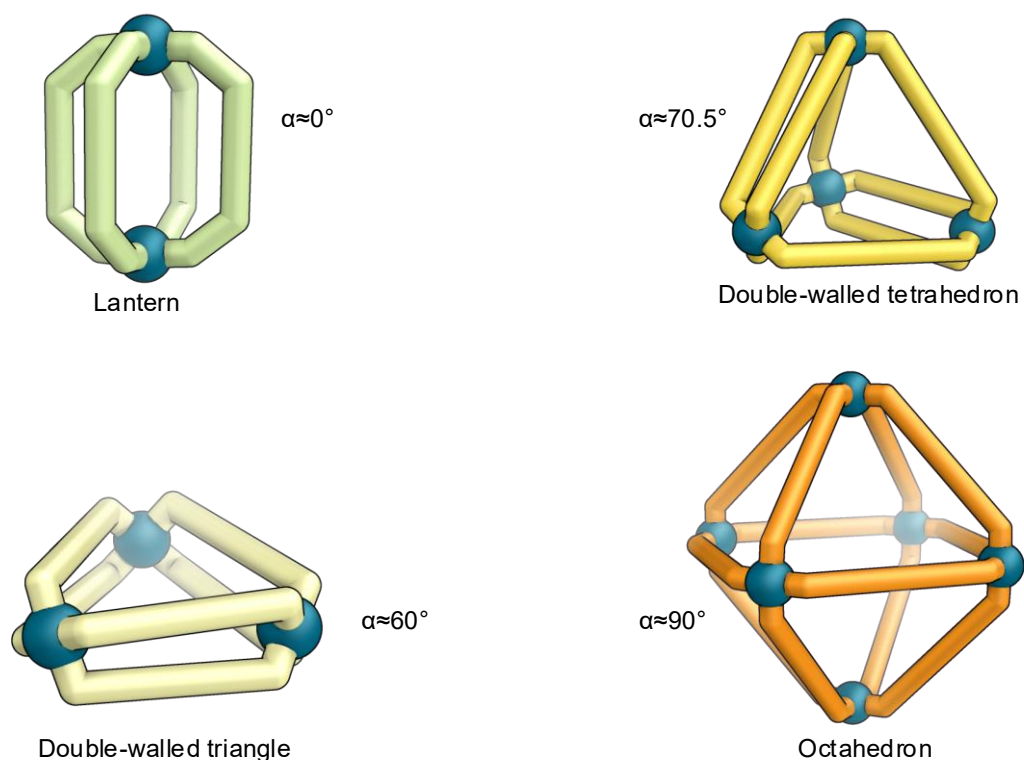


Figure 1. 3D model representation of palladium metal-organic cage geometries and their coordination angles, α , between two ligands (L) bonding to a metal centre (M). Top left: M_2L_4 lantern, top right: M_4L_8 double-walled tetrahedron, bottom left: M_3L_6 double-walled triangle, bottom right: M_6L_{12} octahedron.

The coordination number of a metal ion, as well as the coordination angle of its bonded ligands play a significant role in the geometries we see in MOCs. For instance, considering a metal that is four coordinate and prefers square planar geometry, such as platinum or palladium (Figure 1), if a ditopic ligand binds to it in solution, a range of structures can arise. M_2L_4 complexes, known as lanterns,¹² occur when the coordination angle near 0° ,⁷ while M_6L_{12} octahedrons occur with ligands having larger coordination angles $\sim 90^\circ$.¹³ There is also the possibility of 'double-walled' polyhedra as well, where two ligands occupy a edge of a shape. M_3L_6 double-walled triangles can occur when the coordination angle is $\sim 60^\circ$, while double-walled tetrahedra have coordination angles of $\sim 70.5^\circ$.¹⁴ Larger structures have been reported, such as a $M_{12}L_{24}$ cuboctahedron used to encapsulate a large cutinase-like enzyme.¹⁵

When a cage is characterized by its similarities to a polyhedron, it can either be considered edge-capped or face-capped. The distinction between the two is used to determine where the ligands lie if the structure were to be projected on the polyhedron that describes its shape. For example, when considering a tetrahedron, if the ligands are positioned as to align with the edges, it is edge-capped,¹⁶ and if it were to be aligned with the faces, it is face-capped.¹⁷

Similarly in octahedral complexes, isomerism can also play a role in determining the structure of octahedral and tetrahedral MOCs,¹⁸ specifically, *fac/mer* isomerism and Λ/Δ isomerism, which can appear even when all ligands are the same. While in octahedral complexes *fac/mer* and Λ/Δ isomerism are characterised considering the arrangement of the ligands in reference to the coordination centre, with MOCs, each metal centre must be considered in the structure to determine their individual character.^{19,20} A large part of what determines which isomer forms out the myriad of potential candidates are the properties of things that do not involve the metal ion or the binding site of the ligand, but are rather programmed into the system through other means; it has been shown that simply changing the dihedral angle of the organic components of a cage assembly is enough to affect which structures are possible,²¹ while the solvent effects can affect whether a cage is Λ/Δ isomer.²²

Applications

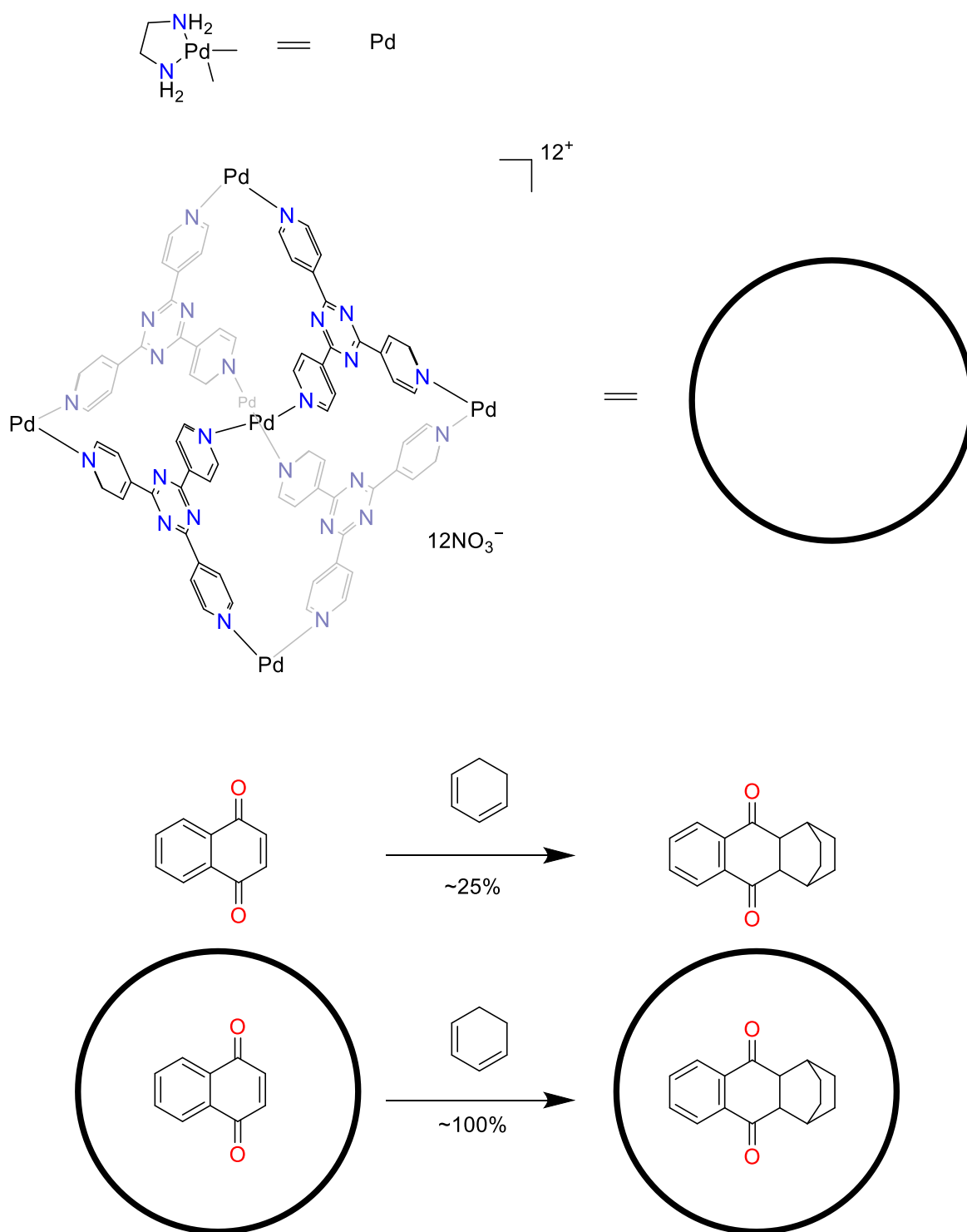
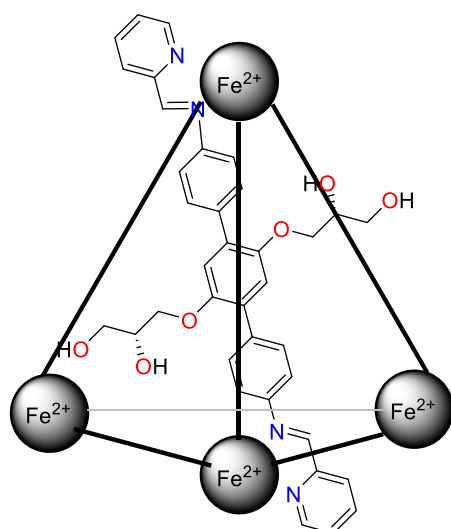


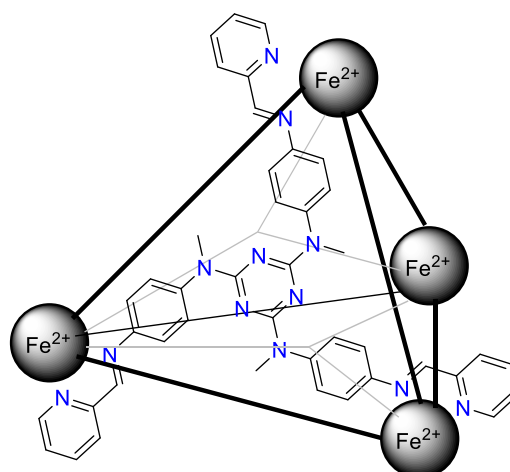
Figure 2. reaction scheme demonstrating the catalytic effects of a Pd_6L_4 octahedral face-capped cage, substituted with a circle. Naphthoquinone normally undergoes 2+4 cycloaddition with 1,3-cyclohexadiene giving yields of ~25%, but when encapsulated by the palladium cage, the reaction has yields nearing 100%.

MOCs show promising applications in catalysis,²³ separation science,²⁴ gas purification,²⁵ and a wide range of biomedical applications.²⁶ Cages have similarities to enzymes in the fact that they are both able to restrict the conformations of other molecules,²⁷ where its cavity acts analogous to the active site of an enzyme allowing for successful collisions to occur more

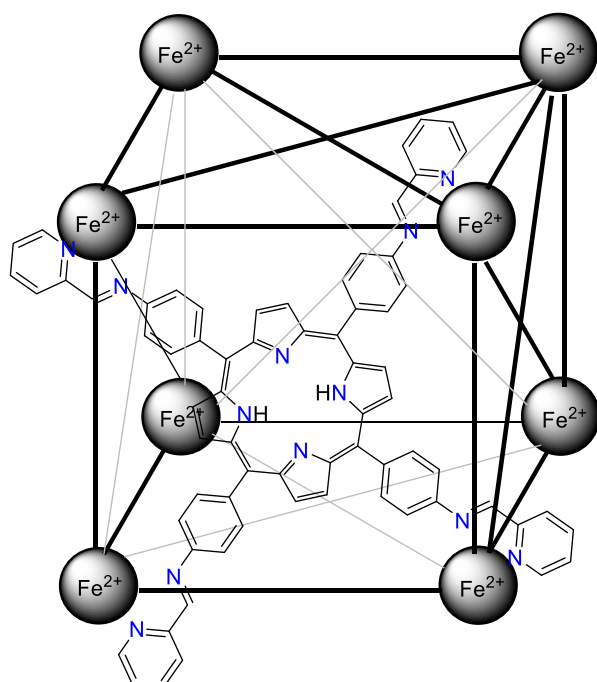
often.^{28,29} When considering catalysis, there have been several cages that increase the yield of the Diels-Alder reaction.^{28,30-33} Fujita and coworkers have done extensive work in this area, first showing how a face capped octahedral $\text{Pd}^{\text{II}}_6\text{L}_4$ cage allows for an encapsulated naphthoquinone molecule to undergo (2+4) cycloaddition with 1,3-cyclohexadiene (Figure 2).³³ Results showed a marked increase the rate of reaction, with a yield of ~100% after 12.5 h while a reaction in the same conditions without the presence of a cage recorded a yield of under 25% within the same time frame. Fujita and coworkers then went onto show the same cage being used to promote (2+4) cycloaddition between naphthalene and maleimide,³² naphthalene being quite resistant to pericyclic reactions.³⁴ Naphthalene had to be substituted with electron donating groups in order for there to be meaningful increases in yield, but in 2015 Fujita and coworkers demonstrated that by changing the ancillary ligands, ligands that bond the palladium but do not occupy an edge or a face of a polyhedron, the volume of the cages void can be manipulated and tuned, allowing for unsubstituted naphthalene to undergo (2+4) cycloaddition.²⁸



Edge-capped $\text{Fe}^{\text{II}}_4\text{L}_6$ tetrahedron



Face-capped $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedron



Face-capped $\text{Fe}^{\text{II}}_8\text{L}_6$ cube

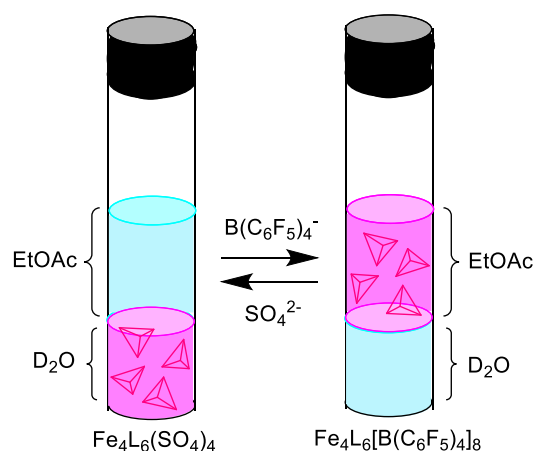


Figure 3. Iron(II) cages used by Nitschke and coworkers to create an ion-controlled phase transport system involving two liquids. An edge-capped $\text{Fe}^{\text{II}}_4\text{L}_6$ tetrahedron (top left), face-capped $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedron (top right) and a face-capped $\text{Fe}^{\text{II}}_8\text{L}_6$ cube (bottom left) were used in with counter-ions SO_4^{2-} and $\text{B}(\text{C}_6\text{F}_5)_4^-$ in a biphasic $\text{EtOAc}/\text{D}_2\text{O}$ system where the solubility of the cage and the phase it resides in is determined by the counter-ion concentration. The experimental setup (bottom right) depicts the reaction involving the face-capped $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedron. The leftmost vial shows the cage-ions in the D_2O phase, with each cage ion accompanied by 4 sulphate ions. With the addition of $\text{B}(\text{C}_6\text{F}_5)_4^-$, which is more soluble in EtOAc , cages will migrate into the EtOAc phase as the concentration of $\text{B}(\text{C}_6\text{F}_5)_4^-$ increases. Increasing the concentration of SO_4^{2-} in the biphasic system causes the cages to move into the D_2O phase.

As detailed previously, cages are excellent at encapsulating molecules in solution, not only hosting guests in their cavity but, also restricting the number of conformations available for a given molecule can have.^{30,31} When considering the application of MOCs in separation science however, the overall aim is to design cages that are stable in a range of environments while having preferential binding to the target host.¹ MOCs have been developed for a range of separation techniques including liquid-liquid extraction,²⁴ liquid-solid extraction,^{35,36} and gas separation, notably CO₂.³⁷⁻³⁹ An emerging field within separation science with MOCs is the use of MOCs to transport species of interest between media, similar to lipid membranes in biological systems, MOCs can act not only as the agent of confinement, but one that can control and mediate the passage of molecules and ions.⁴⁰ Nitschke and coworkers have played a key role in developing this field, initially laying out the framework for the transference of cage molecules both with and without guests between immiscible liquid phases.⁴¹ In their work, using face-capped Fe^{II}₄L₄ and edge-capped Fe^{II}₄L₆ tetrahedral cages, as well as a cubic Fe^{II}₈L₆ face-capped cage, a thermodynamic model was developed, shown in figure 3, relating the amount of cage in each phase of a biphasic system to the response stimuli, in this case ion exchange. The solubility of a cage is influenced by whether the cage and its counter-anion can dissolve, as a salt, in a solvent. Exploiting this property, Nitschke and coworkers were able to control the amount of cage in each phase with a single input, the addition of a hydrophobic anion [B(C₆F₅)₄]⁻ to a solution of the cage. It was also demonstrated that two different cages and their respective guests occupying the same phase can be separated when the amount of anion needed for phase transfer is different for each cage.

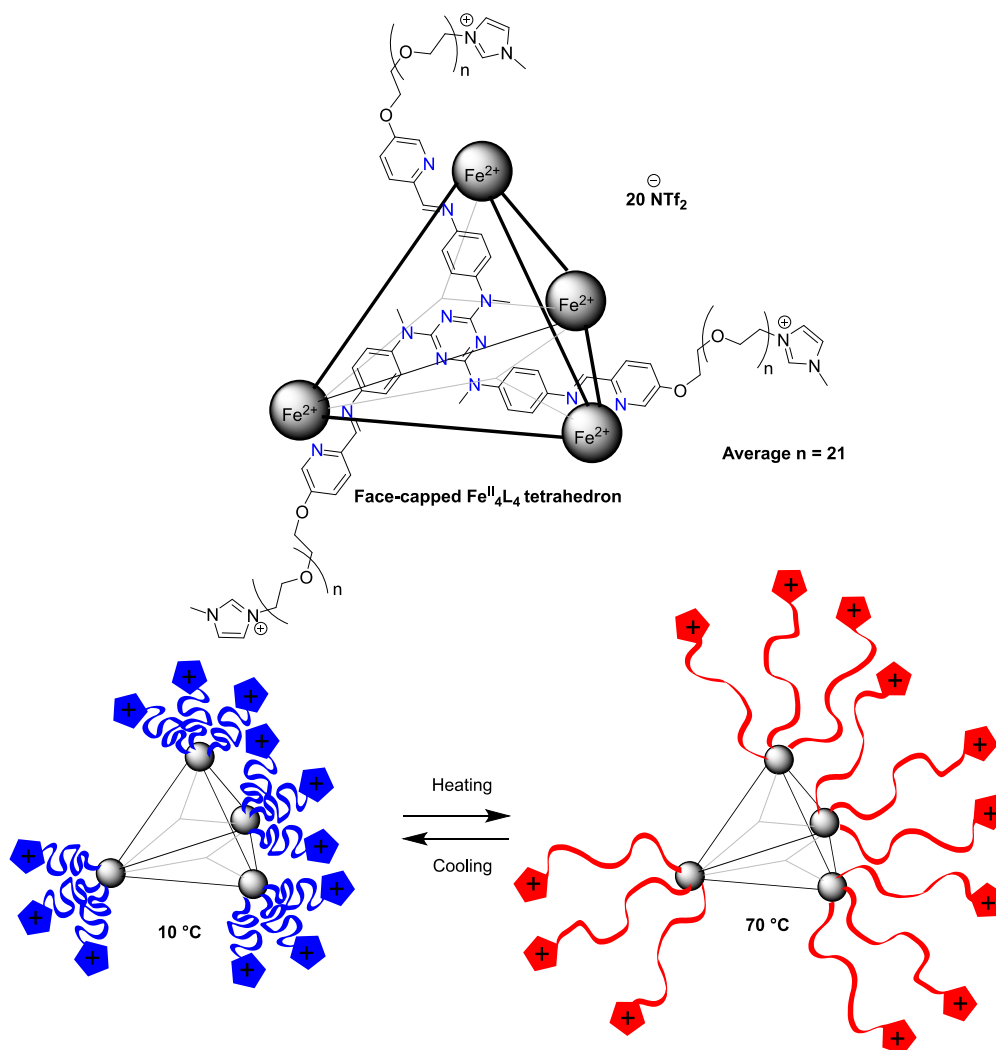


Figure 4. A face-capped $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedral cage with long polyethylene glycol chains (top) used by Nitschke and coworkers for temperature-controlled cargo shuttling in a water/ethyl acetate biphasic system. The solubility of the cage at low temperatures favours water while high temperatures it favours ethyl acetate. This is due to hydrophobic burying of the ethylene groups at low temperatures while higher temperatures cause them to unfurl and be exposed decreasing their solubility in water.

Later the group built upon these concepts but changed the stimulus that governed transitioning between phases, using temperature, while implementing guests, shuttling them between phases akin to cargo.⁴² To do this, long polyethylene glycol (PEG) chains were introduced to the ends of the ligands of an face-capped $\text{Fe}^{\text{II}}_4\text{L}_4$ tetrahedron. In a water/ethyl acetate biphasic system, the cage has a higher solubility in water at low temperatures, with data showing no signs of the cage in ethyl acetate at 10 °C. This is due of the hydrophobic ethylene groups folding in on themselves, into occupying low energy conformations due to low temperatures. these conformations were more soluble in water as hydrogen bonding between the water and the PEG oxygen atoms is more. Upon heating, higher energy conformations become more common, stretching out the chains and exposing hydrophobic groups, decreasing the cages solubility in water until it is completely insoluble at 70 °C. In comparison to their previous method for stimulating phase transfer, the use of heat does not have the drawback of using

anions, as while the movement of the cages between phases can be changed by altering the concentration of the hydrophobic anion in respect to the hydrophobic anion, the system will begin to break down when the solvent becomes saturated. Altering the temperature however does not add any physical media to the biphasic system and therefore transferring cages between phases can be done within a tolerable range of temperatures.

Nitschke and coworkers took this concept further by creating an automatic filtering system using, a triphasic system, with an aqueous middle phase containing cages, while the two end phases are organic.⁴³ The group showed that by adding a chemical that binds strongly to the cage but is insoluble in water in a feedstock phase, the chemical can be shuttled through the aqueous phase and dropped off into a third organic phase. In this work, cages no longer moved in between phases but instead encapsulated guests at phase boundaries, mediating their passage. This was demonstrated using two different tetrahedral cages, a face-capped $\text{Co}^{\text{II}}_4\text{L}_4$ and an edge-capped $\text{Fe}^{\text{II}}_4\text{L}_6$, with naphthalene as the cargo. A concentration gradient was established by filling the feedstock phase with naphthalene, and through a capture release mechanism facilitated by MOCs within the aqueous layer, the receiver phase would be populated by naphthalene as the concentration of the cargo tends towards an equilibrium between both organic phases. The cages were also selective in their binding to naphthalene, experiments using a mixture of organic molecules in the feedstock phase showed preferential binding to naphthalene, with it having the fastest rate of transference to the receiving phase before reaching equilibrium within 25 days. Most recently (2024), Nitschke and coworkers published two additional articles in this field using different variables to promote the transfer of molecules through phase boundaries with the aid of MOCs, with light as their stimuli.⁴³ A face-capped $\text{Zn}^{\text{II}}_4\text{L}_4$ tetrahedral cage was synthesized in a one-pot fashion by adding the zinc salt as well as the aldehyde and an amine into the reaction mixture, allowing for imine formation and complexation to occur in tandem. This resulted in a MOC where at the vertices were photo-switchable diazo groups reside. The stable cage featured diazo groups adopting the *trans* isomer, and when visible light with a wavelength of 350 nm irradiates it, the diazo groups convert into the *cis* isomer, causing a breakage of the cage structure due to steric clashing at the vertices of the cage. Using 500 nm light, the ligands turn into the *trans* isomer which leads to the regeneration of the cage. In a mixture of steroids in CD_3CN , it was shown that it selectively binds to progesterone. Given that the cage is insoluble in cyclopentane while the steroids have a higher solubility in cyclopentane compared to CD_3CN , a separation procedure was developed. The $\text{Zn}^{\text{II}}_4\text{L}_4$ cage was added into a mixture of steroids, including progesterone, in CD_3CN which allowed for preferential binding of progesterone. Cyclopentane is then used to create a biphasic system where the encapsulated progesterone is trapped in the CD_3CN phase with the cage, while the other steroids cross the phase boundary into

cyclopentane. Removing the cyclopentane layer, a new portion of cyclopentane can be added. Irradiation and subsequent breakdown of the cage releases progesterone into the cyclopentane, and the cage can be regenerated through light allowing for the process to be repeated. In the later article published in 2024 Nitschke and colleagues combined ideas from the triphasic system established in their previous work with photoswitching.⁴⁴ Taking inspiration from a thought experiment proposed by James Clerk Maxwell, an edge-capped $\text{Fe}^{\text{II}}_4\text{L}_6$ tetrahedron with a photoswitching guest was situated in an aqueous phase that separated two organic phases creating a triphasic system. The experiment created a sorting system, where the separate organic phases were irradiated with different wavelengths of light, 530 nm corresponding to the formation of the *cis* configuration and 400 nm corresponding to the *trans*. The *cis* isomer has a higher affinity to their cage than the *trans* isomer and so when there both organic layers are irradiated, a concentration gradient is between the two phases that corresponds to this affinity. The system appears to create a concentration gradient without the need of thermodynamic work, where a high concentration of the *trans* isomer is formed as the *cis* isomer travels through the aqueous phase at a faster rate, thermodynamically driven to decrease its concentration in the organic phase irradiated with 530 nm light. Upon entering the 400 nm irradiated phase, the molecule isomerises to the *trans* configuration and is trapped due to its low binding affinity to the cage.

Lanthanide cages

Lanthanide MOCs differ from cages consisting of transition metals due to how their ions behave in terms of bonding to ligands. Specifically, ligand field theory can be used to predict and explain coordination bonding of transition metal complexes, which as detailed earlier underpins the creation of cages as they are fundamentally coordination complexes. Ligand field theory is not suitable for lanthanide complexes as the 4f orbitals is heavily shielded by the orbitals of 5s, 5p and 6s.⁴⁵ Lanthanide ions act like a ball of positive charge that ligands attach to in any way they can, and so available space is more important for predicting bonding than other factors. Despite this, most complexes made from lanthanide 3+ ions are 8 or 9 coordinate, but range from 6 to 12.^{46,47}

Lanthanide cages have similar applications as those detailed previously in the case of transition metal MOCs, including separation,⁴⁸ catalysis.⁴⁹ Lanthanide cages also have applications that are unique to them which include sensing and luminescence.⁵⁰⁻⁵² A face-capped $\text{Eu}^{\text{III}}_4\text{L}_4$ tetrahedron was synthesized by Yan and coworkers that showed luminescent responses to ammonia as well as a range of volatile amines.⁵³ Spin-coating was used to create a thin film using a solution of $\text{Eu}^{\text{III}}_4\text{L}_4$ in THF on quartz plates, with film thickness ranging from 40-80 nm. The study showed that the luminescent response from the lanthanide cage thin film

varied depending on the amine interacting with it, giving different intensities for each compound at concentrations of 100 ppm, while no response was given for oxygen containing vapours that were screened.

PARASHIFT contrast agents

MRI

Before magnetic resonance imaging (MRI) was used in medicine today, the groundwork for the technique was initiated by Isidor Isaac Rabi with the discovery of nuclear magnetic resonance (NMR),⁵⁴ which he published in 1938. It was not until the 1970s that NMR was used to differentiate between different types of biological tissue, with Raymond Damian being the first to differentiate between cancerous and non-cancerous cells,⁵⁵ and then going on to create the first method of performing of what would be considered an MRI scan by today's standards.

Further developments to the technique were made shortly after with the production of MRI images, by both Paul Christian Lauterbur and Peter Mansfield. Lauterbur would go on to publish the first instance of MRI image,⁵⁶ while Mansfield would independently come up with a method to produce images in a shorter time than Lauterbur did, both being awarded the 2003 Nobel Prize in medicine for their contributions.

Currently MRI is one of the most well-known diagnostic techniques used in medicine,⁵⁷⁻⁵⁹ especially in determining diseases and injuries in soft tissue and brain tissue.^{60,61} MRI images use the NMR signal of hydrogen environments in an organism and constructs a two-dimensional (2D) or 3D image, allowing for the differentiation of different types of tissue based on the amount of water within them. To generate an NMR signal, an atom must be spin active. For ^1H each nucleus has a spin value $I = \frac{1}{2}$, and fulfils this condition, allowing for the H_2O to be used.^{61,62}

In an MRI scan, an external magnetic field, B_0 , with its vector described as parallel to the z-axis, is applied, causing the hydrogen's spin to either align with the direction of B_0 , ($+\frac{1}{2}$), or opposite to its direction, ($-\frac{1}{2}$), with those aligned with the direction of the external magnetic field being lower in energy those that are not.⁶² These are called spin states and denoted as m_i .

$$E_{m_i} = \gamma h B_0 / 4\pi$$

Equation 1.

Equation 1 shows the energy of a spin state, where h is Planck's constant and γ is the gyromagnetic ratio, which is the ratio of magnetic moment and angular momentum of the particle.⁶³ ^1H has two spin states, and their difference in energy is equal to (equation 2):

$$E\Delta = \gamma h B_0 / 2\pi$$

Equation 2.

When experiencing the external magnetic field each state will precess around it, directly proportional to its gyromagnetic ratio and the strength of the field.⁶³ The most occupied spin state is parallel to B_0 , but due to the small energy gap created between spin states, temperature effects can increase the population of the higher energy state as temperature increases.⁶² The next stage in the experiment is to send a radio frequency pulsed through the patient 90° in respect to the vector of B_0 .⁶² This causes spins in the $m_i = (-\frac{1}{2})$ spin state to populate the $m_i = (+\frac{1}{2})$ spin state, and their vector to be 90° to B_0 .⁶⁴ After the pulsed is applied the spin states relax and return to their orientations under the effect of just the external magnetic field, releasing energy in the process.⁶⁴ The time for the spin states to return to equilibrium is characterized by two factors, T_1 and T_2 , these two factors are paramount to the production of NMR images which are often either T_1 or T_2 weighted.⁶⁵ T_1 is the spin lattice relaxation time and is the time it takes for the spin states z component, M_z , to reach the equilibrium of being either aligned or unaligned in respect to the vector of B_0 before the 90° radio frequency pulse, in other words, the thermal equilibrium of the distribution of nuclei in both spin states.⁶⁵ T_2 on the other hand is the time it takes for the xy component, M_{xy} , to reach equilibrium after the 90° radio frequency pulse, as the spins interact with each other and dephase from their coherent xy vector.⁶⁵ For both relaxation times, the time taken for relaxation is dependent of the environment, this allows for different tissue to give different T_1 and T_2 values,⁶⁵ and using this information an MRI image is created allowing medical professionals to identify different types of tissues as well as assess whether they are diseased.⁶³

Problems with modern MRI

One of the challenges in MRI is its long scan times and as well as the background signal of biological environments; the majority of which are fats and water situated between 0-12 ppm.⁶⁶ Another issue is the low sensitivity of the technique caused by the small energy gap in spin states once a magnetic field is applied.⁶⁷ As mentioned previously, thermal factors can cause nuclei to move from the lowest energy state to the highest with relative ease, and so strong magnetic fields are used to increase that energy gap. Because of this, MRI machines require liquid nitrogen and liquid helium, as they use superconducting magnets to have high localised magnetic field strengths.⁶⁸ The only other way of increasing the energy gap would be to use a nuclei with a higher gyromagnetic ratio, but in the case of ^1H MRI, ^1H has the second highest gyromagnetic ratio known at 42.6 MHz T^{-1} ,⁶² with ^3H having a higher value but being unusable due to the incredibly low natural abundance.⁶⁹ While other nuclei can and have been used, such as ^{19}F ,⁷⁰ they are also not good candidates due to their low biological abundance as well as their lower gyromagnetic ratio, making ^1H a clear choice despite the intrinsic shortcomings of using it. One of the solutions to this problem is to increase the relaxation time of ^1H Contrast agents, drugs that increase the relaxation time of water molecules within a patient during a

scan, have been deployed since the 1980s, and allow medical practitioners to differentiate between different types of tissues easier due to clearer images being produced.⁷² Most contrast agents use gadolinium(III) metal complexes, such as Dotarem and Gadovist.⁷² This is because gadolinium has the highest number of unpaired electrons in comparison to other lanthanide ions, which interact with water molecules in the biological environment, shortening their relaxation time due to paramagnetic effects and increasing the amount of data that can be acquired in a given time frame.⁷³ The issue with this approach is that although clearer images can be produced, there is still the background signal of other water and biological media that can complicate the interpretation of the image.⁷⁴ This is because the imaging is done indirectly, using the relaxation of water molecules, which are well within the biological window of 0-10 ppm.⁷⁴

PARASHIFT contrast agents, a solution

Due to the issues mentioned above, a new type of contrast agent is being developed, one that increase the relaxation rate of ^1H but also gets rid of the background signal problem. These are PARASHIFT contrast agents.^{70,74-81} PARASHIFT contrast agents work similarly to the traditional contrast agents mentioned above but instead of increasing the relaxation of H_2O in a MRI scan, the lanthanide metal increases the relaxation of a reporter group signal on a ligand within the metal complex.⁷⁴ This allows for direct detection of the contrast agent, where unlike with traditional contrast agents that make spectra from large concentrations of H_2O environments in the body, the PARASHIFT approach needs to only concerns itself with the concentration of the agent administered to the patient.⁷⁴ PARASHIFT contrast agents, as the name suggests, also shift the MR resonance of the reporter group either up or down field through interactions with the paramagnetic lanthanide, with shifts that can go beyond 80 or - 80 ppm.⁷⁶ This allows for images and spectra to be interpreted well outside of the biological background signal range.

Although transition metal PARASHIFT contrast agents have been developed,⁷⁵ there has been much more focus on lanthanide metal-complexes as agents, with this project being one of them. Therefore, only lanthanide complexes will be discussed theoretically.

Theory

For paramagnetic shifts to occur due to metal ions, there needs to be magnetic anisotropy.⁸² Magnetic anisotropy is present when an object's magnetic properties differ based on direction. In the case of paramagnetic lanthanide ions, their unpaired electrons in the f orbital give rise to magnetic anisotropy because there is no degeneracy in secondary orbital states, J_z , that make up the total angular momentum quantum number, J .⁸² This is caused by the high spin-orbital coupling electrons experience in the f orbital in these lanthanide species that is not fully stabilised by the crystal field, leading to a Boltzmann distribution across the J_z states.⁸²

Because these states are vector quantities, the magnetic properties of the lanthanide paramagnetic species are spatially inhomogeneous, therefore magnetically anisotropic.⁸² This property leads to large temperature-dependent chemical shifts when the unpaired electrons interact with other magnetic fields.⁸² The observed chemical shift experienced by resonances interacting with a lanthanide species, δ_{obs} , is equal to $\delta_{dia} + \delta_{FCS} + \delta_{PCS}$, where δ_{dia} is the diamagnetic term, δ_{FCS} is the Fermi contact term and δ_{PCS} is the pseudocontact term.⁸³ Out of these terms, the most important one is the pseudocontact term, as it relates the magnetic interactions between nuclei and lanthanide ions' unpaired electrons to chemical shift. The Bleaney equation (equation 3) is used to describe this shift for Ln(III) ions, and although the equation has issues predicting some systems, it is accurate enough to give reasonable approximations of chemical shifts if the orientation of the principle magnetic axis is known. The equation states (equation 3):

$$\delta_{PCS} = \frac{C_J \mu_B^2}{60(kT)^2} \left[\frac{(3\cos^2\theta - 1)B_0^2}{r^3} + \frac{(\sin^2\theta\cos^2\phi)B_2^2}{r^3} \right]$$

Equation 3

Where C_J is the Bleaney constant that is specific for each Ln(III) ion which is derived from J , μ_B is the Bohr magneton, r is the distance of the nucleus from the Ln(III) ion, θ and ϕ are the angles between the nucleus and the principle magnetic axis of the Ln(III) and B which are second order crystal field terms.⁸² From equation 3 we can see that there are three things determining the effects of PARASHIFT that are important: The lanthanide used, the distance from the lanthanide to the nucleus and the angle between the nucleus and the principle magnetic axis.

For relaxation, the Bloch-Redfield-Wangness theory (equation 4 and 5) can be used to link relaxation rates and to the dipolar interactions between electrons and a nucleus:

$$R_1 = \frac{2}{15} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_N^2 g_{Ln}^2 \mu_B^2 J(J+1)}{r^6} \left[3 \frac{T_{1e}}{1 + \omega_N^2 T_{1e}^2} + 7 \frac{T_{2e}}{1 + \omega_N^2 T_{2e}^2} \right] + \frac{2}{5} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\omega_N^2 \mu_{eff}^4}{(3k_B T)^2 r^6} \left[2\tau_r \frac{3}{2} \frac{\tau_r}{1 + \omega_N^2 \tau_r^2} \right]$$

Equation 4

$$R_2 = \frac{2}{15} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\gamma_N^2 g_{Ln}^2 \mu_B^2 J(J+1)}{r^6} \left[2T_{1e} \frac{3}{2} \frac{T_{1e}}{1 + \omega_N^2 T_{1e}^2} + \frac{13}{2} \frac{T_{2e}}{1 + \omega_N^2 T_{2e}^2} \right] + \frac{2}{5} \left(\frac{\mu_0}{4\pi} \right)^2 \frac{\omega_N^2 \mu_{eff}^4}{(3k_B T)^2 r^6} \left[2\tau_r \frac{3}{2} \frac{\tau_r}{1 + \omega_N^2 \tau_r^2} \right]$$

Equation 5

Where T_{1e} is the longitudinal relaxation time of the electron spin, μ_0 is the vacuum permeability, γ_N is the gyromagnetic ratio of the nucleus, g_{Ln} is the Landé factor of the fundamental multiplet J of the lanthanide ion, μ_B is the Bohr magneton, r is the distance between the lanthanide and the hydrogen nucleus, τ_r is the rotational correlation time, ω_N is the Larmor frequency of the nucleus and μ_{eff} is the effective magnetic moment.⁸⁴ The relaxation rates R_1 and R_2 are the reciprocal of T_1 and T_2 respectively.⁸¹

Designing PARASHIFT probes

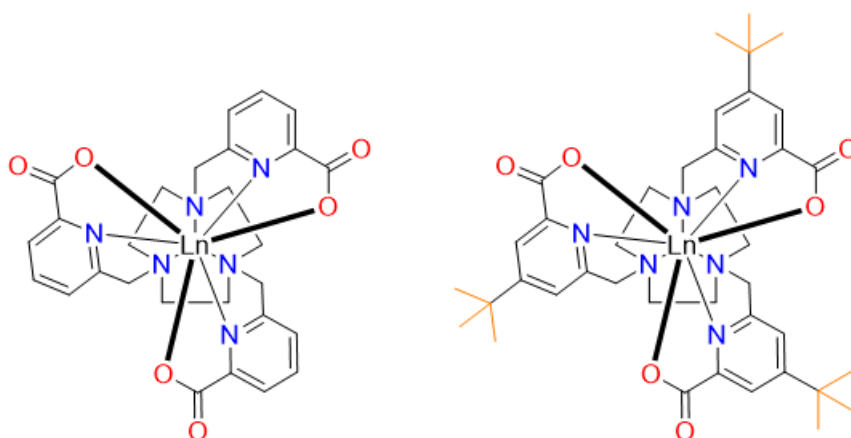


Figure 5. (Left) A lanthanide complex motif used by Nicholas F. Chilton et. al to measure the pseudocontact shifts experienced by the hydrogen in the 4th position on the pyridine rings. A potential PARTASHIFT agent using this motif, reporter tert-butyl groups shown in orange.

As mentioned above in reference to equation 3, the most important aspects to consider in terms of paramagnetic shift are the choice of lanthanide ion, the distance of the reporter nucleus from the lanthanide ion and the angle between the nucleus in respect to the principle magnetic axis of the lanthanide ion.⁸² When considering relaxation rates using equation 4 and 5, only the choice of the lanthanide, reporter nucleus and the distance between them are important. As explained earlier, ^1H is the best candidate for a reporter nucleus due to its high γ_N and availability, this also translates well into design as organic chemists have a plethora of methods of making molecules that contain ^1H . One difficulty in designing PARASHIFT probes is that it is very difficult to predict the position of the principle magnetic axis of the lanthanide once it has formed a complex,^{82,85} with research groups using computational methods based on empirical data to do so.^{86,87} Although the principle magnetic axis is the same for each lanthanide ion in a complex, one must be made to determine its orientation.⁸⁸

This is why, despite dysprosium having the largest magnitude of shift, it is not the only lanthanide used for PARASHIFT probes, and multiple lanthanides are used to make complexes to determine which ones shift outside of the biological background signal window.^{74,76,82,86,87} Relaxation rates are another thing determined by the lanthanide, and similarly to the principle magnetic axis, it is difficult to predict the amount of relaxation a

reporter group will experience without empirical data from previous experiments.⁸⁵ T_2 relaxation must also be short, line broadening will occur, reducing the sensitivity of the spectra produced.⁸¹ To exploit these properties, it's natural to conclude that metal organic complexes must be made, they allow organic molecules to form dative-covalent bonds with lanthanide ions, putting their ^1H environments in close proximity to the lanthanide ion allowing PARASHIFT to occur.⁸⁵ Typical lone pair donors are nitrogen and oxygen, often with heterocyclic, macrocyclic and carboxyl moieties attached, as shown in figure 5. The one factor chemists do have significant control over is r , ligand motifs can be made that allow for the reporter groups to be close enough to the lanthanide ion to be affected by its magnetic anisotropy, and organic chemistry can be used to place these reporter groups on different positions of a ligand in order to find the position that gives the best results.⁶⁶ The functionality of the reporter group can also be changed, with *tert*butyls being a common choice for its high integration value and lack of splitting, but other groups such as *isopropyl* are also used.⁸⁸ For lone pair donors, common atoms used are N and O, are great heteroatoms and allow for fine design in the bite angles of ligands.

There are also other factors to consider when it comes to design such as stability of the complex, the splitting pattern of the reporter group and sensitivity to other factors such as pH and ion concentration allowing for another dimension to be available for interpreting spectra. A common motif to ensure stability is the use of macrocyclic C_8N_4 seen in compounds such as Dotarem, used over linear contrast agents because of its stability and the toxicity of gadolinium ions in the body.

Examples

So far there have been few examples of PARASHIFT,^{79,89} although there have been probes developed that are pH,⁷⁶ anion,⁸⁰ and temperature sensitive.^{77,90,91} The use of *tert*-butyl groups as reporter was first described by Peter Harvey *et. al* in 2013, where the term 'PARASHIFT' was first mentioned.⁷⁴ Here the PARASHIFT probes designed were based on the drug Dotarem, having a macrocyclic ring containing four nitrogen atoms that chelate the lanthanide ion, based on the molecule cyclen.⁹² Peter Harvey *et. al* used the Bleaney equation detailed earlier (equation 3) to explain the paramagnetic shifts caused by lanthanide ions, and so this work was the first to propose and formulate a method for the design of PARASHIFT probes and the potential applications within the field of MRI imaging. Later Morrow and coworkers used a cobalt containing coordination complex for PARASHIFT imaging as an undergraduate experiment, making an argument for the need of more paramagnetic studies into contrast agents and their PARASHIFT capabilities.⁷⁵ Another cobalt containing PARASHIFT probe was developed by Que and coworkers, using fluorine containing reporter groups, showing the detection of reactive oxygen species, where paramagnetic Co^{II} is oxidised to Co^{III} by, allowing

images to be made based on the degree paramagnetically shifted environments. In the NMR spectra, where images showing less paramagnetic shift suggest a higher amount of H_2O_2 .⁷⁰ More recently, Harvey and colleagues have tested several new macrocyclic compounds using transition metals, with new ligands based on a C_6N_3 macrocycle as opposed to C_8N_4 cyclen-based ligands.⁸¹ Finally, a PARASHIFT probe developed by Meade and colleagues was shown to detect the enzyme activity of nitroreductase, where the PARASHIFT probe is reduced by the enzyme, allowing for ratiometric detection.⁷⁸

Metal-organic cages for PARASHIFT imaging

As detailed earlier, metal organic cages offer unique functionality in their ability to encapsulate and carry guest molecules, and PARASHIFT probes have shown to be a promising analytical tools that allow for fast MRI monitoring with added clarity due their reporter groups having chemical shifts well outside the range of 0-12 ppm. The subject of this thesis is the synthesis of these two fields, the development of a theranostic approach to MRI imaging that leverages the magnetic anisotropy of lanthanides, as well as the capabilities of MOC to capture and release molecules, creating a PARASHIFT probe that can administer medication to treat an illness while a patient is undergoing an MRI scan. The property of cages to form highly symmetric structures, also allows them to have hydrogen environments with high integration, which is ideal for the reporter group of a PARASHIFT probe.

Purpose

To date, there have been no published examples of a MOC for PARASHIFT imaging. While there have been examples of lanthanide cages as mentioned in the lanthanide cage section, the ligands used for these cages do not have hydrogen environments with large amounts of equivalent hydrogens such as *tert*-butyl groups, and so the aim of this work is to synthesise ligands motifs with reporter groups that can form lanthanide cages, and display the ideal properties of a PARASHIFT agent as detailed earlier in the Designing PARASHIFT probes section.

Designing

Two different functional groups will be tested for their ability to form coordination bonds with lanthanides, amides, and imines. Firstly, tridentate diamide and diimine ligands will be created, each with a central pyridine moiety and a *tert*-butyl reporter group, where the location of the reporter group will be altered to see the effects of position in respect to the paramagnetic shifts caused by the lanthanide ions. These ligands will be used to make ML_3 mononuclear complexes with lanthanide ions, and paramagnetic NMR be used to see the degree of chemical shift on the reporter groups.

We will then adapt the initial ligand motifs so that there is only one amide or imine group, and a benzyl triazole group will be added. The triazole functional group forms bonds with lanthanide ions, and the benzyl group be replaced by multiple linker groups by performing a copper catalysed azide-alkyne cycloaddition which will allow them to form cages. Mononuclear complexes of with lanthanide ions Lu, Dy, Tb and Tm will be made, and both paramagnetic ^1H NMR and T_1 relaxation experiments will be performed on these complexes and comparisons will be made, ultimately determining the best motif and ion combination for the creation of cages.

Results and Discussion

Imine mononuclear complexes

Imine bonds have appeared in several recent literature publications within the ligands of cages. The nitrogen within this functional group can form dative covalent bonds to metal ions, and with the reaction being a simple condensation reaction between an aldehyde or ketone and an amine. Imine formation can even be done in one pot methods where metal salts are also added to the reaction mixture allowing for cage formation in a single step. A very interesting thing about the imine bond is its ability to change conformations, switching between *E* and *Z* isomers, allowing for molecular switching functionality to be added to metal-organic cages. This phenomenon can be controlled with either heat or light, which allows for the prospect of cages holding their guests with a specific ligand conformation, and with a switch of light, that guest is released. The advantage of using metal-organic cages as PARASHIFT agents would be its ability to deliver drugs through the use of host-guest chemistry, and imine bonds give us another avenue to pursue drug release in localised areas such as tumours close to the skin which can be irradiated with light.

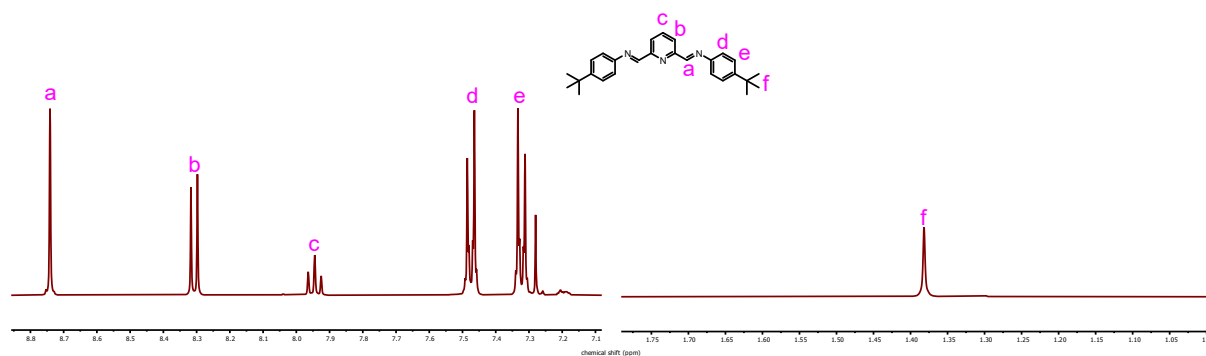
Aim of this work

In order to probe the viability of a lanthanide metal-organic cage with imine moieties, a mononuclear complex will be created. This reduces the amount of steps and risks involved with full cage synthesis while also allowing us to make a bonding motif that can be attached to different backbones as well. Pyridine-2,6-dicarbaldehyde will be used in two separate condensation reactions with amines 4-*tert*-butyl aniline and 2-*tert*-butyl, which are both contain *tert*butyl groups attached to their benzene ring. Once these two ligands are in hand, complexation reactions with the ligands and lanthanide salts will be performed and the complexes will be characterised by HRMS and ¹H NMR techniques, including those that measure relaxation times. Photo switching capabilities will then be probed, and if successful the changes in the complexes' structure can be confirmed with the aforementioned analytical techniques. Then a scheme to create a cage using the imine motif will be created.

Synthesis and characterisation

Pyridine-2,6-dicarbaldehyde (1 equiv.) reacted with 4-*tert*butyl aniline (2.1 equiv.) forming the diimine through imine condensation. HRMS and ¹H NMR found that the imine had decomposed. As the complexation reactions were run at room temperature and did not need the addition of any other compounds, the starting material was checked only to discover that starting material had also decomposed. Upon redoing the initial imine formation and monitoring the product using NMR, the product was only stable for a day. To circumvent this, an *in-situ* method was developed where complexation and imine formation happened in

tandem, hoping that the imine bonds would be stabilised upon complexation but again this, this led to similar results to the two-step process complexation.



Future prospects

Due to the degradation of the ligands, it was decided to abandon the imine motifs early on and focus on the amide motifs.

Diamide mononuclear complexes of ligands 2 and 3

Diamide mononuclear complexes were of interest because the binding motif has been shown to work in other lanthanide complexes, where lone pairs from the amide carbonyl oxygens are coordinated to the metal ion.⁴⁷ Recent literature shows that the functional group can be combined with different functional groups as well other amides in order to make a wide range of bonding motifs for lanthanides. The dipicolinamide bonding motif appears to be easily accessible and was decided to be a good candidate to use for trialling mononuclear complexes that can be modified to form cages.

Synthesis and characterisation

Pyridine-2,6-dicarbonyl chloride was synthesised *via* nucleophilic acyl substitution inspired by literature.⁹³ Pyridine-2,6-dicarboxylic acid and excess thionyl chloride were refluxed for 24 hours yielding a diacyl chloride. Excess thionyl chloride was removed *in vacuo* without isolating the dichloride. Keeping it under inert conditions, dry CH₂Cl₂, 2-*tert*butyl aniline or 4-*tert*butyl aniline, followed by triethylamine were then added, and the sample was refluxed for 6 hours, yielding ligand **L2** and **L3** respectively. The identities of these compounds were confirmed by ¹H NMR, ¹³C NMR, and HRMS.

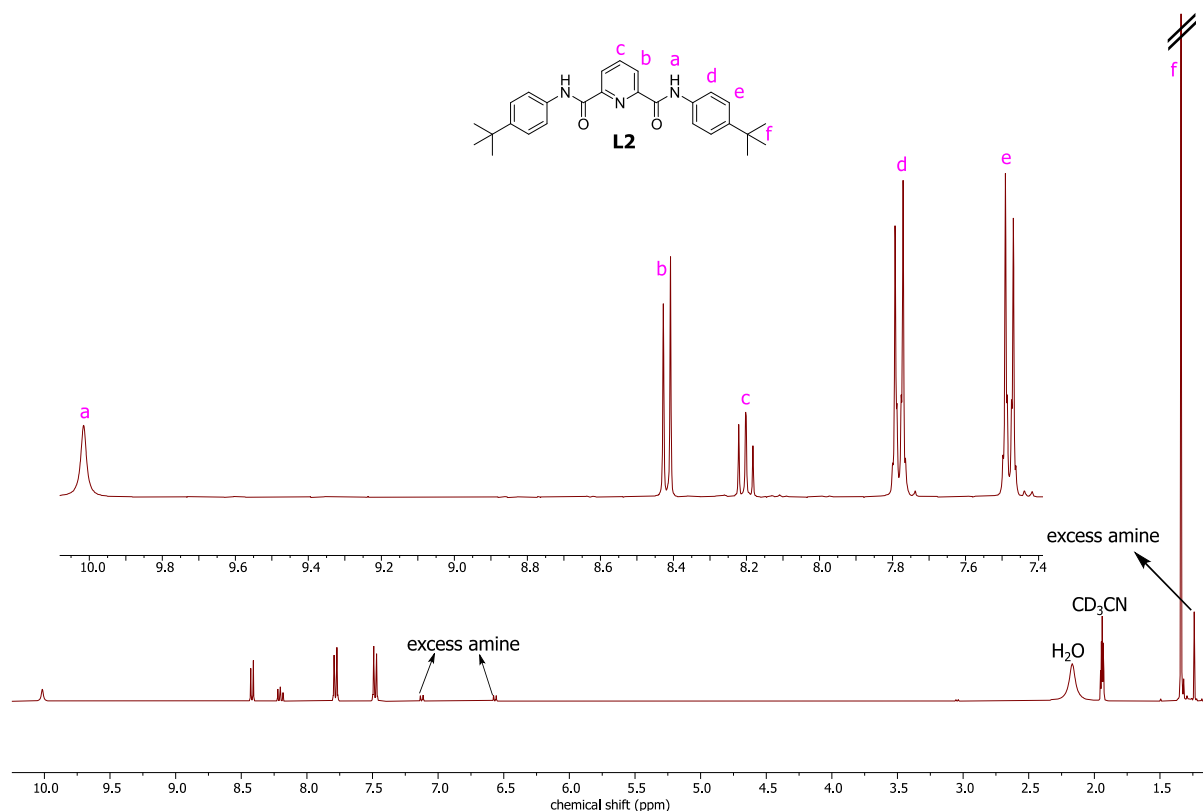


Figure 6. ¹H NMR spectrum (400 MHz, 298 K, CD₃CN) of **L2**

Ligand **L2's** ^1H NMR spectra showed that excess amine was present in the mixture, which remained despite flash chromatography being used to purify the product. This meant that all complexes made using this ligand would have this impurity. It was decided to continue despite this, the product would be used for complexations as it was assumed that complexation between the ligand and the lanthanide ions would dominate rather than coordination with the amine.

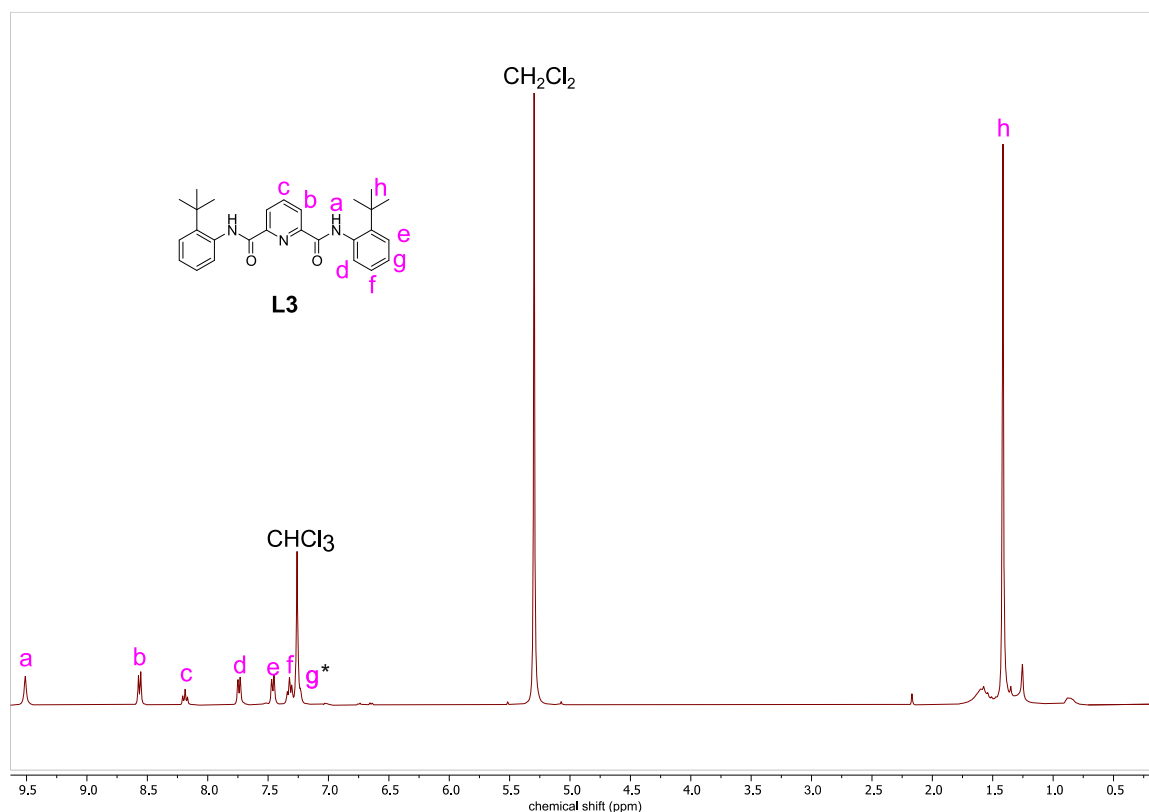


Figure 7. ^1H NMR spectrum (400 MHz, 298 K, CDCl_3) of ligand **L3** Signal b is obscured by the residual solvent peak CHCl_3 .

L3's ^1H NMR spectrum has one of its signals at 7.26 ppm and is hidden by the CHCl_3 peak. The spectrum features CH_2Cl_2 as an impurity due to the solvent not fully evaporating from the product.

Each diamide ligand was used to form three complexes using the triflate salts of lutetium, dysprosium and thulium. The typical experimental procedure for these reactions was to stir ligand (1 equiv.) and lanthanide triflate (0.4 equiv.) in a sample vial containing CD_3CN at room temperature for 1 h. Both ligands (**L2** and **L3**) proved to be sparingly soluble in CD_3CN and upon completion of the reactions there were no solid left in the sample vial for any experiment, indicating complexation was successful.

Table 1. The ligand and lanthanide triflate salt in relation to the metal complex it forms.

Ligand	Triflate salt	Abbreviation
L2	Lu(OTf) ₃	LuL2₃
L2	Dy(OTf) ₃	DyL2₃
L2	Tm(OTf) ₃	TmL2₃
L3	Lu(OTf) ₃	LuL3₃
L3	Dy(OTf) ₃	DyL3₃
L3	Tm(OTf) ₃	TmL3₃

The resulting structures were characterised using HRMS and ¹H NMR spectroscopy; paramagnetic experiments were conducted on the appropriate compounds.

Due to the paramagnetic nature of most of the lanthanide complexes, assigning the spectra of the ¹H NMR spectra was not possible, but evidence of changes in chemical shift showed that this structure was a promising candidate for use as a binding motif for metal-organic cage design.

L2 Complexes

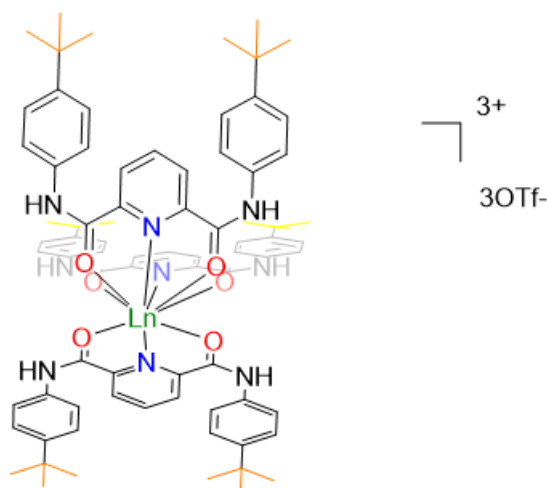


Figure 8. General formula for **LnL2₃** complexes.

¹H NMR of the *in-situ* **LuL2₃** solution was compared to **L2**, which suggested that this complexation reaction returned **L2** as the major component, as shown in figure 9. Signals attributed to **LuL2₃** had a 1:5 integration ratio with those attributed to **L2**. Interestingly there were no signals that correlated to free 4-*tert*-butyl amine, but three signals corresponding to its splitting pattern and integrations were found, albeit shifted in ppm, which could suggest that it has formed complexes with lutetium ions. HRMS showed charge fragments that corresponded

to the theoretical isotopic distribution patterns expected for $[\text{L}_2\text{LuOTf}]^{2+}$ and $[\text{L}_2\text{Lu}]^{3+}$ species, having lost two triflate and three triflate ions respectively.

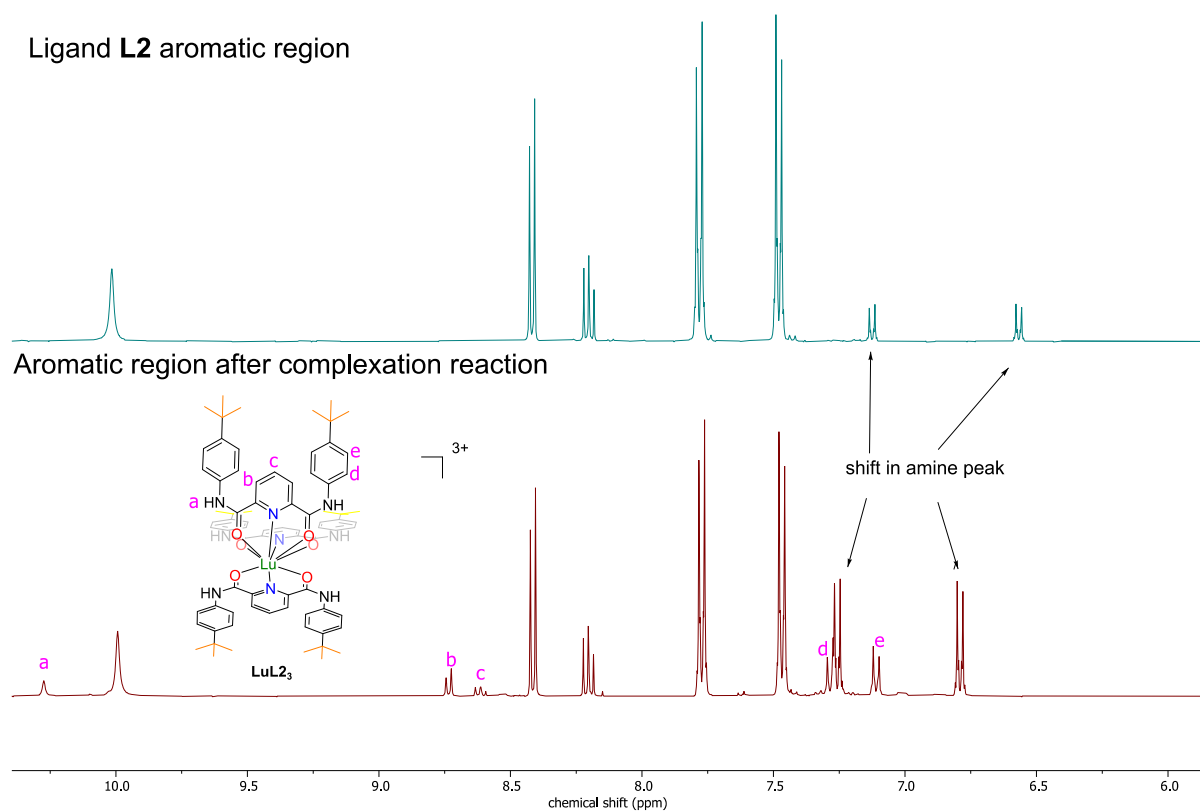


Figure 9. Comparison of **L2**'s ^1H NMR spectrum to that of complex **LuL2₃**, a 1:5 integration ratio was found between labelled and unlabelled signals suggesting that there is a 1:5 ratio of **Lu2₃** and **L2** in the mixture. The shifted peaks are attributed to 4-*tert*butylaniline, with the change in chemical shift suggesting that it has formed.

Table 2. HRMS analysis of **LuL2₃** in CD_3CN .

Formula	Theoretical m/z	Found m/z	Charge
L₂Lu³⁺	487.5547	487.5524	3+
L₂Lu³⁺ + OTf⁻	805.8083	805.8107	2+

^1H NMR analysis indicated a similar lack of complexation for the reactions to form paramagnetic complexes **DyL2₃** and **TmL2₃** as with complex **LuL2₃**. The major constituent in their mixtures was the free ligand **L2**, with the presence of excess amine. Signals attributed to **L2** within **DyL2₃** and **TmL2₃** mixtures showed broadening in comparison to those within **LuL2₃**'s, most likely due to the experimental conditions in paramagnetic NMR. Lack of complexation in all mixtures is most likely because of excess amine which was present in all reactions using ligand **L2**. Despite this, paramagnetic ^1H NMR showed that there were paramagnetic shifts for both diamagnetic lanthanide complexes, notably around -0.5 and -3

ppm for **DyL2₃** and around 0 ppm, 3.2 ppm, and 3.6 ppm for **TmL2₃**. This gave evidence that there had been complexation with lanthanide ions in these solutions.

HRMS showed a peak at 483.8887 m/z, which suggested that the triflate-free 3+ ion species of **DyL2₃** was present, with the theoretical value being 483.8848 m/z. Both the 3+ and 2+ ions. For **TmL2₃** the 2+ and 3+ ions were observed, the HRMS spectrum of the mixture showed values of 802.8021 m/z and 485.5529 m/z which corresponded to the 2+ and 3+ ion species respectively, where the theoretical calculations gave 802.8055 m/z and 485.5530 m/z. The isotopic distribution of the peaks closely matched those calculated theoretically, images of these can be found in the experimental section

Table 3. HRMS analysis of **DyL2₃** and **TbL2₃** in CD₃CN.

Formula	Theoretical m/z	Found m/z	Charge
L2₃Dy³⁺	487.5547	487.5524	3+
L2₃Tm³⁺	485.5530	485.5529	3+
L2₃Tm³⁺ OTf⁻	802.8055	802.8021	2+

L3 Complexes

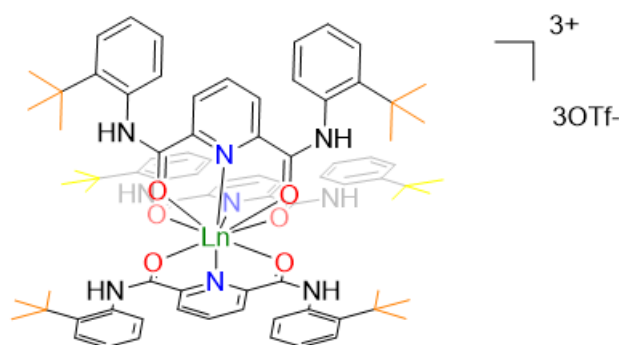


Figure10. General formula for **LnL3₃** complexes

¹H NMR data for **LuL3₃** was inconclusive due to impurities within the mixture, and it was decided that the reaction mixture had become contaminated. The aromatic region contained multiple overlapping signals, but a signal at 9.5 ppm, which was indicative of an amide hydrogen environment, was observed which evidenced that the ligand had not reacted with impurities and was within the mixture. HRMS gave the strongest evidence of the compound's existence, as signals at 487.5553 m/z and 805.8083 m/z matched with the theoretical values for 3+ and 2+ ions, those being 487.5547 m/z and 805.8083 m/z respectively, with the isotopic distribution of these signals matching theoretical calculations.

Table 4. HRMS analysis of **LuL3**₃ in CD₃CN.

Formula	Theoretical m/z	Found m/z	Charge
L3 ₃ Lu ³⁺	487.5547	487.5553	3+
L3 ₃ Lu ³⁺ + OTf ⁻	805.8083	805.8083	2+

Paramagnetic ¹H NMR showed that complexes **DyL3**₃ and **TmL3**₃ experienced significant shifts in ppm for its hydrogen environments. Due to the nature of paramagnetic lanthanide ions affecting each hydrogen environment differently based on the distance between them and the angle of the group in reference to its principle magnetic axis, that is both their chemical shift and relaxation, it is difficult to assign the spectrum of these complexes. The amount of hydrogens that share an identical environment will still increase the integration value of the signal as with regular ¹H NMR spectra. This is why, as mentioned above, the *tert*butyl group is key to our construction of PARASHIFT agents. With this information we can suggest that the signal at -12.96 ppm is the *tert*butyl groups on ligand **L3** within complex **DyL3**₃. The signals at -4.02 ppm, -4.42 ppm, -6.13 ppm and -6.65 ppm follow a splitting pattern similar the aromatic of proton environments **e** and **f** in ligand **L3**'s ¹H NMR, suggesting that these signals belong to groups on the benzene ring that is substituted with a *tert*butyl group. The signal at 24.20 ppm has a lower integration value and may potentially be from the amide proton environment of the ligands in the complex. For **TmL3**₃, there were less pronounced changes in chemical shifts due to thulium ions. The most intense signal at 7.04 ppm was attributed to the *tert*butyl reporter group. Using the same logic that was stated for the previous complex, this signal is most likely representing the *tert*butyl hydrogen environment on the bonded ligand **L3** in the complex. Due to there being little change in chemical shift of the aromatic regions in complex **TmL3**₃ from the paramagnetic effects of the thulium ion, we can compare **TmL3**₃'s paramagnetic ¹H NMR to that of **LuL3**₃'s standard ¹H NMR, allowing us to determine the which parts of the spectrum are signals relating to the product and which ones are impurities by noting which signals share splitting patterns.

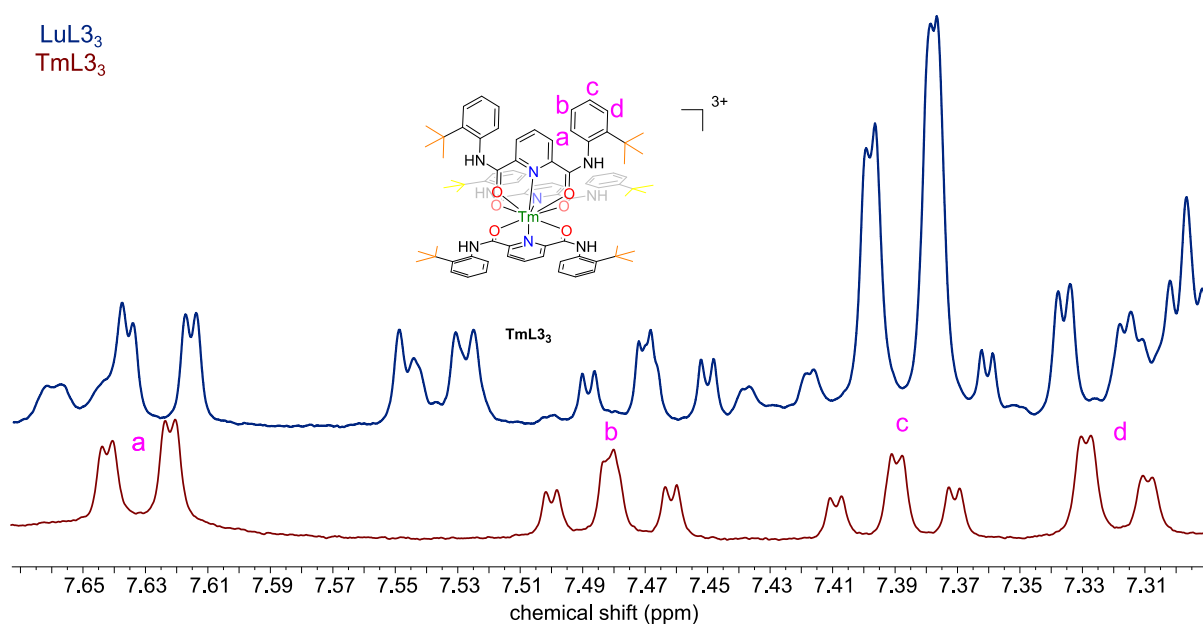


Figure 11. Comparison of **LuL₃**'s and **TmL₃**'s ¹H NMR spectra in CD₃CN showing the similar splitting patterns and integration, which helps to characterize the spectrum of **LuL₃** despite its contaminants.

The signals corresponding to the benzene ring's hydrogen environments are present, shown in figure 11. Signals a, b, c and d share similar chemical shifts to the doublet of doublets and triplet of doublets shown in complex **LuL₃**'s spectrum. The signal corresponding to c is partially hidden by a large doublet of doublets peak but is nonetheless still visible. For thulium compound **TmL₃**'s, the coupling constants for signal a are 8.10 Hz and 1.51 Hz, while for b it is 7.67 Hz and 1.50 Hz. Comparing this to the spectrum of lutetium complex **LuL₃**'s, the coupling constants for the signals correlating to a and b are 8.09 Hz and 1.57 Hz, and 7.65 Hz and 1.59 Hz respectively. Although not exact, these *J* values give more evidence of ligand **L3** within both complexes' NMR mixtures. With this information it can be concluded that there is an impurity in **LuL₃**'s ¹H NMR mixture that is aromatic in nature, as the doublet of doublets is characteristic of disubstituted aromatic rings.

Further analysis of the integration values of peaks a b and c do not correlate with any peaks that have shifted in **LuL₃**'s spectrum. When setting the signal at 7.07 ppm to an integral of 9.00, The integration values of peaks a, b, c and d range from 0.33-0.36. Meanwhile signals at 13.47 ppm, 12.08 ppm, and 11.42 ppm have integrals of 0.95, 0.95 and 1.07 respectively. This tells us that the aromatic impurity is not binding to the lutetium ion. The splitting pattern of the aromatic impurities is characteristic of a 1,2-disubstituted benzene, which fits with the starting material 2-(*tert*-butyl)aniline. Setting signal d to have an integral of 1.00, the signal at 1.45 ppm has an integral of 8.78, with this being within the region of alkyl chemical shifts. Hence, we can conclude that the impurity in is our starting material. Despite the spectrum of

ligand **L3** showing the pure ligand, the spectrum of compounds that used this ligand are shown with starting material which suggests that decomposition of the ligand had occurred. For this to be the case, only one amide bond would have been cleaved, as shifted peaks show a 1:9 integration ratio. A single crystal was grown via vapour diffusion from an NMR mixture which turned out to be a fragment of ligand **L3** that was not bound to any metal. This provided more evidence that there was decomposition of the ligand, with the cleavage of one amide bond to form a carboxylic acid.

HRMS did not return any evidence of charged species corresponding to complex **DyL3₃** and so was inconclusive as to whether the desired complex was made in the reaction. Nonetheless, there must be some lanthanide coordinated species present and experiencing paramagnetic shifts.

Using the mass of this fragment, we were able to show that unexpected complexes had formed in the solution via HRMS. The fragment with a formula of $C_{17}H_{18}N_2O_3$, which we call **F1**, had formed a 1+ ion of $[F1_3Tm^{3+} + 2OTf]$, giving a peak of 1361.3001 m/z, with theoretical calculations being 1361.2329 m/z. Another complex, $[F1_2L34\text{-}tertbutyl\ anilineTm^{3+} + OTf]$, showed that mixed ligand complexes also existed in the mixture, having three different ligands bonding to one lanthanide, with value 746.2839 m/z found, correlating to theoretical value 746.2554 m/z.

Future prospects

Ligand **L2** should be purified and complexation reactions with lanthanides should be redone to obtain clean ^1H NMR data. With this we will be able to measure the paramagnetic characteristics such as T_1 and T_2 , as well as properly characterise the NMR of the lutetium compounds. Because the experiments showed paramagnetic shifts in NMR signals, the *tert*butyl groups on ligands **L2** and **L3** are within range of the anisotropic magnetic fields of the lanthanide ions used. This makes the specific bonding motif a good candidate to consider when building PARASHIFT cages as we no longer need to worry about whether paramagnetic shift can affect our reporter group, and so, designing the molecule will be primarily influenced by the practicalities of making a MOC.

Mononuclear complexes with ligands 4, 5 and 6

With the discovery from the previous experiments showing that *tert*-butyl aniline ligands **L2** and **L3** could form complexes with lanthanide salts, display paramagnetic shifts in our reporter groups, modifications to the ligand structure must be made for cage formation to occur. Considering both phenylamide moieties, at least one of them must change. The binding sites must be designed in a way where our ligand occupies a face or edge of a polyhedron, with the vertices being our metal ion. One way to do this would be using a tritopic linker such as triphenylbenzene group that creates a new ligand with three tridentate binding sites.

Synthesis and characterisation

Ligand synthesis

As our starting material for ligands **L4** and **L5** already contain carboxylic acids, amide bond coupling using benzene-1,3,5-trianiline could be considered, but this could potentially lead to issues with multiple reactions required. A simpler method would be to remove one of the amide functional groups of our desired ligand and use another functional group that can be added in different reaction conditions without disturbing the amide bond, which also makes a dative bond to our lanthanide ion.

Ligand **L6** was synthesised in a four step process: starting with the *tert*butylalkylation of pivalic acid *via* a Minisci reaction inspired by the literature. The reaction conditions were such that radical decarboxylation of pivalic acid (using ammonium persulfate as a base and silver nitrate as a catalyst) creates an alkyl radical which then reacts with the electron deficient aromatic ring. The reaction pathway to all ligands from this project will first activate the carboxylic acid to an acyl chloride and then couple to form an amide, with each precursor for **L4**, **L5** and **L6** using a different amine derivative. Once the amide has been formed, the general procedure for all ligands is the same, with a Sonogashira coupling performed to add a trimethylethynylsilane group, which was deprotected *in-situ* in a one pot alkyne-azide cycloaddition reaction.

All ligands undergo complexation reactions with lutetium, dysprosium, thulium, and terbium. HRMS and NMR techniques were used to analyse the precursors, ligands and complexes obtained and the paramagnetic effects, including T_1 and T_2 relaxation times which were investigated for our *tert*butyl reporter groups.

The new ligands **L4**, **L5** and **L6** have been created using similar functional groups seen in ligands **L2** and **L3**. These would still contain the amide groups, but instead of a diamide, a 1,2,3-triazole would be added to the structure instead, changing the ligand's binding motif. The triazole is a good replacement group as it allows us to access many different linkers through copper catalysed azide-alkyne cycloaddition reactions. These linkers allow us to control the length of our ligands, non-dative bonding regions as well as the denticity of the ligand which helps determine the geometry of a metal-organic cage. For this project, the linker will be substituted for a simple benzyl group for us to test the viability of this binding motif in isolation as well as compare it to the results obtained from the amide complexes.

L4 complexes

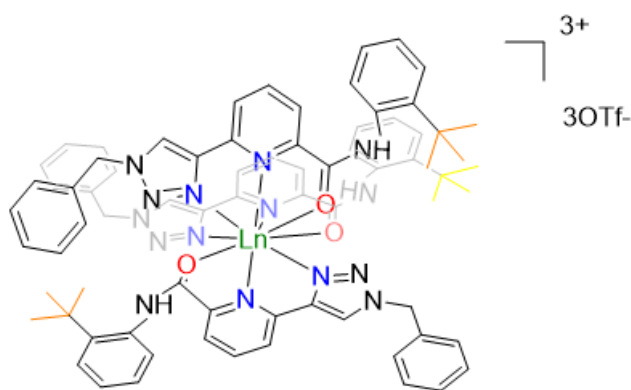


Figure 12. General formula for LnL_4_3 complexes.

Complex **LuL4₃** was the first complex formed using ligand **L4**, using the diamagnetic lanthanide salt $\text{Lu}(\text{OTf})_3$. ^1H NMR data showed that the complex had formed the *meridional* isomer, as there were three separate signals for the *tert*butyl group (1.07, 0.92 and 0.88 ppm) and the amide group's hydrogen environment (10.15, 10.04 and 9.78 ppm), one for each ligand bonding to the lutetium ion. Interestingly, there is a 4th *tert*butyl and amide hydrogen signal (0.88 and 9.62 ppm) that is of a relatively lower integration in comparison the three pairs of peaks assigned to the meridional complex. This is likely due to there being excess ligand within the solution. The aromatic region contains a series of large multiplets along with triplets and doublets. The large multiplet at 7.5 ppm is likely the amalgamation of the aromatic phenyl groups of each of the *fac* isomers as well as some signals of the 1,2-substituted benzene ring that contains the reporter group and our amide, based on the chemical shifts of the signals and the lack of a full set of 12 signals representing each of the expected hydrogen environments. 4 signals, a doublet of doublets at 5.97 ppm, 2 multiplets at 6.11 ppm and 6.47 ppm, and a triplet of doublets at 6.71 ppm integrate in a 1:1 ratio with the amide signals and 1:9 ratio with the *tert*butyl signals previously mentioned which give more evidence that the major isomer in solution is *meridional*. Signals between 8.58 ppm and 7.75 ppm are

overlapping triplets and doublets that match well with the hydrogen environments for the nitrogen containing six membered rings in the centre of the ligand. Due to the stereocentre at the lanthanide ion, it is expected that the two hydrogens on the benzylic position of the ligand are not identical in ^1H NMR and are in fact diastereotopic. Despite this, there are 2 signals that appear as broad singlets at 5.35 ppm and 5.43 ppm, while there is a multiplet at 5.23 ppm. These signals integrate in a 2:1 ratio with the signals in the amide hydrogen region and have chemical shifts typical of hydrogen environments on the benzylic position of a benzyl triazole moiety, despite the disparity in splitting patterns, and so have been assigned to the three benzylic hydrogen environments in the complex.

Formula	Theoretical m/z	Found m/z	Charge
L₄Lu³⁺ + OTf⁻	778.7547	778.7602	2+
L₄Lu³⁺ + 2OTf⁻	1706.4620	1706.4743	1+

Table 5

The full paramagnetic ^1H NMR spectrum of **DyL₄** showed shifts as far as 177 ppm and -113 ppm, although these peaks had low integration and are most likely not the *tert*butyl reporter group peaks. Like complex **LuL₄**, **DyL₄** appeared to have formed a *meridional* isomer; there were three large and broad signals all with similar intensity, at 52.86, 37.02 and 6.57 ppm. We expect these shifted peaks to be *tert*butyl peaks due to their high integration and the size of the paramagnetic shift that was observed in these environments. For example, the signal at -110.45 ppm had an integration ratio of 1:9 with the signals attributed to the *tert*butyl reporter groups. One of the *tert*butyl signals appeared to be in superposition with another signal and due to this as well as it laying inside the biological window, only two of the three signals can have their relaxation properties investigated.

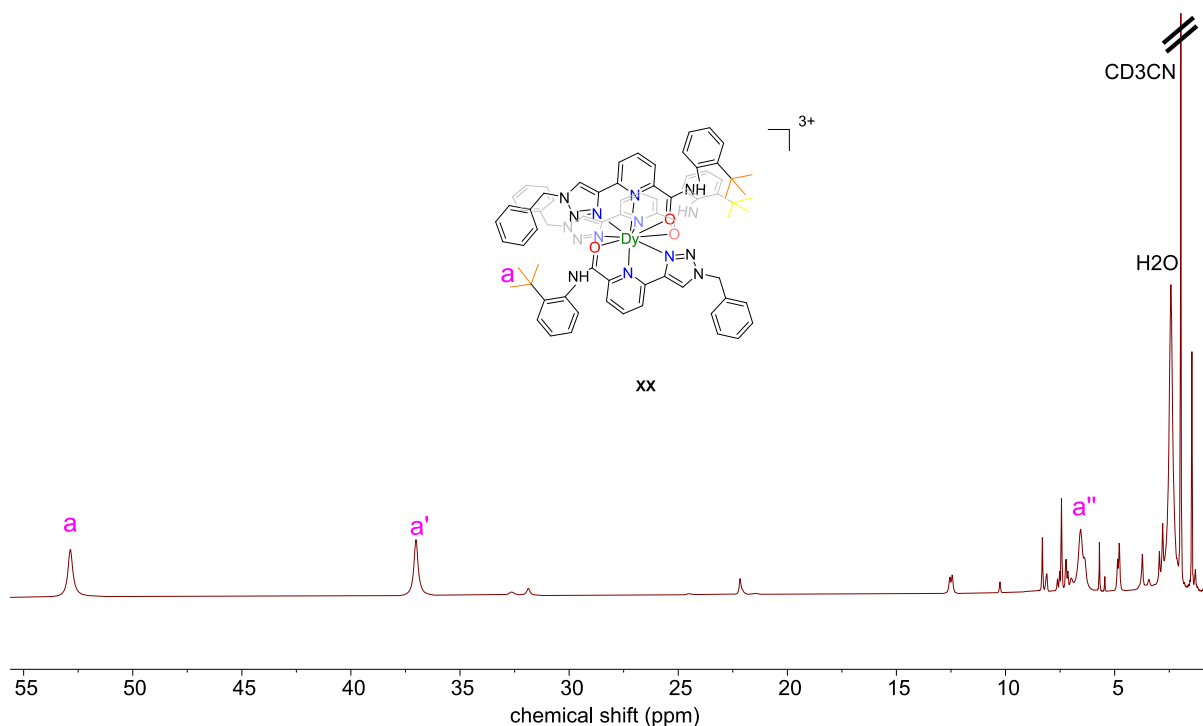


Figure 13. NMR spectra of **DyL43** in CD_3CN

For both signals, R_1 and R_2 calculations show that both a_1 and a_2 have fast R_2 relaxation rates, 317.678 and 278.188 Hz respectively. While fast, considering them in terms of T_1 and T_2 , they are still within the range of milliseconds, which would work well with millisecond pulse times. While faster rates would decrease the time for pulses to be taken and so increase the amount of information we can gain per second, R_2^* is proportional to the broadness of the signal width, as explained in the introduction, and so faster signals can lead to issues with broad lines that overlap and decrease the clarity of the spectra. The signal with the fastest R_2 , a_1 , has a close R_1/R_2^* ratio of 0.932, and in conjunction with its chemical shift, it makes it a good candidate to use as a reporter signal in PARASHIFT imaging.

Signal	Chemical shift δ	R_1 (Hz)	R_2^* (Hz)	R_1/R_2^*
a₁	52.86	296.095 $\pm$ 15.266	317.678	0.932
a₂	37.02	191.073 $\pm$ 55.6168	278.188	0.687

HRMS data gave evidence of the 1+ and 2+ ion species, reporting peaks at 1695.4520 and 773.2575 m/z respectively, in comparison to the theoretical values of 1695.4517 and 773.2497 m/z. Data for other **L4** containing lanthanide complexes can be found in the experimental section.

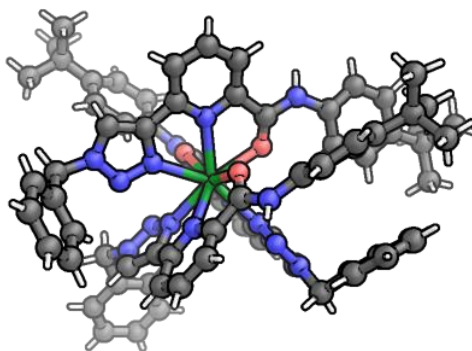


Figure 14. Crystal structure of LuL6₃

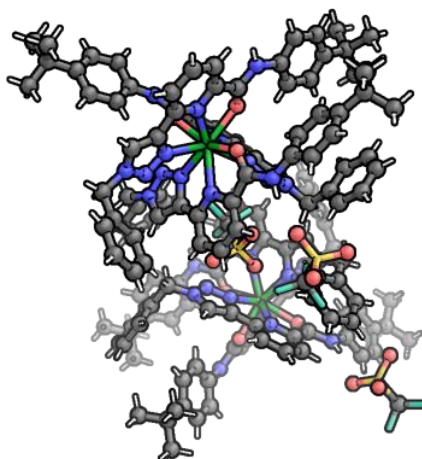


Figure 15. Unit cell of LuL6₃

Paramagnetic NMR and relaxation experiments showed that paramagnetic complexes created from **L6** had fast relaxation times and good R_1/R_2 ratios. This data can be found in the experimental section.

Future prospects

Full characterisation of each complex is needed, and comparisons must be made to determine which ligand motif and lanthanide ion pair is best suited for cage synthesis.

Minisci reaction

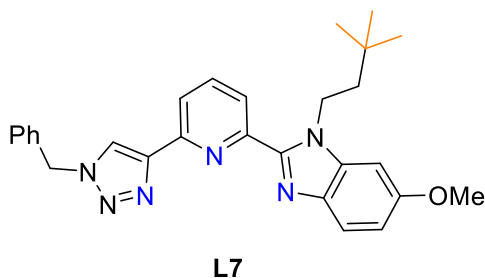


Figure 16

Within the research group, ligand **L7** has been shown to form mononuclear complexes with all *fac* isomerism upon complexation reactions with lanthanides. This is ideal for use as a PARASHIFT agent as it allows there to be a single set of ligand peaks when an NMR experiment is run, making interpretation easier. This isomerism is thought to come from the 2,2-dimethylpropyl group that is part of the benzimidazole moiety. Ligand **L7** forms three dative covalent bonds with lanthanides, one from the triazole, pyridine and benzimidazole, respectively. The final reaction to form ligand **L7** can be altered with other azides, and which would then form cages.

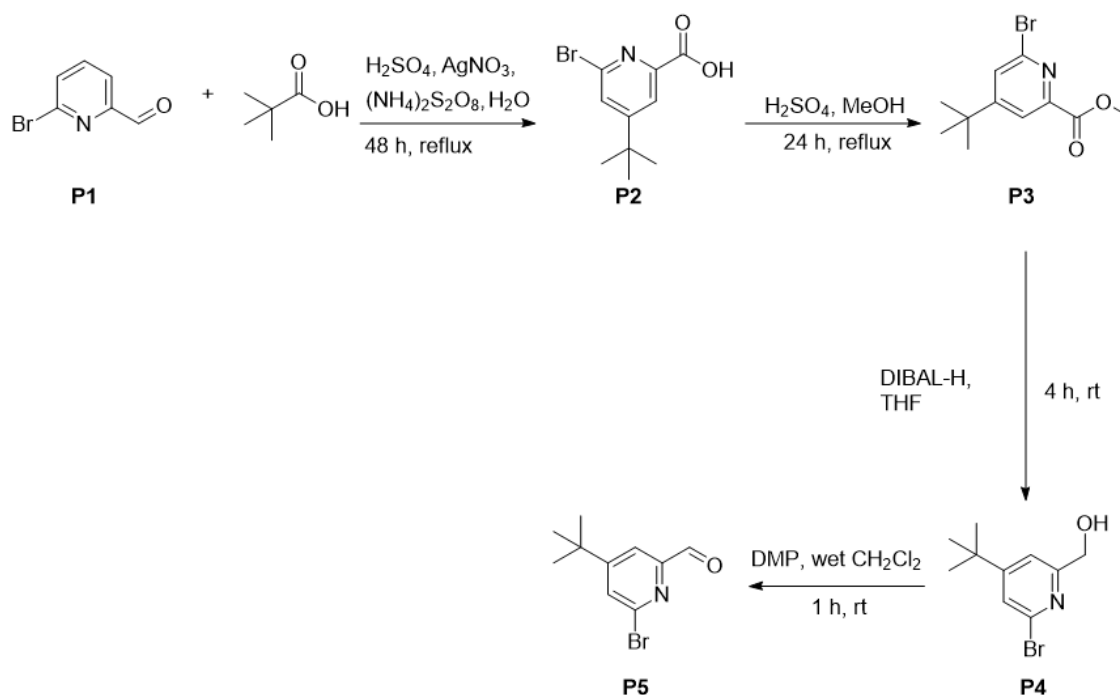


Figure 17

This allows us to control the morphology of the cage to our liking, making benzyl azide a good reagent to use for mononuclear complexes. Triflate lanthanide salts have been shown to form

stable mononuclear complexes within the research group and are the main choice for not only this project but all complexation reactions within this project.

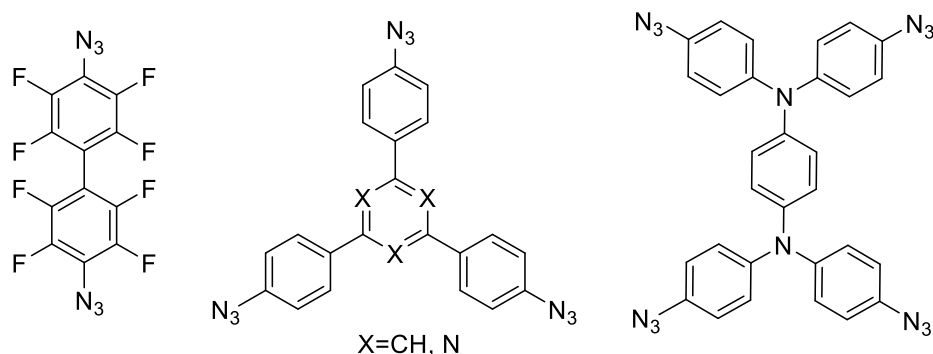


Figure 18

To take advantage of the *tert*butyl group we decided to use the Minisci reaction. This method offers great utility in adding alkyl groups to electron deficient aromatic rings, which are common in cage chemistry due to the dative bonds that are formed between nitrogen atoms and metal ions. With this reaction we can place a *tert*butyl group *para* to the nitrogen in the pyridine moiety. Due to the oxidative conditions of the reaction to get to precursor **P2**, the aldehyde will be converted to a carboxylic acid, this brings the challenge of creating an aldehyde again. To do this, a route was created where Fischer esterification is performed, creating **P4** which is more susceptible to reduction. After the reduction step, Dess-Martin periodinane is used as a mild oxidising agent to regain the aldehyde functional group, now with the *tert*butyl group in place.

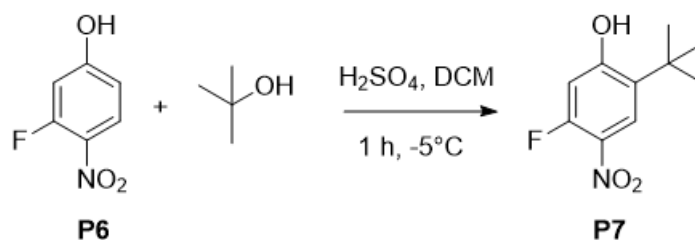


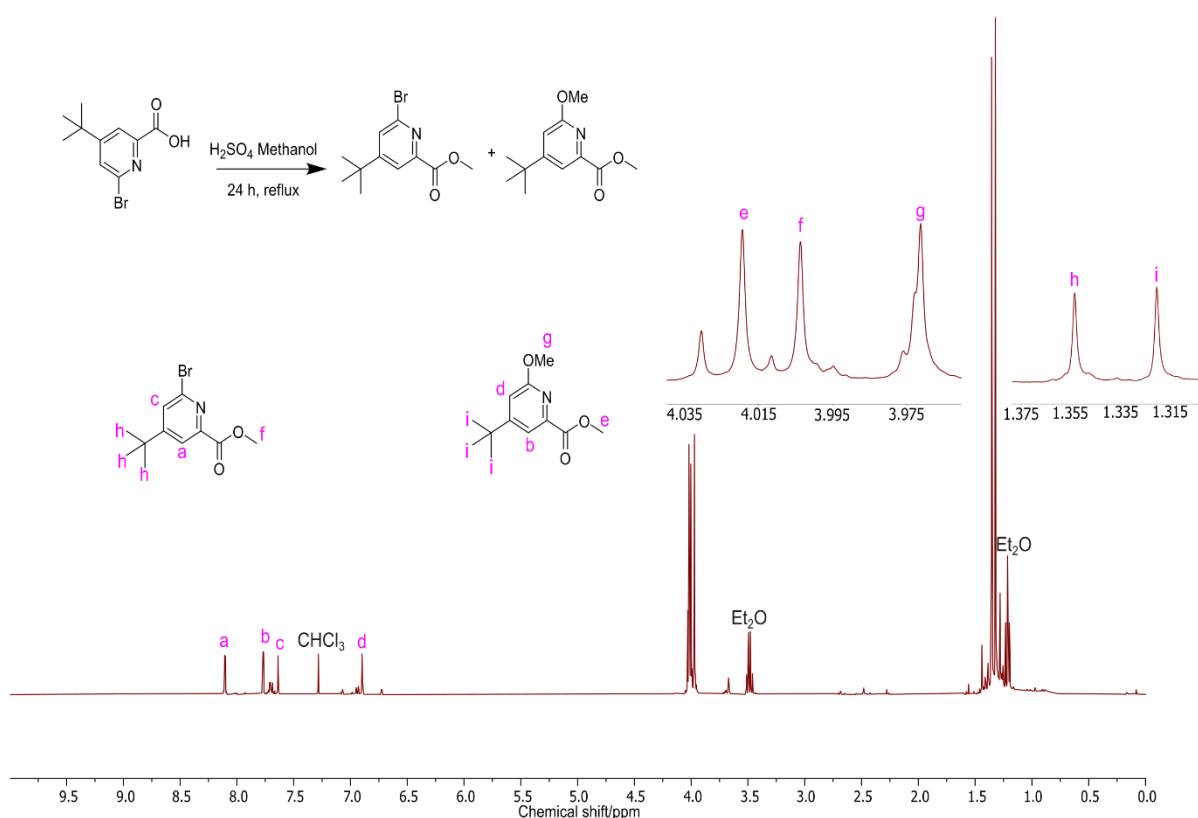
Figure 19

Once precursor P5 and P7 are made, they will be used to make new ligands similar to L7. This would give 2 more groups of 9 equivalent hydrogens on that we can use to form 3 more ligands, one with a 9 equivalent hydrogens environment on each moiety providing a dative covalent bond to the metal centre and two more where either the triazole or the benzimidazole part of the molecule contains a *tert*butyl group but not the other.

Synthesis and characterisation

The first reaction was to place a *tert*butyl group at the *para* position, using pivalic acid to make precursor **P2**. To increase the yield of this reaction we decided to increase the amount of

pivalic acid and oxidant in reference to the starting material. **P1** (1 equiv.) reacted with pivalic acid (11 equiv.), in the presence of AgNO_3 (3.6 equiv.), H_2SO_4 (2.6 equiv.) and $(\text{NH}_4)_2\text{S}_2\text{O}_8$ (11 equiv.). The results of this experiment showed that the desired product was created which was confirmed by both HRMS but there was an excess of unreacted pivalic acid that was difficult to remove from the product. Separation by chromatography proved unviable due to both the product and pivalic acid adhering heavily to the stationary phase. Several subsequent experiments were done, changing the liquids used in liquid-liquid phase separation and centrifugation, and different reactions entirely. Thinking that separation by chromatography would be easier by using an ester instead of an acid, the crude mixture of **P3** (1 g) was used without purification in a Fischer-esterification reaction with excess methanol and H_2SO_4 (13 mL). Unfortunately, this led to a roughly 1:1 mixture of the desired bromine containing ester and one where the bromine was substituted for a methoxy group, based on the ^1H NMR results. What was most likely to have happened is that the reaction conditions also permitted nucleophilic aromatic substitution with bromine as a leaving group.



Seeing as this would mean that Fischer esterification wouldn't be a viable route, we decided to reduce the **P2** outright to **P4** using LiAlH_4 , using the crude mixture from the previous step.

Interestingly, this reaction resulted in the creation of precursor **P5**, supported by both ^1H NMR and HRMS data but the yield of the reaction was negligible.

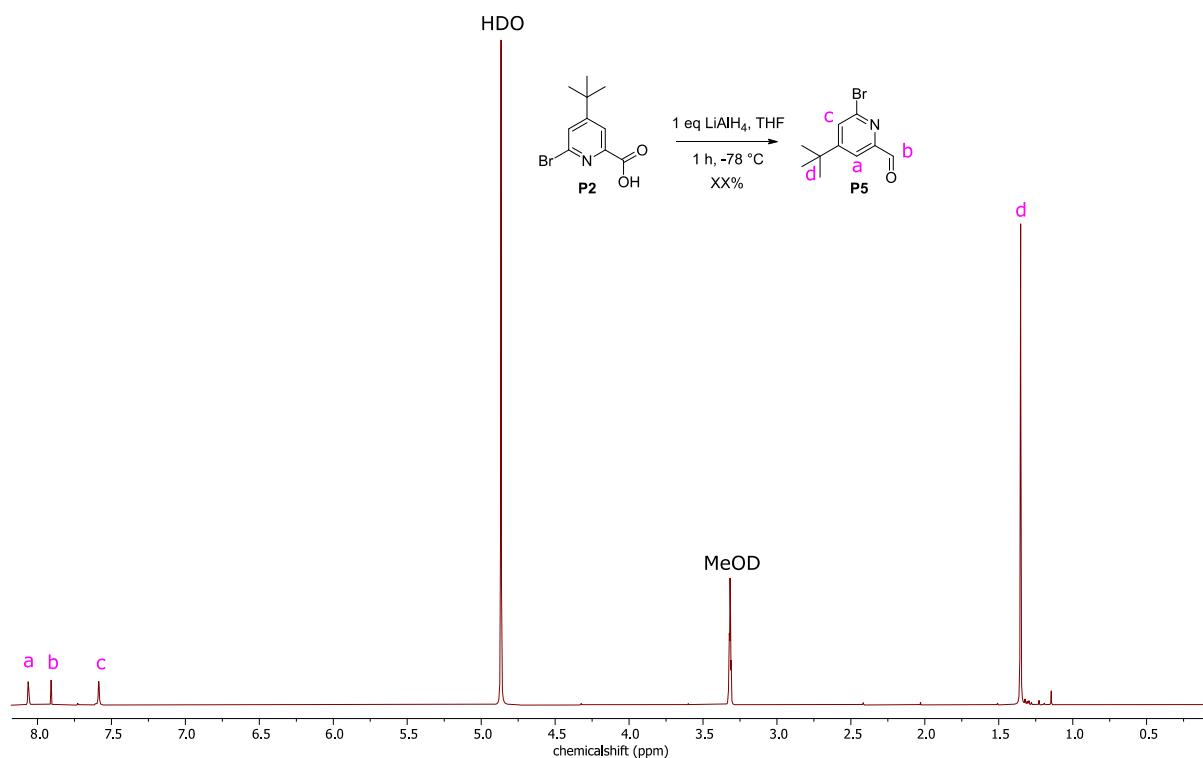
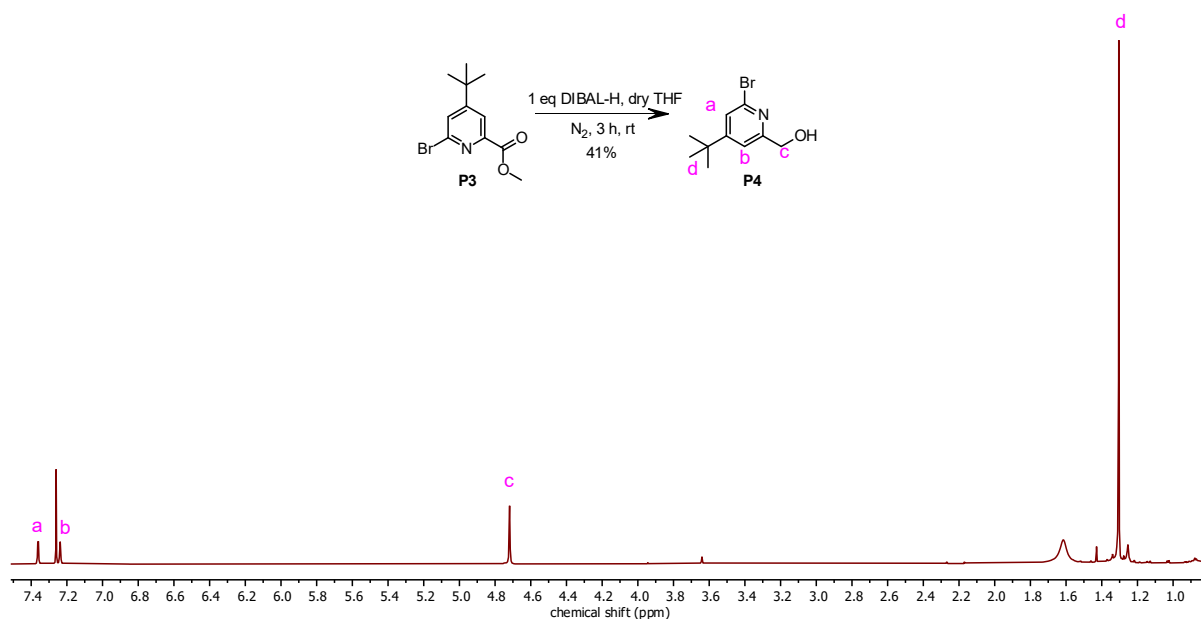


Figure 2

Ultimately, it was decided to use the methylating agent to get the precursor **P3**. **P2** (1 equiv.) reacted with dimethyl sulphate (1 equiv.) in acetone in the presence of K_2CO_3 (1.25 equiv.) This reaction worked well, giving a yield of 52% and the existence of **P3** was confirmed by HRMS and ^1H NMR. Going back to the original step to get to precursor **P4**, the reaction using DIBAL-H was successful, giving a yield of 40%.



But the final step in the synthesis of precursor **P5** was not feasible, despite the reaction working. **P4** (1 equiv.) reacted with Dess-Martin periodinane (1 equiv.) while refluxing in DCM, the reaction did not go to completion with some starting material still present, and only 10 mg of solid crude product was created out the original 61 mg of starting material. For an 8-step synthesis, 4 steps of this being to create a precursor, the overall yield would make this synthetic route incredibly cost-ineffective.

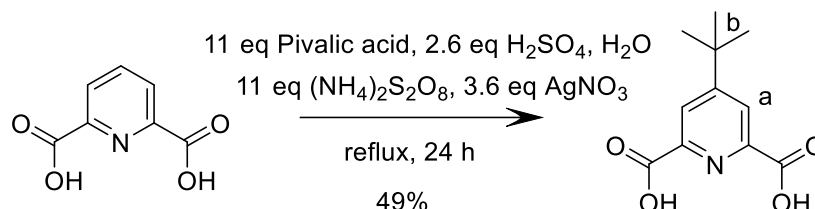
Before abandoning this route, more work was done to purify the crude product of the initial Minisci reaction. After trying many solvents, we managed to separate pivalic acid from the mixture by recrystallizing the crude product in dry toluene, which removed solid impurities, then washing and centrifuging with hexane, which pivalic acid had low solubility in, while **P4** had high solubility. By repeatedly sonicating and then centrifuging the mixture, collecting the hexane each time and concentrated *in vacuo*, pure product was obtained. The yield of this reaction was 52%.

Despite not synthesising all of the ligands within this work, much of the trial and error that went into this process has laid the groundwork for optimising the synthetic route. Discovering the purification method used during the work up of Minisci reactions opens the door for a wide range of picolinic acids, picolinaldehydes and other nitrogen containing heterocycles that can benefit from it. Further optimisation could be done on the oxidation reaction by increasing the time of the reaction or introducing heat to the reaction condition. For the second route for **P3**, more alkylation reactions can be tried in order to find one that is successful. With a successful and optimised route to get ligands, complexation reactions can take place and T₂ experiments

can be done to determine to the PARASHIFT capabilities, and if successful in showing that the *tert*butyl groups are within sufficient distance of the lanthanide ion to experience PARASHIFT, the ligands will be modified to form cages. With cages, binding experiments can be done with guest molecules, and while T_2 experiments can be done on to probe the change in shift, allowing the cages to be distinguished by whether they have encapsulated a guest molecule or not.

Experimental

4-(*tert*-Butyl)pyridine-2,6-dicarboxylic acid



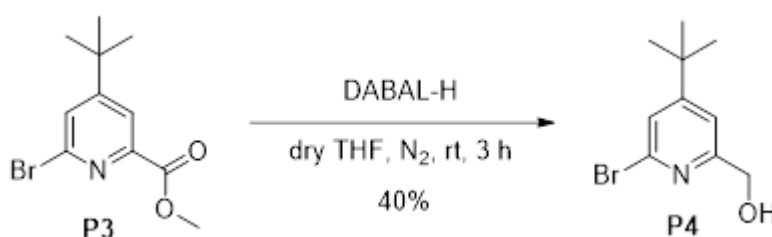
Pyridine-2,6-carboxylic acid (1.01 g, 6.06 mmol), pivalic acid (6.73 g, 65.9 mmol), (NH₄)₂S₂O₈ (15.0 g, 65.7 mmol) and AgNO₃ (0.365 g, 2.15 mmol) were placed into a round bottom flask covered in foil. H₂O (74 mL) and H₂SO₄ (0.74 mL) were subsequently added to the flask and the contents were refluxed and stirred for 24 hours. The mixture was cooled to room temperature and brine (20 mL) was added. EtOAc (3 × 20 mL) was used to extract the mixture. The combined organic layers were dried over Na₂SO₄ and evaporated under reduced pressure to give a dark brown liquid as the crude product. The crude product was washed with hexane, sonicated for 1 min, and centrifuged at 3000 rpm for 15 min × 3. The organic layers were collected and concentrated *in vacuo* to give the pure product (660 mg, 2.96 mmol, 49%) as a grey/pink powder.

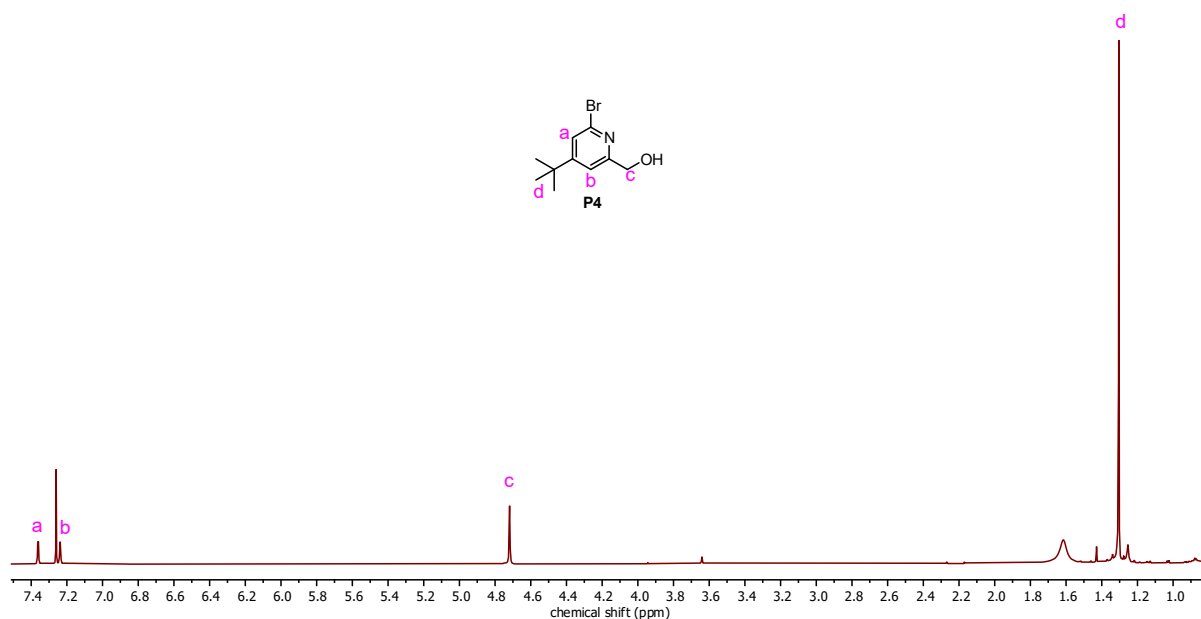
¹H NMR (400 MHz, MeOD) δ 8.38 (s, 2H, a), 1.42 (s, 9H, b).

¹³C NMR (101 MHz, MeOD) δ 166.8, 165.2, 148.3, 125.3, 35.7, 30.0.

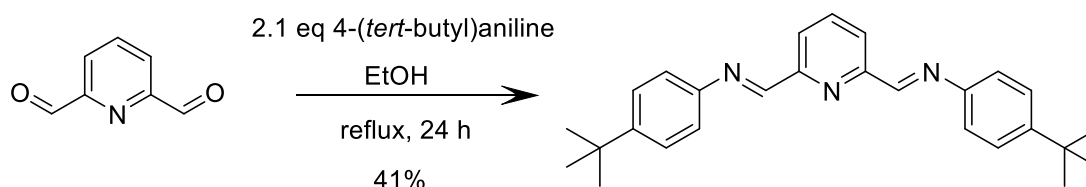
HRMS (ESI, MeOH), m/z: calc for [M+Na]⁺, [C₁₁H₁₃NNaO₄]⁺, 246.0737, found 246.0736

P4





(1E,1'E)-1,1'-(Pyridine-2,6-diyl)bis(N-(4-(tert-butyl)phenyl)methanimine) L1

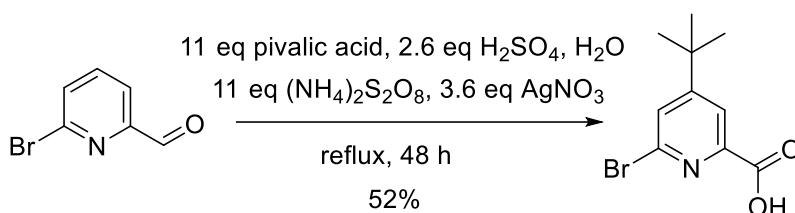


Pyridine-2,6-dicarbaldehyde (505 mg, 3.74 mmol), 4-*tert*-butylaniline (1.24 mL, 7.85 mmol) and EtOH (60 mL) were placed into a round bottom flask and the mixture was refluxed and stirred for 24 h. The mixture was concentrated in *vacuo* and the remained solid was dissolved in CH₂Cl₂ (30 mL) and washed with H₂O (3 × 20 mL), dried over Na₂SO₄ and the solvent was removed in *vacuo* to give the pure product.

¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 2H, a), 8.29 (d, *J* = 7.8 Hz, 2H, b), 7.92 (t, *J* = 7.8 Hz, 1H, c), 7.49 – 7.41 (m, 4H, d), 7.34 – 7.26 (m, 4H, e), 1.36 (s, 18H, f).

¹³C NMR (101 MHz, CDCl₃) δ 159.3, 154.8, 150.3, 148.0, 137.2, 126.2, 123.1, 121.0, 34.6, 31.4.

6-Bromo-4-(*tert*-butyl)picolinic acid



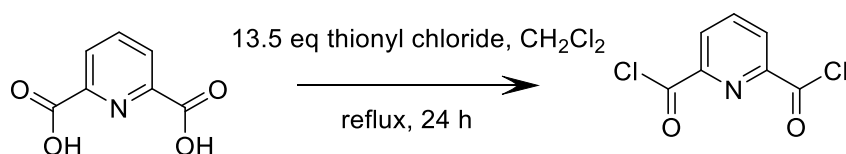
6-Bromopicolinaldehyde (4.00 g, 21.5 mmol), pivalic acid (26.7 mL, 237 mmol), (NH₄)₂S₂O₈ (54.1 g, 237 mmol) and AgNO₃ (1.31 g, 7.74 mmol) were placed into a round bottom flask covered in foil. H₂O (250 mL) and H₂SO₄ (2.5 mL) were subsequently added to the flask and the mixture were refluxed and stirred for 48 h. The mixture was cooled to room temperature and brine (50 mL) was added. EtOAc (3 × 30 mL) was used to extract the mixture. The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo* to give a dark brown liquid as the crude product. The crude product was recrystallized with dry toluene to solidify the impurities, then the mixture was washed with hexane (30 mL), sonicated for 1 min and centrifuged at 3000 rpm for 15 min × 3 to remove the solid impurities. The supernatant liquid from each round of centrifugation was collected and concentrated *in vacuo* to give the pure product (2.90 g, 11.2 mmol, 52%) as a yellow powder

¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 1.6 Hz, 1H, a), 7.70 (d, *J* = 1.5 Hz, 1H, b), 1.36 (s, 9H, c).

¹³C NMR (101 MHz, CDCl₃) δ 166.3, 163.4, 147.0, 141.2, 129.6, 120.7, 77.4, 30.5.

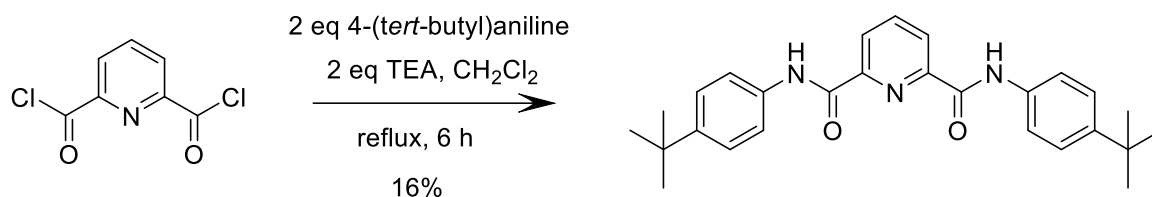
HRMS (ESI, MeOH), *m/z*: calc for [M-H]⁻, [C₁₀H₁₁BrNO₂]⁻, 255.9979, found 255.9982.

Pyridine-2,6-dicarbonyl dichloride



Pyridine-2,6-dicarboxylic acid (500 mg, 2.99 mmol) was placed into a 2-necked flask under nitrogen N₂. Thionyl chloride (1 M solution in CH₂Cl₂, 40.4 mL, 40.4 mmol) was added dropwise and the solution was refluxed and stirred for 24 h. Excess thionyl chloride and CH₂Cl₂ were removed *in vacuo* to give product (580 mg) as a yellow powder. The product was used immediately for reactions with N²,N⁶-bis(4-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide and N²,N⁶-bis(2-(*tert*-butyl)phenyl)pyridine-2,6-dicarboxamide without further purification.

N²,N⁶-bis(4-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide



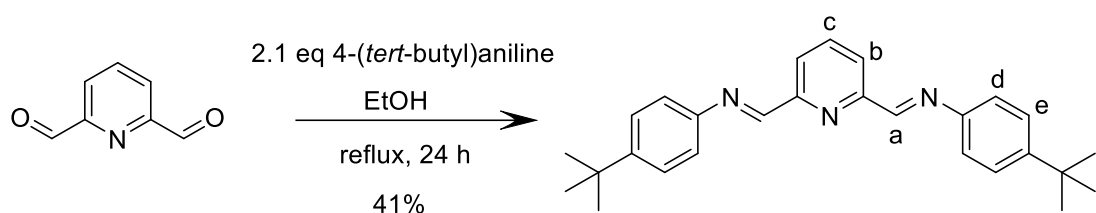
Pyridine-2,6-dicarbonyl dichloride (380 mg, 1.86 mmol) was placed into a 2-necked flask under nitrogen. Dry CH₂Cl₂ (10 mL) was added to mixture. Dry TEA (0.51 mL, 3.73 mmol) was added dropwise, followed by the addition of 4-(*tert*-butyl)aniline (0.59 mL, 3.73 mmol) dropwise. The reaction mixture was refluxed for 6 h, then washed with water (20 mL) and brine (20 mL). The organic layer was dried over Na₂SO₄. CH₂Cl₂ was evaporated in *vacuo*. The solid left was recrystallised in toluene to give product (126 mg, 0.293 mmol, 16%) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.45 (s, 2H, a), 8.51 (d, *J* = 7.8 Hz, 2H, b), 8.15 (t, *J* = 7.8 Hz, 1H, c), 7.73 – 7.65 (m, 4H, d), 7.50 – 7.42 (m, 4H, e), 1.35 (s, 18H, f).

¹H NMR (400 MHz, CD₃CN) δ 10.02 (s, 2H, a), 8.42 (d, *J* = 7.8 Hz, 2H, b), 8.20 (t, *J* = 8.2, 7.4 Hz, 1H, c), 7.82 – 7.74 (m, 4H, d), 7.52 – 7.44 (m, 4H, e), 1.34 (s, 18H, f).

¹³C NMR (101 MHz, CD₃CN) δ 150.3, 136.3, 126.7, 126.1, 121.9, 118.3, 35.1, 31.6, 1.9, 1.7.

N²,N⁶-bis(2-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide

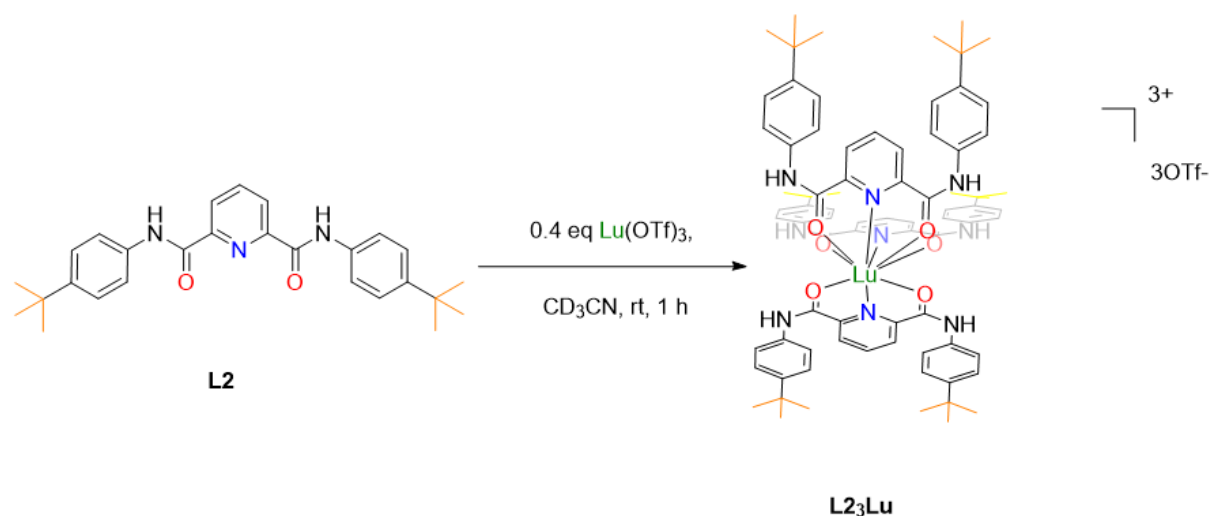


Pyridine-2,6-dicarbonyl dichloride (200 mg, 0.980 mmol) was placed into a 2-necked flask under N₂. Dry CH₂Cl₂ (10 mL) was added to the mixture. Dry TEA (0.27 mL, 1.96 mmol) was added dropwise, followed by the dropwise addition of 2-(*tert*-butyl)aniline (0.31 mL, 1.96 mmol). The reaction mixture was refluxed for 6 h, then washed with water and brine, and the organic layer was dried over Na₂SO₄. CH₂Cl₂ was evaporated in *vacuo* and the resultant solid was recrystallised from toluene to give product (46.7 mg, 0.157 mmol, 16%) as an off-white solid.

^1H NMR (400 MHz, CDCl_3) δ 9.51 (s, 2H, a), 8.56 (d, $J = 7.7$ Hz, 2H, b), 8.19 (t, $J = 7.9$ Hz, 1H, c), 7.74 (d, $J = 7.2$ Hz, 2H, d), 7.46 (d, $J = 7.7$ Hz, 2H, e), 7.32 (t, $J = 7.4$ Hz, 2H, f), 7.25 (t, 2H, g), 1.42 (s, 18H, h).

^{13}C NMR (101 MHz, CDCl_3) δ 162.0, 139.9, 128.0, 127.3, 127.0, 127.0, 126.1, 77.4, 53.6, 34.9, 30.9, 1.2.

L2₃Lu



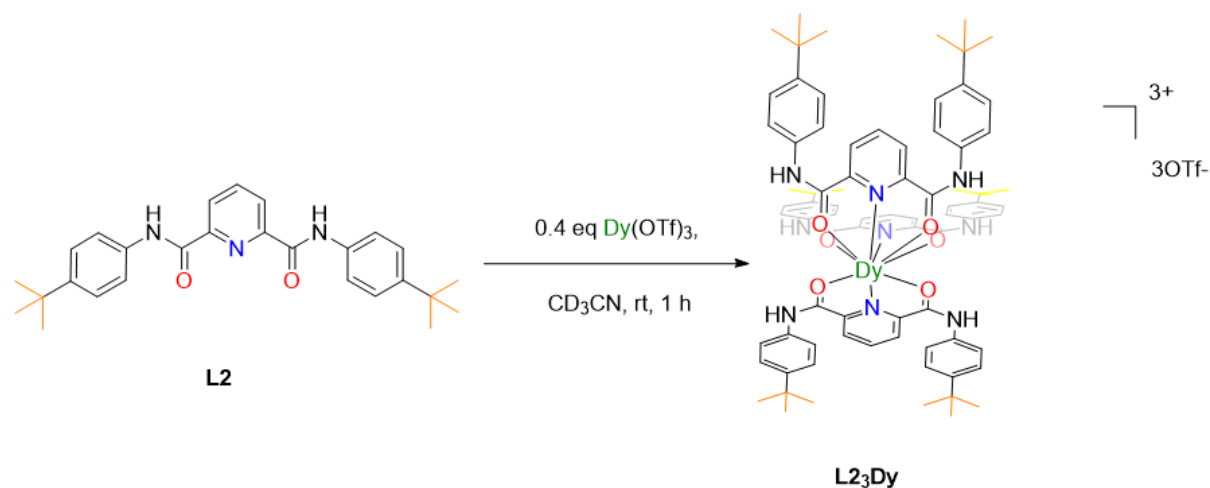
N^2,N^6 -bis(4-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.40 mg, 1.50×10^{-2} mmol) and Lu(OTf)_3 (3.70 mg, 6.00×10^{-3} mmol) were added to a small vial along with CD_3CN (0.6 mL). The mixture was stirred for 1 h to give a solution of complex in CD_3CN .

^1H NMR (400 MHz, CD_3CN) δ 9.99 (s, 2H, a), 8.41 (d, $J = 7.7$ Hz, 2H, b), 8.20 (dd, $J = 8.1$, 7.4 Hz, 1H, c), 7.77 (d, $J = 8.7$ Hz, 4H, d), 7.47 (d, $J = 8.7$ Hz, 4H, e), 1.33 (s, 18H, f).

HRMS (ESI, CD_3CN), m/z : calc for $[\text{ML}_2(\text{OTf})]^{+2}$, $[\text{C}_{82}\text{H}_{93}\text{F}_3\text{LuN}_9\text{O}_9\text{S}]^{2+}$, 8005.8083, found 805.8107.

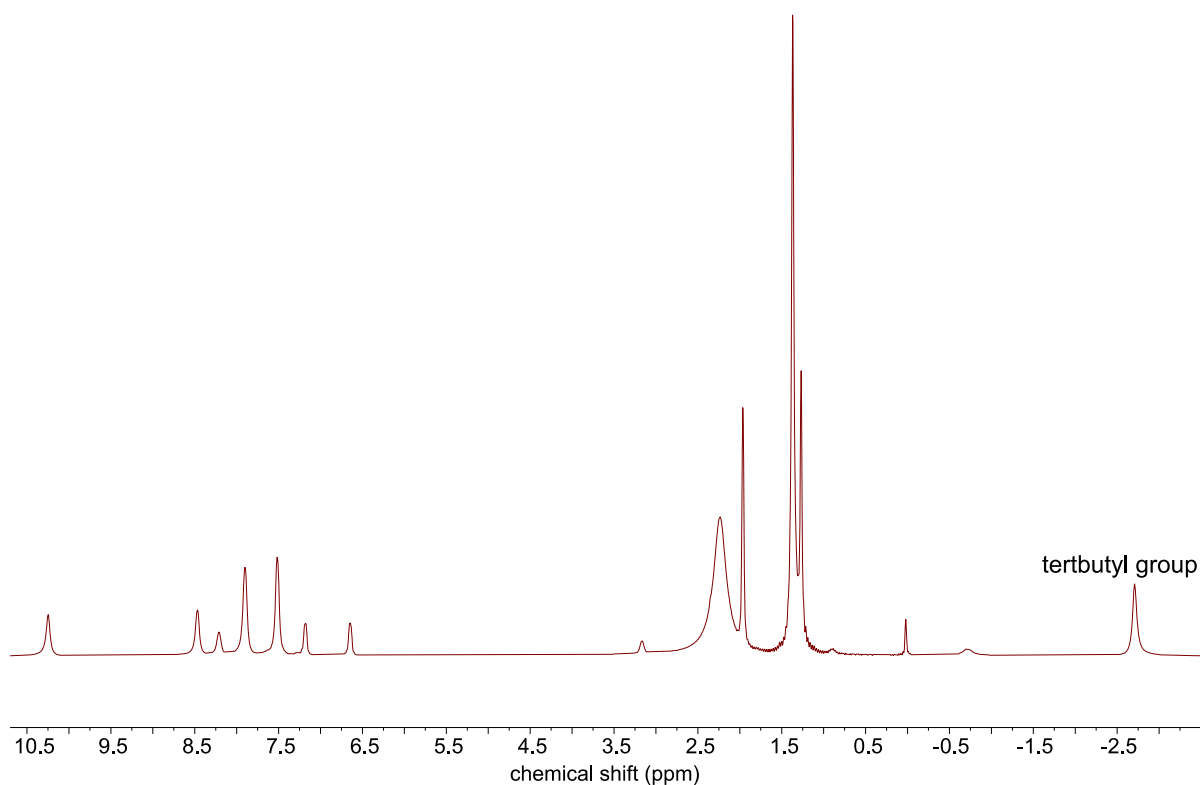
HRMS (ESI, CD_3CN), m/z : calc for $[\text{ML}_2]^{+3}$, $[\text{C}_{81}\text{H}_{93}\text{LuN}_9\text{O}_6]^{3+}$, 487.5552, found 487.5524.

L2₃Dy

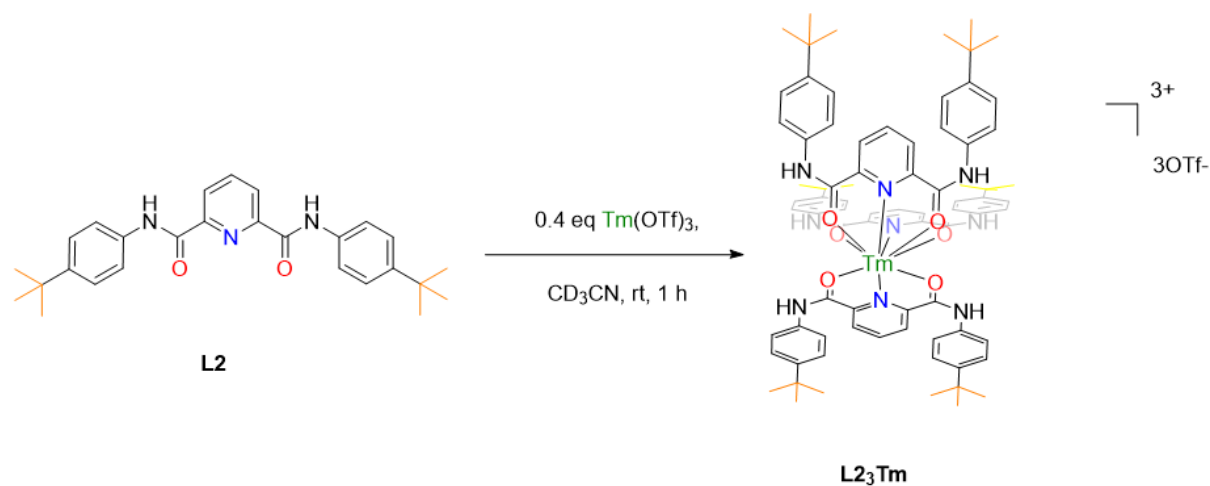


N²,N⁶-bis(4-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.4 mg, 1.50×10^{-2} mmol) and Dy(OTf)₃ (3.7 mg, 6.00×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The mixture was stirred for 1 h to give a solution of complex in CD₃CN.

HRMS (ESI, CD₃CN), m/z: calc for [ML₂₃]³⁺, [C₈₁H₉₃DyN₉O₆]³⁺, 483.8834, found 483.8887.



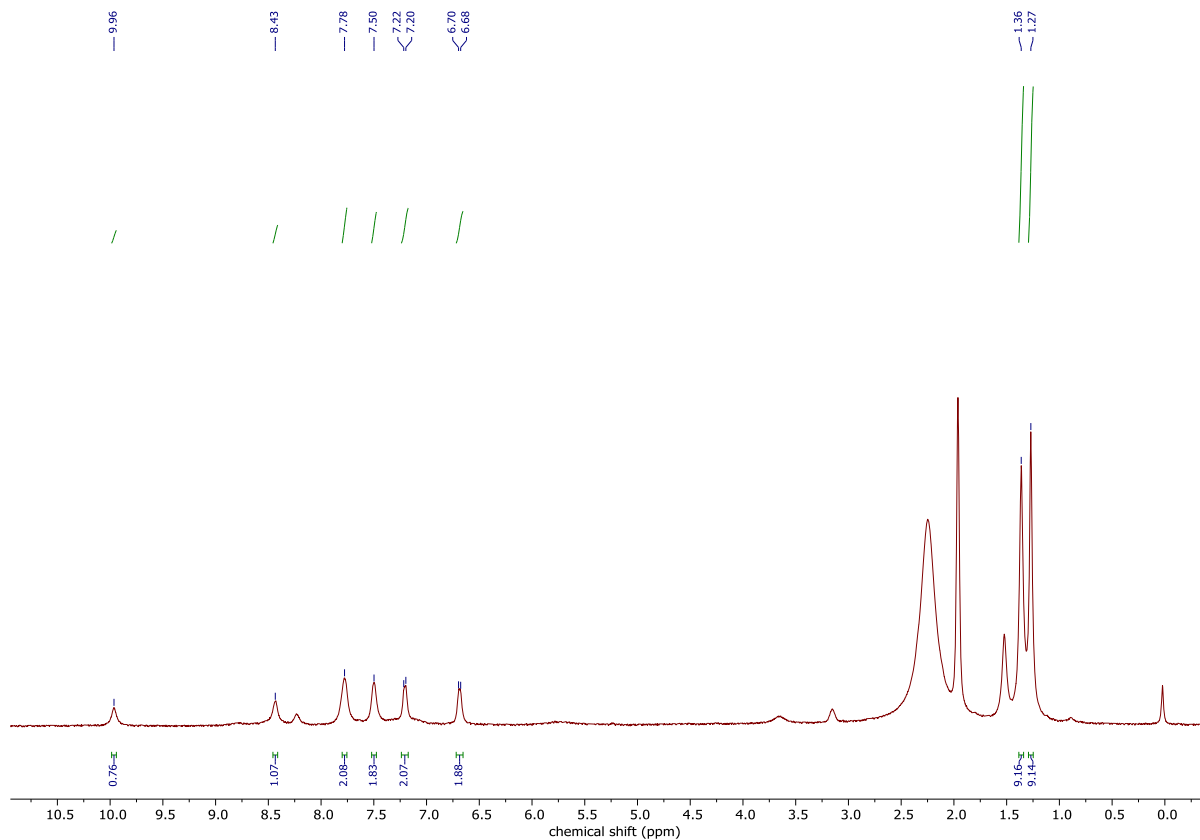
L₂₃Tm



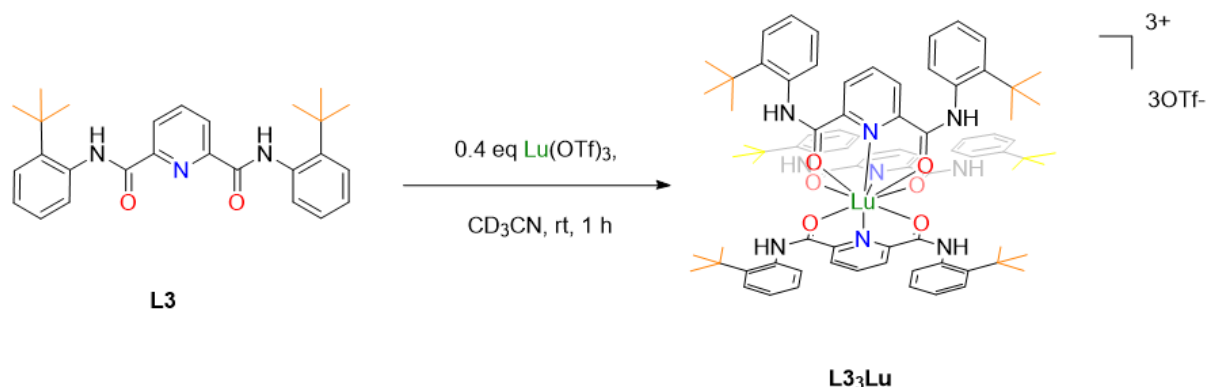
N²,N⁶-bis(4-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.40 mg, 1.50 × 10⁻² mmol) and Tm(OTf)₃ (3.70 mg, 6.00 × 10⁻³ mmol) were added to a small vial along with CD₃CN (0.6 mL). The mixture was stirred for 1 h to give a solution of complex in CD₃CN.

HRMS (ESI, CD₃CN), m/z: calc for [ML₂₃(OTf)]²⁺, [C₈₂H₉₃F₃TmN₉O₉S]²⁺, 802.8055, found 802.8021.

HRMS (ESI, CD₃CN), m/z: calc for [ML₂₃]³⁺, [C₈₁H₉₃TmN₉O₆]²⁺, 485.5530, found 485.5529.



L3₃Lu

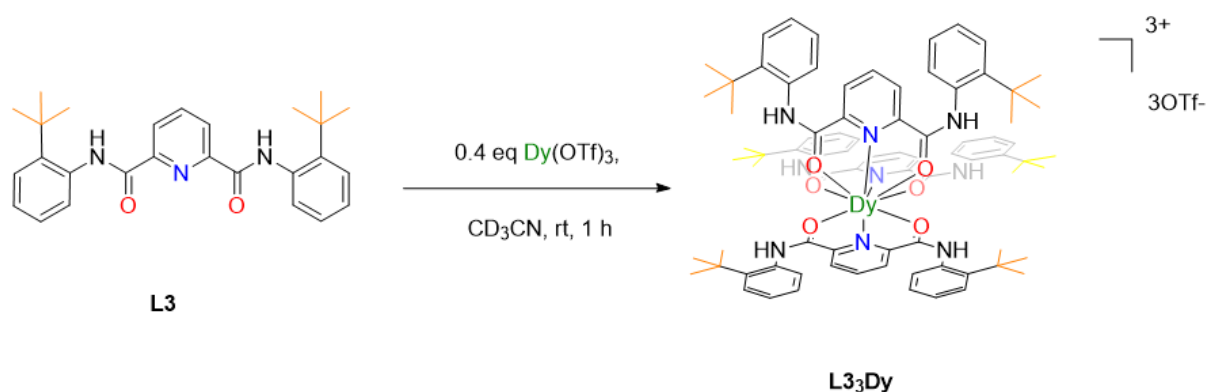


*N*²,*N*⁶-bis(2-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.40 mg, 1.50×10^{-2} mmol) and $\text{Lu}(\text{OTf})_3$ (3.70 mg, 6.00×10^{-3} mmol) were added to a small vial along with CD_3CN (0.6 mL). The mixture vial were stirred for 1 h to give a solution of complex in CD_3CN .

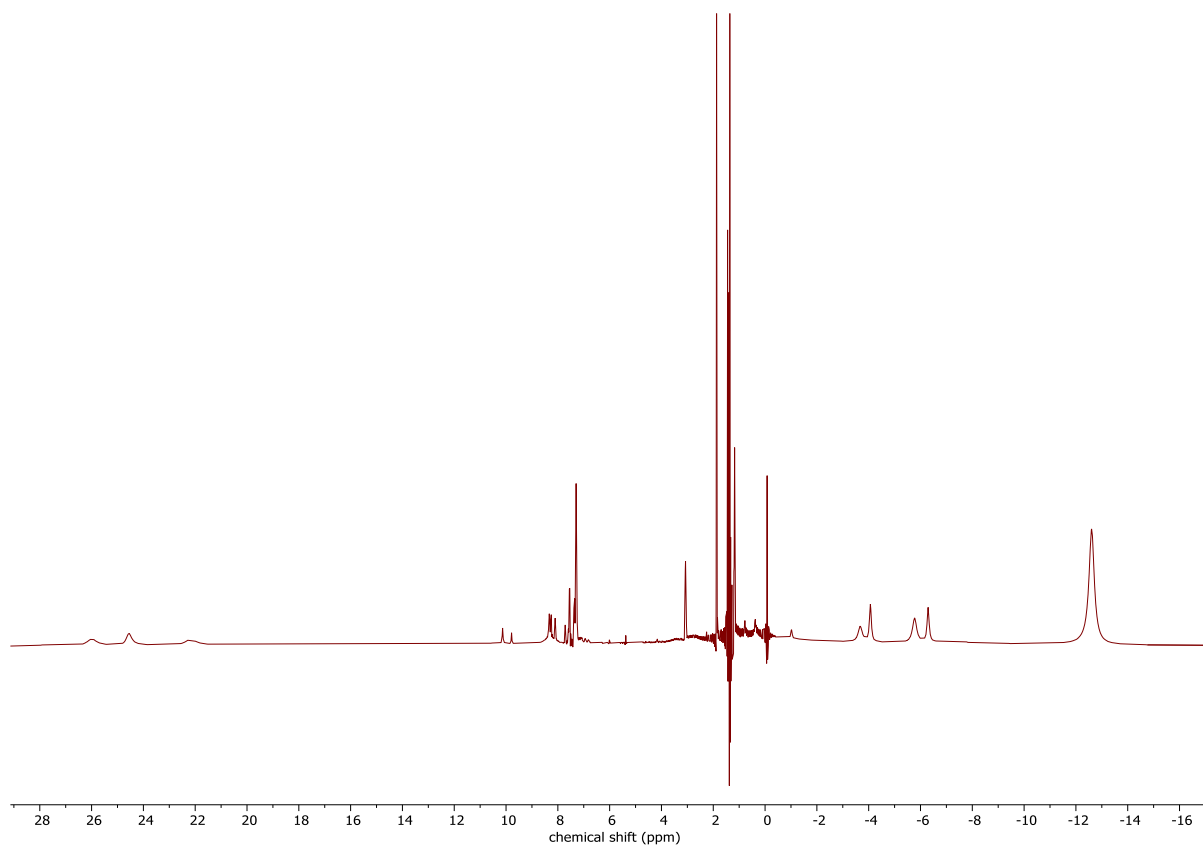
HRMS (ESI, CD_3CN), *m/z*: calc for $[\text{ML}_3]^{+3}$, $[\text{C}_{81}\text{H}_{93}\text{LuN}_9\text{O}_6]^{3+}$, 487.5547, found 487.5553.

HRMS (ESI, CD_3CN), *m/z*: calc for $[\text{ML}_3(\text{Otf})]^{+2}$, $[\text{C}_{82}\text{H}_{93}\text{F}_3\text{LuN}_9\text{O}_9\text{S}]^{2+}$, 805.8083, found 805.8083.

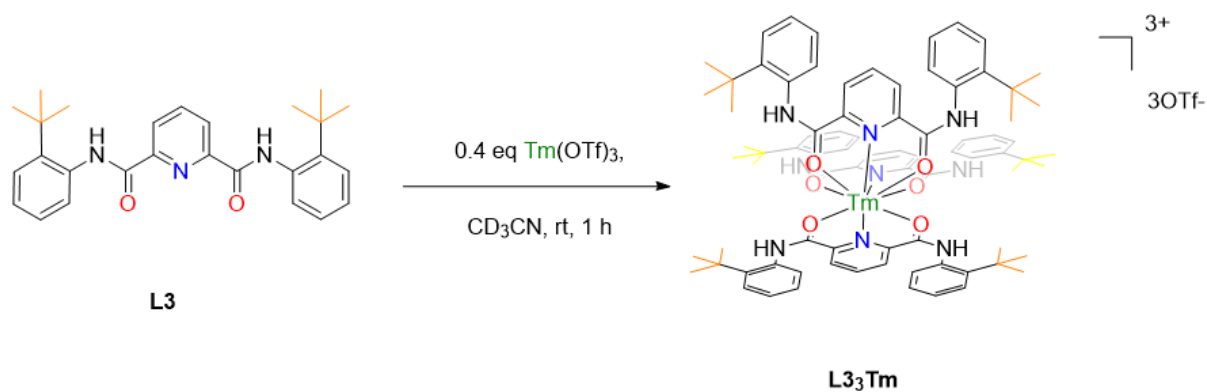
L3₃Dy



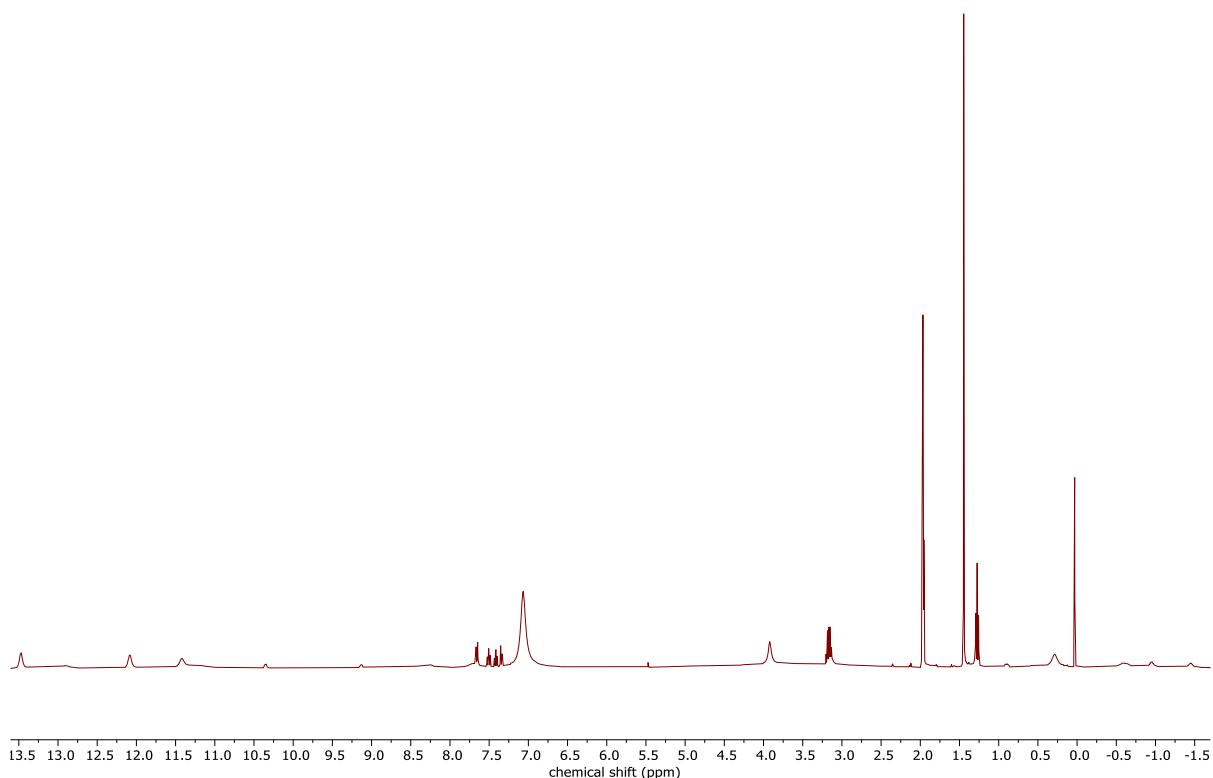
*N*²,*N*⁶-bis(2-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.40 mg, 1.50×10^{-2} mmol) and $\text{Dy}(\text{OTf})_3$ (3.70 mg, 6.00×10^{-3} mmol) were added to a small vial along with CD_3CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD_3CN .



L3₃Tm

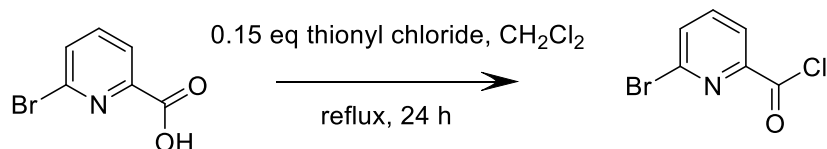


*N*²,*N*⁶-bis(2-(*tert*-Butyl)phenyl)pyridine-2,6-dicarboxamide (6.40 mg, 1.50×10^{-2} mmol) and Tm(OTf)₃ (3.70 mg, 6.00×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.



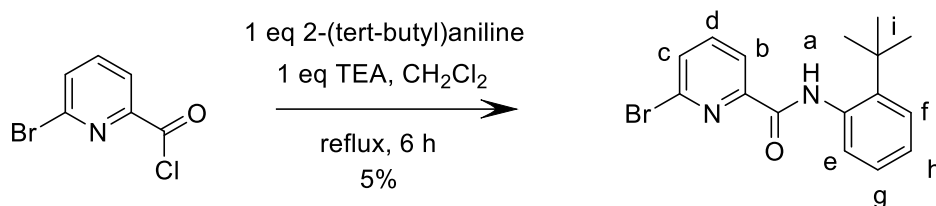
HRMS (ESI, CD₃CN), m/z: calc for [ML₃(OTf)]⁺2, [C₈₂H₉₃F₃TmN₉O₉S]²⁺, 802.8055, found 802.8066.

6-Bromopicolinoyl chloride



6-Bromopicolinoyl chloride (6.00 g, 297 mmol) was placed into a 2-necked flask under N₂. Thionyl chloride (1 M solution in CH₂Cl₂, 44.5 mL, 44.5 mmol) was added dropwise and the solution was heated under reflux and with stirring for 24 h. Excess thionyl chloride and DCM were evaporated *in vacuo* to give crude product (6.10 g) as a yellow powder. The product was used immediately for the reactions to make 6-bromo-N-(2-(*tert*-butyl)phenyl)picolinamide and 6-bromo-N-(4-(*tert*-butyl)phenyl)picolinamide without further purification.

6-Bromo-N-(2-(*tert*-butyl)phenyl)picolinamide



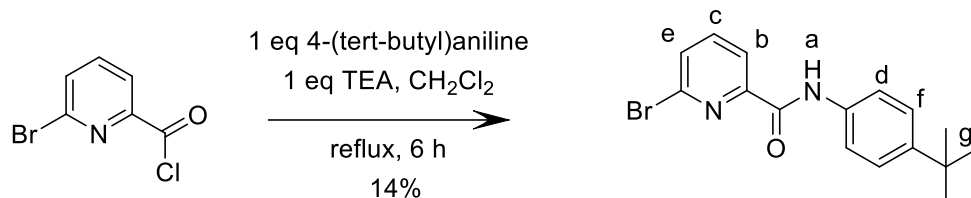
6-Bromopicolinoyl chloride (3.05 g, 13.8 mmol) was placed into a 2-necked flask under N₂. The solid was dissolved in dry CH₂Cl₂ (10 mL). To this mixture, dry TEA (1.9 mL, 13.8 mmol) was added dropwise, followed by the addition of 2-(*tert*-butyl)aniline (2.2 mL, 13.8 mmol) dropwise. The reaction mixture was refluxed for 6 h, then washed with water and brine, and the organic layer was dried over Na₂SO₄. CH₂Cl₂ was reduced *in vacuo* and the resultant solid left was recrystallised from in toluene to give product (250 mg, 0.750 mmol, 5%) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 10.09 (s, 1H, a), 8.26 (ddd, *J* = 11.0, 7.6, 0.9 Hz, 1H, b), 8.17 (ddd, *J* = 10.8, 8.0, 1.5 Hz, 1H, c), 7.90 (t, *J* = 7.8 Hz, 1H, d), 7.53 (dd, *J* = 7.9, 0.9 Hz, 1H, e), 7.45 (dd, *J* = 8.0, 1.6 Hz, 1H, f), 7.31 (dd, *J* = 7.7, 1.6 Hz, 1H, g), 7.29 – 7.21 (m, 1H, h), 1.53 (s, 9H, i).

¹³C NMR (101 MHz, CDCl₃) δ 160.6, 150.1, 147.8, 140.0, 134.9, 131.1, 127.1, 126.2, 126.1, 121.3, 119.8, 115.1, 31.7, 31.5.

HRMS (ESI, MeOH), *m/z*: calc for [M+H]⁺, [C₁₆H₁₈BrN₂O]⁺, 333.0597, found 333.0581

6-Bromo-N-(4-(*tert*-butyl)phenyl)picolinamide



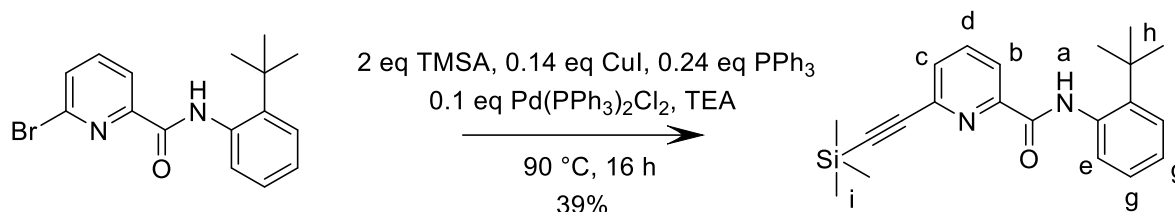
6-Bromopicolinoyl chloride (3.05 g, 13.8 mmol) was placed into a 2-necked flask under N₂. Dry CH₂Cl₂ (10 mL) was added to mixture. Dry TEA (1.9 mL, 13.8 mmol) was added dropwise, followed by the addition of 4-(*tert*-butyl)aniline (2.2 mL, 13.8 mmol) dropwise. The reaction mixture was refluxed for 6 h, then washed with water and brine, and the organic layer was dried over Na₂SO₄. CH₂Cl₂ was reduced *in vacuo* and the resultant solid was recrystallised from toluene to give product (662 mg, 1.99 mmol, 14%) as an off-white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.71 (s, 1H, a), 8.32 (dd, *J* = 7.6, 0.9 Hz, 1H, b), 7.95 (t, *J* = 7.8 Hz, 1H, c), 7.84 – 7.71 (m, 2H, d), 7.59 (dd, *J* = 8.0, 0.9 Hz, 1H, e), 7.53 – 7.45 (m, 2H, f), 1.42 (s, 9H, g).

¹³C NMR (101 MHz, CDCl₃) δ 140.5, 135.3, 127.2, 127.0, 126.7, 125.5, 124.7, 124.4, 121.3, 38.5, 34.6, 30.7.

HRMS (ESI, MeOH), *m/z*: calc for [M+Na]⁺, [C₁₆H₁₇BrN₂NaO]⁺, 355.0416, found 355.0423.

***N*-(2-(*tert*-Butyl)phenyl)-6-(trimethylsilyl)picolinamide**



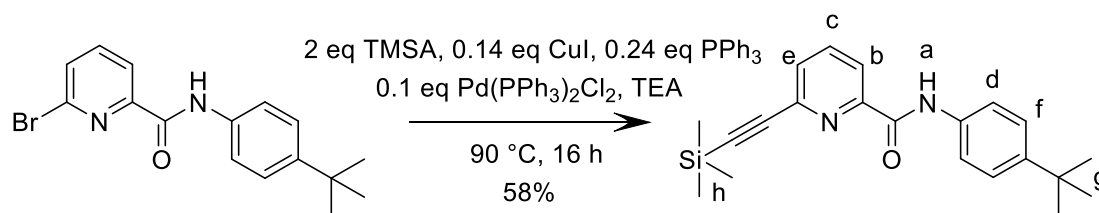
6-Bromo-*N*-(2-(*tert*-butyl)phenyl)picolinamide (250 mg, 0.750 mmol), CuI (20.0 mg, 0.105 mmol), Pd(PPh₃)₂Cl₂ (15.1 mg, 0.750 x 10⁻¹ mmol) and PPh₃ (47.2 mg, 0.180 mmol) were placed in a two-necked round bottom flask and but under nitrogen. Dry TEA (50 mL) was introduced to the flask and it's contents were freeze-pump-thawed. The mixture was heated at 50 °C for 30 minutes then heated to 90 °C. TMSA (0.21 mL, 1.5 mmol) was added dropwise, and the reaction mixture was heated and stirred for 16 hours. The reaction was then cooled, filtered by gravity to removed solids, reduced in *vacuo* and purified via flash chromatography (petroleum ether 40-60 °C 9 : EtOAc 1). The fractions were collected and reduced in *vacuo* to give pure product (103 mg, 0.292 mmol, 39%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 10.39 (s, 1H, a), 8.24 (dd, *J* = 7.8, 1.1 Hz, 1H, b), 8.20 (dd, *J* = 8.0, 1.5 Hz, 1H, c), 7.87 (t, *J* = 7.8 Hz, 1H, d), 7.61 (dd, *J* = 7.8, 1.1 Hz, 1H, e), 7.44 (dd, *J* = 8.0, 1.5 Hz, 1H, f), 7.34 – 7.25 (m, 2H, g), 1.54 (s, 9H, h), 0.30 (s, 9H, i).

¹³C NMR (101 MHz, CDCl₃) δ 229.4, 216.7, 201.6, 167.7, 166.0, 146.9, 138.7, 127.75, 109.4, 92.4, 72.5, 42.6, 30.7.

HRMS (ESI, MeOH), *m/z*: calc for [M+H]⁺, [C₂₁H₂₇N₂OSi]⁺, 351.1887, found 351.1882.

***N*-(4-(*tert*-Butyl)phenyl)-6-(trimethylsilyl)picolinamide**



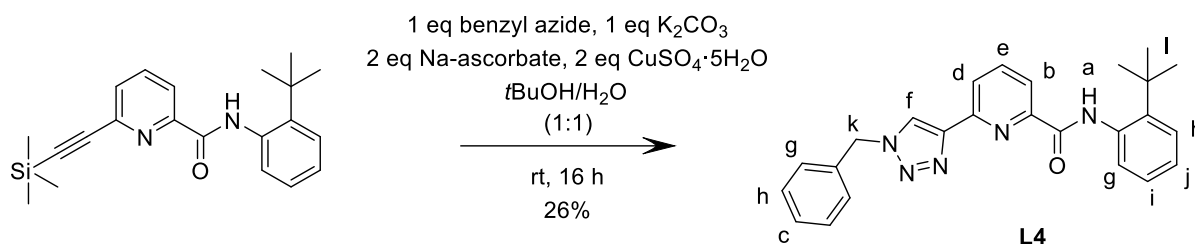
6-Bromo-*N*-(4-(*tert*-butyl)phenyl)picolinamide (661.6 mg, 1.99 mmol), CuI (52.9 mg, 0.278 mmol), Pd(PPh₃)₂Cl₂ (140 mg, 0.199 mmol) and PPh₃ (125 mg, 0.476 mmol) were placed in a two-necked round bottom flask and but under nitrogen. Dry TEA (50 mL) was introduced to the flask and the resultant mixture -was freeze-pump-thawed. The mixture was heated at 50 °C for 30 minutes then heated to 90 °C. TMSA (0.55 mL, 3.98 mmol) was added dropwise, and the reaction mixture was heated and stirred for 16 hours. The reaction was then cooled, filtered by gravity to removed solids, reduced in *vacuo* and purified via flash chromatography (petroleum ether 40-60 °C 9: EtOAc 1). The fractions were collected and reduced *in vacuo* to give pure product (405 mg, 1.15 mmol, 58%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.83 (s, 1H, a), 8.25 (dd, *J* = 7.9, 1.1 Hz, 1H, b), 7.86 (t, *J* = 7.8 Hz, 1H, c), 7.74 – 7.68 (m, 2H, d), 7.62 (dd, *J* = 7.8, 1.1 Hz, 1H, e), 7.44 – 7.37 (m, 2H, f), 1.33 (s, 9H, g), 0.33 (s, 9H, h).

¹³C NMR (101 MHz, CDCl₃) δ 199.6, 174.3, 171.9, 149.0, 137.9, 135.1, 126.0, 119.9, 112.9, 104.4, 86.0, 68.5, 40.1, 31.5, 18.7, 16.0, -0.1.

HRMS (ESI, MeOH), *m/z*: calc for [M+H]⁺, [C₂₁H₂₇N₂OSi], 351.1887, found 351.1883.

6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(2-(*tert*-butyl)phenyl)picolinamide **L4**



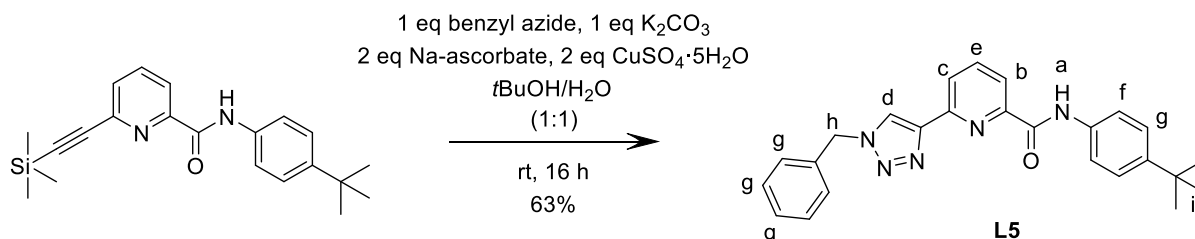
N-(2-(*tert*-Butyl)phenyl)-6-(trimethylsilyl)picolinamide (105 mg, 0.292 mmol), K₂CO₃ (40.4 mg, 0.292 mmol), CuSO₄·5H₂O (146 mg, 0.585 mmol) and Na-ascorbate (115 mg, 0.585 mmol) were placed in a round bottom flask and *t*BuOH/H₂O (14 mL, 1:1) was added. Benzyl azide (36.5 μL, 0.292 mmol) as added and *t*BuOH/H₂O (6 mL, 1:1) was added again to ensure all benzyl azide entered into the solution. The reaction mixture was stirred at room temperature for 16 h, starting as a brown solution and turning into a pale green solution. The mixture was that extracted with CH₂Cl₂ (30 mL) and washed with saturated aqueous EDTA solution (30 mL), ammonia solution 35% (30 mL) and brine (30 mL). The organic layers were collected purified via flash chromatography (petroleum ether 40-60 °C 9: EtOAc 1) and reduced *in vacuo* to give the pure product **L4** (21 mg, 7.53 × 10⁻² mmol, 26%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 10.18 (s, 1H, a), 8.38 (dd, *J* = 7.9, 1.1 Hz, 1H, b), 8.32 (td, *J* = 8.4, 1.5 Hz, 1H, c), 8.25 (dd, *J* = 7.8, 1.1 Hz, 1H, d), 8.01 (t, *J* = 7.8 Hz, 1H, e), 7.94 (s, 1H, f), 7.49 – 7.42 (m, 3H, g), 7.42 – 7.35 (m, 3H, h), 7.30 (t, 1H, i), 7.13 (t, *J* = 8.2, 6.9 Hz, 1H, j), 5.63 (s, 2H, k), 1.36 (s, 9H, l).

¹³C NMR (101 MHz, CDCl₃) δ 161.3, 150.0, 139.5, 139.0, 135.6, 134.1, 129.6, 129.4, 128.9, 127.2, 126.5, 125.1, 124.0, 123.1, 121.9, 121.9, 77.4, 54.8, 34.6, 30.5, 1.2.

HRMS (ESI, MeOH), *m/z*: calc for [M]⁻, [C₂₅H₂₄N₅O]⁻, 410.1986, found 410.1977.

6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(4-(*tert*-butyl)phenyl)picolinamide **L5**



N-(4-(*tert*-Butyl)phenyl)-6-(trimethylsilyl)picolinamide (105 mg, 0.292 mmol), K₂CO₃ (40.4 mg, 0.292 mmol), CuSO₄·5H₂O (146 mg, 0.585 mmol) and Na-ascorbate (115 mg, 0.585 mmol) were placed in a round bottom flask and *t*BuOH/H₂O (14 mL, 1:1) was added. Benzyl azide (36.5 μL, 0.292 mmol) as added and *t*BuOH/H₂O (6 mL, 1:1) was added again to ensure all benzyl azide entered into the solution. The reaction mixture was stirred at room temperature

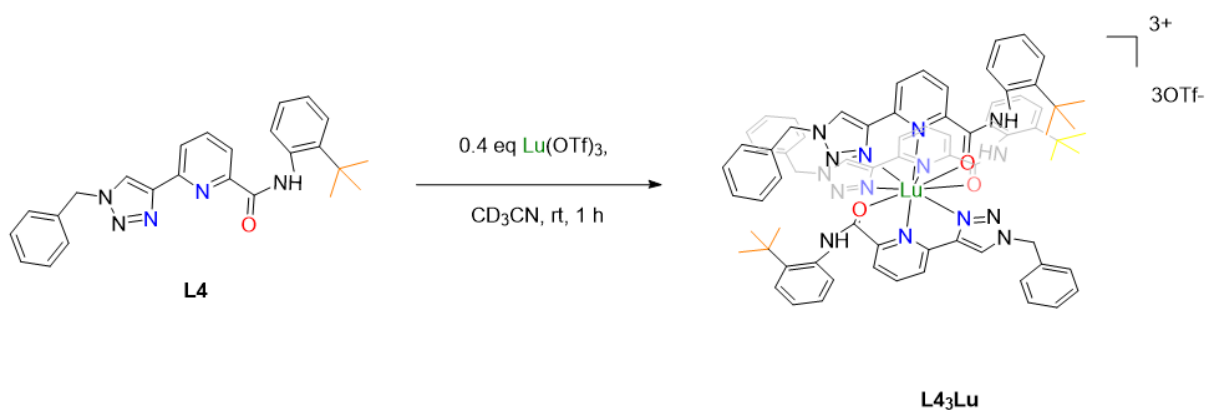
for 16 h, starting as a brown solution and turning into a pale green solution. The mixture was that extracted with CH₂Cl₂ (30 mL) and washed with saturated aqueous EDTA solution (30 mL), ammonia solution 35% (30 mL) and brine (30 mL). The organic layers were collected purified via flash chromatography (hexane 7: EtOAc 3) and reduced *in vacuo* to give the pure product (74.9 mg, 0.182 mmol, 63%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.76 (s, 1H, a), 8.34 (dd, *J* = 7.9, 1.1 Hz, 1H, b), 8.23 (dd, *J* = 7.7, 1.1 Hz, 1H, c), 8.10 (s, 1H, d), 7.99 (t, *J* = 7.8 Hz, 1H, e), 7.68 – 7.61 (m, 2H, f), 7.46 – 7.34 (m, 7H, g), 5.66 (s, 2H, h), 1.33 (s, 9H, i).

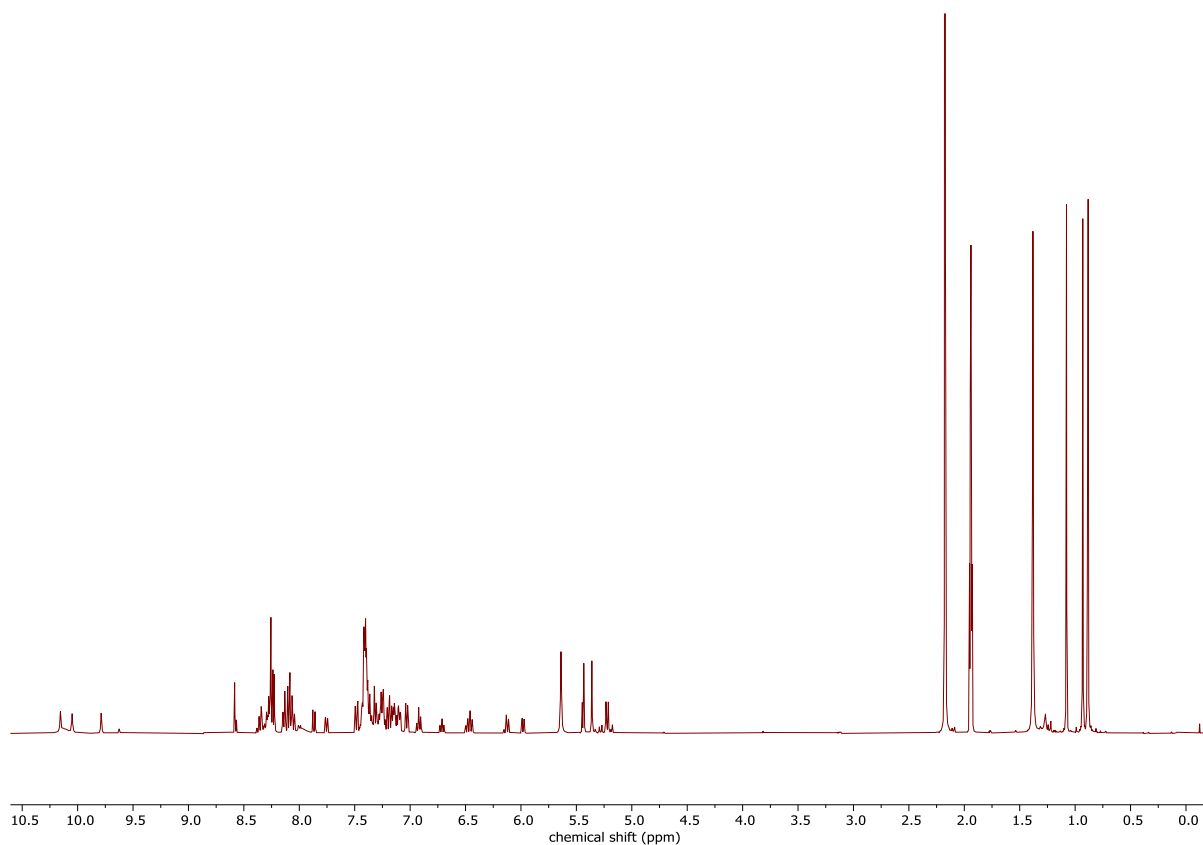
¹³C NMR (101 MHz, CDCl₃) δ 161.9, 149.8, 149.0, 148.0, 138.8, 135.0, 134.6, 129.4, 129.1, 128.2, 126.0, 123.3, 122.2, 121.8, 120.0, 77.4, 54.6, 34.6, 31.5.

HRMS (ESI, MeOH), *m/z*: calc for [M+H]⁺, [C₂₅H₂₆N₅O]⁺, 434.1951, found 434.1944.

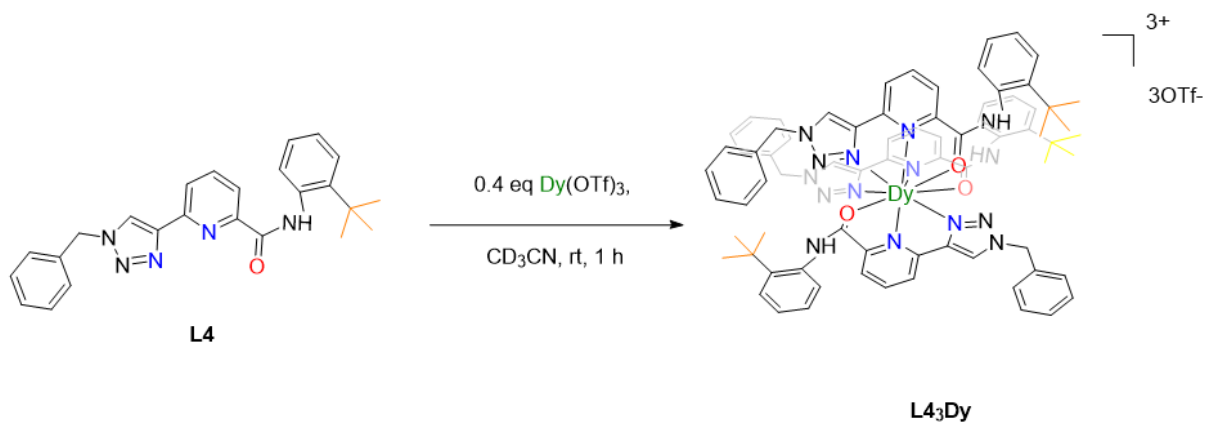
L₄Lu



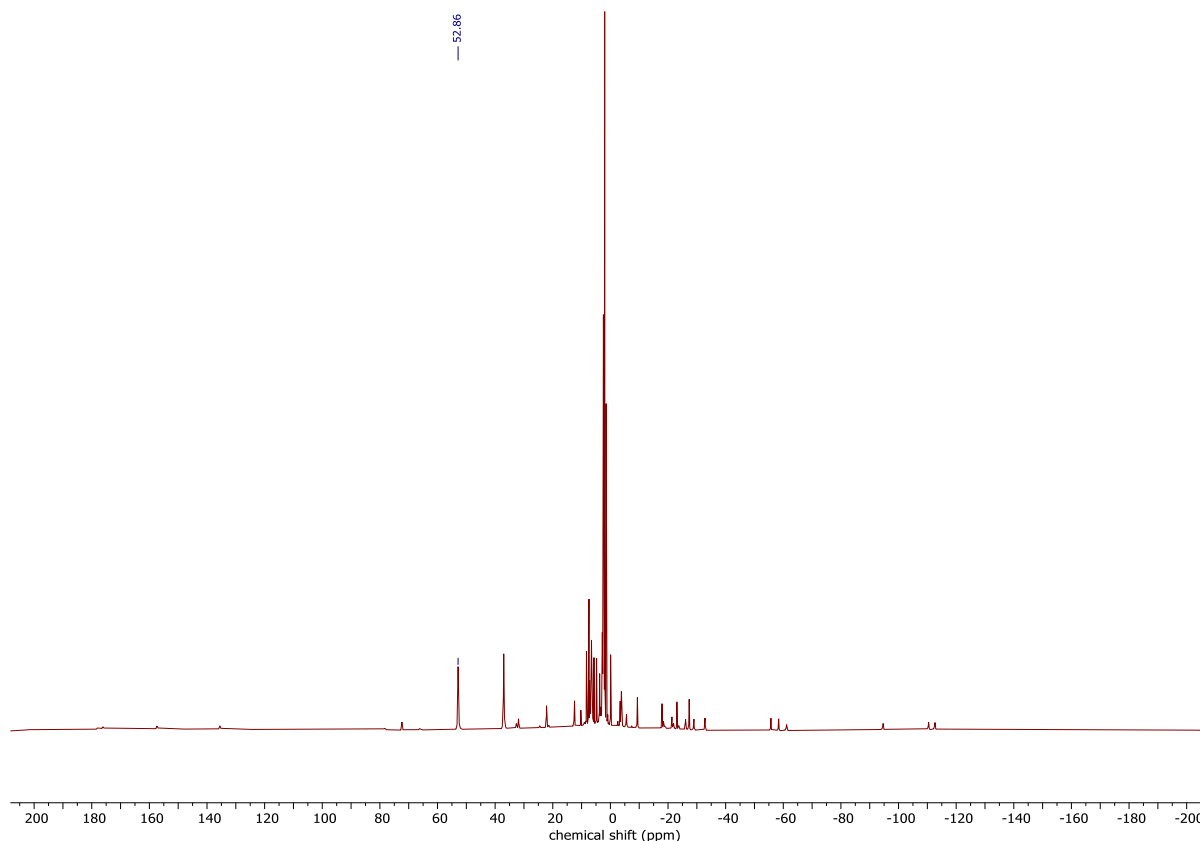
6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(2-(*tert*-butyl)phenyl)picolinamide (7.0mg, 1.70 × 10⁻² mmol) and Lu(OTf)₃ (4.2 mg, 6.80 × 10⁻³ mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.



L4₃Dy



6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(2-(*tert*-butyl)phenyl)picolinamide (7.0 mg, 1.70×10^{-2} mmol) and Dy(OTf)₃ (4.1 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.

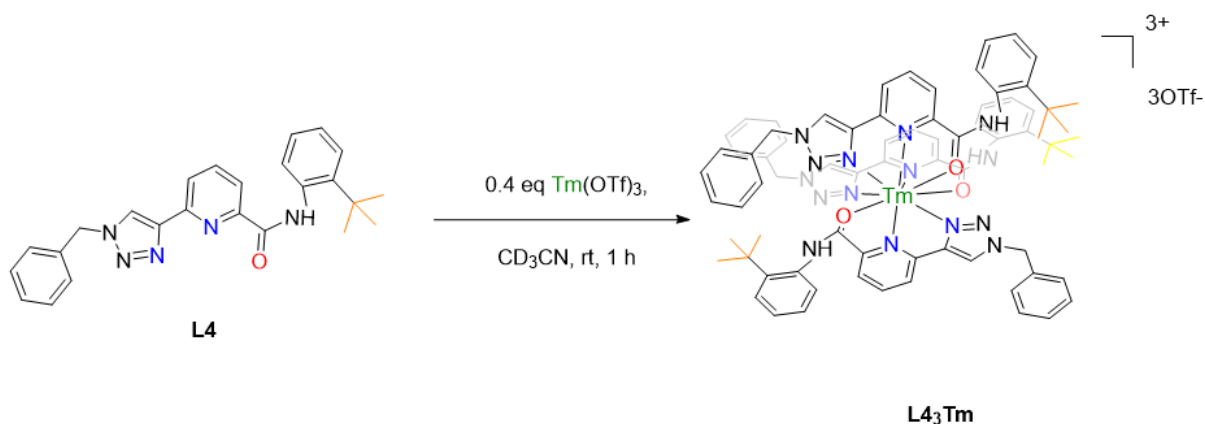


T1 NMR Peak at δ 52.86, $T_1 = 3.38$ ms, $T_2^* = 3.15$ ms, $R_1 = 296.095$ s $^{-1}$, rError = ± 15.266 s $^{-1}$, $R_2^* = 317.678$ s $^{-1}$, $R_1/R_2^* = 0.932$

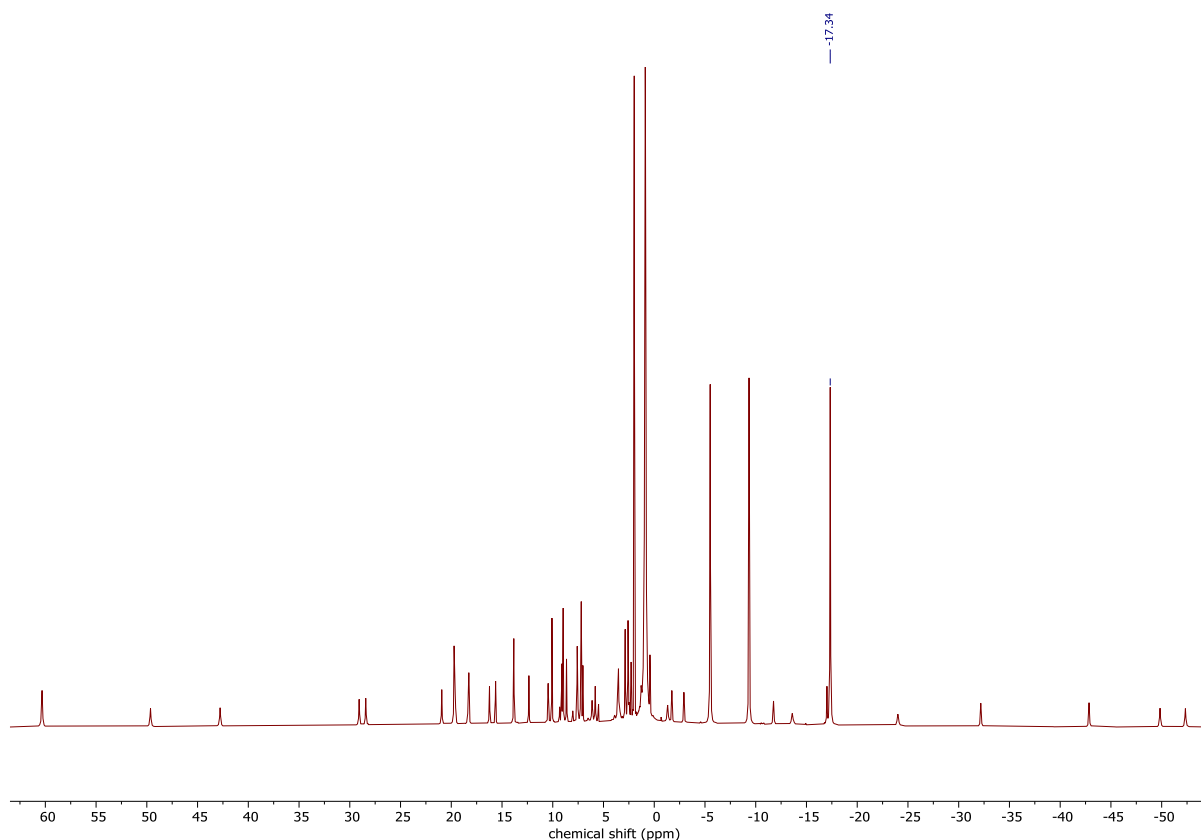
Peak at δ 37.02, $T_1 = 5.23$ ms, $T_2^* = 3.59$ ms, $R_1 = 191.073$ s $^{-1}$, rError = ± 55.6168 s $^{-1}$, $R_2^* = 278.188$ s $^{-1}$, $R_1/R_2^* = 0.687$.

HRMS (ESI, CD₃CN), m/z: calc for [ML₄₃(OTf)₂]⁺, [C₇₇H₇₅F₆DyN₁₅O₉S₂]⁺, 1695.4470, found 1695.4470

L₄Tm



6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(2-(*tert*-butyl)phenyl)picolinamide (7.0 mg, 1.70×10^{-2} mmol) and Tm(OTf)₃ (4.2 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.

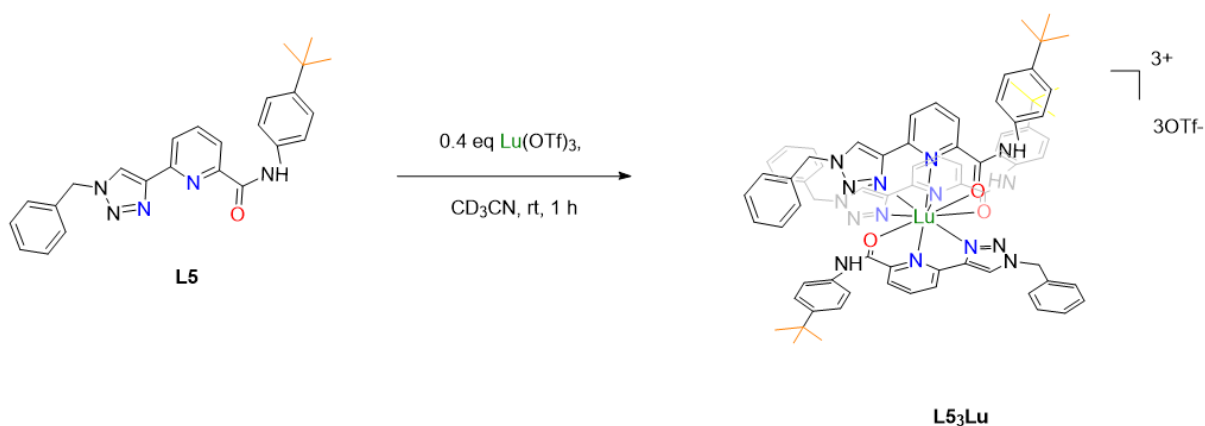


T1 NMR Peak at δ -17.34, $T_1 = 20.1$ ms, $T_2^* = 15.1$ ms, $R_1 = 49.8389$ s $^{-1}$, rError = 3.67108 s $^{-1}$, $R_2^* = 66.036$ s $^{-1}$, $R_1/R_2 = 0.755$.

HRMS (ESI, CD₃CN), m/z: calc for [ML₄₃(OTf)₂]⁺, [C₇₇H₇₅F₆TmN₁₅O₉S₂]⁺, 1695.4470, found 1695.4470.

HRMS (ESI, CD₃CN), m/z: calc for [ML₄₃(OTf)]²⁺, [C₇₆H₇₅F₃TmN₁₅O₆S]²⁺, 775.7520, found 775.7579.

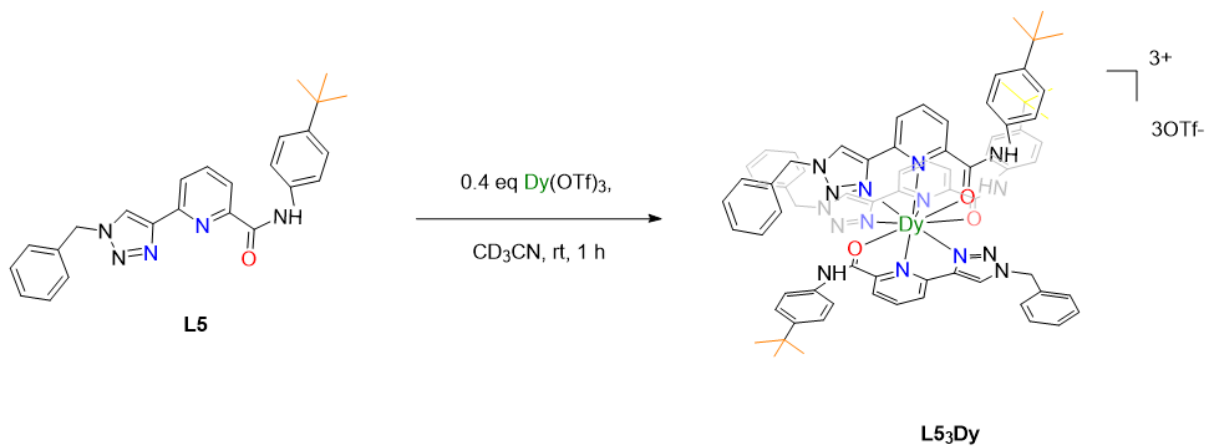
L5₃Lu



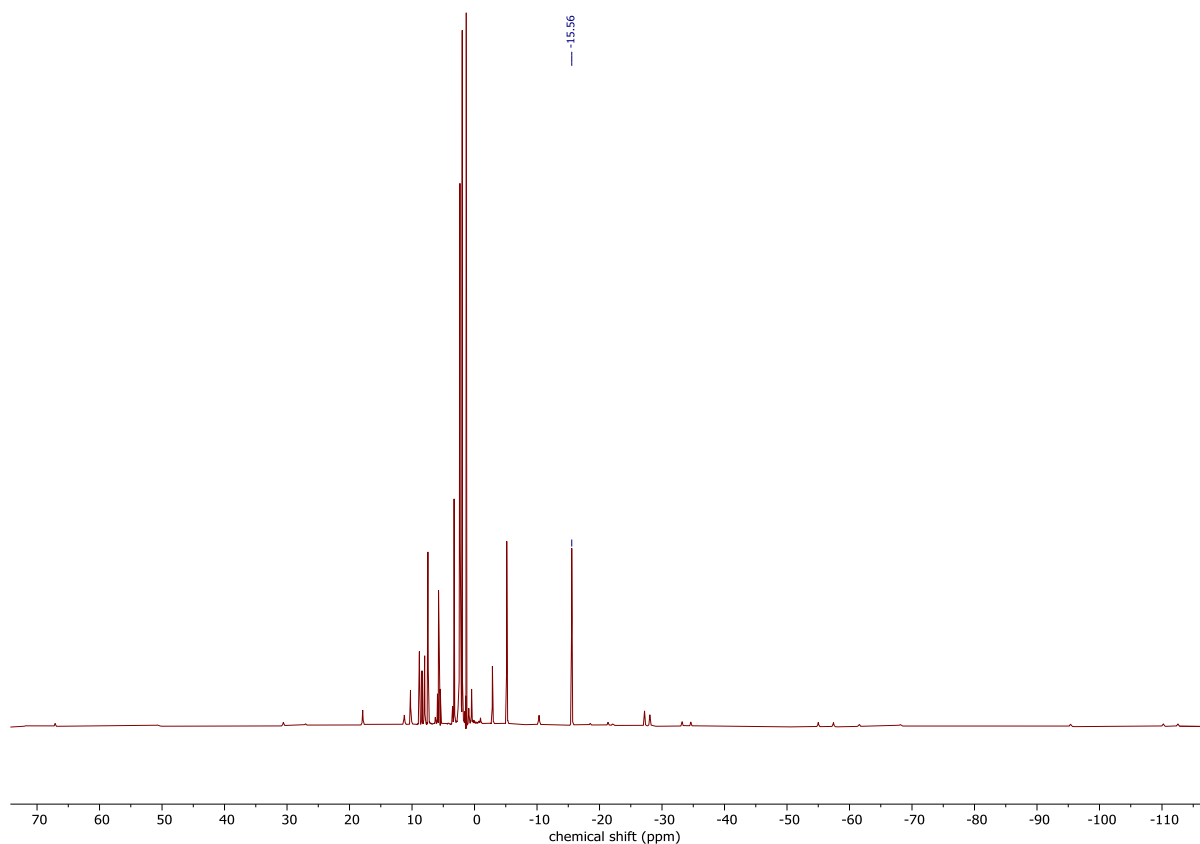
6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(4-(*tert*-butyl)phenyl)picolinamide (7.0 mg, 1.70×10^{-2} mmol) and Lu(OTf)₃ (4.2 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.

HRMS (ESI, CD₃CN), m/z: calc for [ML₅(OTf)]²⁺, [C₇₆H₇₅F₃LuN₁₅O₆S]²⁺, 778.7552, found 778.7552.

L₅Dy

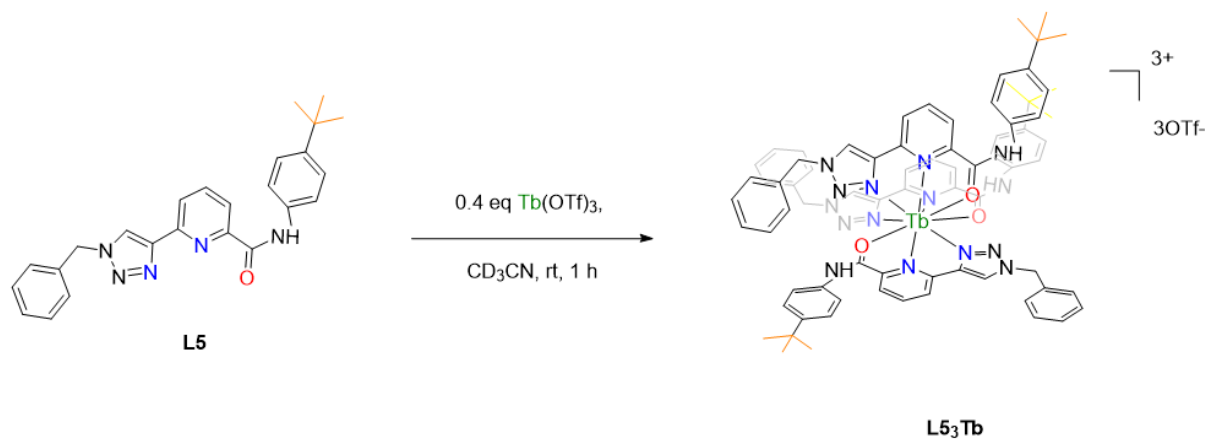


6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(4-(*tert*-butyl)phenyl)picolinamide (7.0mg, 1.70×10^{-2} mmol) and Dy(OTf)₃ (4.1 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.

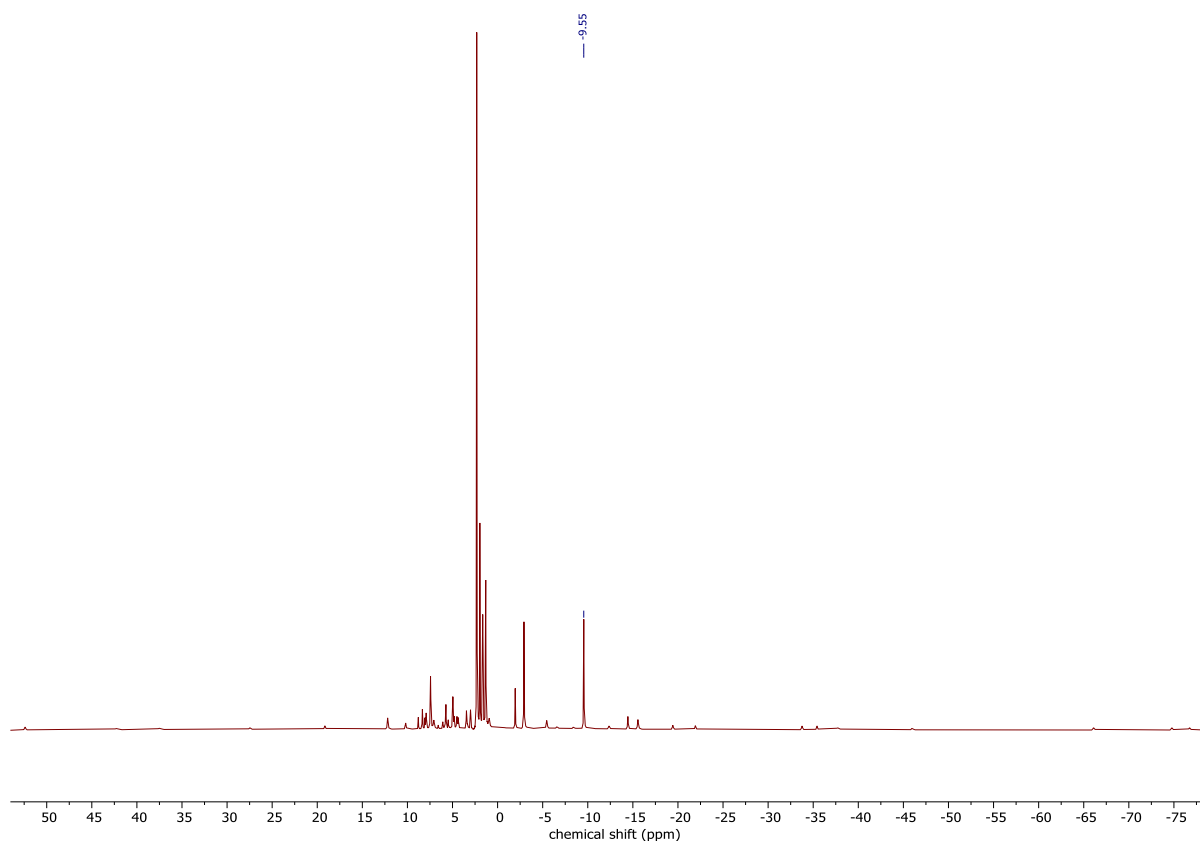


T1 NMR Peak at δ -15.56, $T_1 = 27.8$ ms, $T_2^* = 21.04$ ms, $R_1 = 36.0036$ s⁻¹, rError = 2.85607 s⁻¹, $R_2^* = 47.532$ s⁻¹, $R_1/R_2^* = 0.757$.

L5₃Tb



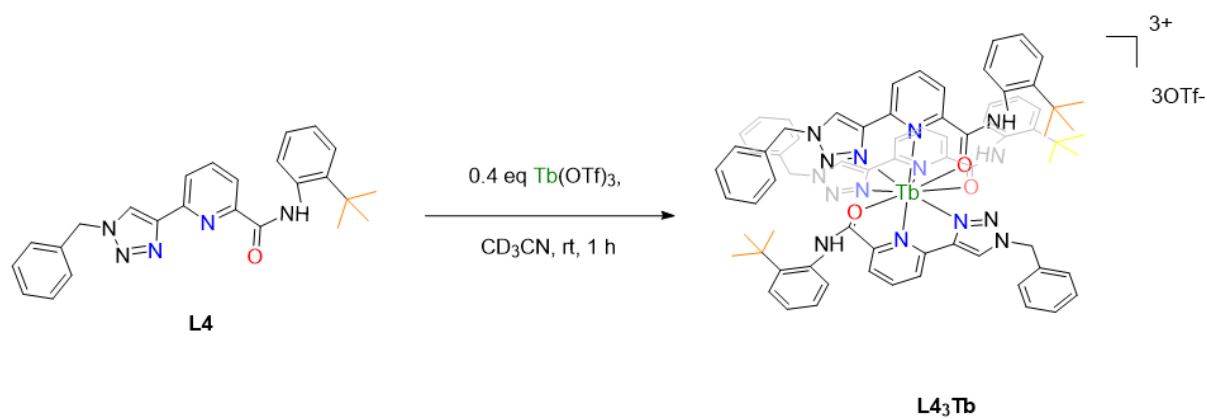
6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-N-(4-(*tert*-butyl)phenyl)picolinamide (7.0 mg, 1.70×10^{-2} mmol) and $\text{Tb}(\text{OTf})_3$ (4.1 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD_3CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD_3CN .



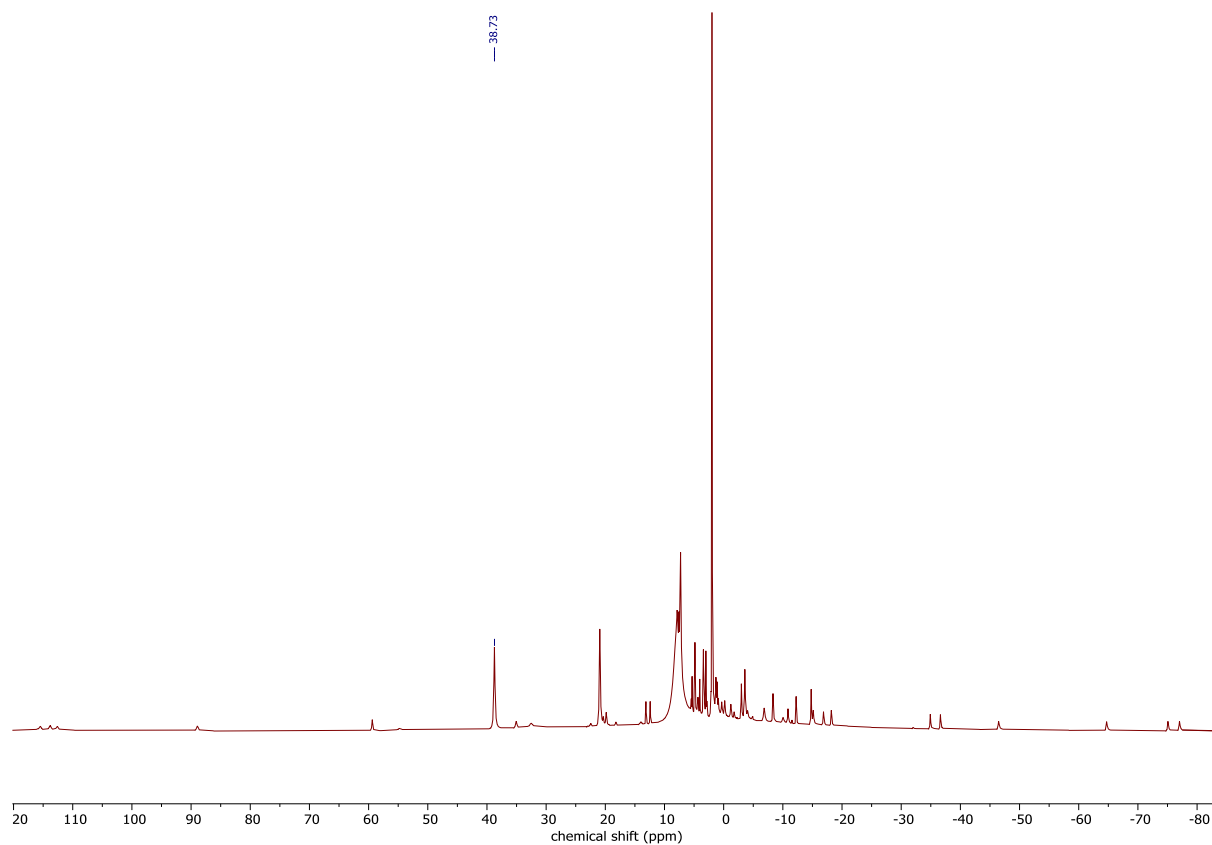
T1 NMR Peak at $\delta -9.56$, $T_1 = 15.0$ ms, $T_2^* = 17.470$ ms, $R_1 = 53.69$ s⁻¹, rError = 4.31635 s⁻¹, $R_2^* = 57.240$ s⁻¹, $R_1/R_2^* = 0.937$.

HRMS (ESI, CD_3CN), m/z : calc for $[\text{ML}_5(\text{OTf})_2]^+1$, $[\text{C}_{77}\text{H}_{75}\text{F}_6\text{TbN}_{15}\text{O}_9\text{S}_2]^+1$, 1690.4471, found 1690.4396.

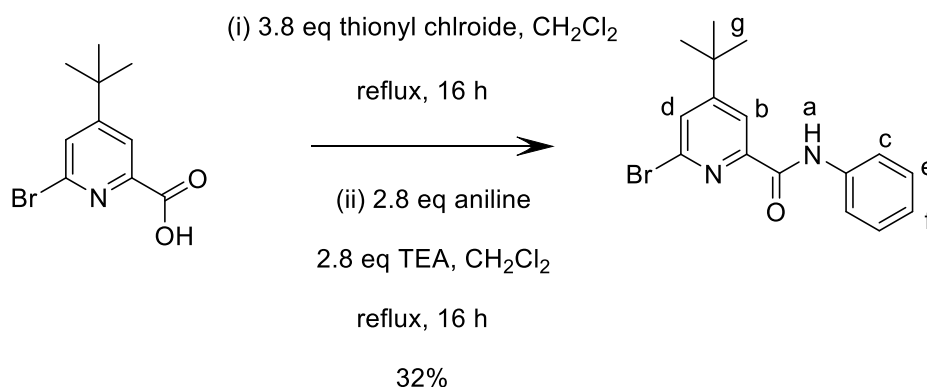
L4₃Tb



Peak at δ 38.73, $T_1 = 4.93$ ms, $T_2^* = 3.45$ ms, $R_1 = 230.084$ s⁻¹, rError = 4.86239 s⁻¹, $R_2^* = 243$ s⁻¹, $R_1/R_2^* = 0.950$.



6-Bromo-4-(*tert*-butyl)-N-phenylpicolinamide



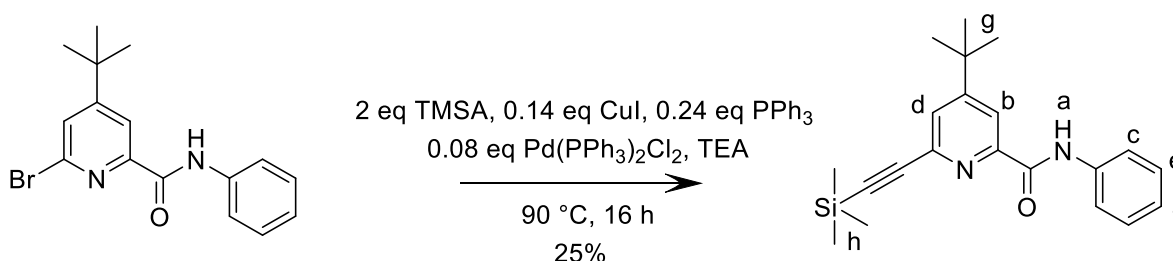
6-Bromo-4-(*tert*-butyl)picolinic acid (1.10 g, 4.26 mmol) was placed into a 2-necked flask and put under nitrogen. Thionyl chloride (1 M solution in CH_2Cl_2 , 16.2 mL, 16.2 mmol) was added dropwise and the solution was refluxed and stirred for 16 h. Excess thionyl chloride and DCM were evaporated *in vacuo* and the flask was put under nitrogen. Dry CH_2Cl_2 (20 mL) was added to mixture. Dry TEA (1.7 mL, 11.9 mmol) was added dropwise, followed by the addition of aniline (1.1 mL, 11.9 mmol) dropwise. The reaction mixture was refluxed for 16 h, then washed with water (20 mL) and brine (20 mL). The organic layers were collected and dried over Na_2SO_4 , purified via flash chromatography (hexane 9: EtOAc 1) and reduced *in vacuo* to give the pure product (452.2 mg, 1.36 mmol, 32%) as an off-white solid.

^1H NMR (400 MHz, CDCl_3) δ 9.70 (s, 1H, a), 8.28 (d, J = 1.6 Hz, 1H, b), 7.77 (td, 2H, c), 7.61 (d, J = 1.6 Hz, 1H, d), 7.39 (ddt, 2H, e), 7.17 (ddt, 1H, f), 1.37 (s, 9H, g).

^{13}C NMR (101 MHz, CDCl_3) δ 165.5, 150.8, 141.0, 137.6, 129.2, 128.0, 124.8, 120.1, 119.3, 77.4, 35.7, 30.5.

HRMS (ESI, MeOH), m/z : calc for $[\text{M}+\text{Na}]^+$, $[\text{C}_{16}\text{H}_{17}\text{BrN}_2\text{NaO}]^+$, 355.0416, found 355.0416.

4-(*tert*-Butyl)-N-phenyl-6-((trimethylsilyl)ethynyl)picolinamide

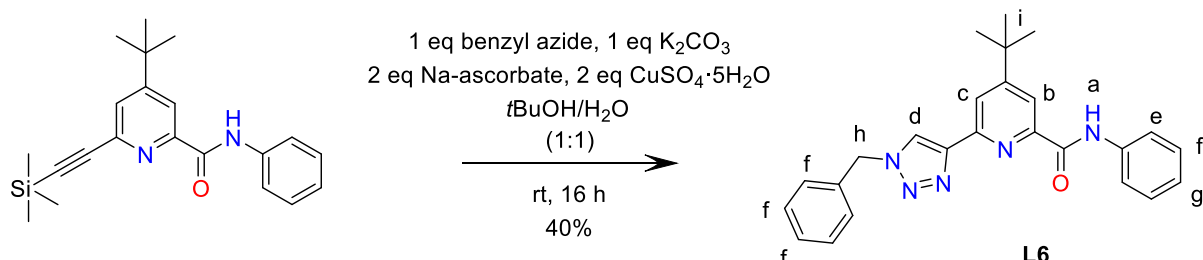


6-Bromo-4-(*tert*-butyl)-N-phenylpicolinamide (452 mg, 1.36 mmol), CuI (36.2 mg, 190 μmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (76.5 mg, 0.109 mmol) and PPh_3 (85.5 mg, 0.326 mmol) were placed in a two-necked round bottom flask under nitrogen. Dry TEA (50 mL) was introduced to the flask and its contents were freeze-pump-thawed. The mixture was heated at 50 °C for 30 minutes then heated to 90 °C. TMSA (0.38 mL, 2.71 mmol) was added dropwise, and the reaction mixture was heated and stirred for 16 hours. The reaction was then cooled, filtered by gravity to remove solids, reduced *in vacuo* and purified via flash chromatography (hexane 9: EtOAc 1). The fractions were collected and reduced *in vacuo* to give pure product (118 mg, 0.337 mmol, 25%) as a yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 9.92 (s, 1H, a), 8.27 (d, *J* = 1.8 Hz, 1H, b), 7.80 (td, 2H, c), 7.61 (d, *J* = 1.9 Hz, 1H, d), 7.39 (ddt, 2H, e), 7.16 (ddt, 1H, f), 1.37 (s, 9H, g), 0.34 (s, 9H, h).

¹³C NMR (101 MHz, CDCl₃) δ 213.9, 166.7, 162.7, 150.2, 141.5, 129.2, 127.4, 124.5, 120.1, 119.5, 95.4, 77.4, 35.3, 30.5, -0.1.

6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4-(*tert*-butyl)-N-phenylpicolinamide L6



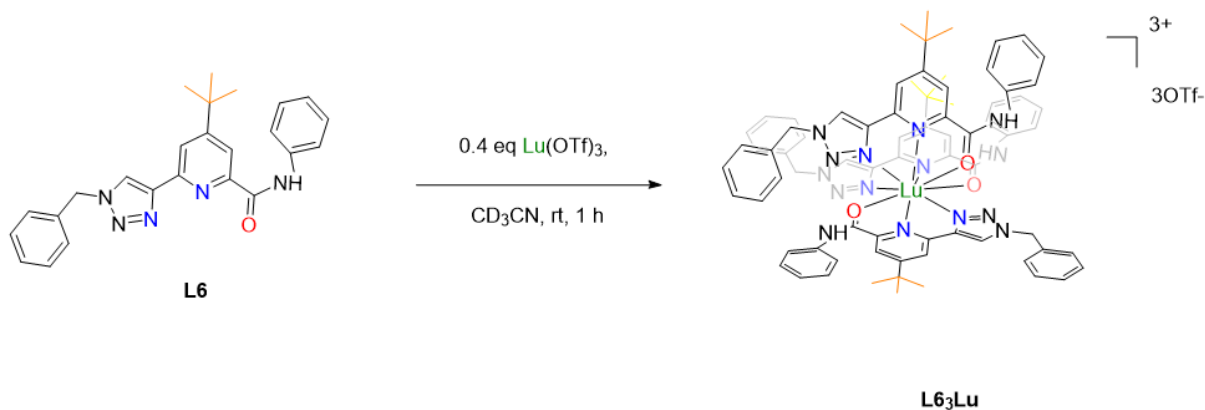
4-(*tert*-Butyl)-N-phenyl-6-((trimethylsilyl)ethynyl)picolinamide (118 mg, 0.337 mmol), K₂CO₃ (93.2 mg, 0.675 mmol), CuSO₄·5H₂O (169 mg, 0.675 mmol) and Na-ascorbate (134 mg, 0.675 mmol) were placed in a round bottom flask and *t*BuOH/H₂O (12 mL, 1:1) was added. Benzyl azide (42.1 μL, 0.337 mmol) was added and *t*BuOH/H₂O (6 mL, 1:1) was added again to ensure all benzyl azide entered into the solution. The reaction mixture was stirred at room temperature for 16 h, starting as a brown solution and turning into a pale green solution. The mixture was extracted with CH₂Cl₂ (30 mL) and washed with saturated aqueous EDTA solution (30 mL), ammonia solution 35% (30 mL), and brine (30 mL). The organic layers were collected, purified via flash chromatography (hexane 9: EtOAc 1) and reduced *in vacuo* to give the pure product (55.2 mg, 0.134 mmol, 40%) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 9.87 (s, 1H, a), 8.37 (d, *J* = 1.9 Hz, 1H, b), 8.27 (d, *J* = 1.8 Hz, 1H, c), 8.10 (s, 1H, d), 7.74 (td, 2H, e), 7.47 – 7.32 (m, 7H, f), 7.16 (ddt, 1H, g), 5.66 (s, 2H, h), 1.42 (s, 9H, i).

¹³C NMR (101 MHz, CDCl₃) δ 215.9, 159.0, 144.1, 137.8, 134.7, 129.4, 129.2, 128.1, 124.5, 122.2, 120.1, 119.2, 105.8, 77.4, 54.6, 37.5, 30.7, 10.5, 1.2.

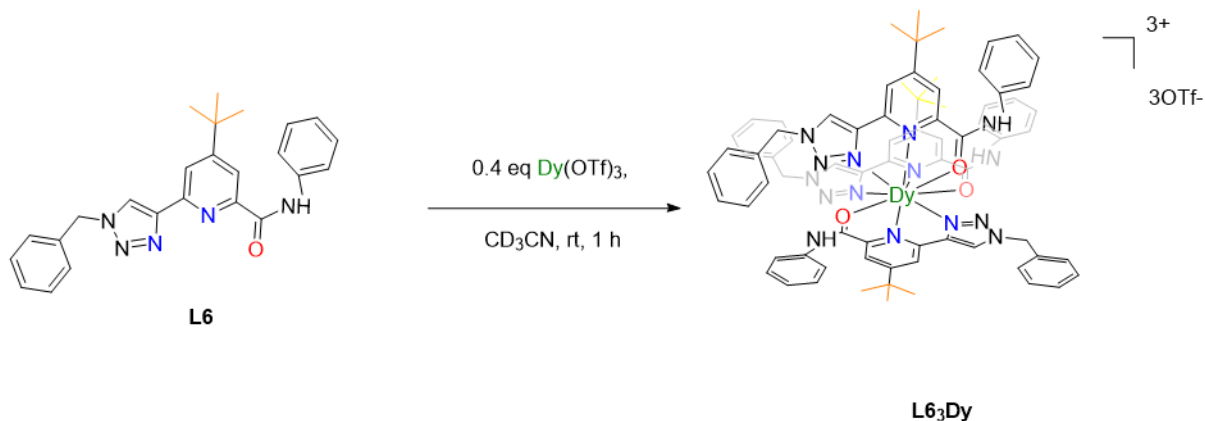
HRMS (ESI, MeOH), *m/z*: calc for [M+Na]⁺, [C₂₅H₂₅N₅NaO]⁺, 434.1951, found 434.1962.

L6₃Lu

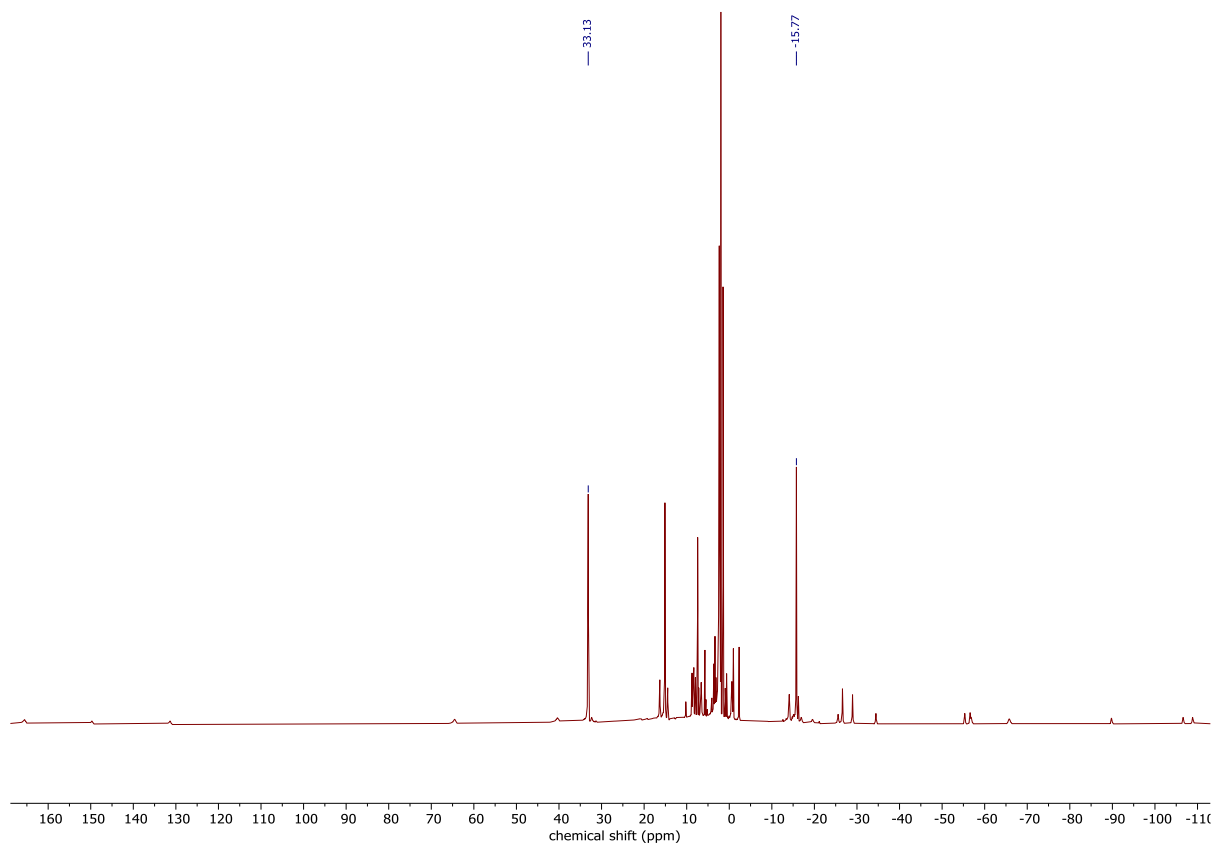


6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4-(*tert*-butyl)-N-phenylpicolinamide (7.0 mg, 1.70×10^{-2} mmol) and Lu(OTf)₃ (4.2 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The mixture was stirred for 1 h to give a solution of complex in CD₃CN.

L6₃Dy



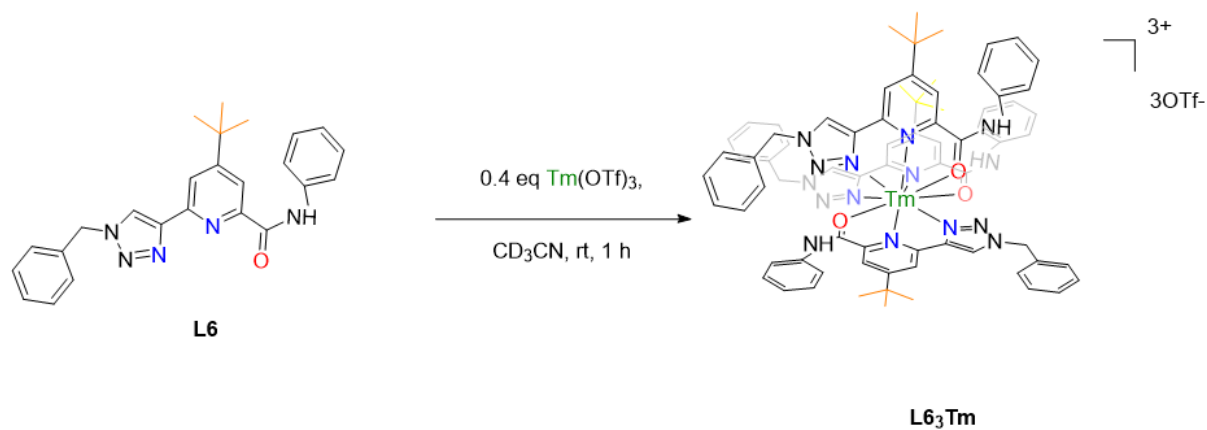
6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4-(*tert*-butyl)-N-phenylpicolinamide (7.0 mg, 1.70×10^{-2} mmol) and Dy(OTf)₃ (4.1 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.



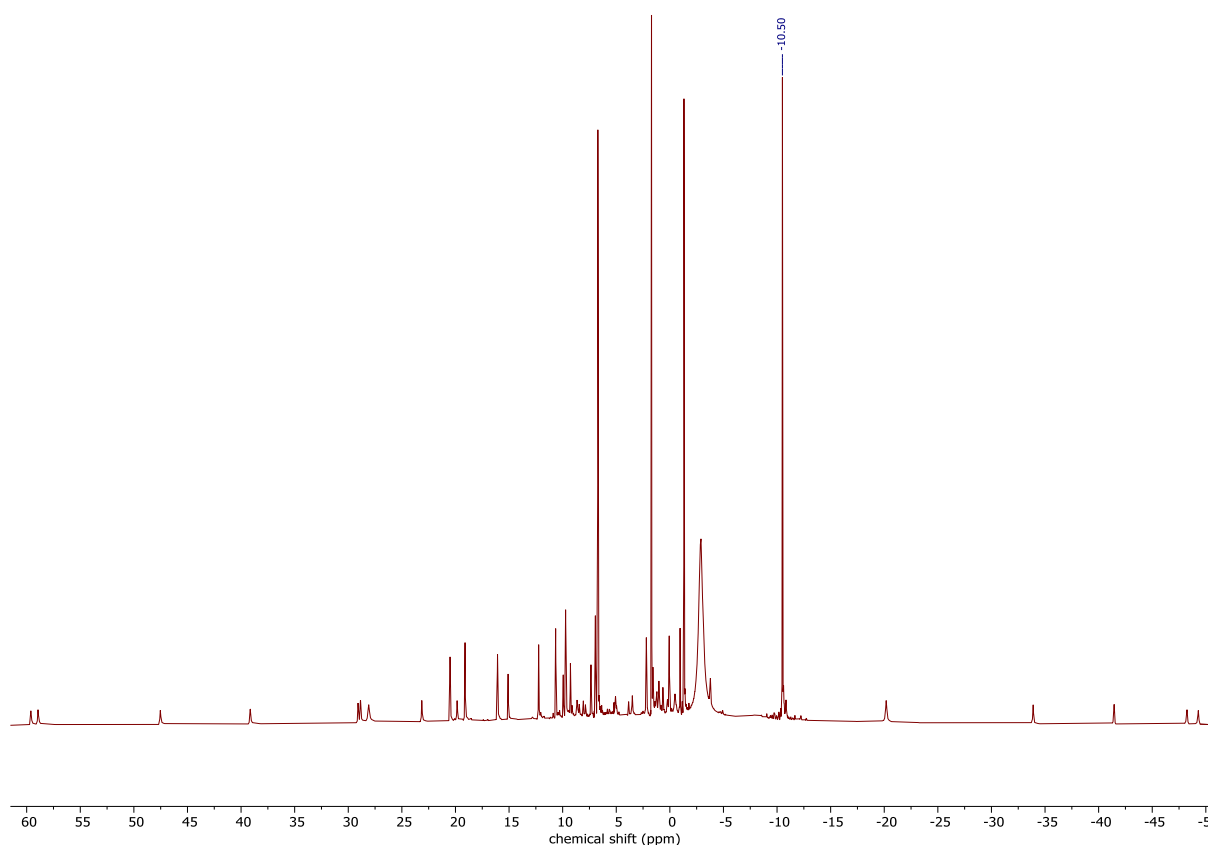
Peak at δ 33.13, $T_1 = 14 \text{ ms}$, $T_2^* = 8.93 \text{ ms}$, $R_1 = 70.6752 \text{ s}^{-1}$, $r\text{Error} = 0.409285 \text{ s}^{-1}$, $R_2^* = 112 \text{ s}^{-1}$, $R_1/R_2^* = 0.63$.

Peak at δ , -15.77 $T_1 = 16.8$ ms, $T_2^* = 11.1$ ms, $R_1 = 59.3438$ s⁻¹, rError = 1.47975 s⁻¹, $R_2^* = 90.4$ s⁻¹, $R_1/R_2^* = 0.66$.

L6₃Tm

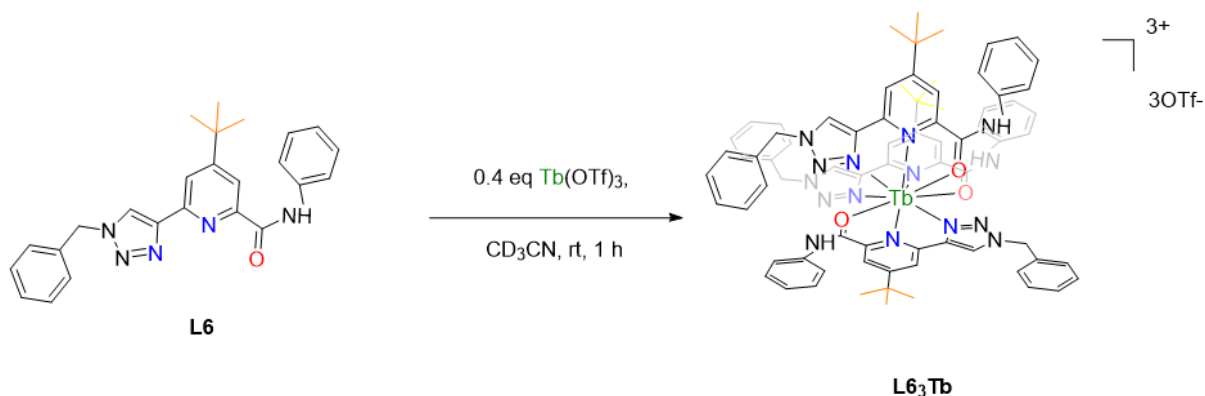


6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4-(*tert*-butyl)-N-phenylpicolinamide (7.0 mg, 1.70×10^{-2} mmol) and **Tm(OTf)₃** (4.2 mg, 6.80×10^{-3} mmol) were added to a small vial along with **CD₃CN** (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in **CD₃CN**.

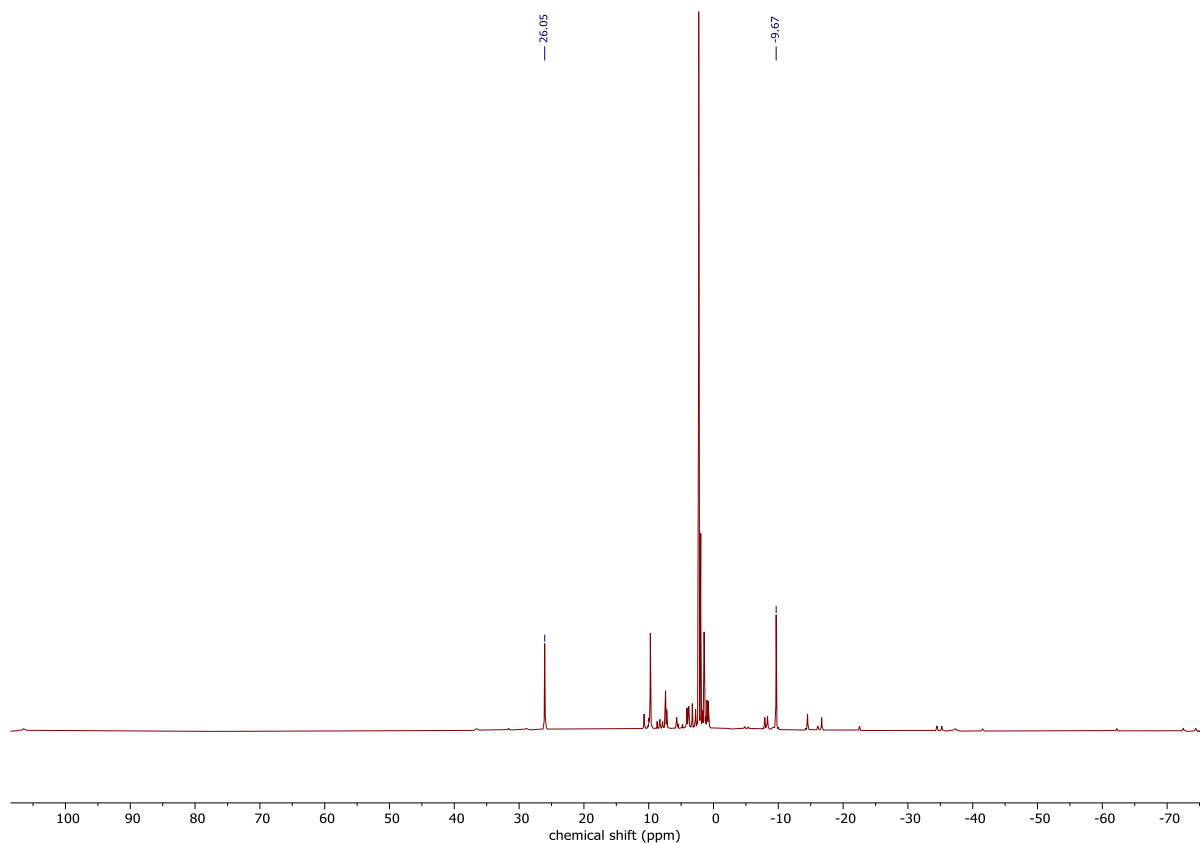


Peak at δ -10.50, $T_1 = 25.7$ ms, $T_2^* = 23.9$ ms, $R_1 = 38.9241$ s⁻¹, rError = 2.29017 s⁻¹, $R_2^* = 41.9$ s⁻¹, $R_1/R_2^* = 0.93$.

L6₃Tb



6-(1-Benzyl-1H-1,2,3-triazol-4-yl)-4-(*tert*-butyl)-N-phenylpicolinamide (7.0 mg, 1.70×10^{-2} mmol) and Tb(OTf)₃ (4.1 mg, 6.80×10^{-3} mmol) were added to a small vial along with CD₃CN (0.6 mL). The contents of the vial were stirred for 1 h to give a solution of complex in CD₃CN.



Peak at δ 26.05, $T_1 = 18.1$ ms, $T_2^* = 12.0$ ms, $R_1 = 54.9842$ s⁻¹, rError = 0.5616 s⁻¹, $R_2^* = 83.5$ s⁻¹, $R_1/R_2^* = 0.66$.

Peak at δ -9.67, $T_1 = 16.4$ ms, $T_2 = 17.5$ ms, $R_1 = 61.1369$ s⁻¹, rError = 0.969616 s⁻¹, $R_2^* = 57.0$ s⁻¹, $R_1/R_2^* = 1.1$.

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