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SYNTHESIS, CHARACTERIZATION AND CATALYTIC ACTIVITY OF CHIRAL TETRAAZAMACROCYCLE - **Pc-L*** - Cu(I) AND Ag (I) COMPLEXES

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Alla mia MAMMA

A papà e Marco

Chaos is a friend of mine.

(Bob Dylan)

INDICE

1 INTRODUCTION

1.1 Macrocylic ligands

A **macrocycle** is defined by IUPAC as *"a cyclic macromolecule or a macromolecular cyclic portion of a molecule."*[1] Generally macrocyclic ligands are defined as cyclic and polydentate molecules possessing heteroatoms that act as donor atoms, which are either incorporated in or attached to a cyclic backbone, that can coordinate to a metal centre.

Macrocyclic ligands have attracted widespread attention due to two unique properties. In 1969 a peculiar property named as macrocyclic effect was initially described in studies of tetraaza macrocycles with copper(II).[2] The macrocyclic effect is the significant enhancement in complex stability constants of macrocyclic ligands relative to their open chain analogues. Moreover it's accepted that a ligand that can bind a metal with more than one atom increases the stability of the generated complex (chelating effect). Compared to the acyclic ones, macrocyclic ligands also have the advantages to be conformationally pre-organized and they show the ability to discriminate among closely related metal ions based on the metal ion radius (ring size effect). In fact the selectivity of a macrocycle for either a metal ion or another substrate is critically dependent on the structure of the macrocycle and electronic effects, i.e. the types of donor atoms.

Macrocyclic molecules are naturally occurring species and they play a vital role in biological system like porphrins, corrins and chlorins. "Synthetic" macrocycles are opposed to the natural ones and they were first synthesized in the early 1960's. N. F. Curtis in 1960 synthesized the first macrocyclic complex by the reaction of tris-ehtylenediamine nickel(II) perchlorate and acetone (figure 1.1).[3]

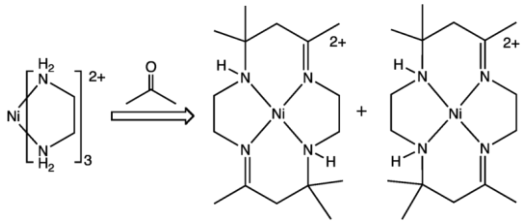


Figure 1.114-membered *N*4 macrocyclic ligands, called Curtis macrocycles, arise from the condensation of acetone and a nickel complex of ethylenediamine.

Since its birth, the development of macrocyclic chemistry has been mainly focused on the synthesis of species as models of the naturally occurring macrocyclic systems, containing predominantly nitrogen donor atoms. In fact the early macrocycles were synthesized to mimic

biologically occurring ones such as the porphyrins, corrins, chlorins, and, more recently, the corphins. Another area of macrocyclic development began in the late 1960s to design molecules as receptors for recognition for modelling biological processes such as ion transport. These macrocycles included the oxygen-based crown ethers of Pedersen,[4] in 1967 named as cyclic polyethers or crown ethers with a variety of ring sizes, constituting a number of oxygen atoms and substituent groups. The ability of these compounds is to coordinate strongly with alkali and alkaline earth metals. Two years later the mixed oxygen–nitrogen bicyclic cryptands were synthetized by Lehn.[5] Several years later, the concept of 'preorganized' cavities resulted in the synthesis of the cavitands by Cram.[6] The award of the 1987 Nobel Prize in Chemistry to Pedersen, Lehn, and Cram has fuelled an exponential growth in macrocyclic chemistry research.

1.1.1 Classification of ligands

As mentioned before, a wide range of macrocyclic ligands have been synthesized in the last decades. Here I report only some selected examples, classified and subdivided thanks to the donor atoms present into the framework.

1.1.1.1 Polyoxa ligands

Polyether macrocycles are the simplest polyoxa macrocycles. The commonly used name for these macrocycles is **crown ethers,**[7] due to their crown-like structure in the solid state. These molecules have been extensively studied as chelating agents for the alkali and alkaline earth metal ions (figure 1.2).

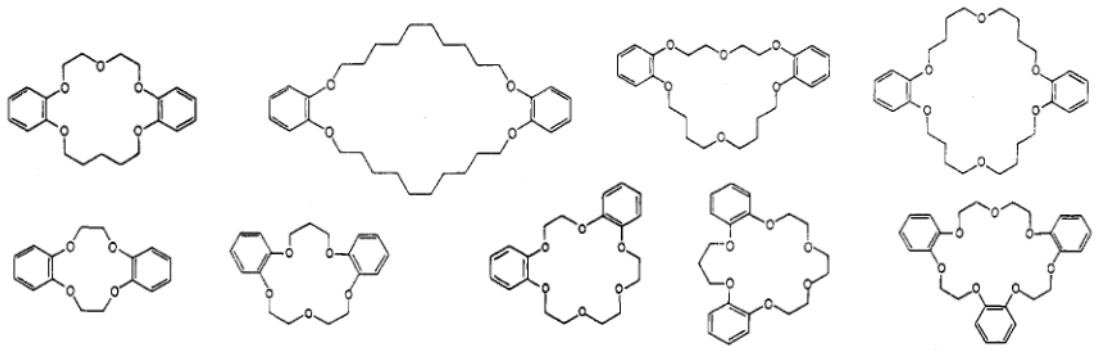


Figure 1.2 Some selected structural formulas of cyclic polyethers presented in Pedersen's paper in 1967.

Up to now more than twenty-five thousand articles have been published on crown ethers. In 2013 about three hundred article were reported, also on detection and recognition of specific molecules. As reported by Archibald,[8] although the crown ether macrocycles have been around for many years and offer less potential for functionalization there are some new and interesting chelators in this group. The well-known chelators can also be used to form unusual species, for

example a crown ether chelator was used to stabilize organotin(IV) compounds and crown ethers (15-crown-5) can be used as a component in the formation of new drug formulations with magnesium oxide.

The **lariat ethers** comprise a subset of the polyether macrocycles, and are identified by their pendant chains.[9] They can be categorized as either *N*-pivot (**A**) or *C*-pivot (**B**), depending on which type of atom the chain is attached (figure 1.3). The trends for structural and thermodynamic aspects are noted to be relatively similar for both the carbon-pivot and nitrogen-pivot types of lariat ethers. Binding strengths and selectivities are dependent on ring size and in general increase as ligand size increases. As for their polyether parents, much of the focus on these macrocycles has been on complexation of alkali and alkaline earth metal ions. In fact strong selectivities are noted for the potassium ion, as in the case for crown ethers.

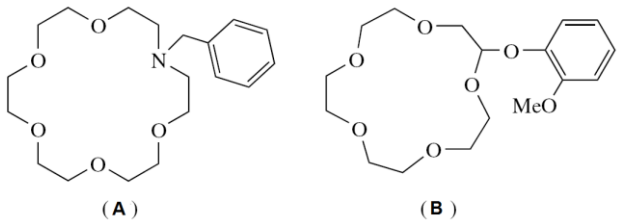


Figure 1.3 Some selected structural formulas of lariat ethers.

Spherands and **Hemispherands**, first reported by Crams in 1985 (figure 1.4),[10]consist of an arrangement of phenyl groups which provide a preorganized cavity for complexation. Spherands are systems of ligands organized prior to complexation so that the orbitals of unshared electron pairs of the binding sites line a roughly spherical cavity enforced by a support structure of covalent bonds. Spherands must be rigid enough so that their parts cannot rotate to fill their own cavities, which ordinarily will be too small to be filled with either solvent or parts of solvent. Thus the cavity should be empty and relatively unsolvated. The crystal structures of a free spherand and the spherand part of its complexes should be very similar.

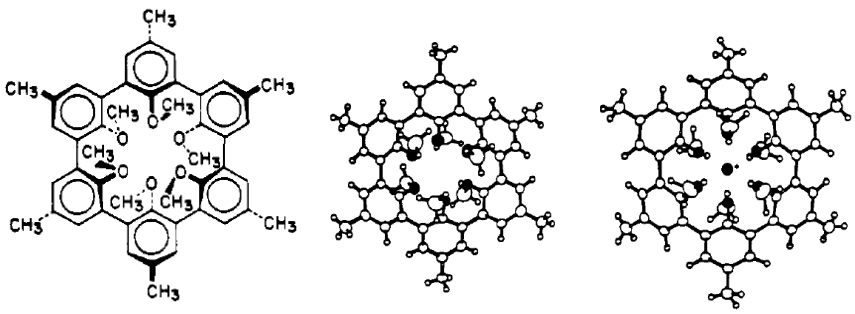


Figure 1.4 Structural formula of spherand **1**, $A(AA)_2A$ ligands and crystal structure of spherands **1**, $A(AA)_2A$ and its **l**-Li+ complex respectively.

Among the polyoxa macrocycle, **calixarenes** are based on the condensation between phenols and an aldehydes.[11] The word calixarene is derived from Greek *calix* or *chalice* because this type of molecule resembles a vase; in fact, they are described by IUPAC as "compounds capable of assuming a basket (or 'calix') shaped conformation".[12] Calixarenes have hydrophobic cavities that can hold smaller molecules or ions and belong to the class of cavitands known in host-guest chemistry. For example in 1990 the water-soluble calixarene **A** (see figure 1.5) was reported. In **A** the 2,2'-bipyridine units show both hydrophilic and chelating properties, forms complexes with Cu^{+} and Cu^{2+} ions. The aqueous solution of **A** treated with $[Cu(CH_3CN)_4]PF_6$ affords the 1:1 complex **B**.[13] Also chiral examples were reported in literature in the same year: the chiral calix[5]arenes ***(R)*-C** and ***(S)*-C**. It was observed that they selectively bind Cu^{2+} over other (Li^{+}, Na^{+}, K^{+}, Mg^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+} and Zn^{2+}) ions.[14]

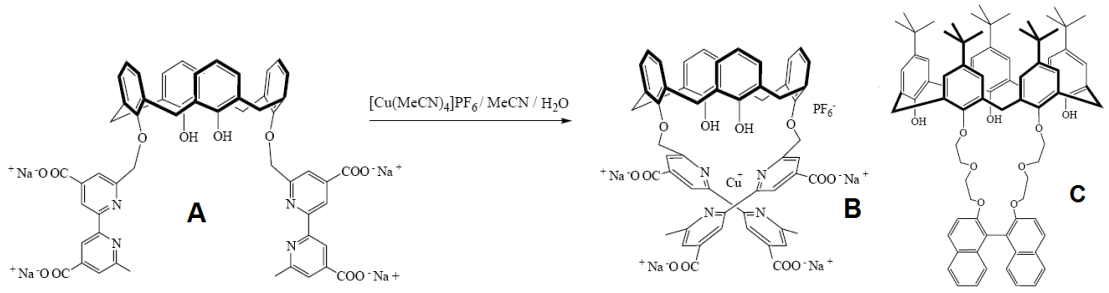


Figure 1.5 Free ligand **A** and corresponding copper complex **B**; chiral ligand **C**.

Only in 2013 more than three hundred article have been published on calixarenes, concerning cataltytic activities like hydride and oxo transfer reactions,[15] palladium and nickel-catalysed cross-coupling[16] and more specifically palladium Suzuki–Miyaura cross-coupling.[17]

1.1.1.2 Polythia, Polyphospha, and Polyarsa ligands

Polythia macrocycles, the thioether analogs of the crown ethers, have been known since the 1930s.[18] These are the most extensively studied macrocycles in line after the polyoxa and polyaza macrocycles. The macrocyclic effect is also noted for thioethers, but to a lesser extent than some of the other macrocyclic ligands. This is due primarily to the reorganizational energy requirements. In fact macrocyclic thioethers must undergo a reorganization of their *exo* lone pairs in order to incorporate metal ions within the cavity. Hence, the favorable macrocyclic effect is more attributable to the entropy changes in the sulfur macrocycles.[19] A comprehensive review of the structural aspects of thia macrocycles can be found.[20] In aqueous solution, thiaether sulfur donor atoms appear to be selective for metal ions in the so-called "copper triangle", specifically Pd(II), Pt(II), Cu(II), Cu(I), Ag(I), Au(I), and Hg- (II). In fact the most important characteristic of thiamacrocyclic ligands is their ability to form stable complexes with

cations of heavy and transition metals, as well as their ability to selectively bind just one cation from a mixture of cations.[21] A study published in 1999 revealed that macrocyclic tetrathiaethers exhibit a greater degree of selectivity for Cu(II) over Ni(II) than any other known class of chelating agents.[22] Structural modification can tune these macrocycles as selective complexing agents - synthetic receptors: for example, adamantane units embedded into the thiamacrocyclic ligands framework (figure 1.6) reduce the conformational mobility of the ligand, defining the shape and size of the cavity of the macrocyclic ring, and therefore, improve the selectivity of complexing cations and in these case Ag(I)-ionophores were obtained.[23]

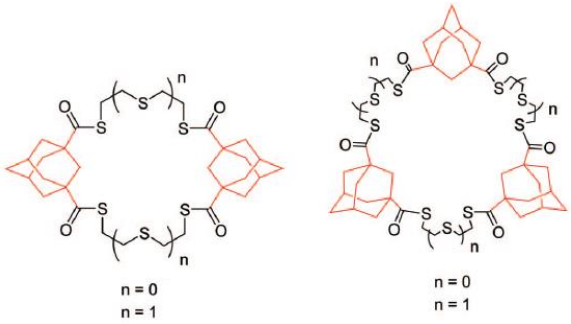


Figure 1.6 Thiamacrocyclic lactones with adamantane and chainlike units embedded into a macrocyclic framework.

The 'pure' **polyphospha macrocycles** (figure 1.7, **A**) (as opposed to the mixed donor phospha macrocycles) were first reported in 1975.[24] These macrocycles have been found to complex a variety of transition metals, but have not received the same attention as the more readily accessible polyaza and polyoxa macrocycles. Phosphorus macrocycles can exist in a variety of conformations, a number of which are stable. The barrier for inversion of phosphate is 146.4 kJ mol^{-1}.[25] Hence for the tetraphosphorus macrocycle **A** there are five possible conformations. Two are preferred: the one in which the macrocyclic benzo groups are *trans (trans*-**A)** and that in which they are *cis* (cis-**A**), figure 1.7.[26]

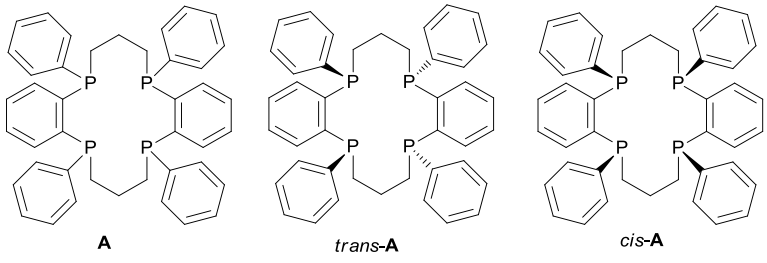


Figure 1.7 Pure tetraphosphorus macrocycle (**A**) and the two most stable isomers *(trans*-**A)** and (*cis*-**A**).

The **polyarsa macrocycles** comprise one of the least common type of macrocycles.[27] More recently, in 2011, 1,4,7-triarsacyclononane ([9]aneAs_3) macrocycles were prepared by

templating a bidentate and monodentate unit around an iron cyclopentadienyl unit and characterized by X-ray crystallography. [9]aneAs_3 was the first characterized example of a nine membered arsamacrocycle.[28]

1.1.1.3 Mixed donor ligands

Cryptands are bicyclic macrocycles which can contain a variety of donor atoms with bridgehead nitrogen atoms. They are highly selective for alkali and alkaline earth metal ions. The term cryptand implies that this ligand binds substrates in a crypt, interring the guest as in a burial. These molecules are three dimensional analogues of crown ethers but are more selective and complex the guest ions more strongly. The resulting complexes are lipophilic. As a selective example, I here report the mixed donor N_3S_3 cryptand **B** (figure 1.8) copper(II) complex that has anion dependent coordination modes with the perchlorate complex hexadentate showing the metal ion bound to all six donor atoms.[29] The bromide complex is five coordinate with four of the donors from the cryptand (N_2S_2) and the halide completing the square pyramidal geometry.

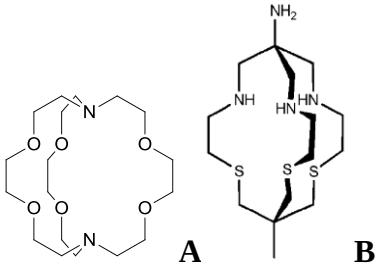


Figure 1.8 The most common and most important cryptand named as [2.2.2]cryptand (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane) **A**. The mixed donor N_3S_3 cryptand **B** reported in 2010.

Catenands are interlocked macrocyclic ligands, which complex a variety of metal ions (figure 1.9).[30] Up to now, comparing with the other classes of cited ligands, catenands are less studied and only few works appeared in the literature mainly devoted to the synthesis and characterization of the novel species.

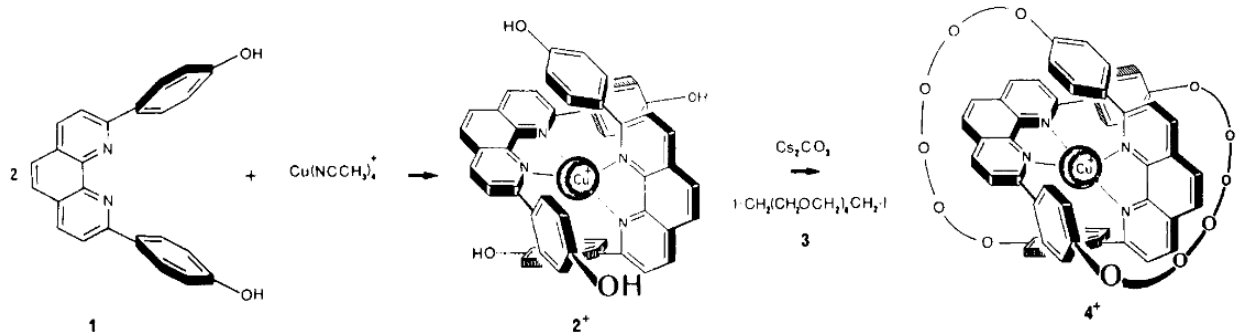


Figure 1.9 Synthesis of a cuprocatenane from a macrocyclic compound.

Compartmental ligands are macrocyclic ligands which contain 'compartments' for housing more than one metal ion.[31] They can have into the framework the same kind of donor atoms, but for simplicity they are listed in this section. Compartmental ligand systems offer an increasing diversity of structures with the control of binding of different metal ions allowing unusual magnetic or catalytic properties to be studied. An example of a mixed donor ligand incorporating different metal ions is the macrocyclic trinucleating ligand (figure 1.10, **A**), which is capable of complexing two 'soft' donor metal centers in addition to a 'hard' alkali or alkaline earth metal.[32] New synthetic methods were investigated for large ring compartmental Schiff's base macrocycles, such as **B** (figure 1.10), using supercritical CO_2 and no organic solvent.[33] High yields were achieved and this methodology offers the advantage of producing empty cavity chelators that do not have solvent molecules bound. A di-iron(III) complex[34] and more recently di-magnesium(II) complexes[35] using ligand **C** (figure 1.10) have been reported by Williams and co-workers as catalysts for the copolymerisation of cyclohexene oxide and carbon dioxide.

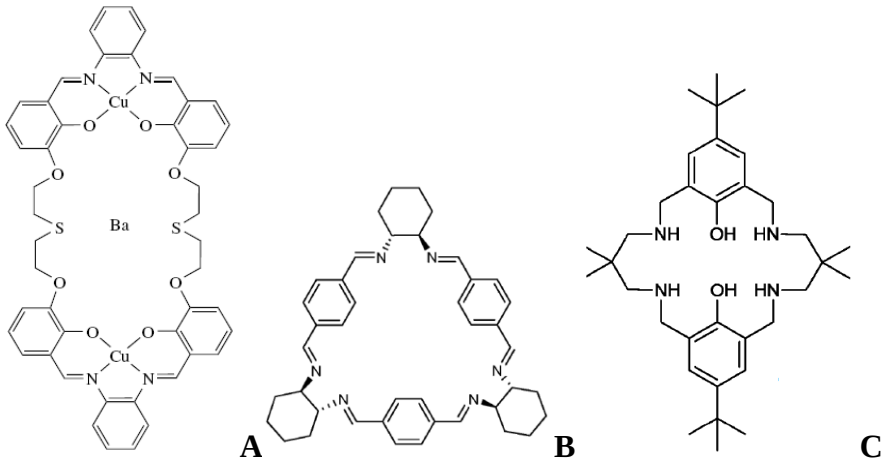


Figure 1.10 Structural formulae of selected compartmental ligands and complex.

In this classification we should mention the wide range of different ligands that have appeared in literature also in recent years, independently on the class to which they belong to. Many are the possible combination between the donors atoms: N/O, N/S, N/P, O/S and N/S/O just to give selected examples.

Chelators which form copper(II) complexes with an N_2S_2 coordination sphere **A** (figure 1.11) have been investigated in detail[36] and the complexes have high stability and could be of relevance for the formation of copper(II) containing radiopharmaceuticals. Cobalt(II) complexes of ligands such as **B** (figure 1.11) show catalytic properties in H_2 production from water at pH 2.2.[37] The ruthenium(II) complex of the P/N chelator **C** (figure 1.11) reduces oxygen to give a

formal peroxide complexes,[38] however full reduction to water was unsuccessful due to decomposition before catalytic oxygen reduction.

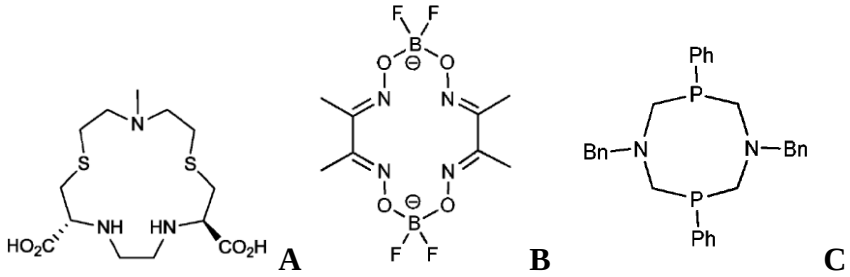


Figure 1.11 Selected examples of mixed donor macrocycles.

1.1.1.4 Polyaza ligands

In general, the polyaza macrocycles form extremely stable complexes with transition metals of the later transition series and they show reduced affinity for alkali and alkaline earth metal ions compared to the oxa macrocycles. Among the polyaza macrocycles, **Cyclam** (1,4,8,11-tetraazacyclotetradecane) and related ligands with extensive varieties of modifications including differing degrees of saturation and ring size, had been the most studied, primarily because of the relationship of these molecules to naturally occurring tetraaza macrocycles, such as the porphyrins and corrins. The larger cyclam macrocycle (with respect to cyclen) has been mainly used in the stabilization of high oxidation state metal complexes that act as catalysts, and in the formation of bifunctional chelators for the attachment of radioisotopes to biological targeting units such as antibodies or peptides. Many examples are reported in literature, as tetramethylcyclam that is frequently used for the stabilization of reactive high valent iron oxo compounds: it formed stable oxoiron(IV) compounds with a variety of anions coordinated trans to the oxo ligand.[39] Monopicolinate cyclam derivatives **A** were reported by Tripier and co-workers and they formed stable copper(II) complexes, demonstrating Cu(II) complexation over other metal ions (figure 1.12).[40] Cyclam units can be also grafted on biomolecules producing an unsymmetric N-functionalized bifunctional chelator version of the cross bridged cyclam (figure 1.12, **C)**, that were extensively studied for their application in the formation of high stability ^{64}Cu complexes as PET radiopharmaceutical imaging agents.[41]

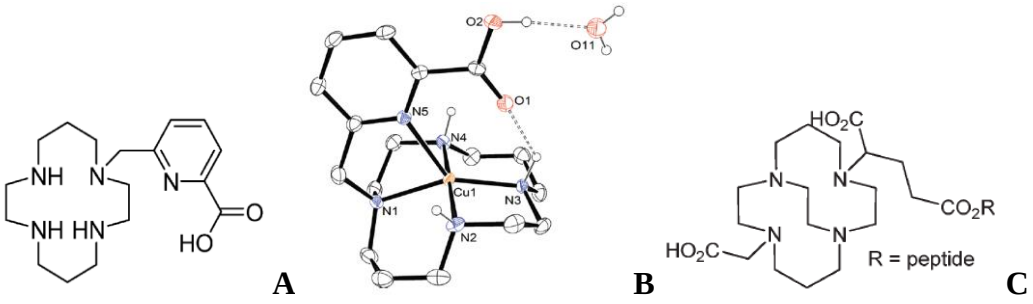


Figure 1.12 Cyclam derivatives (**A**) and ORTEP view of [Cu(**A**)]$(ClO_4)_2 \cdot H_2O$ (**B**) - perchlorate anions and hydrogen atoms bound to carbon atoms are omitted for clarity. Cyclam ligand grafted on peptide (**C**)

Cyclen (1,4,7,10-tetraazacyclododecane) is a macrocycle and the aza analogue of the crown ether 12-crown-4. Many different are the application fields of this macrocycles and their corresponding metal complexes. For example as a NMR probe like the paramagnetic lanthanide(III) chelating protein, pH sensitive that has a bright yellow color which simplifies the protein sample handling (figure 1.13, **A**).[42] As previously reported Tripier and co-workers have developed macrocycles with pinacolate pendent arms, also the cyclen analogue, and tested their copper(II) complexation properties.[40] Coordination of the cyclen derivative switched between the carboxylate and the nitrogen donors depending on pH, whilst in the cyclam derivative the carboxylate was uncoordinated in both protonated and deprotonated forms. The same research group reported another example of cyclen macrocycles with two trans-*N*-acetate arms very selective for Cu(II).[43] The zinc(II) complex of ligand **B** (figure 1.13) binds selectively to thymine bulges in DNA with micromolar affinity. Bismacrocyclic chelators containing a platinum bipyridyl linking unit **C** have been designed to target the amyloid β-peptide, a known Alzheimer's marker.

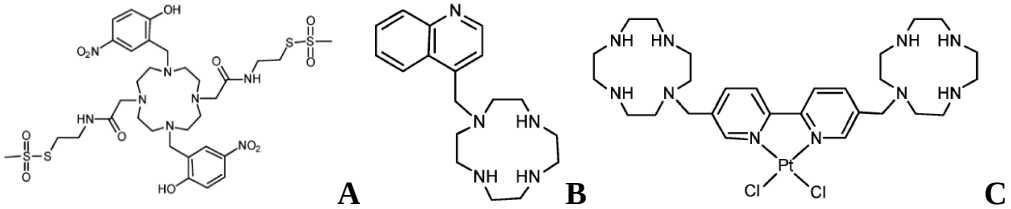


Figure 1.13 Structural formulae of selected cyclam.

Tetraaza macrocycles studied in our research group will be treated in details in the next sections, but we must report some selected examples on tetraaza macrocycles as 'cyclam derivaties' present in literature, mainly in recent year. As examples, in 2012 pyridine-based 12 membered tetraaza macrocycles with quinoline pendant arms were reported (figure 1.14, **A**) that coordinated copper(II); these complexes showed that the *N*-substitution pattern of the quinolone influences reaction kinetics and stability of the complexes.[44] In the field of

radiopharmaceuticals, this pyridine-based 12 membered tetraaza pattern has been used by Cooper and co-workers for ^{64}Cu for labelling of antibodies (figure 1.14, **B**)[45] and by Ferreira and co-workers for the study of pharmacokinetic properties with several radionuclides (figure 1.14, **C**).[46] Another example is the more expanded pyridine-based 14 membered tetraaza macrocycle (figure 1.14, **D**) and its iron(IV) intermediate that have been studied to determine its role as mediators for catalytic epoxidations of cyclooctene and other olefins with H_2O_2.[47]

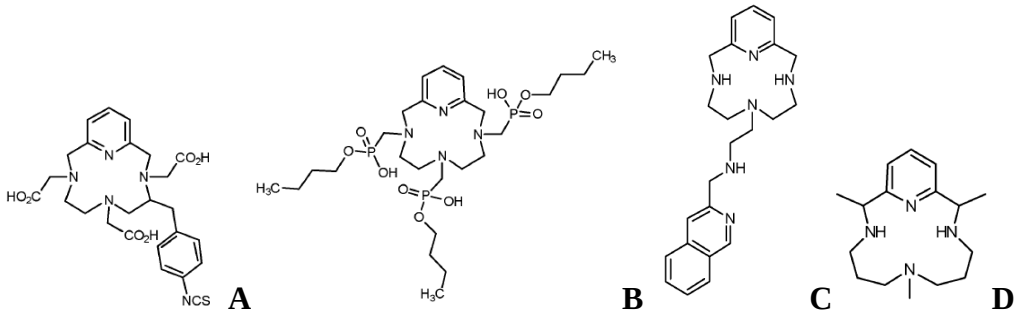


Figure 1.14 Structural formulae of selected examples of 'cyclam derivaties'.

Cyclidenes (1,4,7-triazacyclononane) are a subset of the polyaza macrocycles and are the lacunar ligands first synthesized and extensively studied by D. H. Busch. They coordinate a single metal ion and maintain a 'persistent void' which allows access to small molecules within the vaulted cavity. They are still widely studied and applied as complexes in many different field as catalysis (as example for oxidation[48],[49]), biological target,[50] RNA cleavage,[51] *etc*. Cyclidene based ligands were also used to form a metal organic framework structure for CO_2 absorption.[52] The corresponding zinc(II) complex of ligand **A** (figure 1.15) forms a framework with a high surface area of 1350 m^2 g^{-1} and good selectivity for CO_2 absorption over other gases as CO, CH_4 and N_2. Recently new synthetic methodologies have been developed for the unsymmetric functionalization of their framework in high yields to give chelators such as **B** (figure 1.15**)**.[53]

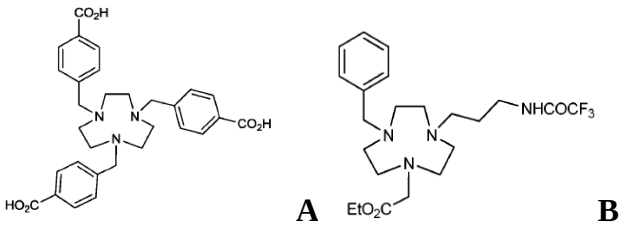


Figure 1.15 Structural formulae of selected examples of cyclidenes.

Sepulchrates are polyaza cage macrocycles (figure 1.16). They are noted for their exceptionally strong hold on encapsulated metal ions.[54]

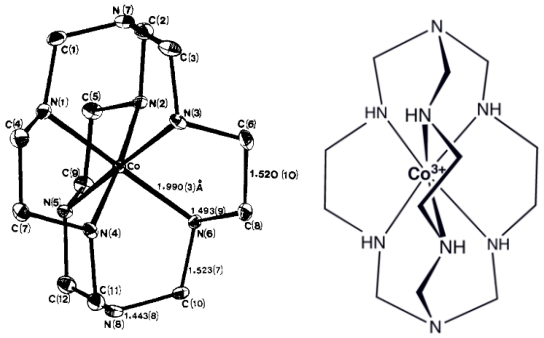


Figure 1.16 ORTEP diagram of Co(sepulchrate)$^{3+}$ repored by Creaser and co-worker.

Porphyrins are tetraaza macrocyclic ligands, many naturally occurring. The overall structure is composed of the tetrapyrrolic macrocycle whose units are connected by methinic bonds. Carbon atoms at positions 5, 10, 15, and 20, which form methinic bonds are known as meso-carbon position; those belonging to positions 2, 3, 7, 8, 12, 13, 17, and 18 are considered β-pyrrolic (figure 1.17, **A**). The porphyrins are found in nature, playing important roles in the metabolism of living beings, and are generally associated with metal ions forming metalloporphyrins. In fact, when the two internal protons of the free-base porphyrin are removed, the porphyrin becomes a tetradentate chelating dianion capable to coordinate a metal ion in the central cavity. So far, porphyrin ligands have been reported to form complexes with all the transition metals, all the lanthanides, several of actinides and some of the main group metals.[55] Metal complexes of this type are possible due to the high electron density of the porphyrin ring, which can coordinate the metal ion.[56] One of the best-known and most abundant natural occurring metalloporphyrin is the complex iron protoporphyrin IX named as heme. Heme is the cofactor of the protein haemoglobin that is also the pigment in red blood human cells (figure 1.17, **B**).

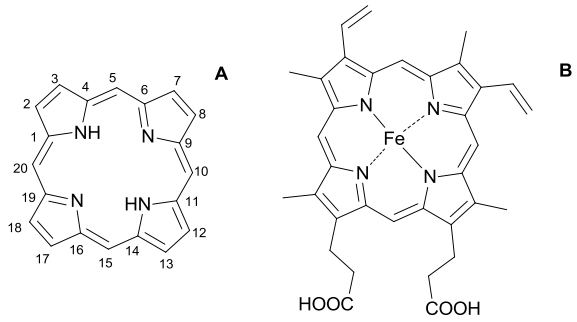
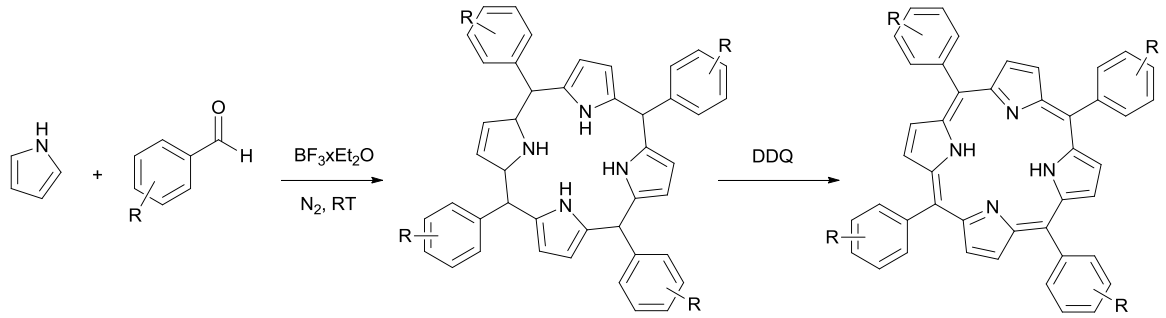


Figure 1.17 Porphine (**A**) - the simplest porphyrin with numbering scheme adopted.; Heme B (**B**)

The first synthesis of a porphyrin was reported by Hans Fisher and Bruno Walach in 1926.[57] After their pioneering work, between the 1930s and 1950s different and continuously improved routes for the preparation of porphyrins have been reported, in particular due to the work of

Rothermund.[58] Despite Rothermund's conditions involved severe limitations in the number of aromatic aldehydes used in these procedures and the low yields, his reactions were historically important. He paved the way for better yields obtained by Adler and Long who performed a one pot reaction between different benzaldehydes and pyrrole with propionic acid at reflux for 30 minutes in an open container with yield up to 20%.[59] Even today this method is used when large amounts of non-symmetrical porphyrins or porphyrin using different aldehydes are needed. In 1986 Lindsey and colleagues proposed the two steps milder variant for the synthesis of porphyrin via porphyrinogen (scheme 1.1), thus avoiding the severe conditions in the method proposed by Adler-Longo, with yield up to 55%.[60]



Scheme 1.1 Synthetic method reported by Linsdey consisting in the coupling between pyrrole and benzaldehyde in DCM in the presence of catalytic amounts of $BF_3 \cdot Et_2O$. The porphyrinogen intermediate can be directly aromatized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

To extend the utility of metalloporphyrin species, synthetic chiral porphyrin derivatives have been developed over the years, having for example enantioselective applications. Chiral porphyrins have been mainly prepared by Groves and Meyers's approach that involves the attachment of chiral units to preformed porphyrins.[61] Then O'Malley and Kodadek showed that chiral substituents can be introduced by allowing a chiral aldheyde to condense with pyrrole through a classic Lindsey procedure.[62] Many different substituted chiral porphyrins appeared in literature. As an example the single-face protected picket fence and picnic basket ones (figure 1.18, **A**, **B** and **C**), first synthetised by Collman in 1993, are still used as ligands in enantioselective catalysis by Rose and co-workers that used iron(III)-chloride complexes of this family of chiral ligands for the asymmetric epoxidation of styrene.[63] The groups of Che and Berkessel tested ruthenium and manganese complexes of the simplest D_4-symmetric double faced porphyrins for stoichiometric and catalytic oxidation,[64] cyclopropanation,[65] and amination[66] reactions of unfunctionalized hydrocarbons, always reaching good to very good results in term of yields. Another important family are the so called "bis-strapped" porphyrins. These systems are characterized by the presence of chiral binaphthyl (BINAP) groups that infer a

significant steric bulk in the vicinity of the active site. These features contribute to high catalytic activity and selectivity. For example, groups of Collman and Rose reported the synthesis of C_2-symmetric bis-binaphthyl chiral porphyrin and the corresponding Fe(III) complex (figure 1.18, **D**) that gave TON of 16000 in the epoxidation of some terminal olefins.[67]

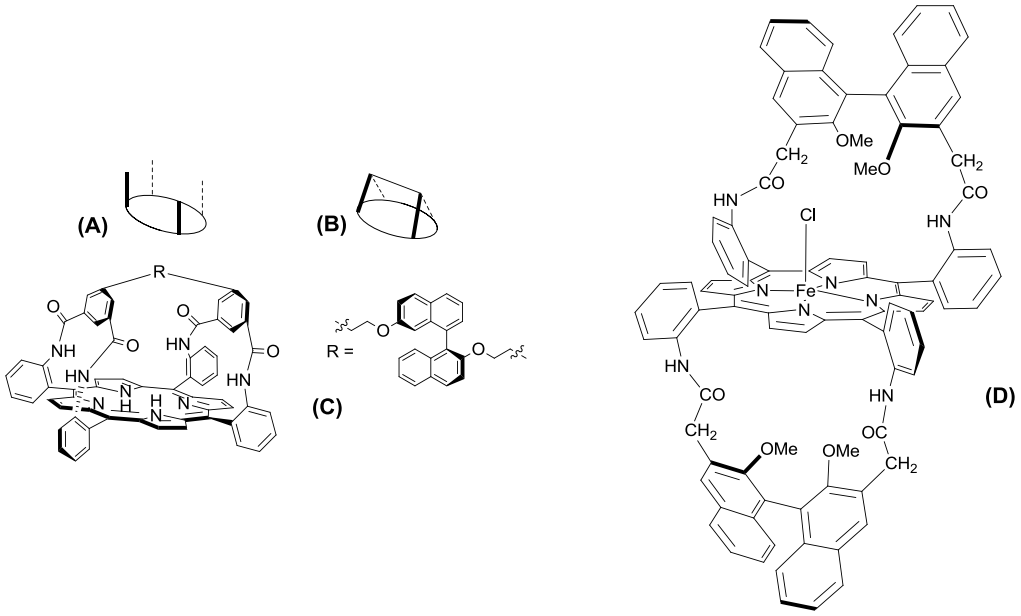


Figure 1.18 Schematic representation of the single-face protected picket fence (**A**) and picnic basket (**B**); picnic basket porphyrin bearing isophthalate amide loops and a binaphthyl dieter linkers (**C**); iron (II) complex of the C_2 bis-strapped porphyrin (**D**).

Up to now, more than sixty thousand papers, about 4000 reviews and books regarding synthesis and uses of porphyrins have been published.

Expanded porphyrins are macrocycles based on the pyrrolic backbone of porphyrins, but are expanded in size to achieve a larger cavity (**A**) or binucleating capabilities (**B**). A review of expanded porphyrin ligands has been published in 1991.**[68]** The cadmium complex of the texaphyrins (figure 1.19, **A**) is found to be planar with pentadentate coordination of the macrocycle to cadmium, which becomes seven-coordinate as a result of axial coordination to two pyridine molecules. The cavity is nearly circular with a center-to-nitrogen distance of 2.39 A˚. Because of the larger size of this macrocycle, metal ion coordination is generally seen with the larger transition metals and lanthanides. The 'accordion' porphyrin (figure 1.19, **B**) is a more flexible expanded porphyrin.

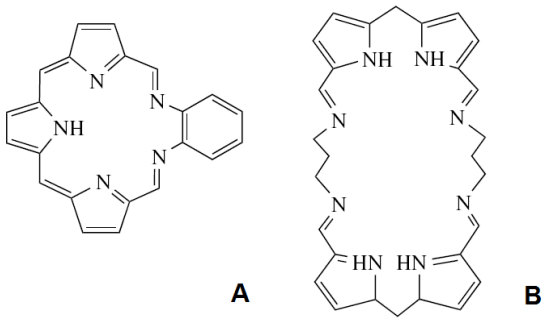


Figure 1.19 Texaphyrins (**A**) and expanded porphyrin (**B**)

Finally **larger polyaza** macrocycles must be citied. They can be classified by increasing macrocyclic ring size and number of donor atoms. For macrocycles with five nitrogen atoms, I here report as example two macrocyclic pentaaza compounds (figure 1.20, **A** and **B**) containing pyridine that were synthetized and evaluated as novel chelating agents in copper(II) and nickel(II).[69] As an example for hexaza macrocycle, two novel copper(II) complexes of ligand **C** (figure 1.20) have been synthesized by a one-pot metal template Mannich reaction and have been shown to produce cleavage of DNA in the presence of H_2O_2 potentially via a hydroxyl radical mediated process.[70] An even more extended system, a octaaza macrocycle (figure 1.20, **D**) has been functionalized with methyl-naphthyl groups for the detection of zinc(II) using chelation enhanced fluorescence.[71] The derived fluorescence by complexation was not switched on by other biologically relevant ions, enhancing its potential as a sensor for biological systems.

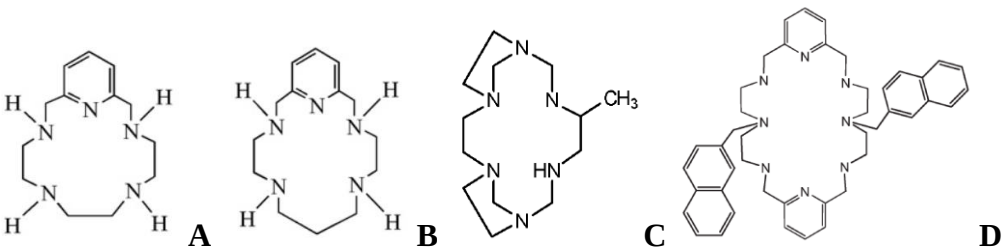
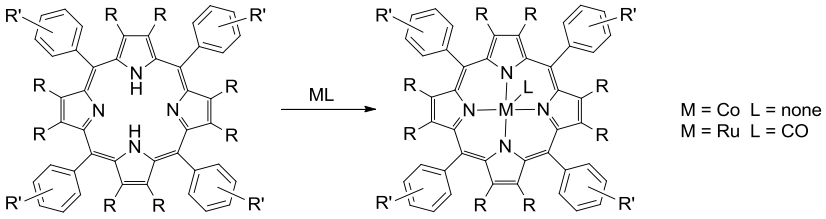


Figure 1.20 Structural formulae of selected examples of penta, hexa and octaaza macrocycle.

1.1.2 Tetraaza macrocycles

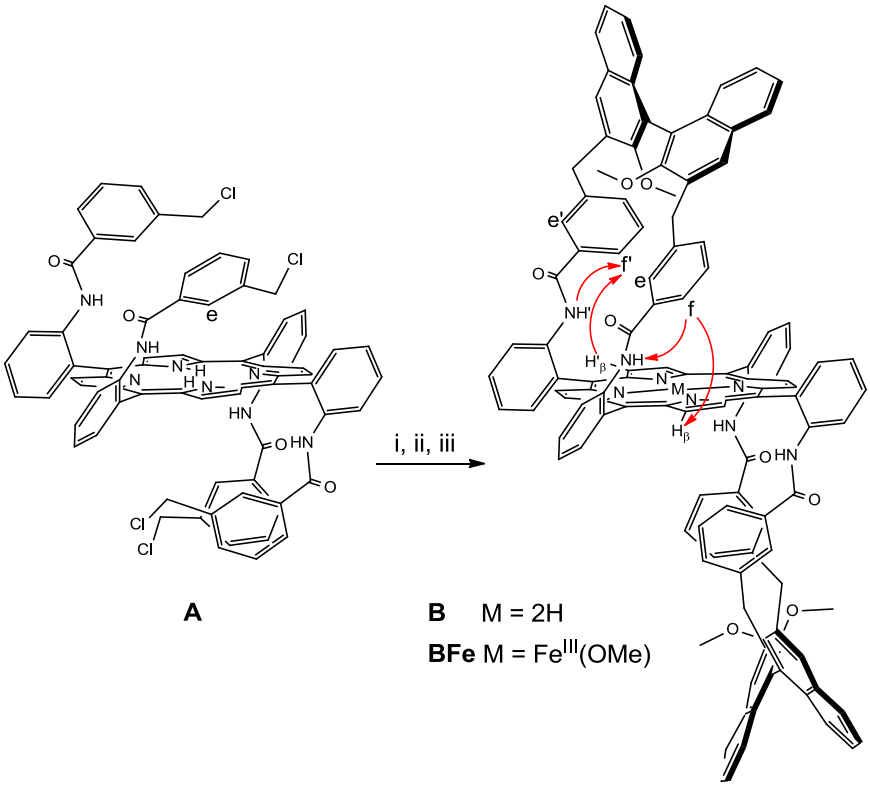
This part of the introduction is devoted to the research conducted on tetraaza macrocycles in our group. Several years ago, we have focused our attention on the synthesis of tetraza macrocycles and we investigated the catalytic activity of their transition metal complexes. We reported the synthesis of Co^{II}-porphyrin complexes that catalysed, for example, the amination of benzylic compounds.[72] Co(porphyrin)- also promoted the amination of 1,2-dihydronaphthalene derivatives promoting an unusual reactivity of dihydronaphthalene towards several aryl azides.[73] The aziridination of olefins using aryl azides as nitrogen sources was observed using

another porphyrin [Ru-(CO)(TPP)] (TPP = dianion of tetraphenylporphyrin) as catalyst.[74] This ruthenium complex has been found to catalyze the direct aziridination of conjugated dienes by aryl azides with high chemoselectivity, to provide *N*-aryl-2-vinylaziridines.[75] More recently, our research group discovered that [Ru-(CO)(TPP)] promoted the amination of both exocyclic and endocyclic benzylic C-H bonds (scheme 1.2).[76]



Scheme 1.2 General scheme for the synthesis of cobalt and ruthenium complexes.

Finally, we have explored cyclopropanation reactions employing a new chiral iron porphyrin (scheme 1.3, **B**), obtaining cyclopropanes with excellent yields (up to 99%), enantio- and diasteroselectivities (ee_{trans} up to 87%, trans/cis ratios up to 99:1) and outstanding TON and TOF values (up to 20,000 and 120,000/h respectively).[77]



Scheme 1.3 Synthesis of C_2-symmetrical binap-*bis*-strapped porphyrin **B** and its iron(III) complex **BFe**; i) (*R*)-(2,2'-dimethoxy-[1,1'-binaphthal-ene]-3,3'-diyl)diboronic acid, $(Ph_3P)_4Pd$, K_2CO_3 (35%); ii) $FeBr_2$/THF, reflux.

Porphyrin complexes have shown excellent catalysts turnovers and unusual selectivities, thanks to the high versatility of the porphyrin ligand and to its ability to give only one way to coordinate the metal. On the other hand several problems arise during the synthesis of these species, especially if some functional groups are introduced on the framework. and when the optical form are synthetised. For example, chiral porphyrin complexes of cobalt(II) and ruthenium(II) were tested in catalytic cyclopropanation[78] and amination reactions.[79] Also the synthetic methodologies reported in literature concerning chiral porphyrins require laborious procedure, expensive reagents and moreover the overall yields are very low. Our attention turned to the development of synthetic pathways that allow to obtain a new class of tetraaza macrocyclic ligands in few synthetic steps, easily functionalised, in good yield, with economic and commercially available starting materials. In collaboration with Prof. Sisti, we synthesised a new type of ligand, containing a pyridinic ring. Sisti and co-workers studied these class of compounds to be employed as ligand for gadolinium(III)[80] since their complexes are useful contrast agents for magnetic-resonance images (MRI), figure 1.21.

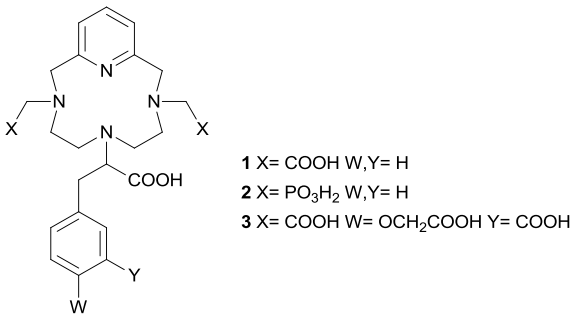
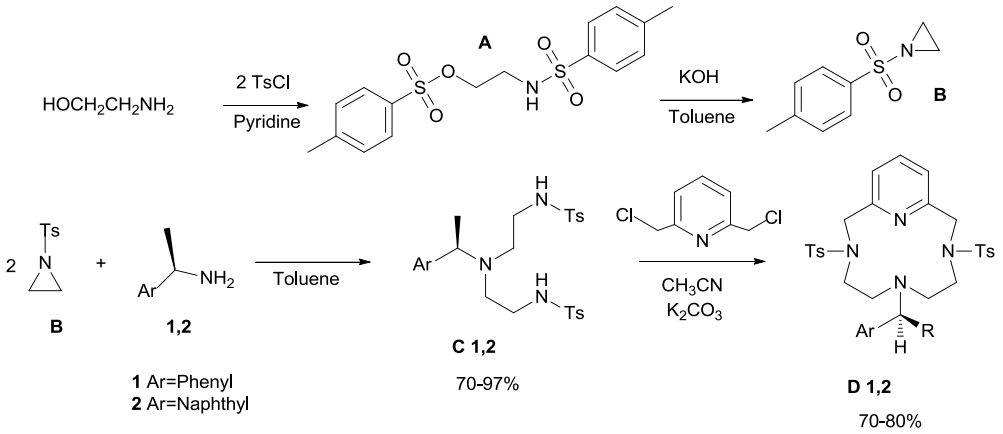


Figure 1.21 Structure of the PC-type ligand.

We decided to modify this kind of ligands in order to make them suitable for catalytic purpose. In 2008 the new pyridine based 12-membered tetraaza-macrocyclic ligands, named Pyridine Containing Ligands (**Pc-L*)** were obtained.[81] The synthetic approach employed to synthesise these macrocyclic ligands, is reported in scheme 1.4.



Scheme 1.4 Synthesis of macrocyclic molecules **Pc-L***.

There are three main steps to obtain the macrocycle. Firstly ethanolamine is reacted with tosyl chloride and the obtained *N,O*-ditosylethanolamine **A** undergoes a ring closure after treatment with base to obtain the tosyl-aziridine **B**. Then a solution of **B** (2 equivalents) is added to commercially available chiral aryl-amine **1** or **2** to yield a substituted amine **C**. Finally, compound **C** is added to a solution of 2,6-bis(chloromethyl)pyridine, yielding the desired macrocycle **D**. It should be pointed out that the crucial step, *i.e.* the macrocyclization, was run under heterogeneous conditions that represent a modification of Richman-Atkins protocol (NaH/DMF). This synthetic methodology allows to avoid high dilution techniques and to obtain the 12 membered macrocycle **D** in 70–80% yields, without any racemisation at the asymmetric carbon. Moreover, it is worth of note that, even conducting the reaction in concentrated condition, we never observed the formation of polymers. These macrocyclic ligands are of particular interest because of the presence of different types of nitrogen, one sp^2 and three sp^3, one of which can bear a chiral moiety (figure 1.22).

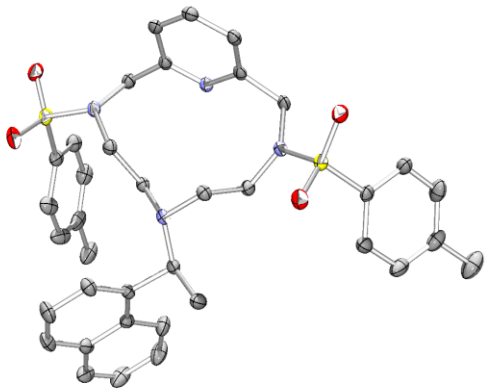
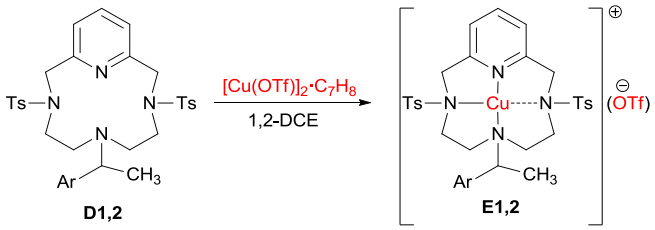


Figure 1.22 Ortep view of compound **D2.** The ORTEP view shows the good conformational degree of freedom of the macrocyclic cavity.

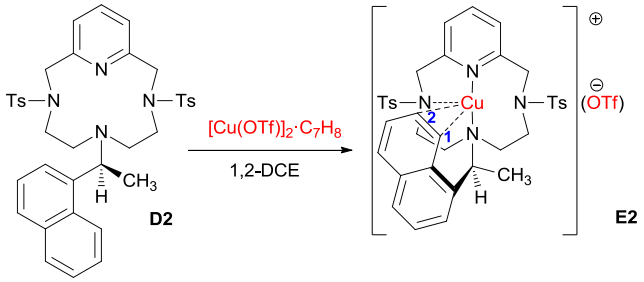
As mentioned before, this synthetic methodology is simple and allow to differently functionalise the macrocyclic framework in order to create stereocenter on the backbone. A modular design of the catalyst is possible by varying for example the structure of the amine nucleophile starting from different commercially available chiral or non chiral amines; the tosyl groups can be removed and replaced with others protecting group.

Metal complex formation with ligands **D1,2** was investigated with copper(I) triflate toluene complex ($[Cu(OTf)]_2 \cdot C_7H_8$) as copper(I) source (scheme 1.5).



Scheme 1.5 Synthesis of the copper(I) complexes **E1,2**.

Treating ligand **D1** with $[Cu(OTf)]_2 \cdot C_7H_8$, a yellow Cu(I) complex **E1** was obtained that undergo oxidation quite readily. On the other hand, by layering with benzene a 1,2-dichloroethane (DCE) solution of ligand **D2** after treatment with an equimolar amount of $[Cu(OTf)]_2 \cdot C_7H_8$ a colourless crystalline solid was obtained (scheme 1.6).



Scheme 1.6 Cu(I) complex formation from ligand **D2**, highlighting the η^2 coordination mode of naphthyl moiety.

All the analytical data confirmed the formation of a mono-metallic Cu(I) complex (45% yield) of formula [Cu**D2**]·(OTf), **E2,** which did not readily oxidize to Cu(II). These complexes have been isolated and fully characterised. As reported by our group,[81] the ^{1}H NMR spectrum of complex **E2** in $CDCl_3$ displays a very low symmetry. In the ^{1}H NMR (figure 1.23) the proton directly bound to carbon **1** shifted to higher frequencies, 8.93 ppm compared to 8.16 ppm for the free ligand **D2**.

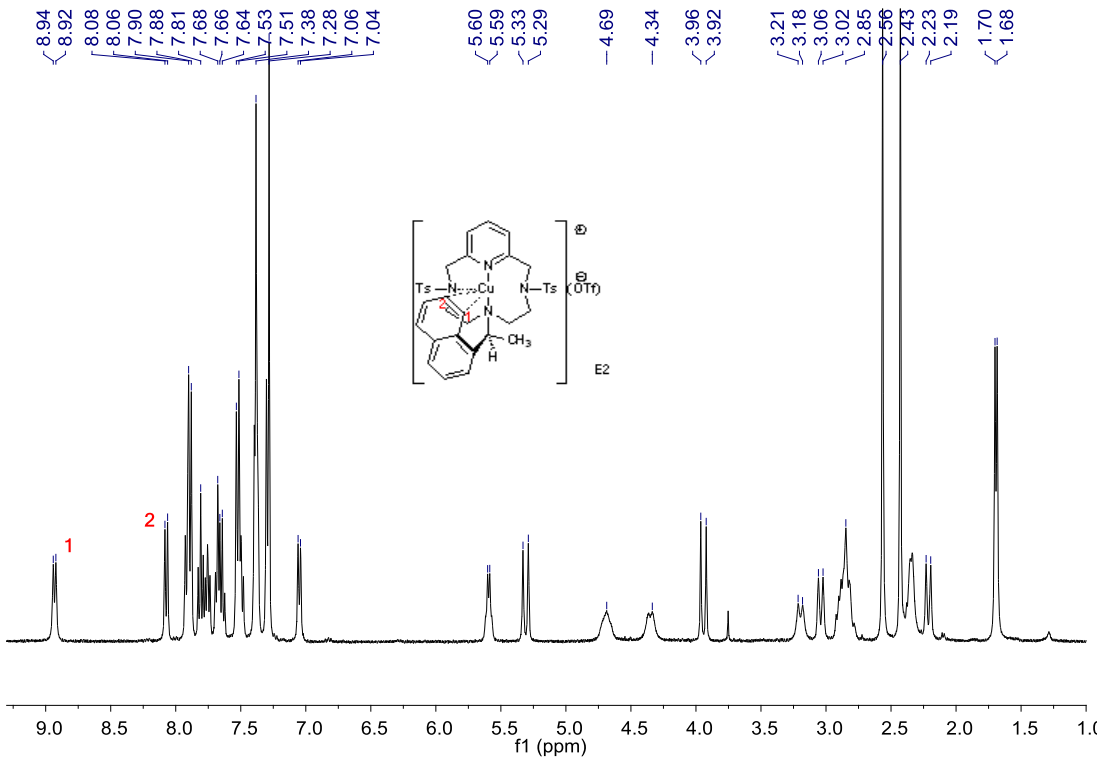


Figure 1.23 ^{1}H NMR spectrum of complex **E2** in $CDCl_3$

Moreover, two sets of signals are observed for the sulphonamide moieties and this can be due to very low symmetry of the molecule, also retained in solution. In fact, the solid state structure of complex **E2** shows that the copper atom is placed in the large macrocyclic cavity of the ligand, which has five potential coordination sites (the four nitrogens and the naphthyl moiety) in a strongly distorted trigonal bipyramidal geometry (figure 1.24).

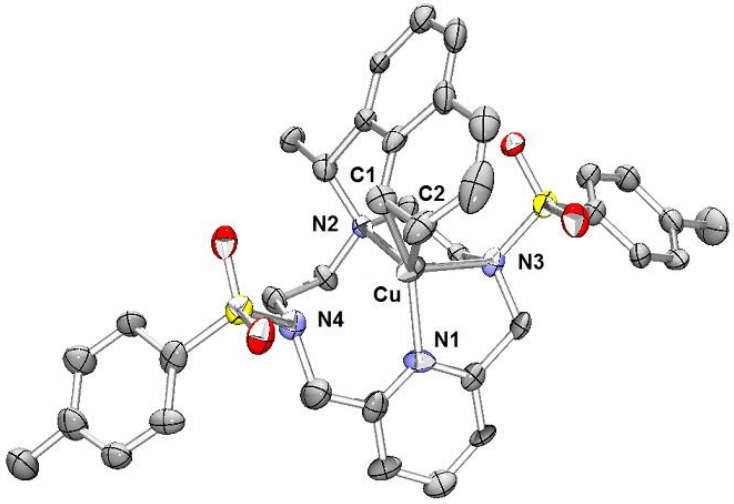
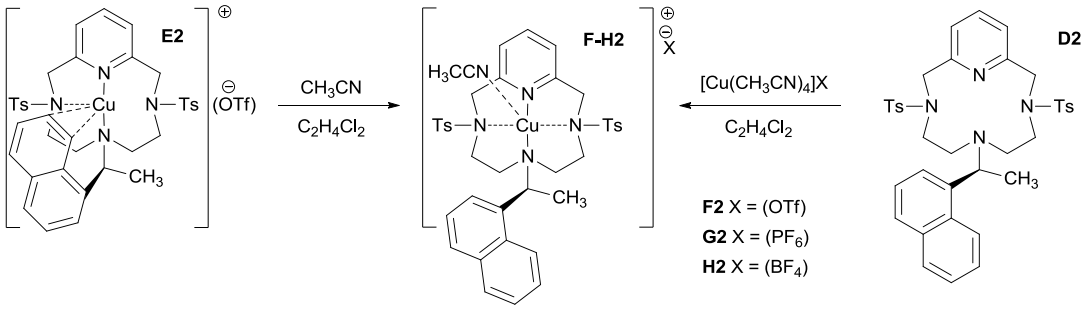


Figure 1.24: Ortep view of the cation of **E2**. Selected bond distances: Cu–N1 1.980 Å, Cu–N2 2.151Å, Cu–N3 2.346 Å, Cu–N4 2.820 Å, Cu–C1 2.017 Å, Cu–C2 2.428 Å.

Actually, in this complex the metal is only tetra-coordinated since for steric reasons its position is shifted to one side of the cavity, away from N4 (at a distance in excess of 2.8 A˚ , well above a regular Cu–N bond). The η^2 coordination mode of the naphthyl on copper(I) in solution has been also observed by ^{13}C NMR studies in $CDCl_3$ solution. A marked low frequency shift of the naphthylic carbon **1** involved in the η^2 bond with copper from 124.5 ppm in the free ligand, to 94.2 ppm in the complex (see figure 1.24 for labelling of the carbon atoms **1** and **2**). Carbon **2** is affected to a lower extent (low frequency shift from 124.6 to 118.2 ppm). The observed coupling constant ^1J (^{13}C, ^1H) of 149 Hz for carbon **1** provides hints of a partial re-hybridisation state from sp^2 to sp^3. Carbon **2**, instead, is less affected and a ^1J (^{13}C, ^1H) of 163 Hz is observed.[82] The effect of the copper complexation to the ligand was shown also by the ^{15}N NMR chemical shifts observed in $CDCl_3$ solution. The ^{15}N NMR spectrum shows a marked shift for the pyridinic nitrogen atom (from 313 to 245 ppm), while the sp^3 nitrogen atom bonded to the asymmetric carbon is affected to a lesser extent (from 39 to 51 ppm). The η^2 coordination mode of the naphthyl on copper(I) can explain not only the better stability of the copper complex with ligand **D2** with respect to **D1**, but also the higher performances in term of enantioselection observed in the catalysis. The reactivity of complex **E2** was also tested with acetonitrile (scheme 1.7).



Scheme 1.7 Reaction of complex **E2** with CH_3CN. Synthesis of complexes **F-G2**.

We first accomplished this by stirring a dicholoroethane solution of **E2** in the presence of excess of acetonitrile (5 equivalents). The ^1H NMR spectrum shows a marked shift of all the signals, especially in the aliphatic region. The ^{15}N NMR spectrum shows that the position of the pyridine nitrogen signal is unaffected while the sp^3 nitrogen atom bonded to the stereogenic carbon is located at 38 ppm. The excess of acetonitrile can be easily removed under reduced pressure to yield [Cu(CH_3CN)**D2**]·(OTf), **F2**, containing only one coordinated acetonitrile molecule (ν_{CN} = 2250 cm^{-1}), as shown by integration of the CH_3CN signal in the ^1H NMR spectrum. The same product, with different counter anions, can also be synthesized by treating the free ligand **D2** with [Cu($CH_3CN)_4$]·(PF_6) or [Cu($CH_3CN)_4$]·(BF_4), to yield complexes **G2**

and **H2**, respectively (scheme 1.7). Both complexes show the same chemical shifts as **F2** for the cation in the ^{1}H NMR spectra, indicating that the counter anion does not affect the symmetry of the product in solution.

All the obtained complexes were fully characterized and in particular for complex **H2** crystals suitable for an X-ray structural determination were obtained by crystallisation from dichloroethane / *n*-hexane. The structure of complex **H2**, (figure 1.25) shows the copper atom placed in the middle of the macrocyclic cavity, again in a fivefold coordination site produced by the four ligand nitrogens and the acetonitrile. At variance from copper complex **E2**, in **H2** Cu is therefore truly pentacoordinated in a strongly distorted trigonal bipyramidal geometry. N3 and N9 occupy particularly elongated axial sites (Cu-N ~2.5 Å), whereas N6, N12 and the acetonitrile are in equatorial positions. As expected, the naphthyl group has been displaced from the coordination sphere of the metal by the incoming acetonitrile molecule. The complex crystallizes in $P2_1$, and the absolute configuration is well established (Flack parameter -0.003(16)).

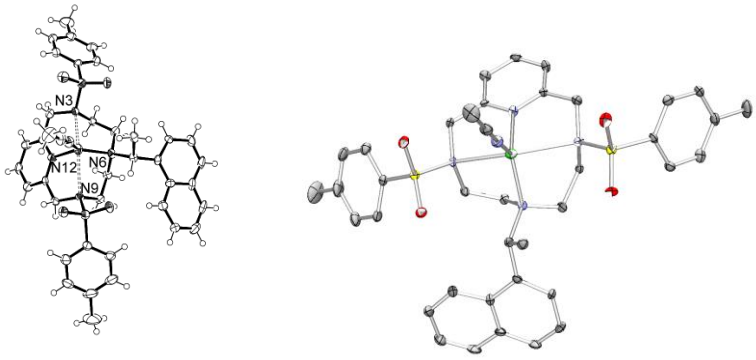


Figure.1.25 Structure of compound **H2** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°): Cu-N12 2.058(4), Cu-N6 2.111(5), Cu-N3 2.567(4), Cu-N9 2.549(5), Cu-N(CH_3C*N*) 1.898(5), N3-Cu-N9 139.1(1).[81] For sake of comparison with **D2** and **E2**, N6---N12 is 3.306(5) and N3---N9 is 4.793(6).

1.2 Cyclopropanation reactions

In recent years cyclopropane derivatives have attracted great interest because of their biological and pharmaceutical applications. Cyclopropane ring systems are ubiquitous in nature and are contained in a large number of natural products,[83] insecticides, and pharmaceutical drug candidates. Designing small molecules that bind to therapeutically important biological targets with high affinity and selectivity is a major goal in contemporary bioorganic and medicinal chemistry. The reactivity of cyclopropanes allows them as versatile intermediates in the synthesis of complex molecules, and the smallest carbon containing ring is frequently employed as versatile building block in organic syntheses. Natural and synthetic cyclopropanes have been found to exhibit diverse biological proprieties and applications ranging from enzyme inhibitions to antibacterial,[84] insecticidal (figure 1.26, **a**),[85] antifungal, herbicidal, antimicrobial,[86] antibiotic, antibacterial, anticancer, antitumor activities. For example Betulins and their derivative containing a cyclopropane moiety were synthesized and were proven to be the most cytotoxic toward human melanoma of the Colo 38 and Bro lines and human ovarian carcinoma of the CaOv line.[87] Cyclopropanes also have antiestrogenic, anti-HIV[88] and antiviral activities like the nucleoside analogue reported in figure 1.26 (**b**).

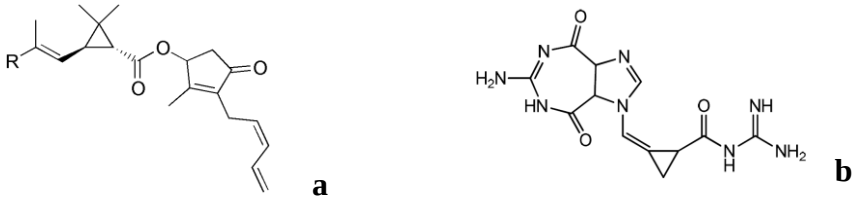
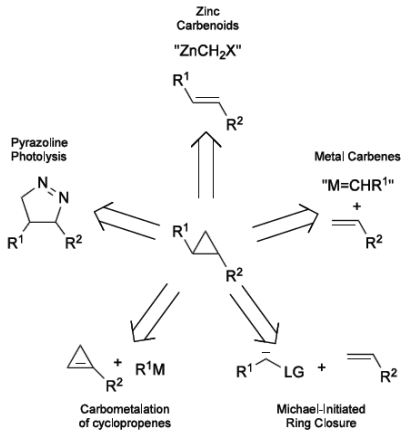


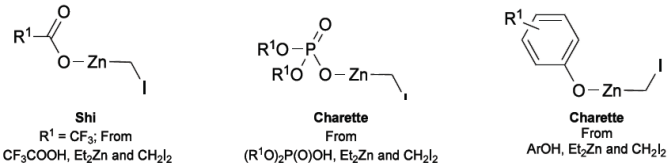
Figure 1.26 a) General structure of pyrethroids; pyrethrin I, R = CH_3; pyrethrin II, R = CO_2CH_3 **b**) (z)-1-[(z-guanidino-carbomoylcyclopropyledene)methyl]-4,5,7,8-tetrahydro-6H-6-iminoimidazo (4,5-e)[1,3]diazipine-4,6-dione.

The cyclopropane rings is present also in molecules produced in industrial scale as antidepressants[89] and drugs for the treatment of sleep disorders.[90] The synthesis and application of multi-substituted cyclopropanes has been a subject of great interest due to their roles as the basic structural elements in a wide range of biologically active compounds and important intermediates in organic synthesis diverse applications in synthetic, agricultural, and medicinal chemistry as well as in material science. Many different methods have been reported up to now for the synthesis of cyclopropane derivatives from various achiral substrates (scheme 1.8).



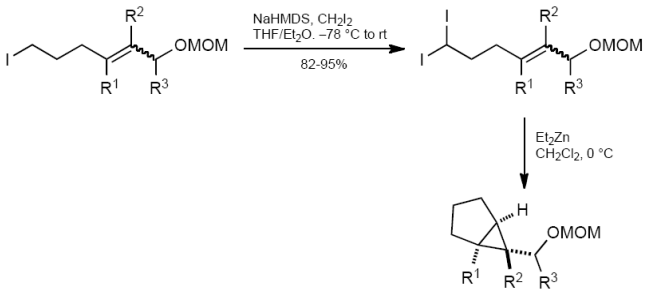
Scheme 1.8 Various approaches to cyclopropane derivatives.

From the historical point of view, since the pioneering work of Emschwiller[91] in 1929, the conversion of alkenes to cyclopropane derivatives was discovered by Simmons and Smith in 1958, using zinc carbenoids.[92] Even today, this method remains one of the most important reactions for the synthesis of cyclopropanes. Several zinc carbenoid reagents have been prepared shortly after Simmons and Smith, Wittig,[93] and Furukawa publication.[94] Recently, several new zinc carbenoids have been prepared to tailor their reactivities and properties to specific applications. Typical modifications involve the replacement of the iodide substituent on iodomethylzinc iodide by another anionic substituent. Notable reagents include zinc carboxylates,[95] zinc phosphates[96] and zinc phenoxides[97] (scheme 1.9).



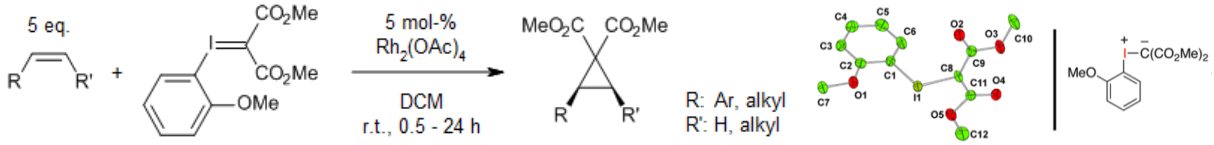
Scheme 1.9 Reagents for the zinc carbenoid-mediated cyclopropanation of alkenes.

Various synthetic strategies have appeared via intramolecular Simmons-Smith cyclopropantion. For example Charette in 2010 proposed the synthesis of substituted bicyclo[n.1.0]alkenes. The reaction conditions allow the construction of substituted bicyclo[3.1.0]hexanes in good yields, where the relative stereochemistry of the cyclopropane is controlled by the double bond geometry, and the chemoselectivity is promoted by the directing ability of the methoxymethyl group (scheme 1.10).[98]



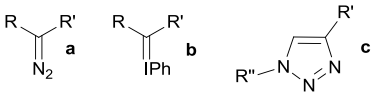
Scheme 1.10 Intramolecular Simmons-Smith cyclopropanation leading to bicyclo[3.1.0]hexanes.

Different alternative routes have been proposed to access also to even more highly functionalized motifs. Zhu and co-workers in 2012 proposed an highly soluble iodonium ylides derived from malonate methyl ester that showed higher reactivity than common phenyliodonium ylides in the Rh-catalysed cyclopropanation under homogeneous conditions (scheme 1.11).[99]



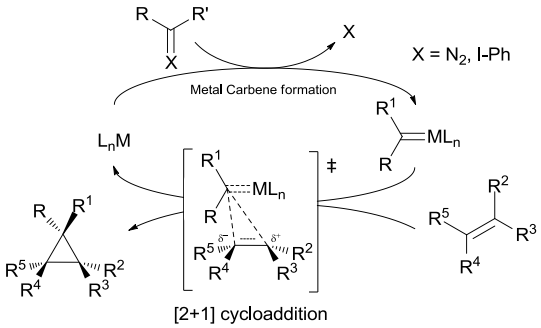
Scheme 1.11 Synthesis of functionalized cyclopropane molecules proposed by Zhu and co-workers.

One of the most useful method to obtaine the cyclopropane ring involves the transition metal catalysed decomposition of a carbene precursor, such as a diazoalkane, an iodonium ylide, or a 1,2,3-triazole, to form a reactive specie (scheme 1.12, **a b, c** respectively).



Scheme 1.12 Most commonly used types of carbene precursors in asymmetric cyclopropanation.

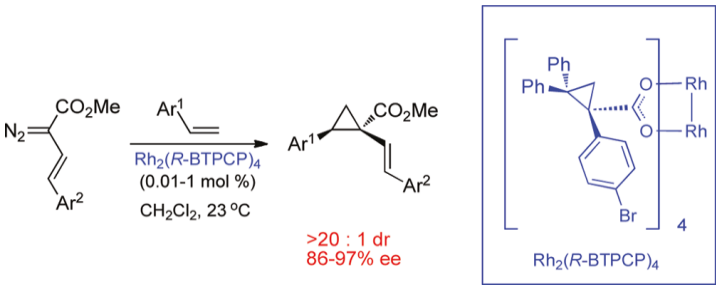
The formed metallo-carbene is then capable of reaction with an alkene to produce a cyclopropane derivative in a concerted, asynchronous [2+1] cycloaddition (scheme 1.13).



Scheme 1.13 General mechanism of the intermolecular cyclopropanation using metal carbenes.

Although a wide variety of transition metal catalysts can be used for this transformation, only rhodium(II), copper(I/II), ruthenium(II), iridium(III), iron(III) and cobalt(II) have proven to

furnish useful levels of stereoinduction, using the appropriate chiral environment around the metal center(s). With these transition metals, the carbene involved has an electrophilic character (Fischer-type carbene) and readily reacts with electron-rich alkenes. The electronic nature of the substituents on the carbene highly influences its reactivity and, thus, the stereoselectivity outcome of the reaction. The cyclopropanation of olefins using the transition metal-catalyzed decomposition of diazoalkanes is one of the most extensively studied reactions. Both inter- and intramolecular versions of this reaction have been developed and exploited in synthesis. The nature of the starting diazo reagent, as well as the type of the reaction to be carried out (inter- *vs* intramolecular), plays a key role in the appropriate selection of the most efficient catalyst for a given transformation.[100] Different type of diazo compounds could be used and according to their electronic proprieties they can be divided in metal carbenes bearing one electron-withdrawing group (type **A**); two electron-withdrawing groups (type **B**); and one electron-donating group and one electron-withdrawing group (type **C**). For example, very recently in 2011, Qin and co-worker used aryl- and styryldiazoacetates for highly enantioselective cyclopropanations with dirhodium tetrakis-(R)-(1-(4-bromophenyl)-2,2-diphenylcyclopropanecarboxylate) (Rh_2(R-BTPCP)$_4$) as catalyst (scheme 1.14).[101]



Scheme 1.14 (Rh_2(R-BTPCP)$_4$) as chiral catalyst for enantioselective cyclopropanation reactions.

In 2013 Zhang[102] *et al* reported the cobalt(II)-catalyzed asymmetric olefin cyclopropanation with α-ketodiazoacetates. These cobalt(II) complex of the D_2-symmetric chiral porphyrin (figure 1.27) achieved very high diasteroselection with enantioselectivity up to 94%.

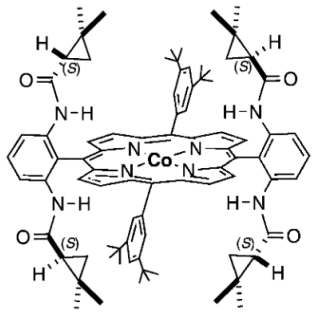
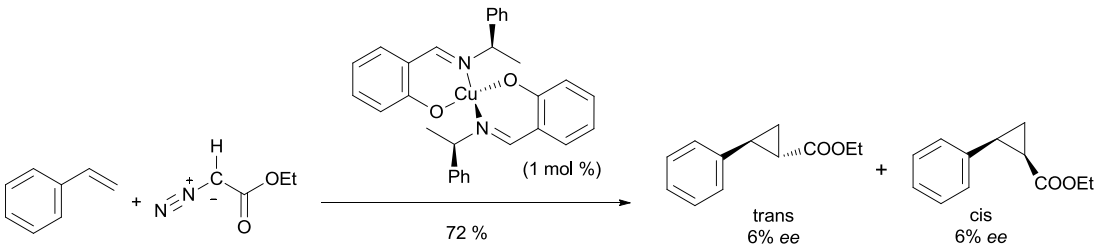


Figura 1.27 Structural formula of D_2-symmetric chiral porphyrin proposed by Zhang.

The reaction of unsubstituted diazocarbonyl compounds (type **A**) with alkenes has attracted the attention of organic chemists for many years and is one of the most well-known transformation in the field of asymmetric cyclopropanation. For instance, ethyl diazoacetate (EDA),[103] which is one of the rare commercially available diazo compounds, is part of this class. This compound readily reacts with transition-metal catalysts in the presence of alkenes to generate the resulting ethyl cyclopropanecarboxylate derivatives. The first example of an enantioselective copper based intermolecular cyclopropanation reaction was reported by Nozaki in 1966.[104] The copper-catalyzed decomposition of ethyl diazoacetate in the presence of an *N*-benzylethylamine-based chiral salicylaldimino complex gave about 6% enantiomeric excess of the corresponding *cis*- and *trans*-cyclopropanecarboxylates (scheme 1.15).



Scheme 1.15 Nozaki's copper catalyzed cyclopropanation.

Although the enantiomeric ratios were modest, this catalyst defined the basis for further ligand optimization. In particular the copper-catalysed enantioselective version of the reaction is now well established, and chiral C_2 symmetric bidentate ligands such as bisoxazolines[105], [106],[107] are the most widely used, also with EDA as carbene source.[108] As an example, very recently Kellehan *et al.* described copper complexes of chiral BOX ligands applied as catalysts to asymmetric cyclopropanation reaction of styrene with ethyldiazoacetate and enantioselectivities of up to 70% were obtained. (figure 1.28).[109]

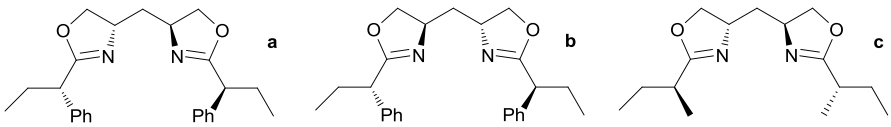


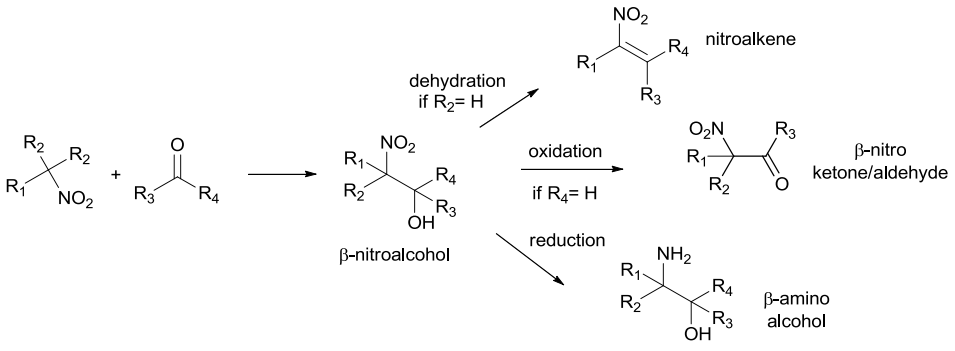
Figure 1.28 Two different PhPrAraBOX (**a** and **b**) and MePrArBOX (**c**) synthetized by Kellehan *et al.*

Another example is reported by S. Gharaati[110] *et al.* that described tin(IV) tetraphenylporphyrinato trifluoromethanesulfonate, $[Sn^{IV}(TPP)(OTf)_2]$, and tin(IV)tetraphenylporphyrinato tetrafluoroborate, $[Sn^{IV}(TPP)(BF_4)_2]$ as catalysts for cyclopropanation of styrene derivatives with EDA. These electron-deficient catalysts catalyzed the cyclopropanation of styrene derivatives in high yields, with very high diasteroselection and under mild conditions. The literature concerning the cyclopropanation reaction is continuously

expanding: new and more efficient methods for the preparation of these functionalities in enantiomerically pure form are still evolving. Few years ago, our group reported the synthesis and characterisation of copper(I) complexes of the previously described (*vide supra*) pyridine containing tetraazamacrocyclic ligands (Pc-L) and preliminary results on their use as catalysts in asymmetric cyclopropanation reactions.[81] As we shall see in the next chapter *Result and Discussion*, section **2.4.2**, we report our new findings concerning the asymmetric cyclopropanation reaction of alkenes exploring the catalytic performances of copper(I) complexes derived from the new synthetized tetraazamacrocyclic ligands (**Pc-L**).[111]

1.3 Henry reactions

Henry or nitroaldol reaction has received much attention as one of the most important C-C bond formation reactions. The reaction, discovered in 1895 by L. Henry,[112] couples nitroalkanes with carbonyl compounds in the presence of a base giving β-nitroalcohols, which are useful intermediates in the synthesis of relevant biologically active compounds. In fact β-nitroalcohols are, for example, important intermediates in the synthesis of pharmaceutically active compounds such as (*S*)-propanolol and (*S*)-pindolol, amino sugars, and alkaloids.[113] Since a base is used to generate the nitronate anion (nucleophile) able to attack the carbonyl moiety (electrophile), a careful control of the experimental conditions is necessary to avoid competitive side-reactions such as aldol condensation (when aliphatic aldehydes are employed), Cannizzaro reaction or base-catalyzed water elimination from β-nitroalcohols to give β-nitroalkenes (scheme 1.16). These last products are easily formed when aromatic aldehydes are employed.[114]



Scheme 1.16 Henry reaction and the other possible collateral reactions.

The excellent review of Luzzio[115] reports a variety of promoters, basic catalysts and conditions employed for simple nitroaldol reactions. Noteworthy, Ballini[114] and coworkers described the possibility to run the condensation between a nitroalkane and an aldehyde in water, in the presence of 0.025 M NaOH and cetyltrimethylammonium chloride as a cationic surfactant. These experimental conditions led to the formation of β-nitroalcohols in high yields and prevented side reactions.

Metal ion complexes as Lewis acid catalysts for the Henry reaction were exploited for the first time in 1992 by Shibasaki *et al.*[116] to obtain enantioenriched β-nitroalcohols. Since then, the interest in the metal ion catalyzed Henry reaction has greatly increased and several reports have been continuously appearing in the literature,[117] mainly devoted to the asymmetric version of the reaction. For example, Trost[118] revealed a novel family of dinuclear zinc complexes (figure

1.29) catalysing the reaction between nitromethane and aldehydes with high level of enantioselectivity (78-93 % *ee*) and high yields (58-90 %).

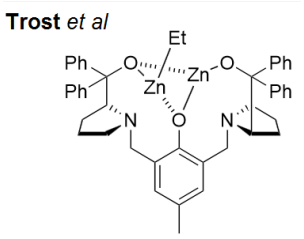
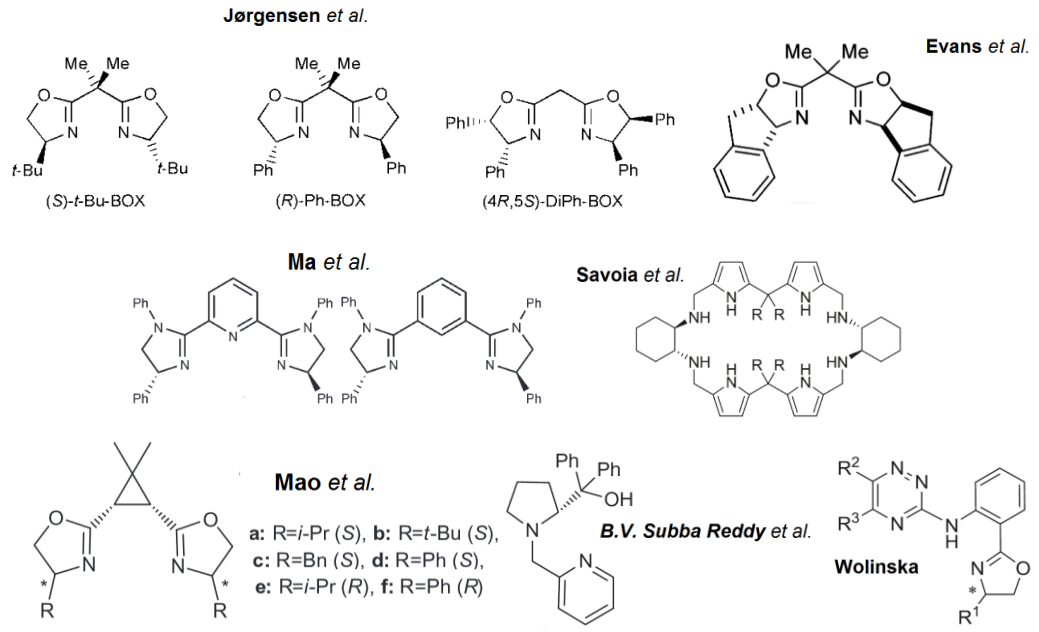


Figure 1.29 Structural formula of dinuclear zinc complex reported by Trost *et al*.

In this context, copper complexes play a relevant role: copper is relatively cheap and displays the ability to form complexes with bi- and polydentate ligands. The first example of an enantioselective copper-catalyzed Henry reaction was reported by Jørgensen[119] and co-workers in 2001 with bisoxazoline ligands. Two years later, Evans[120] *et al*. have formulated that weakly Lewis acidic metal complexes bearing moderately basic, charged ligands may facilitate the deprotonation of nitroalkanes, reporting a catalyst based on copper acetate-bis(oxazoline) obtaining very high *ee* (up to 94%), see scheme 1.17.



Scheme 1.17 Selected examples of polydentate ligands as catalysts for Henry reaztion.

Subsequently, Ma's reported that bisimidazolines[121] are able to promote the reaction at room temperature, tolerating a wide scope of aldehydes (*ee*. 93-98 %). More recently, several different system have been proposed, like perazamacrocyle containing a pyrrole ring by Savoia *et al*.,[122] a functionalized pyrrolidine ligand by B.V. Subba Reddy *et al*.,[123] a cyclopropane-based bisoxazolines by Mao *et al*..[124] In the last year chiral iminopyridine ligands by Chelucci *et*

al.[125] and oxazoline ligands containing a 1,2,4-triazine ring by Wolinska[126] were reported (see scheme 1.17).

In most cases this reaction is catalyzed by Cu(II) complexes and the application of unstable cuprous species is less documented.[127] As mentioned before, studies in our research group demonstrated the efficacy of [Cu(I)/(**Pc-L**)] complexes in the cyclopropanation reaction of various alkenes.[81] The obtained good results prompted us to verify the application and explore the activity of our copper(I) complexes in the Henry reaction. Experimental results, collected during this thesis, were obtained testing the new Cu(I) complexes as Lewis acid catalyst in the condensation between aldehydes and nitroalkanes and they will be treated in details in chapter *Result and Discussion*, section **2.4.1.**.[128]

1.4 Heterogeinesed catalyst

Homogenous catalysis presents some inherent problem, if compared to its heterogenous counterpart. Recyclability and separation of the products from the catalyst and any solvent can be difficult, time-consuming and energy intensive. Heterogeneous catalysis is widely preferred in industry due to the well-known advantages and, very often, the resistance of the catalyst to drastic operation conditions. On the other hand, homogenous catalysts normally show higher chemo- and stereo-selectivities. Extensive effort have been made to develop new methods which combine the ease of catalyst recovery of the heterogeneous systems with the higher performances in terms of activity and selectivity obtained with homogeneous catalysts.[129] The heterogeineization of the known homogenous catalyst on solid support is the ideal combination in order to achieve the advantages of both heterogeneous and homogeneous catalysis.[130]

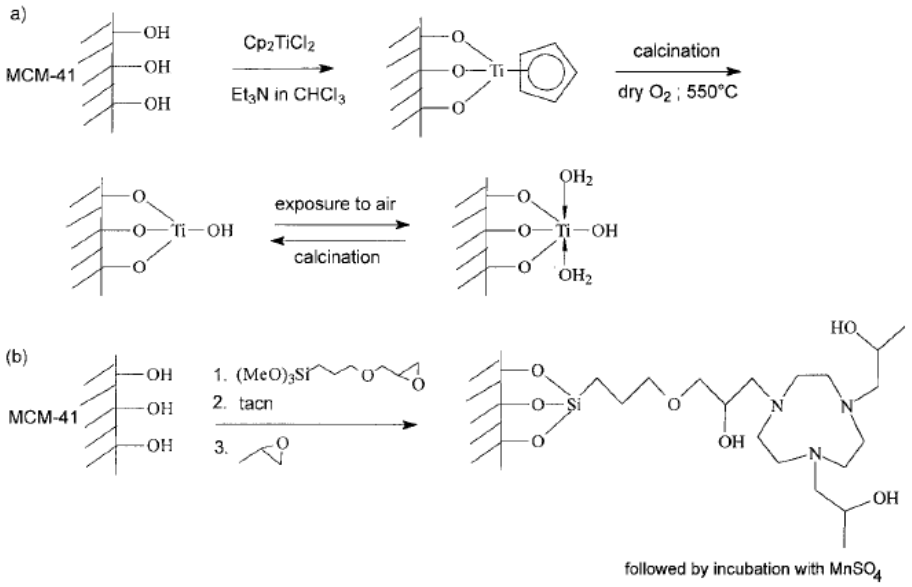
1.4.1 Mesopuorous materials

Several solid supports are suited for heterogeneous catalysis or for heterogenisation of homogeneous catalysts. Molecular sieves are a class of compound that present a porous structure combined with high adsorption capacity. These peculiar proprieties have prompted their application in hetereogenous catalysis as solid support for catalyst. Zeolites are the most widely used supporting materials in industry. They are microporous aluminosilicate minerals with a crystalline structure, with channels and cavities in the range of 5-12 Å, and very high surface area. Their intricate channel structure allows the zeolites to present different types of shape selectivity, i.e., product, reactant, and transition state, which can be used to direct a given catalytic reaction toward the desired product avoiding undesired side reactions. Despite these catalytically desirable properties of zeolites, they become inadequate when reactants with sizes above the dimensions of the pores have to be processed. In this case the rational approach to overcome such a limitation would be to maintain the porous structure, which is responsible for the benefits described above, but to increase their diameter to bring them into the mesoporous region (2,0-50 nm). For example the family of materials generally called M41S is represented by mesoporous silicate and aluminosilicate molecular sieves synthetized with LCT (*Liquid Crystal Templating*) technique. These mesoporous silica have surface areas above 700 m^2 g^{-1}, large channels from 1.5 to 10 nm ordered in a hexagonal (MCM-41), cubic (MCM-48), and laminar (MCM-50) array.[131] As mentioned before, classically, inorganic materials based on

clays, silica, alumina and carbon are used but more recently other supports such as ionic liquids or polymers are employed, too. Research has been devoted towards creating inorganic or polymer-based monoliths as supports. For example, our research group reported Schiff base complexes of cobalt (II) heterogeneised in polimeric membranes. These supported complexes were tested as catalysts in the asymmetric cyclopropanation of olefins by EDA.[132]

1.4.2 Immobilization technique

The development of these mesoporous molecular sieves extended the scope to much larger substrates and guest complexes and in this case metal complexes can be grafted or tethered (via a spacer ligand) to the internal surface (scheme 1.18).



Scheme 1.18 General technique to bind the desired species on silica support.

These methods create covalent bond between the complex and the support but the structural modifications needed to graft the ligand to the support infer also modification onto the catalytic behavior of the supported complex. Especially for chiral catalyst when they are immobilised onto solid surfaces, the interaction between the active metal complex and the surface may reduce the obtained stereoselectivities,[133] and has often a detrimental effect on the observed enantioselectivities.[134] Few years ago an innovative technique called **Supported Hydrogen-Bonded** (**SHB**), based only on weak interactions, was developed. This technique link the silanol groups of the support via hydrogen bonding to the sulfonate tail of the Rh(I) catalyst (figure 1.30).

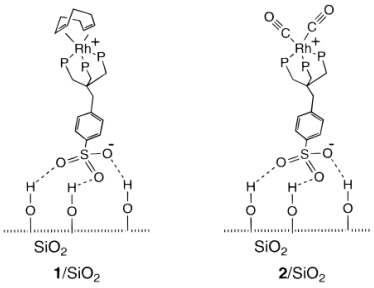
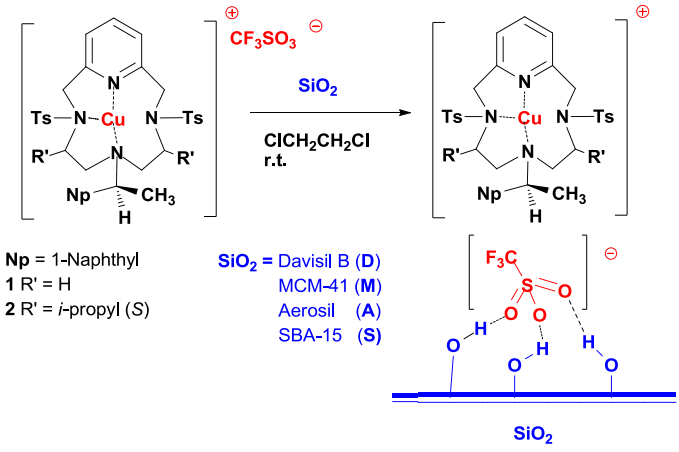


Figure 1.30 Rh(I) catalysts supported on silica with SHB method.

The immobilized zwitterionic Rh(I) catalysts gave good results in hydrogenation and hydroformylation reactions, showing that the immobilized catalyst is more chemoselective than the unsupported analogue.[135] SHB catalysts show some peculiar advantages, with respect to the covalent bound ones, such as remarkably mild grafting protocols and the possibility to easily recover the bound complex for further studies by standard liquid-phase techniques.[135-136] Moreover, the SHB methodology can be applied to cationic metal complexes, with minimal or no ligand modifications of the parent homogeneous complex. In fact a more recent research reported the application of SHB for the immobilization of complexes where only the presence of $CF_3SO_3^-$ counter-anion is necessary.[137]

Recently, in order to improve our catalytic system, we have developed new supported hydrogen-bonded chiral **Pc-L*** copper(I) complexes on different ordered and non-ordered silicas with the collaboration of Dr. Vladimiro Dal Santo of CNR – Istituto di Scienze e Tecnologie Molecolari of Milan (scheme 1.19).



Scheme 1.19 General synthesis of suppored Cu(I) complexes of **Pc-L*** ligands.

These grafted preformed Pc-L* copper(I) complexes on different ordered and non-ordered silicas were tested during my research project as catalysts, under heterogeneous batch conditions, for the olefin cyclopropanation - see section **2.5.1**.[138]

Immobilized catalysts in general can also be used under flow conditions where the reagents continuously pass through the catalytic bed. In general flow reactors carry material as a flowing stream and reactants are continuously fed into the reactor and emerge as a continuous stream of product (figure 1.31).

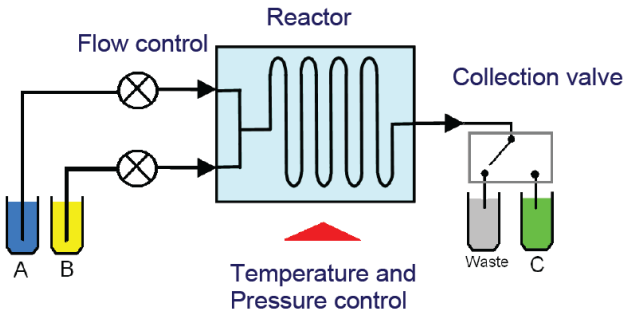


Figure 1.31 General scheme of a flow reactor where reactants A and B are pumped continuously in the reactor.

Despite their many advantages, continuous flow processes have commonly flourished only in the industrial environment of chemical and biotechnological production. Several advantages have been recognized such as facile automation, secured reproducibility, improved safety and process reliability. Indeed, with continuous flow processes constant reaction parameters (temperature, time, amount of reagents and solvents, efficient mixing, etc.) can easily be assured.

Recently flow processes have been miniaturized and thus have appeared as bench sized microstructured devices in the laboratory allowing facile automation, reproducibility, safety and process reliability due to constant reaction parameters also in the lab scale (efficient mixing, temperature, time, amount of reagents and solvent etc.). In some cases, the reaction temperature can be far above the solvent's boiling point due to the ability of being operated under pressure. Importantly also multistep reactions can be arranged in a continuous sequence.

The need for more eco-sustainable and green systems prompted the development of special rigs to conduct catalytic reactions using carbon dioxide as a carrier. In fact $ScCO_2$ is an attractive solvent as it is safe and an ideal substitute for many hazardous and toxic solvents.[139] This kind of catalytic systems have been used for a wide range of reaction such as cyclopropanation reactions,[140] hydroformilation,[129] alkene methatesis.[141]

In this thesis, chapter *Results and Discussion* - section **2.5.2.**, we report on the use of the previously described SHB copper(I) catalysts of **Pc-L*** ligands in asymmetric cyclopropanations under flow condition by using 1,2-DCE or CO_2, thanks to the collaboration with Prof. David J. Cole-Hamilton from the University of St. Andrews (UK).[142]

2 RESULTS and DISCUSSION

2.1 Synthesis of ligands

As mentioned before, a few years ago our group reported the synthesis of pyridine-based 12 membered tetraaza macrocyclic (**Pc-L***).[81] In order to extend our library of tetraazamacrocycles **Pc-L***, we used different non chiral amines: benzylamine and 1-naphthylmethylamine. Moreover to extend our method to the synthesis of new chiral non racemic pyridine containing tetraazamacrocycles, we envisioned that *N*-tosyl aziridine[143] could be useful to prepare chiral 4-substituted -1,4,7-triazaheptanes by nucleophilic ring opening of 2 moles of *N*-tosyl aziridine with the appropriate enantiomerically pure amine. In that way different stereocentres can be created on the macrocyclic framework in positions 4 and 8 (figure .2.1).

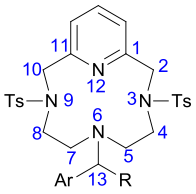
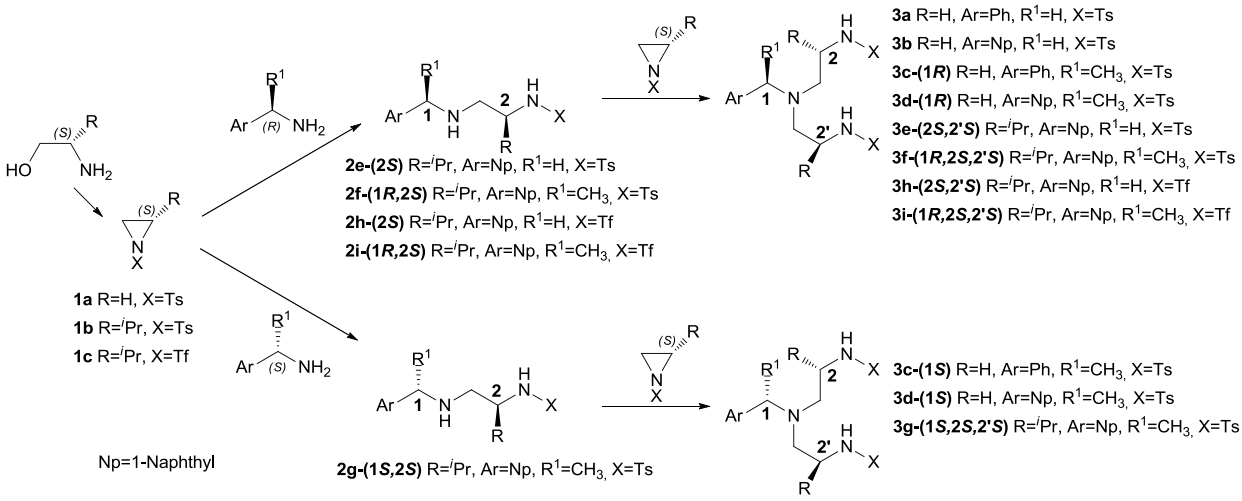


Figure 2.1 General macrocyclic ring system and numbering scheme adopted.

The key step in the synthesis of the macrocyclic ligands, **Pc-L***, is the assembly of the pyridine unit from the reaction of 2,6-bis(chloromethyl) pyridine with an opportunely designed bis(sulphonamide) under heterogeneous reaction conditions. The synthetic approach employed to obtain the starting bis(sulphonamides) is reported in Scheme 2.1.



Scheme 2.1 Synthesis of mono(sulphonamides) **2e-i** and bis(sulphonamides) **3a-l**.

Two are the main steps involved in the synthesis. Firstly, ethanolamine or (*L*)-valinol was reacted with 2 equivalents of tosyl chloride in the presence of a weak base to afford aziridine derivatives **1a** and **1b**,[144] respectively. Use of triflic anhydride in the reaction with valinol in

dichloromethane afforded the aziridine **1c**.[145] Since the aziridines carry electron-withdrawing groups on the nitrogen atom, they are expected to be susceptible to nucleophilic attack. Thus, reaction with commercially available primary aryl amines in refluxing toluene resulted in the formation of the desired bis(sulphonamides) **3a-i** in moderate to good yields (40-97%).

The nucleophilic attack of primary amines on 1-tosylaziridine **1a** occurs readily and the use of two equivalents of aziridine afforded bis(sulphonamides) **3a-3d** directly, without isolation of intermediate **2**.

Recently we have optimised the synthesis of bis(sulphonamide) **3a** with microwave irradiation instead of conventional heating. The desired product **3a** was obtained in quantitative yield and without any further purification in only one hour conducing the reaction in methanol at 120 °C (with conventional heating longer time - 4 hours - and a chromatographic step were required).

When the chiral primary amines 1-benzylethylamine and 1-naphthylethylamine were employed both enantiomers of the chiral sulphonamides **3c** and **3d** were synthesised and fully characterised, as already reported.[81] On the other hand, when bulkier (*S)*-2-isopropyl-*N*-tosylaziridine was used, the ring opening reaction could be stopped after the addition of 1 equiv. of the aziridine and the mono adducts **2e-i** could be isolated, although in moderate yields (13-50%). It was interesting to note that in the present case, using naphthylalkylamines as nucleophiles, no large excess of amine was needed to obtain the mono adduct, contrary to what previously reported in the case of the ring opening of 2-isopropyl-*N*-(triflouromethylsulfonyl)aziridine with benzylamine.[146] These reactions are extremely slow, but higher yields within shorter times were obtained by employing microwave irradiation. It was found that after 3h at 150°C in toluene, a 1.1:1 ratio of aziridine **1b** and amine afforded sulphonamides **2** in 70% yield. Extending the reaction time and using larger amounts of the aziridine relative to the amine did not significantly improve the yield of bis(sulphonamide) **3**. Thus a two-step strategy was followed for their synthesis. Firstly, the reaction was conducted at 150°C under microwave heating. Then, an excess of the aziridine was added to the reaction mixture and the reaction was continued under conventional heating. Under these conditions, bis(sulphonamides) **3e-g** could be obtained in yields up to 74% after chromatographic purification.

As expected, (*S)*-2-isopropyl-*N*-(triflouromethylsulfonyl)aziridine **1c** is more reactive than the corresponding *N*-tosylaziridine analogue and the reaction requires milder conditions. The attack at the terminal position of the aziridine is highly regioselective and we never observed a

competing ring opening reaction at the substituted carbon which was reported in the case of 2-phenylaziridines.[147] This methodology allows extensive structural modifications, since a large number of primary amines can be used as nucleophiles in the ring opening reaction. All products were fully characterised including ^{1}H, ^{13}C NMR, EA, MS. Moreover for mono(sulphonamide) **2h** and bis(sulphonamide) **3h** crystals suitable for X-ray determination were obtained (figure 2.2).

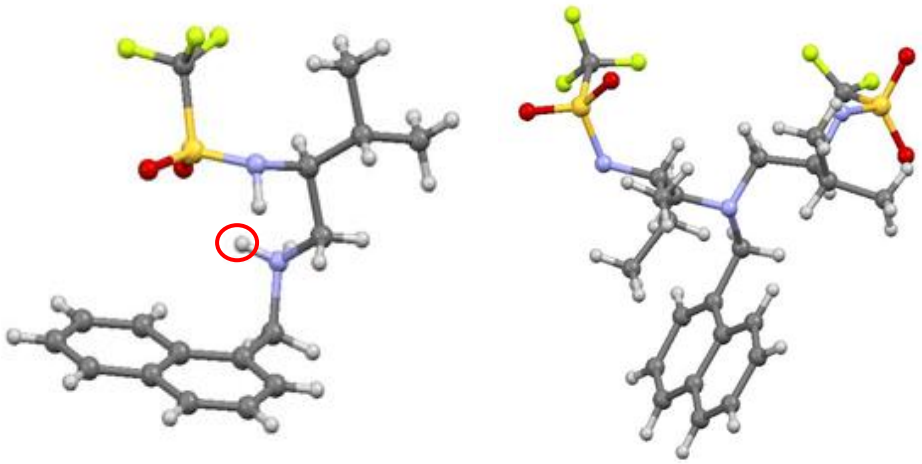
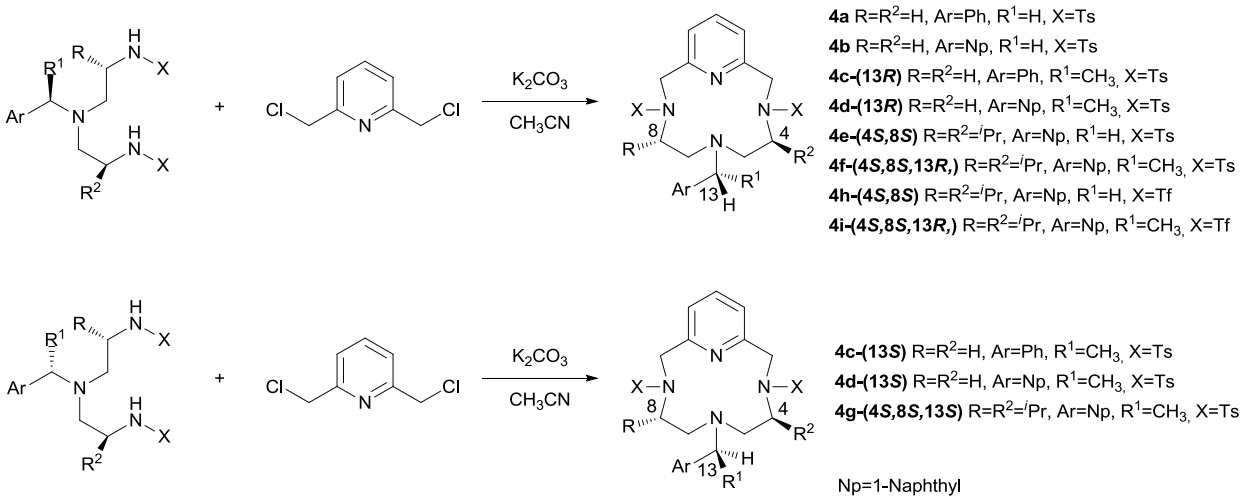


Figure 2.2. Structure of mono(sulphonamide) **2h**, the hydrogen highlighted in red is a disordered proton, coming from the presence of a zwitterionic formula (70%) equilibrating with the neutral molecule; and bis(sulphonamide) **3h** in which NH hydrogens were omitted, respectively.

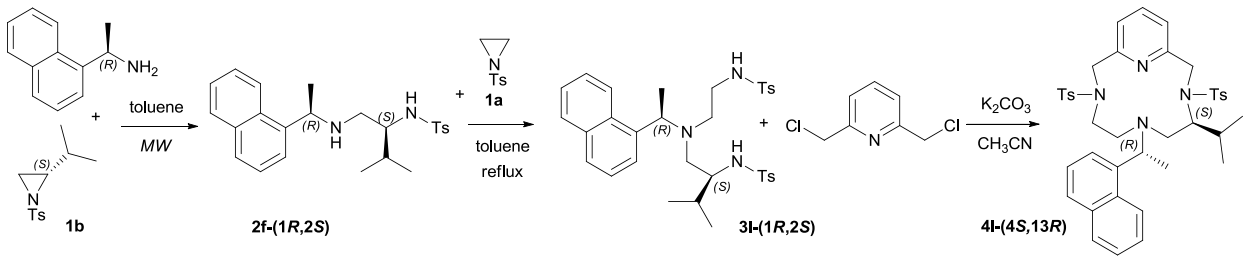
Once bis(sulphonamides) **3a-i** were obtained, the Richman-Atkins cyclisation with 2,6-bis(chloromethyl) pyridine was attempted. As already reported in the introduction, the macrocyclisation was run under heterogeneous conditions.[148] This synthetic methodology allows avoiding high dilution techniques and obtaining the 12 membered macrocycles **4a-i** in 50–85% yields (Scheme 2.2).



Scheme 2.2 Synthesis of the macrocyclic ligands (Pc-L*) **4a-i**

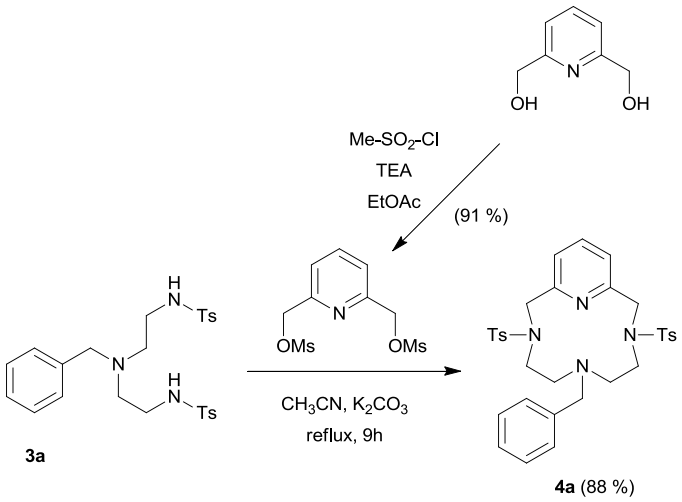
Although the employed conditions allowed for the synthesis of all the target macrocycles, in several cases (see *Experimental part*), the time required was extremely long. In order to accelerate the reaction, we ran the synthesis in a microwave reactor. We initially focused on the synthesis of compound **4i**, that under conventional heating required 110 h of reflux to yield the desired macrocycle in 40% yield after purification. Maintaining the same stoichiometry and concentration of the reactants at 130ºC, 20% of macrocycle **4i** was observed after 2 h. When the temperature was raised to 150 °C, 50% yield was obtained in just 3 h. Nevertheless, upon prolonged reaction times under these conditions, no beneficial effect was observed to the reaction yield. Surprisingly, tosylsulphonamides **3a**-**i** failed to yield the macrocycles under microwave heating. Further studies will be needed to clarify this aspect, in order to shorten the reaction times required for the macrocyclysation step and to improve the global yield.

In order to obtain a non-symmetric ligand **4l-(4*S*;13*R*),** the unsymmetrical bis(sulphonamide) **3l-(1*R*,2*S*)** was synthetized. Sulphonamide **3l**, that bears only one *i*-propyl group substituted side arm, was obtained staring from mono(sulphonamide) **2f** that was reacted with an equimolar quantity of 1-tosylaziridine **1a** to give the desired product in 85% yield. Once bis(sulphonamide) **3l** was obtained, the macrocyclization was conducted with 2,6-bis(chloromethyl) pyridine; macrocycle **4l** was so obtained with 55% of yield in 22 hours (scheme 2.3).



Scheme 2.3 Synthesis for ligand **4l-(4*S*,13*R*).**

Recently we have optimized the synthesis of ligand **4a**, with respect to the method previously reported.[128] Thus, by reacting the *bis*-protected amine **3a** with 2,6-pyridinedimethanol 2,6-dimesylate in refluxing anhydrous acetonitrile in the presence of anhydrous K_2CO_3, the macrocycle **4a** was obtained in 88% yield. 2,6-pyridinedimethanol 2,6-dimesylate was obtained in 91% yield by reaction of 2,6-pyridinedimethanol and an excess of methanesulfonylchloride in ethyl acetate, in the presence of triethylamine (scheme 2.4).[149]



Scheme 2.4 Optimised synthesis of ligand **4a**.

With the employed methodology, a small library of macrocyclic ligands possessing different symmetries, steric and electronic properties was easily obtained, starting from commercially available products in few synthetic steps. The products **2, 3, 4a-l** have been fully characterized including a X-Ray structure determined for **4a**. Crystals suitable for an X-ray structural determination were obtained by crystallization of **4a** from a dichloromethane/toluene solution (figure 2.3).[128] In the absence of chirality, this compound crystallize in centrosymmetric P-1.

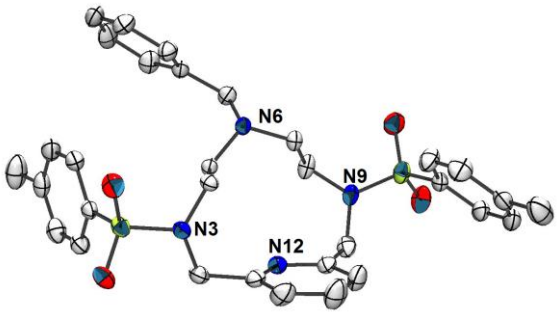


Figure 2.3 Structure of **Pc-L** tetraazamacrocyclic ligand **4a**. Distances within the coordination pocket are: N12-N6 3.933 Å and N3-N9 5.741 Å, the asymmetric unit includes the entire molecule.

A crystal structure for **4f-(4*S*,8*S*,13*R*)** has also been determined through X-ray diffraction on a single crystal, obtained from a $CDCl_3$ solution (figure 2.4). Apart for the rigid conformations induced by the pyridine ring at the 12-1 and 11-12 bonds, all others show a fairly large flexibility. In the free ligands, the conformation of the cycle brings the tosyl bounded nitrogens *antiparallel* and the aromatic ring oriented far from each other.

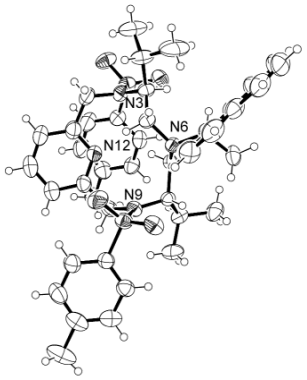
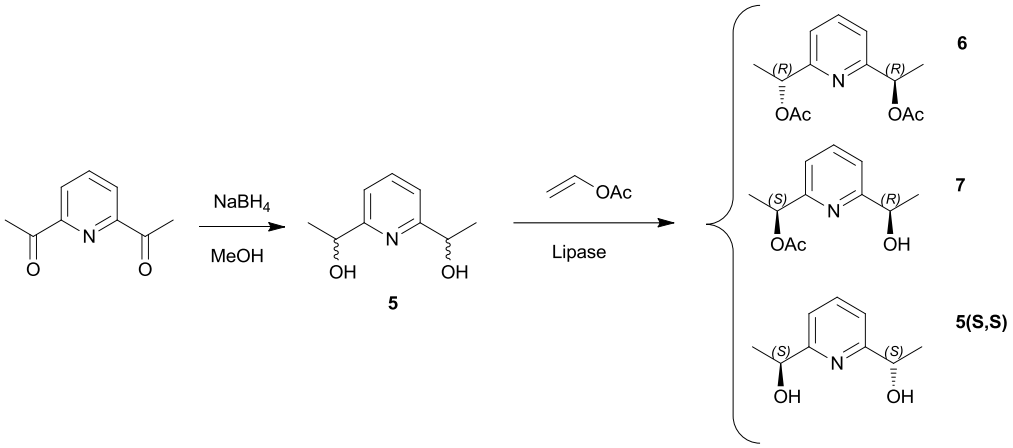


Figure 2.4 Structure of compound **4f-(4*S*,8*S*,13*R*)** (thermal ellipsoids are shown at 50% probability level). Distances within the coordination pocket are: N6---N12 3.629(5) Å and N3---N9 4.910(6) Å.

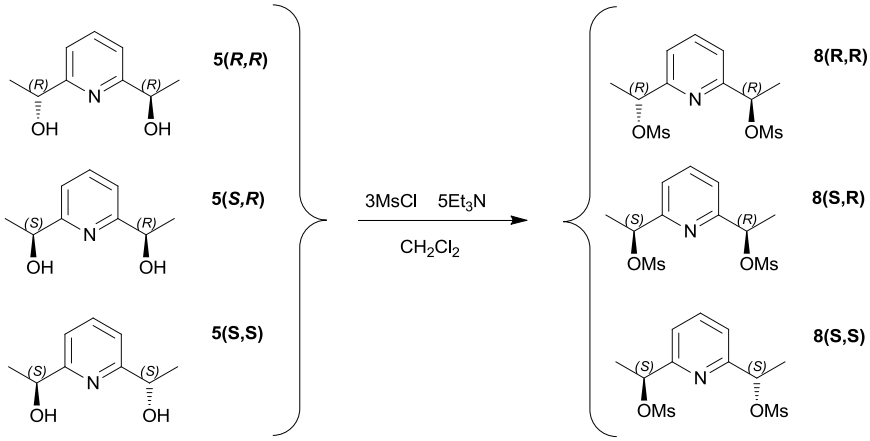
In **4f** the bonds C2-N3 and C10-N9 (see figure 2.1 for labelling of the carbon and nitrogen atoms) are associated with *anti-clinal* conformations that makes the pyridine ring lying on the average plane of the cycle, instead of being significantly tilted as in **4a** - figure 2.3 (same as **4d**, see *Introduction* section **1.1.2** figure **1.22**). In general, the intermolecular packing is not very tight, in the absence of strong hydrogen bonding or other intermolecular interactions. However, we cannot exclude that the observed conformations could also be affected by packing effects. A full investigation of the conformations of the ligands in isolation is currently underway by means of theoretical gas phase quantum chemical calculations. The presence of S atoms allows a correct evaluation of the absolute configuration of the species **4f**, which is in agreement with expectations.

At the same time, to even more expand the library of chiral macrocyclices **Pc-L***, we made some modifications to the pyridine moieties, in order to have two new stereocenters in position 2 and 10 (figure 2.1). Following a well described procedure,[150] we started from the reduction of the commercially available 2,6-diacetylpyridine with $NaBH_4$ to give the 2,6-bis(1-hydroxy-ethyl)pyridine **5** as mixture of the two enantiomers and the *meso*-form. A kinetic acetylation of the mixture of **5** with vinyl acetate in the presence of *Candida antarctica* lipase gave three different products: diacetate **6** in 19% yield, monoacetate **7** in 40% yield and the unacetylated products **5(*S*,*S*)** in 19% yield. In fact this lipase supported on resin is an enzyme that acetylated only the stereocentre in *R* conformation. The three chiral pyridines are separed by silica gel chromatography (scheme 2.5).



Scheme 2.5 General procedure for the reduction and acetylation of the mixture of **5**.

Then, potassium carbonate promoted deacetylation of **6** gave diol **5-(*R,R*)** and diol **5-(*S,R*)** from **7.** We next mesylated each form, by treating a solution of **5** pyridine in CH_2Cl_2 with methanesulfonyl chloride and triethylamine, obtaining the corresponding products **8** in high yields (scheme 2.6).



Scheme 2.6 General procedure for mesylation of **5**.

Once obtained the pure mesylated pyridines, we conducted the reaction between these different substitute pyridine **8** and the 1-naphthylamines to get a new class of macrocycles of C_1 symmetry (from chiral amines) and C_{2v} symmetry (from achiral amine and chiral optical active pyridines). Treating the amines with the mesylated pyridines **8** in refluxing anhydrous acetonitrile in presence of K_2CO_3, we isolated 12 member ligands **4m-p** in yields between 12 and 76% (figure 2.5).

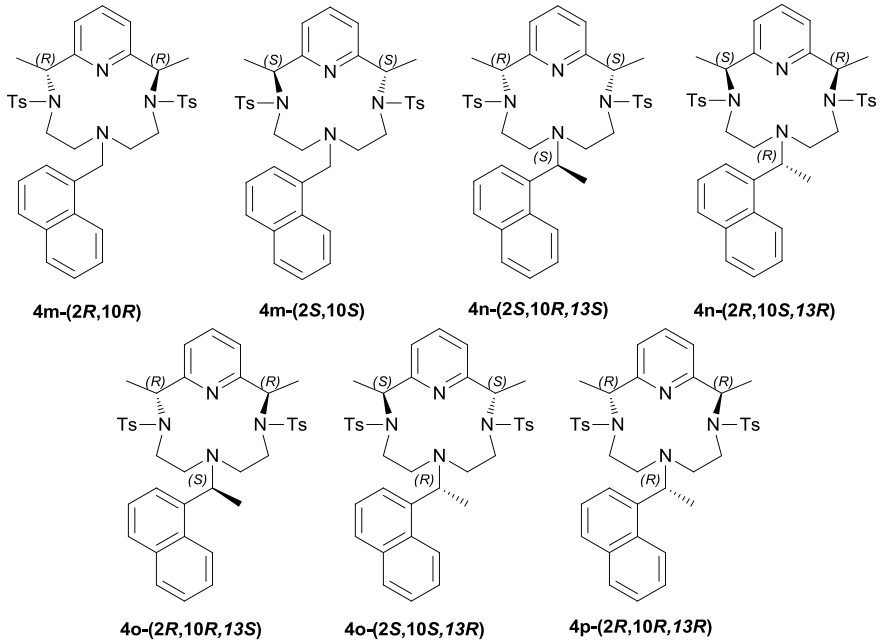


Figure 2.5 Macrocyclic ligands (Pc-L*) **4m-p.**

The nucleophilic attack of the bis(sulphonamides) **3** on the pyridine **8** occurs with SN_2 mechanism and thus the inversion of configuration of the stereocenter present on the pyridine is involved. These new synthesised ligands have been completely characterized, including, ^{1}H, ^{13}C -NMR analysis, MS and specific optical rotation. Moreover crystals suitable for X-ray structural determination were obtained by crystallization of macrocycle **4o-(2*R*,10*R*,13*S*)** from a dichloromethane–toluene solution, proving the involved SN_2 mechanism. Crystals of macrocycle **4n-(2*S*,10*R*,13*S*),** suitable for X-ray structural determination were also obtained (figure 2.6).

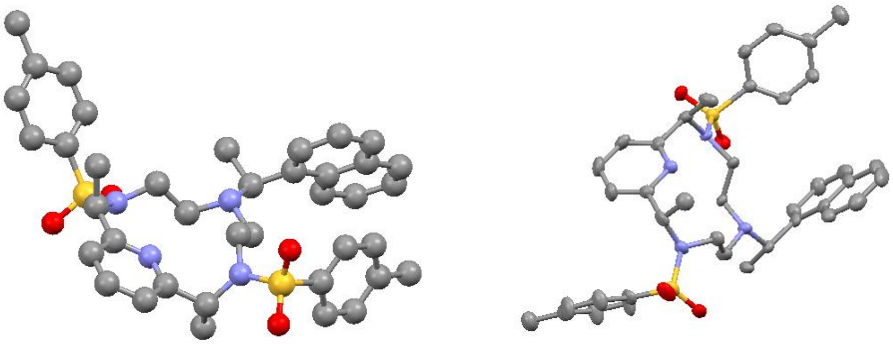
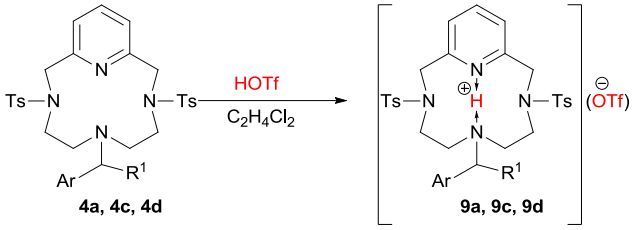


Figure 2.6 X-ray structures of macrocycles **4o-(2*R*,10*R*,13*S*)** and **4n-(2*S*,10*R*,13*S*)** respectively.

The synthesised ligands were used to prepare the corresponding metal complexes and, in selected cases, protonated salts.

2.2 Synthesis of protonated ligands and metal complexes

In order to investigate the relative basicity of the four nitrogen atoms, we synthesised the protonated salts of some of the ligands. In particular, we have isolated compounds **9a**, **9c** and **9d**, by reaction of the ligands with triflic acid in dichloroethane (scheme 2.7)..



Scheme 2.7 Synthesis of the protonated salts **9a, 9c** and **9d**.

Although the reaction was fast and quantitative as determined by ^{1}H NMR, the pure protonated salts were isolated only in modest yields (ca. 50%). The products were fully characterised, including a X-ray structural determination in the case of the proton complex **9d** (see below). The proton, as expected for an ammonium salt, was located at high frequencies in the ^{1}H NMR spectrum (11.82 ppm for **9a**, 11.24 ppm for **9c**, 10.66 ppm for **9d** in $CDCl_3$ at room temperature).

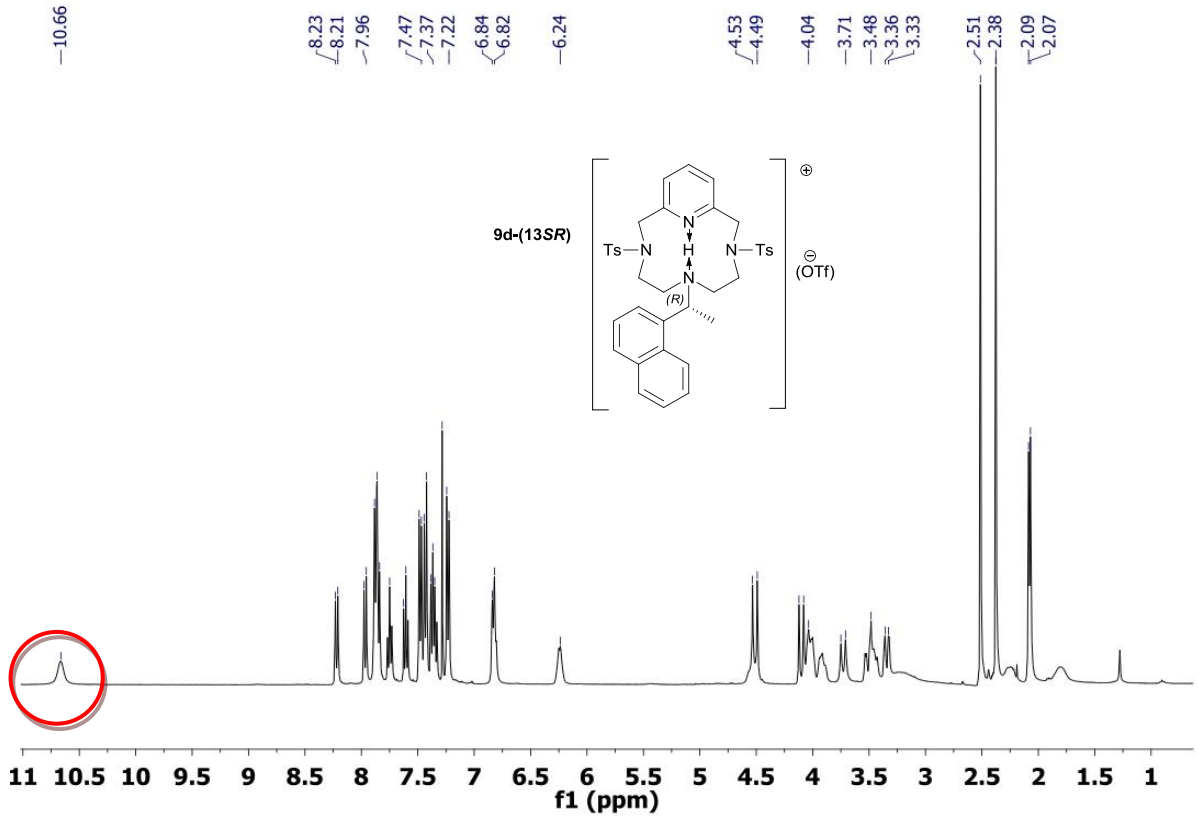


Figure 2.7 ^{1}H-NMR of the protonated ligand **9d.**

Worth of note is the fact that for compound **9d** the ^{15}N NMR chemical shift for the pyridine nitrogen was observed at 282 ppm (solvent $CDCl_3$) instead of 312 ppm in the free ligand **4d**, and the resonance of N-6 (figure 2.1) was shifted from 39 to 52 ppm. This is consistent with a molecule where the proton is coordinated in a bridging position between this two nitrogen atoms and, in fact, this was confirmed by data obtained from X-ray analysis.

As mentioned above, crystals suitable for an X-ray structural determination were obtained by crystallization of **9d** from a dichloroethane solution (figure 2.8). The specie crystallized as salt of $[CF_3SO_3]^-$ in chiral $P2_12_12_1$. **9d** and free ligand **4f** have some similarities in the conformation of the cycle: the bonds C2-N3 and C10-N9 are associated with *anti-clinal* conformations that makes the pyridine ring lying on the average plane of the cycle. On the other hand, overall they are quite different, mainly because of the intra-molecular N-H---N hydrogen bond (d_{N-N} 2.916Å) occurring between the protonated N6 and the pyridine N12. In fact, as we could expect the proton is localized on the more basic sp^3 nitrogen N6, bridging between the latter and the pyridinic nitrogen atom N12. The larger perturbation at N6 is in keeping with the assigned position of the H atom, which was also tentatively refined (resulting in d_{N6-H6} 0.7Å). As this refinement was somewhat unstable, in the final model it was constrained into the stereochemically predicted position. The absolute configuration is confirmed by the X-ray analysis (Flack parameter -0.02(10))

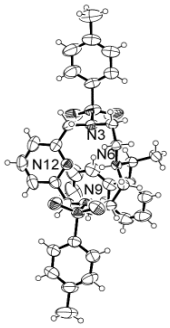
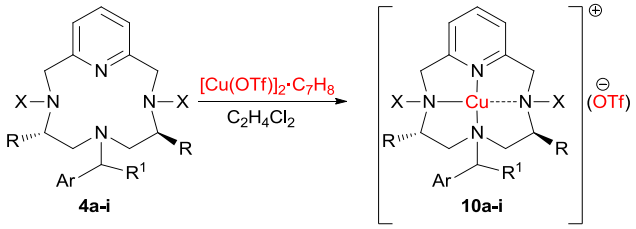


Figure 2.8 Structure of compound **9d** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°) : N6-H2 is fixed at 0.91 , N6-H2-N12 153. For sake of comparison with **4d**, N6---N12 is 2.916(5) and N3---N9 5.090(5),

Metal complex formation with ligands **4a-i** was investigated with different copper salts (scheme 2.8).



Scheme 2.8 Synthesis of the copper(I) complexes **10a-i**.

As already reported in the introduction (section **1.1.2**), treating ligand **4c** with $[Cu(OTf)]_2 \cdot C_7H_8$ gave yellow Cu(I) complex that undergo oxidation quite readily. The same behaviour was observed for Cu(I) complex **10a** derived from free ligand **4a**.[128] This complex has been isolated and fully characterised. It is readily formed by treating a suspension of the copper salt in 1,2-dichloroethane (DCE) at room temperature, yielding a light yellow solution. The addition of toluene to this solution caused the precipitation of a white powder of complex **10a**, in moderate yields. Complex **10a** was characterised by NMR spectroscopy.

The corresponding copper(I) complexes were synthetized also for ligand **4e-l**. As previously reported, the effect of the copper complexation to the ligand was shown also by the ^{1}H, ^{13}C and ^{15}N NMR spectra. Moreover, the presence of a naphthyl substituent seems to confer a major stability to the copper(I) complexes and, although the synthesis is better performed under protecting atmosphere, compounds **10d** and the new **10b** and **10e-i** could be manipulated in air without decomposition. The reason of this major stability is due to the presence of the naphtyl group that can act as a further coordination site for the metal (see *Introduction* section **1.1.2,** pages 18-21). In these cases also, low symmetry is retained in solution, as shown by NMR studies (see figure 2.9 as example for complex **10f**). Again, the ^{15}N NMR spectrum shows a marked shift for the pyridinic nitrogen atom (from 313 to 245 ppm), while the *N*-6 atom bonded to the stereogenic carbon, is affected to a lower extent (from 39 to 51 ppm). All these complexes were isolated in good yields and fully characterised.

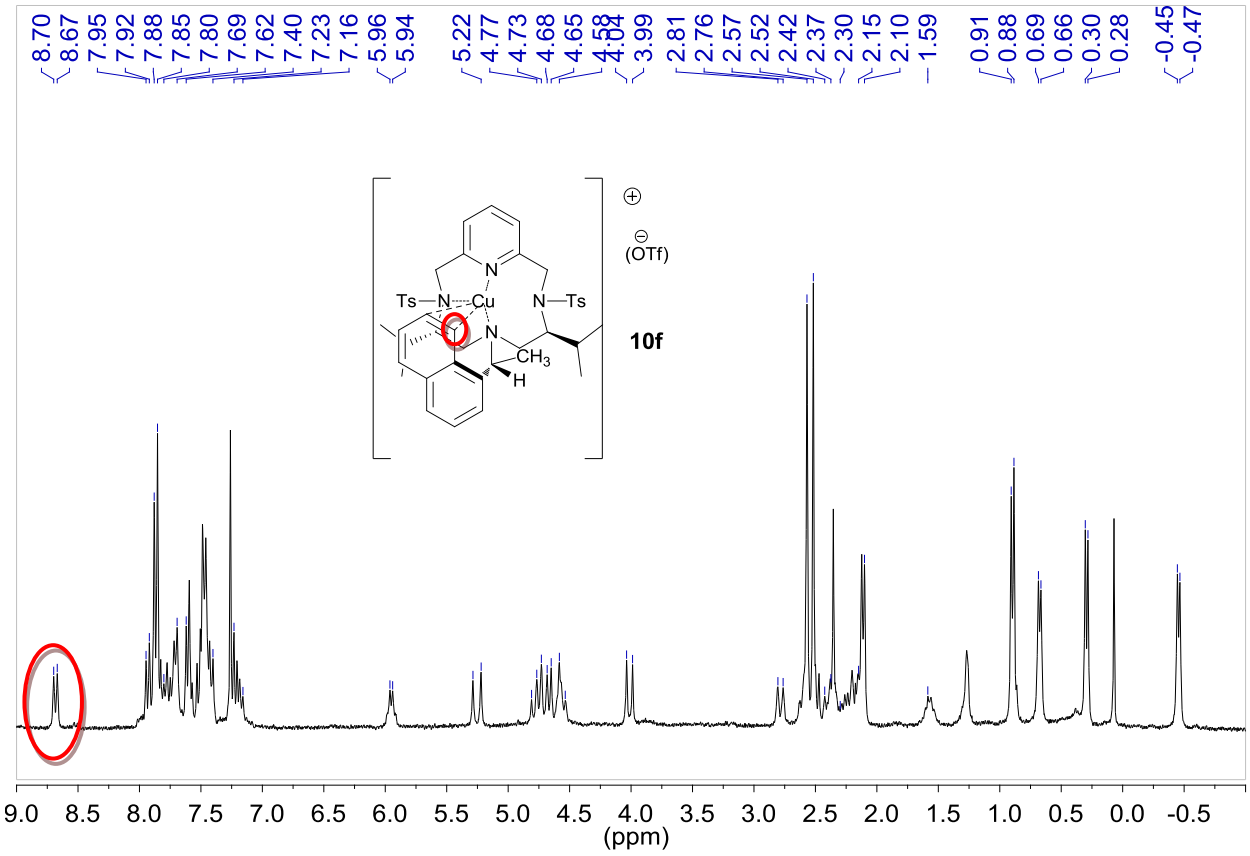
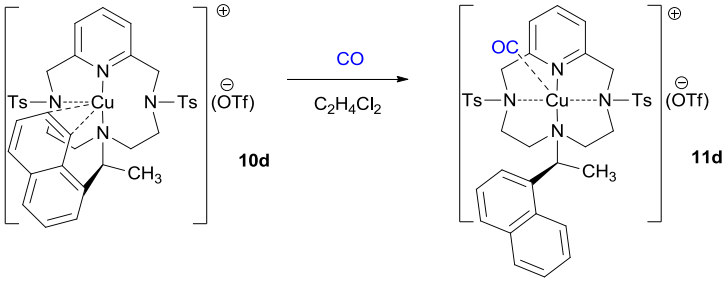


Figure 2.9 ^{1}H NMR relative to complex **10f.** In the ^{1}H NMR the proton directly bound to the highlighted carbon shifted to higher frequencies 8.68 ppm compared to 8.58 ppm for the free ligand **4f.**

In order to investigate the coordination behaviour of the naphthyl group in the presence of an added ligand, we decided to treat complex **10d** with CO in dichloroethane solution (scheme 2.9).



Scheme 2.9 Reaction of complex **10d** with CO to give **11d**.

As revealed by IR in solution, a sharp band at 2111 cm^{-1} was present immediately after (5 min) the exposure to CO at atmospheric pressure. The observed frequency of coordinated CO in complex **11d** is higher than those reported in the case of tetracoordinated copper(I) CO complexes of [bis(2pyridylmethyl)amine],[151] probably due to the lower donating ability of aliphatic amine nitrogen compared to the pyridine one. The experiment was then repeated but exposing a $CDCl_3$ solution of complex **10d** in an NMR tube to ^{13}C doped carbon monoxide

atmosphere. As reported in figure 2.10, a sharp signal at 171.3 ppm was observed, in a typical range for CO coordinated to copper(I).[152]

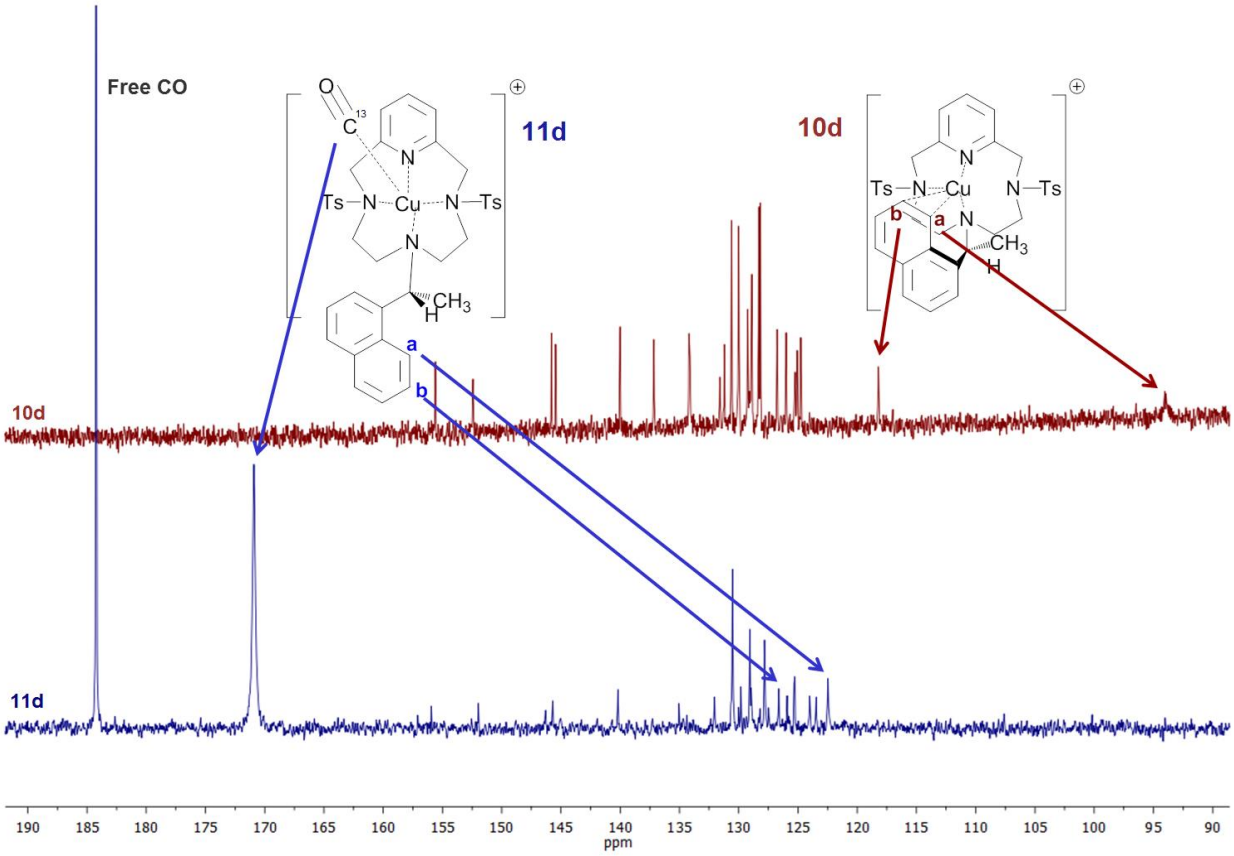
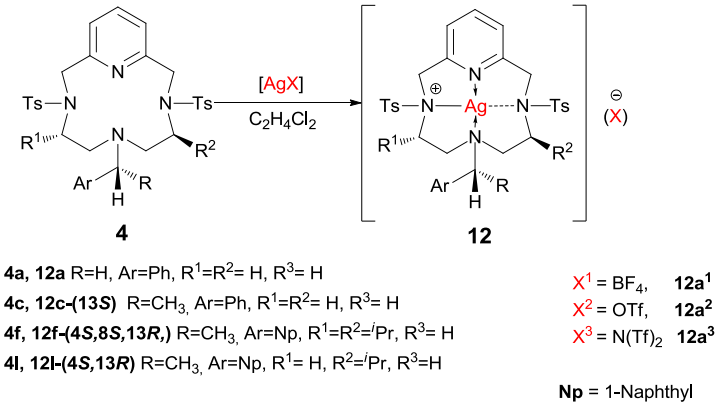


Figure 2.10 ^{13}C NMR spectra of complexes **10d** (upper red line) and **11d** (lower blue line) in $CDCl_3$

On the other hand, signals relative to carbon **a** and **b** were located at 122.9 and 127.0 ppm respectively, thus clearly indicating that the naphthyl group is no more coordinated to the copper atom after the CO uptake. This result is of particular relevance to catalysis, since it is reasonable to assume that the naphthyl moiety can stabilise the coordination sphere of the copper atom, but can be easily displaced by incoming substrates.

Since our ligands are particularly suited for the complexation and stabilization of copper(I) salts, we extend our studies on metal complexes testing them with other metal ions in order to explore the coinage group. We have prepared silver(I) complexes **12** of **Pc-L***: metal complex formation with ligands **4a,c,f,l** was investigated with different silver(I) salts, respectively silver tetrafluoroborate (^{1}), silver triflate (^{2}) and silver *bis*-triflimidate (^{3}) (scheme 2.10).



Scheme 2.10 Synthesis of silver(I) complexes **12** with different anions.

The silver salt was added to the solution of the ligand **4** in DCE and stirred for one hour, keeping the mixture in the dark until the isolation of the final product. Silver complexes **12** are easily obtained evaporating the solvent and by adding *n*-hexane. A white solid is then filtered in yields up to 91%. We also tried to prepare complexes with a coordinating anion such as chloride ion. Neither the direct reaction of the ligand **4a** with silver chloride, nor the anion-exchange reaction of complex 1**2a**^{1} with tetrabutylammonium chloride led to the desired product. In the first case, no reaction occurred whereas in the second, immediate expulsion of the metal from the ligand as silver chloride precipitate was observed. These reactions demonstrated that silver complexes **12** are sensitive to any chloride anion that may be present in solution. All the obtained silver complex **12** have been fully characterized by NMR, ESI-MS, IR and UV-Vis spectroscopy.

The "well-defined" [Ag(I)(Pc-L)] complexes **12** are stable, versatile and can be used under open-air atmosphere. In fact, in sharp contrast with the analogous copper(I) complex **10a**, silver(I) **12**$^{1-3}$ do not suffer from oxidation if exposed to the air atmosphere. On the other hand, they have the tendency to assorb atmospheric moisture to form monoaquo species, as confirmed by single crystal X-ray determination for complex **12a**^{1} (figure 2.11).

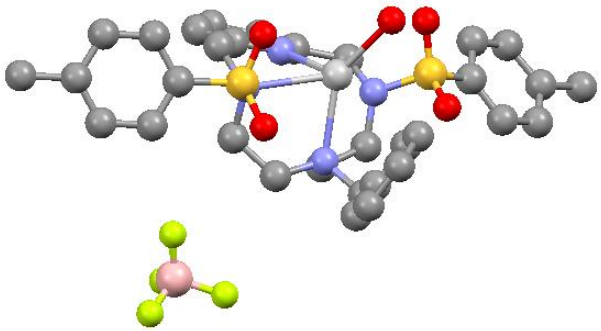


Figure 2.11 Structure of compound **12a**^{1} with a molecule of water coordinated to the metal centre (hydrogen atoms are omitted).

Generally the silver complexes **12** have the tendency to crystallize with a molecule of 1,2-DCE, as revealed by ^{1}H-NMR spectra. Moreover, as previously reported for copper(I) complexes, the effect of the metal complexation to the ligand was shown also by the ^{1}H, ^{13}C NMR. The ^{1}H NMR spectrum of complex **12f^{1}**, for example, in $CDCl_3$ displays a very low symmetry. In the ^{1}H NMR the proton directly bound to carbon **a** (figure 2.12) shifted to higher frequencies 8.69 ppm compared to 8.58 ppm for the free ligand **10f**.

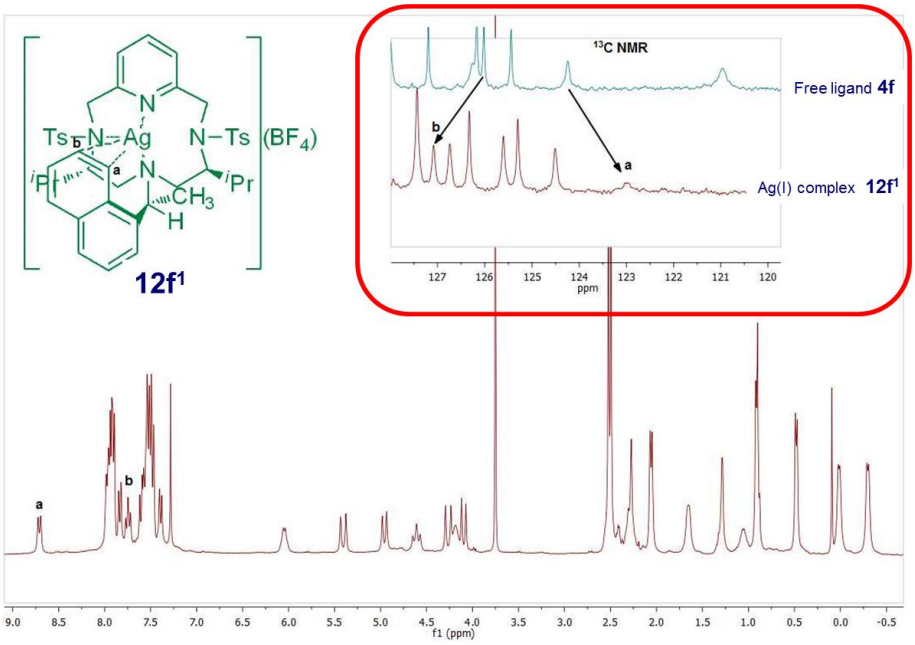


Figure 2.12 ^{1}H NMR of complex **12f^{1}** with carbons **a** and **b** involved in η^2 coordination of the naphthyl on silver(I). In the red box ^{13}C NMR spectra of ligand **10f** and complex **12f^{1}**, respectively, are reported.

The η^2 coordination mode of the naphthyl on silver(I) in solution has been also observed by ^{13}C NMR studies in $CDCl_3$. A low frequency shift of the naphthylic carbon **a** involved in the η^2 bond with silver from 124.0 ppm in the free ligand, to 122.7 ppm in the complex, while for carbon **b** a high frequency shift from 125.8 in **10f** to 127.1 ppm in complex **12f^{1}** were observed. This unsymmetrical shift of the η^2-carbon bond atoms is quite common for strongly distorted double bonds coordinated to a metal atom.[153] Carbon **a** is held in close proximity to the silver atom by steric requirements, while carbon **b** is less strongly coordinated.

For complexes **12a$^{1-3}$** the same pattern was observed in the ^{1}H NMR,^{13}C NMR and ^{15}N NMR spectra, independently from the counter ion. Complexes **12a$^{1-3}$** showed an apparent C_s symmetry of the structure in solution, with two signals for each couple of equivalent methylene groups. The ^{1}H-^{19}F HOESY experiment conduced in $CDCl_3$ solution showed that the tetrafluoroborate anion in complex **12a^{1}** has proximity interactions mainly with the pyridine ring of the ligand (figure 2.13).

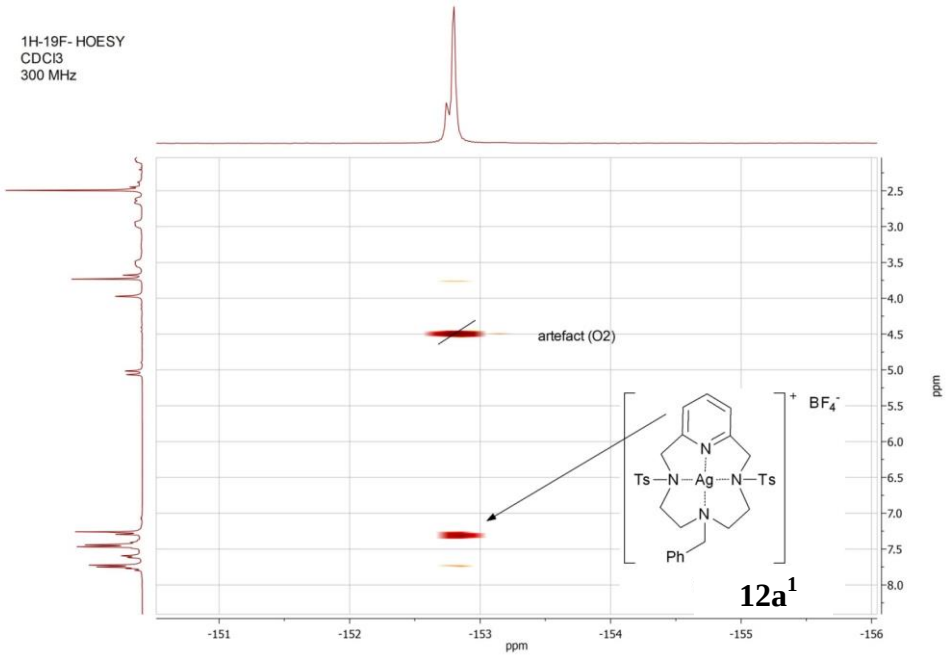


Figure 2.13 ^{1}H-^{19}F HOESY experiment in $CDCl_3$ for complex **12a**[1]

The UV-vis spectra of complex **12a**[1] and **12a**[2] in chloroform showed the absence of absorption bands at wavelength higher than 290 nm, which is consistent with the observed absence of colour and the d^{10} electronic configuration for the metal - no *d-d* transitions allowed (figure 2.14).

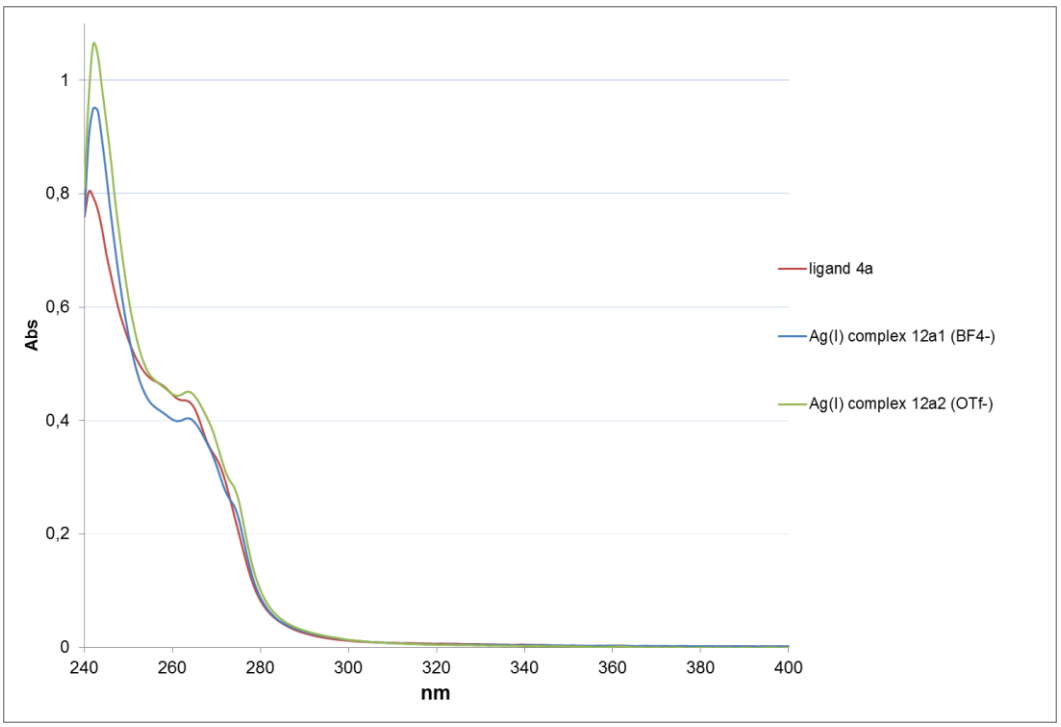


Figure 2.14 Superimposed UV spectra of ligand **4a** and Ag(I) complexes **12** with different anions (10^{-5} M in $CHCl_3$).

The shape of the UV-vis spectra of ligand **4a** does not vary owing to complexation, while the intensities of the absorptions are quite different; so, the bands recorded in the near UV region can be related to ligand-centred transition (figure 2.14).

At the same time we started collaboration with Dr. Giorgio Abbiati for the development of a new catalytic system based on our silver complexes **12a**[1-3] for the effective and selective synthesis of 1-alkoxy-*1H*-isochromenes (see section **2.4.3** for further details).

2.3 Synthesis of supported complexes

As mentioned in the *Introduction* section **1.4.2**, thanks to the collaboration with Dr. Dal Santo we have heterogenised our copper(I) complexes **10** on silica with SHB technique in order to improve our catalytic system and recyclability. The copper(I) complex **10d-(13*S*)** was chosen at first as a model complex to be supported on different silica to be studied as a catalyst in cyclopropanation reactions. Four different silica were investigated as a support: two commercial ones, Davisil LC150 (Grace) and Aerosil 380 (Evonik), and two popular and often applied mesoporous silica support materials, MCM-41[154] and SBA-15[155] The characteristic (pore diameter, pore volume, surface area) are listed in table 2.1.

Table 2.1. Proprieties of the different silica

Ref.	SiO_2 Support	Pore diameter (nm)	Pore volume (mL/g)	Surface area (m^2/g)
M1	MCM-41 (6124) [a]	3.6	0.61	827
M2	MCM-41 (6170) [a]	3.6	0.73	967
D	Davisil LC150	13.3	1.1	279
A	Aerosil 380	-	-	262
S1	SBA-15 (MFDC061) [b,c]	6.7	0.69	786
S2	SBA-15 (MFDC065) [b,d]	9.6	1.02	525

[a] MCM-41 materials were prepared accordingly as already reported.[156] [b] SBA-15 were prepared accordingly to references.[157],[158] [c] Sample prepared at 60 °C. [d] Sample prepared at 130 °C.

The adopted SHB methodology allowed the easy and very mild preparation of the supported **10d**/SiO_2 catalyst (figure 2.15).

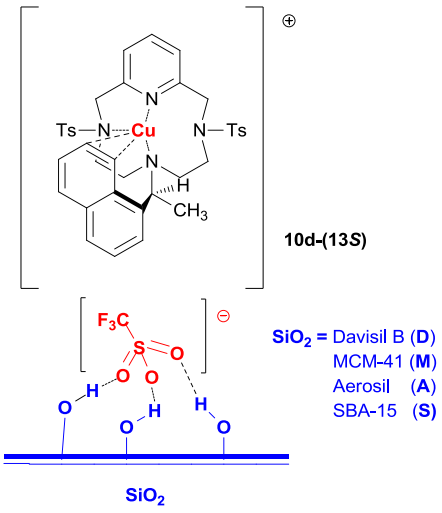


Figure 2.15 Supported copper(I) complex **10d/SiO_2**.

Copper complex **10f** was also grafted on silica and Davisil B was chosen as support. The different catalysts were fully characterized and copper content was determined by ICP-OES. Cu loadings between 0.32 and 1.79 wt. % were obtained, depending on the used silica. In general, higher loadings could be achieved using [Cu^{I}(**Pc-L***)]CF_3SO_3 directly after its synthesis in the dissolved form, without isolation from the solvent (see section **2.5.1.** and **2.5.2.** concerning catalytic data for details). DRIFT spectra were performed, confirming that the SHB technique creates interaction, *via* H-bonding: upon the Cu complex grafting the strong and sharp band located at 3740 cm^{-1}, ascribable to isolated silanols, disappeared almost completely, and a new broad band, located between 3500 and 3400 cm^{-1} (originated by O-H stretching vibration of silanols H-bonded with triflate counter anion) appeared in the spectra (figure 2.16).

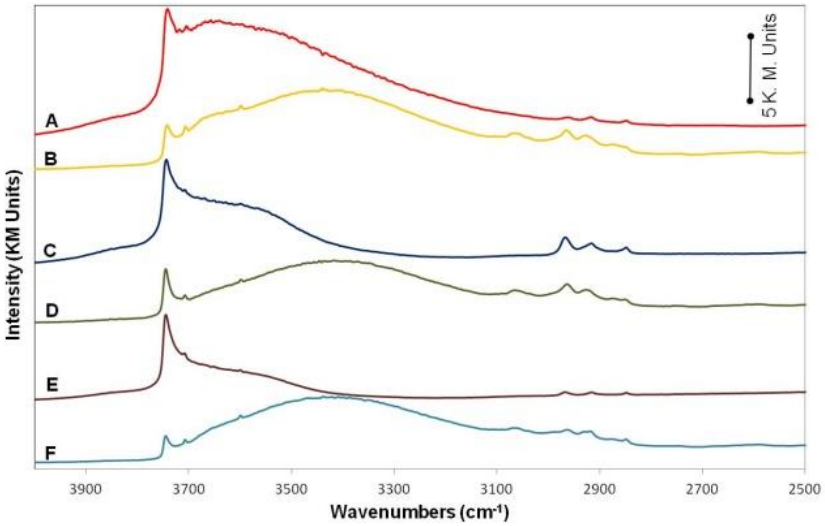


Figure 2.16 DRIFT spectra showing the interaction via H-bonding; **A**, bare Davisil; **B**, **10d/D**; **C**, bare MCM-41 (6124); **D**, **10d**/M1; **E**, bare SBA-15 (MFDC061); **F**, **10d**/S2.

Moreover, DRIFT spectra showed also that the Cu complex is grafted without any modification of the ligand structure, since the IR absorption bands did not show any appreciable modification with respect to solid **10d**, nor in location, nor in intensity (figure 2.17).

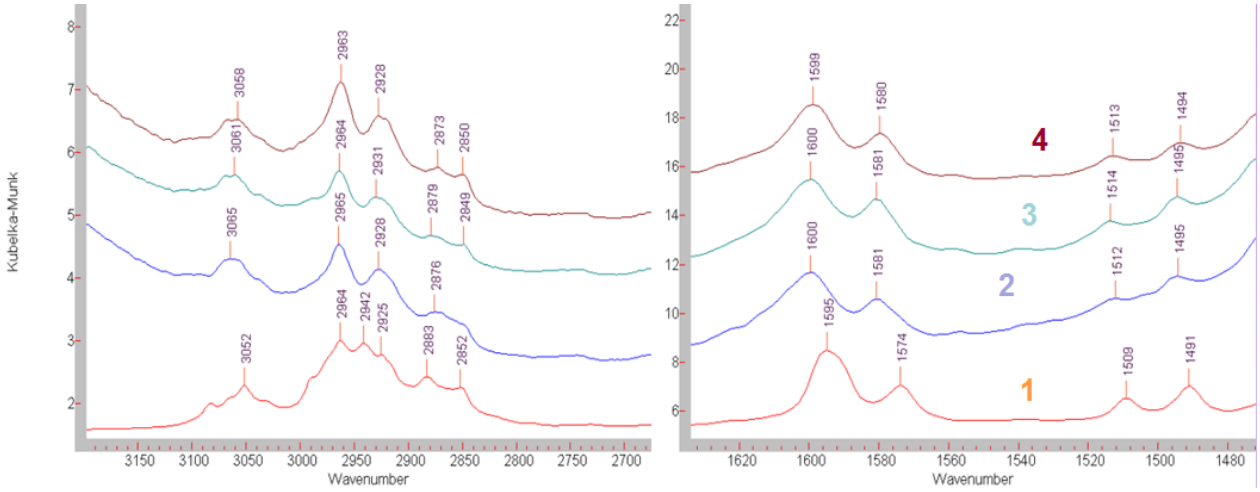


Figure 2.17 DRIFT spectra of [Cu^{I}(Pc-L*)]CF_3SO_3 pure complex **10d** in solid state (mixed with KBr), trace 1; **10d/D** sample, trace 2; **10d/S2a** sample, trace 3; **10d/M1** sample, trace 4.

The nature of the grafted Cu complex was further investigated by CO-DRIFT spectroscopy, since CO is a very good probe molecule for Cu(I) sites. In fact, stretching vibrations of a copper bound CO, ν(C≡O), is very sensitive to the coordination and electronic density on Cu site.[152, 159] Cu complex in the solid state (diluted in KBr, trace **E** in figure 2.18) did not adsorb CO under mild pressure (up to 2 bar), while, when CuL was dissolved in dichloroethane, an intense band located at 2111 cm^{-1} readily appeared in solution (trace **D** in figure 2.18).[111] The observed frequency of the coordinated CO was slightly higher than those reported for the CO adsorbed on tetra coordinated Cu (I) of [bis(2-pyridylmethyl)amine] copper complexes (2097 cm^{-1})[151] probably due to the lower efficiency of aliphatic amines in transferring electron density to the metal centre compared to pyridine. Notably also the grafted complex exposed to CO flow showed the presence of a strong CO band, slightly red-shifted and broadened, located in the range 2115 - 2119 cm^{-1}, (traces **A-C** in figure 2.18) that suggests a "solution like" complete accessibility to the Cu sites of the supported complex to small molecules (like CO).

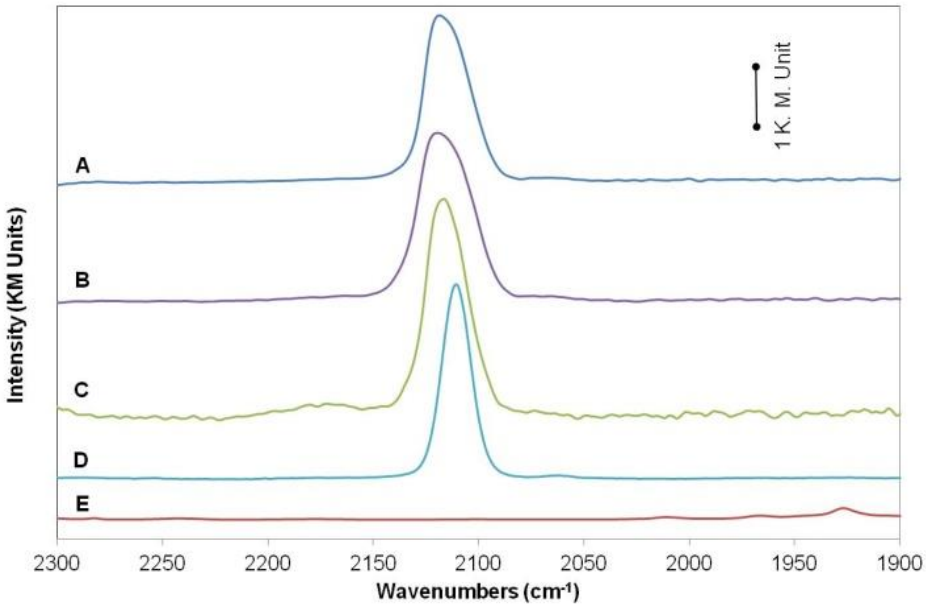


Figure 2.18 CO-DRIFT spectra of Cu(I) Pc-L* supported complex: **A**, **10d/D**; **B**, **10d/M1**; **C**, **10d/S2a**; **D**, **10d** in dichloroethane solution; **E**, **10d** solid state (KBr pellet).

The state of Cu(I) site after the catalytic reactions (see later section **2.5.1**) was further investigated by CO-DRIFT and, in general, CO bands undergo a small redshift to lower wavenumbers at around 2113 cm^{-1} (figure 2.19), possibly due to the reversible coordination of reaction products on copper site.

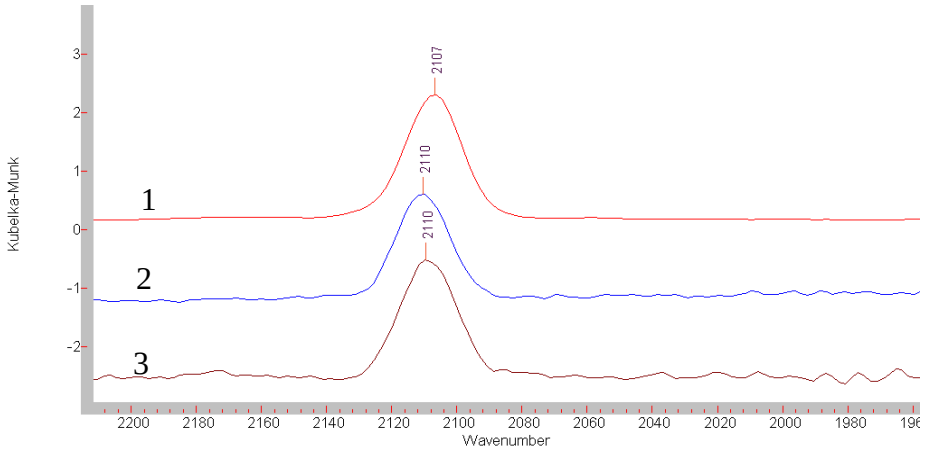
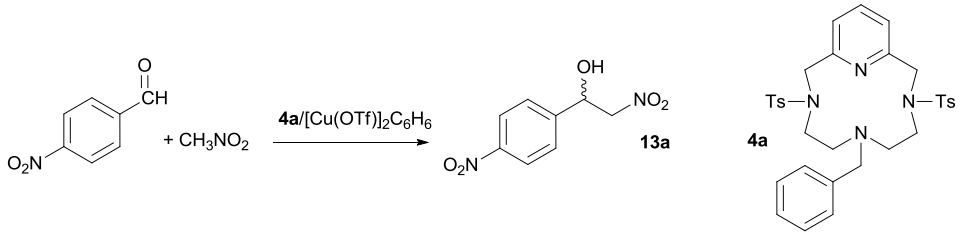


Figure 2.19 CO-DRIFT spectra of: trace 1**, 10d/D**; trace 2, **10d/M1**; trace 3, **10d/S2a** samples after catalysis.

2.4 Homogeneous catalysis

2.4.1 Henry reaction

Here we report the application of the Cu(I) complex **10a** of macrocyclic ligand **4a** as Lewis acid catalyst in the condensation between aldehydes and nitroalkanes.[128] The feasibility study with of the catalysed Henry reaction was initially carried out on 4-nitrobenzaldehyde and nitromethane (scheme 2.11).



Scheme 2.11 Copper catalysed Henry reaction of nitromethane with 4-NO_2-benzaldehyde.

As mentioned before, copper complexes are synthetized in 1,2-DCE and they can be isolated from that solvent. Since identical results were obtained with both the isolated preformed **10a** and the *in situ* formed complex, for practical reasons, all the next experiments were run with the *in situ* generated complex. During the catalysis conduced for the optimization, it was apparent that the course of the reaction critically depende on the nature of the solvent and the catalytic ratio (table 2.2). In order to verify the catalytic efficiency of the system, Henry reactions were performed in absence of any added base (entries 1-6).

Table 2.2. Feasibility study of the catalysed Henry reaction (Scheme 2.11)

Entry	solvent	base	T (°C)	Time (h)	Yield (%)[a]
1[b]	ethanol	-	25	48	61
2[b]	THF	-	25	48	34
3[b]	DCM	-	25	48	88
4[b]	DCM	-	reflux	36	80
5[b,c]	DCM	-	25	24/24/24	91
6[b]	chlorobenzene	-	25	48	19

[a] Isolated yields based on initial 4-nitrobenzaldehyde; unreacted benzaldehyde accounted for the rest of the reaction mass balance. [b] Reactions were performed with a 1:1 Cu(I)/**4a** ratio ($[Cu(OTf)]_2$ (C_6H_6) = 1.5×10^{-2} mmol) in the solvent (5 mL) at a Cu(I)/aldehyde/nitromethane ratio of 1:10:560; reactions were monitored by TLC. [c] After 24 h from the starting addition, two additions of both aldehyde and nitromethane were repeated (same quantities as the initial addition); total yield is reported.

The best results in terms of chemical yields were obtained with *in situ* formed 1:1 ligand **4a**:Cu(OTf) complex, from $[Cu(OTf)]_2 \cdot C_6H_6$, with a catalytic ratio ligand **4a**/Cu(I)/aldehyde/nitromethane = 1:1:10:560 in dichloromethane at room temperature (entry 3, Table 1). Under these experimental conditions, the catalytic cycle can be restored just upon addition of both aldehyde and nitromethane (same quantities as the initial addition) without any loss of catalytic activity: after three cycles, the global isolated yield was 91% (entry 5, Table 1). The reaction is not strongly influenced by the temperature (entry 4, Table 1). Dichloromethane was found to be far superior to more polar and coordinating solvents as ethanol or tetrahydrofuran (entries 1 and 2, Table 1). In aromatic hydrocarbons such as benzene or toluene the reaction did not take place. When $[Cu(CH_3CN)_4](BF_4)$ was used, a slower reaction was observed, while in the presence of copper(II) salts, such as copper(II) acetate or copper(II) chloride, the reaction did not occur. In the absence of ligand **4a** copper(I) triflate was unable to promote the reaction.

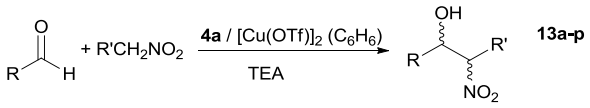
As a prior step to the nucleophilic attack on the carbonyl group of an aldehyde, generation of the activated nitronate species is needed. Nitroalkane activation by base promoted hydrogen transfer must necessarily be part of the catalytic cycle, together with the activation of the acceptor carbonyl through coordination to the copper atom. To study the beneficial effect of a basic co-catalyst, which is well documented in the literature,[160] we added a substoichiometric amount (fivefold excess with respect to the catalyst) of triethylamine (TEA) to the reaction mixture. As reported in Table 2.3, entry 1, in these conditions we observed a dramatic increase in the reaction rate. We were able to reduce the excess of nitromethane to 5 equivalents with respect to the aldehyde (entry 2, Table 2.3) and still to isolate the desired nitroalcohol in good yields. It is important to point out that every step of the Henry reaction is reversible and that large excesses of nitroalkane are usually required to drive the reaction to completion. The catalyst loading can be reduced to 1%, but in this case longer reaction times are needed (entry 4, table 2.3). It should be noted that if the reaction was run in the presence of ligand **4a** without adding any copper(I) salt (entry 6, table 2.3) the desired product was obtained only in very poor yield. Very recently, Darcel and co-workers reported a convenient Henry reaction of aldehydes and nitroalkanes catalysed by 1,4,7,10-tetraaza-cyclododecane (cyclen) in the absence of any added metal ion.[161]

Table 2.3 Optimization of the catalysed Henry reaction (Scheme 2.11)

Entry	solvent	base	Time (h)	Yield (%)[a]
1[b]	DCM	TEA	5	87
2[c]	DCM	TEA	20	75
3[c]	DCM	TEA	5	57
4[d]	DCM	TEA	160	51
5[c]	DCM	DIPEA	20	60
6[e]	DCM	TEA	20	18
7[d]	Ethanol	TEA	88	40

[a] Isolated yields based on initial 4-nitrobenzaldehyde; unreacted benzaldehyde accounted for the rest of the reaction mass balance. Reactions were performed with a 1:1 Cu(I)/**4a** ratio ($[Cu(OTf)]_2$ (C_6H_6) = 1.5×10^{-2} mmol) in the solvent (5 mL) at 25°C [b] Catalytic ratio Cu(I)/base/aldehyde/nitromethane = 1:5:10:560. [c] Catalytic ratio Cu(I)/base/aldehyde/nitromethane = 1:5:10:50. [d] Catalytic ratio Cu(I)/base/aldehyde/nitromethane = 1:5:100:500. [e] The reaction was performed in the same conditions as entry 5, but in the absence of copper. Under these conditions unreacted 4-nitrobenzaldehyde did not account for the rest of the reaction mass balance and by products derived from competitive side reactions were also observed.

These conditions allowed for the synthesis of a range of β-nitroalcohol derivatives **13a-13o** in moderate to excellent yields (scheme 2.12).

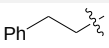


Scheme 2.12 Reaction scope.

All the collected data are summarized in Table 2.4. Best results in term of yields were obtained when an electron withdrawing group was present on the aryl ring (entries 1-5, table 2.4). Good yields have been also observed in the case of benzaldehyde. Using electron rich aromatic aldehydes the reaction was very slow and large excesses of nitromethane were required (entries 7 and 8, table 2.4). This can be rationalised on the basis of the less pronounced electrophilic character of the aldehyde, which probably displaces the reaction equilibrium towards the reagents, so that larger amounts of the pronucleophilic nitroalkane are required to drive the reaction to completion. Bulky aliphatic aldehydes such as pivalaldehyde were less reactive but in the case of cyclohexanecarbaldehyde acceptable yields have been obtained (entry 10, table 2.4). Noteworthy, no trace of the product derived from water elimination in compounds **13a-13p** was ever detected and in all cases selectivities of >99% were observed.

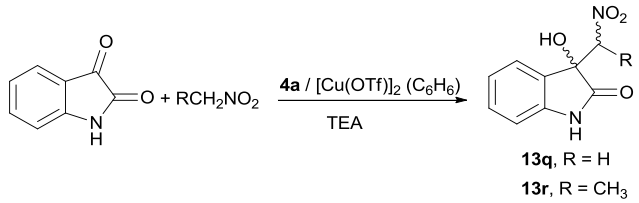
To test the diastereocontrol of our catalytic system, we next run the reaction with nitroethane,[162] obtaining the desired nitroalcohol in good yields, although the observed *syn/anti* ratio was very modest (entries 11 and 12, table 2.4).

Table 2.4 Scope and limitations of the **4a**/copper(I) catalysed Henry reaction reported in Scheme 2.12.[a]

Entry	R	R'	Product	Time (h)	Yield (%)[b]
1	4-NCC_6H_4	H	**13b**	20	96
2	4-$CF_3C_6H_4$	H	**13c**	20	70
3	4-FC_6H_4	H	**13d**	20	76
4	4-ClC_6H_4	H	**13e**	20	68
5	4-BrC_6H_4	H	**13f**	20	56
6	C_6H_5	H	**13g**	20	75
7[c]	4-*n*BuC_6H_4	H	**13h**	96	50
8[c]	3,4,5-$(MeO)_3C_6H_2$	H	**13i**	72	70
9	$(CH_3)_3C$	H	**13l**	40	traces
10		H	**13m**	20	41
11[d]	C_6H_5	CH_3	**13n**	20	65
12[e]	4-$NO_2C_6H_4$	CH_3	**13o**	20	70
13		H	**13p**	40	traces

[a] Reactions were performed with 1:1 Cu/**4a** ratio ($[Cu(OTf)]_2$ (C_6H_6) = 1.5×10^{-2} mmol) in dichloromethane (5 mL) at a Cu(I)/TEA/aldehyde/nitromethane ratio of 1:5:10:50; reactions were monitored by TLC. [b] Isolated yields based on starting aldehyde; unreacted aldehyde accounted for the rest of the reaction mass balance. [c] Without added base; catalytic ratio Cu(I)/aldehyde/nitromethane of 1:10:560. [d] *Syn/anti* ratio = 58:42.[163] [e] *Syn/anti* ratio = 55:45.[163]

Taking into account that the indole nucleus is present in a large number of compounds of biological and/or pharmaceutical interest, we extended the **4a**:Cu(OTf) system to isatine (scheme 2.13).



Scheme 2.13. Reaction with isatine.

The reaction with nitromethane gave the desired 3-hydroxy-3-(nitromethyl)-1,3-dihydro-2H-indol-2-one, **13q**, in 75% yield.[164] Encouraged by this result, isatine was reacted with nitroethane and a mixture of the diastereoisomers **13r** in the ratio 5:1 (figure 2.20) was obtained with an overall yield up to 80%.[165]

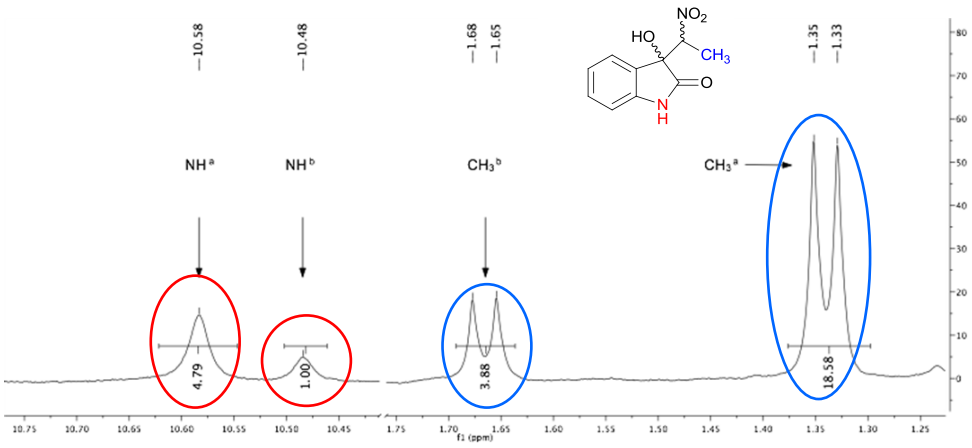


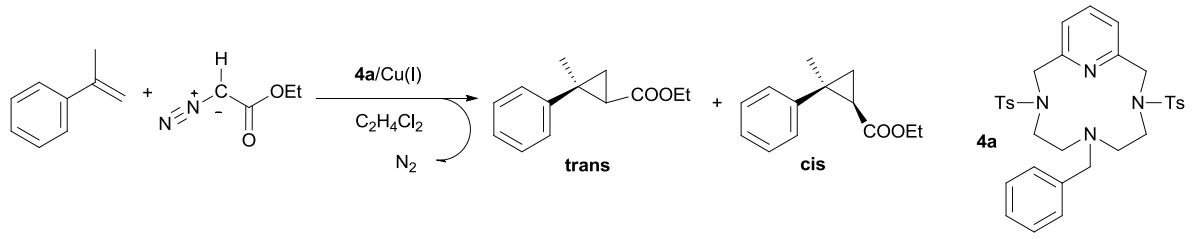
Figure 2.20 Selected part of ^{1}H-NMR spectrum of reaction with isatine and nitroethane.

Although this reaction opens up new routes for the synthesis of oxindole alkaloids, at the date when we have undertaken our studies no reports on the diastereoselective nitroaldol reaction by using isatine as substrate were present. Very recently, an excellent work by Wang and co-workers on the subject has been published.[166]

Preliminary studies were conducted employing the chiral ligand **4c** in the present catalytic system gave only very modest *ee*. Interestingly the diastereoselection of the reaction increased and, for instance, in the case of the reaction between 4-nitrobenzaldheyde and nitroethane the *syn*/*anti* ratio could be improved up to 7:3.

2.4.2 Cyclopropanation reaction

Then our group focused its attention on asymmetric cyclopropanation promoted by copper (I) complexes of ligands **Pc-L***.[111] Preliminary studies were already conducted.[81] Despite the evident potential of this class of C_1 symmetric ligands, their application in asymmetric catalysis has not been fully exploited. Here we report our finding testing the copper(I) complexes **10** of the new tetraazamacrocylces ligands **4** previously described. At first the catalytic activity of copper complexes with ligand **4a** in cyclopropanation reactions was investigated. As model reaction we chose the cyclopropanation of α-methylstyrene with EDA. Catalytic reactions were run by adding EDA to a solution containing the olefin, the ligand and the Cu salt (Cu/**4a**/EDA/olefin ratio 1:1:35:170), following by IR spectroscopy the disappearance of the band due to the stretching of the N_2 moiety (ν = 2114 cm^{-1}) (scheme 2.14).



Scheme 2.14 Benchmark cyclopropanation reaction catalysed by copper complex of ligand **4a**.

We first tested the reaction by changing the copper salt, the solvent, the temperature and the modality of addition of the EDA solution. All reported yields were isolated and based on EDA. In all cases cyclopropanes were obtained as major products. However, the high volatility of the products requires a careful isolation from the eluates. Fumarate and maleate, the homo-coupling product of EDA, were the only detected side products. The results are summarised in Table 2.5. As it can be seen by data reported in Table 2.5, best results in term of yield were obtained at 0 °C by slow addition of EDA with a syringe pump employing $[Cu(OTf)]_2 \cdot C_6H_6$ as copper source (same results were obtained with the more expensive toluene complex) in 1,2-dichloroethane (table 2.5, entry 4). Lower yields were observed when using copper II sources such as $CuCl_2$ or $Cu(OAc)_2$ (table 2.5, entries 7 and 8). Better results were obtained when employing copper(II) triflate instead (table 2.5, entry 6). It is reasonable to assume, anyway, that copper must be reduced to oxidation state (I) by EDA under reaction conditions and that the active species is again a cationic copper(I) complex of the ligand having an outer sphere non coordinating triflate anion.[167]

Table 2.5 Cu(I)/**4a** complexes for asymmetric cyclopropanation of α-methylstyrene [a]

Entry	Copper source	T	solvent	Yield (%)[b]	*cis* : *trans*[c]
1	$[Cu(OTf)]_2 \cdot C_6H_6$	r.t.	$C_2H_4Cl_2$	31	42 : 58
2	$[Cu(OTf)]_2 \cdot C_7H_8$	r.t.	$C_2H_4Cl_2$	33	42 : 58
3	CuI	r.t.	$C_2H_4Cl_2$	32	42 : 58
4[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	$C_2H_4Cl_2$	89	43 : 57
5[d]	$[Cu(CH_3CN)_4] \cdot BF_4$	0 °C	$C_2H_4Cl_2$	45	43 : 57
6[d]	$Cu(OTf)_2$	0 °C	$C_2H_4Cl_2$	89	43 : 57
7[d]	$CuCl_2$	0 °C	$C_2H_4Cl_2$	10	44 : 56
8[d]	$Cu(OAc)_2 \cdot H_2O$	0 °C	$C_2H_4Cl_2$	16	45 : 55
9[d,e]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	$C_2H_4Cl_2$	32	44 : 56
10[d,f]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	$C_2H_4Cl_2$	43	45 : 55
11[d,g]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	$C_2H_4Cl_2$	88	43 : 57
12[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	CH_2Cl_2	44	64 :36
13[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	CH_3CN	10	50 : 50
14[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	toluene	50	77 : 23
15[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	chlorobenzene	47	72 : 28
16[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	THF	19	66 : 34
17[d]	$[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	$C_2H_4Cl_2$[h]	37	40 : 60

[a] Reactions were performed with equimolar amounts of Cu salt (3.0×10^{-2} mmol) and **4a** in solvent . Cu/**4a**/EDA/α-mehylstyrene 1:1:35:170. [b] Isolated yields based on EDA. [c] Determined by GC-MS. [d] Slow addition of EDA over 100 min. [e] In the presence of molecular sieves. [f] Cu/**4a** ratio = 1:2. [g] Synthesised according to ref. 39. [h] Not distilled.

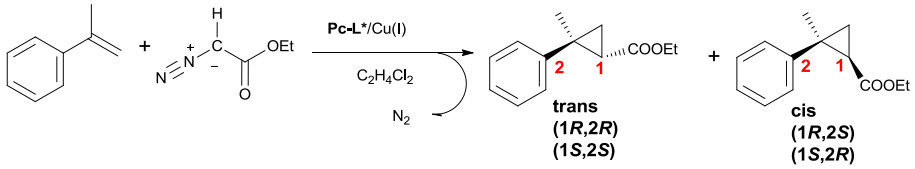
In preliminary experiments, freshly distilled solvents were employed. However, the use of molecular sieves during the reaction was found to be detrimental while yields were not severely affected by the use of not distilled solvents (table 2.5, entries 9 and 17, respectively). Good yields were obtained in other chlorinated solvents such as dichloromethane and chlorobenzene and in toluene, while by using acetonitrile, lower yields were observed. In this case acetonitrile competes with the ligand and the substrates for the coordination to the copper atom. A different explanation instead should be given for the low yield of cyclopropanes formed when using THF.

In this case the product derived from the C-H insertion into the α-CH bond of the solvent was also observed (table 2.5, entry 16).[168]

We next studied the effect of the different ligands under the optimised conditions in $C_2H_4Cl_2$ as solvent. The preformed complexes **10d**, [**10d**/CH_3CN][OTf], [**10d**/CH_3CN][PF_6] and [**10d**/CH_3CN][BF_4] (see section **1.1.2** for details) were also tested. Results are reported in Table 2.6 and table 2.7. All the reported yields in this case were determined by GC with the addition of 2,4-dinitrotoluene as internal standard, confirmed by quantitative ^{1}H NMR analysis of the reaction mixture. In all the cases cyclopropanes were obtained in good to excellent yields; again fumarate and maleate were the only detected side products and accounted for the missing mass balance of the reactions. The presence of the naphthyl group, although confers a better stability to the copper complex, does not alter the reaction course and ligand **4b** essentially gave the same results compared to **4a** (table 2.6, entry 1). In the case of chiral ligands, the presence of a naphthyl substituent seems to be beneficial and the enantioselectivities obtained with ligand **4d** are slightly better than those with ligand **4c** (table 2.6, compare entries 6 and 7 with entries 3 and 4). Further decreasing the temperature did not improve the selectivity of the reaction (table 2.6, entry 5). Best results in terms of enantioselectivities for both *cis* (88%) and *trans* (99%) isomers were obtained with the more sterically hindered ligand **4f** (table 2.6, entry 9). Ligand **4f** has a matching configuration of all the stereocenters and as a result the observed enantioselection was significantly higher than in the case of ligands **4d** and **4e** (table 2.6, compare entries 6 and 8 with entry 9).

On the other hand, a mismatching diastereoselection is observed: ligand **4d** gave preferentially the *cis* isomer, while ligand **4e** the *trans* and, in the case of ligand **4f**, equal amounts of both isomers were obtained. The two diastereoisomers **4g** and **4f** afforded the same enantiomer albeit in different enantiomeric excess (table 2.6, entry 10). The experimental results show that better enantiomeric excesses were obtained if a stereogenic carbon is present in position 13 (figure 2.1). On the other hand, the diastereoselection in favour of the *cis*-isomer is influenced by the presence of bulky substituents on the macrocycle. The presence of the *i*-propyl moieties, in fact, confines the macrocycle in a more rigid environment (figure 2.4). Using ligand **4l**, that presented only one *i*-propyl moiety on the framework, same diasteroselection were obtained with respect to **4d**, but with higher enantioselectivities (table 2.6, entries 13 and 6).

Table 2.6 Cu(I)/**Pc-L*** complexes for asymmetric cyclopropanation of α-methylstyrene [a]



Entry	**Pc-L*** / Cu	T	Yield (%)[b]	*cis* : *trans*[c]	ee (%)[d]	
					cis	*trans*
1	**4b** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	86	43 : 57	-	-
2[e]	**4c-(13*S*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	r.t.	75(53)	55 : 45	-44	-35
3[e]	**4c-(13*S*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	90(70)	65 : 35	-50	-38
4	**4c-(13*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	91(72)	65 : 35	50	38
5	**4c-(13*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	-20 °C	80(59)	64 : 36	53	38
6	**4d-(13*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(83)	60 : 40	53	65
7[e]	**4d-(13*S*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(83)	60 : 40	-53	-65
8	**4e** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(88)	33 : 67	30	50
9	**4f** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	98(57)	50 : 50	88	99
10[e]	**4g** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	66	35 : 65	-57	-52
11[e]	**4h** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	91	52 : 48	-21	-16
12	**4i** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	95	42 : 58	23	59
13	**4l** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	48	60:40	74	79
14[e]	**4m-(2*R*,10*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	79	63:37	-50	-40
15[e]	**4n-(2*R*,10*S*,13*S*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	77	64:36	-47	-58
16[e]	**4o-(2*R*,10*R*,13*S*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	94	63:37	-55	-62
17	**4o-(2*S*,10*S*,13*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	94	63:37	55	62
18[e]	**4p-(2*R*,10*R*,13*R*)** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	66	58:42	-28	-16

[a] Reactions were performed with equimolar amounts of Cu(I) salt (3.0×10^{-2} mmol) and **Pc-L*** with a *S* configuration in dichloroethane (5 mL). Cu/**4a**/EDA/α-mehylstyrene 1:1:35:170. [b] Yields based on EDA determined by GC (isolated yield). [c] Determined by GC. [d] Determined by chiral HPLC; absolute configurations: *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*S*,2*S*). [e] Absolute configurations: *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*).

Surprisingly, when employing ligand **4h** we obtained the opposite enantiomer (table 2.6, entry 11). The stereocenters of this molecule are exactly in the same configuration as those of **4e**. It is reasonable to assume that trifyl moieties induce a different conformation of the macrocyclic ring system. While testing macrocyles with the differently functionalised pyridine moieties **4m-p**, we observed that methyl groups in position 2 and 10 (figure 2.1) did not affect the diasteroselection outcome of the reaction if compared to obtained results with **4d** (table 2.6, comparing entries 14-17 and 6). When another methyl group is added in position 13 (figure 2.1), **4n** and **4o** (table 2.6, entries 15 and 16), we observed an increased in enatioselection especially for the *trans* isomer with respect to **4m** (table 2.6, entry 14). Ligand **4o** has a matching configuration of all the stereocenters and as a result the observed enantioselection was significantly higher than in the case of ligands **4n** (table 2.6, compare entries 16-17 and 15). Finally we also tested ligand **4p** that present a mismatching configuration and as expected lower *ees* were obtained (table 2.6, entry 18) with respect to the ligand previously described **4o**.

When employing the bulkier *tert*-butyl diazoacetate, ^{t}BuDA, (condition as in the caption to table 2.6, **4d**/$[Cu(OTf)]_2 \cdot C_6H_6$ as catalyst) both lower yields (28%) and a decrease of enantioselectivity (ee *cis* 12%, *trans* 46%) were observed with an inversion of the diastereoselectivity (*cis* : *trans* = 27 : 73). Similar effects on increasing the size of the diazoacetate are not unprecedented and have been explained in terms of overcrowding of the transition state.[169]

Identical results were obtained whether preformed **10d** or **4d** / $[Cu(OTf)]_2 \cdot C_6H_6$ were used (comparing table 2.7, entry 4 and entry 2). The presence of acetonitrile in the reaction mixture slightly decreased the yields, without affecting to a major extent the observed steroeselectivities (table 2.7, entries 1–2 and 5-7). This result suggests that the coordinated acetonitrile molecule dissociates in solution before the activation of the EDA, and that the pre-catalyst is **10d** whilst [**10d**/CH_3CN][OTf], [**10d**/CH_3CN][PF_6] and [**10d**/CH_3CN][BF_4] are inactive. The inhibiting effect was observed also upon addition of external acetonitrile (table 2.7, entry 8). Noticeably, the reaction with **4f**/$Cu(OTf)_2$ (table 2.7, entry 3) gave still very good yields with respect to **4f**/$[Cu(OTf)]_2 \cdot C_6H_6$ (table 2.6, entry 9), but a significant drop in the enantioselection.

Table 2.7 Cu(I)/**Pc-L*** complexes for asymmetric cyclopropanation of α-methylstyrene [a]

Entry	**Pc-L*** / Cu	T	Yield (%)[b]	*cis* : *trans*[c]	ee (%)[d]	
					cis	*trans*
1	**4c-(13*R*)** / $[Cu(CH_3CN)_4]\cdot BF_4$	0 °C	78(65)	57 : 43	33	36
2	**4d-(13*R*)** / $[Cu(CH_3CN)_4]\cdot BF_4$	0 °C	70(56)	55 : 45	45	44
3	**4f** / $Cu(OTf)_2$	0 °C	96	52 : 48	70	77
4	**10d**	0 °C	98(82)	57 : 43	55	66
5	[**10d**/CH_3CN][OTf]	0 °C	80(72)	58 : 42	49	63
6	[**10d**/CH_3CN][PF_6]	0 °C	75(65)	57 : 43	45	62
7	[**10d**/CH_3CN][BF_4]	0 °C	85(73)	55 : 45	54	62
8[e]	**4d-(13*R*)** / $[Cu(OTf)]_2\cdot C_6H_6$	0 °C	79(65)	59 : 41	53	65

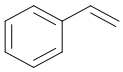
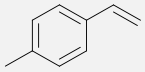
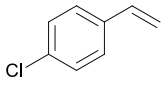
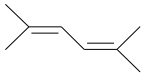
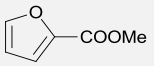
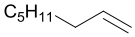
[a] Reactions were performed with equimolar amounts of Cu(I) salt (3.0×10^{-2} mmol) and **Pc-L*** with a *S* configuration in dichloroethane (5 mL). Cu/**4**/EDA/α-mehylstyrene 1:1:35:170. [b] Yields based on EDA determined by GC (isolated yield). [c] Determined by GC. [d] Determined by chiral HPLC; absolute configurations: *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*S*,2*S*). [e] In the presence of added acetonitrile (5 equiv.).

Under optimal conditions, other alkenes were employed to determine the substrate scope of the macrocyclic **Pc-L*** and $[Cu(OTf)]_2\cdot C_6H_6$ in dichloroethane (table 2.8).

At a Cu(I)/EDA/alkene ratio of 1:35:170, the formed complex catalysed the reaction of all the tested substrates yielding the cyclopropanes in good yields and enantioselectivities. The absence of α-substituents on the styrene affected the diastereoselectivity of the reaction (table 2.8, entries 1-9) yielding preferentially to the *trans* isomer (up to a 4 fold excess in the case of 4-Cl-styrene, entry 7). Steric hindrance at the α position does not hamper the reaction and good yields were obtained with 1,1-diphenyl ethylene (table 2.8, entries 10-13). The catalytic activity is not confined to styrenic double bonds With 2,5-dimethyl-2,4-hexadiene, an important precursor to the chrysanthemic acid synthesis,[170] the catalytic reaction yielded the desired cyclopropanes (cyclopropanation of only one double bond was observed)[171] and with reasonable diastereoselectivities, if a large excess of the olefin is employed (table 2.8, entry 14). Good yields (attack only at the non-substituted double bond) and excellent diastereoselectivities in favour of the *trans* isomer (> 99%) were obtained with 2-methylfuroate, (table 2.8, entries 15-18).[172] From this precursor, some years ago Reiser reported a very elegant synthesis of roccellaric acid.[173] Non-activated aliphatic alkenes are known to be less reactive in comparison with aromatic or activated alkenes towards copper mediated cyclopropanations.[174] Chiral catalyst for the enantioselective cyclopropanation of aliphatic 1-alkenes are very often *trans*

selective,[175] although more recent examples of highly *cis* selective catalysts have been reported.[176] When 1-octene was reacted with EDA in the presence of Cu(I)/**4f** the corresponding cyclopropane derivative was obtained in 73% yield, thus extending the scope of **Pc-L*** copper(I) complexes in asymmetric synthesis (table 2.8, entry 19).

Table 2.8 Asymmetric cyclopropanation of alkenes by Cu(I)/**Pc-L*** [a]

Entry	**Pc-L*** / Cu	T	Yield (%)[b]	*cis* : *trans*[c]	ee (%)[d]	
					cis	*trans*
1	**4d-(13*R*)**		72(51)	50 : 50	33	50
2	**4f**		97	38 : 62	99	87
3	**4o-(2*R*,10*R*,13*S*)**		95	54 : 46	47	65
4	**4d-(13*R*)**		66(45)	53 : 47	34	45
5	**4e**		79	25 : 75	33	40
6	**4d-(13*R*)**		88(68)	47 : 53	36	50
7	**4e**		88	19 :81	42	53
8	**4f**		86	42 : 58	66	78
9	**4o-(2*R*,10*R*,13*S*)**		87	51 : 49	n.d.	n.d.
10	**4d-(13*R*)**		64(56)	-	50	
11	**4e**		85	-	62	
12	**4f**		45	-	88	
13	**4o-(2*R*,10*R*,13*S*)**		49	-	32	
14[e]	**4d-(13*R*)**		81(54)	67 : 33	30	15
15	**4d-(13*R*)**		54(45)	> 1 : 99	n.d.	57
16	**4e**		55	> 1 : 99	n.d.	28
17	**4f**		74	> 1 : 99	n.d	76
18	**4o-(2*R*,10*R*,13*S*)**		94	> 1 : 99	n.d	77
19[f]	**4f**		73	38 : 62	75	55

[a] Reactions were performed with slow addition of EDA over 100 min to a solution of $[Cu(OTf)]_2 \cdot C_6H_6$ and **Pc-L*** (3.0×10^{-2} mmol) in dichloroethane (5 mL) at 0 °C; [b] Yields based on EDA determined by GC (isolated yield). [c] Determined by GC-MS. [d] Determined by chiral HPLC; absolute configurations: for entries 1–2, 4-8 *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*S*,2*S*); entry 3 *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*); entries 10-12: the absolute configuration was (1*S*); entry 13 was (1*R*)**.** For entry 14 and 19 the absolute configurations were not determined; for entries 15–17 *trans*-cyclopropane was (1*R*,5*R*,6*R*); for entry 18 *trans*-cyclopropane was (1*S*,5*S*,6*S*). [e] Cu(I)/**4d**/EDA/olefin = 1:1:35:1750. [f] Cu(I)/**4f**/EDA/olefin = 1:1:35:330.

2.4.3 Regiospecific synthesis of 1-Alkoxy-isochromenes

As mentioned before silver complexes **12a**[1-3] were tested in the tandem acetalization/cycloisomerization of ortho-alkynylbenzaldehydes with different primary and secondary alcohols for the synthesis of 1-alkoxy-*1H*-isocromenes.[177]

Isochromene and isochromane nuclei are the core of some interesting bioactive molecules and natural products. For example the methyl 1,5,8-trimethoxy-1*H*-isochromene-3-carboxylate was patented as potential antitumor agent against breast cancer[178] and the related carboxamide derivative BCH2051displayed an interesting activity against the human ovarian cancer cell line SKOV3 and the colon carcinoma cell line HT-29.[179] Moreover, the structure of isochromane is the skeleton of a diterpene from Antarctic sponge Dendrilla Membranosa called membranolide B[180] (figure 2.21). All these compounds are characterized by a cyclic-acetal framework, due to the presence of a methoxy group on C1.

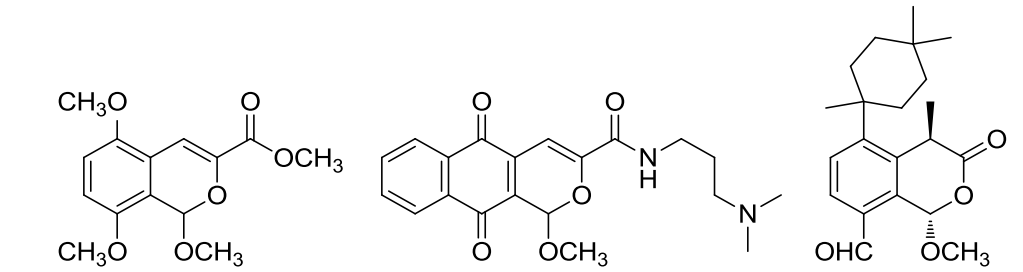
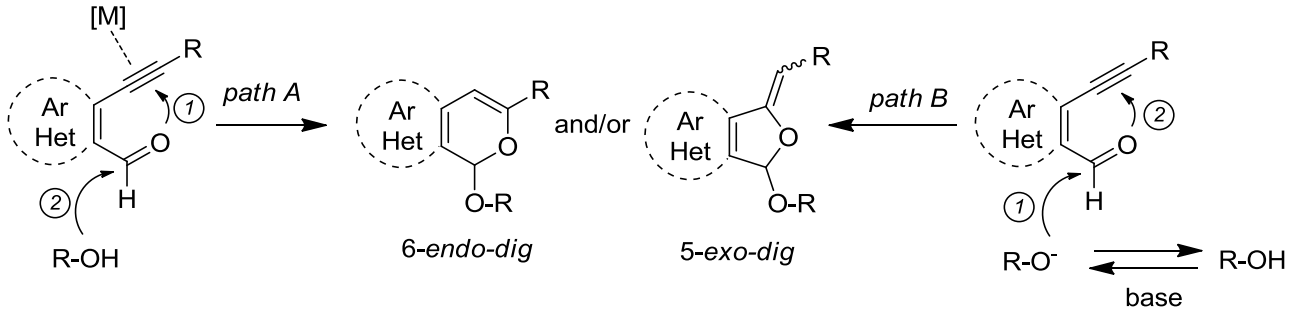


Figure 2.21. Examples of 1-alkoxy-isochromene/ane-containing bioactive molecules.

An efficient method to build-up 4-unsubstituted-1-alkoxyisochromenes and related heteroaryl compounds (e.g., dihydropyranoquinolines) is the regioselective domino addition/cycloisomerization of a properly substituted 2-alkynyl(hetero)arylaldehyde with an alcohol.[181] These reactions are usually catalysed by a metal salt or promoted by a base, but the regioselectivity of the cycloisomerization step (i.e., 5-*exo-dig vs* 6-*endo dig* cyclisation) in not always easy to rationalise[182] (scheme 2.15). In general the reaction promoted by bases lead preferentially to the 5-*exo-dig* cyclisations products (i.e., dihydroisobenzofurans, dihydrofuroquinolines or dihydrofuropyrimidines) via an addition/annulation sequence that probably involves the formation of a hemiacetal anion (scheme 2.15, path B).[183] Conversely, the metal catalysed approaches can lead to both the products depending on several factors, including the nature the aromatic aldehyde (i.e., the presence of one or more nitrogen in the aromatic ring) and the substitution on the triple bond, but usually 6-*endo-dig* cyclisation products predominate

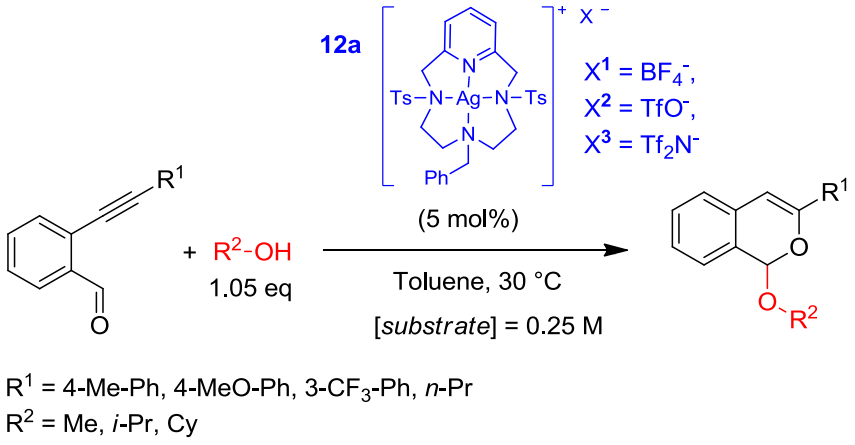
(i.e., isochromenes or dihydropyranoquinoline), whose formation is believed to occur through an highly reactive benzopyrylium intermediate (metal ate complex) followed by the nucleophilic attack from the alcohol as mild nucleophile (Scheme 2.15, path A).



Scheme 2.15. 5-*exo-dig* vs 6-*endo-dig* cyclisation mode of 2-alkynyl(hetero)arylaldehydes and alcohols.

Several metal ions, i.e., Pd(II),[184] Cu(I),[185] Ag(I),[186] Au(I)[187] and In(III)[188] salts, have been used as catalysts for the synthesis of isochromenes and analogues following this approach. An enantioselective version of this reaction, catalysed by chiral gold acyclic diaminocarbene (ADC) complexes has been also recently reported.[189]

In 2010, Dr. Giorgio Abbiati and co-workers reported a regioselective synthesis of substituted 1-methoxy-3-methylen-1,3-dihydroisobenzofurans by microwave-enhanced domino addition/cycloisomerisation reaction of 2-alkynylbenzaldehydes and methanol in the presence of a suitable base.[182] The approach was also successfully transformed in an advantageous multicomponent process.[190] As prosecution of these studies, in this thesis, we focused our attention to the selective synthesis of regioisomeric 1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes **14 (**scheme 2.16**)**.



Scheme 2.16. General synthesis for the isocromenes species promoted by silver(I) complexes **12a**[1-3].

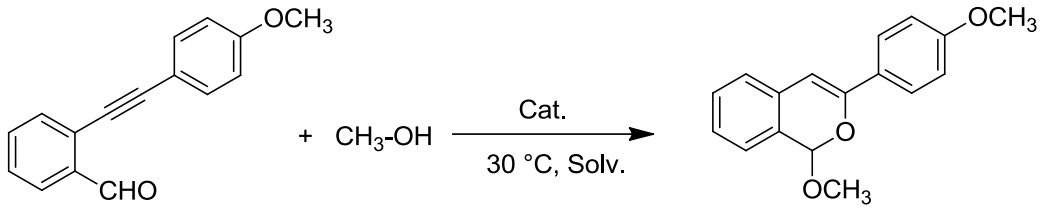
The first experiment was performed on a model reaction with 2-[(4-methoxyphenyl)ethynyl]benzaldehyde **14a** and methanol as reagent/solvent under unoptimised conditions (table 2.9, entry 1). This preliminary test pleasantly revealed that the silver complex **12a**[1] (5 mol%) was able to promote the addition/cycloisomerization of **14a** with methanol yielding regioselectively the corresponding isochromene **15a** in very good yield (83 %) after in 5 h. The TLC analysis of the reaction crude was particularly clean and showed only two spots. Thus, a small amount of the dimethyl acetal **ac-a** was the sole by-product detected by ^{1}H NMR of reaction crude, and accounted for the mass balance of the reaction (table 2.9, entry 1).

To optimize the reaction conditions we performed a series of new experiments. With the aim to find a proper medium to be used with different alcohols and to suppress the formation of the acetal **ac-a**, we tried some different solvents with decreasing relative polarity[191] (table 2.9, entries 2-4) in the presence of 3 equiv of methanol. All the solvent tested gave excellent results and the formation of dimethyl acetal **ac-a** was strongly reduced (table 2.9, entry 3) or completely avoided (table 2.9, entries 2 and 4). Even though the reaction in DCE seems to be a little faster (table 2.9, entry 3), the best yield and cleanness of the reaction were obtained in toluene (table 2.9, entry 4).

The concentration of the substrate seems to have a little effect on the course of the reaction (table 2.9, entries 5 and 6), whereas the reaction with Ag(I) complexes **12a**[2] and **12a**[3], characterised respectively by the presence of a slightly more coordinating counter ion such as triflate[192] or a more bulky and charge delocalized anion as triflimidate,[193] gave slightly lower yields in prolonged reaction times (table 2.9, entries 7, 8). We were pleased to find that the amount of the alcohol can be reduced without loss of yield or increase of reaction times (table 2.9, entries 9, 10). Conversely, the catalyst loading seemed to be a critical factor and amounts of catalysts lower than 5 mol% resulted in extended reaction times and lower reaction yields (table 2.9, entries 11, 12).

Finally, two control experiments in the presence of simple silver salts such as AgOTf (5 mol%) and $AgBF_4$ (5 mol%) as catalysts demonstrated the superiority of our Ag complexes (table 2.9, entries 13 and 14), because in both cases the reactions appeared lower yielding and, in particular, less clean.

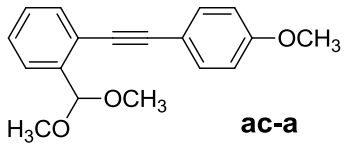
Table 2.9. Optimisation of the reaction conditions



14a **15a**

Entry	Solv.	equiv. MeOH	[**14a**] M	t (h)	Cat.	Cat. loading (mol%)	**15a** (Yield %)
1	MeOH	-	0.25	5	**12a**[1]	5	83[a]
2	Dioxane	3	0.25	5	**12a**[1]	5	88
3	DCE	3	0.25	1	**12a**[1]	5	94[b]
4	**Toluene**	3	**0.25**	2.5	**12a**[1]	5	99
5	Toluene	3	0.125	4	**12a**[1]	5	98
6	Toluene	3	0.50	2.5	**12a**[1]	5	98
7	Toluene	3	0.25	22	**12a**[2]	5	92
8	Toluene	3	0.25	24	**12a**[3]	5	93
9	Toluene	1.5	0.25	2.5	**12a**[1]	5	99
10	Toluene	**1.05**	0.25	2	**12a**[1]	5	99
11	Toluene	1.05	0.25	8	**12a**[1]	2.5	82
12	Toluene	1.05	0.25	36	**12a**[1]	1	70
13	Toluene	3	0.25	4	AgOTf	5	64[c]
14	Toluene	1.05	0.25	3	$AgBF_4$	5	60[c]

[a] Beside dimethyl acetal **ac-a** in 15% yield. [b] Beside traces of acetal **ac-a.** [c] Yields calculated via ^1H NMR using dimethyl terephthalate (DMT) as internal standard.



ac-a

In this regard, it is important to emphasize that one of the additional features of our method is the neatness of the reactions, which allows, in most cases, the isolation of the pure product through a simple work-up, i.e., washing of the crude with $NaHCO_3$ sat. sol. and extraction with dichloromethane. The simplicity of purification step represent an outstanding peculiarity of our

approach, because is well known that the purification of 1-alkoxyisochromenes and related compounds could be quite troublesome.[183,189]

With the best reaction conditions in hands, we tested scope and limitation of the approach. We selected some alkynylaldehydes substituted on alkynyl moiety with an alkyl- or an aryl-group and characterized by the presence on the aryl moiety of electron-donating or electron-withdrawing groups. The 2-alkynylbenzaldehydes **14a-d** were synthesised as previously reported[182] in good to excellent yields starting from commercially available 2-bromobenzaldheyde and a selection of terminal acetylenes by means of a typical Sonogashira coupling,[194] and their reactivity was tested with four alcohols with increasing steric hindrance. The results are reported in Table 2.10.

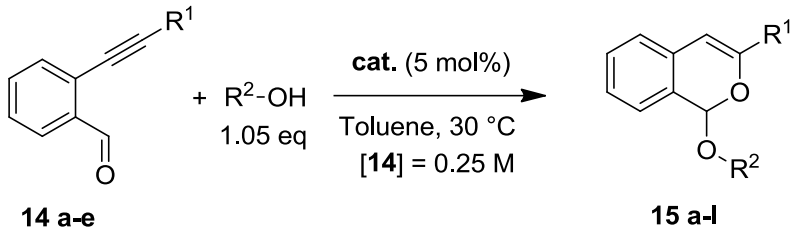
All alkynylbenzaldehydes bearing aryl or alkyl substitution on alkynyl moiety (**14a-d**) reacted with methanol to give the corresponding isochromenes **15a-d** in excellent yields, and the presence of EWG or EDG on the phenyl substituent is well tolerated (table 2.10, entries 1-6). Surprisingly in the presence of the trimethylsilyl group on alkynyl moiety the reaction completely failed, and the starting material **3e** was recovered unreacted also after a prolonged reaction time (table 2.10, entry 7), and under higher reaction temperatures (table 2.10, entries 8,9).

More hindered secondary alcohols, i.e., isopropanol and cyclohexanol, smoothly reacted with alkynylbenzaldehydes **14a-d** to give the desired isochromenes **15e-l** in very high yields (table 2.10, entries 8-20). Unfortunately, all attempts to react **14a** with highly sterically demanding tertiary alcohol such as *tert*-butanol failed, giving rise to a unidentified breakdown products (table 2.10, entries 21 and 22).

Catalysts **12a^2**and **12a^3** gave only slightly poorer results than **12a^1** (table 2.10, cfr. entries 2/3, 5/6, 11/12, 14/15 and 19/20). Aldehyde **14d**, substituted on alkynyl moiety with a *n*-propyl group reacted faster than other aldehydes with all alcohols and catalysts tested.

In some cases the products obtained after the standard work-up were not sufficiently pure and needed a purification by flash column chromatography (table 2.10, entries 5, 14 and 16). In these cases the resulted yields are lower than usual because 1-alkoxyisochromenes are not very stable and during the chromatographic purification partial decomposition of the product was observed.

Table 2.10 Scope and limitation of the approach.



14 a-e **15 a-l**

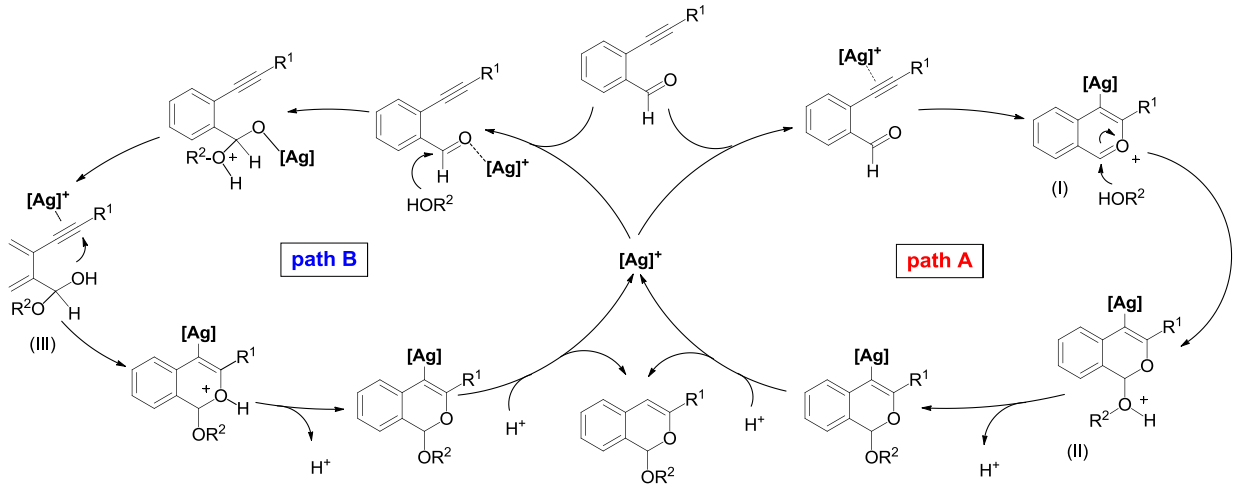
Entry	sub.	cat.	R^1	R^2	t (h)	**15** yield[a] (%)
1	**14a**	**12a**[1]	*p*-MeO-Ph-	Me	2	**15a** 99
2	**14b**	**12a**[1]	*p*-Me-Ph-	Me	22	**15b** 97
3	**14b**	**12a**[3]	*p*-Me-Ph-	Me	24	**15b** 94
4	**14c**	**12a**[1]	*m*-F-Ph-	Me	24	**15c** 98
5	**14d**	**12a**[1]	CH_3-CH_2-CH_2-	Me	2	**15d** 96 (76)[b]
6	**14d**	**12a**[2]	CH_3-CH_2-CH_2-	Me	2	**15d** 95
7	**14e**	**12a**[1]	$(CH_3)_3Si$-	Me	24	- (96 % **14e** rec.)
8	**14e**	**12a**[1]	$(CH_3)_3Si$-	Me	4[d]	- (95 % **14e** rec.)
9	**14e**	**12a**[1]	$(CH_3)_3Si$-	Me	18[c]	- (95 % **14e** rec.)
10	**14a**	**12a**[1]	*p*-MeO-Ph-	*i*-Pr	6	**15e** 99
11	**14b**	**12a**[1]	*p*-Me-Ph-	*i*-Pr	26	**15f** 97
12	**14b**	**12a**[3]	*p*-Me-Ph-	*i*-Pr	22	**15f** 93
13	**14c**	**12a**[1]	*m*-F-Ph-	*i*-Pr	24	**15g** 97
14	**14d**	**12a**$_1$	CH_3-CH_2-CH_2-	*i*-Pr	2	**15h** 89 (62)[b]
15	**14d**	**12a**[3]	CH_3-CH_2-CH_2-	*i*-Pr	4	**15h** 88
16	**14a**	**12a**[1]	*p*-MeO-Ph-	Cy	24	**15i** 92 (67)[b]
17	**14b**	**12a**[1]	*p*-Me-Ph-	Cy	24	**15j** 94
18	**14c**	**12a**[1]	*m*-F-Ph-	Cy	48	**15k** 96
19	**14d**	**12a**[1]	CH_3-CH_2-CH_2-	Cy	2	**15l** 94
20	**14d**	**12a**[2]	CH_3-CH_2-CH_2-	Cy	2	**15l** 86
21	**14a**	**12a**[1]	*p*-MeO-Ph-	*t*-Bu	27	-
22	**14a**	**12a**[1]	*p*-MeO-Ph-	*t*-Bu	72[d]	-

[a] After simple work-up. [b] After column chromatography. [c] Reaction performed at 110 °C. [d] Reaction performed at 80 °C.

In particular, we think that the acidic character of silica is the main responsible of degradation of 1-alkoxyisochromenes due to their acetal nature. To confirm this hypothesis we made two experiments to test the stability of 1-alkoxyisochromenes. A 0.25 M solution of **15a** in ethyl acetate was treated under alkaline or acidic conditions. We observed that in the presence of a

base (TEA, 0.2 equiv) the product remains unmodified also after stirring for 3.5 days, whereas in the presence of an acid (*p*-TSA, 0.2 equiv) the isochromene rapidly decomposes to give a complex mixture of unidentified by-products. The ^{1}H-NMR spectrum of the reaction crude roughly filtered on a silica gel-plug, displayed the preponderance of 2-[2-(4-methoxyphenyl)-2-oxoethyl] benzaldehyde[195] (maybe in equilibrium with its *cis/trans* enol forms) resulting from hydrolysis of **15a**. Nevertheless, also performing the chromatographic purification of new synthetized isochromenes **15** with a basified eluent mixture a slight reduction of yields due to partial decomposition of product was however observed.

As mentioned above, the most accepted mechanism to explain the silver catalysed synthesis of isochromenes invokes the formation of a isochromenilium intermediate (**I**) (metal ate complex) stabilized by resonance, resulting from the direct nucleophilic attack of the aldehyde oxygen to the metal activated triple bond (scheme 2.17, path A).[196] Then, the alcohol can attack the activate isochromenilium intermediate (**I**) to give the intermediate (**II**). A fast protodemetallation lead to the isochromene and restore the catalyst . Nevertheless, the ambivalence of silver salts and complexes, i.e., σ-philic *vs* π-philic character,[197] has been repeatedly established,[186a] so a plausible alternative path could involve the direct nucleophilic attack of the alcohol to the metal activated aldehyde to give a hemiacetal intermediate (**III**), which itself is able to react with the metal activated triple bond (scheme 2.17, path B). Also in this case, the following protodemetallation is the last step that leads to the formation of the isochromene and restore the catalyst.



Scheme 2.17 Plausible reaction mechanisms.

To gain insight into the mechanism, some kinetic ^{1}H NMR experiments were done. In the first experiment, the preliminary reaction conditions were repurposed (see table 2.9, entry 1) reacting **14a** at 30 °C in deuterated methanol in a NMR test tube (figure 2.22).

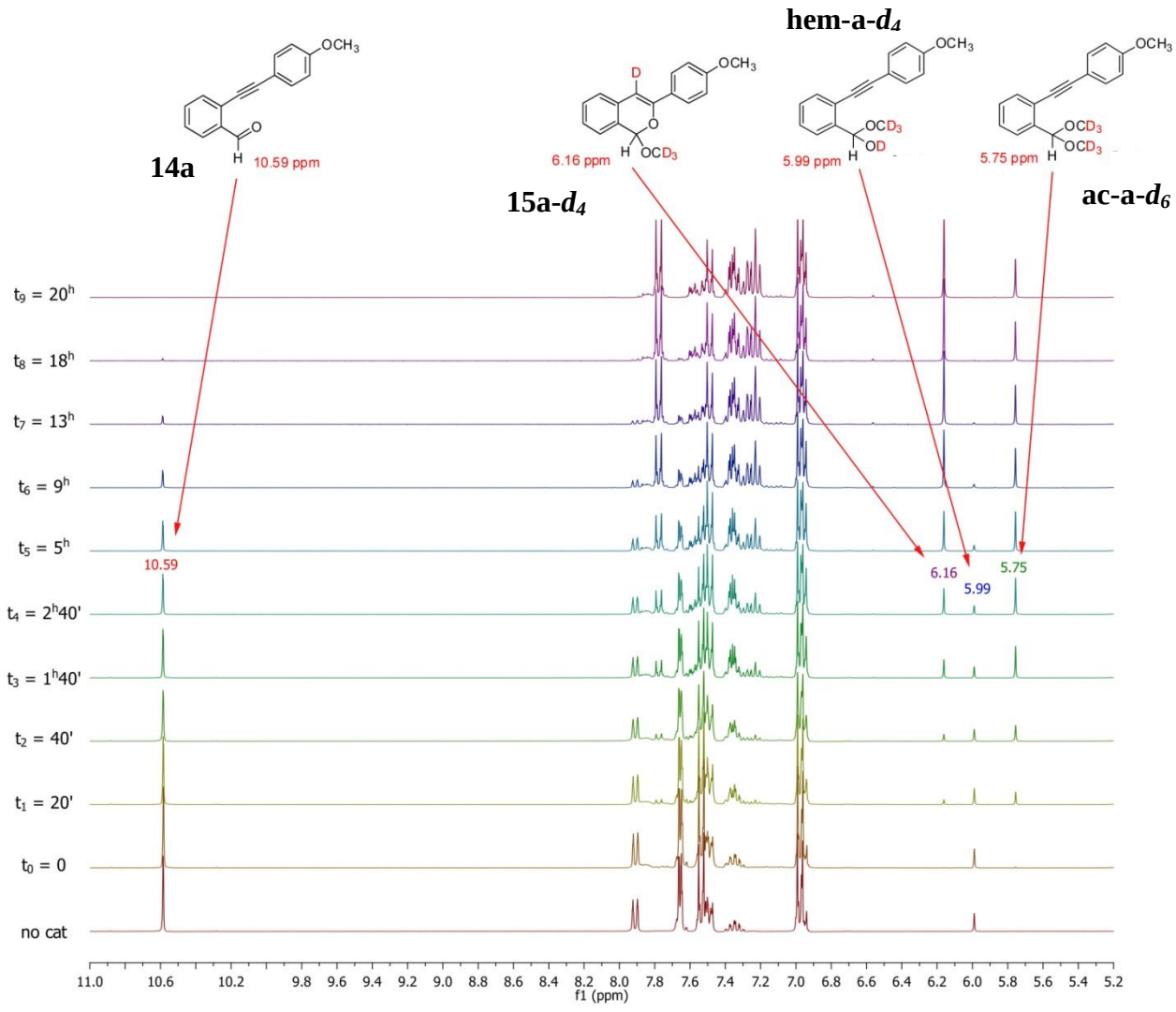


Figure 2.22 Kinetic ^{1}H NMR experiment of **14a** in CD_3OD in the presence of **12a**[1] (5 mol%), T = 30 °C.

In the absence of the catalyst (figure 2.22, no cat spectrum) only the formation of a little amount (≈18%) of the deuteromethyl-hemiacetal **hem-a-***d*$_4$ was observed (signal at 5.99 ppm). The amount of **hem-a-***d*$_4$ was roughly calculated on the basis of relative integration of the hemiacetal proton signal at 5.99 ppm and the aldehydic one at 10.59 ppm. The spectrum shape and the ratio between aldehyde **14a** and hemiacetal **hem-a-***d*$_4$ do not change in time (20 h), thus indicating an equilibrium between the two compounds. Then, **12a**[1] (5 mol%) was added (figure 2.2, T^0 spectrum). After 20 minutes (figure 2.22, T^1 spectrum) two new signals at 5.75 ppm and 6.16 ppm were detected, relative to the deuterodimethyl-acetal **ac-a-***d*$_6$ and the isochromene **15a-***d*$_4$, respectively. The spectra appeared very clean, and then the reaction proceeded with complete disappearance of the signals relative to aldehyde **14a** (10.59 ppm) and methyl-hemiacetal **hem-a-***d*$_4$ (5.99 ppm). The reaction was complete in 20 h (figure 2.22, T^9 spectrum) when only the signals relative to isochromene **15a-***d*$_4$ and the acetal **ac-a-***d*$_6$ were detectable. The signal relative

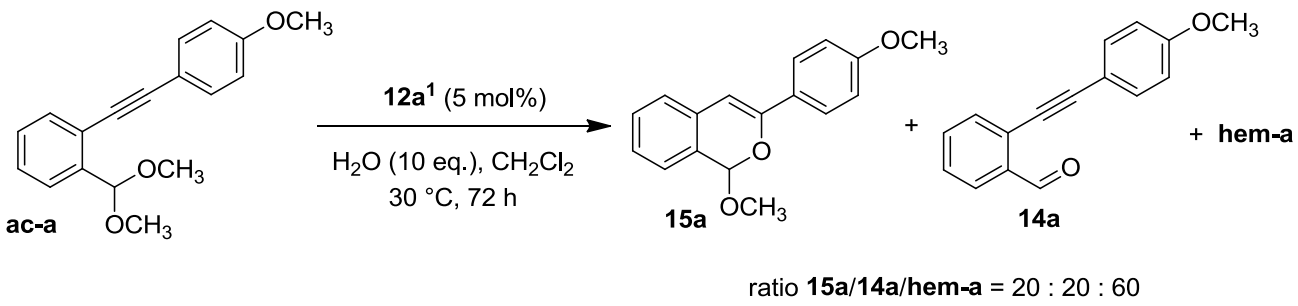
to acetal **ac-a**-d_6 at 5.75 ppm was attributed by comparison with those observed in the spectrum of a pure sample of the dimethyl-acetal **ac-a**. It is interesting to note that in all spectra no signal around 10.1 ppm, attributable to a possible isochromenilium intermediate[198] was ever detected (figure 2.22).

Moreover the analysis of the integrals at different times of the signals relative to deuterodimethyl-acetal **ac-a**-d_6 (5.75 ppm) with respect to those relative to CH_3 of 4-methoxyphenyl moieties chosen as reference (all these signals fall around 3.84-3.85 ppm and their overall integral is invariable), revealed that under these reaction conditions the hydrolysis of deuterodimethyl-acetal **ac-a**-d_6 to give the methyl-hemiacetal **hem-a**-d_4 is a very slow process (table 2.11).

Table 2.11 Integrals of selected signals of kinetic ^{1}H NMR experiment.

Time	ref.(**14a+15a+ ac-a+hem-a**) (3.84-3.85 ppm) $C\underline{H}_3O$-Ph-	Aldehyde **14a** (10.5 ppm) -C$\underline{H}$O	Hemiacetal **hem-a** (5.99 ppm) -C$\underline{H}$(OD)OCH_3	Acetal **ac-a** (5.75 ppm) -C$\underline{H}$$(OCH_3)_2$	Isochromene **15a** (6.16 ppm) -C$\underline{H}$$(OCH_3)$O-
0	3	0.57	0.12	0	0
20’	3	0.48	0.10	0.08	0.03
40’	3	0.43	0.09	0.12	0.05
1^h40’	3	0.33	0.07	0.19	0.11
2^h40’	3	0.27	0.06	**0.22**	0.15
5^h	3	0.20	0.04	**0.23**	0.23
9^h	3	0.12	0.03	**0.24**	0.34
13^h	3	0.06	0.01	**0.23**	0.42
18^h	3	0.02	0	**0.23**	0.48
20^h	3	0	0	**0.23**	0.50

This statement was confirmed by an additional experiment: the reaction of a pure sample of the dimethyl-acetal **a** in CH_2Cl_2 in the presence of **12a**[1] (5 mol%) and 10 equiv of water gave a mixture of isochromene **15a**, aldehyde **14a** and unreacted starting material **hem-a** in 20:20:60 ratio (roughly calculated on the ^{1}H NMR of the reaction crude), after a prolonged reaction time (72 h at 30 °C) (scheme 2.18).



Scheme 2.18. Reactivity of acetal **ac-a**.

From these results, some preliminary consideration could be made: 1) the formation of dimethyl-acetal **ac-a**-d_6 in the reaction performed in deutero-methanol in the presence of complex **12a**[1] confirmed its oxo-philic character (as yet previously observed for Ag(I) salts),[199]and its ability to promote the acetalization of methyl-hemiacetal **hem-a**-d_4; 2) such acetalization is probably a competitive side reaction; 3) when the reaction was performed in deutero-methanol, the methyl-hemiacetal **hem-a**-d_4 is surely an intermediate in the acetalization way, but it can be also an intermediate in the formation of isochromene **15a** (scheme 2.17 path B). Conversely, the absence in ^{1}H NMR spectra of any signal referable to a isochromenilium intermediate (scheme 2.17, **I**) do not seem to be a sufficient evidence to rule out its involvement in the process, probably with a very fast kinetic.

The latter concept seemed to be confirmed by a new kinetic ^{1}H NMR experiment: when the reaction was performed in a NMR tube at 30 °C, using $CDCl_3$ as solvent and in the presence of complex **12a**[1] (5 mol%) and only 2 equiv of methanol no traces of hemiacetal **hem-a**, acetal **ac-a** neither isochromenilium intermediates were observed, but only a slow direct conversion of aldehyde **14a** in the desired product **15a** was detected (figure 2.23).

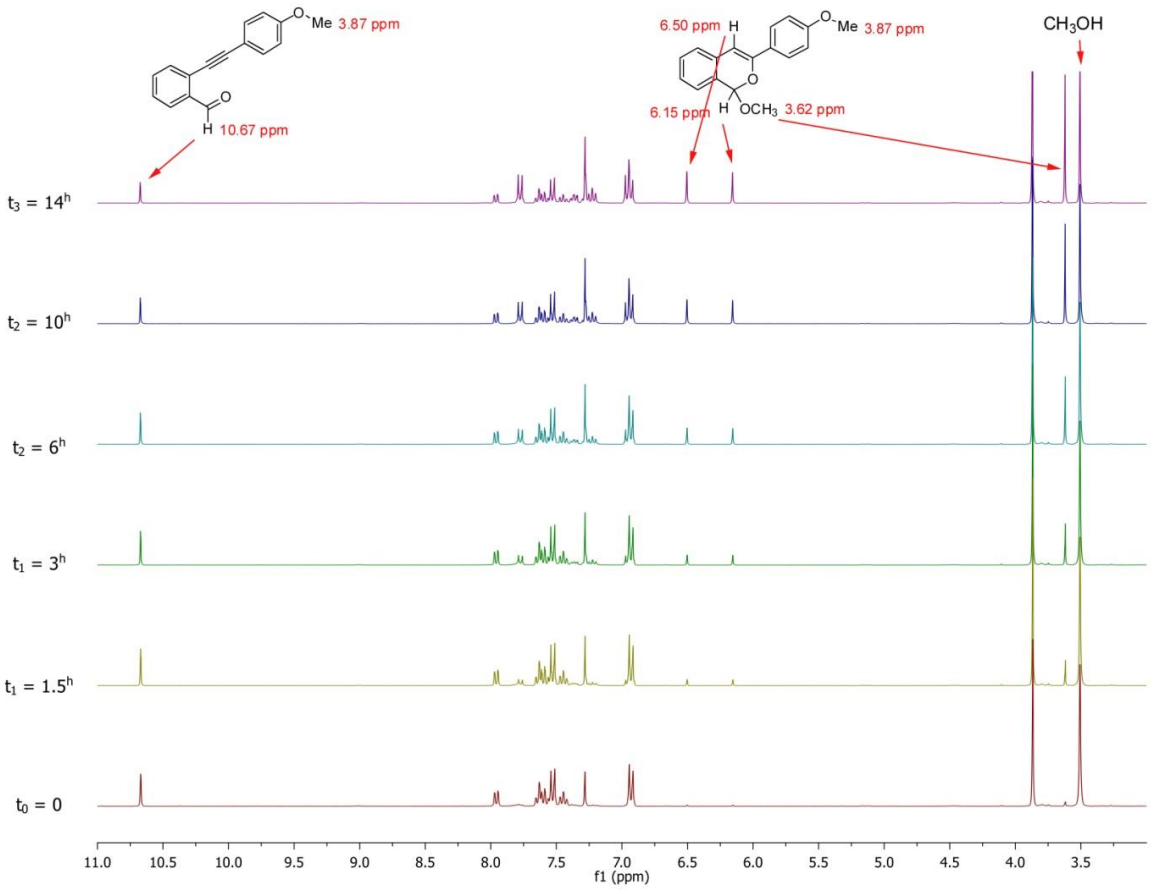
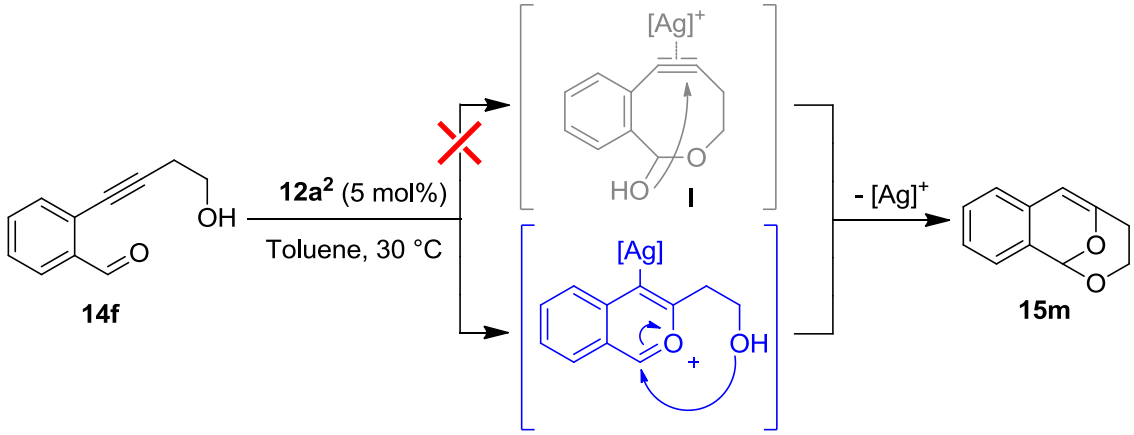


Figure 2.23. Kinetic ^{1}H NMR experiment of **14a** in $CDCl_3$ in the presence of 2 equiv of methanol and **12a**[1] (5 mol%), T = 30 °C.

Thus, to point out the possible involvement of a isochromenilium intermediate in the reaction mechanism, a conclusive intramolecular trapping experiment was made by reacting the new synthesised alkyne **14f**, characterized by the presence of a hydroxyethyl pendant at alkyne terminus, under standard condition in the absence of any other alcohol (scheme 2.19). Due to geometric requirements, the hypothetical formation of the corresponding tricyclic isochromene derivative **15m** can only occur by formation of an isochromenilium intermediate, because an alternative oxa-benzocyclooctyne hemiacetal (**I**) is a strongly improbable intermediate and such oxa-benzocyclooctyne bicyclic structures were never observed in the literature.[200] Moreover, the feasibility of the synthesis of **15m** was yet verified independently by the group of Wu and Hammond by AgOTf [201] and triazole-Au[202] catalysed processes, respectively.



Scheme 2.19 Intramolecular addition/cycloisomerisation of alkyne **14f**.

We were pleased to find that the reaction in the presence of Ag(I) complex **12a**^{2} gave the attained product **15m** in 5h (50 % yield), thus confirming that an isochromenilium ion is presumably the main intermediate involved in the reaction mechanism.

2.5 Heterogeneous catalysis

2.5.1 Cyclopropanation reaction in BATCH

Here we report on the use of SHB copper catalysts (described in section **2.3**) in cyclopropanations by using bare alkanes as reaction solvents in place of the less desirable halogeno-alkanes. The copper(I) complex **10d** was chosen as a model complex to be supported on different silica to be studied as a catalyst in cyclopropanation reactions. Details for every single catalyst (employed silica, impregnation methods and copper content) are reported in table 2.12, for further details see *Experimental part* section **3.6**.

Table 2.12 Impregnation method and Cu loadings (determined by ICP-OES), of $[Cu^{I}(Pc\text{-}L^{*})]CF_3SO_3/SiO_2$ samples.[a]

Entry	SiO_2 support	Impregnation method	Cu loading [wt. %]
10d/M1	MCM-41 (6124) [a]	1	0.62
10d/M2	MCM-41 (6170) [a]	1	0.54
10d/D	Davisil LC150	1	0.66
10d/A	Aerosil 380	2	0.45
10d/S1	SBA-15 (MFDC061)	2	1.09
10d/S2a	SBA-15 (MFDC065)	2	1.59
10d/S2b	SBA-15 (MFDC065)	1	0,45
10f/D	Davisil LC150	1	0.66

[a] **General procedure:** Metal loadings are determined by ICP-OES using a Thermo X Series II apparatus. 15 mg of each sample are mineralized by adding 3 mL of 37% HCl, 1 mL of concentrated HNO_3, 1 mL of 98% H_2SO_4

As model reaction we chosen the cyclopropanation of α-methylstyrene by EDA. Catalytic reactions were run by syringe pump slow addition of a EDA solution to a suspension containing the olefin and the catalyst (Cu/EDA/olefin ratio 1:35:170); the disappearance of the band due to the stretching of the N_2 moiety (ν = 2114 cm^{-1}) was followed by IR spectroscopy. These conditions are very close to those used in the homogeneous phase[111] and allows for a direct comparison of the obtained results. The major difference is that the solvent used in the homogeneous phase, 1,2-dichloroethane, was replaced with the more eco-friendly *n*-hexane. Although the latter is a volatile organic solvent, its use should be intended only as a proof of concept. In fact, for practical applications it may be easily substituted with other hydrocarbons with higher boiling point. All reactions were carried out at 0 °C, since this was the optimal temperature for cyclopropanation reactions catalysed by complex **10d** in the homogeneous phase. We first tested the reaction by changing the employed silica support. The results are

summarised in Table 2.13, compared with a typical result for the cyclopropanation reaction in the homogeneous phase by using the same copper(I) complex **10d** as catalyst. All reported yields have been determined by GC and confirmed by quantitative ^{1}H NMR and based on EDA. In all tested cases we observed a complete conversion of the starting EDA after the end of the addition (100 min) and cyclopropanes were obtained as major products; fumarate and maleate, the homo-coupling product of EDA, were the only other products detected and accounted for the reaction mass balance. The catalyst activity was almost unchanged in the heterogeneous phase with respect to the homogeneous one, although in some cases (entry 5, table 2.13) the yield in cyclopropanation products is somewhat lower, due both to a slight increase in the coupling product fumarate and maleate and to a partial absorption of the cyclopropanes on silica (see next section). Actually, in selected cases, especially when employing *n*-hexane as the solvent, reaction yields in cyclopropane products increase in the second run. This can be explained with a better release of the formed product from the silica (see entries 6, 9, 10 and 13, table 2.13). Experimental data show only a very weak dependence of the reaction efficiency from the surface area characteristics of the employed silica. In particular, we have obtained almost indistinguishable diastereo- and enantio-selectivities using either commercial Davisil or Aerosil 380, either ordered mesoporous silica MCM-41 or SBA-15. The possibility to use commercially available silica as a support in the present system is very interesting and paves the way to the employment of this immobilization technique also in laboratories not equipped for the synthesis of mesoporous materials. Other authors, using covalently bonded bis(oxazoline)-copper complexes on silica, recently reported that in those conditions commercially available silica were not suitable materials, probably due to its acidity.[134] The Sheldon test[203] showed that the catalyst is strongly bound to the support and that the filtered solution has no catalytic activity, while the filtrate keeps the same catalytic activity as the original material (compare entries 2 and 3, table 2.13). After the catalytic run, the filtrate solution was analysed by ICP-OES to determine the copper content and the results (0.1% of total Cu originally present in the catalyst) confirmed that leaching is negligible when employing *n*-hexane as the reaction solvent. A blank test (MCM-41 not loaded with copper complex) showed that the silica has no catalytic activity in the present reaction. As often observed for heterogeneised catalysts, the *ees* were in any case slightly lower if compared to the homogeneous system, especially for the *trans* isomer.[203]

Table 2.13 Cu(I)/**Pc-L*** supported complexes for asymmetric cyclopropanation of α-metyhlstyrene [a]

Entry	Run	catalyst	yield (%)[b]	*cis* : *trans*[b]	ee (%)[c] *cis*	ee (%)[c] *trans*
1	1	**10d**	81	62 : 38	55	62
2	1	**10d/D**	72	72 : 28	35	26
3[d]	1	**10d/D**	< 1	-	-	-
	1		74	76 : 24	35	27
4	1	**10d/D**	65	72 : 28	40	31
	2		68	72 : 28	39	32
	3		56	71 :29	41	30
5	1	**10d/S1**	45	71 : 29	35	25
	2		43	72 : 28	42	33
	3		40	70 : 30	38	29
6	1	**10d/S2a**	91	67 : 33	35	24
	2		78	72 : 28	39	30
	3		52	71 : 29	40	30
7	1	**10d/S2b**	57	70 : 30	36	29
	2		73	73 : 27	38	29
	3		58	72 : 28	46	38
8	1	**10d/M2**	53	68 : 32	29	22
	2		77	71 : 29	34	23
	3		75	72 : 28	23	20
9[e]	1	**10d/M2**	97	63 : 37	39	34
	2		88	62 : 38	37	31
	3		99	63 : 37	33	33
10	1	**10d/M1**	67	69 : 31	36	26
	2		71	70 : 30	37	27
	3		78	71 : 29	37	26
	6		65	70 : 30	37	26
	7[f]		37	70 : 30	34	25
11[d,e]	1	**10d/M1**	< 10	59 : 41	46	58
	1		64	64 : 36	58	54
12[e]	1	**10d/M1**	69	64 : 36	58	54
	2		99	63 : 37	53	47
	3		96	63 : 37	n.d.	n.d.
13	1	**10d/A**	73	67 : 33	39	31
	2		99	69 : 31	39	30
	3		91	68 : 32	39	30
14[e]	1	**10d/A**	99	63 : 37	33	33
	2		95	63 : 37	50	51
	3		98	62 : 38	46	48
15[g]	1	**10f/D**	63	68 : 32	-59	-60
	2		71	65 : 35	-65	-56
	3		65	63 : 37	-67	-60

[a] Reactions were performed with [Cu(I)] (3.0×10^{-2} mmol) in *n*-hexane (5 mL). Slow addition of EDA (1 mmol) in *n*-hexane (1 ml) over 100 min at 0 °C. [b] Determined by GC and ^{1}H NMR, with 2,4-dinitrotoluene as internal standard. [c] Determined by chiral HPLC; absolute configurations: *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*); The opposite enantiomers were obtained in the same *ee* when employing **Pc-L*** with a *R* configuration. [d] Sheldon test (upper row). [e] Reaction performed in 1,2-dichloroethane. [f] In the 7th run reaction was slower and further 45 minutes after the addition were needed to reach completion. [g] Opposite enantiomers were obtained.

Compared to the homogeneous reaction (entry 1, table 2.13), better diastereomeric excesses in favour of the *cis* isomer were obtained in *n*-hexane, a fact that is in agreement with those reported for clay-immobilized copper complexes.[204] In a low polarity solvent, in fact, tight ion pairs are to be expected and it is reasonable to assume that in this case, the steric hindrance of the support must favour the preferential formation of the *cis* isomer.[205] It should be pointed out that complex **1** is not soluble in *n*-hexane and thus the reaction cannot be performed in this solvent under homogeneous conditions. On the other hand, reactions in 1,2-dichloroethane yielded to better enantioselectivities, especially for the *trans* isomer (entries 9, 11, 12 and 14, table 2.13). This may well be due to the enhancement of the polarity of the medium that will affect the strength of ion pairs and ions-silica interactions,[206] finally leading to the observed differences in enantioselectivity (it should be pointed out how cyclopropanation reactions can be affected by several parameters in a complex way). The improvement in the yield of the first run in this last cases can be explained with the better solubility of the cyclopropanes in chlorinated solvents. However, in this last solvent, some leached catalyst could be active in solution, as shown by the Sheldon test performed in 1,2-dichloroethane (entry 11, table 2.13). This may explain the higher enantiomeric excesses obtained in the second and third run of the reaction when employing Aerosil 380 as a support (entry 14, table 2.13), while *ee* obtained in *n*-hexane remains constant during all the consecutive runs (entry 13, table 2.13). To further asses eventual leaching of the catalyst employing dichloroethane as reaction solvent, also in this case the filtered reaction mixture after catalysis was analysed by ICP-OES, showing Cu concentrations below 12.4 ppm, corresponding to a maximum leaching of 4.3% of copper present in the catalysts. It should be pointed out that in such low concentration in solution, complex **10d** is a poor cyclopropanation catalyst, especially at 0° C. Copper leaching in chlorinated solvents should be promoted by the presence of EDA.[135, 207] Given the efficacy of the supported catalyst in the cyclopropanation reaction, we tested their reusability both using *n*-hexane and 1,2-dichloroethane as single solvents. As mentioned previously, *n*-hexane appears as a valuable greener solvent with respect to chlorinated ones. It is noticeable that quantitative conversion was still observed and cyclopropanes were obtained in almost unchanged yields, diastereo- and enantio-selectivities in all consecutive runs. All catalysts were recycled at least three times, without any noticeable deactivation. In particular, in the case of catalyst **10d/M1** the reaction was repeated for several consecutive runs and only after the seventh recycle (two days) a decrease in activity was observed. It is well known that silica can act as ligand for copper leading to non-enantioselective catalytic processes.[208] We guess that this must not be the case in the present system, since if that

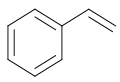
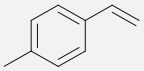
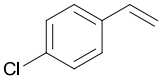
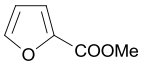
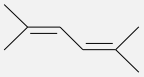
where truth we should expect a progressive decrease in the enantioselectivity after consecutive runs. To further exclude this hypothesis, in order to remove eventual free copper species from the reaction mixture, the catalyst was washed with 1,2-dichloroethane after the first run in *n*-hexane. Then, the reaction was repeated using the hydrocarbon solvent and no change in yield, diastereo- and enantioselectivity was observed.

When employing the bulkier *tert*-butyl diazoacetate, *t*BuDA, (conditions as in the caption to table 2.13, **10d/D** as supported catalyst) together with lower yields (35% average of three runs) we observed a decrease in the enantioselectivities (*ee cis* 19%, *trans* 20%) and a complete drop of the diastereoselectivity (*cis* : *trans* = 50 : 50). Similar negative effects related to the diazoacetate steric hindrance have been observed also in the homogeneously catalysed reaction[81] and have been explained in terms of overcrowding of the transition state.[169]

Finally, since the Cu(I) complex, **10f** of the more sterically hindered ligand, possessing two further stereocenters on the ring skeleton (6-[(*R*)-1-naphthylethyl]-3,9-ditosyl-3,8-[(*S*,*S*)-*iso*-propyl]-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene), gave the best results in term of enantioselectivity in the homogeneous phase,[111] we next studied its reactivity when supported on silica. Again commercial Davisil LC150 was chosen as support. A complete conversion of the starting EDA was observed also in this case (entry 15, Table 1), although we should point out that the reaction in the third run was slightly slower and further 15 minutes after the addition were needed to reach completion. Remarkably, **10d/D** and **10f/D** gave cyclopropane products in very similar yields (compare entry 4 with entry 15, table 2.13). It should be pointed out that complex **10f** under homogeneous conditions gave equal amounts of both isomers whilst, when supported on Davisil, a slight preference for the *cis* isomer is again obtained. As expected, observed enantiomeric excesses were higher (67% for the *trans*, 60% for the *cis* isomer).

Under optimal conditions, other alkenes were employed to determine the substrate scope of the copper catalysed cyclopropanation reactions. Since the results in terms of diastereo- and enantioselectivity were comparable for all tested materials, the less expensive commercial Davisil silica was chosen as support. At a Cu(I)/EDA/alkene ratio of 1:35:170, the formed complex catalysed the reaction of all the tested substrates yielding the cyclopropanes in acceptable yields and enantioselectivities. It should be pointed out that for these substrates, reported yield have been determined by quantitative ^{1}H NMR and based on EDA. However, the high volatility of some cyclopropane products requires a careful removal of the reaction solvent. Fumarate and maleate were again the only detected side products. All the collected data are summarised in table 2.14.

Table 2.14 Asymmetric cyclopropanation of alkenes by **10d/D** [a]

Entry	Alkene	Yield (%)[b]	*cis* : *trans*[b]	ee (%)[c]	
				cis	*trans*
1		36	61 : 39	45	35
		33	61 : 39	37	29
		35	61 : 39	38	30
2		59	58 : 42	42	35
		65	60 : 40	39	35
		68	57 : 43	39	35
3		48	56 : 44	42	38
		61	56 : 44	42	38
		50	56 . 44	42	38
4		33	-	21	
		36	-	23	
		29	-	25	
5		46	> 1 : 99	n.d.	49
		43	> 1 : 99	n.d.	49
		44	> 1 : 99	n.d.	44
6[d]		37	60 : 40	38	33
		37	60 : 40	38	33
7[e]	*n*-octene	50	56 : 44	40	35

[a] Reactions were performed with [Cu(I)] (3.0×10^{-2} mmol) in *n*-hexane (5 mL). Slow addition of EDA (1 mmol) in *n*-hexane (1 ml) over 100 min at 0 °C. [b] Determined by ^{1}H NMR, with 2,4-dinitrotoluene as internal standard. [c] Determined by chiral HPLC; absolute configurations: for entries 1–3 *cis*-cyclopropanes were (1*R*,2*S*), *trans*-cyclopropanes were (1*R*,2*R*); entry 4: the absolute configuration was (1*R*), entry 5: *trans*-cyclopropane was (1*S*, 2*S*, 6*S*)**.** For entries 6 and 7 were not determined. [d] Cu(I)/ EDA/olefin = 1: 35:500; isolated yield. [e] *n*-Octene as the solvent: Cu(I)/ EDA/olefin = 1:35:1060; isolated yield.

The absence of α-substituents on the styrene affected the diastereoselectivity of the reaction, although also in this case a slight *cis* preference was observed compared to the results obtained in the homogeneous phase.[81] We have obtained almost indistinguishable diastereo- and enantioselectivities using styrene (entry 1, table 2.14), 4-methyl styrene (entry 2) and 4-chloro styrene (entry 3). Enantioselectivities obtained for the *cis* cyclopropane products with those substrates were higher than those observed in the homogeneous reactions.[81] Low yields and enantioselectivities were obtained with diphenylethylene (entry 4, table 2.14). Interestingly, benzophenone (less than 10% with respect to starting diphenylethylene) was found in this case amongst the reaction products.

To explore the scope of the reaction, we next studied the cyclopropanation of two different dienes. Excellent diastereoselectivity to yield the desired *trans* isomer (attack only at the non-substituted double bond), was obtained with methyl-2-furoate (entry 5, table 2.14).[172] With 2,5-dimethyl-2,4-hexadiene the catalytic reaction yielded the desired cyclopropanes (cyclopropanation of only one double bond was observed[171]) although in modest yields (37%, isolated yield), if a large excess of the olefin (Cu/EDA/olefin = 1:35:500) is employed (entry 6,

table 2.14). Worth to note, slightly higher *ees* with respect to the homogeneously catalysed reaction were observed.

Even aliphatic alkenes that are generally less reactive in cyclopropanation reactions,[174] gave very good results. For instance, the cyclopropanation occurs also with reasonable yields with the non-activated double bond of *n*-octene, although in this case the olefin has been used as the solvent (entry 7, table 2.14).

As mentioned before in the description of supported catalysts (section **2.3**), they were analysed by DRIFT spectra and by CO-DRIFT spectroscopy. In general they showed very robust catalyst that remained stable under the reaction conditions. Moreover the catalysts were investigated at the end of the catalysis by IR spectroscopy. IR spectra confirmed the intact Cu complex structure, showing the presence of all the bands in the skeletal range of the spectrum typical of **10d**. These results confirmed that the grafted complex is stable under the reaction conditions. The presence of bands at 2986 and 1746 cm^{-1} suggests the presence of adsorbed –COOR compounds (IR spectra of reaction products pure cyclopropanes show similar bands located at 2980 and 1730 cm^{-1}) (figure 2.24).

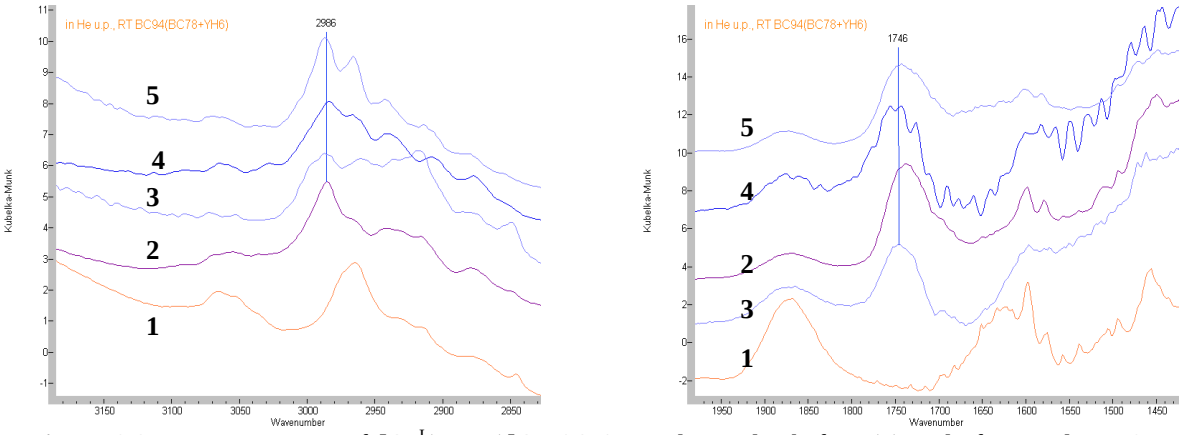


Figure 2.24 DRIFT spectra of [Cu^{I}(Pc-L*)]CF_3SO_3/Davisil samples before (**1**) and after catalysis: **2**, 4-chloro styrene + EDA; **3**, 4-methyl styrene + EDA; **4**, α-methyl styrene + EDA; **5**, α-methyl styrene + EDA (after 3 cycles and washing in 1,2-dichloroethane); characteristic bands of cyclopropanation products (pure cyclopropanes) at 2980 and 1730 cm^{-1}.

Coordination of by-products[206] (diethyl maleate and fumarate) and formation of diazoacetate polymers[209] have been proposed in the literature as possible deactivation processes for bis(oxazoline) copper complexes. Also in the present system slightly longer reaction times, after the third run, were observed.

2.5.2 Cyclopropanation reaction under FLOW conditions

Immobilized catalysts are used in flow conditions, especially in industry, where the reagents and products continuously pass through the catalytic bed. During my PhD research project we have tested our SHB copper(I) catalysts (described in section **2.3**) in asymmetric cyclopropanations under flow condition. We tested, in our catalysis under flow, both DCE and CO_2 as solvent. All the catalysts (table 2.15) were prepared with impregnation method 2, thus the synthetized copper(I) complexes were not isolated from the solvent but directly used after its synthesis in the dissolved form (for further details, see *Experimental Part* section **3.6**).

Table 2.15 Cu loadings (determined by ICP-OES), of $[Cu^{I}(Pc\text{-}L^{*})]CF_3SO_3/SiO_2$ samples.[a]

Entry	SiO_2 support	Cu loading [wt. %]
10d/M2	MCM-41 (6170) [a]	0.850
10d/D	Davisil LC150	0.840
10d/A	Aerosil 380	0.812
10f/D	Davisil LC150	0.657

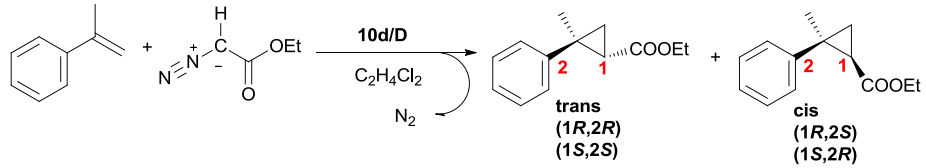
[a] **General procedure:** Metal loadings are determined by ICP-OES using a Thermo X Series II apparatus. 15 mg of each sample are mineralized by adding 3 mL of 37% HCl, 1 mL of concentrated HNO_3, 1 mL of 98% H_2SO_4

The catalytic reactions were carried out on a specially designed rig, the design of which has previously been reported[210] using a stainless steel tubular reactor with a volume of 8.8 cm^3. The supported catalyst was loaded into a metal tubular reactor in a glove box. The bed was fixed with stoppers of dried glass wool used to prevent it being flushed from the reactor. This tube was then held vertically in an aluminium heating block. All reactions were carried out with the tubular reactor held vertical and with the flow being from bottom to top. Substrate ratios and flow rates are described later in table captions. All reported yields and diasteroselectivities have been determined by quantitative ^1H NMR spectroscopy and are based on EDA, using 2,4-dinitrotoluene as internal standard. The average (conversion, selectivity, *cis/trans* ratios and *ees*) values of all collected samples are here reported and for data for each sample see *Experimental Part* section **3.9**. Diethyl-fumarate and maleate, derived from EDA coupling, were the only side products detected and they accounted for the rest of the mass balance of the reaction.

In order to easily compare the results obtained in the homogenous phase[111] with respect those under heterogeneous in flow condition, we optimised the conditions for the benchmark cyclopropanation reaction employing DCE as the solvent. As a benchmark reaction we chosen the cyclopropanation of α-methylstyrene, an alkene which is known to give cyclopropanes with

low diasteroselectivity[211] and that undergoes polymerization less easily with respect to styrene, with EDA. As previously mentioned catalysis in homogenous phase was not performed in *n*-hexane since complex **10d** is not soluble and DCE was found to be the solvent that gave the best results in term of conversion. Optimization of the reaction under flow conditions was subsequently investigated and the collected data for the cyclopropanation in DCE employing catalysts **10d/D** are summarize in Table 2.16, compared with a typical results for the same reaction conducted in the homogenous[111] and in heterogeneous phases under batch conditions.[138]

Table 2.16 Catalyst **10d/D** for asymmetric cyclopropanation of α-methylstyrene [a]



Entry	Run	Flow (mL/min)	Time (min)[b]	Selectivity (%)[c]	Conversion (%)[c]	*cis* : *trans*[c]	*ee* (%)[d] *cis* (1*R*,2*S*)	*ee* (%)[d] *Trans* (1*R*,2*R*)
1[e]	-	-	100	81	>99	62:38	55	62
2[f]	-	-	100	72	>99	72:28	35	26
3	1	0.2	381	66.2	>99	56:44	34	15
	2[g]		399	64.6	39-4	46:54	25	14
	3[h]		385	n.d.	<5	-	-	-
4[i]	1	0.2	394	57.3	>99	59:41	36	23
5	1	0.1	668	56.9	>99	61:39	25	26
6	1	0.5	346	60.5	>99	63:37	58	29
	2[j]		121	55.6	99-11	54:46	38	30

[a] Reactions were performed with [Cu(I)] (5.0×10^{-2} mmol), EDA/α-mehylstyrene ratio = 1:5. [EDA] = 0.17 mol/L in DCE at room temperature. [b] Total time of the single flow run. [c] Conversion and selectivities determined by ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard. Fumarate and maleate accounted for the rest of mass balance. [d] Determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/*i*-PrOH = 99.25:0.75). [e] Reaction was performed with equimolar amounts of [Cu(I)] (3.0×10^{-2} mmol) and **4d** in DCE (5 mL) . Cu/**4d**/EDA/α-mehylstyrene 1:1:35:170, in homogeneous phase. The DCE solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes. [f] Reactions were performed with [Cu(I)] (3.0×10^{-2} mmol) with **10d/D** in *n*-hexane (5 mL). Cu/EDA/α-mehylstyrene 1:35:170, in heterogeneous phase in batch. The *n*-hexane solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes. [g] In this run we observed a progressive deactivation of the catalytic system, and instead of the average conversion value, the range is reported. The selectivities and *ees* reported instead are those averaged. [h] The catalyst became completely inactive at the third run. Only traces of *cis* cyclopropane were detected in the first collected sample. [i] A more dilute system was tested: [EDA] = 0.085 mol/L in DCE. [j] We observed a progressive deactivation of the catalytic system, and instead of the average conversion value, the range is reported. The selectivities and *ees* reported instead are averages.

The ratio between EDA and α-methylstyrene was at first maintained at 1:5 with [EDA] = 0.17 M as in the homogeneous phase. In fact a fivefold excess of the alkene has to be used to minimise the side product derived from EDA self-condensation. Interestingly, we always observed complete conversion of the starting EDA in the first reaction runs, with a good chemoselectivity in cyclopropane products. We performed the reaction by testing different flows

and substrate concentrations.

A 0.2 mL/min flow was first tested and complete conversion with good chemoselectivity (66%) was obtained with the selectivity remaining constant during all the time needed for the reagent solution to be eluted (from the reactor (381 min, entry 3, run 1, table 2.16). The EDA conversion only decreased slightly (91%) in the last collected sample (see *Experimental part* section **3.9.1**). However, the obtained results in term of *cis*/*trans* ratio and enantioselectivities were lower than those obtained in the homogeneous phase and in batch reactions employing *n*-hexane as solvent. The catalyst was then recycled for a second run by flowing a fresh mixture of α-methylstyrene and EDA in DCE (same amounts used for the first run). In this case we noticed that the catalyst has lost its initial activity (39% conversion of the added EDA). Progressively the conversion decreased to <4% at the end of the reaction (TON = 399 – overall 780 minutes, entry 3, run 2, table 2.16). The chemoselectivity of the system in cyclopropanated products, however, remained almost unaffected, while the diastereo- and enantio-selectivities were slightly reduced. In order better to understand the nature of the deactivation process (*i.e.* poisoning of the catalyst by the cyclopropane products), after a DCE washing, new fresh reagents were introduced and a third run was performed (entry 3, run 3, table 2.16). No conversion of EDA was observed meaning that a complete deactivation of the catalyst occurred after prolonged reaction times. Under batch conditions employing DCE as solvent, we observed some apparent copper leaching under the reaction conditions (4.3% of the total copper originally present in the catalyst).[111] ICP-OES analysis of the silica post-catalysis showed a copper content lower than in the starting material (determined copper loading = 0.60%). However, the silica material after catalysis has some adsorbed organic compounds (see below) that can explain the lower copper content. Moreover, the amount of Cu(I) would still be enough to guarantee some catalytic activity and thus leaching alone cannot explain the observed complete deactivation of the supported catalyst. A big difference from our previous work in the homogeneous phase and under heterogeneous batch conditions, was that we did not run the catalytic reaction under a protective atmosphere and we employed commercially available solvents and reagents without any further distillation. So, the deactivation of the catalyst may also due to a reduced stability of the Cu(I)-complex under these conditions.

We next optimized the reaction conditions by changing the reagent concentrations and the flow rate. A more diluted system - half concentration of reagents - was tested (entry 4, table 2.16) In this case a lower chemoselectivity was obtained although diastereo- and enantio-selections were slightly improved. Again, we observed a decrease in the stereoselective outcome of the reaction

after prolonged times. Different flow rates (0.1 and 0.5 mL/min) were subsequently tested. The 0.1 mL/min flow is probably too low because a slight decrease of overall cyclopropane selectivity was observed (entry 5, table 2.16). Better results were achieved with 0.5 mL/min flow (entry 6, run 1, table 2.16). To our delight, under those conditions the best results in term of diastereo- and enantio-selection were obtained, meaning that under those flow conditions the catalytic system worked even better than in batch. Unfortunately, during the second run again a decrease of chemoselectivity was observed together with a decrease in activity (entry 6, run 2, table 2.16). Comparing the collected data with respect to reaction in the homogenous (entry 1, table 2.16) and heterogeneous phases under batch conditions (entry 2, table 2.16) under flow conditions higher TONs based on EDA converted per mol of catalyst were achieved, but with a general decrease in chemoselectivity. Notably in these catalytic system starting materials were mixed together and the reactor was fed straight with the mixture and all the catalysis were performed a R.T. Conversely, in the homogenous phase EDA was slowly added by a syringe pump over 100 minutes at 0°C in order to avoid the formation of the homocoupled products. Despite the higher temperature, however, the *ees* obtained were closed to or even better than those recorded under batch conditions. The leaching of the catalyst employing DCE as a vector, however, is still a problem to be faced. Random samples have been analysed in order to determine the amount of copper leached during the catalysis. In DCE, a copper content up to 3788 ppb (1.9 % of total copper) was found.

Our intent was to shift to a more sustainable and greener system using carbon dioxide in place of DCE as the flowing solvent. CO_2 was chosen because it can reach the supercritical state under moderate conditions of pressure and temperature, avoiding the degradation of thermolabile and volatile substances and providing simultaneously an inert medium suitable for been used as a vector.[139d] The critical point of pure CO_2 is 73.8 bar and 31.1 ^{o}C. However, with the substrates and flow rates involved it is likely that the system should be considered as operating in an expanded liquid phase. Previous studies have shown that such expanded liquids can give superior performance under flow conditions.[210b]

Maintaining the ratio 1:5 with EDA/α-methylstyrene, complex **10d**, grafted on the three different type of silica, was tested under flow condition with carbon dioxide (table 2.17). Reactions in CO_2 were carried out at 40 °C (while the best *ees* in the homogeneous phase reactions were carried out at 0 °C).

Table 2.17 Asymmetric cyclopropanation of α-methylstyrene by EDA with supported complex **10d** under CO_2 flow.[a]

Entry	Run	catalyst	Time (min)[b]	Selectivity (%)[c]	Conversion (%)[c]	*cis* : *trans*[c]	*ee* (%)[d] *cis* (1*R*,2*S*)	*ee* (%)[d] *Trans* (1*R*,2*R*)
1	1	**1/D**	468	65.8	>99	67:33	36	34
	2		159	65.5	>99	68:32	44	26
2[e]	1	**1/D**	543	46.3	>99	62:38	38	25
3[f]	1	**1/D**	603	72.7	>99	72:28	36	27
4	1	**1/M2**	470	87.9	>99	59:41	40	29
5	1	**1/A**	472	72.2	>99	57:43	33	21

[a] Reactions were performed with [Cu(I)] (5.0×10^{-2} mmol), EDA/α-methylstyrene ratio = 1:5, T = 40°C, p_{CO2} = 130 bar, flow CO_2 = 0.5 mL/min, flow HPLC = 0.02 mL/min. [b] Total time of the single flow run. [c] Conversion and selectivities determined by ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard. Fumarate and maleate accounted for the rest of mass balance. [d] Determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75). [e] Reaction was performed with EDA/α-mehylstyrene 1:2. [f] Reaction was performed with EDA/α-mehylstyrene 1:10.

Initially, the catalyst **10d/D**, used for screening catalysis in DCE flow, was tested also under CO_2. The CO_2 pressure was adjusted to 130 bar, with a flow rate of 0,5 mL/min. The reagents were fed at 0,02 mL/min *via* an HPLC pump. Again, complete conversion of EDA was observed and in this case, the reaction products were just collected and weighted every half-hour and analysed by quantitative ^{1}H NMR after the addition of 2,4-dinitrotoluene as internal standard. The chemoselectivity of the reaction towards cyclopropanes was similar to that observed in DCE, but interestingly, in this case the *cis*/*trans* ratio was closer to the value observed in optimised batch conditions employing *n*-hexane as solvent (compare entry 1, table 2.17 with entry 2, table 2.13). Moreover, in this case no deactivation of the catalyst was observed and quantitative conversion of the EDA was also obtained in the second run. We next monitored the effect of different ratio between EDA/α-methylstyrene on the reaction outcome. A decrease of the fivefold excess of alkene to a ratio 1:2 of EDA/α-methylstyrene resulted, as expected, in a lower chemoselectivity, while the *ees* values for both isomers were almost unaffected (entry 3, table 2.17). When a 10-fold excess of α-methylstyrene was used, a better chemoselectivity and a higher diasteroselectivity in favour of the *cis* isomer were observed (entry 3, table 2.17). On the other hand, the enantioselectivity was unaffected by a tenfold excess of alkene.

In last two entries (entries 4 and 5, table 2.17) the complex **10d** grafted on MCM-41 (**10d/M2**) and on Aerosil (**10d/A**) respectively, was used as catalyst, in order to test a possible confinement effect provided by the support. Under batch conditions, experimental data showed only a very weak dependence of the reaction efficiency upon the surface area characteristics of the silica and almost indistinguishable diastereo- and enantio-selectivities using commercial Davisil, Aerosil,

preordered mesoporous MCM-41 silica were obtained.[138] Under CO_2 flow, we observed a slight decrease in the *cis* selectivity with both MCM-41 and Aerosil as a support, but a better yield of cyclopropanes was obtained, especially with **10d/M2** as the catalyst. Again, random samples have been analysed in order to determine the amount of copper leached into the flowing medium. A maximum of 10.8 ppb and 4,3 ppb for compounds **10d/M2** and **10d/D**, respectively, of copper were found by ICP-OES analysis of the reaction products, meaning that under those conditions the copper metal atom is strongly bound to the ligand. Although ultra-pure acids have been used for the mineralization process, ppb amounts of copper have also been found in blank test analyses.

Finally, since the chiral Cu(I) complex **10f** gave the best results in terms of enantioselectivity in the homogeneous phase,[111] and subsequently its reactivity was studied when supported on Davisil B in batch conditions,[138] we next tested the catalytic performances of **10f/D** in asymmetric cyclopropanation reactions under CO_2. The less expensive commercial Davisil silica was chosen as the support. Davisil B was also used as our benchmark silica in heterogeneous phase batch[138] since the possibility of using commercially available silica as a support in the system was very interesting and could pave the way for the employment of this immobilization technique in laboratories not equipped for the synthesis of mesoporous materials. For the sake of clarity, the results obtained using CO_2 under optimised conditions employing catalyst **10f/D** are reported in table 2.18 and compared to those obtained in the homogeneous phase (DCE as solvent, entry 2, table 2.18) and in heterogeneised batch reactions (*n*-hexane as solvent, entry 3, table 2.18) with the same copper(I) complex **10f**. Complex **10f** has the opposite configuration at the α-naphthylic stereogenic carbon C13 (see figure 2.1), thus affording the opposite enantiomeric excesses in the cyclopropanation reaction.

Under CO_2 with catalyst **10f/D**, again complete conversion of EDA was obtained (entry 1, table 2.18). After the first run, a second consecutive reaction was performed, by charging the reactor with fresh α-methylstyrene and EDA in the same concentrations and relative ratios, and the reactor was fed overnight (entry 1, run 2, table 2.18). For that reason, in this case, products were collected only at the end of the run. No deactivation of catalyst was observed, but instead the chemoselectivity of the catalytic system seemed to improve with time (see later). Again, we did not observe any metal leaching and a maximum of 3.2 ppb of copper was found in the collected samples. The catalyst was stable over at least 23 hours, with constant quantitative conversion of added EDA. Again *ees* under CO_2 were similar to those obtained in heterogeneous phase batch reactions, despite the fact that higher temperature are normally detrimental for

enantioselection.[212] In CO_2 the reactions were carried out at 40°C while homogeneous phase and heterogeneous phase batch reactions were run at 0°C.

The turn over number was improved up to 440 with respect to homogenous phase (30) and heterogeneous phase batch (90) reactions. In these last two catalytic system the TON was limited by the slow addition of the EDA solution to the alkene and the high concentration of the catalyst needed for the reaction to proceed to complete conversion.

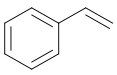
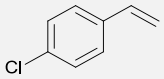
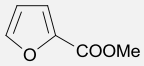
Table 2.18 Catalyst **10f/D** for asymmetric cyclopropanation of α-methylstyrene under CO_2, compared with results obtained with the same copper(I) complex **10f** in homogeneous and heterogeneous phases.

Entry	Run	Time (min)[a]	Selectivity (%)[b]	*cis* : *trans*[b]	*ee* (%)[c] *cis* (1*R*,2*S*)	*ee* (%)[c] *trans* (1*R*,2*R*)	TON
1[d]	1	518	68.6	57:43	58	68	~440
	2	830	74.0	50:50	59	70	
2[e]	-	100	98	50:50	88	99	30
3[f]	1	100	63	68:32	60	59	90
	2	100	71	65:35	56	65	
	3	100	65	63:37	60	67	

[a] Total time of the single flow run. [b] Conversion and selectivities determined by ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard. Fumarate and maleate accounted for the rest of the mass balance. In all cases complete conversion of the starting EDA was observed [c] Determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75). [d] Reactions were performed with [Cu(I)] (4.0×10^{-2} mmol), EDA/α-methylstyrene ratio = 1:5, T =40°C, P_{CO2} = 130 bar, flow CO_2 = 0.5 mL/min, Flow HPLC 0.02 mL/min. For the second run, fresh reagent were added and the reaction was left over night. The reaction products were analysed after the end of the single run. [e] Reaction was performed with equimolar amounts of [Cu(I)] (3.0×10^{-2} mmol) and **4d** in DCE (5 mL) . Cu/**4d**/EDA/α-mehylstyrene 1:1:35:170, in homogeneous phase. The DCE solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes. [f] Reactions were performed with [Cu(I)] (3.0×10^{-2} mmol) with **10d/D** in *n*-hexane (5 mL). Cu/EDA/α-mehylstyrene 1:35:170, in heterogeneous phase in batch. The *n*-hexane solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes.

To explore the substrate scope, different alkenes were tested under the optimized conditions using supported catalyst **10f/D** (table 2.19).

Table 2.19 Asymmetric cyclopropanation of alkenes by **10f/D** under CO_2 [a]

Entry	Run	Alkene	Time (min) [b]	Selectivity (%)[c]	Conversion (%)[c]	*cis* : *trans* [c]	*ee* (%)[d] *cis*	*ee* (%)[d] *trans*
1	1		547	65.5	>99	32:68	62	55
	2 [e]		886	69.8	>99	31:69	56	55
2	1		582	77.7	>99	48:52	43	72
3	1		565	51.7	>99	-	65	
4	1		542	33.1	>99	> 1:99	-	67
5[f]	1	1-octene	477	71.2	>99	48:52	68	40

[a] Reactions were performed with [Cu(I)] (4.0×10^{-2} mmol), EDA/alkene 1:5, T =40°C, P_{CO2} = 130 bar, flow CO_2 = 0.5 mL/min, flow HPLC 0.02 mL/min. All reagents were not distilled but used as received. Reactions were monitored every hour and average values for selectivity, conversion, *cis*/*trans* ratio and *ees* are reported. [b] Total time of the single flow run. [c] Conversion and selectivities determined by ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard. Fumarate and maleate accounted for the rest of the mass balance. [d] Determined by chiral HPLC; absolute configurations: for entries 1–2 *cis*-cyclopropanes were (1*S*,2*R*), *trans*-cyclopropanes were (1*R*,2*R*); entry 3: the absolute configuration was (1*S*)**.** For entry 4 *trans*-cyclopropane was (1*R*,5*R*,6*R*); for entry 5 the absolute configurations were not determined. (See SI for details). [e] Reaction performed overnight and checked only at the end. [f] Reaction was performed with EDA/alkene 1:10.

At an EDA/alkene ratio of 1:5 with [Cu(I)] (4.0×10^{-2} mmol), **10f/D** catalysed the reaction of all the tested substrates and in all cases complete conversion of EDA was observed. Reported conversion and selectivities have been determined by quantitative ^{1}H NMR and are based on EDA. Fumarate and maleate were again the only detected side products. Catalysis was at first performed with styrene in order to study the influence of the absence of α-substituents on the styrenic double bond (entry 1, table 2.19). As expected, the diastereoselectivity of the reaction was strongly affected, in favour of the less hindered *trans* isomer. A similar effect was observed also in the homogenous phase. Again the second run for that alkene was performed overnight (25 hours of continuous reaction).

Reporting the observed chemoselectivity (%) *vs* time (minutes) obtained with α-methylstyrene (table 2.18, entry 1) and styrene (table 2.19, entry 1), we observed that in both cases selectivity increased during the catalysis (figure 2.25). No catalyst deactivation was observed in both cases, indicating that the catalyst could perform catalytic reactions for prolonged times.

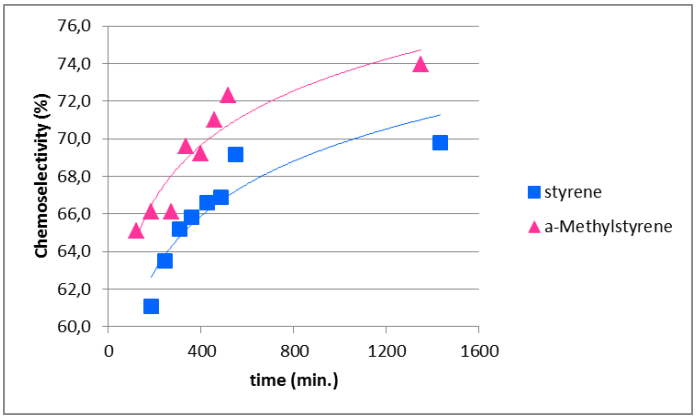


Figure 2.25 Chemoselectivity (%) *vs* time (minutes) of styrene and α-methylstyrene catalysed by **10f/D**.

The observed increase of the chemoselectivity of the reaction upon prolonged times is difficult to rationalise at the present stage, since we could not perform any kinetic study under the employed reaction conditions. In fact, reactants are fed with the same concentration and at the same rate through the catalytic run. It is generally accepted that the copper(I) catalysed cyclopropanation reactions proceed *via* a copper-carbene complex and both mechanistic and computational studies have indicated that copper(I)/olefin complexes in these systems might act as either catalytically active species or resting states[213] Assuming that the formation of the metal-carbene complex is the rate determining step,[214] the chemoselectivity depends on the ratio of the rate constants for the EDA dimerization and the cyclopropanation reaction.[215] To justify the observed improved chemoselectivity to reach a plateau in more than 8 hours of reaction when the relative ratios of EDA and olefins remains unaltered, we can speculate that the silica support has a role in increasing the effective local concentration of the olefin near to the catalytic sites during the reaction progress.

The best yields of cyclopropanes were obtained in the case of 4-chlorostyrene (entry 2, table 2.19), a result that was observed also in the homogenous phase. Also the diastrereoselectivity and the enantioselectivity observed for the *trans* isomer were very close to those obtained employing complex **10f** in DCE. Even in the presence of a bulky substrate such as 1,1-dipheylethylene (entry 3, table 2.19) a conversion up to 99% was achieved, with a selectivity higher than those observed in the homogeneous reactions. The reaction was not limited to aromatic alkenes. Good results were achieved with methyl-2-furoate with excellent diastereoselectivity where only the desired *trans* isomer (attack at the non-substituted double bond), was obtained (entry 4, table 2.19). Also aliphatic alkenes gave very good results. For instance, the cyclopropanation occurred even with the non-activated double bond of 1-octene with good enantioselectivity, although in this case the ratio of alkene / EDA was increased to

10:1 (entry 5, Table 5). A very good chemoselectivity (71%) was achieved and this result is comparable with that for the homogenous counterpart (73%) (see section **3.4.**1 table 2.19). Moreover, enantioselectivities (*ee* up to 72% for the *cis* isomer and up to 42% for the *trans* isomer) very close to those obtained in the homogenous case (75% and 55%), were observed (see section **3.4.1** table 2.19).

Reporting the chemoselectivity (%) *vs* time (minutes) for all the tested alkenes, selectivity generally increased during the catalytic run (figure 2.26). Only in the case of methyl-2-furoate as substrate was a progressive decrease of this value over time observed.

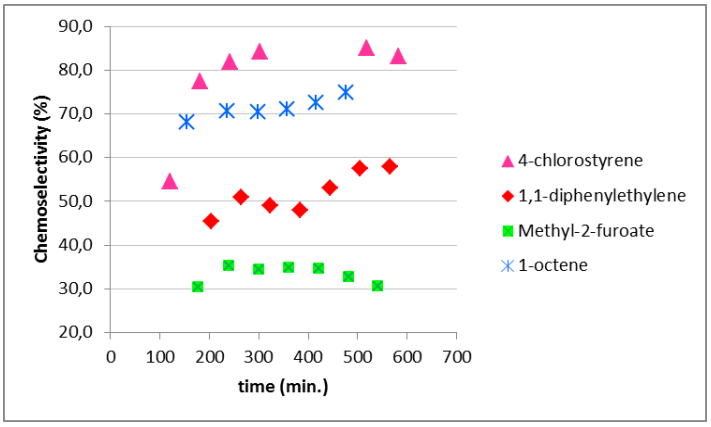


Figure 2.26 Chemoselectivity (%) *vs* time (minutes) of the cyclopropanation reaction of different olefins catalysed by **10f/D**.

In order to check the effect of different substrates on copper leaching employing CO_2, random samples of all the performed catalytic tests were also analysed by ICP-OES (for the complete series of collected data see *Experimental Part* section **3.9.2**). Again, negligible copper leaching was observed in all cases, except for methyl-2-furoate, where values up to 122.5 ppb of copper were obtained. This last results demonstrate that effectively, the presence of an oxygen donor atom in the substrate might be detrimental for the catalyst stability.

At the end of the catalysis, supported catalyst were analysed by DRIFT spectra and by CO-DRIFT spectroscopy. Consistently with the previously characterization of supported copper(I) catalysts in heterogeneous phase in batch, section **2.5.1**, DRIFT spectra showed that the Cu complexes are grafted without any modification of the ligand structure, since the IR absorption bands, detected for **10d/ D, A, M** and **10f/D**, did not show any appreciable modification with respect to solid **10d** or **10f**, either in location, or in intensity.

Grafted complexes were investigated also after the catalytic runs. DRIFT spectroscopy, again, confirmed that the structures of Cu complexes are stable under the reaction conditions, showing the presence of all the bands in the skeletal range of the spectrum typical of **10d** and **10f** (figure 2.27).

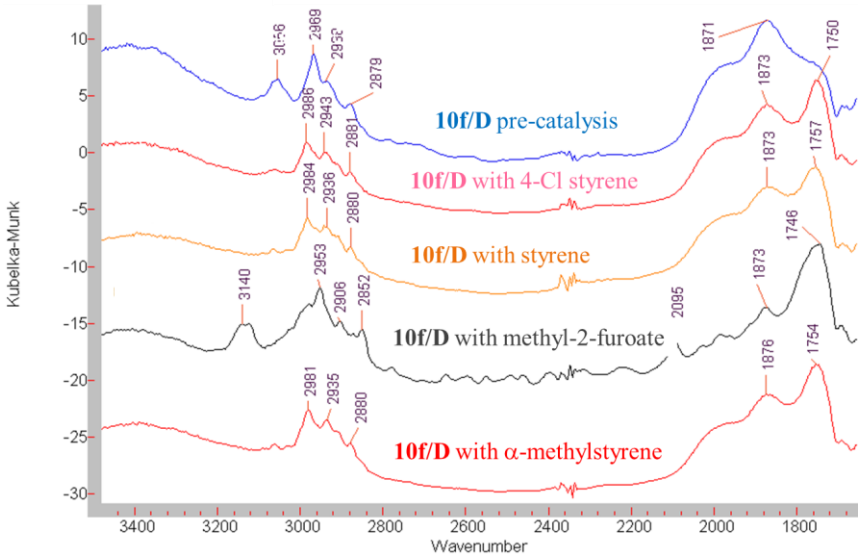


Figure 2.27 DRIFT spectra showing the comparison of catalyst **10f/D** pre- and post-catalysis with different alkenes and EDA.

However, in most cases the presence of an intense absorption band, located around 1750 cm^{-1}, in samples collected at the end of catalytic runs, suggest the presence of adsorbed reaction intermediates. Preliminary experiments, conducted in dichloroethane solutions, revealed the occurrence of an interaction between ethyl maleate and ethyl fumarate and the copper complex, that give rise to a band at 1713 cm^{-1}(figure 2.28 and 2.29). Thus, products, adsorbed on the sample after reactions seems, to be of different nature.

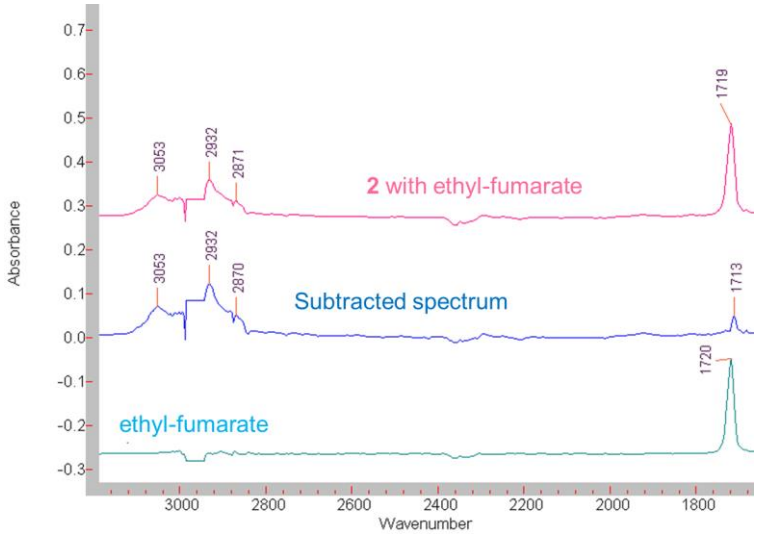


Figure 2.28 Spectra in 1,2-DCE of catalyst **10f** with ethyl-fumarate, showing the interaction of this molecule with the catalyst.

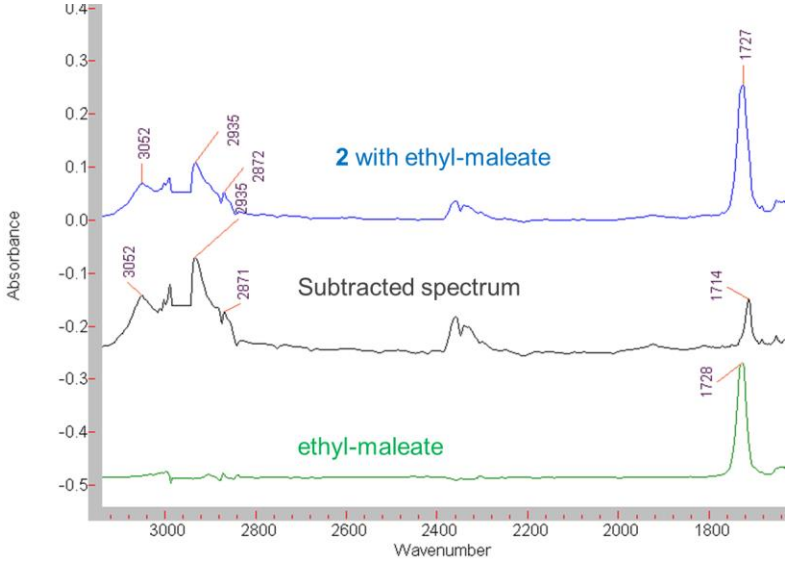


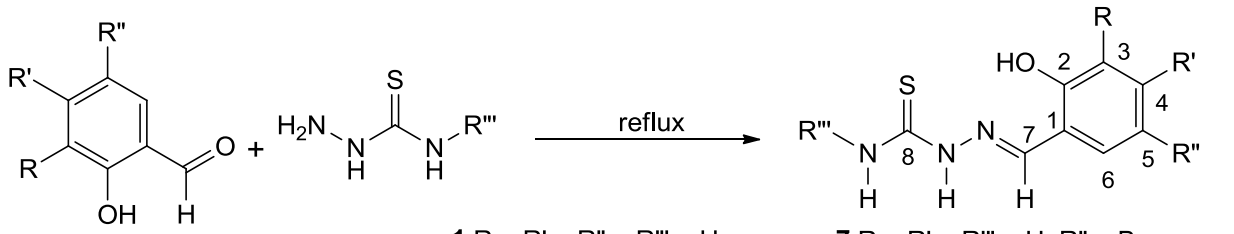
Figure 2.29 Spectra in 1,2-DCE of catalyst **10f** with ethyl-maleate, showing the interaction of this molecule with the catalyst.

2.6 Tiosemicarbazone complexes

2.6.1 Synthesis of ligands and complexes

Our group has recently reported that Schiff bases derived from the condensation of hydrazinecarbothioamide or phenyl thiosemicarbazone with 3-acetyl-2*H*-chromen-2-one are suitable ligands for the synthesis of copper (II) complexes very active as cyclopropanation catalysts.[216] The structure of the thiosemicarbazide moiety confers a good chelating capacity and the latter can be increased by employing a suitable aldehyde or ketone for the formation of the Schiff base possessing a further donor atom to render the ligand tridentate.[217]

During the course of my thesis, we synthetized Schiff bases derived from the condensation reaction of hydrazinecarbothioamide with substituted salicylaldehydes that are suitable ligands for copper. Ligands were synthesized by reacting hydrazinecarbothioamide with substituted salicylaldehydes in refluxing ethanol (scheme 2.20).



1 R = R' = R'' = R''' = H
2 R = R'' = t-Bu; R' = R''' = H
3 R = OMe; R' = R'' = R''' = H
4 R = R'' = R''' = H; R' = NEt_2
5 R = R'' = Cl; R' = R''' = H
6 R = R'' = Br; R' = R''' = H

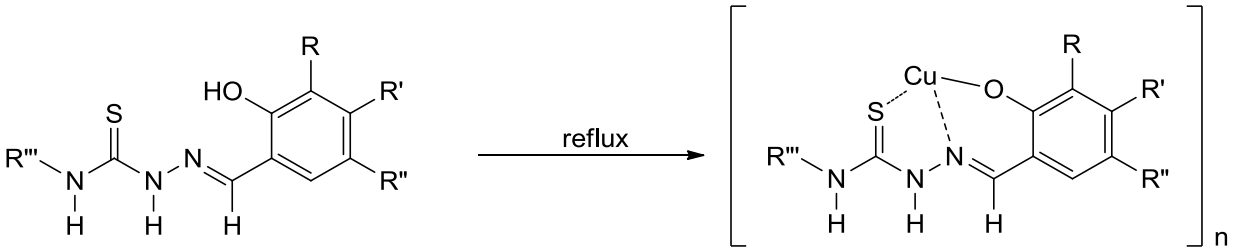
7 R = R' = R''' = H; R'' = Br
8 R = R'' = F; R' = R''' = H
9 R = R' = R'' = H ; R''' = Et
10 R = R' = R'' = H ; R''' = Ph
11 R = R'' = t-Bu; R' = H; R''' = Ph

Scheme 2.20 Formation of the tiosemicarbazone ligands H_2L (**1-11**) and numbering scheme adopted.

Pure ligands could be obtained by simple recrystallization from ethanol. Only in the case of ligand **2** it was necessary to perform a column chromatography over silica in order to obtain a compound free from traces of hydrazinecarbothioamide.

The copper complexes were synthesized by treating the ligands in refluxing ethanol with copper(II) acetate monohydrate dissolved in the minimum required amount of methanol (scheme 2.21). In all cases the formation of a dark green or brown precipitate was observed at the very beginning of the addition of the copper acetate. The reaction mixture was then refluxed and the product collected upon filtration after cooling at room temperature. A recrystallization step from hot ethanol was needed to obtain a crystalline powder. Traces of water could be removed only

after repeated washing with ethanol and diethyleter. Both ligands and complexes were obtained in good yields.



12 R = R' = R'' = R''' = H
13 R = R'' = t-Bu; R' = R''' = H
14 R = OMe; R' = R'' = R''' = H
15 R = R'' = R''' = H; R' = NEt_2
16a R = R'' = Cl; R' = R''' = H
17 R = R'' = Br; R' = R''' = H
18 R = R' = R''' = H; R'' = Br
19 R = R'' = F; R' = R''' = H
20 R = R' = R'' = H ; R''' = Et
21 R = R' = R'' = H ; R''' = Ph
22 R = R'' = t-Bu; R' = H; R''' = Ph

Scheme 2.21. Formation of the copper complexes $[CuHL]_n$ (**12-22**).

2.6.2 Analysis of ligands and metal complexes

All ligands and related copper complexes were fully characterized including NMR spectroscopy, electron impact spectra, IR spectroscopy, UV-vis and molar conductivities. The mass spectra (EI) of the Schiff base ligands **1-8** and **10-11** revealed molecular ion peaks which are coincident with the formula weights for these ligands and support the identity of their structures. Although numerous reports in the literature on the use of thiosemicarbazide derived Schiff bases have been published in the last years,[218] reported spectroscopic and analytical data are often scant; ^{13}C NMR spectra are seldom described and in some cases, especially concerning IR spectra, reported data are not in good relative agreement.

The ^{1}H and ^{13}C NMR spectra of the ligands are in agreement with the proposed structure. Enol and keto tautomers are very close in energy for Schiff bases and may compete for stability. As expected for phenol Schiff bases derivatives, the enol form prevails and we never observed any keto-enol tautomerism in DMSO-d_6 (nor in $CDCl_3$) solutions.[219]

The IR spectra of powders show the characteristic intense bands in the range 1618-1590 cm^{-1} associated with the $\nu_{(C=N)}$ frequencies. The $\nu_{(OH)}$ band of the phenolic oxygen is found almost at the same frequencies for all ligands, in the range 3468-3409 cm^{-1}, whilst the medium to intense band in the region 3300-2900 cm^{-1} have been attributed to $\nu_{(NH2)}$ and $\nu_{(NH)}$. The free ligands exhibit medium intensity bands in the region 1099-1011 cm^{-1} and 859-793 cm^{-1}, attributed respectively to $\nu_{(C=S)}$ and to $\nu_{s(CS)}$. There is no general agreement in the literature data in the identification of $\nu_{s(CS)}$, that for some authors is at lower frequencies (see for example ref.[218b]);

however, reported data in the experimental section are in accordance with those reported by Campbell in his review.[220] This band is particularly diagnostic for transition metal complexes of thiosemicarbazide and thiosemicarbazones, since upon coordination could be shifted almost 100 cm^{-1} to lower frequencies. A shift of this order would indicate a considerable change in the bond order, such as would result from the formation of a strong metal-sulphur bond. As expected, for all the synthesized copper complexes, the frequencies corresponding to $\nu_{s(CS)}$ were found in the range 809-730 cm^{-1}, therefore indicating the coordination of the copper ion to the S atom. This fact is supported even by the disappearance of the $\nu_{(C=S)}$ band at around 1050 cm^{-1}. The complexation of the metal ion is accompanied also by a negative shift of the frequencies corresponding to $\nu_{(C=N)}$ (from the spectral region 1618-1590 cm^{-1} to lower wave numbers) and to $\nu_{amideII}$ (from 1550-1537 cm^{-1} to 1527-1465 cm^{-1}) and a positive shift of the $\nu_{(CO)}$ (from 1271-1245 cm^{-1} to 1318-1278 cm^{-1}).[218f] All these data support that the ligand donor atoms, O, N, S, chelate the copper atom in a tridentate manner. Noteworthy, we observed for all metal complexes the persistence of a sharp band in the region 3484-3404 cm^{-1}. Normally absorption bands assigned to the $\nu_{(OH)}$ modes of lattice water appear as broad and rather intense bands in the spectral region of 3550-3200 cm^{-1} (antisymmetric and symmetric OH stretchings) and are accompanied by $\delta_{(OH)}$ in the region 1630-1600 cm^{-1}, which are not observed in the present case. It should be pointed out, however, that also the OH group in hydroxo complexes lacks the HOH bending mode near 1600 cm^{-1}.[221] The absence of coordinated water molecules within the coordination sphere of these complexes (with the exception of complex **16b**, see experimental section) is further supported by the absence of bands in the 950-930 cm^{-1} and 635-615 cm^{-1} regions, due to H_2O rocking and wagging, respectively. On the other hand, the existence of coordinated water molecules within the coordination sphere of complex $[CuL^5 \cdot 2H_2O]$ (**16b**) is supported by the presence of bands at 3480, 1610, 950 and 630 cm^{-1}, due to OH stretching, HOH deformation, H_2O rocking and H_2O wagging respectively. The complexes under study did not show any band which may be attributed to acetate ligand coordinated to the central metal atom.[221]

The molar conductivities Λ_m of the metal complexes **12-22** dissolved in DMSO at 10^{-3} M were found to be in the range 1-8 $\Omega^{-1}cm^2mol^{-1}$. These low values indicate that these complexes are non-electrolytes due to the absence of any counter ion in their structures.[222]

The absence of water, as well as of coordinate acetate ions, in the metal complexes is also indicated by the elemental analyses, which are in perfect agreement with a 1:1 ratio metal/ligand of general formula $[CuHL]_n$ (with the exception of complex **16b**, which is in agreement with the

formula $CuL^5 \cdot 2H_2O$). This general formula is supported also by the result of the FAB mass analysis of the metal complexes. In general the fast atom bombardment (FAB) gives rise to molecular ions of the type $[M^+ + 1]$ and, to the best of our knowledge, very seldom $[M^+ + 2]$ peaks are observed. For all copper complexes (with the exception of **16b**) we observed a clean base peak corresponding to a general formula $[CuHL^+ + 1]$, which seems to indicate that the ligand has just lost one hydrogen atom in the complexation reaction and thus cannot behave as a dianionic ligand, as would be expected. The mass spectra of complex **13** is reported in Figure 2.30 and compared with the spectrum simulated for the cluster $[CuHL^2]^+$.

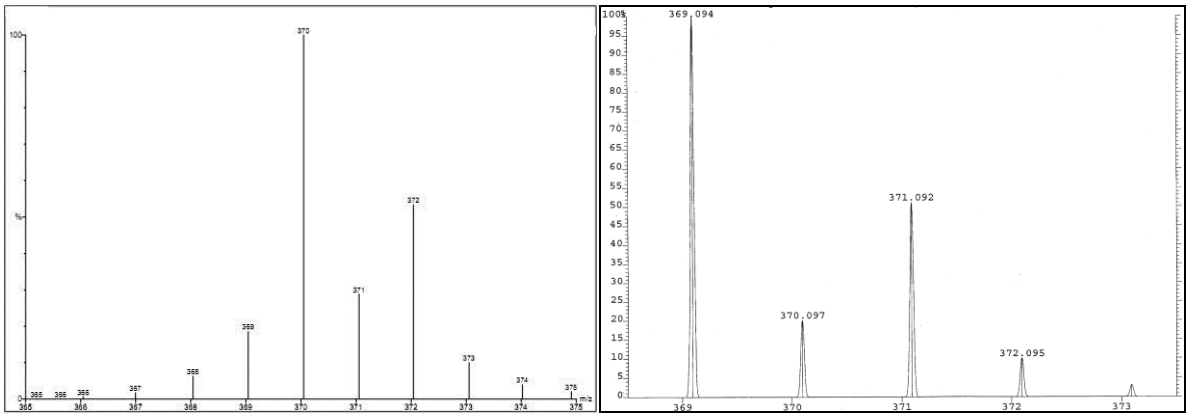


Figure 2.30 FAB mass spectrum of complex **13** (left) compared with the simulated spectra for the cluster $[CuHL^2]^+$.

It can be seen that, even if with low intensity, an ion peak corresponding to the molecular formula $[CuL^+ + 1]$ (369 m/e) is present. The same pattern is found in all the mass spectra of the metal complexes (see *Experimental part*).

If we assume, as all analytical and spectroscopic data support, that the metal to ligand ratio is 1:1 and that we do not have any other ancillary ligand present in the metal complexes, we must conclude that the copper complexes are not monomeric in the solid state and that dimeric (or oligomeric) structures are formed. If the ligand behaves as monoanionic (**A**, figure 2.31), then, to balance charges, the copper atom must have been reduced to a formal I oxidation state. On the other hand, if the ligand behave as dianionic (**B**, figure 2.31), the metal ion should be formally described as copper(II).

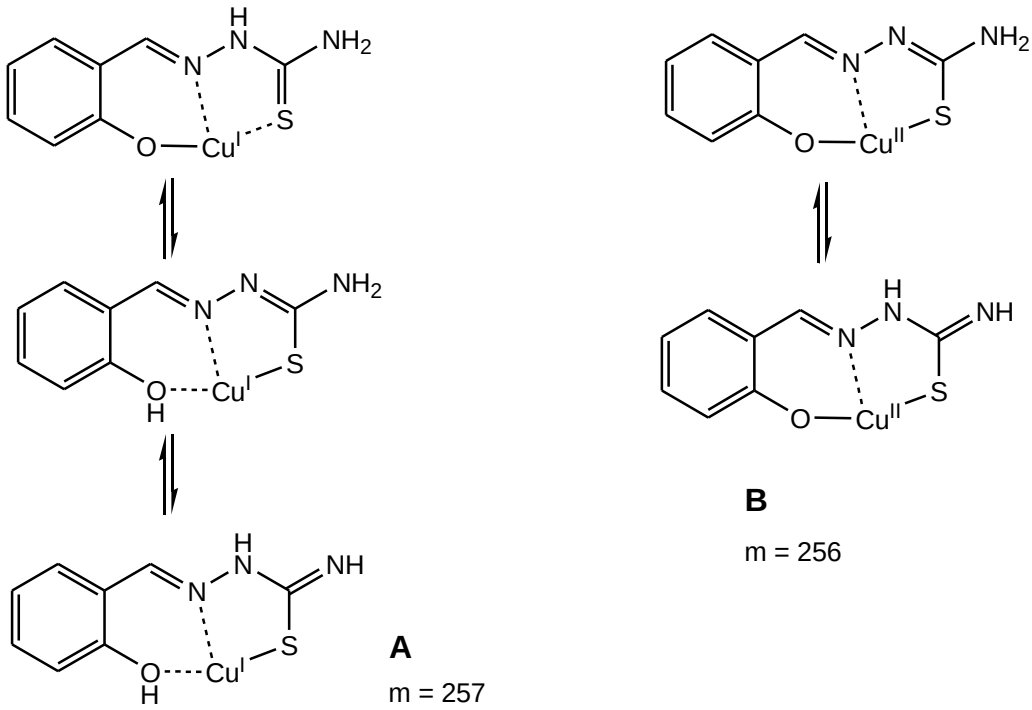


Figure 2.31 Possible molecular formulae (sketched as monomers) for complex **12**: **A** (monoanionic ligand); **B** (dianionic ligand).

The two structures **A** and **B** differ only for one proton, and for the copper oxidation state. In the absence of coordinating solvents, we must assume that these molecules are not monomers, but must aggregate. Actually, all these metal complexes are almost insoluble in most organic solvents, and a good solubility is observed only in DMSO and DMF. Unfortunately, any attempt to grow crystals suitable for X-ray structural determination from these solvents met with failure. When we tried to record NMR spectra in deuterated DMSO, we observed broad signals that prevented any attribution of the chemical shifts. The only complex that showed a good solubility even in chlorinated solvents was **20**. In this case, it was possible to record a ^{1}H NMR spectrum in $CDCl_3$ that is in agreement with a diamagnetic complex. The solid copper complexes **12**, **13** and **14** are diamagnetic at room temperature. The typical magnetic momentum value for mononuclear copper(II) compounds with a S = ½ spin state are expected in the range 1.79-1.95 B.M.[223] Only in the case of complex **18** we measured a room temperature magnetic moment of 1.18 B.M. which seems to indicate a partial antiferromagnetic coupling of spins at this temperature.[224] Further studies on the magnetism of these molecules at low temperature will be the subject of a study in the next future.

The UV-vis spectra of the thiosemicarbazone ligands in DMSO (10^{-5} M) showed broad bands in the range 270-275 nm assignable to the phenyl ring $\pi \rightarrow \pi^*$ transitions. This band is not affected to a major extent upon coordination of the copper atom. The $n \rightarrow \pi^*$ transitions

associated with the C=N group[225] around 350 nm in the spectra of the free ligands are generally shifted to higher energy on complexation. In the spectra of some complexes this latter band shifts to higher energies. The shifts of these bands with respect to those of the free ligand indicate coordination of phenolic oxygen and azomethine thioenol moieties to the metal ions. There are also charge-transfer transitions partially responsible for the intense colours of some of the complexes. The absorption bands with high intensity observed at 420-430 nm are assigned to charge transfer transitions. The UV-Vis spectra of the complexes (10^{-3} M in DMSO) showed broad single band at 570-590 nm (ε in the range 200-300 M^{-1} cm^{-1}, figure 2.32) which is consistent with a distorted square pyramidal geometry at a Cu(II) metal atom.[218g]

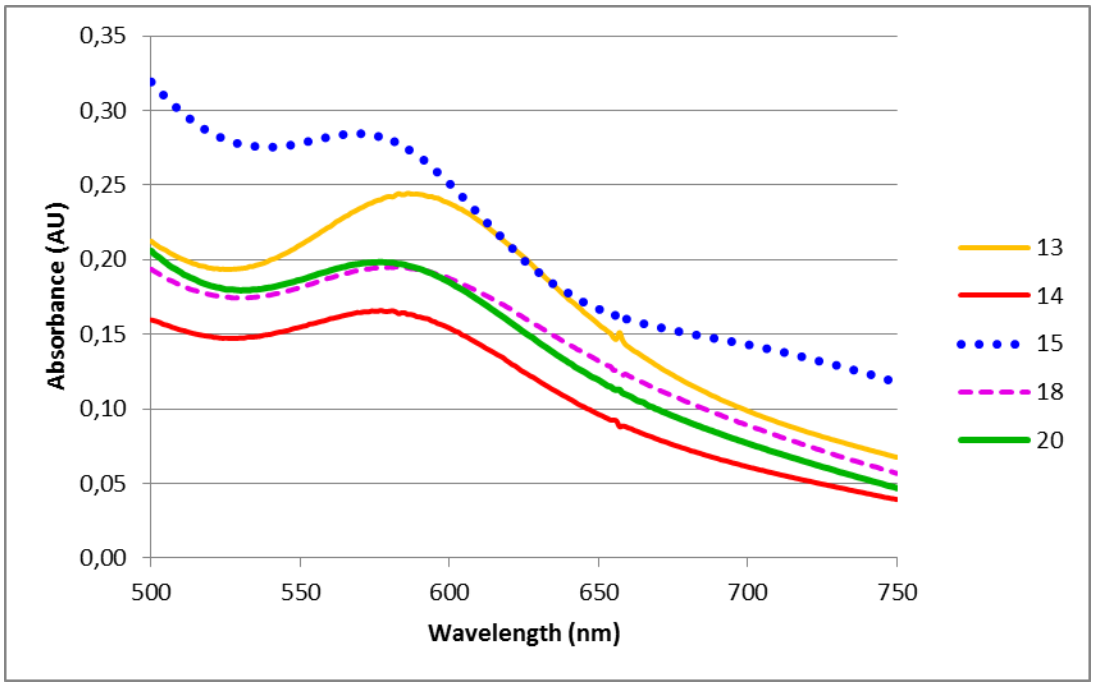


Figure 2.32 UV-vis spectra for complexes **13**, **14**, **15**, **18** and **20** (see legend) in the region 500-700 nm; 10^{-3} M solutions in DMSO.

These experimental data provide grounds for suggesting a polynuclear structure for the metal complexes **12-22** with a spin-spin interaction between the paramagnetic copper ions. This polymeric chain would break upon dissolution in strongly coordinating solvents such as DMSO or DMF. It should be pointed out that Cu(I) complexes are not stable toward oxidation and that the experimental conditions used in the present work and the high dilutions needed to record an UV-vis spectrum in DMSO hampers the characterization of copper(I) in solution. On the other hand, only the presence of copper in the oxidation state (I) would explain the ion peaks of general formula [$CuHL^+$ + 1] observed in the mass spectra. To gain a better insight to the oxidation state of the central metal atom, we decided to carry out an X-ray photoelectron

spectroscopy (XPS) analysis of selected complexes. XPS analysis, in fact, is helpful in identifying the oxidation states of elements in various compounds because the binding energy (BE) measured for the core electrons undergoes a "chemical shift" as a result of changes in the chemical environment of the atoms.[226] The Cu2p spin-orbit doublets ($2p_{1/2}$ and $2p_{3/2}$) obtained from complex **12** are illustrated in Figure 2.33. A characteristic feature of the Cu^{2+} ($3d^9$) is a shift in the Cu2p photoelectron peak doublet to higher BE side compared to Cu^{+} ($3d^{10}$). This can be appreciated in the $Cu2p_{3/2}$ peak that is actually splitted in two components: one major peak at -932 eV (**A**, figure 2.33) that can be ascribed to copper (I), and a smaller peak at -935 eV (**B**, figure 2.33), in the typical range for a copper (II) atom. A small shake-up satellite (**C** figure 2.33) can be seen on the lower kinetic energy (KE) (higher BE), which is normally associated with copper (II). Similar spectra were obtained for complexes **13** and **20**.

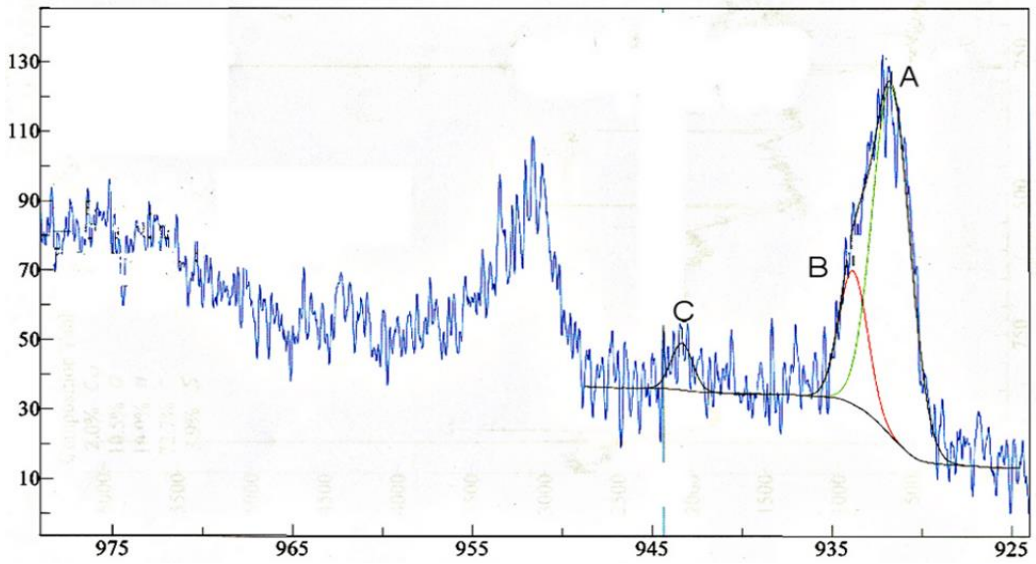


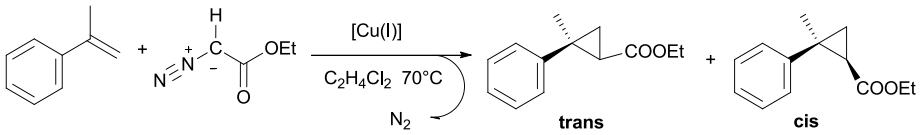
Figure 2.33 The Cu_{2p} spin-orbit doublets obtained for complex **12**.

These data suggest that copper is present as copper(I) in the complexes. The fact that small peaks due to the presence of some Cu(II) are present suggests that the surface of the particles was easily oxidized. We must underline that XPS analysis is a surface technique and that a partial oxidation of the surface may always occur.[226] To investigate if the employed solvent (ethanol) in the reaction may be responsible for the reduction of copper during the complexation, complex **16b** was synthesized in methanol instead. In this case we isolated a paramagnetic complex of copper(II) ($\mu_{eff.}$ (25°C) = 1.79 B.M.) corresponding to the molecular formula $[CuL^5 \cdot 2H_2O]$. When the reaction was repeated in isopropanol (a better reducing agent than ethanol) a less pure product but with a chemical composition similar to **16a** was obtained instead (see experimental). The fact that copper (II) is reduced to copper (I) in reaction with

thioylcarbamoyl ligand[227] and with tiosemicarbazones[228] is not unprecedented. However, in in reported cases, reduction took place in the absence of alcohols. To clarify the role played by the alcohol in the reduction from Cu(II) to Cu(I), we have conducted a GC analysis of the reaction mixture to detect if an oxidation product from ethanol was observed. In order to do this, we had to run the reaction in the absence of methanol, that under our experimental conditions interfere with the detection of acetic aldehyde, by dissolving the copper acetate in the minimum of water and performing the reaction in a pressure tube to avoid any possible evaporation of the formed volatile products. Under these conditions, we were able to detect a reasonable amount of acetic aldehyde after the reaction took place.

2.6.3 Catalytic activity

The catalytic activity of complexes **12-22** in cyclopropanation reactions has been investigated. As a model reaction we choose the cyclopropanation of α-methylstyrene by EDA (scheme 2.22).



Scheme 2.22 Benchmark reaction catalysed by complex **12-22.**

Catalytic reactions were run by slow addition of EDA by syringe pump (100 min) to a stirred solution containing the olefin and the metal complex in dichloroethane under dinitrogen (Cu/EDA/α-methylstyrene ratio 1:500:1000) at 70 °C. In all cases a quantitative conversion of the starting EDA was observed at the end of the addition, as judged by IR spectroscopy, checking the disappearance of the band due to the stretching of the N_2 moiety (ν=2114 cm^{-1}).

All tested copper complexes exhibited a remarkable catalytic activity toward the decomposition of ethyl diazoacetate, and the subsequent transfer of the carbene moiety to the C=C double bond. In Table 2.20 are collected all the obtained results in the cyclopropanation reaction of α-methylstyrene with the different catalysts. In all cases cyclopropanes were obtained in yields from good to excellent. Fumarate and maleate, the homo-coupling product of EDA, were the only other product detected and accounted for the missing mass balance of the reactions. The diastereoselective outcome of the reaction is rather poor in all cases (almost equimolar amount of *trans* and *cis* cyclopropanes) and does not seem to be influenced by the steric and/or electronic requirement of the tiosemicarbazone ligand.

Table 2.20. Catalytic cyclopropanation of α-methylstyrene by EDA.[a]

Entry	catalyst	conversion (%)[b]	yield (%)[c]	*trans*/*cis*[c]
1	**12**	>99%	79	56:44
2	**13**	>99%	78	56:44
3	**14**	>99%	58	55:44
4	**15**	>99%	62	56:44
5	**16a**	>99%	97 (68)[d]	57:43
6	**16b**	>99%	97	57:43
7	**17**	>99%	93	55:45
8	**18**	>99%	92	56:44
9	**19**	>99%	54	54:46
10	**20**	>99%	81	56:44
11	**21**	>99%	87	57:43
12	**22**	>99%	88	55:45

[a] Experimental conditions: EDA (2,52 mmol) dissolved in $C_2H_4Cl_2$ (1 ml) was slowly added (100 min) to a hot (70 °C) solution of cat (5.1 x 10^{-3} mmol) and α-methylstyrene (5.1 mmol) in dichloroethane (9 mL). [b] Conversion of the starting EDA. [c] Determined by GC (yield based on EDA). [d] Isolated yield.

Remarkably, almost no difference in the chemical yield was observed employing a catalyst where copper is present as Cu(I) or complex **16b**, the only monomeric copper(II) catalyst tested. This finding, however, is not surprising, since it is commonly accepted that EDA reduces Cu(II) to Cu(I).

We next optimised the reaction conditions and catalyst loadings, employing complex **16b**. The results are summarised in Table 2.21.

Table 2.21. Cyclopropanation of α-methylstyrene with EDA catalysed by complex **16b**, $CuL^5(H_2O)_2$.[a]

Entry	cat/EDA/olefin	time(min.)	conversion(%)[b]	Yield (%)[c]	*trans*/*cis*[c]
1	1/500/1000	7/5/5[d]	> 99	87	57:43
2[e]	1/1000/1500	100/100/100[d]	> 99	95	57:43
3[f]	1/10000/20000	380	92	77	56:44
4[g]	1/20000/40000	420	92	74	55:45

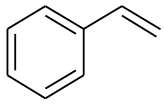
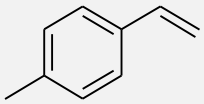
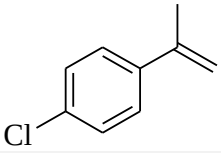
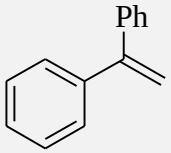
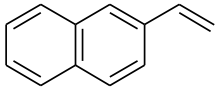
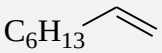
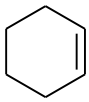
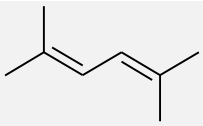
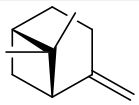
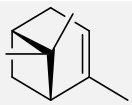
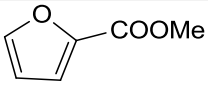
[a] Experimental conditions: EDA was added to a solution of **16b** (2.73 mg, 7.5 x 10^{-3} mmol) and α-methylstyrene in dichloroethane (10 mL) at 70 °C. [b] Conversion of the starting EDA. [c] Determined by GC (yield based on EDA). [d] After complete consumption of the starting EDA, the catalytic cycle was restored twice by addition of EDA and α-methylstyrene; global yield is reported. [e] **16b** (1.35 mg, 3.7 x 10^{-3} mmol) in 9 mL of dichloroethane was used; EDA dissolved in $C_2H_4Cl_2$ (1 mL) was slowly added. [f] This solution was prepared by dissolving **16b** (1.35 mg, 3,7 x 10^{-3} mmol) in dichloroethane (10 mL); 1 mL of this solution was added to the solution of α-methylstyrene in 9 mL of dichloroethane. [g] This solution was prepared by dissolving **16b** (1.35 mg, 3,7 x 10^{-3} mmol) in dichloroethane (10 mL); 0.5 mL of this solution were added to the solution of α-methylstyrene in 9,5 mL of dichloroethane.

When EDA was added in one portion to the reaction mixture (entries 1, 3 and 4, table 2.21), an induction period was observed, that, in the case of complex **16b**, can be necessary to reduce copper(II) to copper(I). In fact, this induction period is not observed upon the second and third additions (entry 1, table 2.21). Noteworthy, the copper complex does not lose its catalytic activity after 3 consecutive runs. In contrast to the prolonged EDA addition time generally required to reduce the formation of homo-coupling products in cyclopropanation, we found complex **16b** to be rather insensitive to this: if we compare entry 1, table 2.21 with entry 6, table 2.20, a decrease only from 97% to 87% in cyclopropane yield is observed. At a **16b**/EDA/α-methylstyrene ratio of 1/1000/1500 with slow addition of EDA products are obtained with excellent yields (entry 2, table 2.21). A 1.5 fold excess of olefin with respect to EDA is however necessary to reduce the formation of homo-coupling products. We were able to further reduce the catalyst loading and TON up to 18,400 has been obtained (entry 4, table 2.21). Even if a poor diastereoselection was observed, to the best of our knowledge, this is the higher TON reported for a single site copper catalyst in homogeneous catalytic cyclopropanation.[216a] A TON of 100,000 has been recently reported by us with a dinuclear copper polyoxometalate catalyst.[229]

To determine the general applicability of copper tiosemicarbazone complexes, cyclopropanation reactions of a series of styrene derivatives with varied electronic and steric properties were carried out, using EDA as carbene source (table 2.22). At a cat/EDA/olefin ratio of 1/500/1000 at 70 °C, the complexes catalysed the cyclopropanation of a range of substrates

with a quantitative conversion and with selectivities ranging from good to excellent. The results are summarised in Table 2.22.

Table 2.22. Cyclopropanation of olefins with EDA.[a]

Entry	Olefin	Cat	Time (min.)	conversion(%)[b]	yield(%)[c]	*trans*/*cis*[c]
1		**16b**	12	> 99	68	72:28
2[d]		**16b**	100[d]	> 99	99 (90)	92:8
3[d]		**16b**	100 [d]	> 99	82 (68)	57:43
4		**16b**	100 [d]	> 99	90 (63)	-
5		**16b**	31	> 99	76	71:29
6		**12** **16b** **16a** **21** **22**	100 [d] 19 100 [d] 100 [d] 100 [d]	> 99 > 99 > 99 > 99 > 99	63 65 75 76 78	68:32 69:31 80:20 73:27 66:44
7		**16b** **16a**	11 100 [d]	> 99 > 99	67 92	91:9 91:9
8		**16b** **16a**	32 100 [d]	> 99 > 99	82 98	64:36 50:50
9[e]		**16b**	100 [d]	> 99	85 (51)	58:41:1:0
10[f]		**16b**	100 [d]	> 99	90 (84)	> 99
11		**21**	100 [d]	> 99	15	> 99

[a] Experimental conditions: EDA was added to a solution of cat (5.1 x 10^{-3} mmol) and olefin in dichloroethane (10 mL) at 70 °C. [b] Conversion of the starting EDA. [c] Determined by GC; isolated yield in parenthesis (yield based on EDA). [d] EDA dissolved in $C_2H_4Cl_2$ (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 ml). [e] The two major products were determined to be (1R, 2R, 2'R) and (1R, 2R, 2'S) by comparison with literature data[230] The fourth possible diastereoisomer was not detected. [f] Only one diasteroeisomer (1R, 2R, 2'R) was isolated.[230]

When styrene was employed as substrate, we observed a decrease in the reaction rate and in cyclopropane products with respect to the case of α-methylstyrene (compare entry 1, table 2.22 and entry 6, table 2.22). However, in this case the diastereoselectivity is improved (*trans*/*cis* = 2.6). Better yields in cyclopropane products and higher diastereoselectivities (*trans*/*cis* = 11.5) were obtained when electron donating substituents are present in the *para* position of the aromatic ring (entry 2, table 2.22). If 4-chloro-α-methylstyrene was employed as substrate, a slight decrease in the yield was observed instead (entry 3, table 2.22). It can be seen that in the absence of an α-substituent on the styrene derivative the formation of the *trans* cyclopropane is always favoured (entries 1, 2 and 5, table 2.22). Steric hindrance at the α position does not hamper the reaction and good yields were obtained with 1,1-diphenyl ethylene (entry 4, table 2.22).

Even aliphatic alkenes that are generally less reactive in cyclopropanation reactions, gave excellent results. Though the time of the cyclopropanation reaction for these substrates increased slightly if compared to what observed for styrene derivatives (compare entries 6, 7 and 8, table 2.22, with entry 6, table 2.20) yields ranging from good to excellent were always obtained. Even in these cases *trans* cyclopropane compounds were obtained as major products and a remarkable diastereoselectivity (*trans*/*cis* = 10.1) was observed for cyclohexene (entry 7, table 2.22). With 2,5-dimethyl-2,4-hexadiene, an important precursor to chrysanthemic acid[170], the catalytic reaction yielded the desired cyclopropanes (cyclopropanation of only one double bond was observed,[171] in very good yields (98 %) (entry 8, table 2.22), without the need for a large excess of the olefin.

Out of the four possible diastereoisomers that could be obtained in the cyclopropanation of (-)β-pinene, two major isomers were obtained. The two major isomers are those deriving from a formal attack of the carbene moiety on the less sterically hindered side of the olefin.[230] On the other hand, when (-)α-pinene was used as the substrate, only one diastereoisomer (1R,2R,2'R, ref. 230) was isolated as a clean product in good yield (entry 10, table 2.22). The only substrate that failed to give good yields in the present study was methylfuroate, (entry 11, table 2.22). However, in this case, even if in low yield, only the trans isomer (attack only at the non-substituted double bond) was detected.[172]

2.7 Concluding remarks

In conclusion, we have prepared and fully characterised a small library of non-chiral and chiral pyridine containing macrocyclic ligands (**Pc-L**) possessing the same donor properties but with either C_1, C_2 or C_{2v} symmetry. The strategy adopted for the synthesis of these macrocyclic ligands is very flexible and allows for structural modifications. Relative basicity of the four nitrogens atoms and metal complexation of Pc-L ligands with different copper(I) salts were studied.

The use of [Cu(I)(Pc-L)] complexes was investigated at first in Henry catalytic reaction under mild conditions. The remarkable diastereoselectivity observed when isatine was reacted with nitroethane under the optimised catalytic conditions is worth to note, considering the easy access to a highly functionalized isatine skeleton. However, further studies on the ligand steric requirements in order to achieve significant enantioselectivities are required.

Then [Cu(I)(Pc-L)] complexes were tested as competent catalysts in asymmetric cyclopropanation reactions, at first under homogenous conditions in 1,2-dichloroethane. Cyclopropanes were obtained in good to excellent yields and enantiomeric excesses up to 99%. Thanks to the collaboration with Dr. Dal Santo, we have developed supported hydrogen-bonded (SHB) chiral copper(I) complexes. These supported catalysts showed good performances in cyclopropanation reactions under heterogeneous conditions in batch. The heterogeneised systems showed higher or comparable activities than the homogeneous counterpart and a good recyclability, allowing the use of more environmentally friendly *n*-hexane as solvent in place of 1,2-dichloroethane. Cyclopropanes were obtained in good to excellent yields and enantiomeric excesses up to 67%. We did not observe any significant Cu leaching when employing *n*-hexane as a reaction medium and the catalytic system is of truly heterogeneous nature, since the filtered solution is not catalytically active. The observed confinement effects are more dependent on the employed solvent (non-polar *vs* halogenated) than to the kind of support (ordered or non-ordered). Worth to note is the fact that even commercial silica can be used as a support, without any need of structural modification of the ligand in order to strongly graft the complex.

Thanks to the three month collaboration with Prof. David J. Cole-Hamilton from the University of St. Andrews (UK), these catalytic system based on SHB chiral copper(I) complexes were also tested as competent catalysts for asymmetric cyclopropanation reactions under flow conditions allowing the use of more eco-sustainable CO_2 as a vector instead of solvents normally used for these reactions. The heterogeneised systems under flowing CO_2

showed comparable or even higher chemoselectivities than the homogeneous counterpart. In terms of enantioselection excellent results were obtained also with non-activated alkenes like 1-octene where *ees* are comparable to those observed in the homogenous phase. Interestingly, all the data in CO_2 were obtained at 40°C, while the best temperature for the cyclopropanation reaction in the homogenous phase was 0°C. Moreover supported catalysts showed a good recyclability and the TON number has been increased (up to 440). The catalysts system remained active up to 25 h without any loss in catalytic activity and chemoselectivity improved upon prolonged reaction times. Catalyst were stable and robust with a negligible copper leaching (0.007% of total copper). Future studies will be devoted to optimise the ligand design in order to improve the stereo-selective outcome of the reaction.

Collaborating with Dr. Giorgio Abbiati, we next extend our studied on metal complexes testing our ligands with other metal ions in order to explore the coinage group. We have prepared silver(I) complexes of **Pc-L*** with different silver(I) salts. The [Ag(I)(Pc-L)] complexes demonstrated to be suitable catalysts for the synthesis of 1-alkoxyisocromenes starting from various 2-alkynylbenzaldehydes and different primary and secondary alcohols. Best results were obtained with BF_4^- complex. The approach is characterised by absolute regioselectivity, mild reaction condition, good to excellent reaction yields, cleanness of the reaction, reduced purification steps. The [Ag(I)(Pc-L)] complexes are quite stable, versatile and can be used under open-air atmosphere. The reaction mechanism was investigated by in depth NMR studies and an aimed intramolecular trapping experiment. Our efforts are now devoted to the development of an enantioselective version of this transformation.

Finally the synthesis of several tiosemicarbazide derived Schiff base copper complexes has been reported. They have been fully characterised with spectral and analytical experiments. All synthesised complexes showed excellent catalytic activities in cyclopropanation reactions and TON up to 18,400 could be obtained. In contrast to the prolonged EDA addition time generally required to reduce the formation of homo-coupling products in cyclopropanation, we found those complexes very selective. Furthermore, a single addition of EDA is required to yield the desired cyclopropanes in excellent yields. Moreover, the catalysts are very robust and no decrease in yield was observed even after three catalytic runs. Several cyclopropanes have been obtained in good to excellent yields even from non-activated olefins. In the case of the cyclopropanation of (-)α-pinene, out of four possible diastereoisomers, only one product was formed that could be isolated pure in 84% yield.

3 EXPERIMENTAL PART

3.1 General procedure

NMR spectra were recorded on Bruker Avance 300-DRX or Avance 400-DRX spectrometers. Chemical shifts (ppm) are reported relative to TMS. The ^{1}H NMR signals of the compounds described in the following have been attributed by COSY and NOESY techniques. Assignments of the resonance in ^{13}C NMR were made using the APT pulse sequence and HSQC and HMBC techniques. The ^{15}N NMR signals of the compound described have been attributed by HMBC technique. Infrared spectra were recorded on a BIO-RAD FTS-7 spectrophotometer. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University. GC-MS analysis were performed on a Shimadzu GCMS-QP5050A instrument. UV/Vis spectra were recorded on an Agilent 8453E instrument. Data collections for the crystal structure determinations were carried out using a Bruker Apex II difractometer or an Agilent SuperNova Mo microsource, Al[231] filtered and working at 50 kV and 0.8 mA. All crystal structures were solved by direct methods using SHELXS97 and refined with SHELX97,[232] within the wingx suite of programs.[233] H atoms were rigidly modelled on the riding C or N atoms. Optical rotation were measured on a Perkin Elmer instruments model 343 plus; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Microwave assisted reactions were performed with a MILESTONE® microSYNT multimode labstation, using 12 mL sealed glass vessels. The internal temperature was detected with a fiber optic sensor. The water and air sensitive compounds were handled in a dry-box, model "MB-10-Compact". Metal loadings are determined by ICP-OES using a Thermo X Series II apparatus. 15 mg of each sample are mineralized by adding 3 mL of 37% HCl, 1 mL of concentrated HNO_3, 1 mL of 98% H_2SO_4. CO-DRIFT spectra of the samples were recorded using a FTS-60A spectrophotometer consisting of a homemade reaction chamber. After purging the apparatus with ultra-pure He, spectra of the samples were recorded at RT in He and CO flow, before and after catalysis. HPLC analyses were performed on a Hewlett-Packard 1050 instrument equipped with DAI-CEL CHIRALCEL, IB, OJ and AD chiral columns. Unless otherwise specified, all the reactions were carried out in a dinitrogen atmosphere employing standard Schlenk techniques and magnetic stirring. Solvents were dried prior use by standard procedures and stored under dinitrogen. α-Methyl styrene was distilled over CaH_2 and stored under dinitrogen. Benzaldehyde, 4-(*n*-butyl)-benzaldehyde and pivalaldehyde were distilled and stored under dinitrogen prior to use. Copper(I) triflate benzene complex and copper(I) tetrakis-

acetonitrile tetrafluoro borate complex were synthesized following literature methods.[234] Davisil (Grace Davison, LC 150 Å, 35-70 micron) and Aerosil (380, Evonik) are commercially available. All other starting materials were commercial products and were used as received. CO_2 (99.9995%) was purchased from BOCgases. For the part dedicated to catalysis in flow, the catalytic reactions were carried out on a specially designed rig, the design of which has previously been reported[210] using a stainless steel tubular reactor with a volume of 8.8 cm^3.

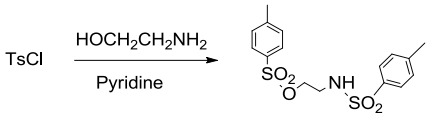
For aziridine, sulphonamide and ligand numerations see *Result and Discussion* section **2.1**.

For protonated ligand and complex numerations see *Result and Discussion* in section **2.2**.

For supported complex numerations see *Result and Discussion* in section **2.3** and **2.5**.

3.2 Synthesis of aziridines and amines

3.2.1 2-tosyl ammine ethyl toluene sulphonate



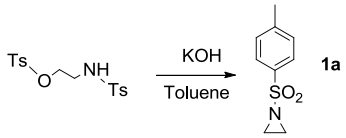
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Tosyl chloride	190.65	80.26	-	-	421	2.1
Ethanol amine	61.08	12.22	1.012	12.1	200	1

A solution of ethanol amine in pyridine (20 mL) was added drop wise to a suspension of tosyl chloride in pyridine (50 mL) cooled at -40 C°. The suspension was vigorously stirred for 2 hours at -10 C° then transferred in an ice bath. Ice was added to the suspension end the solid, filtered and washed with water, was dissolved in chloroform and washed with water. The product obtained was recrystallized from ethanol as a yellow solid. (MW 369.46 g/mol)

yield = 40,87g , 55,3%

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.76 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.72 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.37 (2H, d, *J* = 8.0 Hz, Ar*H*), 7.32 (2H, d, *J* = 8.0Hz, Ar*H*), 4.83 (1H, t, *J* = 6.1 Hz, NH), 4.07 (2H, t, *J* = 5.1 Hz, CH_2O), 3.25 (2H, pq *J* = 5.5 Hz, CH_2NH), 2.48 (3H, s, CH_3), 2.45 (3H, s, CH_3).

3.2.2 Tosyl aziridine -1a



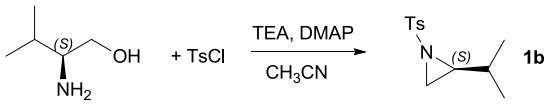
Reagents	MW (g/mol)	g	mmol	EQ
2-tosyl ammine ethyl toluene sulphonate	369.46	10.651	28.83	1
KOH	56.10	5.516	98.32	3.4

Reaction was carried out in air. A solution of KOH in 30 mL of water was added drop wise to a suspension of 2-tosyl ammine ethyl toluene sulphonate in 80 mL of toluene. The resulting solution was stirred for 2 hours at room temperature, then diluted with water and toluene. The organic phase was washed with water obtaining a white solid **1a**. (MW 197.25 g/mol).

yield = 5.004 g, 25.37 mmol, 88%

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.85 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.37 (2H, d, *J* = 8.2 Hz, Ar*H*), 2.47 (4H, s, CH_2), 2.39 (3H, s, CH_3).

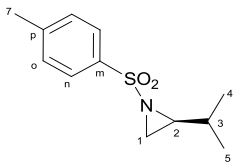
3.2.3 (*S*)-2-isopropyl-1-tosylaziridine - 1b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
L-valinol	103.16	2.08	-	-	20	10
Tosyl chloride	190.65	8.01	-	-	42	21
Et_3N	101.19	8.70	0.726	12	86	43
4-(Dimethylamino)pyridine	122.17	0.25	-	-	2	1

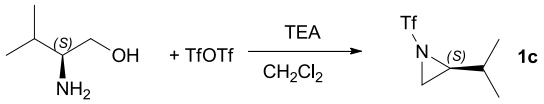
Distilled TEA was added to a solution of L-valinol in distilled CH_3CN (100 mL), cooled to 0°C. Then TsCl and DMAP were added to the solution kept at 0°C. The resulting mixture was stirred for 5 hours and 30 minutes at room temperature. Then reaction was dried under vacuum and the mixture was dissolved in ethyl acetate and washed with brine. The mixture was dried, obtaining a white powder **1b** (MW 239.33 g/mol).

yield = 4.507 g, 18.8 mmol, 96.7%



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.83 (2H, d, *J* = 8.6 Hz, H^n), 7.33 (2H, dd, *J* = 8.9 Hz, *J* = 0.8 Hz, H^o), 2.61 (1H, d, *J* = 7.0 Hz, H^1), 2.55-2.49 (1H, m, H^2), 2.45 (3H, s, CH_3^7), 2.10 (1H, d, *J* = 4.8 Hz, $H^{1'}$), 1.42 (1H, m, *J* = 7.0 Hz, H^3), 0.90 (3H, d, *J* = 6.8 Hz, CH_3^4), 0.80 (3H, d, *J* = 7.0 Hz, CH_3^5).

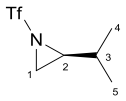
3.2.4 (S)-2-isopropyl-1-((trifluoromethyl)sulfonyl)aziridine - 1c



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
L-valinol	103.16	1.821	-	-	17.7	1.8
Triflic anhydride	282.14	10.0	1.667	6	35.3	3.6
Et_3N	101.19	3.63	0.726	5	9.88	1

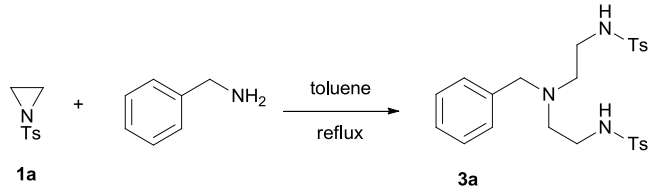
Triflic anhydride was added dropwise to a solution of L-valinol and distilled TEA in distilled CH_2Cl_2 (60 mL), cooled to -78°C. The solution was kept at -30°C and stirred overnight. Organic phase was washed with a cooled HCl 0.1M solution (3 x 30 mL) and then with a cooled saturated Na_2CO_3 solution (3 x 30 mL). The mixture was dried, obtaining a white powder **1c** (MW 217.21 g/mol).

yield = 2.563g, 11.6 mmol, 67%



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 2.88 (2H, m, $H^{1\text{-}2}$), 2.47 (1H, d, J = 4.7 Hz, $H^{1'}$), 1.78 (1H, m, H^3), 1.08 (3H, d, J = 7.0 Hz, CH_3^4), 1.05 (3H, d, J = 7.1 Hz, CH_3^5).

3.2.5 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane (conventional heating) - 3a



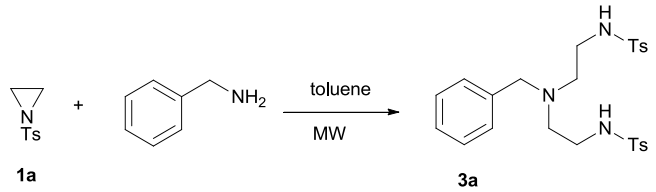
1a 3a

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
tosyl aziridine	197.25	6.094	-	-	30.89	2.2
Benzylamine	107.15	1.588	0.981	1.6	14.82	1

Reaction was carried out in air. A solution of **1a** and benzylamine in toluene (20 mL) was stirred and refluxed for 4 h. The mixture was dried and purified by column chromatography on silica using ethyl acetate:hexane = 50:50 as eluant, obtaining a yellow oil **3a**. (MW 501.66g/mol).

yield = 7.245 g, 14.44 mmol, 97%.

3.2.6 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane (microwave heating)

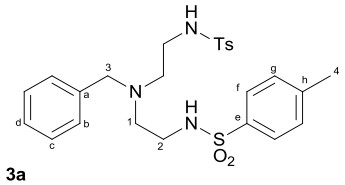


1a 3a

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
tosyl aziridine	197.25	1.603	-	-	8.125	2.2
Benzylamine	107.15	0.396	0.981	0.40	3.693	1

Reaction was carried out in air. A solution of **1a** and benzylamine in toluene (15mL) was stirred and heated by microwave irradiation for 1 h at 120 °C. The mixture was dried and used without any further purification. (MW 501.66g/mol).

yield = 1.853 g, 3.693 mmol, quantitative.



3a

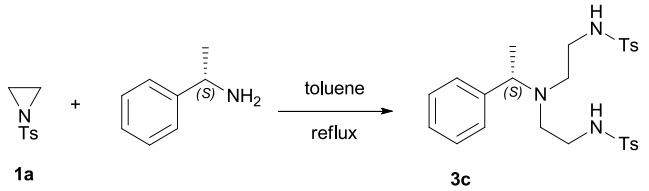
^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.73 (4 H, d, *J*= 8.0 Hz, H^f), 7.29 (4 H, d, *J*=8.0 Hz, H^g), 7.27–7.25 (3 H, m, Ar*H*), 7.13 (2 H, m, Ar*H*), 5.17 (2H, br s, N*H*), 3.44 (2 H, s, H^3), 2.95 (4 H, m, CH_2^1), 2.57 (4 H, m, CH_2^2), 2.42 (6 H, m, CH_3^4).

^{13}C NMR (100 MHz; $CDCl_3$; T = 300 K): δ 143.8 (C^h), 138.2 (C^e), 137.1 (C^a), 130.2 (C^fH), 129.3 (C^bH), 128.9 (C^cH), 127.8 (C^dH), 127.5 (C^gH), 58.8 (C^3H_2), 53.6 (C^1H_2), 41.0 (C^2H_2), 21.9 (C^4H_3).

Elemental analysis: found: C, 60.0; H, 6.2; N, 8.6%; calc. for $C_{25}H_{31}N_3O_4S_2$: C, 59.9; H, 6.2; N, 8.4%.

MS (EI):m/z 501 (M+ 100%).

3.2.7 1,7-ditosyl-4-[(*S*)-1-phenylethyl]-1,4,7-triazaheptane - 3c-(1*S*)

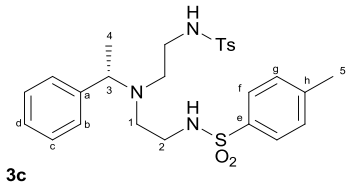


1a 3c

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
tosyl aziridine	197.25	4.707	-	-	23.86	2.2
(*S*)-α-methylbenzylamine	121.18	1.360	0.940	1.45	11.22	1

This synthesis can be performed in the air. A solution of **1a** and (S)-(−)-1-phenylethylamine in toluene (13 mL) was stirred and heated under reflux for 4 hours. The mixture was dried and purified by chromatographic column on silica using ethyl acetate : hexane = 50:50 as eluant, obtaining a yellow oil **3c-(13*S*)**. (MW 515.69 g/mol).

yield = 3.987 g, 7.731 mmol, 70%



3c

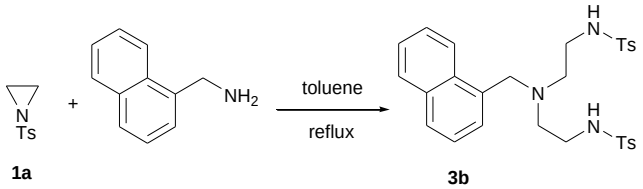
^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.72 (4H, d, *J* = 8.4 Hz, H^{f}), 7.34–7.28 (7H, m, H^{g}, H^{b} and H^{c}), 7.18–7.16 (2H, m, $H^{b'}$ and $H^{c'}$), 4.85 (2H, brs, N*H*), 3.73 (1H, q, *J* = 6.9 Hz, H^{3}), 2.88 (4H, m, CH_2^{2}), 2.61 (2H, m, $CH_2^{1'}$), 2.43 (6H, m, CH_3^{5}), 2.42 (2H, m, CH_2^{1}), 1.30 (3H, d, *J* = 6.9 Hz, CH_3^{4}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K): δ 143.9 (*C*), 137.2 (*C*), 136.7, 130.3 (C^{g}H), 128.8 (C^{b}H), 128.4 (C^{c}H), 127.8 (C^{d}H), 127.55 (C^{f}H), 58.8 (C^{3}H), 50.5 ($C^{1}H_2$), 41.6 ($C^{2}H_2$), 21.9 ($C^{5}H_3$), 21.5.

MS: m/z 516.4 (M^{+}1), 538.4 (90), 1053.1 (100).

1,7-ditosyl-4-[(*R*)-1-phenylethyl]-1,4,7-triazaheptane **3c-(13*R*)** was synthesized in the same way by employing (*R*)-α-methyl benzyl amine instead.yield = 1.853 g, 3.693 mmol, quantitative.

3.2.8 1,7-ditosyl-4-naphthyl-1,4,7-triazaheptane - 3b

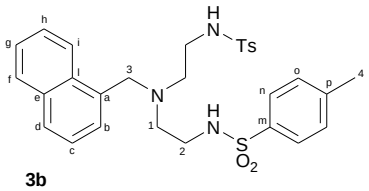


1a **3b**

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Tosyl aziridine	197,25	2,238	-	-	11,346	2,2
1-Naphthylmethylamine	157,21	0,811	1,073	0,756	5,157	1

This synthesis can be performed in the air. A solution of **1a** and 1-naphthylmethylamine in distilled toluene (11 mL) was stirred and heated under reflux for 5 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 6:4 as eluant, obtaining pure amine **3b**. (MW 551.72 g/mol).

yield = 2.14 g, 5.04 mmol, 75%



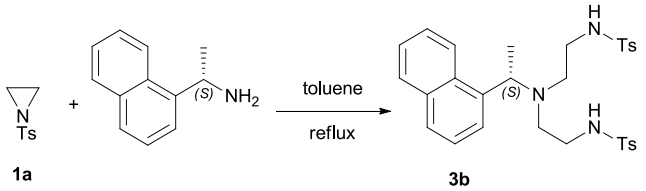
3b

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.14 (1H, d, *J* = 8.3 Hz, *H*^{i}), 7.86 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.78 (1H, m, Ar*H*), 7.54 (4H, d, *J* = 8.0 Hz, *H*^{n}) overlapping with 7.61-7.49 (2H, m, Ar*H*), 7.42-7.32 (2H, m, Ar*H*), 7.19 (4H, d, *J* = 8.0 Hz, *H*^{o}), 4.83 (2H, bs, N*H*), 4.00 (2H, br, CH_2^3), 2.90 (4H, m, CH_2), 2.66 (4H, m, CH_2), 2.38 (6H, s, CH_3^4).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 143.5 (*C*), 136.7 (*C*), 134.0 (*C*), 132.0 (*C*), 129.8 (*C*H), 129.0 (*C*^{0}H), 127.1 (*C*^{n}H), 126.3 (*C*H), 125.4 (*C*H), 123.7 (*C*^{i}H), 54.2(*C*H_2), 40.8 (*C*$^{3}H_2$), 21.6 (*C*$^{4}H_3$). Signals relative to quaternary carbons, aromatic *C*H and *C*H_2 were not detected.

Elemental Analysis: Found: C, 63.1; H, 6.2; N, 7.5% Calc. for $C_{29}H_{33}N_3O_4S_2$: C, 63.1; H, 6.0; N, 7.6%.

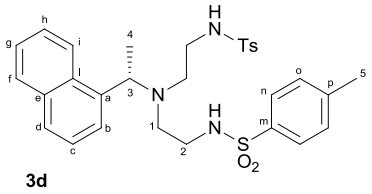
3.2.9 1,7-ditosyl-4-[(*S*)-1-(1-naphthyl)ethyl]-1,4,7-triazaheptane - 3d-(1*S*)



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Tosyl aziridine	197,25	1.433	-	-	7.266	2,2
(S)-1-(1-naphthyl)ethyl amine	171.24	0,566	1.067	0.530	3.303	1

This synthesis can be performed in the air. A solution of **1a** and (S)-1-(1-naphthyl)ethyl amine in toluene (9 mL) was stirred and heated under reflux for 10 hours. The mixture was dried and purified by chromatographic column on silica using ethyl acetate : hexane 40:60 as eluant, obtaining a yellow oil **3d-(1*S*).** (MW 565.75g/mol).

yield = 1,820g, 3.217mmol, 97%.

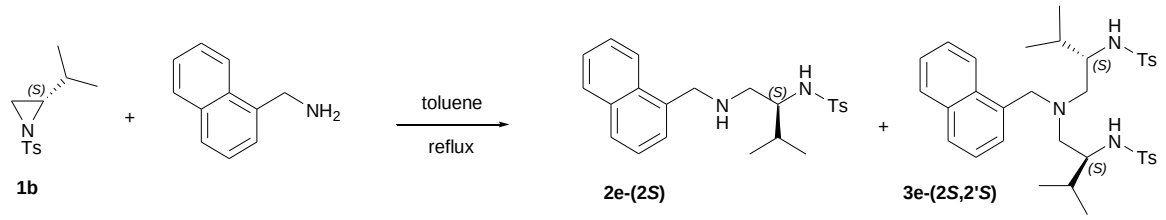


^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 8.36 (1 H, d, *J* = 8.6 Hz, Ar*H*), 7.86 (1 H, d, *J* = 7.5 Hz, H^{n}), 7.76 (1 H, m, H^{c}), 7.67 (1 H, m, Ar*H*), 7.54 (1 H, m, Ar*H*), 7.50 (4 H, d, *J* = 8.0, H^{o}), 7.41–7.40 (2 H, m, H^{b}), 7.24 (4 H, d, *J* = 8.0, Ar*H*), 4.69 (1 H, q, *J* = 6.7, C*H*), 4.63 (2 H, brs, N*H*), 2.82–2.71 (2 H, m, $CH_2^{1'}$), 2.69 (4 H, m, CH_2^{2}), 2.56 (2 H, m, CH_2^{1}), 2.42 (6 H, s, CH_3^{5}), 1.46 (3 H, d, *J* = 6.7 Hz, CH_3^{4}).

^{13}C NMR (100 MHz; $CDCl_3$; T = 300 K) δ 143.2 (*C*H), 138.3 (C^{h}H), 136.7 (C^{a}H), 134.9 (*C*H), 133.9 (C^{i}H), 131.6 (C^{p}H), 129.7 (*C*H), 128.3 (C^{c}H), 126.6 (C^{o}H), 124.2 (*C*H), 57.1 (*C*H), 51.1 ($C^{3}H_2$), 41.8 ($C^{i}H_2$), 21.5 ($C^{5}H_3$), 12.7 ($C^{4}H_3$).

1,7-ditosyl-4-[(*R*)-1-(1-naphthyl)ethyl]-1,4,7-triazaheptane **3d-(1*R*)** was synthesized in the same way by employing (*R*)-1-(1-naphthyl)ethyl amine instead.

3.2.10 Synthesis of 2e-(2*S*) and 3e-(2*S*,2'*S*)



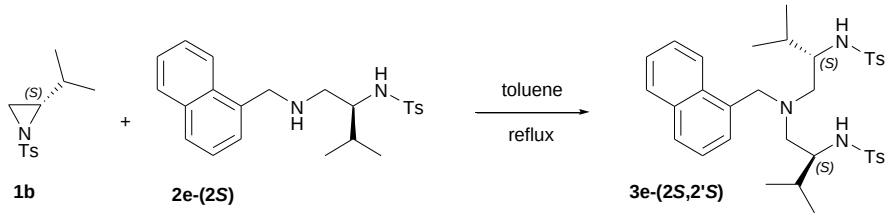
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1b-tosylaziridine	239.33	1.732	-	-	7.23	2,2
1-naphthylmethylamine	157.21	0.494	1.073	0.46	3.14	1

This synthesis can be performed in the air. A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and 1-naphthylmethylamine (0.494 g, 3.14 mmol) in distilled toluene (15 mL) was stirred and heated under reflux for 5 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining:

monoamine **2e-(2*S*)** = (MW 369.55 g/mol) 0.875 g, 2.21 mmol, yield: 70%

pure amine **3e-(2*S*,2'*S*)** = (MW 635.88 g/mol) 0.600 g, 0.944 mmol, yield: 30%.

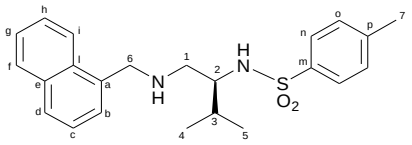
3.2.11 Synthesis of 3e-(2*S*,2'*S*) from 2e-(2*S*) (conventional heating)



Reagents	MW (g/mol)	g	mmol	EQ
1b-tosylaziridine	239.33	0.258	1.08	2,2
2e-(2*S*)	396.55	0.349	0.88	1

A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and monoamine **2e-(2*S*)** in toluene (10 mL) was stirred and heated under reflux for 33 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining the amine **3e-(2*S*,2'*S*).** (MW 635.88 g/mol).

yield = 0.330 g, 0.519 mmol, 74%



2e-(2S)

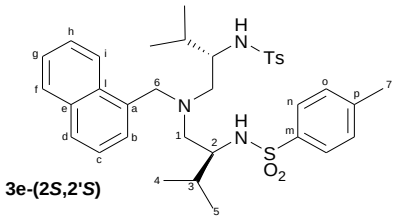
^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.02 (1H, dd, *J* = 7.7 Hz, *J* = 1.3 Hz, H^{i}), 7.89 (1H, dd, *J* = 7.7 Hz, *J* = 1.3 Hz, H^{f}), 7.81 (1H, dd, *J* = 7.7 Hz, *J* = 1.3 Hz, H^{d}), 7.62 (2H, d, *J* = 7.9 Hz, H^{n}), 7.55 (1H, t, *J* = 7.7 Hz, H^{g}), 7.54 (1H, t, *J* = 7.7 Hz, H^{h}), 7.42 (1H, t, *J* = 7.7 Hz, H^{c}), 7.38 (1H, d, *J* = 7.7 Hz, H^{b}), 7.08 (2H, d, *J* = 7.9 Hz, H^{o}), 4.14 (1H, d, *J* = 13.4 Hz, H^{6}), 4.08 (1H, d, *J* = 13.4 Hz, $H^{6'}$), 3.09 (1H, ddd, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 4.4 Hz, H^{2}), 2.73 (1H, dd, *J* = 12.4 Hz, *J* = 6.8 Hz, $H^{1'}$), 2.60 (1H, dd, *J* = 12.4 Hz, *J* = 4.4 Hz, H^{1}), 2.29 (3H, s, CH_3^{7}), 1.85 (1H, m, H^{3}), 0.81 (3H, d, *J* = 6.81 Hz, CH_3^{4}), 0.79 (3H, d, *J* = 6.81 Hz, CH_3^{5}). The signals relative to NH were not detected.

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 129.6 (C^{n}H), 129.0 (C^{f}H), 128.5 (C^{d}H), 127.2 (C^{o}H), 126.7 (*C*H), 126.6 (*C*H), 126.1 (*C*H), 125.5 (*C*H), 123.6 (C^{i}H), 58.2 (C^{2}H), 50.9 ($C^{6}H_2$), 49.0 ($C^{1}H_2$), 30.5 (C^{3}H), 21.5 ($C^{7}H_3$), 18.9 ($C^{4}H_3$), 18.4 ($C^{5}H_3$). The signals relative to quaternary carbons were not detected.

Elemental Analysis: Found: C, 69.8; H, 7.0; N, 6.9% Calc. for $C_{23}H_{28}N_2O_2S$: C, 69.7; H, 7.1; N, 7.1%.

MS (EI): m/z 397 (M^{+}+1).

$[\alpha]_D^{20}$ = - 3.611° (c 1.082 in $CHCl_3$).



3e-(2*S*,2'*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.18 (1H, d, *J* = 8.0 Hz, H^{i}), 7.85-7.76 (2H, m, H^{d} and H^{f}), 7.75 (4H, d, *J* = 8.2 Hz, H^{n}), 7.51-7.38 (3H, m, H^{c}, H^{h} and H^{g}), 7.34 (1H, d, *J* = 8.0 Hz, H^{b}), 7.23 (4H, d, *J* = 8.2 Hz, H^{o}), 4.99 (2H, d, *J* = 6.0 Hz, N*H*), 4.04 (1H, d, *J* = 13.1, H^{6}), 3.80 (1H, d, *J* = 13.1 Hz, $H^{6'}$), 3.45 (2H, m, H^{2}), 2.55-2.35 (4H, m, H^{1}), overlapping with 2.38 (6H, s, CH_3^{7}), 1.79 (2H, m, H^{3}), 0.53 (6H, d, *J* = 6.9 Hz, CH_3^{4}), 0.52 (6H, *J* = 6.9 Hz, CH_3^{5}).

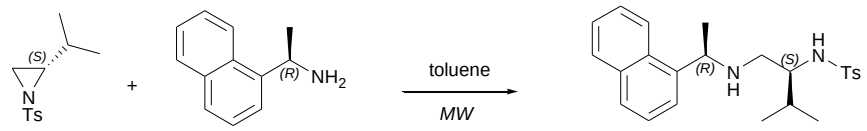
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 143.2 (*C*), 138.6 (*C*), 133.9 (*C*), 132.2 (*C*), 129.6 ($C^{n}H$), 128.6 (*C*H), 128.2 (*C*H), 127.1 ($C^{o}H$), 126.3 (*C*H), 125.8 (*C*H), 125.3 (*C*H), 124.3 ($C^{i}H$), 56.9 ($C^{6}H_2$), 55.9 ($C^{2}H$), 54.9 ($C^{1}H_2$), 29.3 ($C^{3}H$), 21.6 ($C^{7}H_3$), 17.9 ($C^{4}H_3$), 16.9 ($C^{5}H_3$). A signal relative to a quaternary carbon was not detected.

Elemental Analysis: Found: C, 66.3; H, 7.2; N, 6.3% Calc. for $C_{35}H_{45}N_3O_4S_2$: C, 66.1; H, 7.1; N, 6.6%.

MS (EI): m/z 636 (M^{+}+1).

$[\alpha]_D^{20}$ = + 9.92 (*c* 1.31 in $CHCl_3$).

3.2.12 Synthesis of 2f-(1*R*,2*S*) (microwave heating)

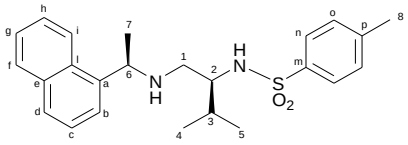


1b **2f-(1*R*,2*S*)**

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1b-tosylaziridine	239.33	0.811	-	-	3.39	1.1
(*R*)-1-(1-naphthyl)ethyl amine	171.24	0.529	1.067	0.496	3.09	1

This synthesis can be performed in the air. A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and (*R*)-1-(1-naphthyl)ethyl amine in toluene (21 mL) was added in a microwave tube. The solution was stirred and heated by microwave irradiation for 3 h at 150 °C. The resulting mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a yellow solid **2f-(1*R*,2*S*)** (MW 410.57 g/mol)

yield = 0.904 g, 2.20 mmol, 71%).



2f-(1*R*,2*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.03 (1H, m, H^{i}), 7.89 (1H, m, Ar*H*), 7.78 (2H, d, *J* = 8.4 Hz, H^{n}) overlapping with 7.79-7.75 (1H, m, Ar*H*) 7.52-7.45 (4H, m, Ar*H*), 7.25 (2H, d, *J* = 8.4 Hz, H^{o}), 5.22 (1H, br, N*H*), 4.35 (1H, q, *J* = 6.6 Hz, H^{6}), 3.08 (1H, m, H^{2}), 2.46-2.42 (2H, m, H^{1}), 2.40 (3H, s, $CH_3{}^{8}$), 1.85 (1H, dh, *J* = 13.4 Hz, *J* = 6.8 Hz, H^{3}), 1.36 (3H, d, *J* = 6.6 Hz, $CH_3{}^{7}$), 0.81 (3H, d, *J* = 6.8 Hz, $CH_3{}^{4}$), 0.78 (3H, d, *J* = 6.8 Hz, $CH_3{}^{5}$) One NH signal is too broad to be detected.

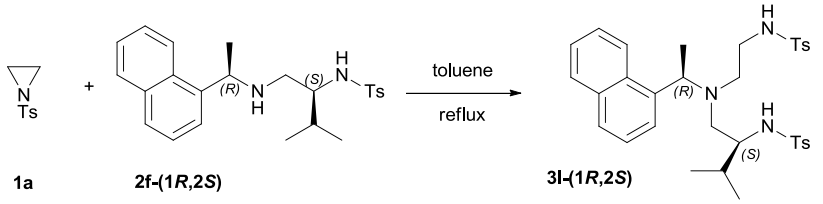
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) *δ* 143.2 (*C*), 140.8 (*C*), 138.2 (*C*), 134.1 (*C*),131.3 (*C*),129.6 (C^{o}H), 129.1 (*C*H),127.4 (*C*H), 127.2 (*C*H), 125.9 (*C*H), 125.7 (*C*H), 125.5 (*C*H), 122.8 (C^{i}H),122.6 (*C*H), 59.0 (C^{2}H), 53.3 (C^{6}H), 47.4 ($C^{1}H_2$), 30.4 (C^{3}H), 23.5 ($C^{7}H_3$), 21.5 ($C^{8}H_3$), 18.8 ($C^{4}H_3$), 18.4 ($C^{5}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) *δ* 98.0 (*N*HTs), 40.1 (*N*HC^{6}).

Elemental Analysis: Found: C, 70.4; H, 7.4; N, 6.6% Calc. for $C_{24}H_{30}N_2O_2S$: C, 70.2; H, 7.4; N, 6.8%.

$[\alpha]_D^{20}$ = + 9.92 (*c* 1.31 in $CHCl_3$).

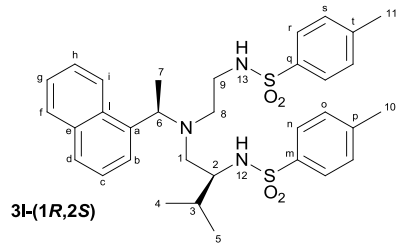
3.2.13 Synthesis of 3l-(1*R*,2*S*) from monoamine 2f-(1*R*,2*S*)



Reagents	MW (g/mol)	g	mmol	EQ
tosylaziridine	197.25	0.579	2.94	1.1
2f-amine	410.57	1.091	2.66	1

A solution of 1-tosylaziridine **1a** and amine **2f-(1*R*,2*S*)** in toluene (22 mL) was stirred and heated under reflux for 40 hours.The mixture was dried and purified by chromatographic column on silica using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining as white solid **3l-(1*R*,2*S*)** (MW 607.83 g/mol).

yield = 1.368 g, 2.25 mmol, 85%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.08 (1 H, d, *J* = 8.2 Hz, H^{i}) 7.85 (1H, m, H^{f}), 7.77 (1H, m, H^{c}), 7.71 (2H, d, *J* = 8.2 Hz, H^{n}),7.59 (2H, d, *J* = 8.2 Hz, H^{r}),7.52 (2H, m, H^{g} and H^{h}), 7.42 (2H, m, H^{b} and H^{d}) 7.28-7.24 (4H, m, H^{o} and H^{s}), 4.82 (1H, m, NH^{13}), 4.63 (1H, q, *J* = 6.6 Hz, H^{6}), 4.30 (1H, d, *J* = 7.5 Hz, NH^{12}), 3.14 (1H, m, H^{2}), 2.83 (2H, m, H^{9} and $H^{9'}$), 2.70 (2H, m, H^{8} and $H^{8'}$), 2.46 (2H, m, H^{1} and $H^{1'}$), 2.42 (6H, br, CH_3^{10} and CH_3^{11}), 1.40 (3H, d, *J* = 6.6 Hz, CH_3^{7}) overlapping with 1.41-1.39 (1H, m, H^{3}), 0.44 (6H, d, *J* = 6.9 Hz, CH_3^{4}), 0.17 (6H, d, *J* = 6.8 Hz, CH_3^{5}).

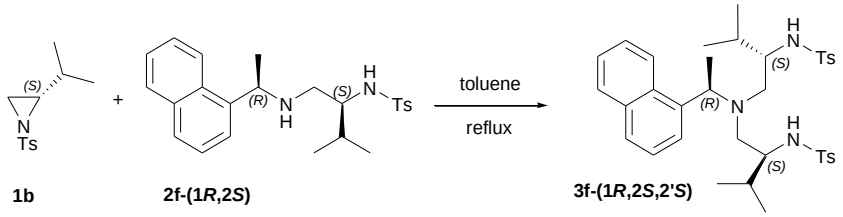
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 143.5 (C^{n}), 143.2 (C^{q}), 138.3 (C^{p}), 137.9 (C^{a}), 137.2 (C^{t}), 134.2 (*C*), 131.9 (C^{l}), 129.8 (C^{s}H), 129.7 (C^{o}H), 129.1 ($C^{f}H$), 128.4 (*CH*), 127.3 (C^{r}H), 127.2 (C^{n}H), 126.4 (*CH*), 125.9 (*CH*), 125.2 (*CH*), 124.9 (*CH*), 123.7 (C^{i}H), 57.4 (C^{2}H), 55.7 (C^{6}H), 53.5 ($C^{1}H_2$), 51.4 ($C^{8}H_2$), 41.6 ($C^{9}H_2$), 28.4 ($C^{3}H$), 21.7 ($C^{11,10}H_3$), 18.6 ($C^{4}H_3$), 15.6 ($C^{5}H_3$), 14.0 ($C^{7}H_3$).

Elemental Analysis: Found: C, 65.61; H, 7.02; N, 6.58% Calc. for $C_{33}H_{41}N_3O_4S_2$: C, 65.21; H, 6.80; N, 6.91%.

$[\alpha]_D^{20}$ = -32.88 (*c* 0.420 in $CHCl_3$)

MS: m/z 608 (M^{+}1).

3.2.14 Synthesis of 3f-(1R,2S,2'S) from 2f-(1R,2S) (conventional heating)

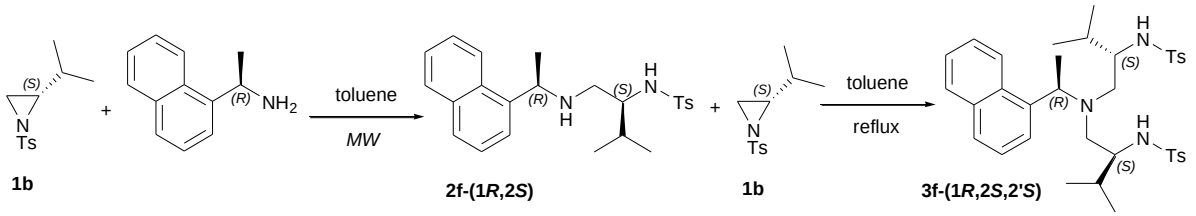


Reagents	MW (g/mol)	g	mmol	EQ
1b-tosylaziridine	239.33	0.307	1.28	1.1
2f-(1*R*,2*S*)	410.57	0.478	1.16	1

A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and monoamine **2f-(1*R*,2*S*)** in toluene (10 mL) was stirred and heated under reflux for 90 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a yellow solid **3f-(1*R*,2*S*,2'*S*)** (MW 649.91 g/mol)

yield = 0.302 g, 0.464 mmol, 40%

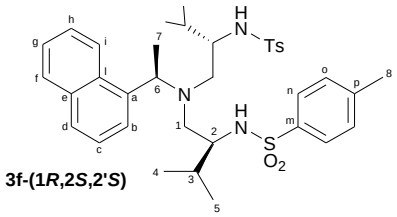
3.2.15 Direct synthesis of 3f-(1*R*,2*S*,2'*S*)



Entry	Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1	**1b**-tosylaziridine	239.33	0.781	-	-	3.21	1.1
	(*R*)-1-(1-naphthyl)ethyl amine	171.24	0.514	1.067	0.482	3.0	1
2	**1b**-tosylaziridine	239.33	0.785	-	-	3.28	1.1

A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and (*R*)-1-(1-naphthyl)ethyl amine (entry 1) in toluene (21 mL) was added in a microwave tube. The solution was stirred and heated by microwave irradiation for 3h at 150°C. The resulting mixture, without any purification, was added to a solution of **1b** (entry 2) in distilled toluene (4 mL) and was stirred and heated under reflux for 45 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a yellow solid **3f-(1*R*,2*S*,2'*S*)** (MW 649.91 g/mol)

yield = 0.785 g, 1.21 mmol, 40%).



3f-(1*R*,2*S*,2'*S*)

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.94 (1H, m, H^{i}) 7.79(4H, d, *J* = 8.0 Hz, H^{n}) overlapping with 7.79 (1H, m, Ar*H*), 7.73 (1H, dd, *J* = 5.8 Hz, *J* = 3.4 Hz, Ar*H*), 7.45-7.42 (2H, m, Ar*H*), 7.40-7.39 (2H, m, Ar*H*), 7.29 (4H, d, *J* = 8.0 Hz, H^{o}), 4.66 (2H, d, *J* = 7.9 Hz, N*H*), 4.59 (1H, q, *J* = 6.6 Hz, H^{6}), 3.26 (1H, m, H^{2}), 2.46 (2H, dd, *J* = 13.4 Hz, *J* = 5.1 Hz, H^{1}), 2.41 (6H, s, CH_3^{8}), 1.55 (2H, m, H^{3}), 1.20 (3H, d, *J* = 6.6 Hz, CH_3^{7}) 0.56 (6H, d, *J* = 6.9 Hz, CH_3^{4}), 0.19 (6H, d, *J* = 6.8 Hz, CH_3^{5}).

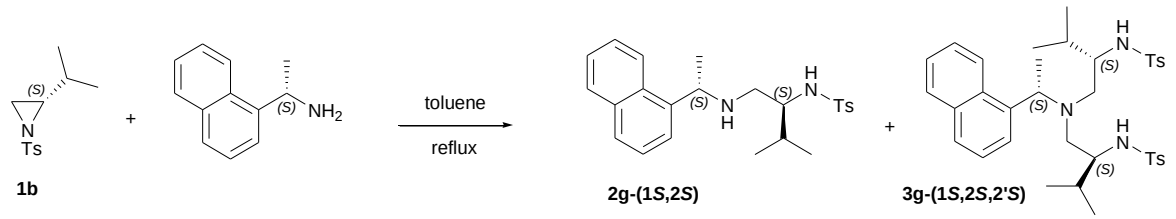
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 143.4 (*C*), 138.2 (*C*), 138.0 (*C*), 134.1 (*C*), 132.1 (*C*), 129.7 (C^{n}H), 128.8 (*C*H), 128.2 (*C*H), 127.3 (C^{o}H), 125.6 (*C*H), 125.5 (*C*H), 125.1 (*C*H), 125.0 (*C*H), 123.9 (*C*H), 56.6 (C^{2}H), 53.6 (C^{6}H), 52.3 ($C^{1}H_2$), 27.6 (C^{3}H), 21.6 ($C^{8}H_3$), 19.3 ($C^{4}H_3$), 14.8 ($C^{5}H_3$), 12.4 ($C^{7}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 94.0 (*N*HTs), 38.3 (*N*HC^{6}).

Elemental Analysis: Found: C, 66.6; H, 7.6; N, 6.5% Calc. for $C_{36}H_{47}N_3O_4S_2$: C, 66.5; H, 7.3; N, 6.5%.

$[\alpha]_D^{20}$ = - 47.22 (*c* 1.37 in $CHCl_3$).

3.2.16 Synthesis of 2g-(1*S*,2*S*) and 3g-(1*S*,2*S*, 2'*S*)

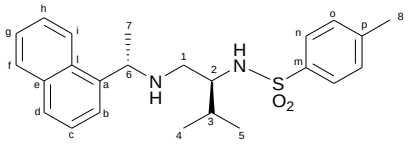


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1b-tosylaziridine	239.33	2.080	-	-	8.70	3
(*S*)-1-(1-naphthyl)ethyl amine	171.24	0.498	1.067	0.467	2.90	1

This synthesis can be performed in the air. A solution of (*S*)-2-isopropyl-1-tosylaziridine **1b** and (*S*)-1-(1-naphthyl)ethyl amine in distilled toluene (38 mL) was stirred and heated under reflux for 220 h. The mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining:

monoamine **2g-(1*S*,2*S*)** = (MW 410.57 g/mol) 0.686 g, 1.67 mmol, yield: 58%

pure amine **3g-(1*S*,2*S*, 2'*S*)** = (MW 649.91 g/mol) 0.754 g, 1.16 mmol, yield: 40%.



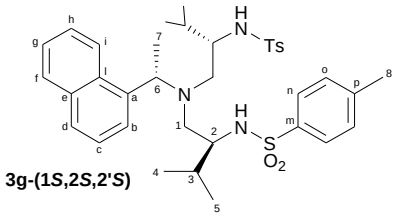
2g-(1*S*,2*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.15 (1 H, m, Ar*H*), 7.90 (1H, m, Ar*H*), 7.78 (1H, dd, *J* = 7.9 Hz, *J* = 1.8 Hz, Ar*H*), 7.55-7.43 (6H, m, Ar*H*), 6.96 (2H, d, *J* = 7.9 Hz, Ar*H*), 5.09 (1H, bs, N*H*), 4.38 (1H, q, *J* = 6.5 Hz, H^6), 2.92 (1H, m, H^2), 2.59 (1H, dd, , *J* = 12.3 Hz, *J* = 5.5 Hz, H^1), 2.26 (3H, s, $CH_3{}^8$), 2.19 (1H, dd, *J* = 12.3 Hz, *J* = 4.5 Hz, $H^{1'}$), 1.84 (1H, m, H^3), 1.40 (3H, d, *J* = 6.5 Hz, $CH_3{}^7$), 0.88 (3H, d, *J* = 6.8 Hz, $CH_3{}^4$), 0.83 (3H, d, *J* = 6.8 Hz, $CH_3{}^5$).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 142.9 (*C*), 140.9 (*C*), 137.7 (*C*), 134.2 (*C*), 131.4 (*C*), 129.4 (*C*H), 129.1 (*C*H), 127.5 (*C*H), 127.0 (*C*H), 125.9 (*C*H), 125.8 (*C*H), 125.6 (*C*H), 123.3 (*C*H), 123.1 (*C*H), 59.3 (C^2H), 54.5 (C^6H), 48.0 (C^1H_2), 30.3 (C^3H), 23.7 (C^7H_3), 21.4 (C^8H_3), 19.0 (C^4H_3), 18.8 (C^5H_3).

Elemental Analysis: Found: C, 70.3; H, 7.5; N, 6.7% Calc. for $C_{24}H_{30}N_2O_2S$: C, 70.2; H, 7.4; N, 6.8%.

$[\alpha]_D{}^{20}$ = - 45.09 (c 1.02 in $CHCl_3$).



3g-(1*S*,2*S*,2'*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.73 (1H, d, *J* = 8.2 Hz, *H*^{i}), 7.73 (2H, d, *J* = 7.8 Hz, Ar*H*), 7.70 (4H, d, *J* = 8.3 Hz, *H*^{n}), 7.56 (1H, pt, *J* = 8.2 Hz, Ar*H*), 7.43-7.37 (2H, m, Ar*H*), 7.29 (1H, m, Ar*H*), 7.24 (4H, d, *J* = 8.3 Hz, *H*^{o}), 5.36 (2H, d, *J* = 5.4 Hz, N*H*), 5.13 (1H, q, *J* = 6.5 Hz, *H*^{6}), 3.68 (2H, m, *H*^{2}), 2.48-2.42 (4H, m, *H*^{1}), overlapping with 2.42 (6H, s, C*H*$_3$^{8}), 1.76 (2H, m, *H*^{3}), 1.48 (3H, d, *J* = 6.5 Hz, C*H*$_3$^{7}), 0.68 (6H, d, *J* = 7.0 Hz, C*H*$_3$^{4}), 0.35 (6H, d, *J* = 7.0 Hz, C*H*$_3$^{5})

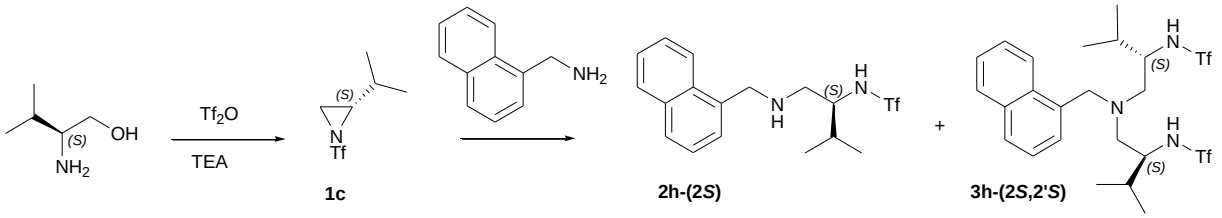
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 143.0 (*C*^{p}), 139.3 (*C*), 137.9 (*C*), 134.1 (*C*), 131.7 (*C*), 129.5 (*C*^{n}H), 128.4 (*C*H), 127.4 (*C*H), 127.1 (*C*^{o}H), 125.9 (*C*H), 125.2 (*C*H), 124.9 (*C*H), 124.6 (*C*H), 54.7 (*C*^{2}H), 53.3 (*C*^{6}H), 48.1 (*C*^{1}H$_2$), 29.6 (*C*^{3}H), 21.7 (*C*^{8}H$_3$), 18.0 (*C*^{4}H$_3$), 15.9 (*C*^{5}H$_3$), 11.1 (*C*^{7}H$_3$). A signal relative to an aromatic carbon was not detected.

Elemental Analysis: Found: C, 66.4; H, 7.3; N, 6.7% Calc. for $C_{36}H_{47}N_3O_4S_2$: C, 66.5; H, 7.3; N, 6.5%.

MS (EI): m/z 650 (M^++1).

$[\alpha]_D^{20}$ = - 33.65 (*c* 0.28 in $CHCl_3$).

3.2.17 Direct synthesis of 2h-(2*S*) and 3h-(2*S*,2'*S*)



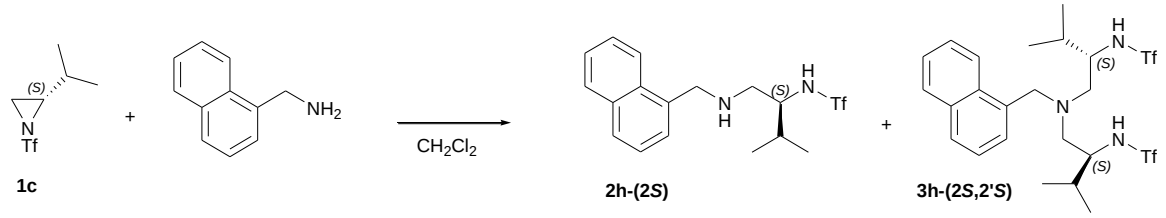
Entry	Reagents	MW (g/mol)	g	d	mL	mmol	EQ
	L-valinol	103.16	0.837	-	-	8.12	2.9
1	Et_3N	101.19	1.742	0.726	2.4	17.2	6.1
	$(CF_3SO_2)_2O$	282.14	5.031	1.677	3.0	17.8	6.4
2	1-naphthylmethylamine	157.21	0.441	1.073	0.4	2.80	1

Triethylamine was added to a solution of L-valinol in CH_2Cl_2 (30 mL). Then trifluoromethanesulfonic anhydride was added dropwise to the solution cooled to -78°C (entry 1). The resulting yellow solution was heated to -30 °C and stirred overnight. The solution was washed with HCl 0.1 M (120 mL) and brine (120 mL); organic phase was anhydrified with Na_2SO_4, filtered and diluted with CH_2Cl_2 (30 mL). The solution was cooled to -40 °C and a solution of 1-naphthylmethylamine in CH_2Cl_2 (10 mL) was added dropwise (entry 2). After 30', the solution was carried to room temperature. A white suspension immediately formed. After 48 h, reaction was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant. Main product was monoamine **2h-(2*S*)** (560 mg, 1.50 mmol, yield: 53%), while amine **3h-(2*S*,2'*S*)** was obtained mixed with unreacted aziridine **1c** and was recrystallized from n-hexane in CH_2Cl_2 (182 mg, 0.310 mmol, yield: 11%).

Crystals suitable for X-Ray analysis of monoamine **2h-(2*S*)** were obtained from CH_2Cl_2.

Crystals suitable for X-Ray analysis of amine **3h-(2*S*,2'*S*)** were obtained by layering n-hexane (4 mL) to a CH_2Cl_2 solution (5 mL).

3.2.18 Synthesis of 2h-(2*S*) and 3h-(2*S*,2'*S*)

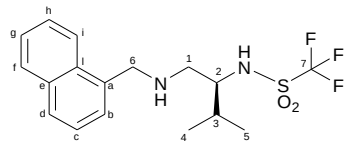


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1c-triflylaziridine	217.21	0.879	-	-	4.01	2
1-naphthylmethylamine	157.21	0.306	1.073	0.285	1.94	1

A solution of 1-naphthylmethylamine in distilled CH_2Cl_2 (10 mL) was added dropwise to a solution of (*S*)-2-isopropyl-1-triflylaziridine **1c** in distilled CH_2Cl_2 (20 mL) cooled to.-40°C. After 30 minutes the solution was carried to room temperature. A white suspension immediately formed. The reaction was followed by TLC. After 48 h the white suspension was filtered giving:

pure monoamine **2h-(2*S*)** = (MW 374.42 g/mol) 0.226 g, 0.604 mmol, yield: 31%;

pure amine **3h-(2*S*,2'*S*)** = (MW 591.63 g/mol) 0.600 g, 1.01 mmol, yield: 52% was obtained by layering *n*-hexane (5 mL) to a CH_2Cl_2 solution (5 mL).



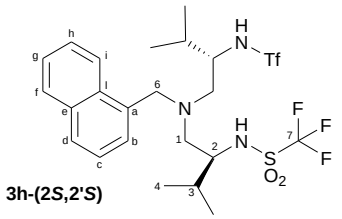
2h-(2*S*)

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 8.09 (1H, d, *J* = 8.0 Hz, H^i), 7.88 (1H, d, *J* = 8.0 Hz, H^f), 7.80 (1H, pst, *J* = 8.0 Hz, Ar*H*), 7.61-7.48 (2H, m, $H^{h\text{-}g}$), 7.43-7.42 (2H, m, Ar*H*), 4.28 (1H, d, *J* = 13.2 Hz, $H^{6'}$), 4.25 (1H, d, *J* = 13.2 Hz, H^6), 3.35 (1H, ddd, *J* = 8.0 Hz, *J* = 4.2 Hz, *J* = 4.8 Hz, H^2), 3.02 (1H, dd, *J* = 12.9 Hz, *J* = 4.2 Hz, $H^{1'}$), 2.80 (1H, dd, *J* = 12.9 Hz, *J* = 4.8 Hz, H^1), 1.86 (1H, dq, *J* = 8.0 Hz, *J* = 6.8 Hz, H^3), 0.97 (3H, d, *J* = 6,8 Hz, CH_3^4), 0.92 (3H, d, *J* = 6,8 Hz, CH_3^5), 0.51 (1H, bs, N*H*).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 129.0 (*C*H), 128.5 (C^4H), 126.5 (*C*H), 126.0 (*C*H), 125.4 (C^iH), 123.6 (C^gH), 61.0 (C^2H), 52.1 (C^6H_2), 49.5 (C^1H_2), 30.4 (C^3H), 19.2 (C^4H_3), 18.8 (C^5H_3). Signals relative to quaternary carbons were not detected.

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ -77.7 (m).

Elemental Analysis: Found: C, 54.7; H, 5.8; N, 7.3% Calc. for $C_{17}H_{21}F_3N_2O_2S$: C, 54.5; H, 5.6; N, 7.5%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.14 (1H, d, *J* = 8.1 Hz, H^{i}), 7.86 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.81 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.58-7.42 (4H, m, Ar*H*), 5.04 (2H, br, N*H*), 4.21 (1H, d, *J* = 13.2 Hz, H^{6}), 4.05 (1H, d, *J* = 13.2 Hz, $H^{6'}$), 3.61 (2H, m, H^{2}), 2.72-2.58 (4H, m, H^{1}), 1.92 (2H, m, H^{3}), 0.81 (6H, d, *J* = 6.9 Hz, CH_3^{4}), 0.65 (6H, d, *J* = 6.9 Hz, CH_3^{5}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 134.1 (*C*), 133.1 (*C*), 132.2 (*C*), 128.9 (*C*H), 128.8 (*C*H), 128.6 (*C*H), 126.5 (*C*H), 126.1 (*C*H), 125.4 (*C*H), 123.9 (C^{i}H), 119.5 (C_7, q, *J* = 321 Hz), 58.7 (C^{2}H), 57.0 ($C^{6}H_2$), 56.2 ($C^{1}H_2$), 29.4 (C^{3}H), 18.4 ($C^{4}H_3$), 16.6 ($C^{5}H_3$).

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ -77.6 (bs).

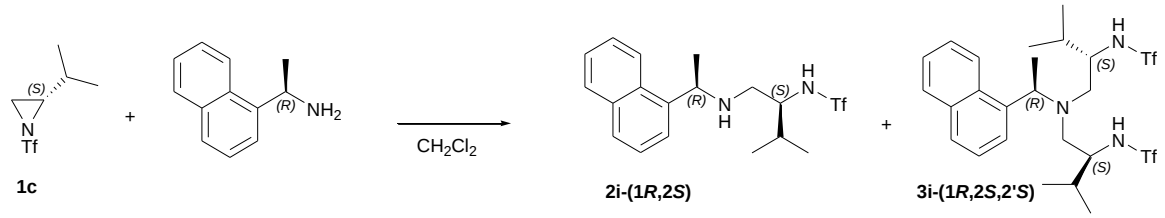
Elemental Analysis: Found: C, 46.6; H, 5.4; N, 7.1% Calc. for $C_{23}H_{31}F_6N_3O_4S_2$: C, 46.7; H, 5.3; N, 7.1%.

Crystals suitable for X-Ray analysis were obtained for:

- mono(sulphonamide) **2h** from CH_2Cl_2.

- bis(sulphonamide) **3h** by layering n-hexane (4 mL) to a CH_2Cl_2 solution (5 mL).

3.2.19 Synthesis of 2i-(1*R*,2*S*) and 3i-(1*R*,2*S*,2'*S*)

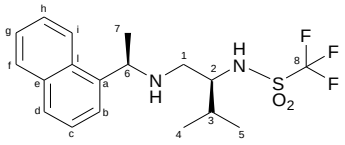


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1c-triflylaziridine	217.21	0.968	-	-	4.46	2
(*R*)-1-(1-naphthyl)ethyl amine	171.24	0.374	1.067	0.350	2.18	1

A solution of (*R*)-1-(1-naphthyl)ethyl amine in distilled CH_2Cl_2 (10 mL) was added dropwise to a solution of (*S*)-2-isopropyl-1-triflylaziridine **1c** in distilled CH_2Cl_2 (30 mL) cooled to.- 40 °C. After 30 minutes the solution was carried to room temperature. A white suspension immediately formed. The reaction was followed by TLC. After 90 h, the mixture was dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining:

monoamine **2i-(1*R*,2*S*)** = (MW 388.45 g/mol) 0.0932 g, 0.240 mmol, yield: 11%

pure amine **3i-(1*R*,2*S*,2'*S*)** = (MW 605.66 g/mol) 1.180 g, 1.95 mmol, yield: 89%.



2i-(1*R*,2*S*)

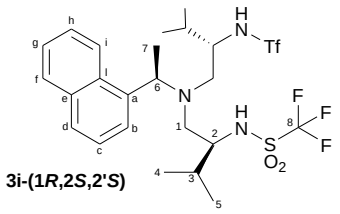
^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.15 (1H, d, *J* = 8.2 Hz, *H*^{i}), 7.90 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.79 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.59-7.47 (4H, m, Ar*H*), 4.67 (1H, q, *J* = 6.5 Hz, *H*^{6}), 3.33 (1H, m, *H*^{2}), 3.20 (2H, br, N*H*), 2.84 (1H, dd, *J* = 13.0 Hz, *J* = 5.0 Hz, *H*^{1}), 2.70 (1H, dd, *J* = 13.0 Hz, *J* = 4.3 Hz, *H*$^{1'}$), 1.87 (1H, m, *H*^{3}), 1.57 (3H, d, *J* = 6.6 Hz, C*H*$_3$^{7}), 0.93 (3H, d, *J* = 6.8 Hz, C*H*$_3$^{4}), 0.84 (3H, d, *J* = 6.8 Hz, C*H*$_3$^{5}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 139.7 (*C*), 134.2 (*C)*, 131.2 (*C*), 129.3 (*C*H), 128.1(*C*H), 126.4 (*C*H), 125.9 (*C*H), 125.8 (*C*H), 122.9 (*C*H), 122.6 (*C*^{i}H), 119.9 (*C*^{8}, q, *J* = 321 Hz*)*, 60.9 (*C*^{2}H), 53.8 (*C*^{6}H), 47.8 (*C*^{3}H$_2$), 30.5 (*C*^{3}H), 23.1 (*C*^{7}H$_3$), 19.2 (*C*^{4}H$_3$), 18.8 (*C*^{5}H$_3$).

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ -77.4 (s).

Elemental Analysis: Found: C, 55.7; H, 6.2; N, 7.0% Calc. for $C_{18}H_{23}F_3N_2O_2S$: C, 55.7; H, 6.0; N, 7.2%.

MS (EI): m/z 388 (M^+), 373 (M^+-CH_3), 255 (M^+-Tf), 184 (M^+-204).



3i-(1*R*,2*S*,2'*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.01 (1H, d, *J* = 9.4 Hz, H^{i}), 7.85 (1H, d, *J* = 9.4 Hz, Ar*H*), 7.80 (1H, d, *J* = 7.8 Hz, Ar*H*), 7.54-7.48 (3H, m, Ar*H*), 7.46 (1H, pst, *J* = 7.4 Hz, Ar*H*), 4.88 (1H, q, *J* = 6.5 Hz, H^{6}), 4.68 (2H, br, N*H*), 3.56 (2H, m, H^{2}), 2.75 (2H, dd, *J* = 13.5 Hz, *J* = 4.9 Hz, H^{1}), 2.63 (2H, dd, *J* = 13.5 Hz, *J* = 9.7 Hz, $H^{1'}$), 1.70 (2H, m, H^{3}), 1.57 (3H, d, *J* = 6.7 Hz, CH_3^{7}) 0.88 (6H, d, *J* = 6.9 Hz, CH_3^{4}), 0.31 (6H, d, *J* = 6.8 Hz, CH_3^{5}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 137.4 (*C*), 134.3 (*C)*, 132.1 (*C*), 129.1 (*C*H), 128.7(*C*H), 125.9 (*C*H), 125.8 (*C*H), 125.3 (*C*H), 125.1 (*C*H), 123.5 (C^{i}H), 119.6 (C^{8}, q, *J* = 321 Hz*)*, 59.2 (C^{2}H), 53.9 (C^{6}H), 53.2($C^{1}H_2$), 27.7 (C^{3}H), 19.5 ($C^{4}H_3$), 14.6 ($C^{5}H_3$), 12.4 ($C^{7}H_3$).

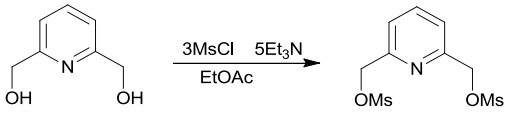
^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ - 77.56 (s).

Elemental Analysis: Found: C, 47.4; H, 5.8; N, 6.6% Calc. for $C_{24}H_{33}F_6N_3O_4S_2$: C, 47.6; H, 5.5; N, 6.9%.

MS (EI): m/z 590 (M^{+}-CH_3), 401 (M^{+}-Tf).

3.3 Modified pyridine

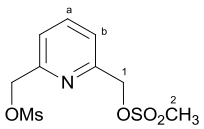
3.3.1 Synthesis.of 2,6-bis(methanesulfonyloxymethyl)pyridine[235]



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Pyridine$(OH)_2$	167.21	0.497	-	-	3.57	1
MsCl	114.55	1.27	1.480	0.86	11.1	3
Et_3N	101.19	1.82	0.726	2.5	17.9	5

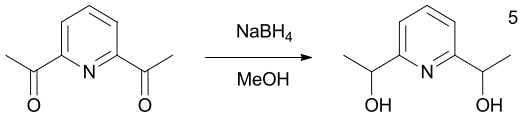
The reaction was performed in air. 2,6-bis(hydroxymethyl)pyridine was suspended in ethyl acetate (10 mL), triethylamine was added and the mixture was cooled to 0°C. Methanesulfonylchloride was added with caution and the mixture was stirred for 15 min, after which the reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate The organic extract was washed with brine and dried over Na_2SO_4, obtaining as a white solid. (MW 295.33 g/mol).

yield = 0,957 g, 3,24 mmol, 91% yield.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.88 (1H, t, *J* = 7.8 Hz, H^a), 7.52 (2H, d, *J* = 7.8 Hz, H^b), 5.36 (4H, s, CH_2^1), 3.13 (6H, s, CH_3^2).

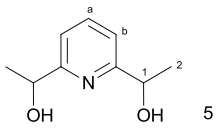
3.3.2 Reduction of 2,6-diacetyl pyridine[150]



Reagents	MW (g/mol)	g	mmol	EQ
2,6-diacetyl pyridine	163.17	2.50	15.3	1.5
$NaBH_4$	37.83	0.386	10.2	1

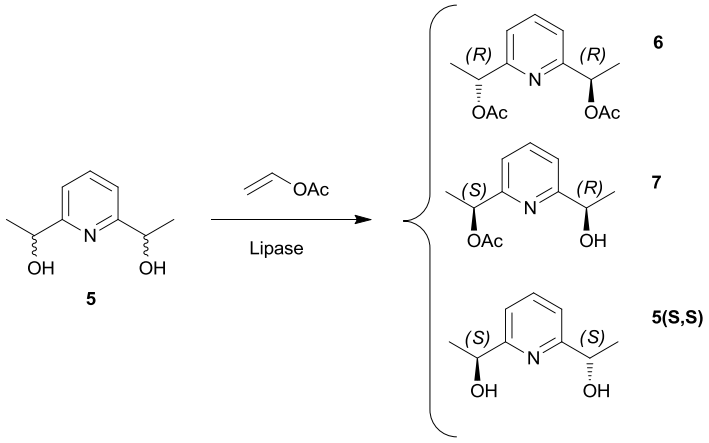
To a solution of 2,6-bisacetylpyridine in MeOH (30 mL), $NaBH_4$ was added in small portions at 0 °C and the mixture was stirred for 1h at room temperature. The reaction mixture was quenched with water and extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, obtaining 2,6-bis(1-hydroxy-ethyl)pyridine **5** as a colorless oil. (MW 167.21 g/mol).

yield: = 1.61 g, 9.61 mmol, 63 %



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.67 (1H, t, *J* = 7.7 Hz, H^a), 7.20 (2H, d, *J* = 7.7 Hz , H^b), 4.87 (2H, q, *J* = 6.6 Hz, H^1), 4.21 (2 H, brs, O*H*), 1.49 (6H, d, *J* = 6.6 Hz, CH_3^2).

3.3.3 Acetylation of 2,6-bis(1-hydroxy-ethyl)pyridine.[150]

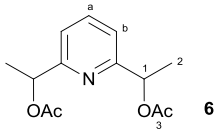


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
5-pyridine	167.21	0.366	-	-	2.19	1
Vinyl acetate	86.09	4.90	0.934	5.25	57.0	26
enzyme	-	0.919	-	-	-	-
molecular sieves	-	0.659	-	-	-	-

A mixture of **5**-pyridine, enzyme (Lipase acrylic resin from *Candida antarctica*), MS 4A and vinyl acetate was stirred for 10 h at room temperature. The mixture was dried and the crude purified by silica gel chromatography using:

a) *n*-hexane:ethyl acetate = 3:7 as eluant, obtaining (1'*R*,1''*R*)-2,6-bis(1-acetoxyethyl)pyridine **6** (MW 251.28 g/mol).

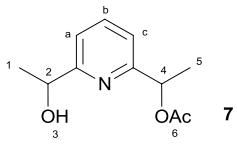
yield = 0.104 g, 0.413 mmol, 19 %



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.64 (1H, t, *J* = 7.7 Hz, H^a), 7.21 (2H, d, *J* = 7.7 Hz, H^b), 5.89 (2H, q, *J* = 6.6 Hz, H^1), 2.09 (6H, s, CH_3^3), 1.55 (6H, d, *J* = 6.6 Hz, CH_3^2).

b) *n*-hexane:ethyl acetate = 1:1 as eluant, obtaining (1'*R*,1''*S*)-2-(1-acetoxyethyl)-6-(1'-idroxyethyl)pyridine **7** (MW 209.24 g/mol).

yield = 0.185 g, 0.882 mmol, 40%



7

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.65 (1H, d, *J* = 7.8 Hz, H^b), 7.23 (1H, d, *J* = 7.8 Hz, H^a), 7.17 (1H, d, *J* = 7.8 Hz, H^c), 5.92 (1H, q, *J* = 6.6 Hz, H^4), 4.83 (1H, q, *J* = 6.6 Hz, H^2), 4.52 (1H, bs, OH^3), 2.12 (3H, s, CH_3^6), 1.60 (3H, d, *J* = 6.6 Hz, CH_3^1), 1.50 (3H, d, *J* = 6.6 Hz, CH_3^5).

c) ethyl acetate as eluant, obtaining (1'*S*,1''*S*)-2,6-bis(1-hydroxyethyl)pyridine **5(*S*,*S*)** (MW 167.21 g/mol).

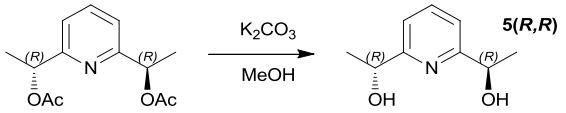
yield = 0.071 g, 0.425 mmol, 19 %

The spectroscopic (^{1}H NMR) and analytical data are in agreement with those reported in section **3.3.2**.

3.3.4 General Method for deacetylation to 5.[150]

Pyridine **6** (or **7**) - 0.1 M - in MeOH and K_2CO_3 were stirred for 10 min at room temperature. The mixture was then diluted with water and extracted with $CHCl_3$. The organic extract was washed with brine, and dried over Na_2SO_4, obtaining **5.** (MW 167.21 g/mol).

3.3.4.1 Deacetylation of 6.



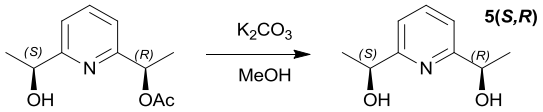
Reagents	MW (g/mol)	g	mmol	EQ
6-pyridine	251.28	0.243	0.967	1
K_2CO_3	138.21	0.401	2.90	3

(1′*R*,1″*R*)-2,6-Bis(1-hydroxyethyl)pyridine **5(*R*,*R*).**

yield = 0.1098 g , 0.657 mmol, 68%

The spectroscopic (^{1}H NMR) and analytical data are in agreement with those reported in section **3.3.2**.

3.3.4.2 Deacetylation of 7.



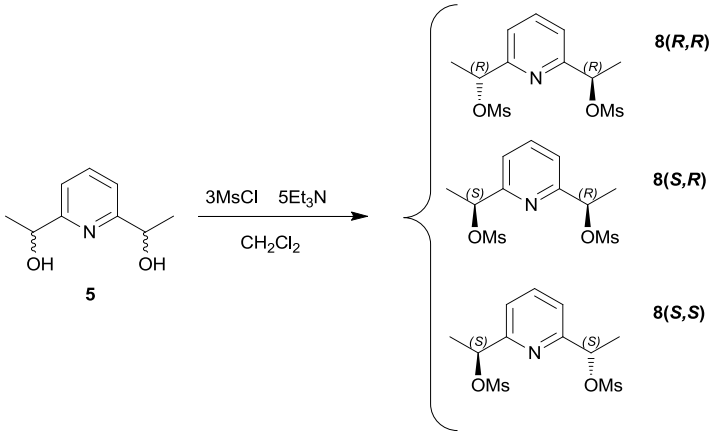
Reagents	MW (g/mol)	g	mmol	EQ
7-pyridine	209.24	1.582	7.561	1
K_2CO_3	138.21	3.13	22.7	3

meso-2,6-Bis(1-hydroxyethyl)pyridine **5(*S*,*R*).**

yield = 0.761 g , 4.55 mmol, 60%

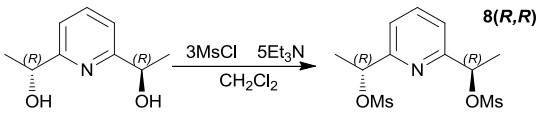
The spectroscopic (^{1}H NMR) and analytical data are in agreement with those reported in section **3.3.2**.

3.3.5 General Method for Mesylation: Preparation of 8.[150]



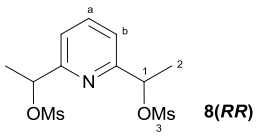
To a stirred solution of 2,6-Bis(1-hydroxyethyl)pyridine **5** (0.1 M) in CH_2Cl_2, Et_3N and MsCl were added at 0 °C. The mixture was stirred for 10 min at room temperature, diluted with water, and extracted with $CHCl_3$. The organic extract was washed with brine and dried over Na_2SO_4. The residue was purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining **8**. (MW 323.29 g/mol).

(1′*R*,1′′*R*)-2,6-Bis(1-methanesulfonyloxyethyl)pyridine 8(*R*,*R*)



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
5(*R*,*R*)	167.21	0.350	-	-	2.13	1
MsCl	114.55	0.731	1.480	0.494	6.38	3
Et_3N	101.19	1.08	0.726	1.48	10.6	5

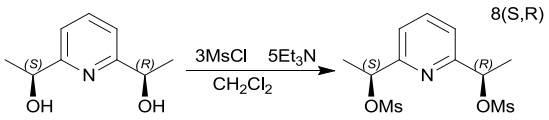
yield = 0.5522 g, 1.71 mmol, 80 %



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.82 (1H, t, *J* = 7.9 Hz, H^a), 7.45 (2H, d, *J* = 7.9 Hz, H^b), 5.78 (2H, q, *J* = 6.6 Hz, H^1), 2.98 (s, 6H, CH_3^3), 1.76 (6H, d, *J* = 6.6 Hz, CH_3^2);

$[\alpha]_D^{20}$ = +94.8 (*c* 0.5 in $CHCl_3$). $[\alpha]_{D\ reported}^{20}$= +121; optical purity = 78 %

meso-2,6-Bis(1-methanesulfonyloxyethyl)pyridine 8(*S,R*)



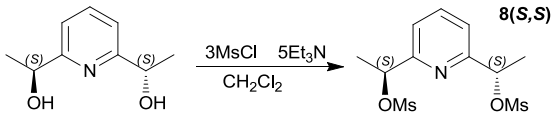
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
5(*S,R*)	167.21	0.761	-	-	4.55	1
MsCl	114.55	1.56	1.480	1.06	13.6	3
Et_3N	101.19	2.30	0.726	3.17	22.8	5

yield = 1.4465 g, 4.47 mmol, 98%

The spectroscopic data (^{1}H NMR) are in agreement with those reported for **8(*R,R*).**

$[\alpha]_D^{20}$ = +2.708 (*c* 0.5 in $CHCl_3$).

(1′S,1′′S)-2,6-Bis(1-methanesulfonyloxyethyl)pyridine 8(*S,S*)



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
5(*S,S*)	167.21	0.290	-	-	1.73	1
MsCl	114.55	0.595	1.480	0.402	5.20	3
Et_3N	101.19	0.877	0.726	1.21	8.66	5

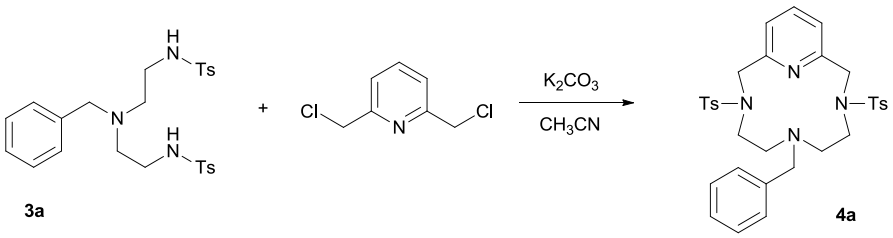
yield = 0.560 g, 1.73 mmol, quantitative

The spectroscopic data (^{1}H NMR) are in agreement with those reported for **8(*R,R*).**

$[\alpha]_D^{20}$ = -106 (*c* 0.5, $CHCl_3$) $[\alpha]_{D\ reported}^{20}$= -112; optical purity = 94,6%

3.4 Synthesis of macrocycles

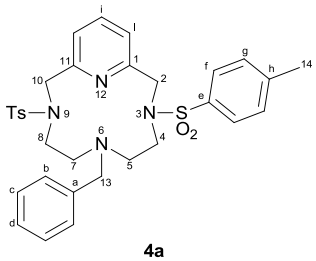
3.4.1 6-benzyl-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene - 4a - (A)



Reagents	MW (g/mol)	g	mmol	EQ
3a-amine	501.66	3.356	6.690	1
2,6-bis(chloromethyl)pyridine	176.04	1.177	6.723	1
K_2CO_3	138.21	2.770	20.07	3

A solution of 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane **3a**, 2,6-bis(chloromethyl)pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (30 mL) was stirred and heated under reflux for 11 h. The mixture was washed with water and extracted with ethyl acetate. The product was then crystallized slowly, adding *n*-hexane to a warm solution in ethyl acetate, yielding a white solid **4a**. (MW 604.78 g/mol).

yield = 3.439 g, 5.686 mmol, 85%.



4a

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.78 (1H, t, *J* = 7.7 Hz, H^{i}), 7.61 (4H, d, *J* = 8.0 Hz, H^{f}), 7.38 (2H, d, *J* = 7.7 Hz, H^{l}), 7.34–7.32 (3H, m, Ph*H*), 7.27 (4H, d, *J*= 8.0 Hz, H^{g}), 7.20 (2H, m, Ph*H*), 4.37 (4H, m, CH_2^{10} and CH_2^{2}), 3.52 (2H, s, H^{13}), 3.13 (4H, m, CH_2^{4} and CH_2^{8}), 2.45 (6H, s, CH_3^{14}), 2.32 (4H, m, $CH_2^{5}$and CH_2^{7}).

^{13}C NMR (100 MHz; $CDCl_3$; T = 300 K): δ 154.9 (C^{1}), 143.3 (C^{h}), 139.2 (C^{e}), 138.8 (C^{i}H), 136.0 (C^{a}), 129.7 (C^{g}H), 128.6 (C^{Ph}H), 128.3 (C^{Ph}H), 128.2 (C^{Ph}H), 127.1 (C^{f}H), 124.0 (C^{l}H), 59.4 ($C^{13}H_2$), 54.3 ($C^{5}H_2$), 50.0 ($C^{2}H_2$), 44.2 ($C^{4}H_2$), 21.5 ($C^{14}H_3$).--> quello pubblicato su aricolo Henry

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): δ 312 (N^{12}), 94 (*N*-Ts), 32 (N^{6}).

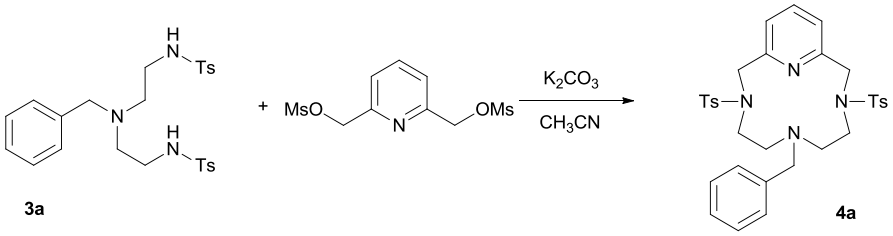
Elemental analysis: found: C, 63.6; H, 6.2; N, 9.2%; calc. for $C_{32}H_{36}N_4O_4S_2$: C, 63.6; H, 6.0; N, 9.3%.

MS (FAB): m/z (%)605 (80) $[MH]^+$, 449 (100) $[M – Ts]^+$

UV-vis: (*c* 5.2 10^{-5} mol/L in $CHCl_3$ in 1 cm cuvettes): λ_{max} [nm], (log ε) = 241 (4.19); 263 (3.93) nm.

Crystals suitable for X-ray structural determination were obtained by crystallization of macrocycle **4a** from a dichloromethane–toluene solution.

3.4.2 6-benzyl-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene - 4a - (B)

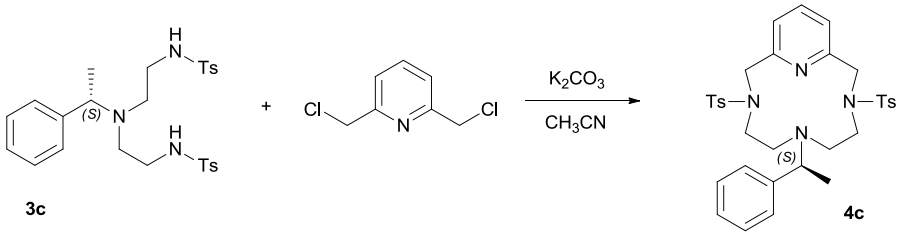


Reagents	MW (g/mol)	g	mmol	EQ
3a-amine	501.66	1.853	3.693	1
Pyridine$(OMs)_2$	295.33	1.091	3.696	1
K_2CO_3	138.21	1.531	11.08	3

A solution of 1,7-ditosyl-4-benzyl-1,4,7-triazaheptane **3a**, pyridine$(OMs)_2$ and micronized anhydrous potassium carbonate in distilled acetonitrile (85 mL) was stirred and heated under reflux for 9 h. The mixture was washed with water and extracted with ethyl acetate. The product was then crystallized in ethyl acetate, yielding a white solid **4a**. (MW 604.78 g/mol).

yield = 1.96 g, 3.25 mmol, 88%.

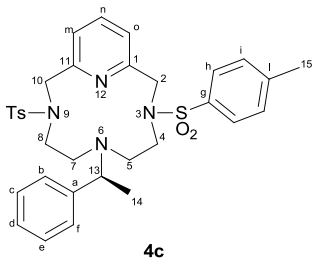
3.4.3 6-[(*S*)-1-phenylethyl]-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene - 4c-(13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
3c-amine	515.69	3.040	5.505	1
2,6-bis(chloromethyl)pyridine	176.04	0.969	5.505	1
K_2CO_3	138.21	3.043	22.02	4

A solution of 1,7-ditosyl-4-[(*S*)-1-phenylethyl)]-1,4,7-triazaheptane **3c**, 2,6-bis(chloromethyl)pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (30 mL) was stirred and heated under reflux for 11 hours. The mixture was washed with water end extracted with ethyl acetate. The product was then crystallized layering *n*-hexane on a warm solution in ethyl acetate, yielding a white solid **4c-(13*S*).** (MW 618.81 g/mol).

yield = 2.460 g, 3.975 mmol, 72%.



4c

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.78 (1H, t, *J* = 7.7 Hz, H^{n}), 7.57 (4H, d, *J* = 8.1 Hz, H^{h}), 7.40 (2H, d, *J* = 7.7 Hz, H^{o}), 7.34–7.32 (3H, m, Ar*H*), 7.26 (4H, d, *J* = 8.1 Hz, Ar*H*), 7.20 (2H, m, Ar*H*), 4.32 (4H, m, CH_2^{2}), 3.58 (1H, q, *J*= 6.6 Hz, H^{13}), 3.13 (2H, m, CH_2), 3.00–2.92 (2H, m, CH_2), 2.44 (6H, s, $C^{15}H_3$), 2.23–2.19 (4H, m, CH_2^{4}), 1.24 (3H, d, *J* = 6.6 Hz, CH_3^{14}).

^{13}C NMR (75 MHz, $CDCl_3$; T = 300 K) δ 155.3 (*C*), 145.4 (*C*), 139.2 (C^{n}H), 136.2 (*C*H), 130.1 (*C*H), 128.7 (*C*H), 127.6 (C^{i}H), 127.5 (C^{f}H), 127.3 (C^{h}H), 124.6 (C^{o}H), 61.7 (*C*H), 54.8 ($C^{2}H_2$), 50.1 ($C^{4}H_2$), 45.7 ($C^{5}H_2$), 21.9 ($C^{15}H_3$), 20.5 ($C^{14}H_3$). One signal relative to an aromatic quaternary carbon was not detected.

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): *δ* 312 (N^{12}), 95 (*N*-Ts), 41 (N^{6}).

Elemental Analysis: Found: C, 64.0; H, 6.2; N, 9.1% Calc. for $C_{33}H_{38}N_4O_4S_2$: C, 64.05; H, 6.2; N, 9.05%.

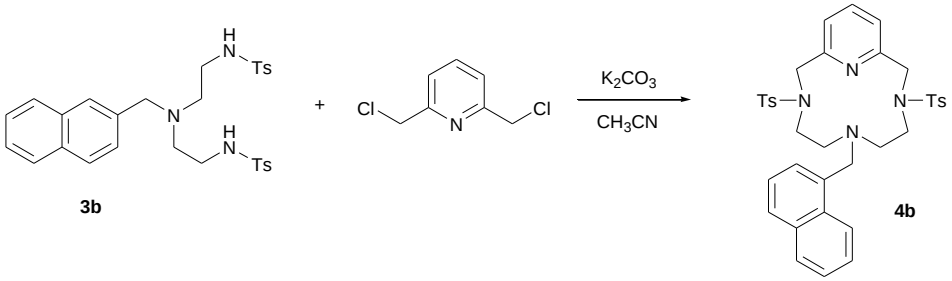
MS: m/z 619 (M^{+}100%), 516 (45).

IR ν (cm^{-1}) = 1743.6 (w), 1594.1 (w), 1492.0 (w), 1460.1 (w), 1344.6 (m), 1160.6 (s).

$[\alpha]_D^{20}$ = -50 (*c* 1 in $CHCl_3$).

6-[(*R*)-1-phenylethyl]-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene **4c-(13*R*)** was synthesized in the same way. $[\alpha]_D^{20}$ = +50 (*c* 1 in $CHCl_3$).

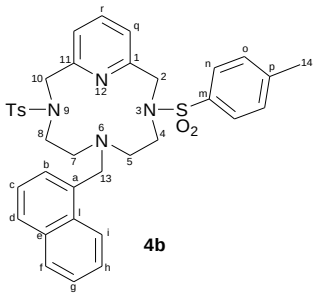
3.4.4 6-methyl(1-naphthyl)-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene - 4b



Reagents	MW (g/mol)	g	mmol	EQ
3b-amine	551.72	0.842	1.53	1
2,6-bis(chloromethyl)pyridine	176.04	0.269	1.53	1
K_2CO_3	138.21	0.633	4.58	3

A solution of amine **3b** and 2,6-bis(chloromethyl)pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (35 mL) was stirred and heated under reflux for 45 hours. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using toluene:dichloromethane:2-propanol = 90:10:5 as eluant, obtaining a white solid **4b** (MW 654.84 g/mol).

yield = 0.508 g, 0.776 mmol, 51%).

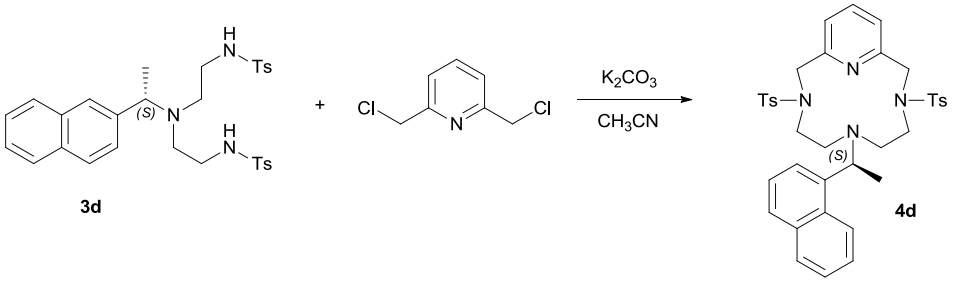


^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.11 (1H, d, *J* = 8.1 Hz, *H*^{i}), 7.90-7.83 (2H, m, Ar*H*), 7.76 (1H, pst, *J* = 7.8 Hz, *H*^{r}), 7.50 (4H, d, *J* = 8.2 Hz, *H*^{n}), overlapping with 7.52-7.23 (6H, m, Ar*H*), 7.19 (4H, d, *J* = 8.2 Hz, *H*^{o}), 4.31 (4H, br, C*H*$_2^{2}$), 3.93 (2H, br, C*H*$_2^{13}$), 3.07 (4H, m, C*H*$_2^{4}$), 2.39 (6H, s, C*H*$_3^{14}$) overlapping with 2.36 (4H, m, C*H*$_2^{5}$).

^{13}C NMR (75 MHz, $CDCl_3$; T = 400 K) δ 155.0 (*C*), 143.3 (*C*), 138.8 (*C*^{r}H), 135.9 (*C*), 134.5 (*C*), 133.9 (*C*), 129.7 (*C*^{o}H), 128.4 (*C*H), 128.1 (*C*H), 127.0 (*C*^{n}H), 125.6 (*C*H), 125.6 (*C*H), 125.3 (*C*H), 124.7 (*C*^{i}H), 124.0 (*C*H), 58.1 (*C*^{13}H$_2$), 54.3 (*C*^{2}H$_2$), 50.4 (*C*^{5}H$_2$), 44.3 (*C*^{4}H$_2$), 21.5 (*C*^{14}H$_3$). A signal relative to an aromatic quaternary carbon and an aliphatic carbon were not detected.

Elemental Analysis: Found: C, 66.2; H, 5.8; N, 8.4% Calc. for $C_{36}H_{38}N_4O_4S_2$: C, 66.0; H, 5.8; N, 8.6%.

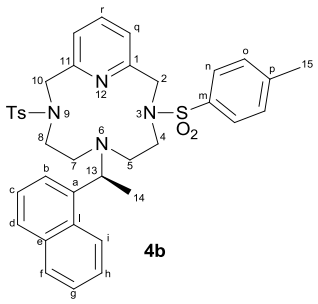
3.4.5 6-[(*S*)-1-(1-naphthyl)ethyl]-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene - 4d-(13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-amine	565.75	2.451	4.231	1
2,6-bis(chloromethyl)pyridine	176.04	0.745	4.231	1
K_2CO_3	138.21	2.339	16.92	4

A solution of 1,7-ditosyl-4-[(*S*)-1-(1-naphthyl)-ethyl)]-1,4,7-triazaheptane **3d**, 2,6-bis-chloromethylpyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (25 mL) was stirred and heated under reflux for 10 hours. The mixture was washed with water and extracted with ethyl acetate. The product was then crystallized layering hexane over a warm solution in ethyl acetate, yielding a white solid **4d-(13*S*)**. (MW 668.87g/mol).

yield = 2.275 g, 3.401 mmol, 80.4%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 K): δ 8.16 (1H, d, *J* = 8.4 Hz, H^{i}), 7.94 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.87-7.77 (2H, m, Ar*H*), 7.56–7.54 (4H, m, Ar*H*), 7.43 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.41 (4H, d, *J* = 8.1 Hz, H^{n}), 7.13 (4H, d, *J* = 8.1, H^{o}), 4.37 (1H, q, *J* = 6.5 Hz, H^{13}), 4.27 (4H, m, CH_2^{2} and CH_2^{10}), 3.09 (2H, m, CH_2^{7} and $CH_2^{7'}$), 2.82-2.85 (2H, m, CH_2^{5} and $CH_2^{5'}$), 2.37 (6H, s, CH_3^{15}), 2.28-2.32 (4H, m, CH_2^{4} and CH_2^{8}), 1.34 (3H, d, *J* = 6.5 Hz, CH_3^{14}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 155.3 (*C*), 143.6 (*C*), 140.5 (*C*), 139.2 (*C*), 136.0 (*C*), 134.4 (*C*), 132.0 (*C*), 130.0 (C^{n}H), 129.1 (*C*H), 127.9 (*C*H), 127.4 (C^{o}H), 126.1 (*C*H), 125.8 (*C*H), 125.7 (*C*H), 124.8 (*C*H), 124.6 (*C*H), 124.5 (*C*H), 58.2 (C^{13}H), 54.8 ($C^{2}H_2$), 50.2 ($C^{4}H_2$), 45.6 ($C^{5}H_2$), 21.8 ($C^{15}H_3$), 14.5 ($C^{14}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): δ 313 (N^{12}), 39 (N^{6}).The signals relative to *N*(Ts) were not detected.

Elemental Analysis: Found: C, 66.2; H, 6.2; N, 8.3% Calc. for $C_{37}H_{40}N_4O_4S_2$: C, 66.4; H,

6.0; N, 8.4%.

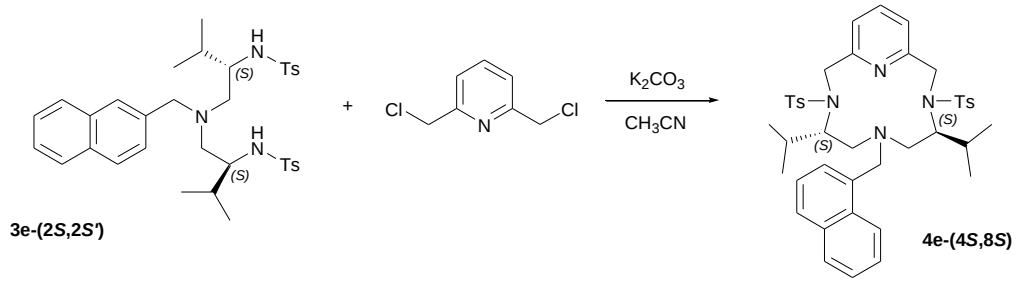
MS: m/z 669 (M^+ 100%).

IR ν (cm^{-1}) = 1595.1 (w), 1457.7 (w), 1357.0 (w), 1339.8 (s), 1253.4 (w), 1158.0 (s).

$[\alpha]_D^{20}$ = -43 (*c* 1 in $CHCl_3$).

6-[(*R*)-1-(1-naphthyl)ethyl]-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1]pentadeca-1(15),11,13-triene **4d-(13*R*)** was synthesized in the same way. $[\alpha]_D^{20}$ = +43 (*c* 1 in $CHCl_3$).

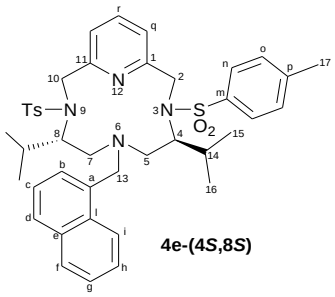
3.4.6 Synthesis of 4e-(4S,8S)



Reagents	MW (g/mol)	g	mmol	EQ
3e-amine	635.88	0.330	0.520	1
2,6-bis(chloromethyl)pyridine	176.04	0.0914	0.520	1
K_2CO_3	138.21	0.228	1.65	3.2

A solution of amine **3e-(2*S*,2*S'*)**, 2,6-bis(chloromethyl) pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (12 mL) was stirred and heated under reflux for 45 hours. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using toluene:dichloromethane:2-propanol = 90:10:5 as eluant, obtaining a white solid **4e-(4*S*,8*S*)**. (MW 739.00 g/mol).

yield = 0.215 g, 0.291 mmol, 56%.



4e-(4*S*,8*S*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.35 (1H, d, *J* = 8.0 Hz, H^{i}), 7.86 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.76 (1H, d, *J* = 8.0 Hz, Ar*H*) 7.66-7.58 (3H, m, Ar*H*), 7.53 (1H, pt, *J* = 7.6 Hz, Ar*H*), 7.43 (1H, pt, *J* = 7.6 Hz, Ar*H*), 7.29-7.11 (6H, m, Ar*H*), 7.02 (4H, d, *J* = 7.8 Hz, H^{o}), 4.72 (2H, d, *J* = 15.6 Hz, H^{2}), 4.30 (1H, d, *J* = 13.5 Hz, H^{13}), 4.18 (1H, d, *J* = 13.5 Hz, $H^{13'}$), 3.78 (2H, d, *J* = 15.6 Hz, $H^{2'}$), 3.68 (2H, dd, *J* = 15.6 Hz *J* = 6.9 Hz, H^{5}), 3.51 (2H, m, H^{4}), 2.29 (6H, s, CH_3^{17}), 2.19 (2H, m, $H^{5'}$), 1.19 (2H, m, *H*), 0.58 (6H, d, *J* = 6.9 Hz, CH_3^{15}), 0.48 (6H, br, CH_3^{16}).

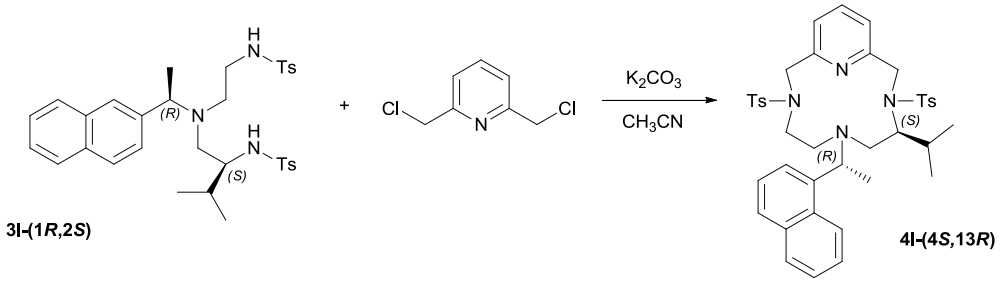
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 156.5 (*C*), 142.3 (*C*), 139.3 (*C*), 137.2 (*C*H), 135.7 (*C*), 134.0 (*C*), 132.7 (*C*), 128.9 (*C*H), 128.5 (*C*H), 128.0 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 125.9 (*C*H), 125.7 (*C*H), 125.4 (*C*H), 125.0 (*C*H), 120.2 (*C*H), 65.6 (C^{4}H), 57.2 ($C^{13}H_2$), 53.1 ($C^{5}H_2$), 48.9 ($C^{2}H_2$), 30.5 (C^{14}H), 21.4 ($C^{17}H_3$), 20.4 ($C^{15}H_3$), 20.2 ($C^{16}H_3$).

Elemental Analysis: Found: C, 68.4; H, 6.8; N, 7.4% Calc. for $C_{42}H_{50}N_4O_4S_2$: C, 68.3; H, 6.8; N, 7.6%.

MS (FAB): m/z 739 (M^{+}+1).

$[\alpha]_D^{20}$ = + 1.04 (*c* 1.01 in $CHCl_3$).

3.4.7 Synthesis of 4l-(4*S*,13*R*)



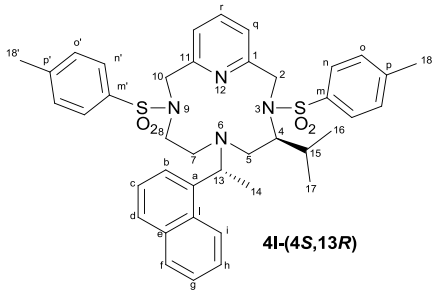
3l-(1*R*,2*S*)

4l-(4*S*,13*R*)

Reagents	MW (g/mol)	g	mmol	EQ
3l-amine	607.83	0.220	0.361	1
2,6-bis(chloromethyl)pyridine	176.04	0.0636	0.361	1
K_2CO_3	138.21	0.200	1.44	4

A solution of amine **3l-(1*R*,2*S*)**, 2,6-bis(chloromethyl) pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (17 mL) was stirred and heated under reflux for 22 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a white solid **4l-(4*S*,13*R*)**.(MW 710.95 g/mol).

yield = 0.142 g, 0.200 mmol, 55%).



4l-(4*S*,13*R*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.25 (1H, m, H^{i}), 7.87 (1H, m, Ar*H*), 7.77 (1H, d, *J* = 7.6 Hz, Ar*H*) 7.65-7.62 (2H, m, Ar*H*), 7.50-7.40 (7H, m, Ar*H*), 7.26 (4H, covered by solvent residual peak), 7.17 (2H, m, Ar*H*), 4.80-4.20 (4H, m, CH_2), 3.80-2.60 (4H, m, CH_2), 2.43 (3H, s, CH_3^{18}), 2.37 (3H,s, C$H_3^{18'}$), 2.00-1.76 (1H, m, CH_2), 1.46 (3H, d, *J* = 6.2 Hz, CH_3^{14}), 0.77 (3H, m, CH_3^{16}), 0.59 (3H, m, CH_3^{16}). Some signals were too broad to be detected.

^{1}H NMR (400 MHz; $C_6D_5CD_3$; T = 373 k) δ 8.36 (1H, d, *J* = 8.6 Hz, H^{i}), 7.68 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.60-7.54 (3H, m, Ar*H*), 7.48-7.44 (3H, m, Ar*H*), 7.38 (1H, pst, *J* = 7.5 Hz, Ar*H*), 7.31 (1H, d, *J* = 7.0 Hz, Ar*H*), 7.27 (1H, d, *J* = 7.0 Hz, Ar*H*), 7.10-6.80 (7H, m, Ar*H* overlapped with toluene), 4.59 (1H, q, *J* = 6.1 Hz, H^{13}), 4.29-4.14 (4H, m, CH_2^{2} and CH_2^{10}), 3.77 (1H, m, , CH_2^{8}), 3.28-3.08 (4H, m, CH_2^{4} and CH_2^{7}), 2.93 (1H, m, CH_2^{5}), 2.08 (3H, s, C$H_3^{18'}$), 2.05 (3H, s, CH_3^{18}), 2.01 (1H, m, CH_2^{5}), 1.88 (1H, m, H^{15}),1.46 (3H, d, J = 6.6 Hz, CH_3^{14}), 0.90 (3H, d, J = 6.7 Hz, CH_3^{17}), 0.69 (3H, d, J = 6.7 Hz, CH_3^{16}).

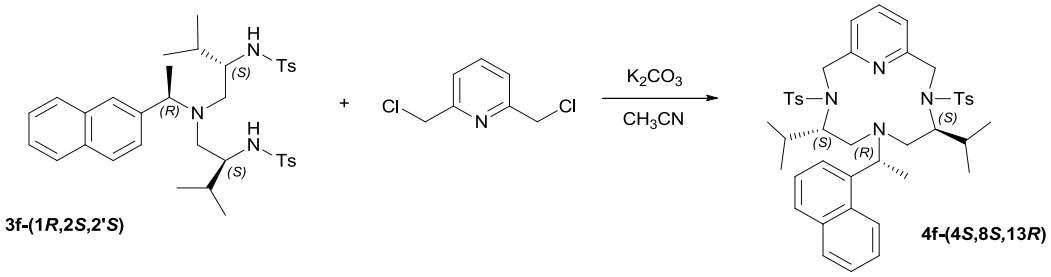
^{13}C NMR (75 MHz; $C_6D_5CD_3$; T = 300 k) δ 156.3 (*C*), 156.2 (*C*), 141.9 *(C*), 134.5 (*C*), 132.1 (*C*),129.2 (*C*H), 128.9 (*C*H), 128.8 (*C*H), 128.7 (*C*H), 127.8 (*C*), 127.8 (*C*H), 127.4 (*C*H), 126.9 (*C*H) 125.3 (*C*H), 125.2 (*C*H), 125.0 (*C*H), 124.0 (*C*^{i}H),), 123.2 (*C*H), 20.8 (*C*H), 20.7 (*C*H), 20.6 (*C*H). Signals relative to aromatic and aliphatic carbons were not detected.

Elemental Analysis: Found: C, 67.1; H, 6.9; N, 7.6% Calc. for $C_{40}H_{46}N_4O_4S_2$: C, 67.6; H, 6.5; N, 7.9%.

MS (EI): m/z 555 (M-NaphCH_3CH), 155 (NaphCH_3CH).

$[\alpha]_D^{20}$ = - 60.7 (*c* 1.01 in $CHCl_3$).

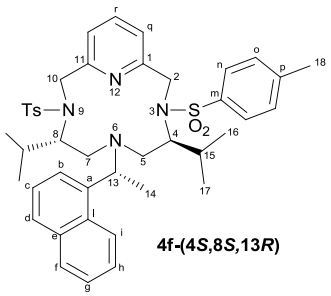
3.4.8 Synthesis of 4f-(4*S*,8*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
3f-amine	649.91	0.715	1.10	1
2,6-bis(chloromethyl)pyridine	176.04	0.194	1.10	1
K_2CO_3	138.21	0.608	4.40	4

A solution of amine **3f-(1*R*,2*S*,2'*S*)**, 2,6-bis(chloromethyl) pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (37 mL) was stirred and heated under reflux for 116 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 6:4 as eluant, obtaining a white solid **4f-(4*S*,8*S*,13*R***).(MW 753.03 g/mol).

yield = 0.471 g, 0.626 mmol, 57%).



4f-(4*S*,8*S*,13*R*)

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.58 (1H, d, *J* = 8.1 Hz, H^{i}), 7.89 (1H, m, Ar*H*), 7.83 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.69 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.64-7.42 (8H, m, Ar*H*), 7.12 (4H, d, *J* = 7.8 Hz, H^{o}), 7.05 (2H, m, Ar*H*), 5.18 (1H, m, H^{13}), 4.72 (2H, m, H^{2}), 3.94-3.82 (6H, m, *H*), 2.63-2.60 (2H, m, *H*), 2.40 (2H, m, *H*) overlapping with 2.33 (6H, s, CH_3^{18}), 1.57 (3H, d, *J* = 6.5 Hz, CH_3^{14}), 0.44 (12H, m, $CH_3^{16\text{-}17}$).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 156.5 (*C*), 142.5 (*C*), 142.2 (*C*), 138.9 (*C*), 137.0 (*C*H), 134.2 (*C*), 131.7 (*C*), 129.2 (C^{o}H), 128.9 (*C*H), 127.8 (C^{n}H), 127.0 (*C*H), 126.0 (*C*H), 125.9 (*C*H), 125.8 (C^{h}H), 125.2 (*C*H), 124.0 (C^{i}H), 120.7 (*C*H), 66.5 (*C*H), 50.8 (CH_2), 49.5 (CH_2), 30.0 (*C*H), 23.8 ($C^{14}H_3$), 21.5 ($C^{18}H_3$), 21.1 ($C^{16}H_3$). A signal relative to a CH was not detected.

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 33.2 (N^{6}). The signals relative to *N*-Ts and N^{12} were not detected.

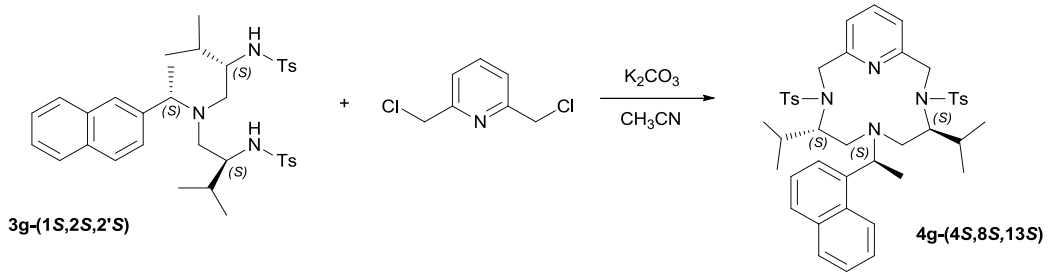
^{1}H NMR (300 MHz; $C_6D_5CD_3$; T = 300 k) δ 8.74 (1H, d, *J* = 8.8 Hz, H^{i}), 7.99 (1H, d, *J* = 7.2 Hz, H^{b}), 7.68 (4H, pst, *J* = 8.0 Hz, H^{n}) overlapping with 7.69-7.66 (1H, m, H^{g}), 7.57-7.47 (2H, m, H^{d} and H^{h}), 7.38 (1H, pst, *J* = 7.5 Hz, H^{c}), 7.29 (1H, pst, *J* = 7.5 Hz, H^{f}), 7.05-7.03 (1H, m, H^{r}), 6.86 (4H, d, *J* = 8.0 Hz, H^{o}), 6.68 (2H, d, *J* = 7.8 Hz, H^{q}), 5.39 (1H, q, *J* = 6.6 Hz, H^{13}), 4.62 (2H, d, *J* = 15.9 Hz, H^{2}), 4.14-4.06 (4H, m, H^{4} and H^{5}), 4.02-3.93 (2H, m, $H^{2'}$), 2.96 (2H, d, *J* = 15.0 Hz, $H^{5'}$), 2.02 (6H, s, CH_3^{18}), 1.68 (3H, d, *J* = 6.6 Hz, CH_3^{14}), 1.39 (2H, m, H^{15}), 0.58 (12H, m, $CH_3^{16\text{-}17}$).

^{13}C NMR (75 MHz; $C_6D_5CD_3$; T = 300 k) δ 157.4 (*C*), 142.7 (*C*), 141.9 *(C*), 140.4 (*C*), 136.3 (C^{r}H), 134.9 (C), 132.5 (C), 129.0 (C^{o}H), 128.2 (C^{n}H), 127.2 (C^{d}H), 126.3 (C^{b}H), 125.9 (C^{d}H) overlapping with 125.9 (C^{h}H), 125.2 (C^{f}H), 124.5 (C^{i}H), 120.5 (C^{q}H), 66.4 (C^{4}H), 57.2 (C^{13}H), 51.4 ($C^{2\text{-}5}H_2$), 30.9 (C^{15}H), 23.5 ($C^{14}H_3$), 21.0 ($C^{16}H_3$), 20.8 ($C^{18}H_3$). A signal relative to an aromatic carbon was not detected.

Elemental Analysis: Found: C, 68.4; H, 7.4; N, 7.1% Calc. for $C_{43}H_{52}N_4O_4S_2$: C, 68.6; H, 7.0; N, 7.4%.

MS (FAB): m/z 753 (M^{+}+1).

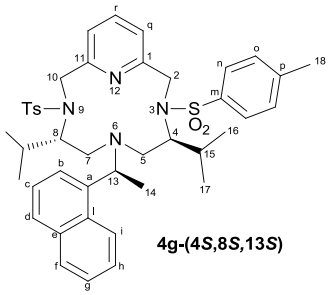
3.4.9 Synthesis of 4g-(4S,8S,13S)



Reagents	MW (g/mol)	g	mmol	EQ
3g-amine	649.91	0.0888	0.137	1
2,6-bis(chloromethyl)pyridine	176.04	0.0240	0.136	1
K_2CO_3	138.21	0.0700	0.506	4

A solution of amine **3g-(1*S*,2*S*,2'*S*)**, 2,6-bis(chloromethyl) pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (6 mL) was stirred and heated under reflux for 53 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using n-hexane:dichloromethane:2-propanol = 80:17.5:2.5 as eluant, obtaining a white solid **4g-(4*S*,8*S*,13*S*)**. (MW 753.03 g/mol).

yield = 0.0512 g, 0.0679 mmol, 50%.



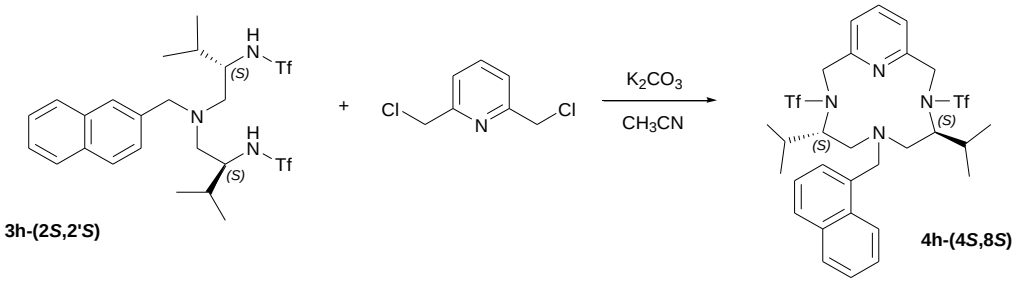
^{1}H NMR (300 MHz; $CDCl_3$;T = 300 k) δ 8.54 (1H, m, H^{i}), 7.89 (1H, m, Ar*H*), 7.85 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.77 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.64-7.41 (8H, m, Ar*H*), 7.09-6.99 (6H, m, Ar*H*), 5.01 (1H, m, H^{13}), 4.76 (2H, m, H^{2}), 3.86 (2H, m, $H^{2'}$), 3.77 (2H, m, H^{4}), 3.55 (2H, m, H^{5}), 2.36 (2H, m, $H^{5'}$), 2.29 (6H, s, CH_3^{18}), 1.48 (3H, d, *J* = 6.6 Hz, CH_3^{14}), 1.34-1.23 (2H, m, H^{15}), 0.60 (6H, m, CH_3^{16}), 0.38 (6H, m, CH_3^{17}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 156.3 (*C*), 142.3 (*C*), 141.4 (*C*), 139.2 (*C*), 137.3 (*C*H), 134.1 (*C*), 132.5 (*C*), 128.9 (C^{n}H), 128.8 (*C*H), 127.7 (C^{o}H), 127.6 (*C*H), 126.7 (*C*H), 126.2 (*C*H), 125.4 (*C*H), 124.1 (*C*H), 120.7 (*C*H), 66.0 (C^{4}H), 56.0 (C^{13}H), 51.0 ($C^{5}H_2$), 49.3 ($C^{2}H_2$), 30.2 (C^{15}H), 21.4 ($C^{18}H_3$), 20.8 ($C^{14}H_3$), 20.1 ($C^{16}H_3$) overlapping with 20.1 ($C^{17}H_3$).

Elemental Analysis: Found: C, 68.6; H, 7.2; N, 7.4% Calc. for $C_{43}H_{52}N_4O_4S_2$: C, 68.6; H, 7.0; N, 7.4%.

MS (FAB): m/z 753 (M^{+}+1).

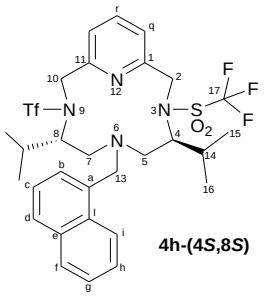
3.4.10 Synthesis of 4h-(4*S*,8*S*)



Reagents	MW (g/mol)	g	mmol	EQ
3h-amine	591.63	0.350	0.592	1
2,6-bis(chloromethyl)pyridine	176.04	0.108	0.612	1
K_2CO_3	138.21	0.245	1.75	3

A solution of amine **3h-(2*S*,2'*S*)** (0.350 g, 0.592 mmol), 2,6-bis(chloromethyl) pyridine (0.108 g, 0.612 mmol) and micronized anhydrous potassium carbonate (0.245 g, 1.75 mmol) in distilled acetonitrile (15 mL) was stirred and heated under reflux for 28 h. The mixture was dried and purified by silica gel chromatography using toluene:dichloromethane:2-propanol = 85:10:5 as eluant, obtaining a yellow oil **4h-(4*S*,8*S*)**. (MW 694.75 g/mol).

yield = 0.218 g, 0.314 mmol, 53%.



4h-(4*S*,8*S*)

^{1}H NMR (400 MHz; C_6D_6; T = 300 k) δ 7.78-7.76 (2H, m, Ar*H*), 7.72-7.66 (2H, m, Ar*H*), 7.45-7.37 (2H, m, Ar*H*), 7.27-7.22 (1H, m, Ar*H*),7.17-7.07 (3H, m, Ar*H*), 4.77-4.47 (4H, m, C*H*), 3.89-3.85 (4H, m, *H*), 3.10-3.05 (2H, m, *H*), 1.09 (2H, m, H^{14}), 0.69 (6H, bs, CH_3^{15}), 0.40 (6H, bs, CH_3^{16}). Two C*H* signals were not detected. At room temperature, this compound gives very broad signals in $CDCl_3$.

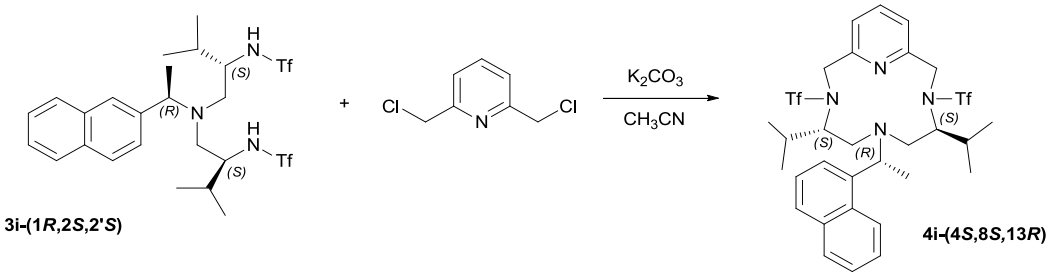
^{13}C NMR (100 MHz; C_6D_6; T = 300 k) δ 136.9 (*C*H), 129.1 (*C*H), 128.4 (*C*H), 128.3 (*C*H), 126.2 (*C*H), 126.0 (*C*H), 125.4 (*C*H), 56.9 (C^2H), 53.2 ($C^{13}H_2$), 49.9 (CH_2), 29.4 (C^{14}H), 19.9 ($C^{15}H_3$), 19.6 ($C^{16}H_3$). Signals relative to quaternary carbons and aromatic *C*H were not detected. ^{19}F NMR (376 MHz; C_6D_6; T = 300 k) δ - 74.5 (bs).

Elemental Analysis: Found: C, 51.8; H, 5.4; N, 8.0% Calc. for $C_{30}H_{36}F_6N_4O_4S_2$: C, 51.9; H, 5.2; N, 8.1%.

MS (FAB): m/z 695 (M^++1), 561 (M^+-Tf).

$[\alpha]_D^{20}$ = - 0.85 (*c* 0.860 in $CHCl_3$).

3.4.11 Synthesis of 4i-(4*S*,8*S*,13*R*) (conventional heating)

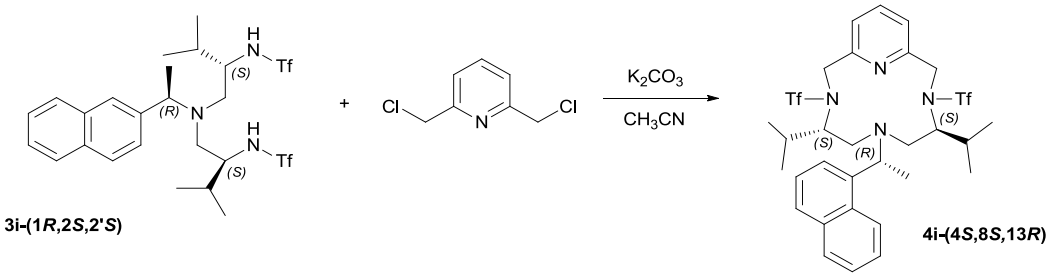


Reagents	MW (g/mol)	g	mmol	EQ
3i-amine	605.66	0.402	0.665	1
2,6-bis(chloromethyl)pyridine	176.04	0.118	0.671	1
K_2CO_3	138.21	0.290	2.10	3

A solution of amine **3i-(1*R*,2*S*,2'*S*)**, 2,6-bis(chloromethyl) pyridine and micronized anhydrous potassium carbonate in distilled acetonitrile (20 mL) was stirred and heated under reflux for 110 hours. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using toluene:dichloromethane:2-propanol = 85:10:5 as eluant, obtaining a white solid **4i-(4*S*,8*S*,13*R*)** (MW 708.78 g/mol).

yield = 0.192 g, 0.271 mmol, 39%.

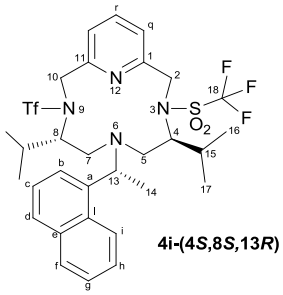
3.4.12 Synthesis of 4i-(4*S*,8*S*,13*R*) (microwave heating)



Reagents	MW (g/mol)	g	mmol	EQ
3i-amine	605.66	0.387	0.639	1
2,6-bis(chloromethyl)pyridine	176.04	0.116	0.658	1
K_2CO_3	138.21	0.265	1.92	3

This synthesis can be performed in the air. A solution of amine **3i-(1*R*,2*S*,2'*S*)**, 2,6-bis(chloromethyl) pyridine and micronized potassium carbonate in distilled acetonitrile (13 mL) was added in a microwave tube. The mixture was stirred and heated by microwave irradiation for 4 hours and 30 minutes at 150°C. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using toluene:dichloromethane:2-propanol = 85:10:5 as eluant, obtaining a white solid **4i-(4*S*,8*S*,13*R*)**. (MW 708.78 g/mol).

yield = 0.250 g, 37.8 mmol, 59%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.42 (1H, m, H^{i}), 7.81-7.78 (2H, m, Ar*H*), 7.68-7.62 (2H, m, Ar*H*), 7.52-7.40 (3H, m, Ar*H*), 7.20-7.17 (2H, m, Ar*H*), 5.16 (1H, q, *J* = 6.3 Hz, H^{13}), 4.91 (2H, d, *J* = 16.0 Hz, H^{2}), 4.40 (2H, d, *J* = 16.0 Hz, $H^{2'}$), 3.82 (2H, m, H^{5}), 2.98 (2H, m, $H^{5'}$), 1.65 (2H, m, H^{4}), 1.51 (3H, d, *J* = 6.3 Hz, CH_3^{14}), 0.73 (6H, bs, CH_3^{16}), 0.44 (6H, bs, CH_3^{17}). Two CH signals were not detected.

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 155.1 (*C*), 141.2 (*C*), 137.9 (*CH*), 134.2 (*C*), 131.6 (*C*), 128.9 (*C*H), 127.2 (*C*H), 126.4 (*C*H), 126.0 (*C*H), 125.3 (*C*H), 123.6 (*C*H), 122.1 (*C*H), 69.1 (C^{4}H), 57.4 (C^{13}H), 50.9 ($C^{2}H_2$), 50.4 ($C^{5}H_2$),29.9 (C^{15}H), 24.0 ($C^{14}H_3$), 21.0 ($C^{16}H_3$), 19.3 ($C^{17}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 31.35 (N^{6}), The signal relative to *N*-Tf and N^{12} were not detected.

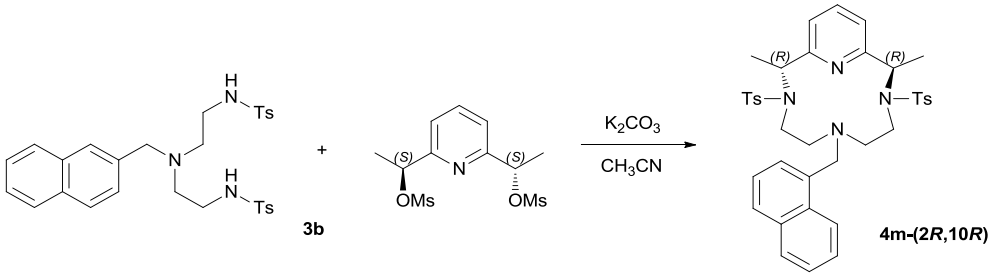
^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ - 74.15 (s).

Elemental Analysis: Found: C, 52.4; H, 5.3; N, 8.0% Calc. for $C_{31}H_{38}F_6N_4O_4S_2$: C, 52.5; H, 5.4; N, 7.9%.

MS (FAB): m/z 709 (M^{+}+1), 575 (M^{+}-133).

$[\alpha]_D^{20}$ = + 117 (*c* 0.005 in CH_2Cl_2).

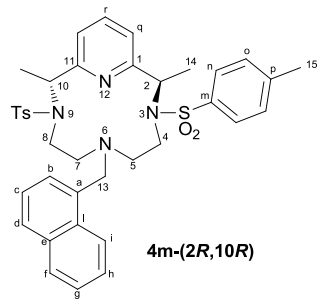
3.4.13 Synthesis of 4m-(2R,10R)



Reagents	MW (g/mol)	g	mmol	EQ
3b-amine	551.72	0.948	1.72	1
8(*S*,*S*)	323.39	0.556	1.72	1
K_2CO_3	138.21	0.713	5.16	3

A solution of amine **3b**, pyridine **8(*S*,*S*)**and micronized anhydrous potassium carbonate in distilled acetonitrile (17 mL) was stirred and heated under reflux for 10 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a solid **4m-(2*R*,10*R*)**. (MW 682.89 g/mol).

yield = 0.144 g, 0.211 mmol, 12%.



4m-(2*R*,10*R*)

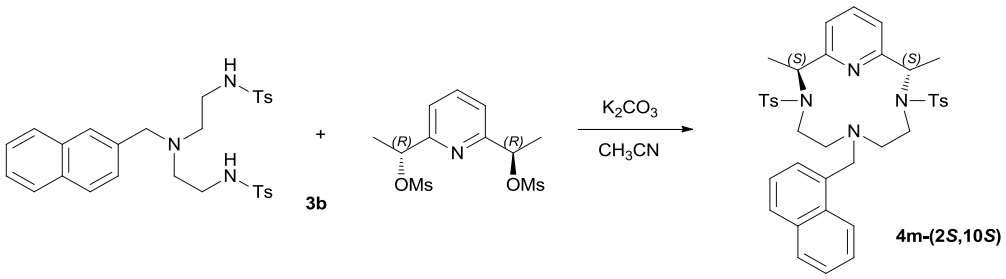
^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.09 (1H, m, H^{i}), 7.87(1H, m, Ar*H*), 7.79 (1H, d, *J* = 8.1 Hz, H^{r}), 7.71 (4H, d, *J* = 8.1 Hz, H^{n}), 7.66 (2H, pst, *J* = 7.8 Hz, Ar*H*), 7.49-7.46 (3H, m, Ar*H*), 7.42 (1H, pst, *J* = 8.0 Hz, Ar*H*), 7.32-7.21 (3 H, m, Ar*H* and H^{q}), overlapping with 7.27 (4H, d, *J* = 8.1 Hz, H^{o}), 5.15 (2H, q, *J* = 6.9 Hz, H^{2}), 3.97 (1H, d, *J* = 13.4 Hz, CH_2^{13}), 3.88 (1H, d, *J* = 13.4 Hz, $CH_2^{13'}$), 3.37-3.27 (2H, m, CH_2^{5} and CH_2^{7}), 3.12-3.04 (2H, m, $CH_2^{5'}$ and $CH_2^{7'}$), 2.85-2.75 (2H, m, CH_2^{4} and CH_2^{8}), 2.53-2.45 (2H, m, $CH_2^{4'}$ and $CH_2^{8'}$), 2.42 (6H, s, CH_3^{15}), 1.39 (6H, d, *J* = 6.9 Hz, CH_3^{14}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 159.3 (C^{1}), 143.1 (C^{p}), 138.3 (*C*), 138.0 (C^{r}H), 134.6 (*C*), 134.0 (*C*), 132.5 (*C*), 129.7 (C^{o}H), 128.6 (*C*H), 128.1 (*C*H), 127.3 (C^{n}H), 127.1 (*C*H), 125.8 (*C*H), 125.6 (*C*H), 125.3 (*C*H), 124.7 (C^{i}H), 121.8 (C^{q}H), 58.1 (C^{2}H), 57.2 ($C^{13}H_2$), 51.2 ($C^{4}H_2$), 40.4 ($C^{5}H_2$), 21.6 ($C^{15}H_3$), 16.6 ($C^{14}H_3$).

MS (FAB): m/z 683 (M^{+}+1), 527 (M-Ts)

$[\alpha]_D^{20}$ = + 36.7 (*c* 0.5 in $CHCl_3$).

3.4.14 Synthesis of 4m-(2S,10S)



Reagents	MW (g/mol)	g	mmol	EQ
3b-amine	551.72	0.867	1.57	1
8(*R*,*R*)	323.39	0.508	1.57	1
K_2CO_3	138.21	0.651	4.71	3

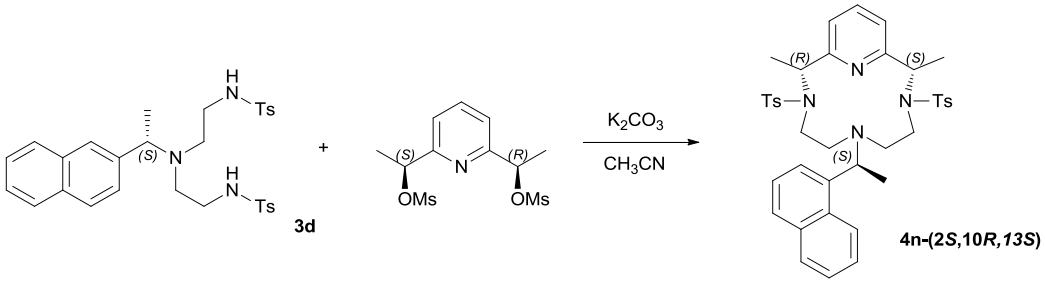
A solution of amine **3b**, pyridine **8(*R*,*R*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (15 mL) was stirred and heated under reflux for 10 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a white solid **4m-(2*S*,10*S*)**. (MW 682.89 g/mol).

yield = 0.370 g, 0.542 mmol, 34%.

The spectroscopic (^{1}H and ^{13}C NMR) and analytical data are in agreement with those reported for **4m-(2*R*,10*R*)** in section **3.4.13**.

$[\alpha]_D^{20}$ = - 52.0 (*c* 0.5 in $CHCl_3$).

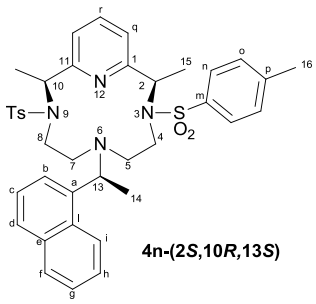
3.4.15 Synthesis of 4n-(2*S*,10*R*,13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-(*1S*)	565.22	0.997	1.76	1
8(*S*,*R*)	323.39	0.571	1.76	1
K_2CO_3	138.21	0.731	5.29	3

A solution of amine **3i**, pyridine **8(*S*,*R*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (16 mL) was stirred and heated under reflux for 7 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 8:2 as eluant, obtaining a solid **4n-(2*S*,10*R*,13*S*)**. (MW 696.92 g/mol).

yield = 0.324 g, 0.465 mmol, 26%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.21 (1H, m, H^{i}), 7.90 (1H, m, Ar*H*), 7.83 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.64 (2H, d, *J* = 7.4 Hz, Ar*H*), 7.61 (1H, m, Ar*H*), 7.53-7.46 (4H, m, Ar*H*), 7.34 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.27-7.25 (2H, m, Ar*H*), 7.17 (2H, d, *J* = 7.7 Hz, Ar*H*), 7.14 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.14 (2H, dq, *J* = 6.6 Hz, H^{2} and $H^{10,}$), 4.42 (1H, q, *J*= 6.6 Hz, H^{13}), 3.38 (1H, m, CH_2), 3.30 (1H, m, CH_2), 3.18 (1H, m, CH_2), 3.06 (1H, m, CH_2), 2.95 (1H, m, CH_2), 2.43 (3H, s, CH_3^{16}), 2.38 (3H, s, C$H_3^{16'}$), 2.22 (1H, m, CH_2), 1.56 (1H, m, CH_2), 1.35 (3H, d, *J*= 6.6 Hz, CH_3^{14}), 1.26 (3H, d, *J*= 6.6 Hz, CH_3^{15}), 1.18 (3 H, d, *J*= 6.6 Hz, C$H_3^{15'}$), 0.90 (1H, m, CH_2).

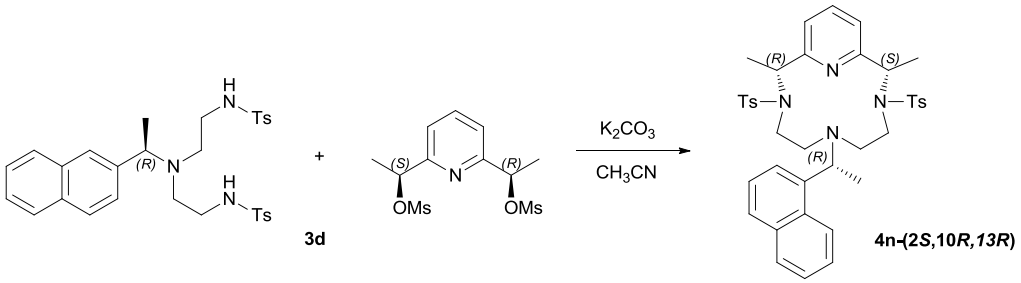
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 157.8 (*C*), 157.5 (*C*), 143.4 (*C*), 143.0 (*C*), 139.9 (*C*), 138.4 (*C*H), 137.9 (*C*), 137.8 (*C*), 134.1 (*C*), 132.0 (*C*), 129.8 (*C*H), 129.6 (*C*H), 128.8 (*C*H), 127.6 (C^{r}H), 127.4 (*C*H), 127.1 (*C*H), 125.8 (*C*H), 125.6 (*C*H), 125.4 (*C*H), 124.7 (*C*H), 124.6 (C^{i}H), 124.1 (*C*H), 124.0 (*C*H), 58.9 (C^{13}H), 56.8 (C^{10}H), 56.5 (C^{2}H), 43.2 (*C*H_2), 41.9 (*C*H_2), 31.7 (*C*H_2), 31.1 (*C*H_2), 22.8 (*C*H_2), 21.7 ($C^{16}H_3$), 15.1 ($C^{14}H_3$), 14.3 ($C^{15}H_3$), 14.3 ($C^{18'}H_3$).

MS (FAB): m/z 697 (M^{+}+1), 541 (M-Ts), 387 (M-2Ts),155 (Ts).

$[\alpha]_D^{20}$ = - 27.2 (*c* 0.5 in $CHCl_3$).

Crystals suitable for X-ray structural determination were obtained by crystallization of macrocycle **4n-(2*S*,10*R*,13*S*)**. from a dichloromethane–toluene solution.

3.4.16 Synthesis of 4n-(2*S*,10*R*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-(1*R*)	565.22	0.908	1.61	1
8(*S*,*R*)	323.39	0.520	1.61	1
K_2CO_3	138.21	0.666	4.82	3

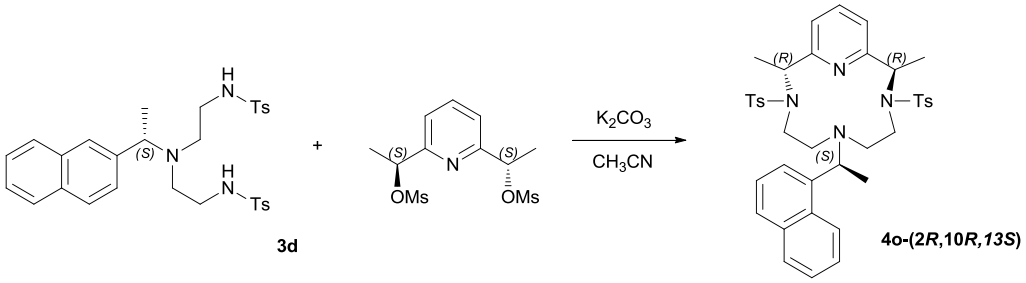
A solution of amine **3d-(1*R*)**, pyridine **8(*S*,*R*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (16 mL) was stirred and heated under reflux for 7 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 8:2 as eluant, obtaining a solid **4n-(2*S*,10*R*,13*R*)**. (MW 696.92 g/mol).

yield = 0.335 g, 0.480 mmol, 30%.

The spectroscopic (^{1}H and ^{13}C NMR) and analytical data are in agreement with those reported for **4n-(2*S*,10*R*,13*S*)** in section **3.4.15**.

$[\alpha]_D^{20}$ = + 16.7 (*c* 0.5 in $CHCl_3$).

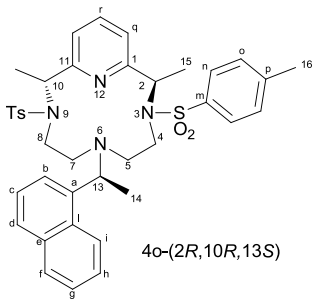
3.4.17 Synthesis of 4o-(2*R*,10*R*,13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-(1*S*)	565.22	0.457	0.808	1
8(*S*,*S*)	323.39	0.261	0.808	1
K_2CO_3	138.21	0.335	2.42	3

A solution of amine **3d**, pyridine **8(*S*,*S*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (8 mL) was stirred and heated under reflux for 15 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a white solid **4o-(2*R*,10*R*,13*S*)**. (MW 696.92 g/mol).

yield = 0.256 g, 0.367 mmol, 45%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.21 (1H, m, H^{i}), 7.89 (1H, m, Ar*H*), 7.81 (1H, dd, *J* = 7.1 Hz, *J* = 2.1 Hz, Ar*H*), 7.65 (1H, pst, *J* = 7.8 Hz, H^{r}), 7.56 (4H, d, *J* = 8.2 Hz, H^{n}), 7.48-7.43 (3H, m, Ar*H*), 7.23-7.19 (2H, m, Ar*H*), overlapping with 7.20 (4H, d, *J* = 8.2 Hz, H^{o}), 5.12 (2H, q, *J* = 6.9 Hz, H^{2}), 4.38 (1H, q, *J* = 6.5 Hz, H^{13}), 2.99-2.73 (6H, m, CH_2), 2.46 (2H, m, CH_2), 2.41 (6H, s, C$H_3{}^{16}$), 1.40 (3H, d, *J* = 6.5 Hz, C$H_3{}^{14}$), 1.35 (6H, d, *J* = 6.9 Hz, C$H_3{}^{15}$).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 159.3 (C^{1}), 143.0 (C^{p}), 139.9 (C^{a}), 138.1 (*C*), 138.0 (C^{r}H), 134.2 (*C*) 131.8 (C^{a}), 129.6 (C^{o}H), 128.8 (*C*H), 127.7 (*C*H), 127.1 (C^{n}H), 125.7 (*C*H), 125.5 (*C*H), 125.3 (*C*H), 124.9 (*C*H), 124.5 (*C*H), 121.8 (C^{q}H), 58.3 (C^{13}H), 49.8 ($C^{5}H_2$), 42.0 ($C^{4}H_2$), 21.6 ($C^{16}H_3$), 19.5 ($C^{14}H_3$), 17.0 ($C^{15}H_3$).

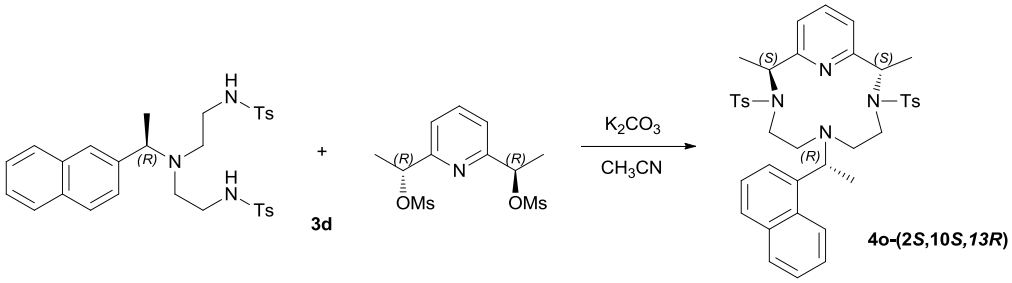
^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): δ 303 (N^{12}), 100 (*N*Ts), 41 (N^{6}).

MS (FAB): m/z 697 (M^{+}+1), 541 (M-Ts), 387 (M-2Ts).

$[\alpha]_D{}^{20}$ = + 26.4 (*c* 0.4 in $CHCl_3$).

Crystals suitable for X-ray structural determination were obtained by crystallization of macrocycle **4o-(2*S*,10*R*,13*S*)**. from a dichloromethane–toluene solution.

3.4.18 Synthesis of 4o-(2*S*,10*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-(1*S*)	565.22	0.252	0.445	1
8(*R*,*R*)	323.39	0.144	0.445	1
K_2CO_3	138.21	0.184	1.33	3

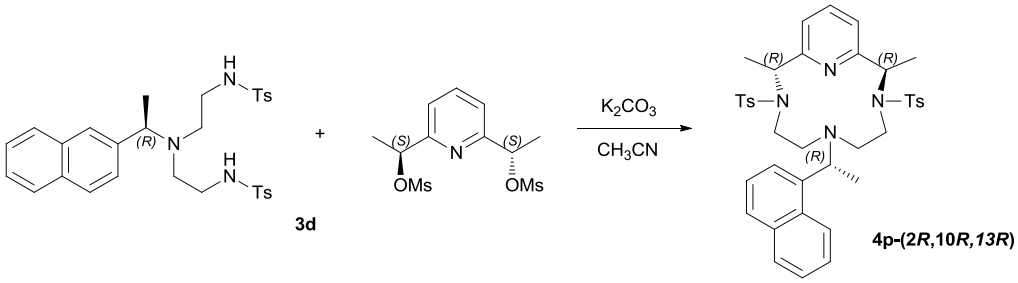
A solution of amine **3d**, pyridine **8(*R*,*R*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (14 mL) was stirred and heated under reflux for 15 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 7:3 as eluant, obtaining a white solid **4o-(2*S*,10*S*,13*R*)**. (MW 696.92 g/mol).

yield = 0.165 g, 0.237 mmol, 53%.

The spectroscopic (^{1}H and ^{13}C NMR) and analytical data are in agreement with those reported for **4o-(2*R*,10*R*,13*S*)** in section **3.4.17**.

$[\alpha]_D^{20}$ = -38.6 (*c* 0.3 in $CHCl_3$).

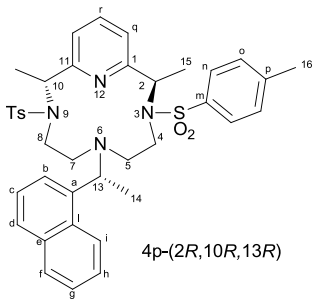
3.4.19 Synthesis of 4p-(2*R*,10*R*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
3d-(1*R*)	565.22	0.695	1.23	1
8(*S*,*S*)	323.39	0.398	1.23	1
K_2CO_3	138.21	0.510	3.69	3

A solution of amine **3d**, pyridine **8(*S*,*S*)** and micronized anhydrous potassium carbonate in distilled acetonitrile (39 mL) was stirred and heated under reflux for 18 h. The resulting mixture was washed with water end extracted with ethyl acetate, dried and purified by silica gel chromatography using *n*-hexane:ethyl acetate = 6:4 as eluant, obtaining a white solid **4p-(2*R*,10*R*,13*R*)**. (MW 696.92 g/mol).

yield = 0.655 g, 0.940 mmol, 76%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.18 (1H, m, H^{i}), 7.90 (1H, m, Ar*H*), 7.78 (1H, d, *J* = 5.6 Hz, Ar*H*), 7.68 (1H, pst, *J* = 5.8 Hz, H^{r}), 7.62 (4H, d, *J* = 6.2 Hz, H^{n}), 7.50-7.44 (4H, m, Ar*H*), 7.26 (2H, d, *J* = 5.8 Hz, H^{q}), 7.20 (4H, d, *J* = 6.2 Hz, H^{o}), 5.15 (2H, q, *J* = 5.2 Hz, H^{2} and H^{10}), 4.42 (1H, q, *J* = 6.2 Hz, H^{13}), 3.28 (2H, m, CH_2^{5} and CH_2^{7}), 3.06 (2H, m, $CH_2^{5'}$ and $CH_2^{7'}$), 2.81 (2H, m, CH_2^{4} and CH_2^{8}), 2.38 (6H, s, CH_3^{16}), 2.32 (2H, m, $CH_2^{4'}$ and $CH_2^{8'}$), 1.40 (3H, d, *J* = 6.2 Hz, CH_3^{14}) overlapping with 1.42 (6H, d, *J* = 5.2 Hz, CH_3^{15}).

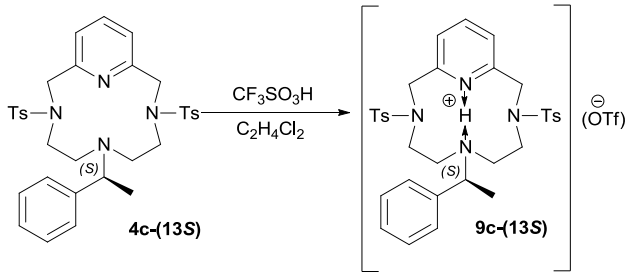
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 159.4 (*C*), 143.1 (*C*), 141.3 (*C*), 138.4 (*C*), 138.2 (*C*H), 134.3 (*C*), 129.7 (*C*H), 129.1 (*C*H), 127.5 (*C*H), 127.2 (*C*H), 125.5 (*C*H), 125.4 (*C*H), 123.9 (*C*H), 123.7 (*C*H), 121.9 (*C*H), 58.3 (C^{13}H), 48.8 (CH_2), 40.7 (CH_2), 31.7 (CH_2), 22.8(CH_2), 21.6 ($C^{16}H_3$), 17.0 ($C^{14}H_3$), 14.9 ($C^{15}H_3$).

MS (FAB): m/z 697 (M^{+}+1), 543 (M-Ts).

$[\alpha]_D^{20}$ = + 40.4 (*c* 0.6 in $CHCl_3$).

3.5 Synthesis of protonated ligands and metal complexes

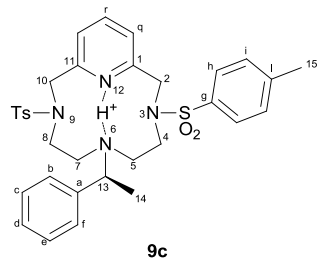
3.5.1 Synthesis of 9c-(13*S*)



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4c-(13*S*)	618.81	0.200	-	-	0.323	1
CF_3SO_3H	150.08	0.053	1.70	0.03	0.355	1.1

Ligand **4c-(13*S*)** was dissolved in distilled dichloroethane (5 mL). Triflic acid was added and the solution stirred for 2 hours. The solution was dried, then *n*-hexane (10 mL) was added and the solid **9c-(13*S*)** filtered in air. (MW 768.89 g/mol).

yield = 0.055 g, 0.071 mmol, 22%.



9c

^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 11.38 (1H, s, N*H*), 7.80 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.71 (1H, pt, *J* = 7.7 Hz, Ar*H*), 7.61 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.52 (2H, m, Ar*H*), 7.45-7.39 (5H, m, Ar*H*), 7.34 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.22 (1H, d, *J* = 7.7 Hz, Ar*H*), 7.04 (1H, d *J* = 7.7 Hz, Ar*H*), 5.60 (1H, q, *J* = 7.0 Hz, *H*^{13}), 4.65 (1H, d, *J* = 17.1 Hz, C*H*$_2$), 4.17 (1H, d, *J* = 17.1 Hz, C*H*$_2$), 4.16-4.09 (2H, m, C*H*$_2$), 3.88 (1H, m, C*H*$_2$), 3.74-3.64 (3H, m, C*H*$_2$), 3.50-3.39 (3H, m, C*H*$_2$), 2.50 (3H, s, C*H*$_3$), 2.45 (3H, s, C*H*$_3$) overlapping with 2.45-2.40 (1H, m, C*H*$_2$), 1.85 (3H, d, *J* = 7.0 Hz, C*H*$_3$^{14}) overlapping with 1.85-1.80 (1H, m, C*H*$_2$).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 156.8 (*C*), 155.5 (*C*), 145.4 (*C*), 144.8 (*C*), 139.6 (*C*H), 134.4 (*C*), 133.4 (*C*), 132.7 (*C*), 130.7 (*C*H), 130.6 (*C*H), 130.4 (*C*H), 129.9 (*C*H), 129.5 (*C*H), 127.9 (*C*H), 127.6 (*C*H), 122.8 (*C*H), 122.2 (*C*H), 58.3 (*C*^{13}H), 52.8 (*C*H$_2$), 51.7 (*C*H$_2$), 51.5 (*C*H$_2$), 46.2 (*C*H$_2$), 44.4 (*C*H$_2$), 21.8 (*C*H$_3$Ts), 21.7 (*C*H$_3$Ts). One *C*H$_2$ and *C*^{14}H$_3$ signals were not detected.

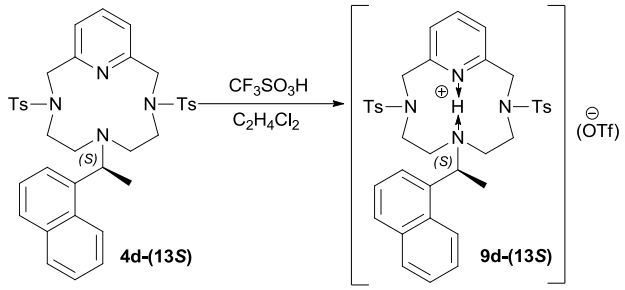
^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 282.0 (*N*^{12}), 52.2 (*N*^{6}). The signals relative to *N*-Ts were not detected.

Elemental Analysis: Found: C, 52.9; H, 5.1; N, 7.6% Calc. for $C_{34}H_{39}F_3N_4O_7S_3$: C, 53.1; H, 5.1; N, 7.3%.

MS (FAB): m/z 619.2 (M^+ - $CF_3SO_3^-$).

9c-(13*R*) was synthesized in the same way starting from **4c-(13*R*)**.

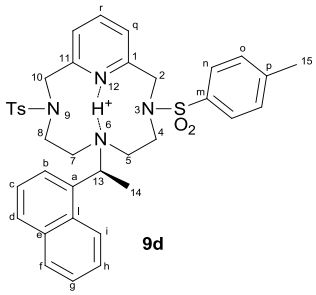
3.5.2 Synthesis of 9d-(13*S*)



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4d-(13*S*)	668.87	0.200	-	-	0.299	1
CF_3SO_3H	150.08	0.051	1.70	0.03	0.340	1.1

Ligand **4d-(13*S*)** was dissolved in distilled dichloroethane (5 mL). Triflic acid was added and the solution stirred for 2 hours. The solution was dried, then *n*-hexane (10 mL) was added and the solid **9d-(13*S*)** filtered in air. (MW 818.94 g/mol).

yield = 0.118 g, 0.144 mmol, 48%.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 10.68 (1H, s, NH), 8.20 (1H, d, *J* = 8.6 Hz, Ar*H*), 7.94 (1H, d, *J* = 8.2 Hz, Ar*H*), 7.87-7.81 (4H, m, Ar*H*), 7.72 (1H, pt, *J* = 7.7 Hz, Ar*H*), 7.58 (1H, pt, *J* = 7.7 Hz, Ar*H*), 7.45 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.41 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.36-7.30 (2H, m, Ar*H*), 7.21 (2H, d, *J* = 8.1 Hz, Ar*H*), 6.81-6.77 (2H, m, Ar*H*), 6.22 (1H, q, *J* = 6.6 Hz, *H*^{13}), 4.53 (1H, m, C*H*$_2$) overlapping with 4.48 (1H, d, *J* = 16.6 Hz, C*H*$_2$), 4.07 (1H, d, *J* = 16.6 Hz, C*H*$_2$), 4.00-3.86 (3H, m, C*H*$_2$), 3.70 (1H, d, *J* = 16.3 Hz, C*H*$_2$), 3.52-3.30 (3H, m, C*H*$_2$), 2.49 (3H, s, C*H*$_3$), 2.35 (3H, s, C*H*$_3$), 2.20 (1H, m, C*H*$_2$), 2.06 (3H, d, *J* = 6.6 Hz, C*H*$_3^{14}$), 1.73 (1H, m, C*H*$_2$).

^{13}C NMR (100 MHz; $CDCl_3$; T = 300 k) δ 157.4 (*C*), 156.9 (*C*), 145.5 (*C*), 144.7 (*C*), 140.0 (*C*H), 133.9 (*C*), 133.8 (*C*), 132.5 (*C*), 131.5 (*C*H), 130.7 (*C*H), 130.7 (*C*), 130.1 (*C*H), 129.4 (*C*H), 129.3 (*C*), 128.0 (*C*H), 127.9 (*C*H), 127.5 (*C*H), 126.9 (*C*H), 126.8 (*C*H), 126.1 (*C*H), 122.8 (*C*H), 122.7 (*C*H), 121.9 (*C*H), 55.2 (*C*^{13}H), 54.3 (*C*H$_2$), 53.8 (*C*H$_2$), 53.5 (*C*H$_2$), 52.9 (*C*H$_2$), 47.8 (*C*H$_2$), 47.2 (*C*H$_2$), 21.8 (*C*H$_3$Ts), 21.6 (*C*H$_3$Ts), 11.3 (*C*^{14}H$_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 282,1 (*N*^{12}), 52.0 (*N*^{6}). The signals relative to *N*-Ts were not detected.

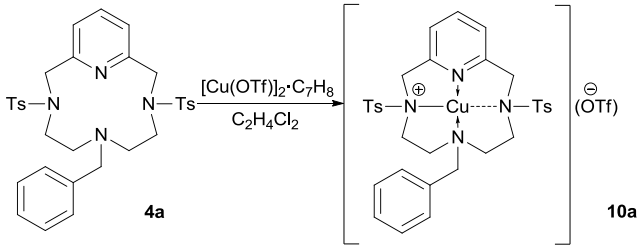
Elemental Analysis: Found: C, 55.4; H, 5.2; N, 6.4% Calc. for $C_{38}H_{41}F_3N_4O_7S_3$: C, 55.7; H, 5.0; N, 6.8%.

MS (FAB): m/z 669.2 (M^+-$CF_3SO_3^-$).

$[\alpha]_D^{20}$ = - 168 (*c* 0.5 in CH_2Cl_2).

9d-(13*R*) was synthesized in the same way starting from **4d-(13*R*)**. $[\alpha]_D^{20}$ = + 168 (*c* 0.5 in CH_2Cl_2)

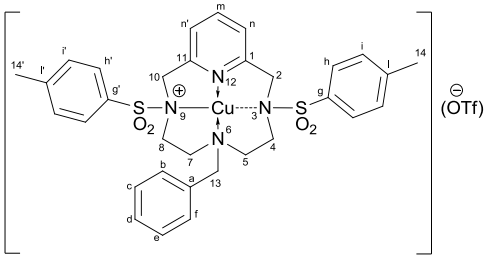
3.5.3 Synthesis of copper complex 10a



Reagents	MW (g/mol)	g	mmol	EQ
4a	604.78	0.100	0.165	1
$(CF_3SO_3Cu)_2\ C_6H_5CH_3$	517.37	0.042	0.0812	0.5

Copper(I) triflate toluene complex was added to a solution of **4a** in dichloroethane (5 mL). The solution was stirred at room temperature for 1 h, and then 10 mL of toluene was layered. After standing at room temperature for 16 h the solid was filtered and dried in *vacuo* under nitrogen, obtaining complex **10a** as a solid. (MW 817.40 g/mol).

yield = 0.059 g, 0.0722 mmol, 44%.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.79 (4H, m, ArH_{Ts}), 7.74 (1H, m, Ar*H*), 7.64 (1H, m, Ar*H*), 7.58–7.53 (2H, m, Ar*H*), 7.46 (2H, m, Ar*H*), 7.42–7.40 (4H, m, ArH_{Ts}), 7.34 (1H, m, Ar*H*), 7.09 (1H, m, Ar*H*), 5.14 (1H, m, CH_2), 4.94 (2H, m, CH_2[13]), 4.50 (1H, d, *J* = 17.2 Hz, CH_2), 4.39 (1H, m, CH_2), 4.23 (1H, d, *J* = 17.2 Hz, CH_2), 4.07 (1H, m, CH_2), 3.82 (2H, m, CH_2), 3.40 (1H, m, CH_2), 3.26–3.10 (3H, m, CH_2), 2.51 (3H, s, CH_3), 2.48 (3H, s, CH_3), 2.28 (1H, m, CH_2).

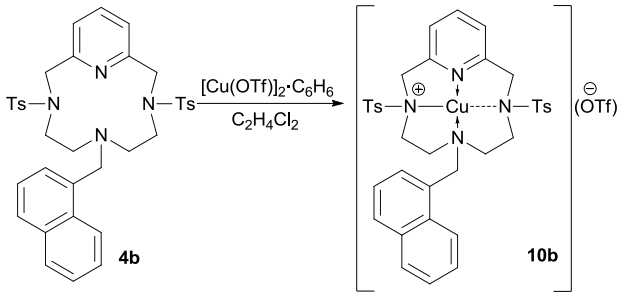
^{13}C NMR (100 MHz; $CDCl_3$; T = 300 K) δ 157.1 (*C*), 139.4 (*C*), 139.0 (*C*), 131.3 (*C*H), 130.6 (*C*H), 130.4 (*C*H), 130.3 (*C*), 130.0 (*C*H), 128.7 (*C*H), 127.8 (*C*H), 125.9 (*C*H), 124.1 (*C*H), 121.5 (*C*H), 58.7 (*C*H_2), 56.1 (*C*H_2), 53.9 (*C*H_2), 52.8 (*C*H_2), 50.1 (*C*H_2), 48.4 (*C*^{13}H_2), 45.6 (*C*H_2), 21.6 (*C*H_3).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): δ 278 (*N*^{12}), 92 (*N*Ts), 46 (N^{6}).

^{19}F NMR (376 MHz; $CDCl_3$; T= 300 K): δ -78.3.

Elemental analysis: found: C, 48.6; H, 4.6; N, 6.7%; calc. for $C_{33}H_{36}CuF_3N_4O_7S_3$: C, 48.5; H, 4.4; N, 6.9%.

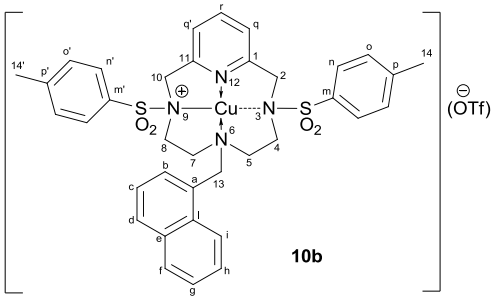
3.5.4 Synthesis of copper complex 10b



Reagents	MW (g/mol)	g	mmol	EQ
4b	654.84	0.0891	0.136	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0298	0.0591	0.5

Copper (I) triflate benzene complex was added to a solution of macrocycle **4b** in dichloroethane (10 mL). The solution was stirred at room temperature for one hour, concentrated to 5 mL and then 10 mL of *n*-hexane were layered. Then the solid was filtered and dried *in vacuo* under nitrogen, obtaining complex **10b** as a solid. (MW 867.46 g/mol).

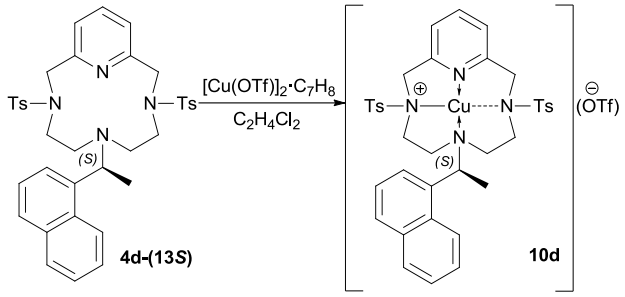
yield = 0.114 g, 0.132 mmol, 97%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.97 (1H, d, *J* = 7.8 Hz, H^i), 8.08-8.05 (2H, m, Ar*H*), 7.92 (1H, m, Ar*H*), 7.85-7.75 (2H, m, H^r) 7.65-7.52 (7H, m, Ar*H*), 7.42-7.37 (4H, m, Ar*H*), 7.27-7.17 (2H, m, Ar*H*), 4.89 (2H, d, *J* = 14.7 Hz, H^2 and H^{10}), 4.46 (2H, m, $CH_2{}^{13}$), 3.68 (2H, d, *J* = 14.7 Hz, H^2 and H^{10}), 3.53 (2H, m, H^4 and H^8), 2.93 (2H, m, H^4 and H^8), 2.82 (2H, m, H^5 and H^7), 2.50 (6H, s, $CH_3{}^{14}$), overlapping with 2.58-2.50 (2H, m, H^5 and H^7).

Elemental Analysis: Found: C, 51.4; H, 4.3; N, 6.1% Calc. for $C_{37}H_{38}CuF_3N_4O_7S_3$: C, 51.2; H, 4.4; N, 6.6%.

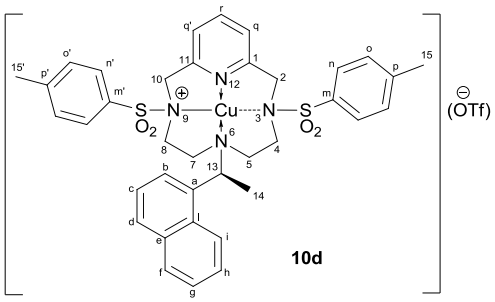
3.5.5 Synthesis of copper complex 3d-(13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
4d-(13*S*)	668.87	0.200	0.299	1
$(CF_3SO_3Cu)_2\ C_6H_5CH_3$	517.37	0.077	0.150	0.5

Copper (I) triflate toluene complex was added to a solution of **4d** in dichloroethane (5 mL). The solution was stirred at room temperature for one hour, concentrated at 5 mL and then 10 mL of benzene were layered. After standing at room temperature for 16 h the solid was filtered and dried in *vacuo* under nitrogen obtaining **10d-(13*S*)**. (MW 881.48 g/mol).

yield = 0.259 g, 0.294 mmol, 98%.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 8.93 (1H, d, *J* = 8.1 Hz, H^{i}), 8.07 (1H, d, *J* = 8.3 Hz, H^{f}), 7.92–7.88 (3H, m, Ar*H*), 7.82–7.74 (2H, m, Ar*H*), 7.69–7.62 (2H, m, H^{b} and H^{c}), 7.53–7.48 (3H, m, Ar*H*), 7.39–7.36 (3H, m, Ar*H*), 7.29 (2H, m, H^{o}), 7.05 (1H, d, *J* = 7.5 Hz, H^{q}), 5.59 (1H, q, *J* = 6.5 Hz, H^{13}), 5.31 (1H, d, *J* = 16.4 Hz, CH_2^{10}), 4.69 (1H, m, CH_2^{7}), 4.35 (1H, m, CH_2^{2}), 3.94 (1H, d, *J* = 16.6 Hz, $CH_2^{10'}$), 3.18 (1H, m, $CH_2^{2'}$), 3.04 (1H, d, *J* = 14.2 Hz, CH_2^{8}), 2.88–2.82 (3H, m, CH_2), 2.56 (3H, s, $CH_3^{15'}$), 2.42 (3H, s, CH_3^{15}), 2.34 (2H, m, CH_2), 2.21 (1H, d, *J* = 14.2 Hz, CH_2^{5}), 1.69 (3H, d, *J* = 6.5 Hz, CH_3^{14}).

^{13}C NMR (100 MHz; $CDCl_3$; T = 300 K) δ 156.2 (C^{11}), 152.9 (C^{2}), 146.2 (*C*H), 145.9 (*C*H), 140.0 (C^{r}H), 137.2 (C^{a}), 134.1 (C^{f}H), 131.9 (*C*H), 131.5 (*C*H), 130.6 ($C^{o'}$H), 130.0 (C^{o}H), 129.2 (C^{n}H), 128.9 (*C*H), 128.3 (*C*H), 128.2 (*C*H), 126.7 (C^{b}H), 126.0 (C^{c}H), 125.2 ($C^{q'}$H), 124.7 (C^{g}H), 124.6 (*C*H), 124.1 (*C*H), 118.2 (C^{h}H), 94.2 (C^{i}H), 56.5 ($C^{2}H_2$), 56.1 ($C^{10}H_2$), 53.1 (C^{13}H), 51.0 ($C^{5}H_2$), 48.9 ($C^{7}H_2$), 45.9 ($C^{4}H_2$), 21.7 ($C^{15'}H_3$), 21.5 ($C^{15}H_3$), 12.9 ($C^{14}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 245 (N^{12}), 51 (N^{6}). The signals relative to *N*-Ts were not detected.

^{19}F NMR (376 MHz; $CDCl_3$; T = 300 k) δ - 78.6 (s).

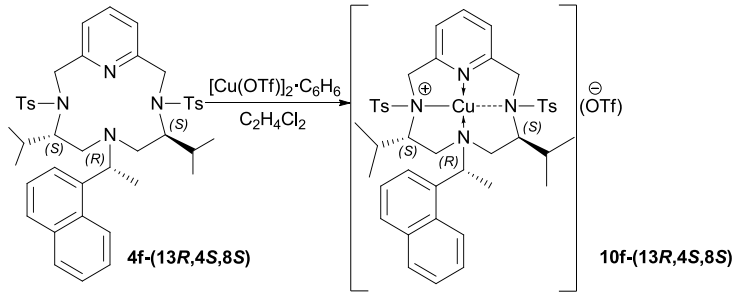
IR ν (cm^{-1}) = 1447.0 (w), 1343.5 (w), 1223.5 (w), 1260.9 (s), 1223.5 (m), 1165.4 (s), 1085.3 (w), 1029.5 (s), 802.6 (w), 759.7 (m), 720.4 (m), 710.0 (m), 660.5 (s), 637.6 (s).

Elemental Analysis: Found: C, 51.6; H, 4.9; N, 6.7%; Calc. for $C_{38}H_{40}CuF_3N_4O_7S_2$: C, 51.9; H, 4.6; N, 6.4%.

$[\alpha]_D^{20}$ = - 115 (*c* 0.5 in $CHCl_3$).

Cu(OTf) complex of 6-[(*R*)-1-(1-naphthyl)ethyl]-3,9-ditosyl-3,6,9,15-tetraazabicyclo[9,3,1] pentadeca-1(15),11,13-triene **10d-(13*R*)** was synthesized in the same way. $[\alpha]_D^{20}$ = +115 (*c* 1 in $CHCl_3$).

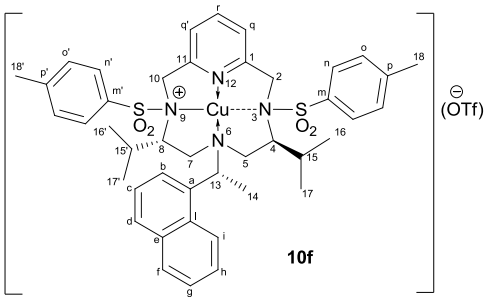
3.5.6 Synthesis of copper complex 10f-(4*S*,8*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
4f-(4*S*,8*S*,13*R*)	753.03	0.0891	0.118	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0298	0.0591	0.5

Copper (I) triflate benzene complex was added to a solution of macrocycle **4f** in dichloroethane (10 mL). The solution was stirred at room temperature for one hour, concentrated to 5 mL and then 10 mL of *n*-hexane were layered. Then the solid was filtered and dried *in vacuo* under nitrogen, obtaining complex **10f-(4*S*,8*S*,13*R*)** as a solid. (MW 965.64 g/mol).

yield = 0.111 g, 0.115 mmol, 97%.



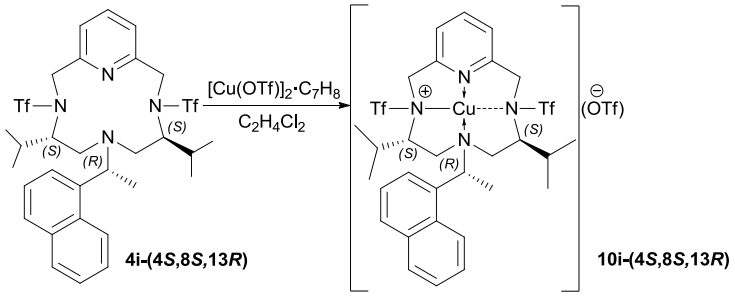
^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.68 (1H, d, *J* = 8.7 Hz, H^{i}), 7.93 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.87 (4H, d, *J* = 8.1 Hz, H^{n} and $H^{n'}$), 7.80-7.69 (3H, m, Ar*H*), 7.62-7.40 (7H, m, Ar*H*), 7.23-7.16 (2H, m, Ar*H*), 5.95 (1H, q, *J* = 6.6 Hz, H^{14}), 5.25 (1H, d, *J* = 20 Hz, H^{2}), 4.79 (1H, d, *J* = 12.7 Hz, H^{7}), 4.71 (1H, d, *J* = 14.6 Hz, H^{10}), 4.62 (1H, d, *J* = 20 Hz, $H^{2'}$), overlapping with 4.61 (1H, m, H^{8}), 4.01 (1H, d, *J* = 14.6 Hz, $H^{10'}$), 2.78 (1H, d, *J* = 12.7 Hz, $H^{7'}$), 2.57 (3H, s, $CH_3^{18 \text{ or } 18'}$), overlapping with 2.57 (1H, m, H^{4}), 2.52 (3H, s, $CH_3^{18' \text{ or } 18}$), 2.42-2.37 (1H, m, H^{5}), 2.30-2.15 (2H, m, $H^{5'}$ and $H^{15'}$), 2.10 (3H, d, *J* = 6.8 Hz, CH_3^{14}), 1.59 (1H, m, H^{15}), 0.90 (3H, d, *J* = 6.7 Hz, $CH_3^{16'}$), 0.68 (3H, d, *J* = 6.2 Hz, CH_3^{17}), 0.29 (3H, d, *J* = 6.5 Hz, $CH_3^{17'}$), -0.49 (3H, d, *J* = 6.2 Hz, CH_3^{16}).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 155.7 ($C^{1 \text{ or } 11}$), 151.2 ($C^{11 \text{ or } 1}$), 145.6 ($C^{p'}$), 145.3 (C^{p}), 140.4 (*C*H), 134.8 (C^{a}), 134.5 (C^{l}), 133.9 (*C*), 132.1 (*C*), 131.5 (*C*H), 130.4 (C^{o}), 129.8 (*C*H), 129.3 (*C*H), 128.9 (*C*H), 127.7 (CH^{h}), 127.3 (*C*H), 126.4 (*C*H), 125.2 (*C*H), 124.8 (*C*H), 124.5 (*C*H), 123.9 (*C*H), 122.8 (C^{i}), 64.7 (C^{4}H), 62.0 (C^{8}H), 57.4 ($C^{5}H_2$), 57.1 ($C^{10}H_2$), 56.4 (C^{13}H), 55.5 ($C^{7}H_2$), 46.8 ($C^{2}H_2$), 29.9 ($C^{15'}$H), 27.1 (C^{15}H), 24.5 ($C^{14}H_3$), 22.4 ($C^{16'}H_3$), 21.9 ($C^{18 \text{ and } 18'}H_3$), 21.3 ($C^{17'}H_3$), 20.3 ($C^{17}H_3$), 18.5 ($C^{16}H_3$).

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 k) δ - 78.58 (s).

Elemental Analysis: Found: C, 54.7; H, 5.2; N, 5.7% Calc. for $C_{44}H_{52}CuF_3N_4O_7S_3$: C, 54.7; H, 5.4; N, 5.8%.

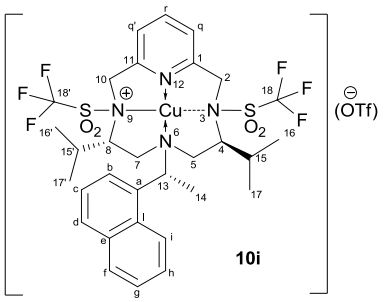
3.5.7 Synthesis of copper complex 10i-(4S,8S,13R)



Reagents	MW (g/mol)	g	mmol	EQ
4i-(4*S*,8*S*,13*R*)	708.78	0.0860	0.121	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0305	0.0607	0.5

Copper (I) triflate benzene complex was added to a solution of macrocycle **4i-(4*S*,8*S*,13*R*)** in dichloroethane (7 mL). The solution was stirred at room temperature for one hour and then 50 mL of *n*-hexane were layered. Then the solid was filtered and dried *in vacuo* under nitrogen, obtaining complex **10i-(4*S*,8*S*,13*R*)** as a solid. (MW 921.39 g/mol).

yield = 0.0502 g, 0.054 mmol, 45%.

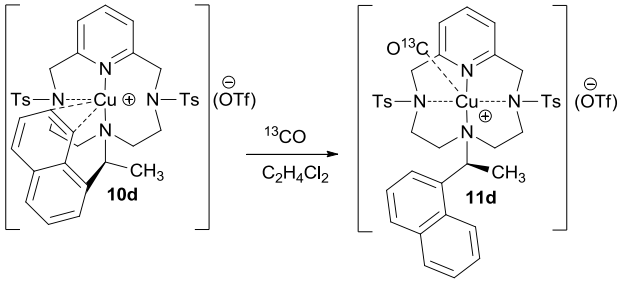


^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si; T = 300 k) δ 8.16 (1H, d, *J* = 8.9 Hz, H^i), 8.01 (2H, pst, *J* = 7.5 Hz, Ar*H*), 7.80 (1H, pst, *J* = 7.7 Hz, Ar*H*), 7.73 (1H, m, Ar*H*), 7.68-7.63 (3H, m, Ar*H*), 7.31 (1H, m, Ar*H*), 7.20 (1H, m, Ar*H*), 6.46 (1H, m, H^{13}), 5.10-4.70 (5H, m, *H*), 4.40-4.01 (3H, m, *H*), 3.50 (1H, m, *H*), 2.95 (1H, m, *H*), 2.50-2.36 (1H, m, *H*), 2.06 (3H, d, *J* = 6.8 Hz, CH_3^{14}), 1.52 (1H, m, *H*), 1.27 (3H, bs, $CH_{3i\text{-}prop}$), 1.10 (3H, bs, $CH_{3i\text{-}prop}$), 0.80 (3H, bs, $CH_{3i\text{-}prop}$), 0.47 (3H, bs, $CH_{3i\text{-}prop}$).

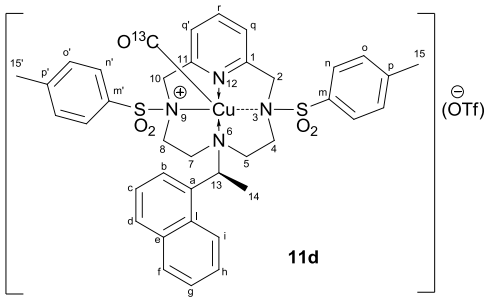
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 139.3 (*C*H), 131.7 (*C*H), 130.4 (*C*H), 128.5 (*C*H), 127.4 (*C*H), 125.7 (*C*H), 122.6 (*C*H), 121.3 (C^iH), 57.1 (CH_2), 43.6 (CH_2), 31.7 (CH_2), 28.8 (*C*H), 22.8 (CH_2), 21.3 ($C^{14}H_3$), 20.8 ($CH_{3\ i\text{-}prop}$), 14.3 ($CH_{3\ i\text{-}prop}$). Signals relative to quaternary carbons, aromatic *C*H, aliphatic *C*H and CH_3 were not detected.

Elemental Analysis: Found: C, 41.8; H, 3.7; N, 5.8% Calc. for $C_{32}H_{38}CuF_9N_4O_7S_3$: C, 41.7; H, 4.2; N, 6.1%.

3.5.8 Synthesis of 11d



20 mg of copper(I) complex **10d** were added to anhydrous and degassed $CDCl_3$ in a NMR tube and the solution was saturated with ^{13}CO, obtaining **11d**.



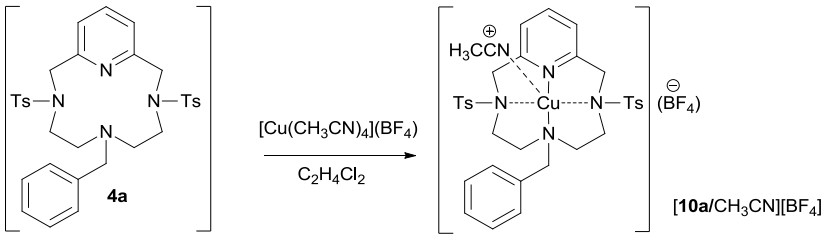
^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.77 (1H, d, *J* = *8.7* Hz, H^{i}), 7.96 (1H, d, *J* = *8.3* Hz, Ar*H*), 7.88 (2H, d, *J* = 8.5 Hz, $H^{n \text{ or } n'}$), 7.84-7.82 (1H, m, Ar*H*) overlapping with 7.81 (2H, d, *J* = 8.2 Hz, $H^{n' \text{ or } n}$), 7.73 (1H, m, H^{h}), 7.68-7.59 (2H, m, Ar*H*), 7.53 (2H, d, *J* = 8.5 Hz, $H^{o \text{ or } o'}$), 7.49 (1H, m, Ar*H*), 7.40 (2H, d, *J* = *8.2* Hz, $H^{o' \text{ or } o}$), 7.31 (1H, m, Ar*H*), 7.23-7.16 (2H, m, Ar*H*), 6.19 (1H, q, *J* = 6.8 Hz, H^{13}), 5.24 (1H, d, *J* = 17.7 Hz, $H^{10 \text{ or } 2}$), overlapping with 5.19 (1H, d, *J* = 15.0 Hz, $H^{2 \text{ or } 10}$), 4.80 (1H, m, H^{7}), 4.30 (1H, m, H^{7}), 3.98 (1H, d, *J* = 17.7 Hz, $H^{10 \text{ or } 2}$), 3.64 (1H, d, *J* = 15.0 Hz, $H^{2 \text{ or } 10}$), 3.09-2.64 (4H, m, CH), 2.56 (3H, s, $CH_3^{15 \text{ or } 15'}$), 2.47 (3H, s, $CH_3^{15' \text{ or } 15}$), 2.36-2.28 (1H, m, $H^{7 \text{ or } 5}$), 2.16 (3H, *J* = *6.8* Hz, CH_3^{14}) overlapping with 2.15-2.07 (1H, m, $H^{8 \text{ or } 4}$). Highlighted signals are relative to compound **9d** (see page 321).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 184.4 (free ^{13}CO), 171.1 (^{13}CO), 156.1 (*C*), 152.2 (*C*), 145.9 (*C*), 140.4 (*CH*), 135.2 (*C*), 134.6 (*C*), 132.2 (*C*), 130.7 (2 CH_{Ts}), 130.0 (*C*H), 129.2 (CH_{Ts}), 129.2 (*C*H), 128.0 (CH_{Ts}), 126.8 ($C^{h}H$), 126.1 (*C*H), 125.5 (2 *C*H), 124.2 (*C*H), 123.6 (*C*H), 122.7 ($C^{i}H$), 56.8 ($C^{2}H_2$), 56.4 ($C^{2'}H_2$), 55.3 ($C^{13}H$), 52.7 ($C^{8}H_2$), 51.9 ($C^{5}H_2$), 50.7 ($C^{7}H_2$), 47.5 ($C^{4}H_2$), 23.4 ($C^{14}H_3$), 21.9 ($C^{15}H_3$), 21.7 ($C^{15'}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 k) δ 243.5 (N^{12}), 39.8 (N^{6}). The signals relative to *N*-Ts were not detected.

IR (CH_2Cl_2 solution) ν_{CO} = 2111 cm^{-1}.

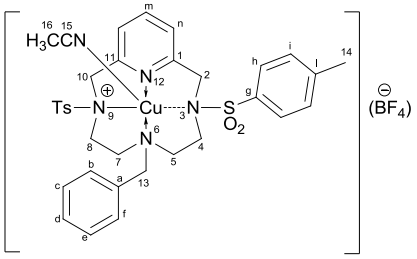
3.5.9 Synthesis of [10a/CH₃CN][BF₄]



Reagents	MW (g/mol)	g	mmol	EQ
4a	604.78	0.100	0.165	1
$[Cu(CH_3CN)_4](BF_4)$	314.56	0.052	0.165	1

Copper(I) tetra(acetonitrile)tetrafluoroborate was added to a solution of **4a** in 1,2-dichloroethane (5 mL). The yellowish solution was stirred at room temperature for 1 h; addition of toluene (10 mL) to this solution caused the precipitation of [**10a**/CH_3CN][BF_4] as a white powder. (MW 796.19 g/mol).

yield = 0.045 g, 0.0565 mmol, 34%.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.81 (4H, d, *J* = 8.0 Hz, H^h), 7.79–7.75 (1H, m, H^m), 7.62–7.57 (1H, m, Ar*H*), 7.50 (4H, d, *J* = 8.0 Hz, H^i), 7.42–7.37 (4H, m, Ar*H* and H^n), 7.27–7.25 (2H, m, Ar*H*), 5.22 (2H, d, *J* = 15.3 Hz, CH_2), 4.55 (2H, s, CH_2^{13}), 3.72 (2H, d, *J* = 15.3 Hz, CH_2), 3.70–3.60 (2H, m, CH_2), 3.12–3.09 (2H, m, CH_2), 2.62–2.55 (2H, m, CH_2), 2.53 (6H, s, CH_3^{14}), 2.29 (3H, bs, CH_3^{16}) 2.15–2.07 (2 H, m, CH_2).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 k) δ 153.5 (C^1), 145.3 (C^l), 139.4 (C^mH), 132.7 (C^g), 131.4(C^a), 131.1 (*C*H), 130.5 (C^iH), 128.6 (*C*H), 128.4 (*C*H),128.1 (C^hH), 124.2 (C^nH), 57.6 ($C^{13}H_2$), 56.1 (*C*H_2), 52.7 (*C*H_2), 48.1 (*C*H_2), 21.7 ($C^{14}H_3$), 1.9 ($C^{16}H_3$); one quaternary carbon atom (C^{15}) was not detected.

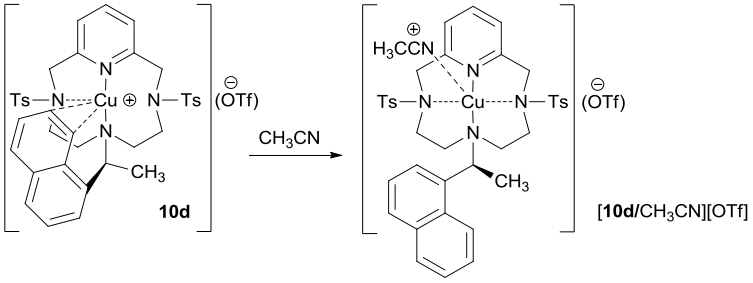
^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): δ 248 (N^{12}), 97 (N^{Ts}), 26 (N^6).

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 K): δ - 153.6.

IR ($CHCl_3$) ν (cm^{-1}) = 2250 (CN).

Elemental analysis: found: C, 51.4;H, 5.0; N, 8.9%; calc. for $C_{34}H_{39}BCuF_4N_5O_4S_2$: C, 51.3; H,4.9; N, 8.8%.

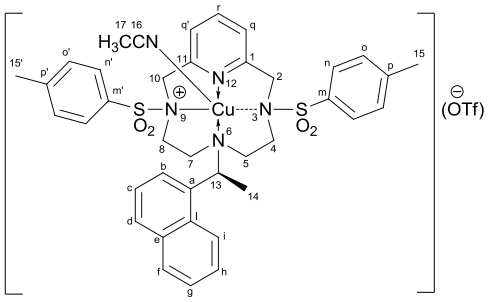
3.5.10 Synthesis of [10d/CH₃CN][OTf]



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
10d	881.48	0.051	-	-	0.0579	1
CH_3CN	41.05	0.012	0.786	0.015	0.295	5

Complex **10b** was dissolved in dichloroethane (3 mL). CH_3CN was added and the resulting solution was stirred at room temperature for 20 min. Solvent was removed *in vacuo* and the solid residue was kept under reduced pressure at 40 °C for 4 h. *n*-Hexane (3 mL) was added and complex [**10d**/CH_3CN][OTf] was collected and dried *in vacuo* as a white powder. (MW 922.53 g/mol).

yield = 0.050 g, 0.0542 mmol 94%.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.83 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.98 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.87 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.83–7.65 (6H, m, H aromatics), 7.60–7.54 (2H, m, Ar*H*), 7.52 (2 H, d, *J* = 8.1 Hz, Ar*H*), 7.38 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.25-7.20 (2H, m, Ar*H*), 5.98(1H, br, H^{13}), 5.17 (2H, d, *J* = 14.7 Hz, CH_2), 4.62–4.49 (1H, m, CH_2), 5.14–5.05 (1H, m, CH_2), 4.23-3.95 (1H, m, CH_2), 3.70 (2H, d, *J* = 14.7 Hz, CH_2), 3.67 (1H, m, CH_2), 3.54–3.34 (1H, m, CH_2), 2.83–2.71 (2H, m, CH_2), 2.56 (3H, s, CH_3^{15}), 2.47 (3H, s, C$H_3^{15'}$) overlapping with 2.47 (1H, m, CH_2), 2.28 (3H, br s, CH_3^{17}), 2.04 (3H, br, CH_3^{14}).

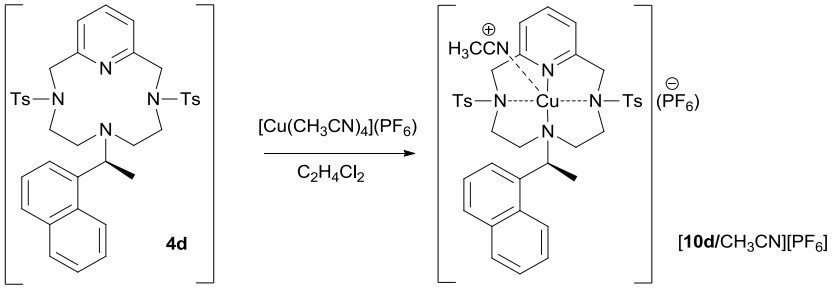
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 155.0 (*C*), 146.0 (*C*), 145.6 (*C*), 139.7 (*C*H), 136.6 (*C*), 134.7 (*C*), 132.4 (*C*), 131.0 (*C*H), 130.8 (*C*H), 130.7 (*C*H), 130.4 (*C*H), 129.1 (*C*H), 128.3 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 126.0 (*C*H), 125.9 (*C*H), 125.8 (*C*H), 124.9 (*C*H), 122.9 (*C*H), 122.2 (*C*H), 116.1 (C^{16}N), 57.0 (*C*H_2), 56.6 (*C*H_2), 54.5 (C^{13}H), 52.0 (*C*H_2), 51.7 (*C*H_2), 47.4 (*C*H_2), 43.8 (*C*H_2), 22.1 ($C^{15}H_3$), 21.9 ($C^{15'}H_3$), 12.1 ($C^{14}H_3$), 3.3 ($C^{17}H_3$).

^{15}N NMR (40 MHz; $CDCl_3$; T = 300 K): *δ* 251 (N^{12}), 95 (N^{Ts}), 38 (N^{6}).

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 K): *δ* -78.7.

IR ($CHCl_3$) ν (cm^{-1}) = 2250 (CN).

3.5.11 Synthesis of [10d/CH₃CN][PF₆]



Reagents	MW (g/mol)	g	mmol	EQ
4d	668.87	0.200	0.299	1
$[Cu(CH_3CN)_4](PF_6)$	372.72	0.112	0.299	1

Tetrakis(acetonitrile)copper(I) hexafluorophosphate was added to a solution of **4d** in dichloroethane (5 mL). The solution was stirred at room temperature for one hour, then solvent was removed *in vacuo*. *n*-Hexane was added to the residue and [**10d**/CH_3CN][PF_6] was collected as a white powder under nitrogen. (MW 918.43 g/mol).

yield = 0.265 g, 0.288 mmol, 97%.

The same pattern reported for [**10d**/CH_3CN][OTf] in section **3.5.10** is found in the ^{1}H NMR,^{13}C NMR and ^{15}N NMR spectra.

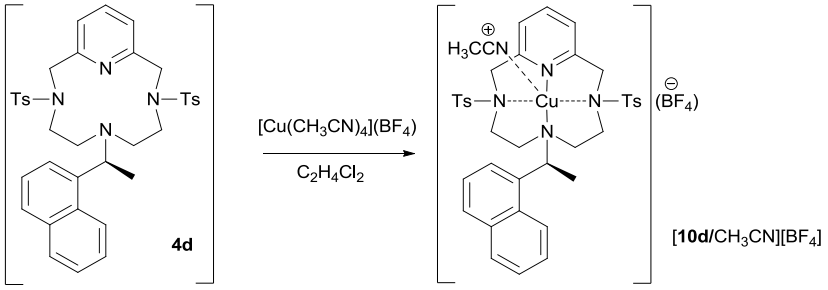
^{19}F NMR (282 MHz; $CDCl_3$; T = 300 K): δ -73.6 (d, $J_{F\text{-}P}$ = 711 Hz).

^{31}P NMR (121 MHz; $CDCl_3$; T = 300 K): δ -144.2 (hept., $J_{P\text{-}F}$ = 711 Hz).

IR ($CHCl_3$) ν (cm^{-1}) = 2250 (CN).

Elemental Analysis: Found: C, 51.5; H, 4.4; N, 7.9%; M+, 918. Calc. for $C_{39}H_{43}BCuF_6N_5O_4PS_2$: C, 51.0; H, 4.7; N, 7.6%.

3.5.12 Synthesis of [10d/CH_3CN][BF_4]



Reagents	MW (g/mol)	g	mmol	EQ
4d	668.87	0.200	0.299	1
$[Cu(CH_3CN)_4](BF_4)$	314.56	0.094	0.299	1

Copper(I) tetra(acetonitrile)tetrafluoroborate was added to a solution of **4d** in 1,2-dichloroethane (5 mL). The yellowish solution was stirred at room temperature for 1 h; then solvent was removed *in vacuo*. *n*-Hexane (10 mL) was added to the residue and [**10d**/CH_3CN][BF_4] was collected as a white powder under dinitrogen. (MW 860.27 g/mol).

yield = 0.235 g, 0.273 mmol, 91%.

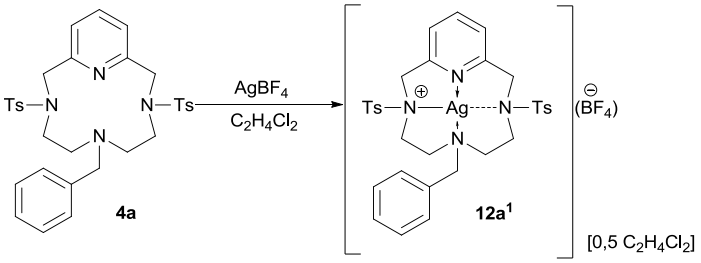
The same pattern reported for [**10d**/CH_3CN][OTf] in section **3.5.10** is found in the ^{1}H NMR,^{13}C NMR and ^{15}N NMR spectra.

^{19}F NMR (282 MHz; $CDCl_3$; T = 300 K): δ -153.6.

IR ($CHCl_3$ solution) ν (cm^{-1})= 2250 (CN).

Elemental Analysis: Found: C, 54.4; H, 5.4; N, 7.9%; M+, 860. Calc. for $C_{39}H_{43}BCuF_4N_5O_4S_2$: C, 54.5; H, 5.0; N, 8.1%.

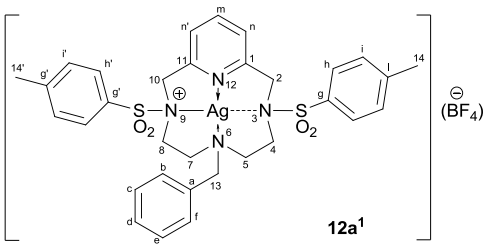
3.5.13 Synthesis of 12a[1]



Reagents	MW (g/mol)	g	mmol	EQ
4a	604.78	0.513	0.849	1
$AgBF_4$	194.67	0.165	0.849	1

Silver tetrafluoroborate was added to a solution of **4a** in dichloroethane (43 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then concentrated close to dryness, then distilled hexane was added. Sovents were now evaporated to dryness and the product recovered by filtration (MW 848.94 g/mol considering **12a[1]**:DCE/1:05).

yield = 0.656 g, 0.772 mmol 91%.



12a[1]

^{1}H NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.75 (4H, d, *J* = 8.0 Hz, H^{h}), overlapping with 7.70 (1H, t, *J* = 7.7 Hz, H^{m}), 7.62 (2H, d, *J* = 6.3 Hz, Ar*H*), 7.45 (4H, d, = 8.0 Hz, H^{i}) overlapping with 7.40 (3H, m, Ar*H*), 7.25 (2H, d, *J* = 7.7 Hz, H^{n}), 5.02 (2H, d, *J* = 15.2 Hz, CH_2^{2}), 3.96 (2H, m, CH_2^{13}), 3.65 (2H, d, *J* = 15.2 Hz, CH_2^{2}), 3.47 (2H, m, CH_2), 2.92 (2H, m, CH_2), 2.53 (2H, m, CH_2) overlapping with 2.47 (6H, s, $C^{14}H_3$), 1.98 (2H, m, CH_2).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 153.4 (*C*), 145.9 (*C*), 140.5(*C*H), 135.6(*C*), 130.9 (*C*H), 130.7 (*C*H), 130.6 (*C*), 128.8 (*C*H), 128.6 (*C*H), 128.4 (*C*H), 125.0 (*C*H), 58.4 ($C^{13}H_2$), 53.6 ($C^{2}H_2$), 52.9 (CH_2), 47.5 (CH_2), 43.6 (CH_2 of DCE), 21.9 ($C^{14}H_3$).

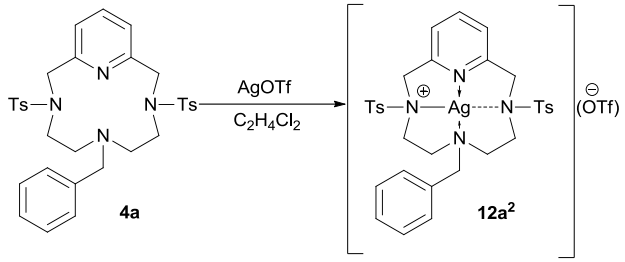
^{19}F NMR (282 MHz; $CDCl_3$; T= 300 K): δ -152.7 ($^{10}BF_4$), -152.8 ($^{11}BF_4$).

Elemental Analysis: Found: C, 46.0; H, 4.7; N, 6.2%; Calc. for $C_{33}H_{38}AgBF_4N_4O_4S_2$: C, 46.6; H, 4.5; N, 6.6%.

MS (FAB): m/z (%) 711 (100) [M^+ – BF_4], 605 (94) [MH – $AgBF_4$]$^+$.

UV-vis: (*c* 5.23 10^{-5} mol/L in $CHCl_3$ in 1 cm cuvettes): λ_{max} [nm], (log ε) = 243 (4.26); 263 (3.89) nm.

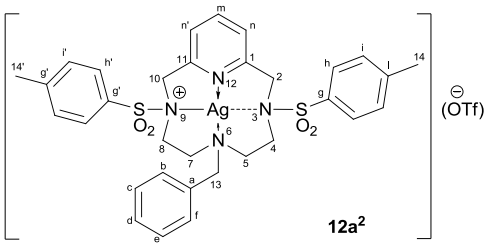
3.5.14 Synthesis of 12a²



Reagents	MW (g/mol)	g	mmol	EQ
4a	604.78	0.209	0.345	1
AgOTf	256.94	0.0887	0.345	1

Silver triflate was added to a solution of **4a** in dichloroethane (17 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then concentrated close to dryness, then distilled hexane was added. Sovents were now evaporated to dryness and the product **12a²** recovered by filtration (MW 861.72 g/mol).

yield = 0.218 g, 0.252 mmol 73%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.82 (1H, m, Ar*H*), 7.76 (4H, d, *J* = 8.2 Hz, H^h), 7.69 (2H, d, *J* = 7.1 Hz, Ar*H*), 7.52 (2H, m, Ar*H*), overlapping with 7.50 (4H, d, *J* = 8.2 Hz, H^i), 7.41 – 7.29 (1H, m, Ar*H*),overlapping with 7.37 (1H, d, *J* = 7.7 Hz, Ar*H*), 5.06 (2H, d, *J* = 14.9 Hz, CH_2^2), 3.94 (2H, s, CH_2^{13}), 3.57 (2H, m, CH_2), 3.09 (2H, m, CH_2), 2.91 (2H, m, CH_2), 2.55 (6H, s, $CH^{14}{}_3$), 2.24 (2H, m, CH_2).

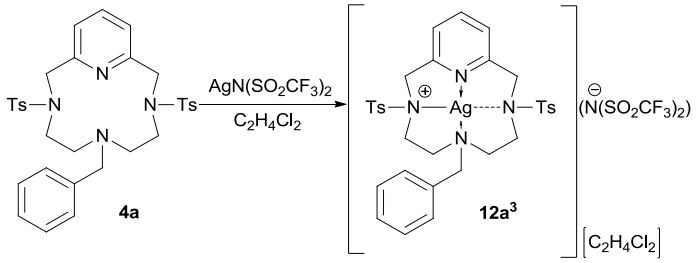
^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 153.7 (*C*), 145.9 (*C*), 140.5(*C*H), 136.0(*C*), 130.9 (*C*H), 130.7 (*C*H), 130.6 (*C*), 129.1 (*C*H), 128.7 (*C*H), 128.2 (*C*H), 125.0 (*C*H), 58.9 ($C^{13}H_2$), 56.4 (C^2H_2), 53.5 (*C*H_2), 47.7 (*C*H_2), 43.6 (*C*H_2 of DCE), 21.8 ($C^{14}H_3$).

^{19}F NMR (282 MHz; $CDCl_3$; T= 300 K): δ -78.45

MS (FAB): m/z (%) 711 (100) $[M^+ – CF_3SO_3]$, 605 (90) $[MH – AgCF_3SO_3]^+$.

UV-vis: (*c* 5.13 10^{-5} mol/L in $CHCl_3$ in 1 cm cuvettes): λ_{max} [nm], (log ε) = 242 (4.32); 263 (3.94) nm.

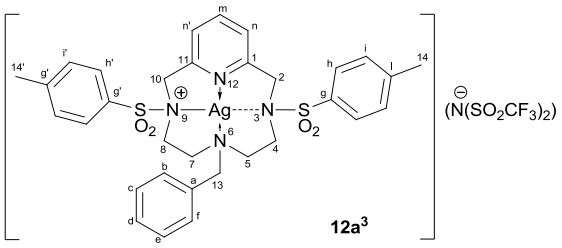
3.5.15 Synthesis of 12a[3]



Reagents	MW (g/mol)	g	mmol	EQ
4a	604.78	0.181	0.300	1
$AgN(SO_2CF_3)_2$	388.09	0.116	0.300	1

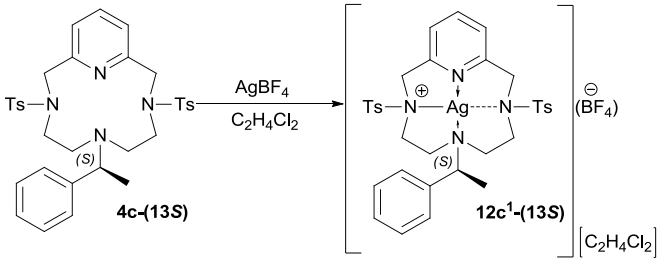
Silver triflimide was added to a solution of **4a** in dichloroethane (13 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then concentrated close to dryness, then distilled hexane was added. Sovents were now evaporated to dryness and the product recovered by filtration (MW 1091.76 g/mol considering **12a[3]**:DCE/1:1).

yield = 0.176 g, 0.161 mmol 54%).



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, t *J* = 7.7 Hz, Ar*H*), 7.71 (4H, d, *J* = 8.0 Hz, H^h), 7.63 (2H, d, *J* = 7.1 Hz, Ar*H*), 7.56-7.38 (3H, m, Ar*H*) overlapping with 7.46 (4H, d, *J* = 8.0 Hz, H^i), 7.28 (2H, m, Ar*H*), 5.05 (2H, d, *J* = 14.9 Hz, CH_2^2), 3.90 (2H, s, CH_2^{13}), 3.70 (2H, DCE), 3.53 (2H, m, CH_2), 3.01 (2H, m, CH_2), 2.72 (2H, m, CH_2), 2.51 (6H, s, $CH^{14}{}_3$), 2.17 (2H, m, CH_2).

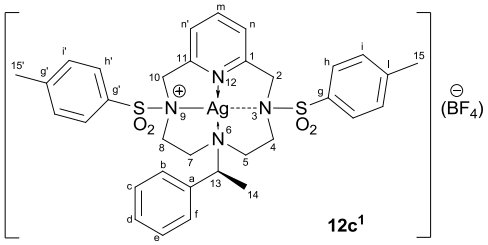
3.5.16 Synthesis of 12c[1]-(13*S*)



Reagents	MW (g/mol)	g	mmol	EQ
4c-(13*S*)	618.81	0.246	0.398	1
$AgBF_4$	194.67	0.077	0.398	1

Silver tetrafluoroborate was added to a solution of **4c** in dichloroethane (15 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then evaporated to dryness, then distilled hexane was added and the product recovered by filtration (MW 912.44 g/mol considering **12c[1]-(13*S*)**:DCE/1:1).

yield = 0.217 g, 0.238 mmol 60%.

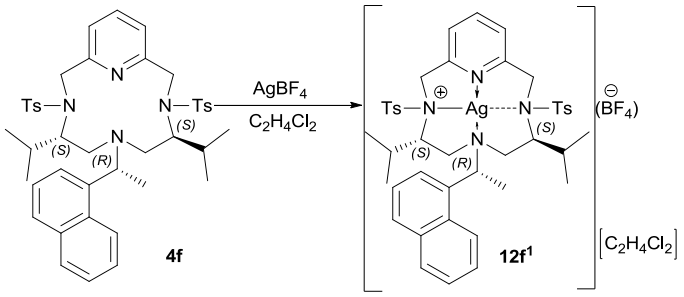


^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (4H, m, Ar*H*), 7.68 (1H, t, *J* = 7.7 Hz, H^m), 7.48-7.35 (10 H, m, Ar*H*) 7.22 (1H, d, *J* = 7.7 Hz, H^n), 5.14 (1H, d, *J* = 15.9 Hz, CH_2^2), 4.80 (2H, m, CH_2^{10} and H^{13}), 4.01 (1H, m, CH_2), 3.85 (1H, d, *J* = 15.9 Hz, CH_2^2), 3.73 (3H, DCE) OVERLLAPPING WITH 3.73 (1H, m, CH_2), 3.59 (1H, d, *J* = 14.9 Hz, $CH^{10}{}_2$), 2.97 (1H, m, CH_2), 2.57 (1H, m, CH_2), 2.48 (6H, bs, $CH^{15}{}_3$ and $CH^{15'}{}_3$), 2.35 (1H, m, CH_2), 2.12 (1H, m, CH_2), 1.77 (3H, d, *J* = 6.0 Hz, $CH^{14}{}_3$) overlapping with 1.72 (2H, m, CH_2).

^{13}C NMR (75 MHz; $CDCl_3$; T = 300 K) δ 154.0 (C^1), 152.6 (C^{11}), 146.1 (*C*), 145.8 (*C*), 140.4 (*C*H), 137.5 (*C*), 131.3 (*C*), 130.8 (*C*H), 130.7 (*C*H), 129.5 (*C*H), 129.3 (*C*), 128.9 (*C*H), 128.2 (*C*H), 127.9 (*C*H), 125.5 (*C*H), 124.8 (*C*H), 56.7 (CH_2), 56.6 (*C*H), 56.3 (CH_2), 49.0 (CH_2), 48.4 (CH_2), 48.0 (CH_2), 46.1 (CH_2), 43.7 (DCE), 21.8 ($C^{15}H_3$), 19.6 ($C^{14}H_3$).

^{19}F NMR (225 MHz; $CDCl_3$; T= 300 K): δ -152.85

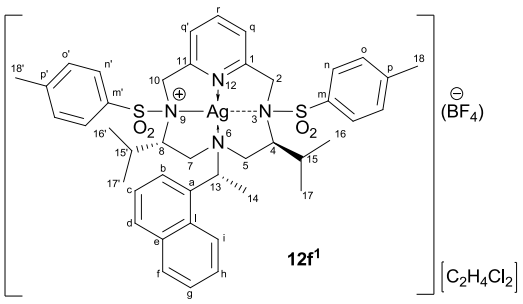
3.5.17 Synthesis of 12f¹-(4*S*,8*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
4f-(4*S*,8*S*,13*R*)	753.03	0.143	0.190	1
$AgBF_4$	194.67	0.037	0.190	1

Silver tetrafluoroborate was added to a solution of **4f** in dichloroethane (7 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then evaporated to dryness, then distilled hexane was added and the product recovered by filtration (MW 1044.64 g/mol considering **12f¹-(4*S*,8*S*,13*R*)**:DCE/1:1).

yield = 0.0943 g, 0.0902 mmol 48%.



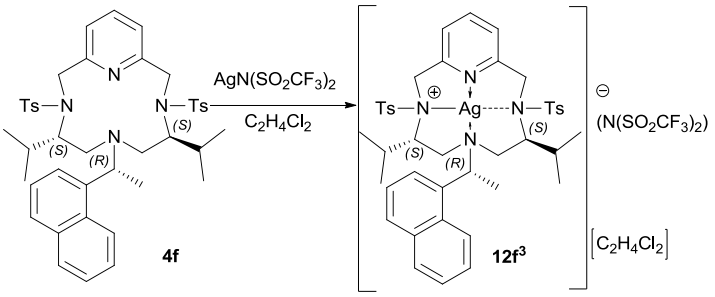
12f[1]

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (1H, d, *J* = 8.4 Hz, *H*^{i}), 7.96 – 7.87 (6H, m, Ar*H*), 7.81 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.72 (1H, m, Ar*H*), 7.59 -7.44 (8H, m, Ar*H*), 7.37 (1H, d, *J* = 7.5 Hz, Ar*H*), 6.02 (1H, q, *J* = 6.5 Hz, *H*^{13}), 5.38 (1H, d, *J* = 17.5 Hz, C*H*$_2^{2}$), 4.93 (1H, d, *J* = 14.0 Hz, C*H*$_2^{10}$), 4.59 (1H, pt, *J* = 12.1 Hz, C*H*$_2^{5}$), 4.24 (1H, d, *J* = 17.5 Hz, C*H*$_2^{2}$), 4.17 (1H, m, C*H*^{8}) 4.07 (1H, d, *J* = 14.0 Hz, C*H*$_2^{10}$), 3.73 (3.5H, DCE), 2.50 (3H, s, C*H*$_3^{18}$), 2.47 (3H, s, C*H*$_3^{18'}$) overlapping with 2.49 (1H, m, C*H*$_2^{7}$), 2.25 (2H, m, C*H*^{15} and C*H*^{4}), 2.04 (3H, d, *J* = 6.5 Hz, C*H*$_3^{14}$), 1.62 (2H, m, C*H*$_2$), 1.03 (1H, m, C*H*$^{15'}$), 0.88 (3H, m, C*H*$_3^{16}$), 0.46 (3H, d, *J* = 5.6 Hz, C*H*$_3^{17}$), -0.02 (3H, d, *J* = 5.0 Hz, C*H*$_3^{16'}$), -0.32 (3H, d, *J* = 5.6 Hz, C*H*$_3^{17'}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8 (*C*), 152.6 (*C*), 145.8 (*C*), 145.5 (*C*), 141.3 (*C*H), 135.3 (*C*), 134.5 (*C*), 134.5 (*C*), 134.4 (*C*), 132.5 (*C*), 130.8 (*C*H), 130.6 (*C*H), 129.8 (*C*H), 128.8 (*C*H), 128.4 (*C*H), 127.7 (*C*H), 127.2 (*C*H), 126.8 (*C*^{h}H), 126.5 (*C*H), 126.0 (*C*H), 125.3 (*C*H), 125.0 (*C*H), 124.2 (*C*H), 122. (*C*^{i}H), 63.6 (*C*^{15}H), 59.1 (*C*^{8}H), 57.1 (*C*^{10}H$_2$), 54.4 (*C*^{13}H), 52.5 (*C*H$_2$), 49.1 (*C*^{2}H$_2$), 43.7 (DCE), 31.7 (*C*^{4}H), 28.4 (*C*$^{15'}$H), 22.7 (*C*^{17}H$_3$), 21.8 (*C*^{18}H$_3$), 21.1 (*C*^{16}H$_3$), 21.0 (*C*$^{17'}$H$_3$), 17.7 (*C*$^{16'}$H$_3$).

^{19}F NMR (225MHz, CDCl3, T = 300 K) δ = -153.13

3.5.18 Synthesis of 12f³-(4*S*,8*S*,13*R*)



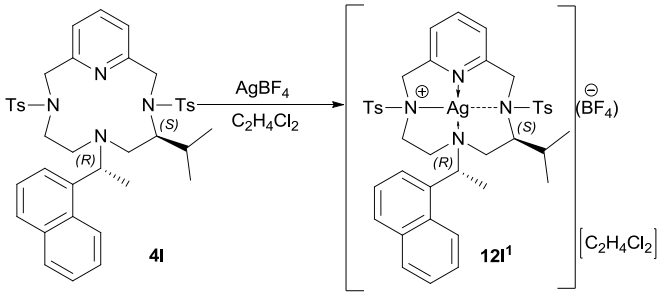
Reagents	MW (g/mol)	g	mmol	EQ
4f-(4*S*,8*S*,13*R*)	753.03	0.124	0.164	1
$AgN(SO_2CF_3)_2$	388.09	0.0637	0.164	1

Silver trifilimide was added to a solution of **4f** in dichloroethane (7 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then evaporated to dryness, then distilled hexane was added and the product recovered by filtration (MW 1237.98 g/mol considering **12f³-(4*S*,8*S*,13*R*)**:DCE/1:1).

yield = 0.135 g, 0.109 mmol 67%.

The same pattern reported for **12f¹** in section **3.5.17** is found in the ^{1}H and ^{13}C NMR NMR spectra.

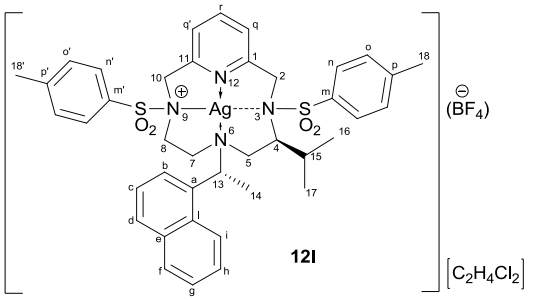
3.5.19 Synthesis of 12l'-(4*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
4l-(4*S*,13*R*)	710.95	0,311	0,438	1
$AgBF_4$	194.67	0,0852	0,438	1

Silver tetrafluoroborate was added to a solution of **4l** in dichloroethane (22 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then evaporated to dryness, then distilled hexane was added and the product recovered by filtration (MW 1044.64 g/mol considering **12l^1-(4*S*,13*R*)**:DCE/1:1).

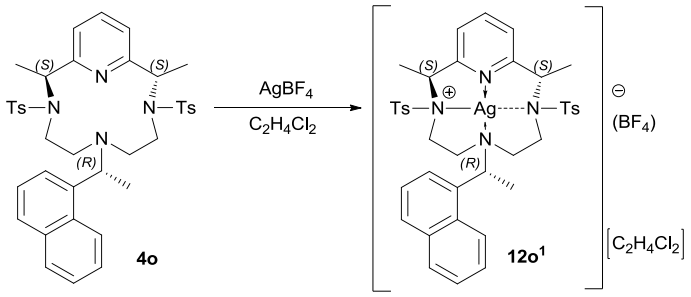
yield = 0.188 g, 0.187 mmol 43%.



^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (1H, d, *J* = 8.5 Hz, *H*^{i}), 7.94 – 7.71 (8H, m, Ar*H*), 7.62–7.47 (5H, m, Ar*H*), 7.42–7.34 (3H, m, Ar*H*), 7.23 (1H, d, *J* = 7.6 Hz, *H*^{q}), 6.00 (1H, q, *J* = 6.7 Hz, *H*^{13}), 5.58 (1H, d, *J* = 17.7 Hz, C*H*$_2^2$), 4.55 (2H, m), 4.13 (1H, d, *J* = 17.7 Hz, C*H*$_2^2$), 3.99 (1H, m, C*H*$_2$), 3.54 (1H, d, *J* = 15.0 Hz, C*H*$_2^{10}$), 2.91 (1H, m), 2.71-2.54 (2H, m), 2.46 (3H, s, C*H*$_3^{18}$), 2.48 (3H, s, C*H*$_3^{18'}$), 1.96 (3H, d, *J* = 6.7 Hz, C*H*$_3^{14}$) overlapping with 1.96 (2H, m), 0.98 (1H, m), 0.06 (3H, d, *J* = 6.7 Hz, C*H*$_3^{17}$), -0.33 (3H, d, *J* = 5.4 Hz, C*H*$_3^{16}$).

^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 (*C*), 152.7 (*C*), 146.2 (*C*), 145.8 (*C*), 140.7 (*C*H), 136.0 (*C*), 134.5 (*C*), 134.3 (*C*), 132.3 (*C*), 130.8 (*C*H), 130.7 (*C*H), 129.9 (*C*H), 129.1 (*C*H), 128.5 (*C*H), 127.2 (*C*H), 126.7 (*C*H), 125.7 (*C*H), 125.5 (*C*H), 123.4 (*C*H), 122.1 (*C*^{i}H), 59.9 (*C*^{4}H), 56.0 (*C*H$_2$), 53.8 (*C*^{13}H), 51.3 (*C*H$_2$), 50.9 (*C*H$_2$), 49.0 (*C*H$_2$), 46.7 (*C*H$_2$), 43.7 (DCE), 31.7 (*C*H$_2$), 28.6 (*C*^{15}H), 22.4 (*C*^{14}H$_3$), 21.9 (*C*^{18}H$_3$), 21.8 (*C*$^{18'}$H$_3$), 20.9 (*C*^{16}H$_3$), 17.8 (*C*^{17}H$_3$).

3.5.20 Synthesis of 12o[1]-(2*S*,10*S*,13*R*)



Reagents	MW (g/mol)	g	mmol	EQ
4o-(2*S*,10*S*,13*R*)	696.92	0.0777	0.114	1
$AgBF_4$	194.67	0.0217	0.114	1

Silver tetrafluoroborate was added to a solution of **4o** in dichloroethane (5 mL). The solution (kept in the dark until the final isolation of the product) was stirred at room temperature for one hour. The solvent was then evaporated to dryness, then distilled hexane was added and the product recovered by filtration (MW 990.55 g/mol considering **12o[1]-(2*S*,10*S*,13*R*)**:DCE/1:1).

yield = 0.0450 g, 0.0465 mmol 41%.

This synthesis has not been optimised and has been performed only once. Since the collected product was very unpure, the ^{1}H NMR spectrum has not been tabulated (see figure page 328).

3.6 SHB [Cu(Pc-L*)]CF_3SO_3 supported catalysts on silica

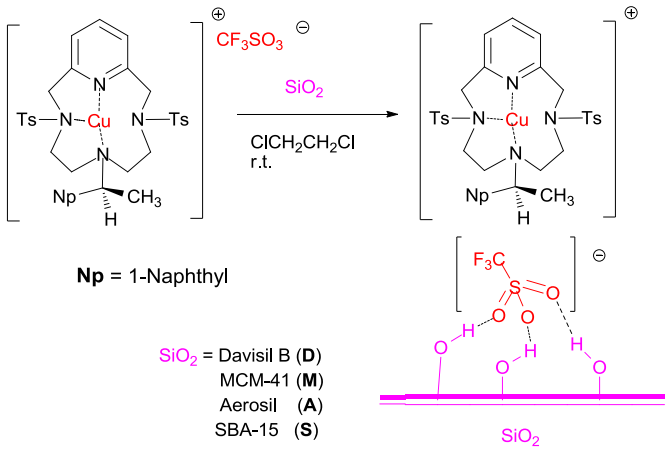
Before use, MCM.41 and SBA-15 were calcinated at 550 °C for 8 h in air.

Activation of all silicas was performed in a Schlenk flask at 300 °C for 2-3 h in air, subsequently in high vacuum (at least 10^{-5} mbar) overnight.

3.6.1 Grafting: Method 1

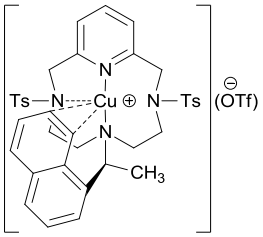
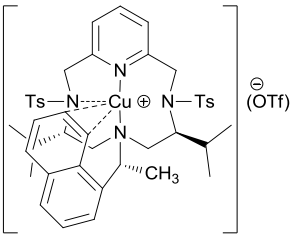
Complex **10d-(13*S*)** (0.0461 g, 0.0629 mmol) was dissolved in CH_2Cl_2 (10 mL). The resulting colourless solution was added to activated Davisil B (0.400 g), the mixture was stirred at RT for 4 h under inert atmosphere, filtered, the solid washed with CH_2Cl_2 (3 x 5 mL) and dried overnight to yield the immobilized copper(I) complex.

3.6.2 Grafting: Method 2



$[Cu(OTf)]_2 \cdot (C_6H_6)$ (0.140 g, 0.277 mmol) was added to a $C_2H_4Cl_2$ (28 mL) solution of **4d-(13*S*)** ligand (0.371 g, 0.555 mmol). The resulting colorless solution was stirred for 1 h, than 5,5 mL of solution was added to activated SBA-15 (0.340 g), the mixture was stirred at RT for 4 h under inert atmosphere, filtered, the solid washed with $C_2H_4Cl_2$ (3 x 5 mL) and dried overnight to yield the immobilized copper(I) complex.

3.6.3 Supported catalysts

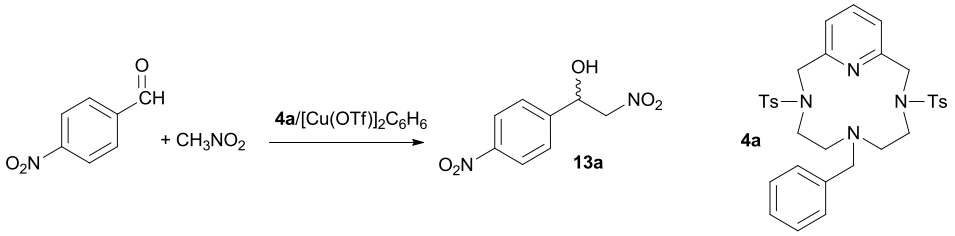
	Complex	Silica	Ref.
10d		Davisil B	**10d/D**
		MCM-41	**10d/M**
		SBA-15	**10d/S**
		Areosil	**10d/A**
10f		Davisil B	**10f/D**

Metal loadings are determined by ICP-OES using a Thermo X Series II apparatus. 15 mg of each sample are mineralised by adding 3 mL of 37% HCl, 1 mL of concentrated HNO_3, 1 mL of 98% H_2SO_4. For further details see *Results and discussion* section **2.3**

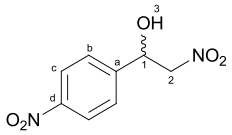
3.7 Homogenous Catalysis

3.7.1 Henry reaction

3.7.1.1 Optimization of the catalyzed Henry reaction



All the reactions carried out for the optimization were conducted between 4-nitrobenzaldehyde and nitromethane with ligand **4a.** Reactions were performed with a 1:1 Cu(I)/**4a** ratio, $[Cu(OTf)]_2 \cdot (C_6H_6)$ (0.0078 g 0.015 mmol) and **4a** (0.0181 g 0.0030 mmol) dissolved in the specified solvent (5 mL) and stirred for 1 h at room temperature. Then 4-nitrobenzaldehyde and the specified base were added to the solution. Finally CH_3NO_2 was added by syringe, and the resulting yellowish solution was kept under stirring at specified temperature. The reaction progress was monitored by thin-layer chromatography (TLC). The solvent was evaporated under vacuum and the crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane : 2/3), obtaining the β-nitroalcohol **13a**. (MW 212.16 g/mol). All the repored yields are isolated yields based on initial 2,4-nitrobenzaldehyde; unreacted benzaldehyde accounted for the rest of the reaction mass balance.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.30-8.25 (2H, m, Ar*H*), 7.63 (2H, dd, *J* = 8.8 Hz, *J* = 1.5 Hz, Ar*H*), 5.61 (1H, s, H^1), 4.60-4.57 (2H, m, $CH_2{}^2$), 3.13 (1H, s, OH^3).

3.7.1.1.1 Catalysis 1

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
EtOH	25	48

yield = 0.0388 g, 0.183 mmol, 61%.

3.7.1.1.2 Catalysis 2

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
THF	25	48

yield = 0.0216 g, 0.102 mmol, 34%.

3.7.1.1.3 Catalysis 3

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	48

yield = 0.0560 g, 0.264 mmol, 88%.

3.7.1.1.4 Catalysis 4

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	reflux	36

yield = 0.0509 g, 0.240 mmol, 80%.

3.7.1.1.5 Catalysis 5

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	24/24/24

After 24 h from the starting addition, two additions of both aldehyde and nitromethane were repeated (same quantities as the initial addition); total yield is reported.

yield = 0.174 g, 0.819 mmol, 91%.

3.7.1.1.6 Catalysis 6

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
chlorobenzene	25	48

yield = 0.0121 g, 0.0570 mmol, 19%.

3.7.1.1.7 Catalysis 7

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	5

yield = 0.0554 g, 0.261 mmol, 87%.

3.7.1.1.8 Catalysis 8

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	20

yield = 0.0477 g, 0.225 mmol, 75%.

3.7.1.1.9 Catalysis 9

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	5

yield = 0.0363 g, 0.171 mmol, 57%.

3.7.1.1.10 Catalysis 10

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.453	-	-	3.0	100
CH_3NO_2	61.04	0.916	1.127	0.810	15	500
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	160

yield = 0.0325 g, 0.153 mmol, 51%.

3.7.1.1.11 Catalysis 11

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
DIPEA	129.24	0.0194	0.742	0.0261	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	20

yield = 0.0382 g, 0.180 mmol, 60%.

3.7.1.1.12 Catalysis 12

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Solvent	T (°C)	Time (h)
EtOH	25	88

yield = 0.0255 g, 0.120 mmol, 40%.

3.7.1.1.13 Catalysis 13

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-NO_2benzaldehyde	151.12	0.0450	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0212	-	-	0.030	1

Solvent	T (°C)	Time (h)
CH_2Cl_2	25	20

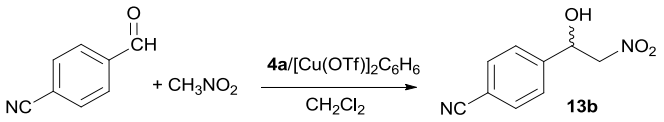
yield = 0.0115 g, 0.0540 mmol, 18%.

3.7.1.2 Reaction scope with nitromethane

General Procedure for the Catalyzed Henry Reaction.

$[Cu(OTf)]_2 \cdot (C_6H_6)$ (0.0078 g 0.015 mmol) and **4a** (0.0181 g 0.0030 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred for 1 h at room temperature. Then, aldehyde (0.30 mmol) and triethylamine (0.15 mmol) were added to the solution. Finally CH_3NO_2 (0.08 mL, 1.5 mmol) was added by syringe, and the resulting yellowish solution was kept under stirring at room temperature for 20 h. The reaction progress was monitored by thin-layer chromatography (TLC). The solvent was evaporated under vacuum and the crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane).

3.7.1.2.1 Catalysis with 4-cyanobenzaldehyde

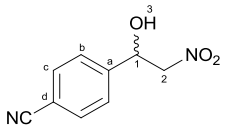


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(CN)benzaldehyde	131.13	0.0395	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

(MW 192.17 g/mol).

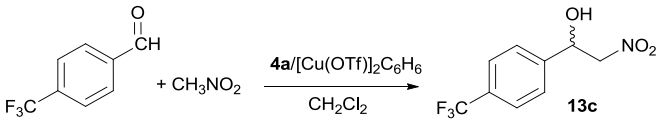
yield = 0.0553 g, 0.288 mmol, 96%.

eluant EtOAc/*n*-hexane = 1/5



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.73 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.58 (2H, d, *J* = 8.0 Hz, Ar*H*), 5.58-5.54 (1H, m, H^1), 4.64-4.60 (2H, m, CH_2^2), 3.19 (1H, bs, OH^3).

3.7.1.2.2 Catalysis with 4-(trifluoromethyl)benzaldehyde

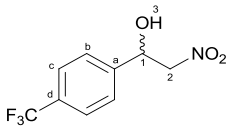


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(CF_3)benzaldehyde	174.12	0.0522	1.275	0.0410	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

(MW 235.16 g/mol).

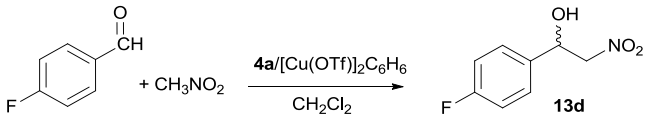
yield = 0.0494 g, 0.210 mmol, 70%.

eluant EtOAc/*n*-hexane = 1/4.5



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.68 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.55 (2H, d, *J* = 8.1Hz , Ar*H*), 5.56-5.53 (1H, m, H^1), 4.60-4.54 (2H, m, $CH_2{}^2$), 3.03 (1H, d, *J* = 3.7 Hz, OH^3).

3.7.1.2.3 Catalysis with 4-fluorobenzaldehyde

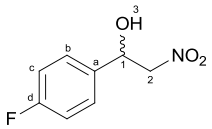


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(F)benzaldehyde	124.11	0.0372	1.157	0.0322	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

(MW 185.15 g/mol).

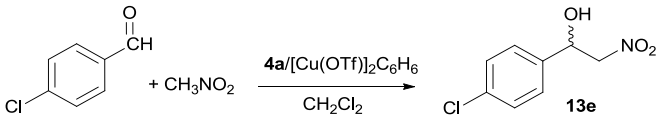
yield = 0.0422 g, 0.228 mmol, 76%.

eluant EtOAc/*n*-hexane = 1/5



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.41 (2H, d, *J* = 5.2 Hz, Ar*H*), 7.11 (2H, d, *J* = 8.8 Hz , Ar*H*), 5.47 (1H, m, H^1), 4.69-4.51 (2H, m, $CH_2{}^2$), 2.87 (1H, bs, OH^3).

3.7.1.2.4 Catalysis with 4-chlorobenzaldehyde

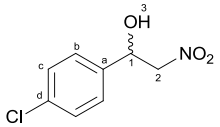


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(Cl)benzaldehyde	140.57	0.0422	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

(MW 201.61 g/mol).

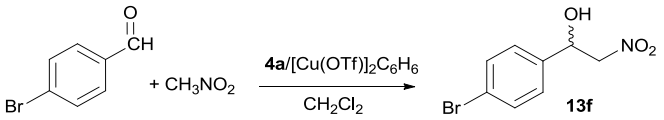
yield = 0.0411 g, 0.204 mmol, 68%.

eluant EtOAc/*n*-hexane = 1/4



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.39 (4H, m, Ar*H*), 5.46 (1H, dd, *J* = 8.9 Hz, *J* = 3.5 Hz, H^1), 4.61-4.52 (2H, m, $CH_2{}^2$), 3.09 (1H, bs, OH^3).

3.7.1.2.5 Catalysis with 4-bromobenzaldehyde

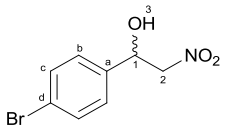


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(Br)benzaldehyde	185.02	0.0556	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

(MW 246.06 g/mol).

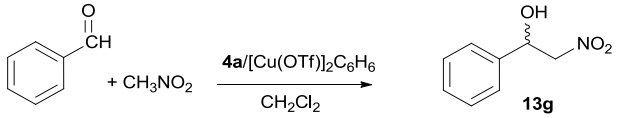
yield = 0.0413 g, 0.168 mmol, 56%.

eluant EtOAc/*n*-hexane = 1/5



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.55-7.53 (2H, m, Ar*H*), 7.29 (2H, d, *J* = 8.8 Hz, Ar*H*), 5.47-5.42 (1H, m, H^1), 4.61-4.47 (2H, m, $CH_2{}^2$), 2.89 (1H, d, *J* = 4,4 Hz OH^3).

3.7.1.2.6 Catalysis with benzaldehyde

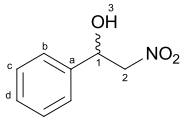


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
benzaldehyde	106.12	0.0318	1.044	0.0300	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

(MW 167.16 g/mol).

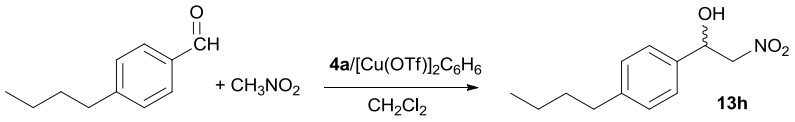
yield = 0.0376 g, 0.225 mmol, 75%.

eluant EtOAc/*n*-hexane = 1/4



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.43-7.36 (4H, m, Ar*H*), 7.28-7.23 (1H, m, H^d), 5.49(1H, dd, *J* = 3,2 Hz, *J* = 9.4 Hz, H^1), 4.60-4.57 (2H, m, $CH_2{}^2$), 2.88 (1H, bs, OH^3).

3.7.1.2.7 Catalysis with 4-butylbenzaldehyde

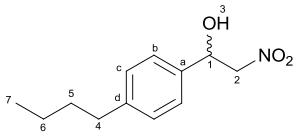


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-butylbenzaldehyde	162.23	0.0487	0.968	0.0503	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

Without added base; time : 96 h. (MW 223.27 g/mol).

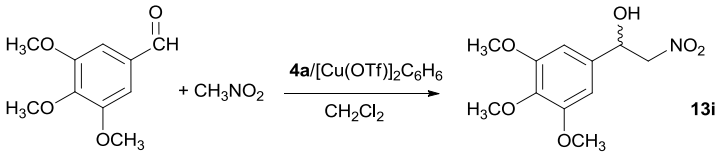
yield = 0.0355 g, 0.150 mmol, 50%.

eluant EtOAc/*n*-hexane = 1/7



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.31 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.21 (2H, d, *J* = 8.1 Hz, Ar*H*), 5.44(1H, dd, *J* = 9.6 Hz, *J* = 2.9 Hz, H^1), 4.62 (1H, dd, *J* = 13.3 Hz, *J* = 9.6 Hz, CH_2^2), 4.50 (1 H, dd, *J* = 13.0 Hz, *J* = 3.0 Hz, $CH_2^{2'}$), 2.76 (1H, d, *J* = 3.6 Hz, OH^3), 2.64 (2H, m, CH_2^4), 1.61 (2H, m CH_2^5), 1.35 (2H, m, CH_2^6), 0.93 (3H, td, *J* = 7.2 Hz, *J* = 6.5 Hz, CH_3^7).

3.7.1.2.8 Catalysis with 3,4,5-trimethoxybenzaldehyde

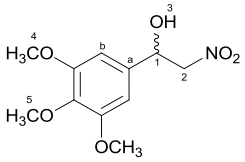


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
3,4,5-$(OMe)_3$benzaldehyde	196.20	0.0589	-	-	0.30	10
CH_3NO_2	61.04	1.01	1.127	0.921	17	560
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Without added base; time : 72 h. (MW 257.24 g/mol).

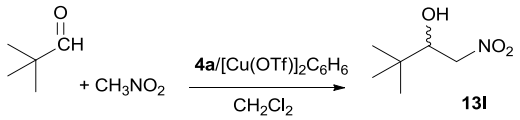
yield = 0.0540 g, 0.210 mmol, 70%.

eluant EtOAc/*n*-hexane = 1/2



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.28-7.15 (1H, m, Ar*H*), 6.63 (1H, s, Ar*H*), 5.71-5.69 (1H, m, H^1), 4.65- 4.59 (1H, m, CH_2^2), 4.54- 4.53 (1 H, m, $CH_2^{2'}$), 3.96- 3.95 (3H, m, CH_3^5), 3.89- 3.85 (6H, m, CH_3^4), 2.92 (1H, d, *J*= 3.2 Hz, OH^3).

3.7.1.2.9 Catalysis with pivalaldehyde

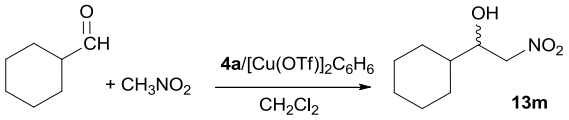


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Trimethylacetaldehyde	86.13	0.0258	0.793	0.0330	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

time : 40 h. (MW 147.17 g/mol).

yield = trace

3.7.1.2.10 Catalysis with cyclohexanecarbaldehyde

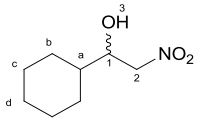


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Cyclohexylcarbaldehyde	112.17	0.0366	0.926	0.0360	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

(MW 173.21 g/mol).

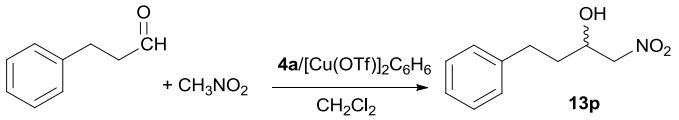
yield = 0.0213 g, 0.123 mmol, 41%.

eluant EtOAc/*n*-hexane = 2/3



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 4.51 (1H, dd, *J* = 13.1, 2.9 Hz, CH_2^2), 4.41 (1H, dd, *J* = 13.1, 8.9 Hz, C$H_2^{2'}$), 4.12 (1H, m, H^1), 2.46 (1H, m, H^a), 1.87-1.71 (5H, m), 1.50 (1H, m), 1.31-1.11 (4H, m).

3.7.1.2.11 Catalysis with 3-Phenylpropionaldehyde



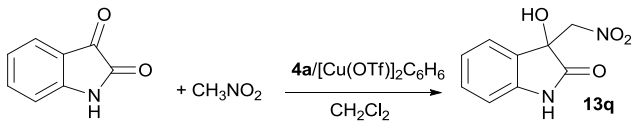
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Hydrocinnamaldehyde	134.18	0.0403	1.019	0.0400	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

Time: 40 h. (MW 195.22 g/mol).

yield = traces

eluant EtOAc/*n*-hexane = 3/7

3.7.1.2.12 Catalysis with isatin

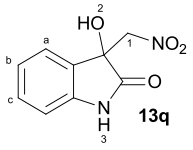


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
isatin	147.13	0.0441	-	-	0.30	10
CH_3NO_2	61.04	0.0916	1.127	0.0810	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

(MW 208.17 g/mol).

yield = 0.0468 g, 0.225 mmol, 75%.

eluant EtOAc/*n*-hexane = 1/3



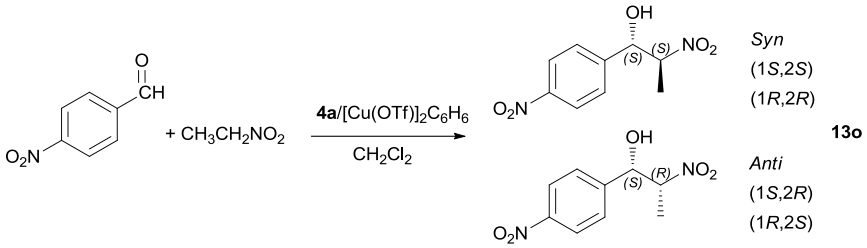
^{1}H NMR (300 MHz; DMSO-d_6; T = 300 k) δ 10.53 (1H, s, N*H*^{3}), 8.12-6.75 (4H, m, Ar*H*), 5.32 (1H, m, CH_2^{1}).

3.7.1.3 Catalysis with nitroethane

General Procedure for the Catalysed Henry Reaction.

$[Cu(OTf)]_2 \cdot (C_6H_6)$ (0.0078 g 0.015 mmol) and **4a** (0.0181 g 0.0030 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred for 1 h at room temperature. Then, aldehyde (0.30 mmol) and triethylamine (0.15 mmol) were added to the solution. Finally $CH_3CH_2NO_2$ (0.10 mL, 1.5 mmol) was added by syringe, and the resulting yellowish solution was kept under stirring at room temperature for 20 h. The reaction progress was monitored by thin-layer chromatography (TLC). The solvent was evaporated under vacuum and the crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane).

3.7.1.3.1 Catalysis with 4-nitrobenzaldehyde[163]

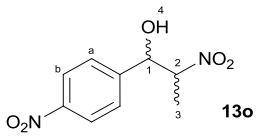


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(NO_2)benzaldehyde	151.12	0.0450	-	-	0.30	10
$CH_3CH_2NO_2$	75.07	0.113	1.045	0.100	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

(MW 226.19 g/mol).

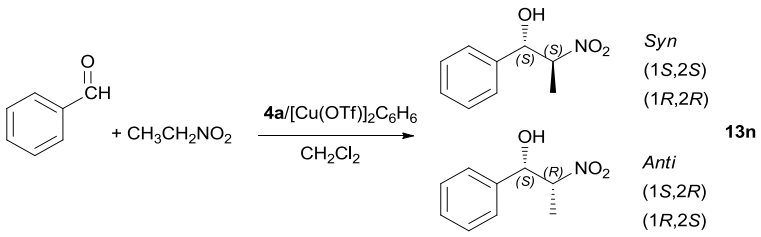
yield = 0.0475 g, 0.210 mmol, overall 70%; *Syn/Anti* ratio = 55:45

eluant EtOAc/*n*-hexane = 3/7



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 8.26 (4H, m, Ar*H*), 7.62 (4H, m, Ar*H*), 5.59 (1H, s, *H anti*), 5.21 (1H, s, *H syn*), 4.79-4.67 (2H, m, *H*), 3.00-2.92 (2 H, bs, O*H*^{4}), 1.49-1.45 (6H, m, *J* = 6.8 Hz, C*H*$_3$^{3}).

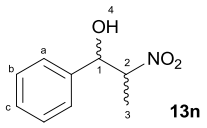
3.7.1.3.2 Catalysis with benzaldehyde[163]



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
benzaldehyde	106.12	0.0318	1.044	0.0300	0.30	10
$CH_3CH_2NO_2$	75.07	0.113	1.045	0.100	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

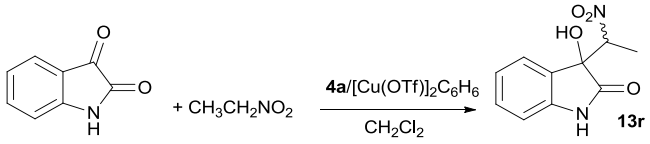
(MW 181.19 g/mol).

yield = 0.0353 g, 0.195 mmol, overall 65%; *Syn/Anti* ratio = 58:42.



^{1}H NMR (300 MHz; $CDCl_3$; T = 300 k) δ 7.40-7.33 (10H, m, Ar*H*), 5.40 (1H, d, *J* = 3.6 Hz, *H anti*), 5.03 (1H, d, *J* = 9.0 Hz, *H syn*), 4.82-4.75 (1H, m, *H*), 4.75-4.66 (1H, m, *H*), 2.77 (2H, br s, O*H*^{3}), 1.50 ppm (3H, d, *J* = 6.9 Hz, C*H*$_3$^{3} *anti*), 1.32 ppm (3H, d, *J* = 6.9 Hz, C*H*$_3$^{3} *syn*).

3.7.1.3.3 Catalysis with isatin

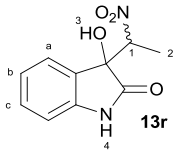


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
isatin	147.13	0.0441	-	-	0.30	10
$CH_3CH_2NO_2$	75.07	0.113	1.045	0.100	1.5	50
EtN_3	101.19	0.0152	0.726	0.0210	0.15	5
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

(MW 222.20 g/mol).

yield = 0.0533 g, 0.240 mmol, overall 80%; diasteroisomeric ratio = 5:1

eluant EtOAc/*n*-hexane = 1/3



Minor Isomer

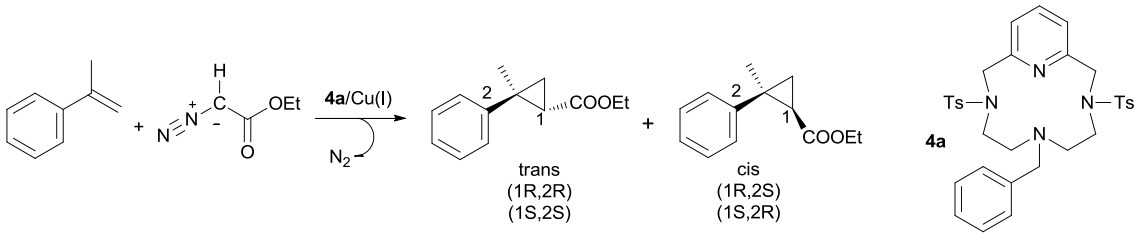
^{1}H NMR (300 MHz; DMSO-d_6; T = 300 k) δ 10.58 (1H, s, NH^4), 8.12-6.75 (4H, m, Ar*H*), 5.03 (1H, m, H^1), 1.34 (3H, d, *J* = 6.8 Hz, CH_3^2).

Major Isomer

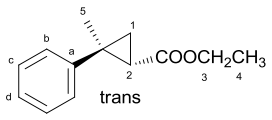
^{1}H NMR (300 MHz; DMSO-d_6; T = 300 k) δ 10.48 (1H, s, NH^4), 8.12-6.75 (4H, m, Ar*H*), 5.04 (1H, m, H^1), 1.66 (3H, d, *J* = 6.8 Hz, CH_3^2).

3.7.2 Cyclopropanation reaction

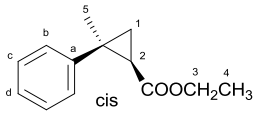
3.7.2.1 Optimization of the catalysed cyclopropanation reaction



All the reactions carried out for the optimization were conducted between α-methlstyrene and ethyldiazoacetate (EDA) with ligand **4a.** Reactions were performed with a 1:1 Cu(I)/**4a** ratio, with equimolar amounts of Cu salt (0.030 mmol) and **4a** in the specified solvent. Copper salt, the ligand **4a** (0.030 mmol) and α-methylstyrene (0.650 mL, 5.0 mmol) were dissolved in distilled solvent (5 mL) and the solution stirred for one hour at the specified temperature. Catalytic reactions were run by adding EDA to the solution containing the copper salt, the ligand **4a** and a-methylstyrene, (Cu/**4a**/EDA/olefin ratio 1/1/35/170). The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). The solvent was evaporated under vacuum and the crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane : 0.3/10), obtaining the two diasteroisomers of the cyclopropane molecules. (MW 204.26 g/mol). All reported yields were isolated and based on EDA. Fumarate and maleate accounted for the rest of the reaction mass balance. The diasteroisomeric ratio was determined by GC-MS.



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.33-7.22 (5H, m, Ar*H*), 4.22 (2H, q, *J* = 7.2 Hz, CH_2^3), 1.97 (1H, dd, *J* = 8.3 Hz, *J* = 2.3 Hz, H^2), 1.55 (3H, s, CH_3^5), 1.47-1.44 (2H, m, CH_2^1), 1.32 (3H, t, *J* = 7.2 Hz, CH_3^4).



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.33-7.22 (5H, m, Ar*H*), 1.92 (1H, m, CH_2^3), 1.80 (1H, t, *J* = 4.9 Hz, *H*^{2}), 1.49 (3H, s, CH_3^5), 1.17 (1H, m, CH_2^1), 0.96 (3H, t, *J* = 7.1 Hz, CH_3^4).

3.7.2.1.1 Catalysis 1

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	r.t.	one pot

yield = 0.0633 g, 0.310 mmol, 31%;
cis:trans = 42:58

3.7.2.1.2 Catalysis 2

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_7H_8	517.37	0.00780	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	r.t.	one pot

yield = 0.0674 g, 0.330 mmol, 33%;
cis:trans = 42:58

3.7.2.1.3 Catalysis 3

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
CuI	190.45	0.00570	-	-	0.030	1

Solvent	T (°C)	modality addition EDA
1,2-DCE	r.t.	one pot

yield = 0.0655 g, 0.320 mmol, 32%;

cis:trans = 42:58

3.7.2.1.4 Catalysis 4

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.182 g, 0.890 mmol, 89%;

cis:trans = 43:57

3.7.2.1.5 Catalysis 5

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$[Cu(CH_3CN)_4]\cdot BF_4$	314.56	0.0095	-	-	0.030	1

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.0919 g, 0.450 mmol, 45%; *cis:trans* = 43:57

3.7.2.1.6 Catalysis 6

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$Cu(CF_3SO_3)_2$	361.68	0.0108	-	-	0.030	1

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.182 g, 0.890 mmol, 89%; *cis:trans* = 43:57

3.7.2.1.7 Catalysis 7

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$CuCl_2$	134.45	0.00400	-	-	0.030	1

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.0204 g, 0.100 mmol, 10%; *cis:trans* = 44:56

3.7.2.1.8 Catalysis 8

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$Cu(OAc)_2 \cdot H_2O$	199.65	0.00600	-	-	0.030	1

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.0327 g, 0.160 mmol, 16%; *cis:trans* = 45:55

3.7.2.1.9 Catalysis 9

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

In presence of moleculare sieves.

yield = 0.0654 g, 0.320 mmol, 32%; *cis:trans* = 44:56

3.7.2.1.10 Catalysis 10

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0363	-	-	0.060	2
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

yield = 0.0878 g, 0.430 mmol, 43%; *cis:trans* = 45:55

3.7.2.1.11 Catalysis[234] 11

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

Copper(I) trifluoromethanesulfonate benzene complex synthetized according to ref. 234.

yield = 0.180 g, 0.880 mmol, 88%; *cis:trans* = 43:57

3.7.2.1.12 Catalysis 12

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
CH_2Cl_2	0	100 min

yield = 0.0899 g, 0.440 mmol, 44%; *cis:trans* = 64:36

3.7.2.1.13 Catalysis 13

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
CH_3CN	0	100 min

yield = 0.0204 g, 0.100 mmol, 10%; *cis:trans* = 50:50

3.7.2.1.14 Catalysis 14

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
toluene	0	100 min

yield = 0.102 g, 0.500 mmol, 50%; *cis:trans* = 77:23

3.7.2.1.15 Catalysis 15

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
chlorobenzene	0	100 min

yield = 0.0960 g, 0.470 mmol, 47%; *cis:trans* = 72:28

3.7.2.1.16 Catalysis 16

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
THF	0	100 min

yield = 0.0388 g, 0.190 mmol, 19%; *cis:trans* = 66:34

3.7.2.1.17 Catalysis 17

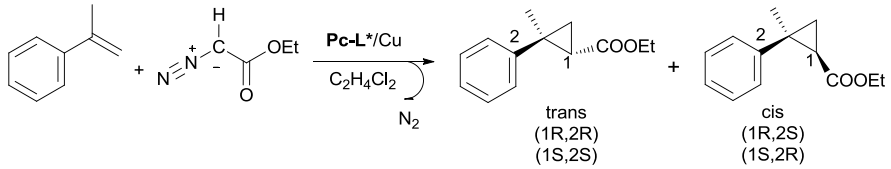
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4a	604.78	0.0181	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

Solvent	T (°C)	modality addition EDA
1,2-DCE	0	100 min

Solvent not distilled.

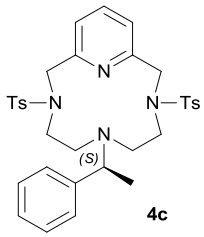
yield = 0.0756 g, 0.370 mmol, 37%; *cis:trans* = 40:60

3.7.2.2 Asymmetric cyclopropanation of α-methylstyrene



All the reactions carried out for this section were conducted between α-methlstyrene and ethyldiazoacetate (EDA) with different ligand or preformed complexes **.** Reactions were performed with a 1:1 Cu(I)/ligand ratio in 1,2-dichloroethane. Copper salt (0.030 mmol), the specified ligand (0.030 mmol) and α-methylstyrene (0.650 mL, 5.0 mmol) were dissolved in distilled 1,2-dichloroethane (5 mL) and the solution stirred for one hour at 0 °C. Catalytic reactions were run by slow addition of EDA over 100 min with a syringe pump to the solution containing the copper salt, the ligand and α-methylstyrene, (Cu/ligand/EDA/olefin ratio 1/1/35/170). The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yields were determined by GC with the addition of 2,4-dinitrotoluene as internal standard, confirmed by quantitative ^1H NMR analysis of the reaction mixture. Isolated yields are reported in parentheses. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75).

3.7.2.2.1 Catalysis 1

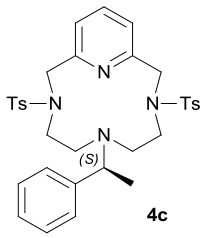


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4c-(13*S*)	618.81	0.0186	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

T (°C) = r.t.

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.153	0.750	75(53)	55:45	44	35

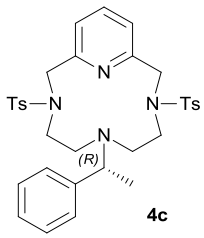
3.7.2.2.2 Catalysis 2



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4c-(13*S*)	618.81	0.0186	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.184	0.900	90(70)	65:35	50	38

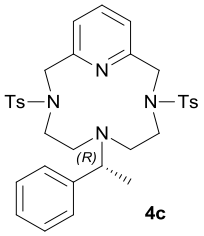
3.7.2.2.3 Catalysis 3



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4c-(13*R*)	618.81	0.0186	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.186	0.910	91(72)	65:35	50	38

3.7.2.2.4 Catalysis 4

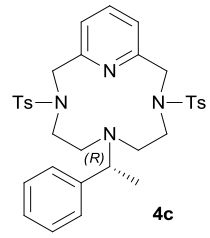


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4c-(13*R*)	618.81	0.0186	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.00750	-	-	0.015	0.5

T (°C) = -20

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.163	0.800	80(59)	64:36	53	38

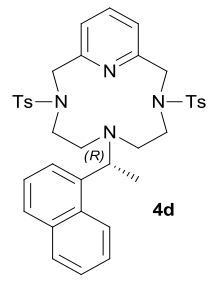
3.7.2.2.5 Catalysis 5



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4c-(13*R*)	618.81	0.0186	-	-	0.030	1
$[Cu(CH_3CN)_4]\cdot BF_4$	314.56	0.0095	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.159	0.780	78(65)	57:43	33	36

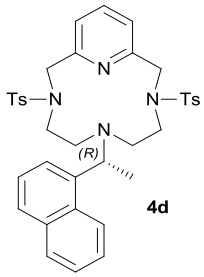
3.7.2.2.6 Catalysis 6



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$[Cu(CH_3CN)_4]\cdot BF_4$	314.56	0.0095	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.143	0.700	70(56)	55:45	45	44

3.7.2.2.7 Catalysis 7

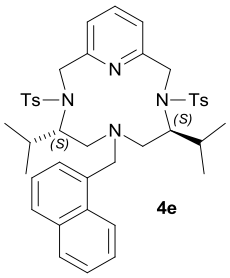


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.202	0.990	99(83)	60:40	53	65

Same results were obtained using the opposite enantiomer **4d-(13*S*)**with the opposite enantiomeric excess.

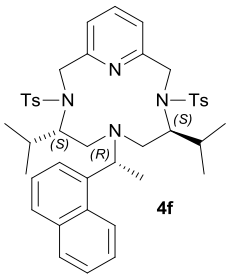
3.7.2.2.8 Catalysis 8



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4e-(4*S*,8*S*)	739.00	0.0222	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.202	0.990	99(88)	33:67	30	50

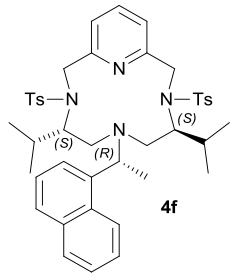
3.7.2.2.9 Catalysis 9



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.00750	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.200	0.980	98(57)	50:50	88	99

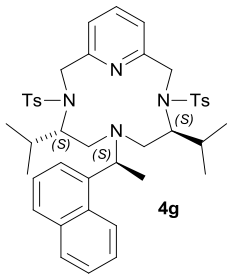
3.7.2.2.10 Catalysis 10



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$Cu(CF_3SO_3)_2$	361.68	0.0108	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.196	0.960	96	52:48	70	77

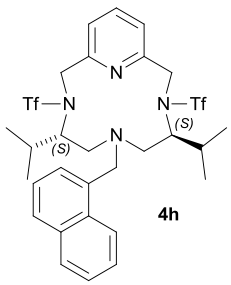
3.7.2.2.11 Catalysis 11



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4g-(4*S*,8*S*,13*S*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.135	0.660	66	35:65	57	52

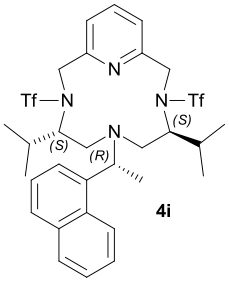
3.7.2.2.12 Catalysis 12



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4h-(4*S*,8*S*)	694.75	0.0208	-	-	0.030	1
$(CF_3SO_3Cu)_2\ C_6H_6$	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.186	0.910	91	52:48	21	16

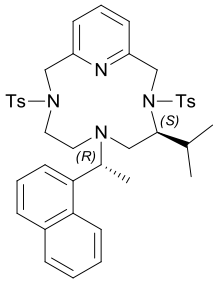
3.7.2.2.13 Catalysis 13



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4i-(4*S*,8*S*,13*S*)	708.78	0.0213	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.194	0.950	95	42:58	23	59

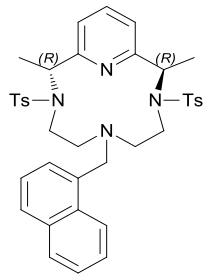
3.7.2.2.14 Catalysis 14



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4l-(4*S*,13*R*)	710.95	0.0213	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.098	0.480	48	60:40	74	79

3.7.2.2.15 Catalysis 15

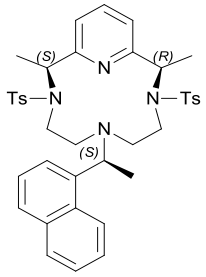


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4m-(2*R*,10*R*)	682.89	0.0206	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.161	0.790	79	63:37	50	40

Same results were obtained using the opposite enantiomer **4m-(2*S*,10*S*)**with the opposite enantiomeric excess.

3.7.2.2.16 Catalysis 16

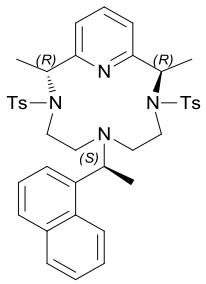


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4n-(2*R*,10*S*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.157	0.770	77	64:36	47	58

Same results were obtained using the opposite enantiomer **4n-(2*S*,10*R*,13*R*)** with the opposite enantiomeric excess.

3.7.2.2.17 Catalysis 17

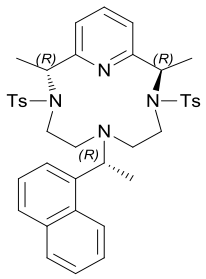


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.192	0.940	94	63:37	55	62

Same results were obtained using the opposite enantiomer **4o-(2*S*,10*S*,13*R*)** with the opposite enantiomeric excess.

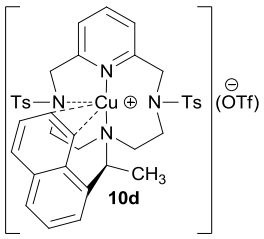
3.7.2.2.18 Catalysis 18



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4p-(2*R*,10*R*,13*R*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.135	0.660	66	58:42	28	16

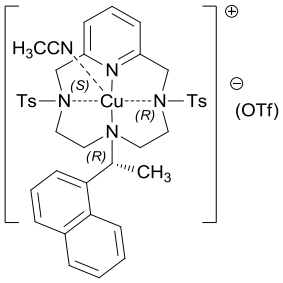
3.7.2.2.19 Catalysis 19



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d	879.47	0.0264	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.200	0.980	98(82)	57:43	55	66

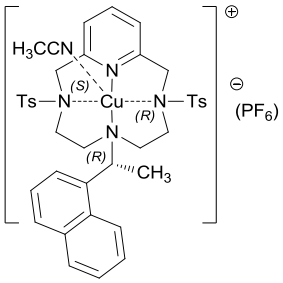
3.7.2.2.20 Catalysis 20



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
[**10d**/CH_3CN][OTf]	922.53	0.0277	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.163	0.800	80(72)	58:42	49	63

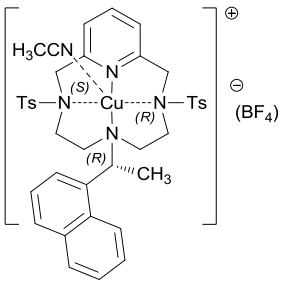
3.7.2.2.21 Catalysis 21



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
[**10d**/CH_3CN][PF_6]	918.43	0.0276	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.153	0.750	75(65)	57:43	45	62

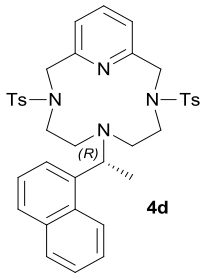
3.7.2.2.22 Catalysis 22



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
[**10d**/CH_3CN][BF_4]	860.27	0.0258	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.174	0.850	85(73)	55:45	54	62

3.7.2.2.23 Catalysis 23



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

In presence of added acetonitrile (5 eq).

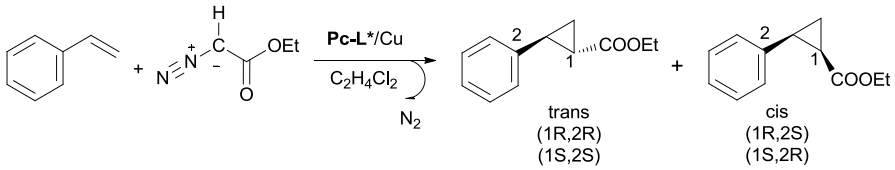
g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.161	0.790	79(65)	59:41	53	65

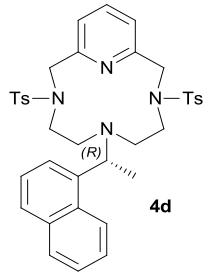
3.7.2.3 Reaction scope with different ligands

General procedure for the catalytic cyclopropanation reactions

In a typical experiment, $[Cu(OTf)]_2 \cdot (C_6H_6)$ (0.0075 g, 0.015 mmol), the ligand (0.030 mmol) and the olefin (5.0 mmol) were dissolved in distilled dichloroethane (5 mL) and the solution stirred for one hour at 0° C. Then a dichloroethane solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yields were determined by the addiction of 2,4-dinitrotoluene as internal standard and the solution was then evaporated to dryness *in vacuo* and analysed by quantitative ^1H NMR. Isolated yields are reported in parentheses. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC.

3.7.2.3.1 Styrene with ligand 4d-(13R)





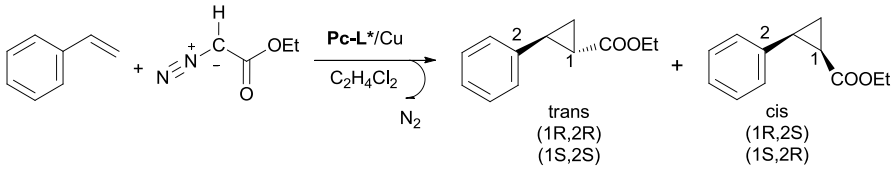
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
styrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

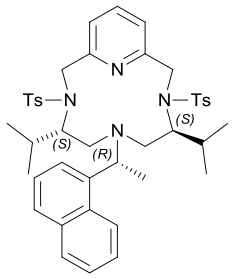
(MW 190.24 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.137	0.720	72(51)	50:50	33	50

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 98:2), λ = 230 nm.

3.7.2.3.2 Styrene with ligand 4f-(4S,8S,13R)





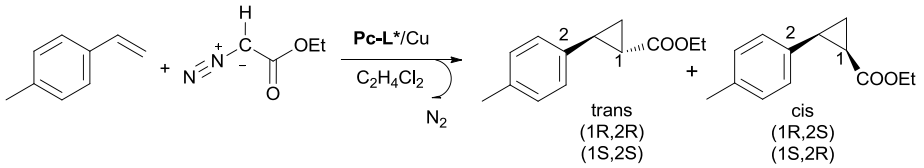
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
styrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

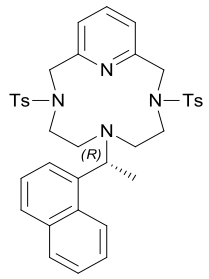
(MW 190.24 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.184	0.970	97	38 : 62	99	87

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 98:2), λ = 230 nm.

3.7.2.3.3 4-Methylstyrene with ligand 4d-(13R)





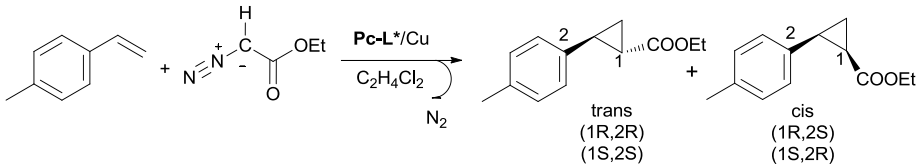
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-methylstyrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

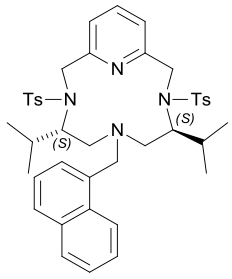
(MW 204.26 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.135	0.660	66(45)	53 : 47	34	45

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.4 4-Methylstyrene with ligand 4e-(4S,8S)





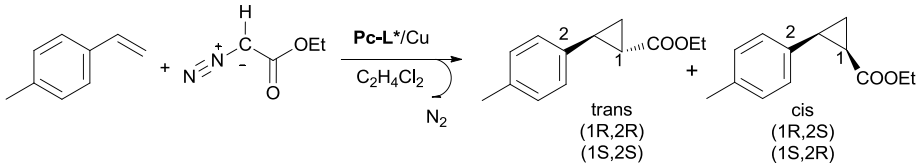
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-methylstyrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4e-(4*S*,8*S*)	739.00	0.0222	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

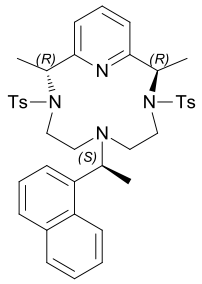
(MW 204.26 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.161	0.790	79	25 : 75	33	40

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.5 4-Methylstyrene with ligand 4o-(2R,10R,13S)





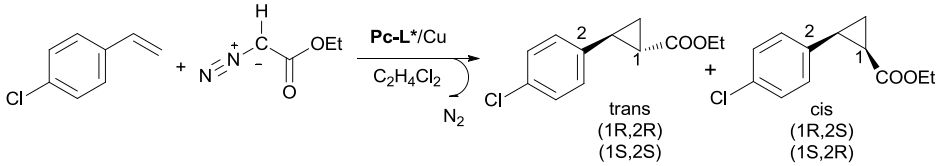
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-methylstyrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_7H_8	517.37	0.0078	-	-	0.015	0.5

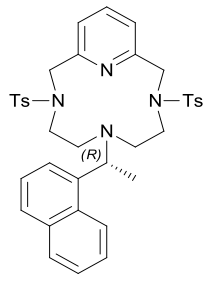
(MW 204.26 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.194	0.950	95	54 : 46	47	65

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.6 4-chlorostyrene with ligand 4d-(13R)





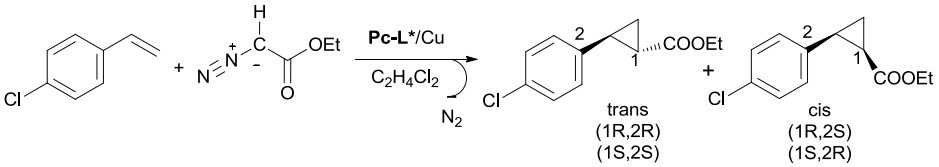
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene	138.59	0.693	1.038	0.640	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

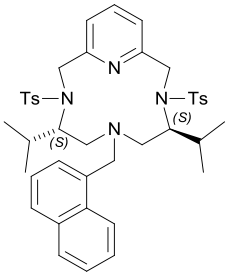
(MW 224.68 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.198	0.880	88(68)	47 : 53	36	50

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.7 4-chlorostyrene with ligand 4e-(4S,8S)





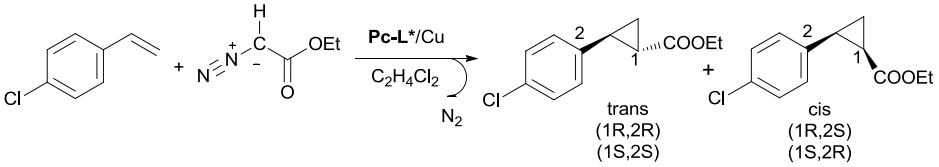
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene	138.59	0.693	1.038	0.640	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4e-(4*S*,8*S*)	739.00	0.0222	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

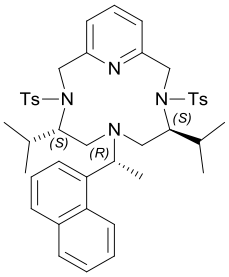
(MW 224.68 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.198	0.880	88	19 :81	42	53

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.8 4-chlorostyrene with ligand 4f-(4S,8S,13R)





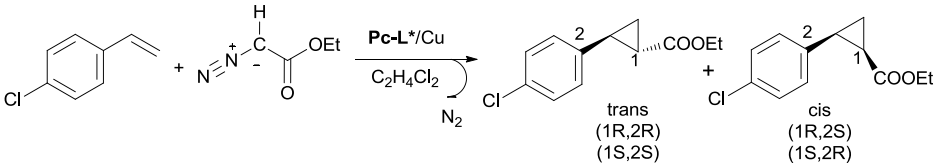
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene	138.59	0.693	1.038	0.640	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

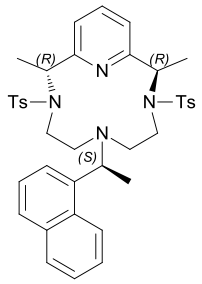
(MW 224.68 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.193	0.860	86	42 : 58	66	78

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.9 4-chlorostyrene with ligand 4o-(2R,10R,13S)





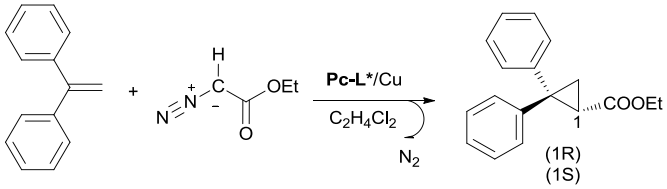
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene	138.59	0.693	1.038	0.640	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

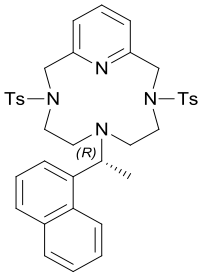
(MW 224.68 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans*
0.195	0.870	87	51 : 49	n.d.	n.d.

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.7.2.3.10 1,1-diphenylethylene with ligand 4d-(13R)





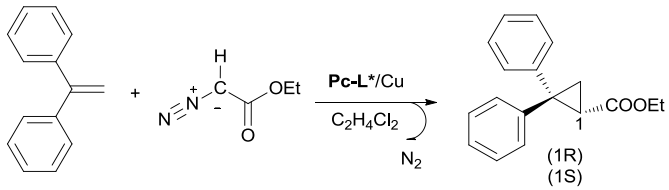
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.901	1.021	0.883	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

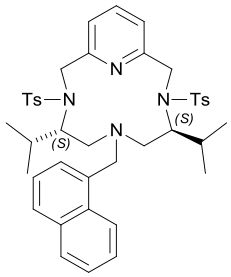
(MW 266.13 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) (1*S*)
0.170	0.640	64(56)	-	50

HPLC equipped with DAICEL CHIRALPAK A-D (*n*-hexane/ *i*-PrOH = 99.66:0.33), λ = 230 nm.

3.7.2.3.11 1,1-diphenylethylene with ligand 4e-(4S,8S)





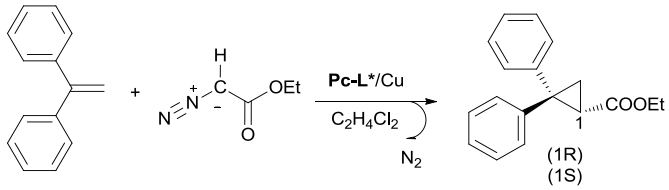
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.901	1.021	0.883	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4e-(4*S*,8*S*)	739.00	0.0222	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

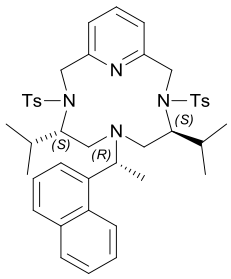
(MW 266.13 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) (1*S*)
0.226	0.850	85	-	62

HPLC equipped with DAICEL CHIRALPAK A-D (*n*-hexane/ *i*-PrOH = 99.66:0.33), λ = 230 nm.

3.7.2.3.12 1,1-diphenylethylene with ligand 4f-(4S,8S,13R)





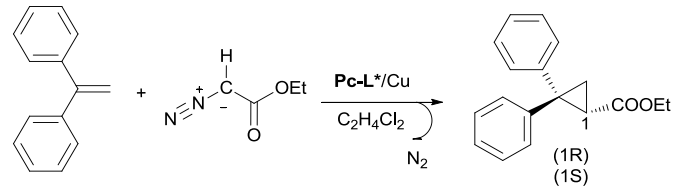
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.901	1.021	0.883	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

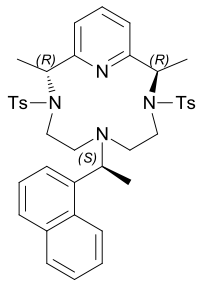
(MW 266.13 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) (1*S*)
0.120	0.450	45	-	88

HPLC equipped with DAICEL CHIRALPAK A-D (*n*-hexane/ *i*-PrOH = 99.66:0.33), λ = 230 nm.

3.7.2.3.13 1,1-diphenylethylene with ligand 4o-(2R,10R,13S)





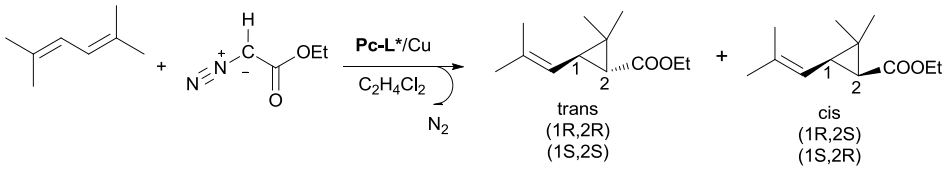
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.901	1.021	0.883	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

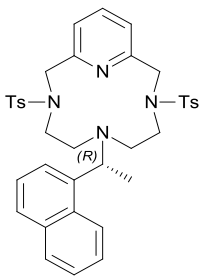
(MW 266.13 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) (1*R*)
0.120	0.450	49	-	32

HPLC equipped with DAICEL CHIRALPAK O-DH (*n*-hexane/ *i*-PrOH = 99.8:0.2), λ = 230 nm.

3.7.2.3.14 2,5-dimethyl-2,4-hexdiene with ligand4d-(13R)





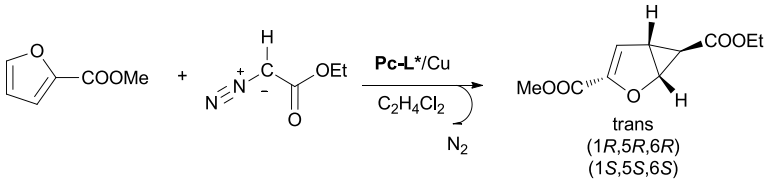
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
2,5-dimethyl-2,4-hexdiene	110.20	5.78	0.773	7.48	52.5	1750
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

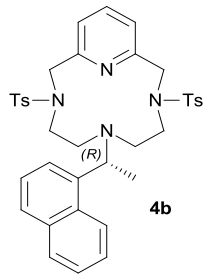
(MW 196.29 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
0.159	0.810	81(54)	67 : 33	30	15

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99.975:0.025), λ = 230 nm.

3.7.2.3.15 Methyl-2-furoate with ligand 4d-(13R)





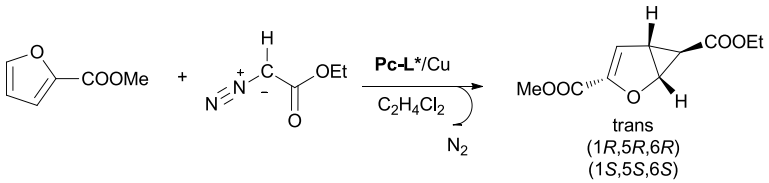
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.630	1.179	0.535	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4d-(13*R*)	668.87	0.0200	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

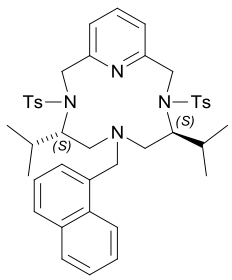
(MW 212.20 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*R*,5*R*,6*R*)
0.115	0.540	54(45)	> 1 : 99	n.d.	57

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 90:10), λ = 254 nm.

3.7.2.3.16 Methyl-2-furoate with ligand 4e-(4S,8S)





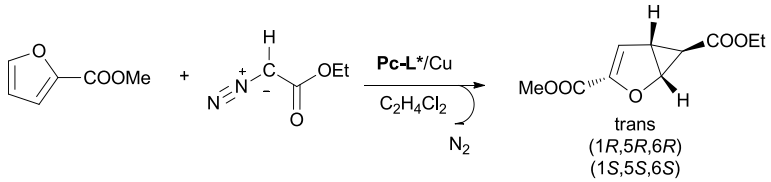
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.630	1.179	0.535	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4e-(4*S*,8*S*)	739.00	0.0222	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

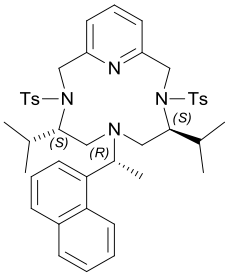
(MW 212.20 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*R*,5*R*,6*R*)
0.117	0.550	55	> 1 : 99	n.d.	28

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 90:10), λ = 254 nm.

3.7.2.3.17 Methyl-2-furoate with ligand 4f-(4S,8S,13R)





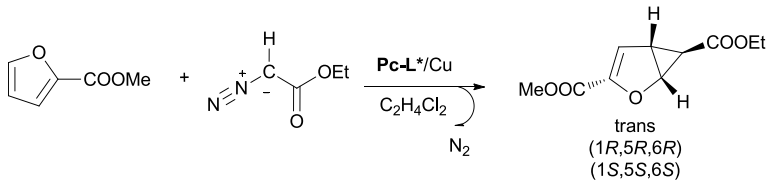
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.630	1.179	0.535	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

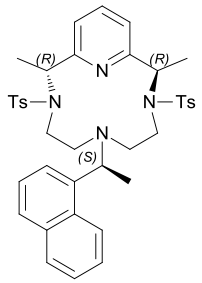
(MW 212.20 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*R*,5*R*,6*R*)
0.157	0.740	74	> 1 : 99	n.d	76

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 90:10), λ = 254 nm.

3.7.2.3.18 Methyl-2-furoate with ligand 4o-(2R,10R,13S)





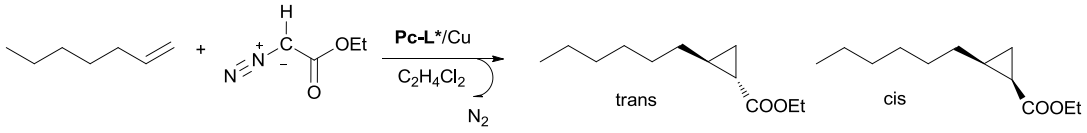
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.630	1.179	0.535	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

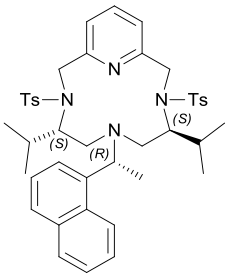
(MW 212.20 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*S*,5*S*,6*S*)
0.199	0.940	94	> 1 : 99	n.d	77

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 90:10), λ = 254 nm.

3.7.2.3.19 1-octene with ligand 4f-(4S,8S,13R)





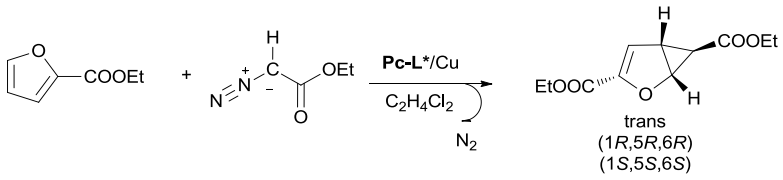
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	1.12	0.715	1.570	10	332
EDA	114.11	0.114	1.082	0.105	1.0	33
4f-(4*S*,8*S*,13*R*)	753.03	0.0226	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

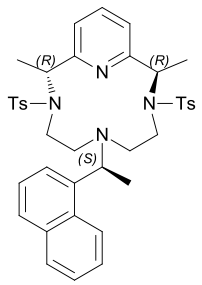
(MW 198.30 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (n.d.)	*ee* (%) *trans* (n.d.)
0.145	0.730	73	38 : 62	75	55

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 236 nm.

3.7.2.3.20 Ethyl-2-furoate with ligand 4o-(2R,10R,13S)





Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Ethyl-2-furoate	140.14	0.701	1.117	0.627	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
4o-(2*R*,10*R*,13*S*)	696.92	0.0209	-	-	0.030	1
$(CF_3SO_3Cu)_2$ C_6H_6	503.34	0.0075	-	-	0.015	0.5

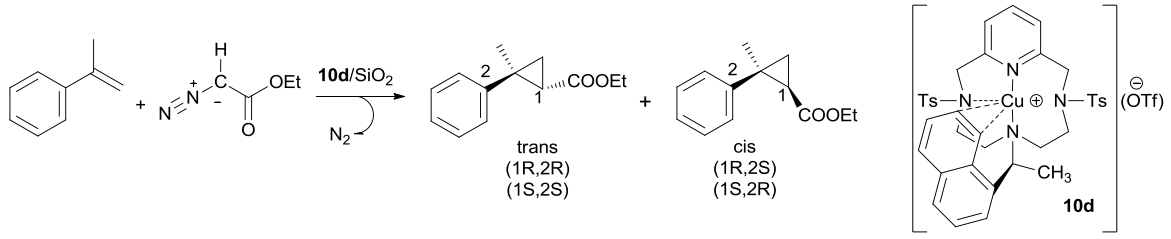
(MW 226.23 g/mol).

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (n.d.)
0.138	0.610	61	> 1 : 99	n.d	71

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 95:10), λ = 254 nm.

3.8 Heterogenous Catalysis - in BATCH

3.8.1 Cyclopropanation rection



All the reactions carried out for this section were conducted between α-methlstyrene and ethyldiazoacetate (EDA) with different supported complexes. (for details relate to the single catalyst see *Results and Discussion*). Reactions were performed with [Cu(I)] (0.0030 mmol) in n-hexane (5 mL). Catalytic reactions were run by slow addition of EDA (1 mmol) in n-hexane (1 mL) over 100 min at 0 °C, with a syringe pump to the solution containing the supported catalyst and α-methylstyrene, (Cu//EDA/olefin ratio 1//35/170). The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All catalysts were recycled at least three times and the reaction was repeated for consecutive runs after the solution was filtrate off from the catalysts, manteining the same catalytic ratio and quantities. All the reported yields were determined by GC with the addition of 2,4-dinitrotoluene as internal standard, confirmed by quantitative ^1H NMR analysis of the reaction mixture. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75).

3.8.1.1 Catalysis 1

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/D (Cu:0.66%)	-	0.289	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
0.147	0.720	72	72 : 28	35	26

3.8.1.2 Catalysis 2

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/D (Cu:0.66%)	-	0.289	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.133	0.650	65	72 : 28	40	31
2	0.139	0.680	68	72 : 28	39	32
3	0.114	0.560	56	71 : 29	41	30

3.8.1.3 Catalysis 3

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/S1 (Cu:1.09%)	-	0.175	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.092	0.450	45	71 : 29	35	25
2	0.088	0.430	43	72 : 28	42	33
3	0.082	0.400	40	70 : 30	38	29

3.8.1.4 Catalysis 4

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/S2a (Cu:1.59%)	-	0.120	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.186	0.910	91	67 : 33	35	24
2	0.159	0.780	78	72 : 28	39	30
3	0.106	0.520	52	71 : 29	40	30

3.8.1.5 Catalysis 5

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/S2b (Cu:0.45%)	-	0.424	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.116	0.570	57	70 : 30	36	29
2	0.149	0.730	73	73 : 27	38	29
3	0.118	0.580	58	72 : 28	46	38

3.8.1.6 Catalysis 6

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/M2 (Cu:0.54%)	-	0.354	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

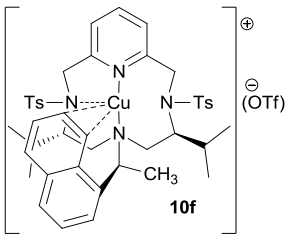
Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.108	0.530	53	68 : 32	29	22
2	0.157	0.770	77	71 : 29	34	23
3	0.153	0.750	75	72 : 28	23	20

3.8.1.7 Catalysis 7

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/A (Cu:0.45%)	-	0.424	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.149	0.730	73	67 : 33	39	31
2	0.202	0.990	99	69 : 31	39	30
3	0.186	0.910	91	68 : 32	39	30

3.8.1.8 Catalysis 8



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10f/D (Cu:0.66%)	-	0.290	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)
1	0.129	0.630	63	68 : 32	59	60
2	0.145	0.710	71	65 : 35	65	56
3	0.133	0.650	65	63 : 37	67	60

3.8.1.9 Catalysis 9

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/M1 (Cu:0.62%)	-	0.308	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.137	0.670	67	69 : 31	36	26
2	0.145	0.710	71	70 : 30	37	27
3	0.159	0.780	78	71 : 29	37	26
4	0.116	0.570	57	72 : 28	37	26
5	0.143	0.700	70	70 : 30	35	26
6	0.133	0.650	65	70 : 30	37	26
7	0.076	0.370	37	70 : 30	34	25

In the 7th run reaction was slower and further 45 minutes after the addition were needed to reach completion.

3.8.1.10 Catalysis 10

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
t-BuDA	114.11	0.114	1.082	0.105	1.0	33
10d/M2 (Cu:0.54%)	-	0.354	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Solvent: distilled 1,2-dichloroethane.

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.198	0.970	97	63 : 37	39	34
2	0.180	0.880	88	62 : 38	37	31
3	0.202	0.990	99	63 : 37	33	33

3.8.1.11 Catalysis 11

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/M1 (Cu:0.62%)	-	0.308	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Solvent: distilled 1,2-dichloroethane.

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%)	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)
1	0.141	0.690	69	64 : 36	58	54
2	0.202	0.990	99	63 : 37	53	47
3	0.196	0.960	96	63 : 37	n.d.	n.d.

3.8.1.12 Catalysis 12

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/A (Cu:0.45%)	-	0.424	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Solvent: distilled 1,2-dichloroethane.

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%)	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)
1	0.202	0.990	99	63:37	33	33
2	0.194	0.950	95	63:37	50	51
3	0.200	0.980	98	62:38	46	48

3.8.1.13 Catalysis 13 - Sheldon Test

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/D (Cu:0.66%)	-	0.289	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Sheldon Test: Syringe pump was stopped after 5 minutes (0.05 mL of EDA solution). Solution was filtrated off from the catalyst and put in an other flask. The remaining EDA solution was completely added into the flask containg the filtered solution. Then we repeted the catalysis on the filtrate to prove that the filtrate has the same catalytic activity as the original material.

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	-	-	< 1	-	-	-
1	0.151	0.740	74	76:24	35	27

3.8.1.14 Catalysis 14 - Sheldon Test

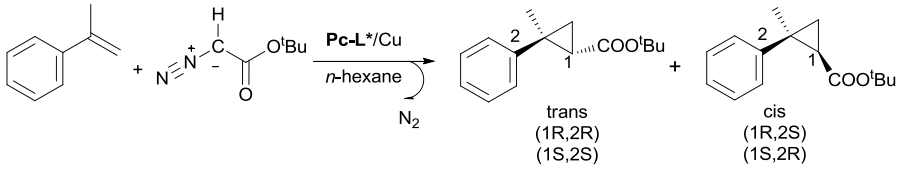
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.590	0.909	0.650	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33
10d/M1 (Cu:0.62%)	-	0.308	-	-	-	-
Cu	63.546	0.00191	-	-	0.030	1

Solvent: distilled 1,2-dichloroethane.

Sheldon Test: Syringe pump was stopped after 5 minutes (0.05 mL of EDA solution). Solution was filtrated off from the catalyst and put in an other flask. The remaining EDA solution was completely added into the flask containg the filtered solution. Then we repeted the catalysis on the filtrate to prove that the filtrate has the same catalytic activity as the original material.

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	-	-	< 10	59 : 41	46	58
1	0.131	0.640	64	64 : 36	58	54

3.8.1.15 Catalysis 15 - with *t*-BuDA

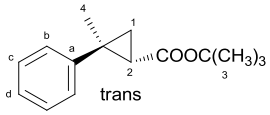


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	0.445	0.909	0.490	3.8	171
tert-butyl diazoacetate	142.16	0.108	1.026	0.105	0.76	34
10d/D (Cu:0.66%)	-	0.212	-	-	-	-
Cu	63.546	0.0014	-	-	0.022	1

The crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane : 0.3/10).

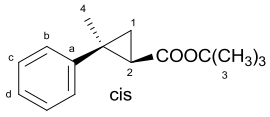
Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1				50 : 50		
2	0.0618	0.266	35	50 : 50	19	20
3				50 : 50		

(MW 232.36 g/mol)



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.38-7.19 (5H, m, Ar*H*), 1.93 (1H, dd, *J* = 8.3 Hz, *J* = 6.1 Hz, H^2), 1.54 (3H, s, CH_3^4), 1.52 (9H, s, CH_3^3), 1.47-1.44 (2H, m, CH_2^1).

MS : m/z 176 [M+1 - $C(CH_3)_3$], 131 (M^+1-COO^tBu)



^{1}H NMR (400 MHz; $CDCl_3$; T = 300 k) δ 7.35-7.16 (5H, m, Ar*H*), 1.82 (1H, dd, *J* = 7.7 Hz, *J* = 5.4 Hz, H^2), 1.73 (1H, t, *J = 5.0* Hz), 1.47 (3H, s, CH_3^4), 1.16 (9H, s, CH_3^3), 1.08 (1 H, dd, *J* = *7.7* Hz, *J = 4.5* Hz).

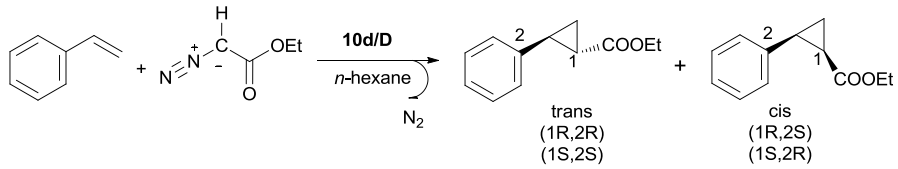
MS : m/z 176 [M+1 - $C(CH_3)_3$], 131 (M^+1-COO^tBu)

3.8.2 Reaction scope with different ligands

General procedure for the catalytic cyclopropanation reactions

Under optimal conditions, the reaction scope was explored using catalyst **10d/D** with different alkenes, with Cu(I)/EDA/alkene ratio of 1:35:170. In a typical experiment, **10d/D** [Cu:0.66%] (0.289 g) corrispondig to Cu (0.00191 g, 0.030 mmol) and the olefin (5.0 mmol) were dissolved in distilled *n*-hexane (5 mL) at 0° C. Then a *n*-hexane solution (1 mL) of EDA (0.114 g, 0.105 mL, 1 mmol) was slowly added by a syringe pump during 100 minutes. All catalysts were recycled at least three times and the reaction was repeated for consecutive runs after the solution was filtrate off from the catalysts, manteining the same catalytic ratio and quantities. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yield have been determined by quantitative ^1H NMR and based on EDA by the addiction of 2,4-dinitrotoluene as internal standard. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC.

3.8.2.1 Styrene



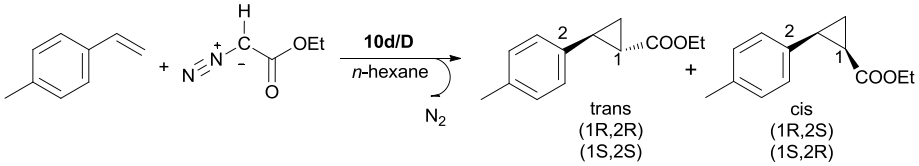
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
styrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 190.24 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.0735	0.360	36	61 : 39	45	35
2	0.0674	0.330	33	61 : 39	37	29
3	0.0715	0.350	35	61 : 39	38	30

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 98:2), λ = 230 nm.

3.8.2.2 4-Methylstyrene



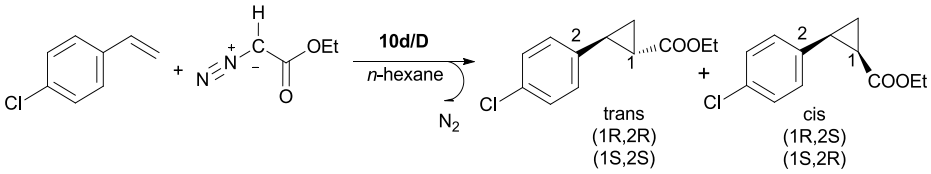
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-methylstyrene	104.15	0.521	0.906	0.575	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 204.26 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.120	0.590	59	58 : 42	42	35
2	0.133	0.650	65	60 : 40	39	35
3	0.139	0.680	68	57 : 43	39	35

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.8.2.3 4-chlorostyrene



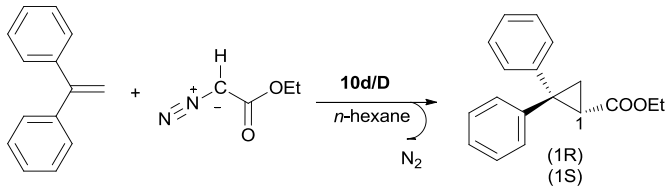
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene	138.59	0.693	1.038	0.640	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 224.68 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	0.0980	0.480	48	56 : 44	42	38
2	0.125	0.610	61	56 : 44	42	38
3	0.102	0.500	50	56 . 44	42	38

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 220 nm.

3.8.2.4 1,1-diphenylethylene



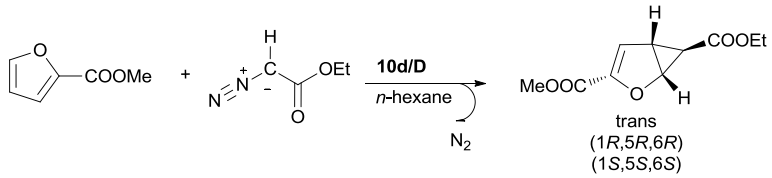
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.901	1.021	0.883	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 266.13 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) (1*R*)
1	0.0674	0.330	33	-	21
2	0.0735	0.360	36	-	23
3	0.0592	0.290	29	-	25

HPLC equipped with DAICEL CHIRALPAK A-D (*n*-hexane/ *i*-PrOH = 99.66:0.33), λ = 230 nm.

3.8.2.5 Methyl-2-furoate



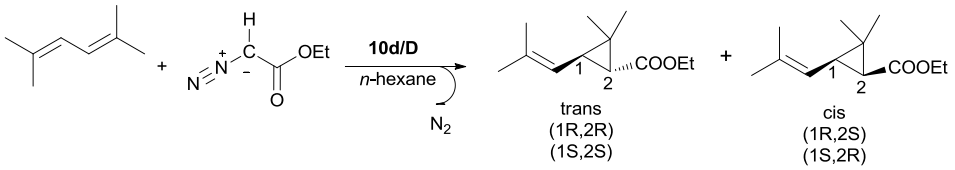
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.630	1.179	0.535	5.0	166
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 212.20 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (n.d.)	*ee* (%) *trans* (1*S*,5*S*,6*S*)
1	0.0940	0.460	46	> 1 : 99	n.d.	49
2	0.0878	0.430	43	> 1 : 99	n.d.	49
3	0.0899	0.440	44	> 1 : 99	n.d.	44

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 90:10), λ = 254 nm.

3.8.2.6 2,5-dimethyl-2,4-hexdiene



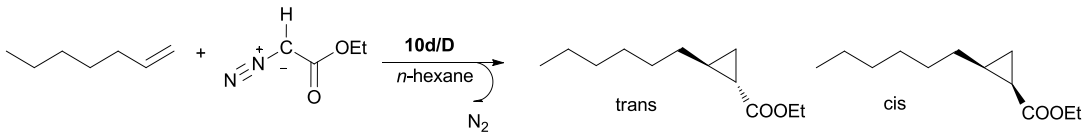
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
2,5-dimethyl-2,4-hexdiene	110.20	1.65	0.773	2.14	15	500
EDA	114.11	0.114	1.082	0.105	1.0	33

(MW 196.29 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*R*,2*R*)
1	0.0940	0.460	46	> 1 : 99	n.d.	49
2	0.0878	0.430	43	> 1 : 99	n.d.	49

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99.975:0.025), □ = 230 nm.

3.8.2.7 1-octene



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	3.59	0.715	5	32	1060
EDA	114.11	0.114	1.082	0.105	1.0	33

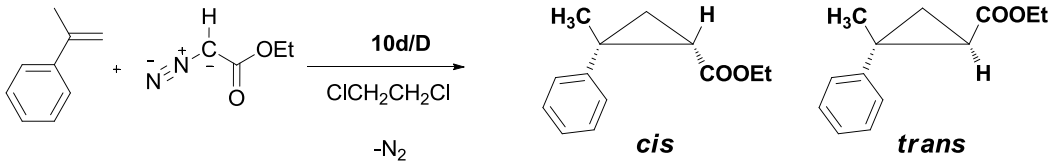
(MW 198.30 g/mol).

Run	g	mmol	yield (%)	*cis:trans*	*ee* (%) *cis* (n.d.)	*ee* (%) *trans* (n.d.)
1	0.102	0.500	50	56 : 44	40	35

HPLC equipped with DAICEL CHIRALPAK O-J (*n*-hexane/ *i*-PrOH = 99:1), λ = 236 nm.

3.9 Heterogenous Catalysis - in FLOW

3.9.1 Cyclopropanation with 1,2-DCE as solvent with 10d/D



General procedure. In a typical procedure, the tubular reactor previously loaded with the supported catalyst **10d/D** (0.427 g, 0.0565 mmol of Cu) was fixed onto the rig. A fresh mixture of α-methylstyrene (7.9 mL, 61 mmol), EDA (0.17 M, 12 mmol) in DCE (72 mL) was pumped through the reactor at room temperature and at different constant flow rates using an HPLC pump. Samples were collected and analysed every 30 min. Conversion, selectivity, *cis/trans* ratios values were determined by quantitative ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard after evaporation of the collected samples. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75). (EDA was at 92% wt in DCE)

3.9.1.1 Catalysis 1

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	7.208	0.909	7.9	61	5
EDA	114.11	1.519	1.082	1.4	12	1
10d/D (Cu:0.84%)	-	0.4274	-	-	-	-
Cu	63.546	0.00359	-	-	0.0565	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.2 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b] *cis* (1*R*,2*S*)	*ee* (%)[b] *Trans* (1*R*,2*R*)
1	218	99	65.2	58:42	38	18
2	249	99	65.7	57:43	39	16
3	280	99	65.4	57:43	36	14
4	300	99	64.8	57:43	31	13
5	328	99	64.3	55:45	29	11
6	354	99	65.0	56:44	26	12
7	381	90,6	73.5	54:46	38	18

3.9.1.2 Catalysis 2

The catalyst, used for **catalysis 1,** was recycled for this second run by flowing fresh mixture of α-methylstyrene, EDA in DCE (same amounts used for the first run).

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	7.208	0.909	7.9	61	5
EDA	114.11	1.519	1.082	1.4	12	1
10d/D (Cu:0.84%)	-	0.4274	-	-	-	-
Cu	63.546	0.00359	-	-	0.0565	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.2 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b] *cis* (1*R*,2*S*)	*ee* (%)[b] *Trans* (1*R*,2*R*)
1	226	39,2	61.2	49:51	29	15
2	256	33,1	62.4	48:52	28	15
3	287	24,9	63.7	46:54	26	14
4	322	14,7	65.5	44:56	24	11
5	352	nd	nd	nd	24	12
6	378	4,2	67.3	45:55	20	16
7	399	3,8	67.3	nd	14	13

3.9.1.3 Catalysis 3

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	3.60	0.909	4	30	5
EDA	114.11	0.759	1.082	0.7	6.1	1
10d/D (Cu:0.84%)	-	0.4022	-	-	-	-
Cu	63.546	0.00338	-	-	0.0532	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.2 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b] *cis* (1*R*,2*S*)	*ee* (%)[b] *Trans* (1*R*,2*R*)
1	180	99	54.9	70:30	54	24
2	212	99	54.7	62:38	40	23
3	243	99	54.4	61:39	36	21
4	273	99	57.3	60:40	34	22
5	303	99	56.5	58:42	30	21
6	334	99	59.9	56:44	29	23
7	364	99	59.6	55:45	32	29
8	394	99	61.6	54:46	31	24

3.9.1.4 Catalysis 4

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	7.208	0.909	7.9	61	5
EDA	114.11	1.519	1.082	1.4	12	1
10d/D (Cu:0.84%)	-	0.4068	-	-	-	-
Cu	63.546	0.00342	-	-	0.0538	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.1 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b]		Cu leaching	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)	Cu (ppb)	Cu lost (%)
1	487	99	57.6	61:39	30	28		
2	517	99	56.8	61:39	28	26	1143	0.67
3	547	99	57.1	60:40	19	27		
4	578	99	58.1	58:42	22	27		
5	608	99	52.5	71:29	24	20		
6	638	99	58.7	57:43	26	25	3788	1.86
7	668	99	57.5	57:43	n.d	n.d		

3.9.1.5 Catalysis 5

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	14.4	0.909	15.8	123	5
EDA	114.11	3.04	1.082	2.8	25	1
10d/D (Cu:0.84%)	-	0.4081	-	-	-	-
Cu	63.546	0.00343	-	-	0.0539	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.5 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b]	
					cis (1*R*,2*S*)	*Trans* (1*R*,2*R*)
1	92	99	48.7	77:23	39	26
2	122	99	53.4	67:33	36	24
3	153	99	59.2	64:38	46	26
4	183	99	65.8	57:43	55	32
5	213	99	70.6	57:43	68	32
6	244	nd	nd	nd	67	33
7	274	99	71.2	58:42	68	33
8	304	99	65.4	59:41	68	30
9	335	99	57.9	62:38	63	29
10	346	99	52.3	65:35	67	28

3.9.1.6 Catalysis 6

The catalyst, used for **catalysis 5,** was recycled for this second run by flowing fresh mixture of α-methylstyrene, EDA in DCE.

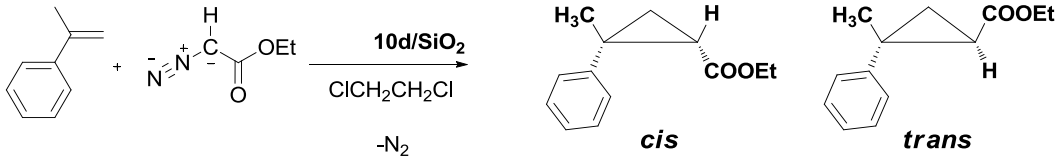
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	5.16	0.909	5.7	44	5
EDA	114.11	1.08	1.082	1.0	8.7	1
10d/D (Cu:0.84%)	-	0.4081	-	-	-	-
Cu	63.546	0.00343	-	-	0.0539	-

Solvent: 1,2-dichloroethane 72 mL

Flow 0.5 mL/min

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)[b]	
					cis (1*R*,2*S*)	*Trans* (1*R*,2*R*)
1	30	99	58.6	54:46	55	30
2	60	78	55.6	54:46	46	30
3	91	59	52.6	56:44	12	nd
4	121	11	nd	nd	nd	nd

3.9.2 Cyclopropanation in CO_2 as solvent with 10d/D



General procedure. In a typical procedure, the tubular reactor previously loaded with the supported catalyst **10d/D** (0.400 g, 0.0529 mmol of Cu) was fixed onto the rig. The rig was pressurised to the desired pressure and the reactor heater and pre-heater raised to the desired temperature (40 °C). Two streams, one a fresh mixture of α-methylstyrene (11.4 mL, 87.8 mmol), EDA (17.5 mmol) and the other CO_2 were mixed by passing through a coil preheater and then passed into the reactor. The liquid substrate mixture was delivered at a constant rate through an HPLC pump and the CO_2 was passed through a cooled head HPLC pump . The pressure was controlled by a back pressure regulator.

T = 40°C, P_{CO2} = 130 bar, flow CO_2 = 0.5 mL/min, flow HPLC = 0.02 mL/min.

The collected material was removed from the vessel and analysed every 30 min. Conversion, selectivity, *cis/trans* ratios values were determined by quantitative ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard after evaporation of the collected samples. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC equipped with DAICEL CHIRALPAK I-B (*n*-hexane/ *i*-PrOH = 99.25:0.75). (EDA was at 92% wt in DCE)

3.9.2.1 Catalysis 1 with 10d/D

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	10.4	0.909	11.4	88	5
EDA	114.11	2.17	1.082	2.0	17	1
10d/D (Cu:0.84%)	-	0.4003	-	-	-	-
Cu	63.546	0.00336	-	-	0.0529	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)		Cu leaching	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)	Cu (ppb)	Cu lost (%)
1	191	99	61.2	63:37	39	33		
2	222	99	64.6	60:40	37	32		
3	254	99	65.7	66:34	37	32		
4	285	99	66.7	68:32	37	33		
5	317	99	67.1	66:34	36	34	4.3	0.0016
6	347	99	67.5	69:31	33	41		
7	377	99	67.8	71:29	32	42		
8	407	99	66.7	67:33	38	29		
9	438	99	66.1	70:30	36	33		
10	468	99	64.4	66:34	38	31		

3.9.2.2 Catalysis 2 with 10d/D

The catalyst, used for **catalysis 1,** was recycled for this second run by flowing fresh mixture of α-methylstyrene, EDA.

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	1.54	0.909	1.7	13	5
EDA	114.11	0.299	1.082	0.3	2.6	1
10d/D (Cu:0.84%)	-	0.4003	-	-	-	-
Cu	63.546	0.00336	-	-	0.0529	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)
1	30	99	64.7	68:32	44	25
2	91	99	66.0	70:30	43	27
3	129	99	66.3	66:34	45	23
4	159	99	65.1	69:31	42	28

3.9.2.3 Catalysis 3 with 10d/D

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	10.4	0.909	11.4	87.8	2
EDA	114.11	4.99	1.082	5	43.7	1
10d/D (Cu:0.84%)	-	0.3943	-	-	-	-
Cu	63.546	0.00331	-	-	0.0521	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *trans* (1*R*,2*R*)
1	147	99	48.9	64:36	36	20
2	178	99	45.3	64:36	42	22
3	208	99	45.4	65:35	40	26
4	239	99	44.6	64:36	43	28
5	270	99	44.4	62:38	41	25
6	300	99	44.9	63:37	39	25
7	330	99	45.2	62:38	31	26
8	361	99	46.1	61:39	39	27
9	391	99	45.8	60:40	37	26
10	422	99	46.8	60:40	36	26
11	452	99	46.6	61:39	38	25
12	483	99	47.3	60:40	38	25
13	513	99	48.1	59	35	25
14	543	99	49.0	60	38	25

3.9.2.4 Catalysis 4 with 10d/D

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	14.5	0.909	15.9	122	10
EDA	114.11	1.40	1.082	1.4	12.2	1
10d/D (Cu:0.84%)	-	0.3393	-	-	-	-
Cu	63.546	0.002847	-	-	0.0448	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (1*R*,2*S*)	*ee* (%) *Trans* (1*R*,2*R*)
1	148	99	67.2	63:37	36	26
2	179	99	74.5	70:30	37	27
3	210	99	75.3	69:31	37	27
4	240	99	77.1	69:31	32	31
5	270	99	77.6	70:30	36	30
6	301	99	73.8	79:21	36	28
7	331	99	73.1	83:17	29	29
8	362	99	73.2	79:21	45	25
9	393	99	64.4	90:10	41	23
10	512	99	75.8	70:30	38	26
11	543	nd	nd	nd	nd	nd
12	573	99	70.9	69:31	38	27
13	603	99	69.2	72:28	32	28

3.9.2.5 Catalysis 5 with 10d/M

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	10.4	0.909	11.4	87.8	5
EDA	114.11	2.00	1.082	2.00	17.5	1
10d/M (Cu:0.85%)	-	0.4044	-	-	-	-
Cu	63.546	0.003437	-	-	0.0541	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)		Cu leaching	
					cis (1*R*,2*S*)	*trans* (1*R*,2*R*)	Cu (ppb)	Cu lost (%)
1	131	99	87.6	58:42	29	32		
2	162	99	87.4	58:42	41	35		
3	192	99	87.5	59:41	41	32	10.8	0.0074
4	223	99	87.3	60:40	42	26		
5	255	99	87.6	60:40	42	28		
6	285	99	87.5	59:41	41	29		
7	316	99	87.5	59:41	40	28	7.18	0.0041
8	346	99	87.9	58:42	42	25		
9	378	99	88.5	58:42	42	29		
10	408	99	88.5	58:42	42	29		
11	439	99	88.5	57:43	42	29		
12	470	99	88.5	59:41	34	30		

3.9.2.6 Catalysis 6 with 10d/A

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	10.4	0.909	11.4	87.8	5
EDA	114.11	2.00	1.082	2.00	17.5	1
10d/A (Cu:0.81%)	-	0.4229	-	-	-	-
Cu	63.546	0.003434	-	-	0.0540	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%)	
					cis (1*R*,2*S*)	*Trans* (1*R*,2*R*)
1	137	99	66.3	58:42	34	26
2	228	99	71.7	58:42	24	28
3	290	99	69.1	58:42	34	18
4	351	99	72.6	59:41	33	23
5	412	99	73.1	53:47	40	17
6	472	99	80.7	54:46	38	15

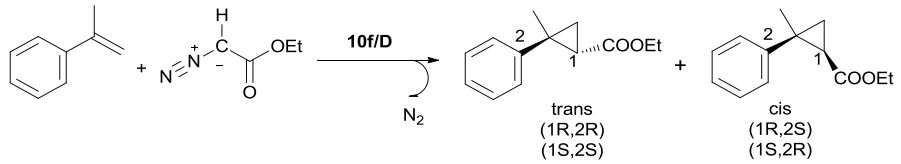
3.9.3 Reaction scope in CO_2 as solvent with 10f/D

General procedure. In a typical procedure, the tubular reactor previously loaded with the supported catalyst **10f/D** (0.416 g, 0.0430 mmol of Cu) was fixed onto the rig. The rig was pressurised to the desired pressure and the reactor heater and pre-heater raised to the desired temperature (40 °C). A fresh mixture of α-methylstyrene (11.4 mL, 87.8 mmol), EDA (17.5 mmol) and CO_2 were all introduced as separate streams, which were mixed by passing through a coil preheater and then passed into the reactor. Liquid substrate was delivered at a constant rate through an HPLC pump and the CO_2 was passed through a pressure valve and a preheated (40°C) mixing coil. After equilibration of the system, the substrate was pumped in at constant rate, and liquid CO_2 was pumped through a Pickel pump to maintain the total pressure.

T = 40°C, P_{CO2} = 130 bar, flow CO_2 = 0.5 mL/min, flow HPLC = 0.02 mL/min.

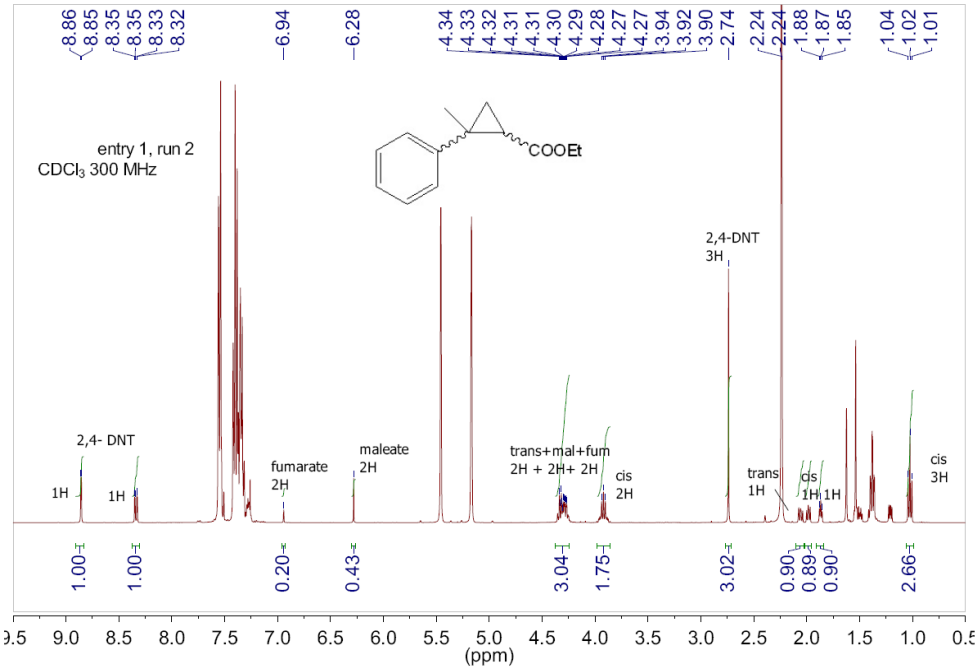
The collected material was removed from the vessel and analysed every hour. Conversion, selectivity, *cis/trans* ratios values were determined by quantitative ^{1}H NMR in $CDCl_3$ based on EDA using 2,4-dinitrotoluene as internal standard after evaporation of the collected samples. Fumarate and maleate accounted for the rest of the reaction mass balance. The enantiomeric excess was determined by chiral HPLC. (EDA was at 92% wt in DCE)

3.9.3.1 α-methylstyrene

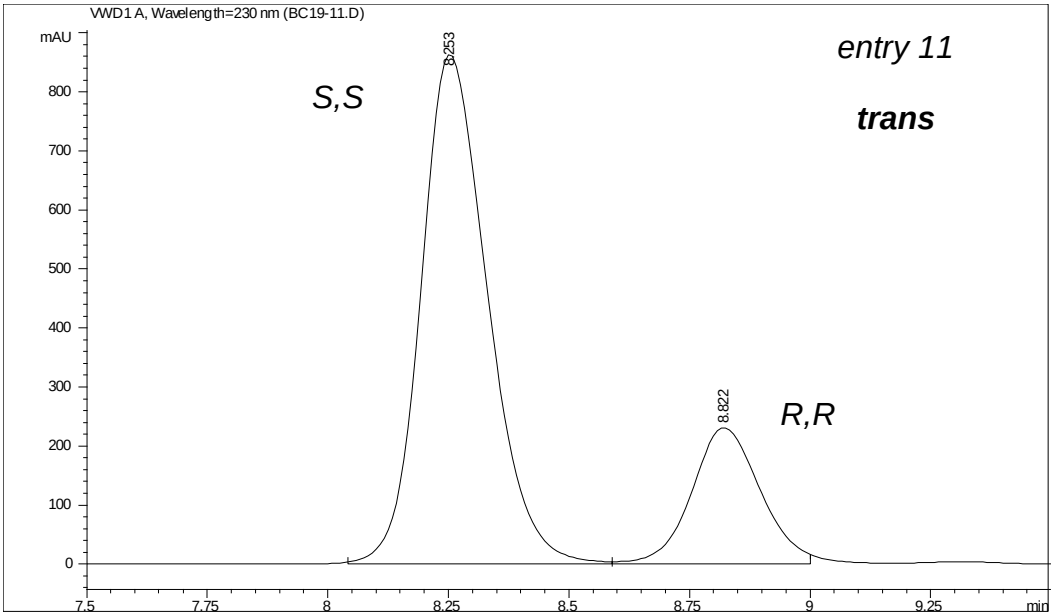


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α–methylstyrene	118.08	10.4	0.909	11.4	87.8	5
EDA	114.11	2.00	1.082	2.00	17.5	1
10f/D (Cu:0.66%)	-	0.4157	-	-	-	-
Cu	63.546	0.002732	-	-	0.0430	-

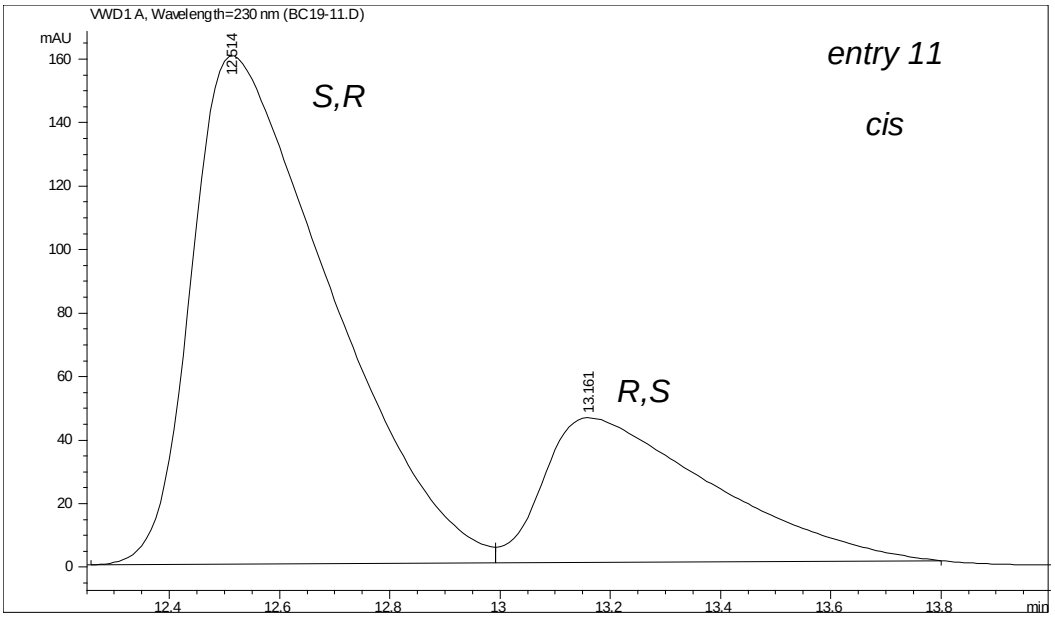
Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)	Cu leaching Cu (ppb)	Cu leaching Cu lost (%)
1	92	99	67.3	59:41	57	67		
2	122	99	65.1	57:43	60	70		
3	153	99	66.0	58:42	59	70		
4	183	99	66.1	59:41	60	67		
5	273	99	66.1	57:43	63	70		
6	336	99	69.6	57:43	59	68		
7	366	99	67.8	57:43	56	67	3.2	0.0022
8	397	99	69.2	57:43	58	68		
9	427	99	69.7	55:45	58	69		
10	457	99	71.0	56:44	57	69		
11	488	99	72.4	55:45	56	66		
12	518	99	72.3	58:42	57	66		



HPLC equipped with DAICEL CHIRALPAK I-B (n-hexane/ i-PrOH = 99.25:0.75. λ =230 nm).

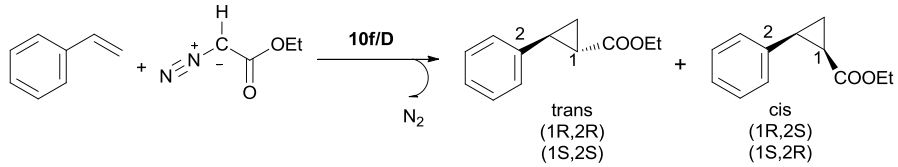


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.253	BV	0.1465	8188.98730	862.73212	82.8398
2	8.822	VBA	0.1544	1696.34167	230.14224	17.1602



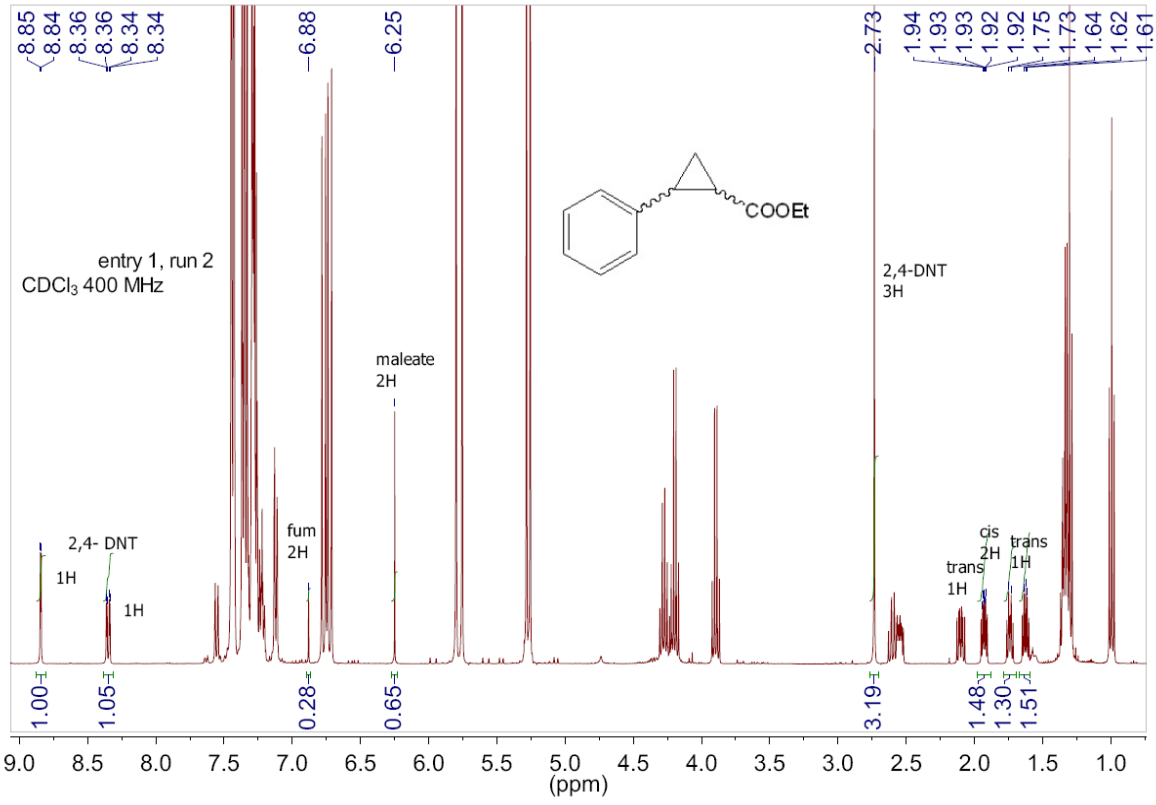
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.514	PV	0.2607	2803.21631	159.08958	77.9257
2	13.161	VBA	0.6884	794.07599	40.98441	22.0743

3.9.3.2 Styrene

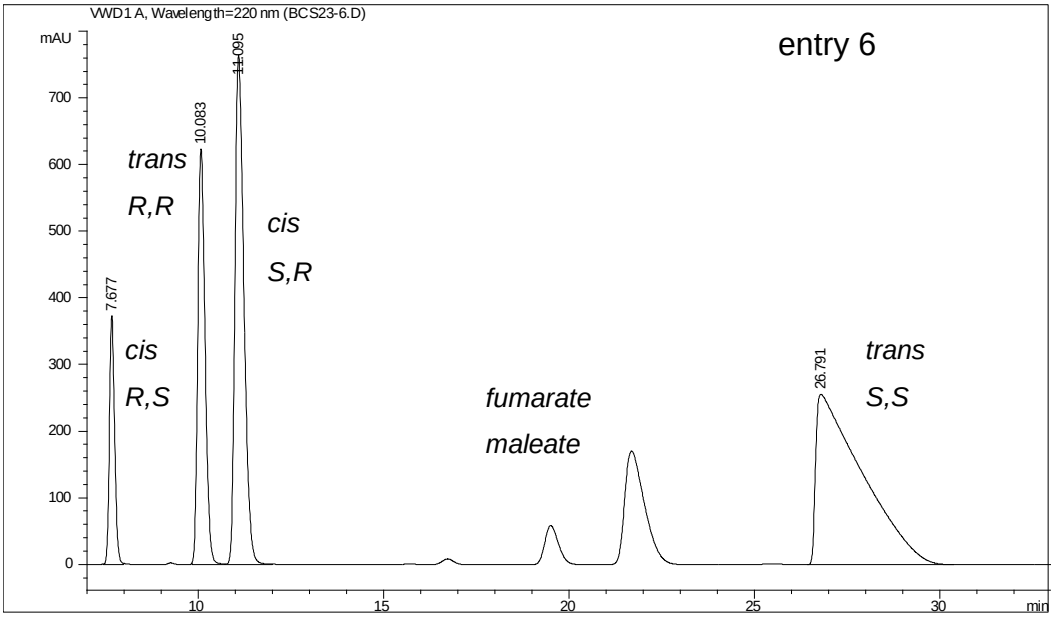


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
styrene	104.15	11.0	0.909	12.1	105	5
EDA	114.11	2.40	1.082	2.40	21	1
10f/D (Cu:0.66%)	-	0.4022	-	-	-	-
Cu	63.546	0.002643	-	-	0.0416	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)	Cu (ppb)
1	185	99	61.1	33:67	58	55	
2	245	99	63.5	33:67	63	57	10.2
3	306	99	65.2	32:68	60	56	
4	360	99	65.8	31:69	59	56	
5	427	99	66.6	31:69	63	55	
6	487	99	66.9	36:64	66	54	
7	547	99	69.1	30:70	65	54	

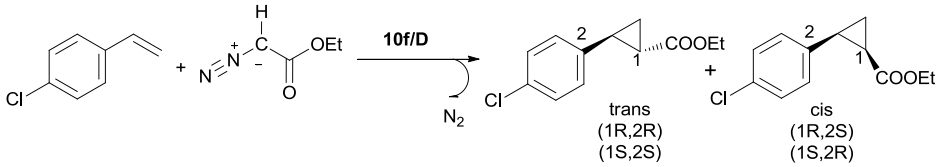


HPLC equipped with DAICEL CHIRALPAK O-J (n-hexane/i-PrOH = 98:2. λ =220 nm).



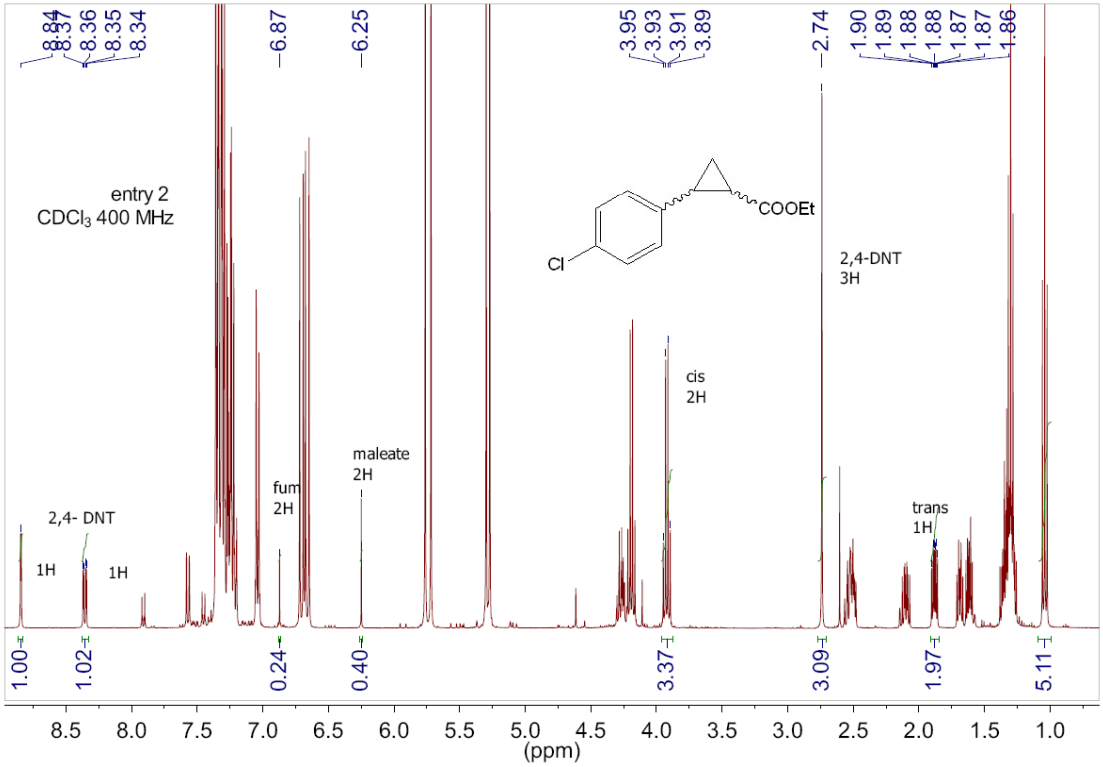
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.677	BBA	0.1509	2577.09375	373.36185	5.8077
2	10.083	BV	0.2108	6766.42627	623.50507	15.2487
3	11.09	VBA	0.2581	1.27766e4	763.63251	28.7930
4	26.791	BB	3.2947	2.22538e4	253.87247	50.1507

3.9.3.3 4-chlorostyrene

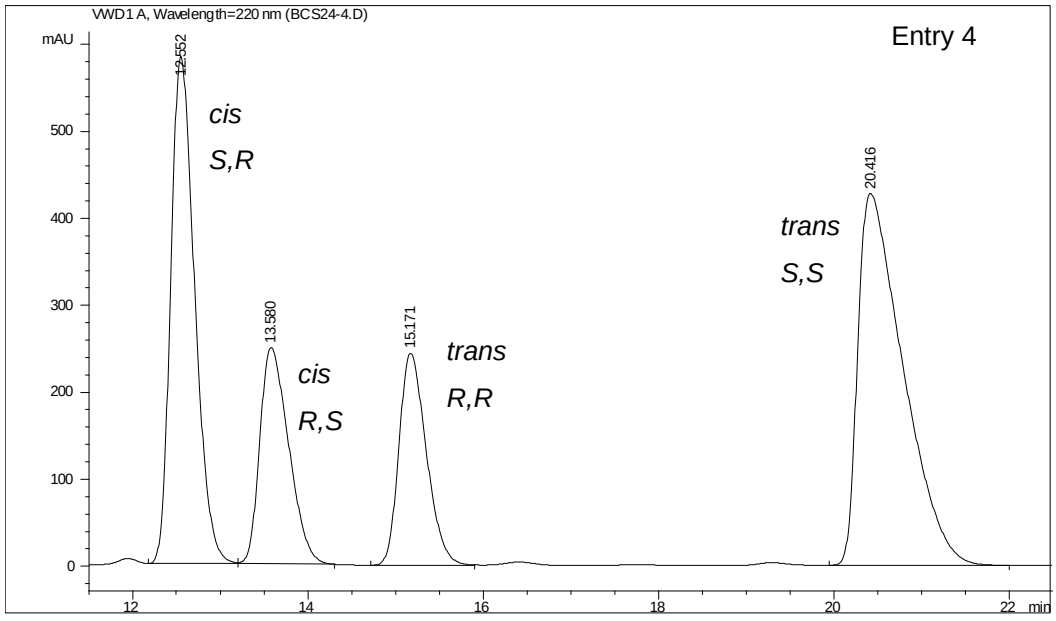


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-chlorostyrene (97%)	138.59	11.2	1.155	10	80.8	5
EDA	114.11	1.85	1.082	1.8	16.2	1
10f/D (Cu:0.66%)	-	0.4020	-	-	-	-
Cu	63.546	0.002643	-	-	0.0416	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (1*S*,2*R*)	*ee* (%) *trans* (1*S*,2*S*)	Cu (ppb)
1	121	99	54.6	56:44	44	69	
2	182	99	77.5	48:52	41	71	
3	242	99	81.9	47:53	44	69	24.9
4	302	99	84.2	46:54	42	76	
5	518	99	85.1	46:54	44	73	
6	582	99	83.2	46:54	44	73	

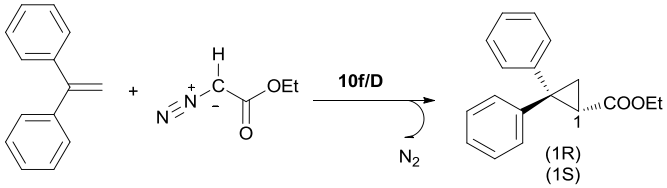


HPLC equipped with DAICEL CHIRALPAK O-J (n-hexane/i-PrOH = 99:1. λ =220 nm).



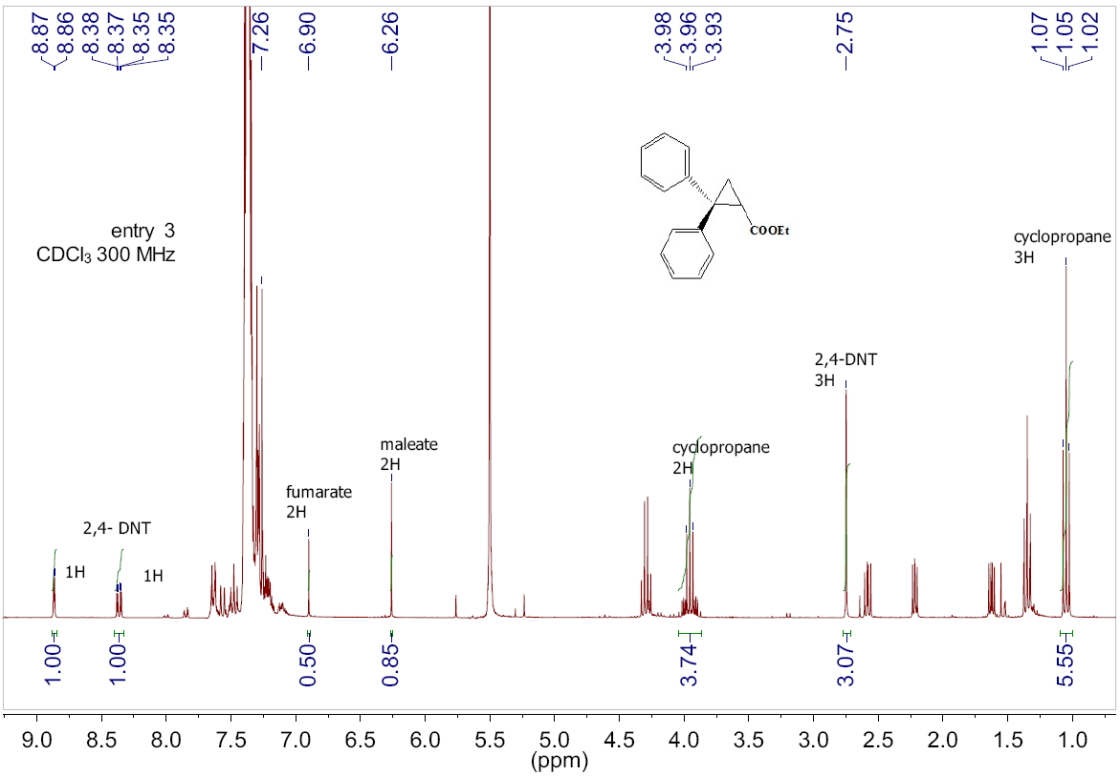
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.552	PV	0.2937	1.10495e4	582.71674	33.0939
2	13.580	VBA	0.3095	4541.09814	247.01970	13.6008
3	15.171	BBA	0.2705	2494.49854	243.77048	7.4712
4	20.416	BPA	0.5325	1.53033e4	427.60849	45.8341

3.9.3.4 1,1-diphenylethylene

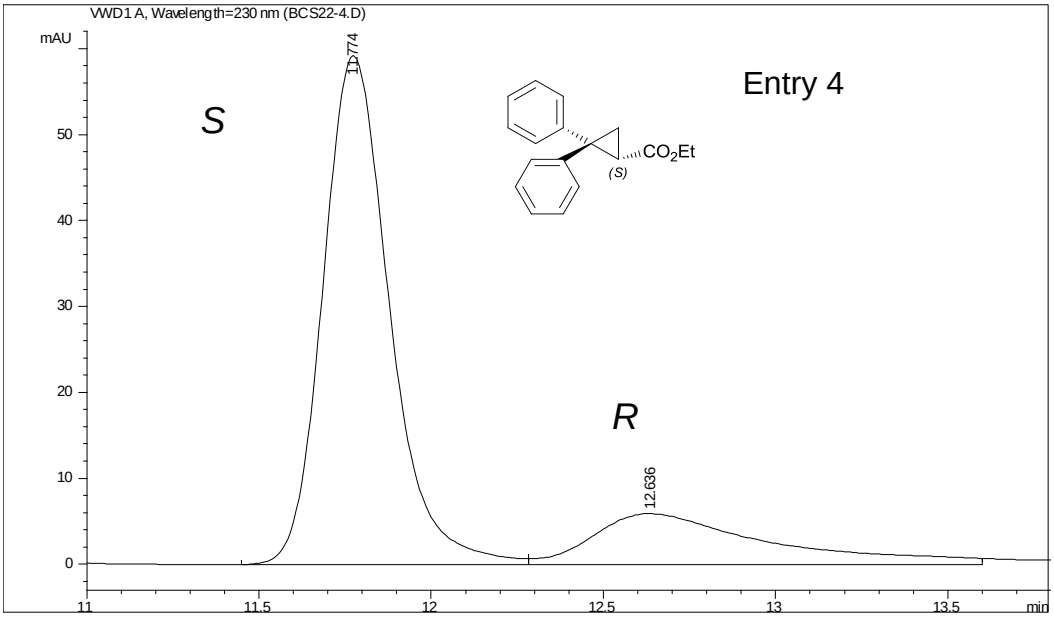


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-diPhethylene (97%)	180.25	9.51	1.021	9.6	52.7	5
EDA	114.11	1.20	1.082	1.2	10.5	1
10f/D (Cu:0.66%)	-	0.3969	-	-	-	-
Cu	63.546	0.002643	-	-	0.0410	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) (1*S*)	Cu (ppb)
1	143	n.d.	n.d.	-	n.d.	
2	203	99	45.5	-	62	
3	264	99	51.0	-	62	24.9
4	324	99	49.1	-	72	
5	384	99	48.0	-	64	
6	445	99	53.1	-	66	
7	505	99	57.5	-	67	
8	565	99	57.9	-	64	

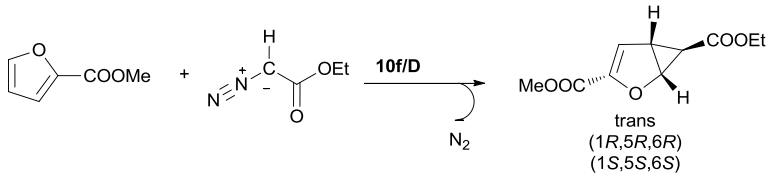


HPLC equipped with DAICEL CHIRALPAK O-J (n-hexane/i-PrOH = 99.66:0.33. λ =220 nm).



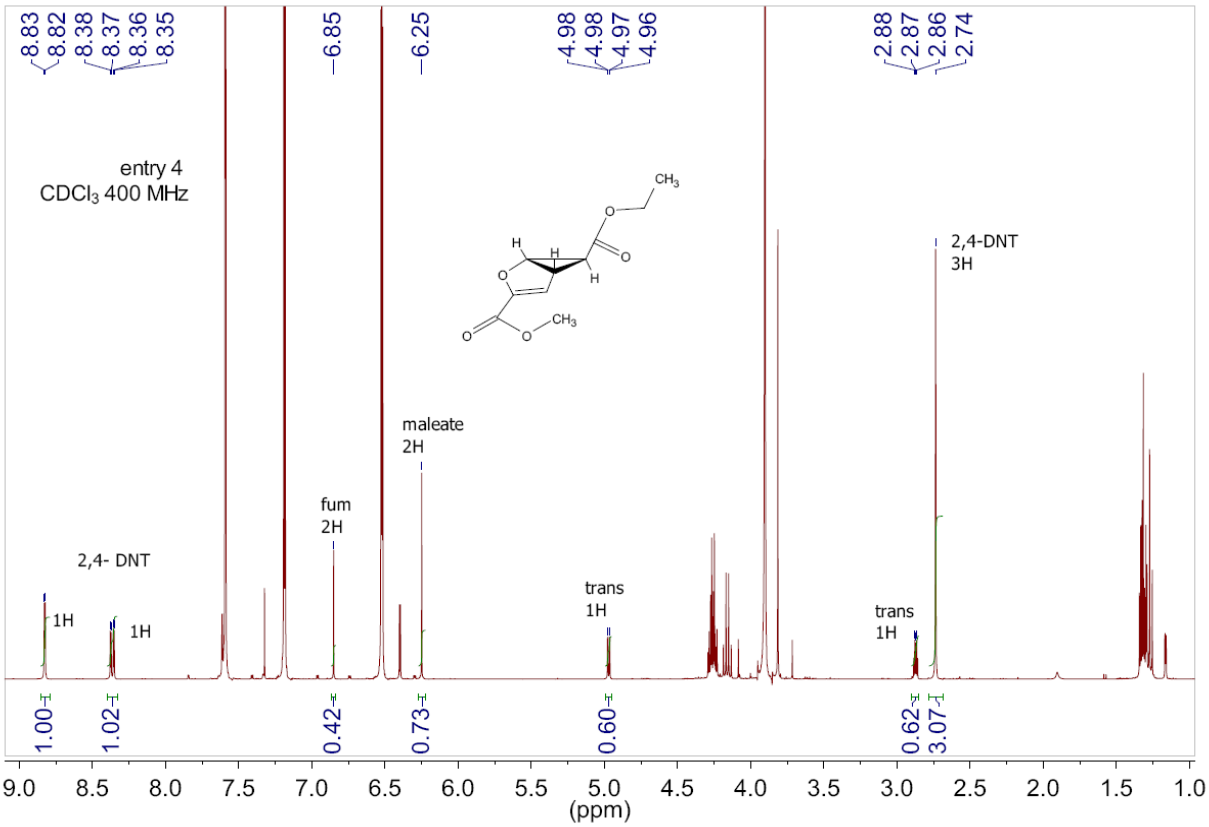
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.774	BV	0.2067	795.80957	59.25520	86.2357
2	12.636	VBA	0.3140	127.02103	5.95084	13.7643

3.9.3.5 Methyl-2-furoate

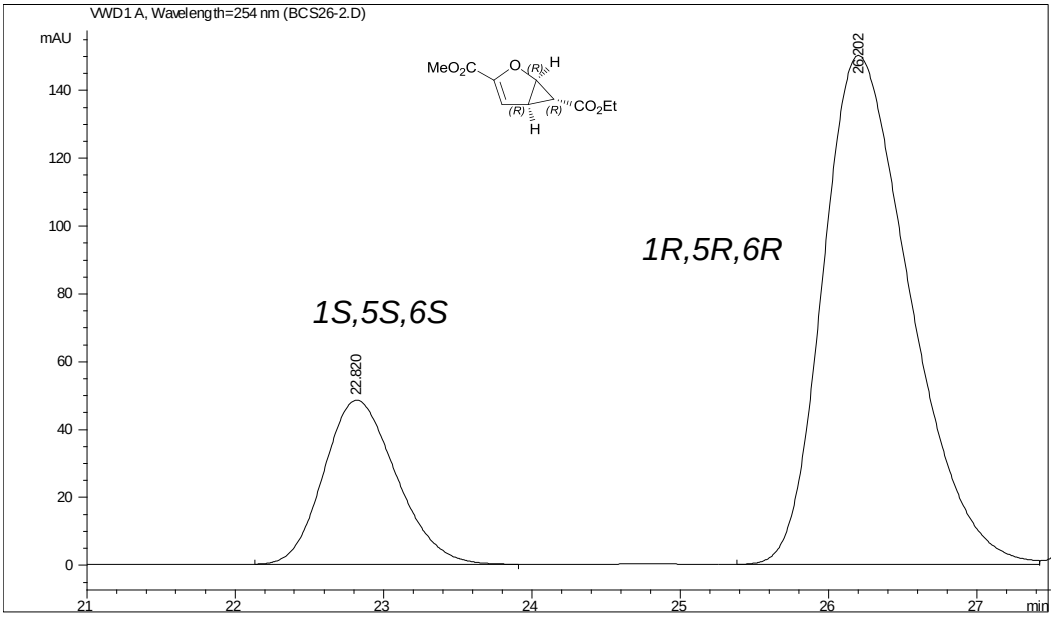


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	16.6	1.021	14	131	5
EDA	114.11	3.00	1.082	3	26	1
10f/D (Cu:0.66%)	-	0.4064	-	-	-	-
Cu	63.546	0.002669	-	-	0.0420	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis*	*ee* (%) *trans* (1*R*,5*R*,6*R*)	Cu leaching Cu (ppb)	Cu leaching Cu lost (%)
1	178	99	30.1	>1: 99	-	68		
2	239	99	35.1	>1: 99	-	67		
3	300	99	34.3	>1: 99	-	68		
4	362	99	34.7	>1: 99	-	66		
5	422	99	34.5	>1: 99	-	66	122.5	0.0905
6	482	99	32.5	>1: 99	-	66		
7	542	99	30.3	>1: 99	-	65	39.8	

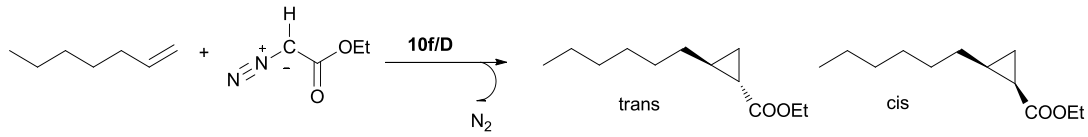


HPLC equipped with DAICEL CHIRALPAK O-J (n-hexane/i-PrOH = 90:10. λ =254 nm).



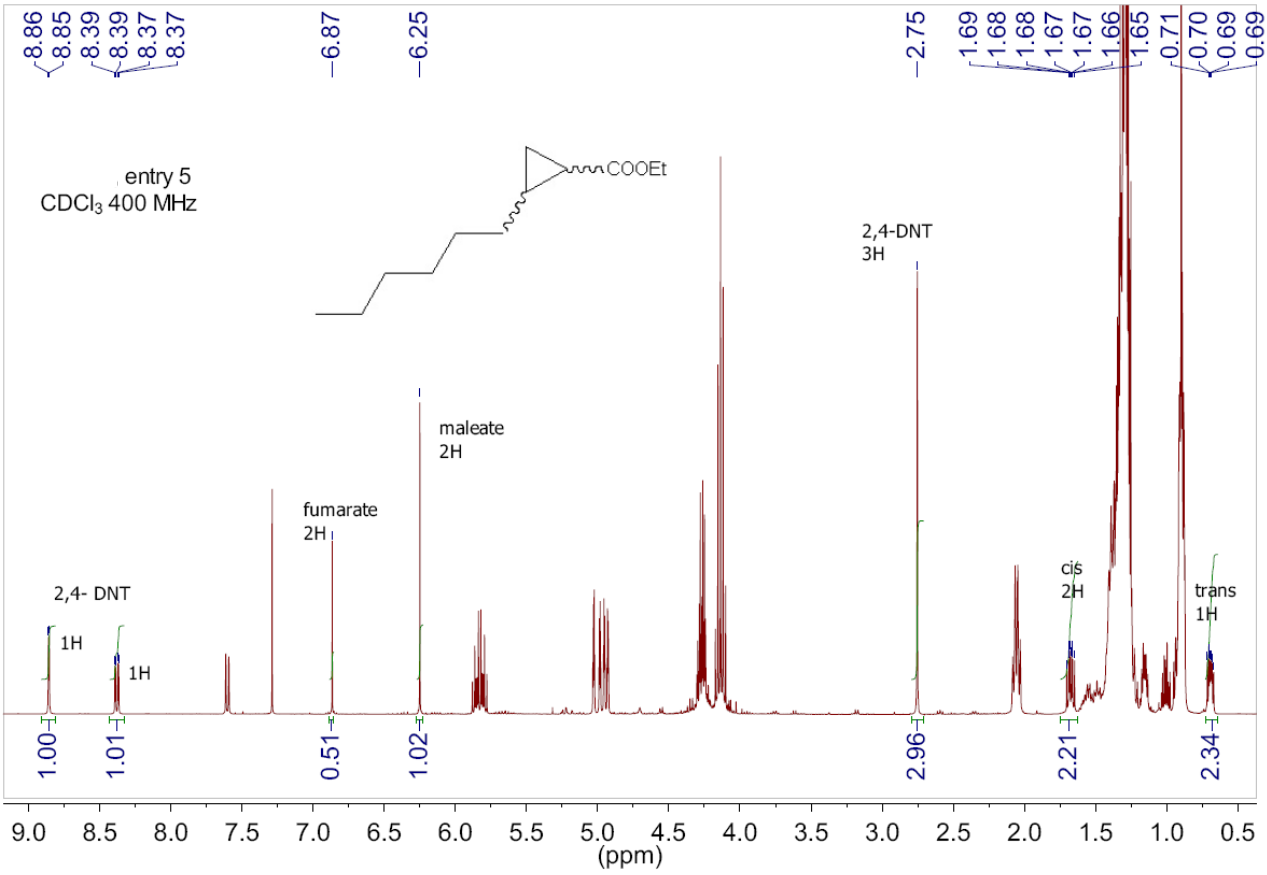
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.820	BBA	0.4114	1195.53821	48.42975	16.3399
2	26.202	BV	0.6283	6121.13330	150.07933	83.6601

3.9.3.6 1-octene

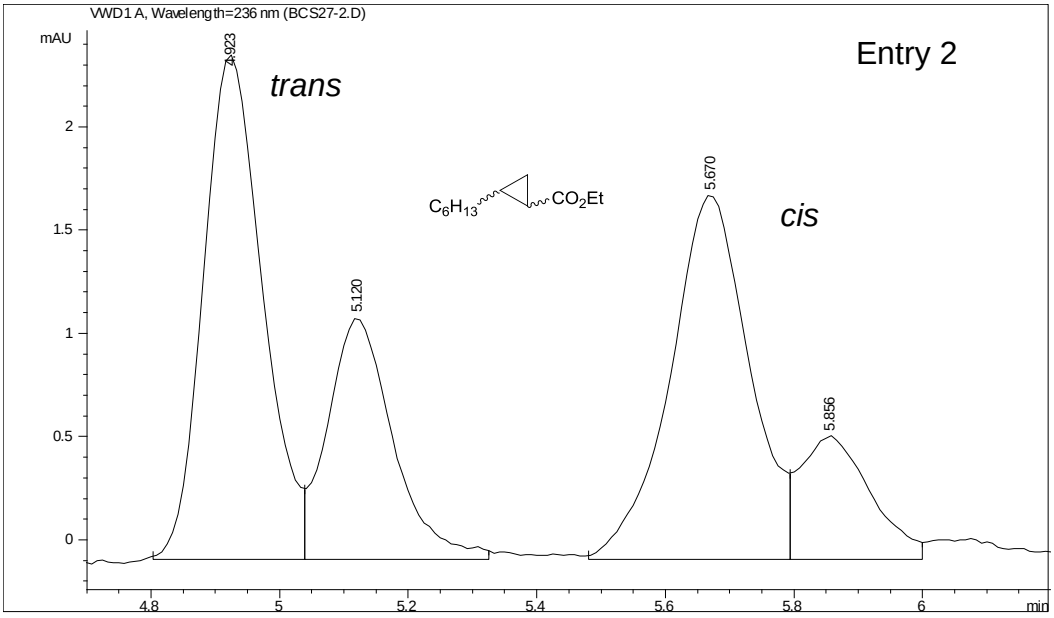


Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	112.21	9.87	0.715	13.8	88	10
EDA	114.11	0.998	1.082	1.00	8.8	1
10f/D (Cu:0.66%)	-	0.4097	-	-	-	-
Cu	63.546	0.002694	-	-	0.0424	-

Entry	time (min)	conversion (%)	selectivity (%)	*cis:trans*	*ee* (%) *cis* (nd)	*ee* (%) *trans* (nd)	Cu (ppb)
1	154	99	68.0	48: 52	72	39	
2	237	99	70.6	47: 53	72	42	8.1
3	298	99	70.4	47: 53	71	41	
4	357	99	71.0	48: 52	63	39	
5	417	99	72.6	49: 51	64	41	
6	477	99	74.8	49: 51	63	39	



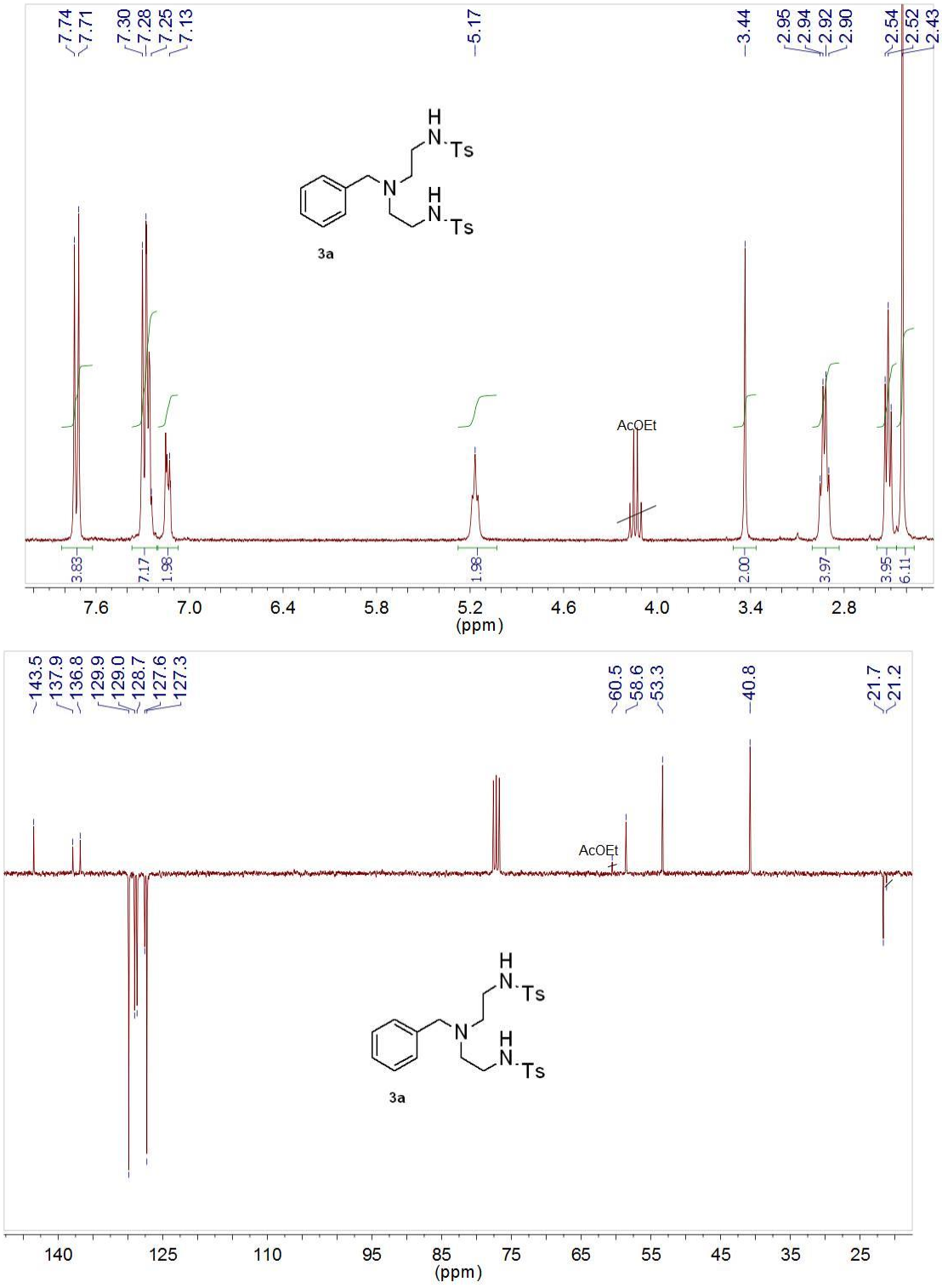
HPLC equipped with DAICEL CHIRALPAK O-J (n-hexane/i-PrOH = 99.9:0.1. λ =236 nm).

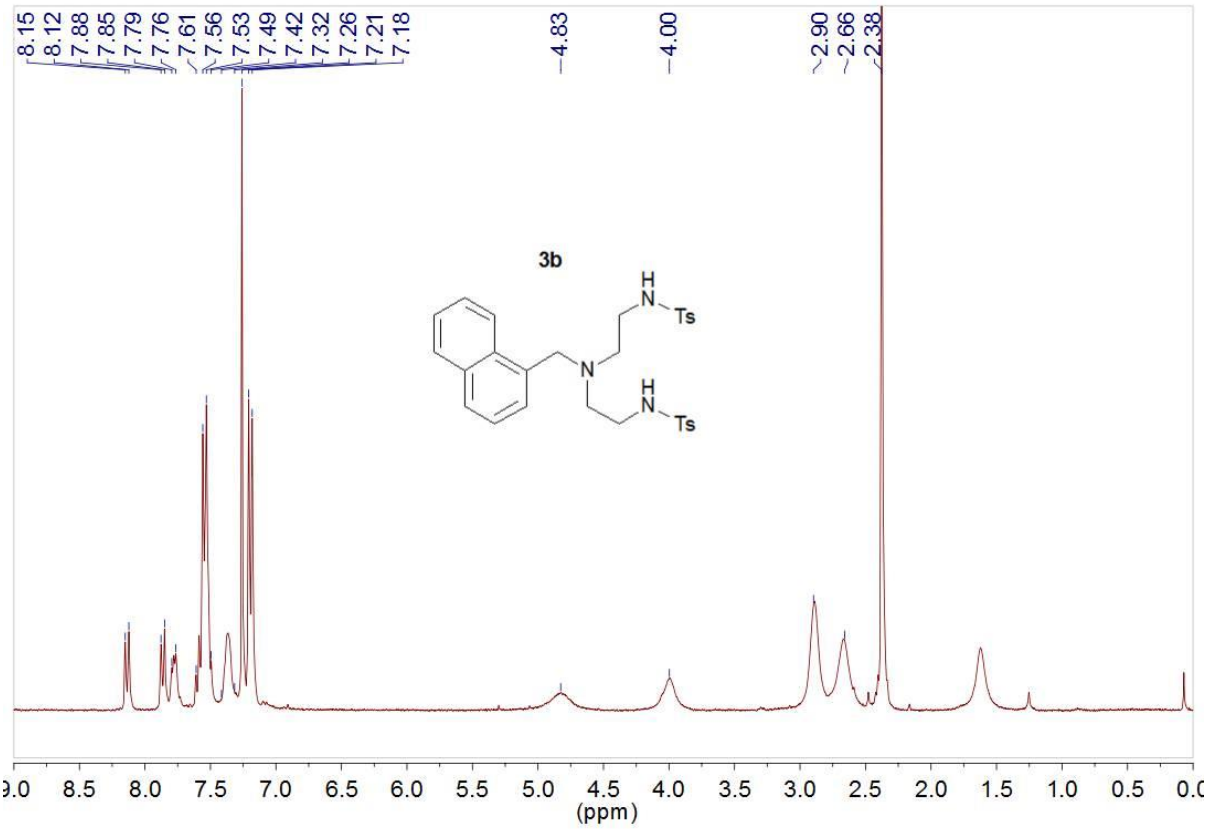


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.923	BV	0.1106	16.45330	2.47873	40.4158
2	5.120	VB	0.0923	6.67279	1.20476	16.3910
3	5.670	BV	0.1435	15.15985	1.76023	37.2386
	5.856	VBA	0.0699	2.42410	5.77861e-1	5.9545

3.10 ^{1}H and ^{13}C NMR for selected ligands and metal complexes.

3.10.1 Mono- and bis(sulphonamides).

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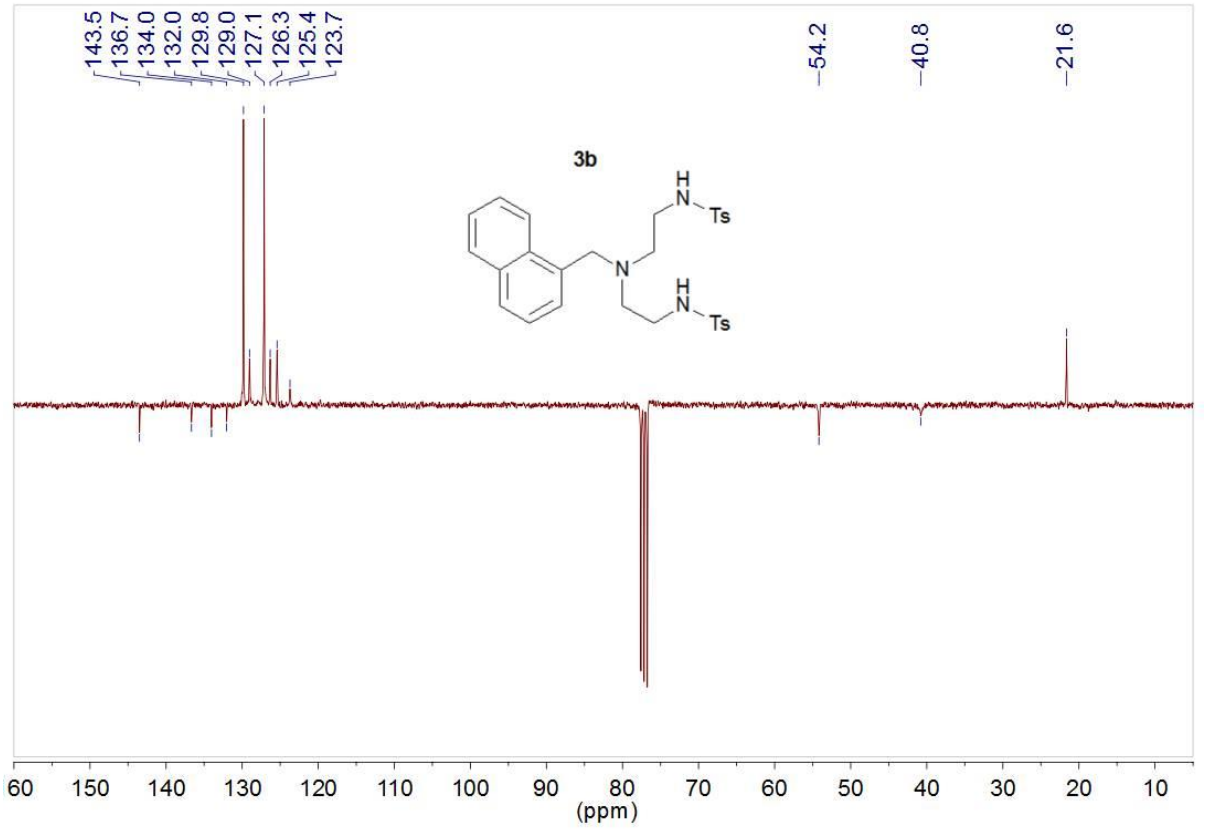
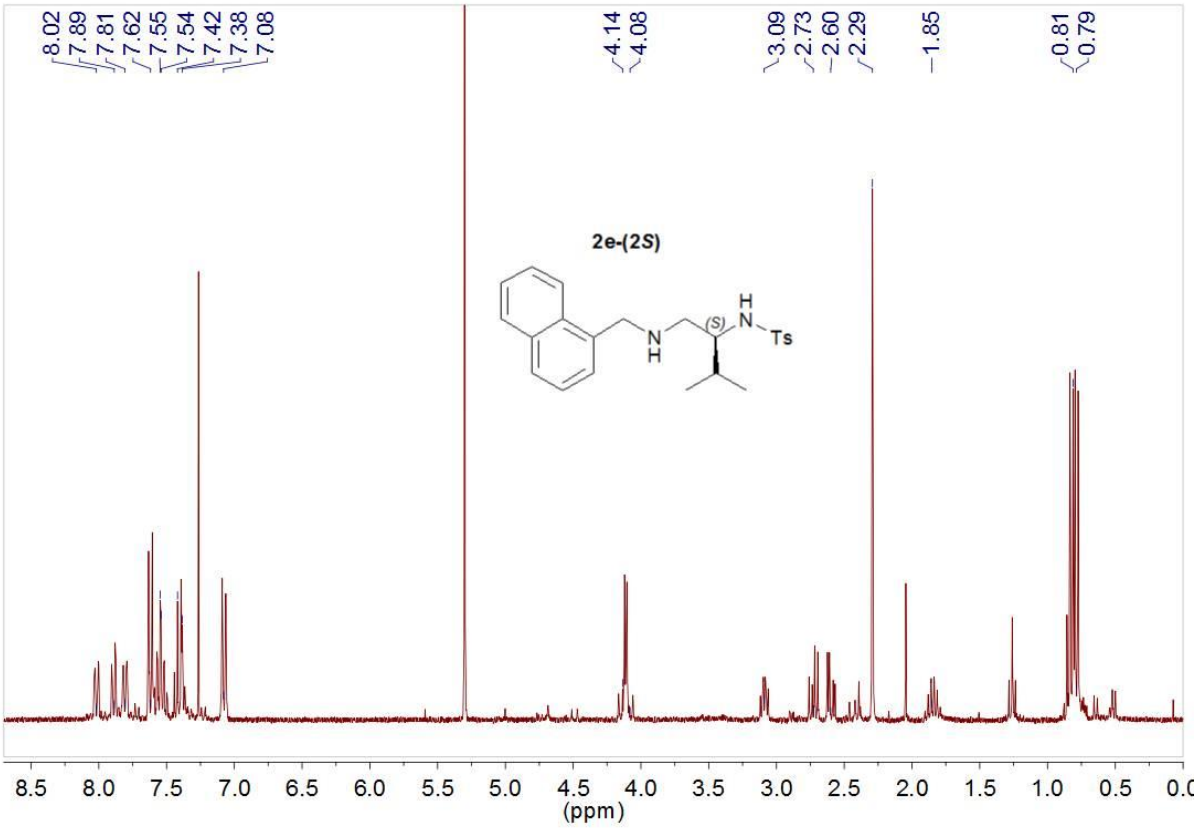
8.12
7.88
7.85
7.79
7.76
7.61
7.56
7.53
7.49
7.42
7.32
7.26
7.21
7.18
4.83
4.00
2.90
2.66
2.38
3b
H
N
Ts
N
H
N
Ts
(ppm)


143.5
136.7
134.0
132.0
129.8
129.0
127.1
126.3
125.4
123.7
54.2
40.8
21.6
3b
H
N
Ts
N
H
N
Ts
(ppm)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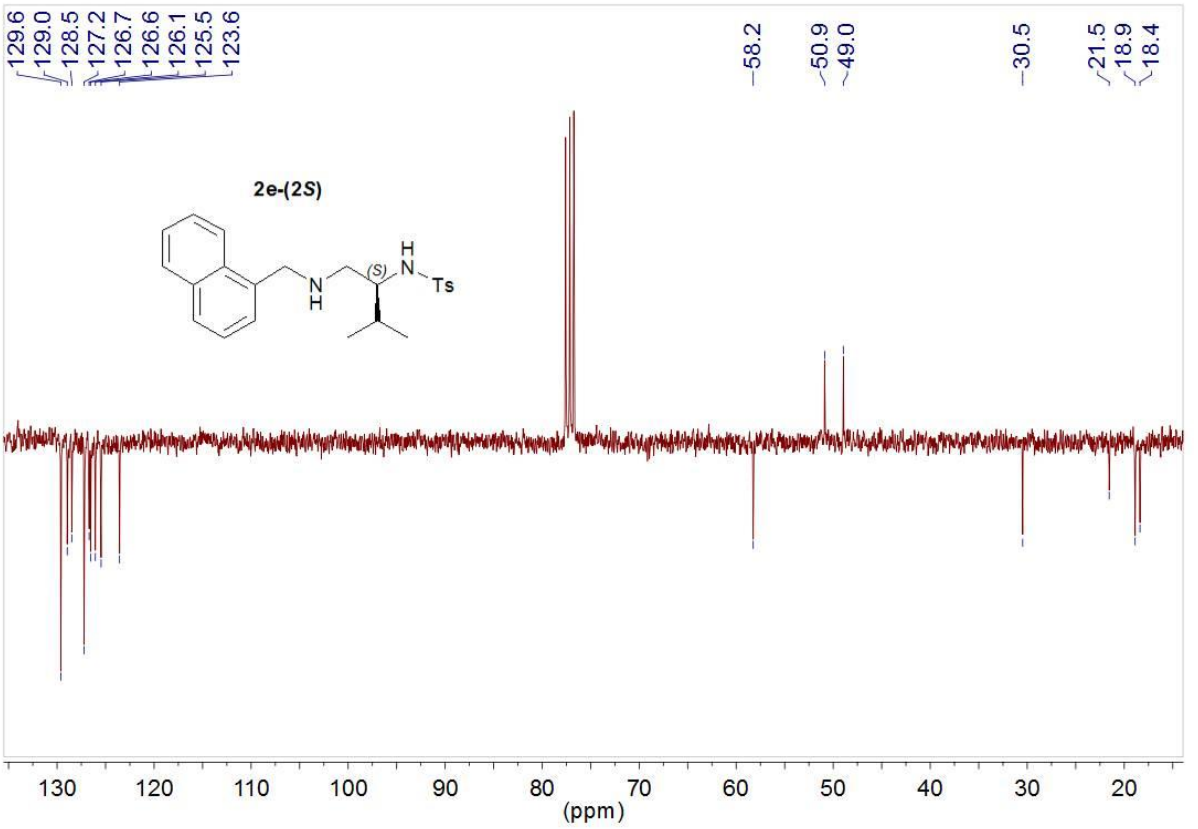
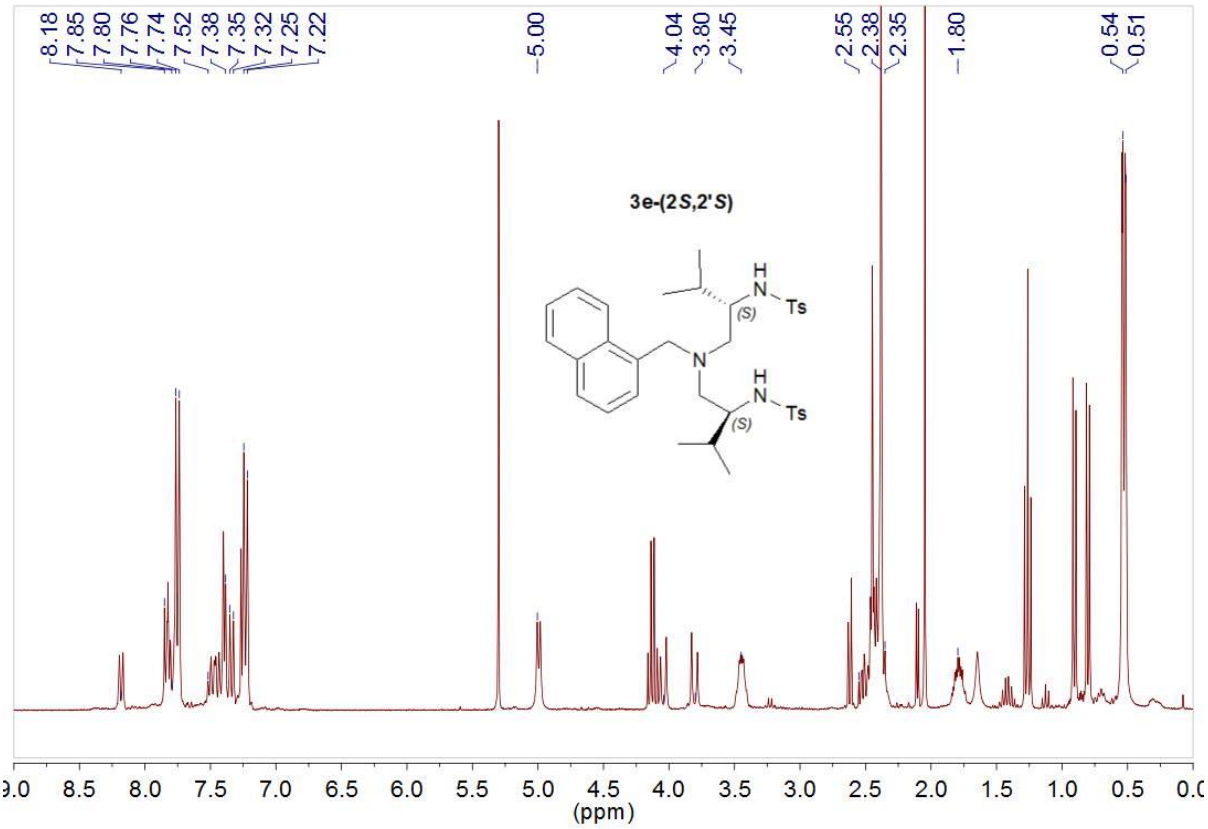
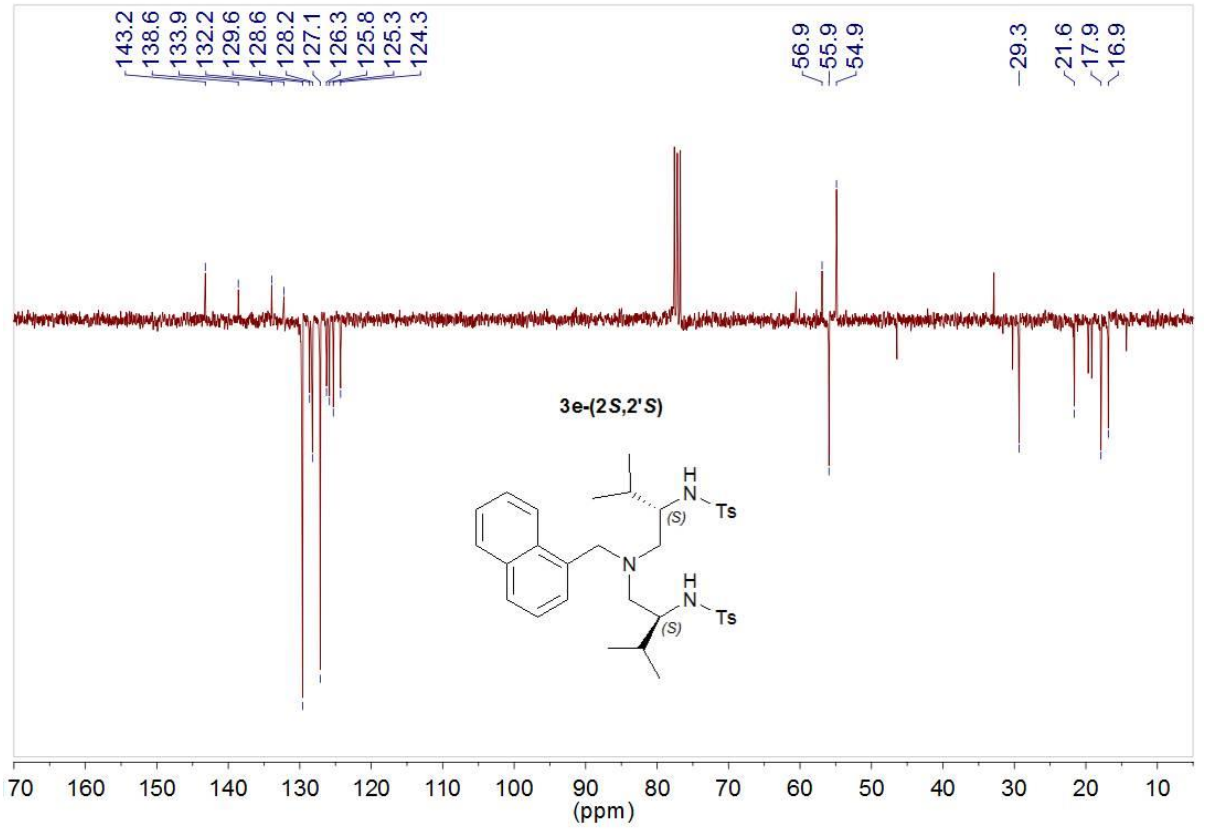
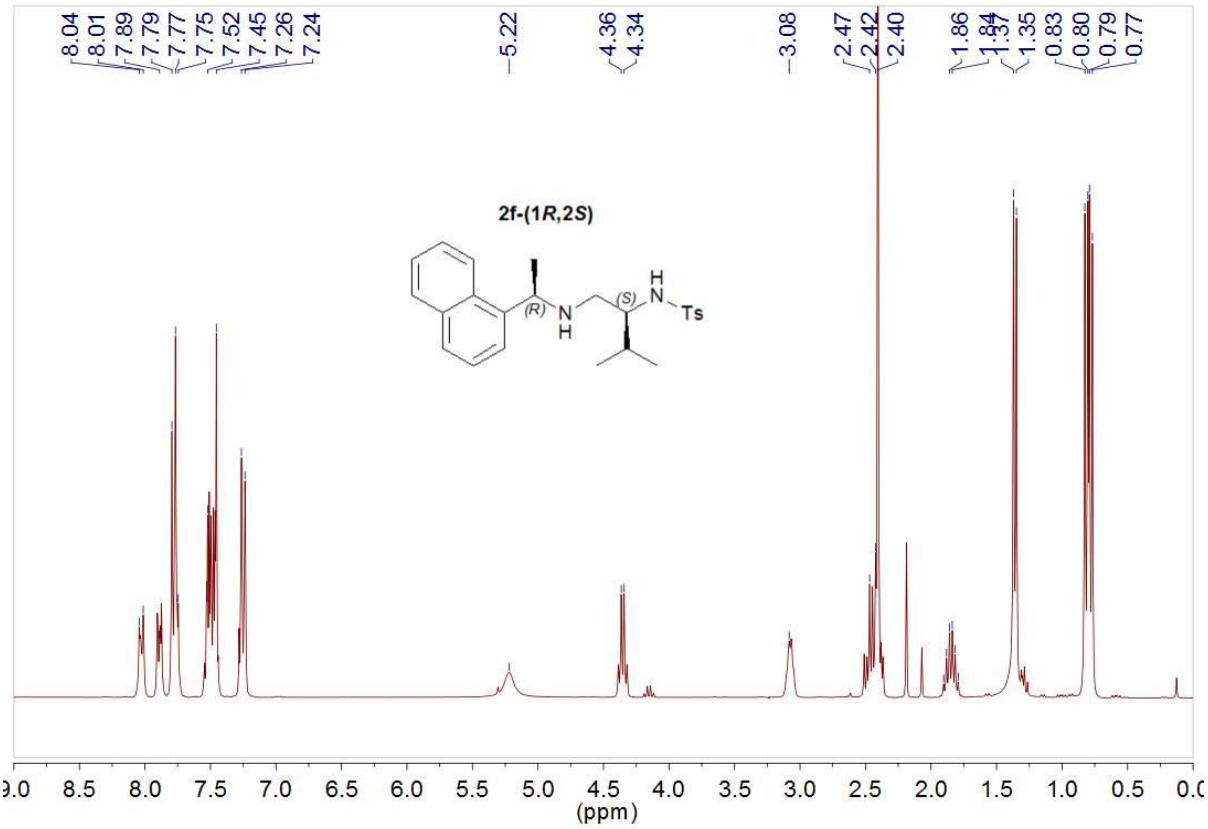
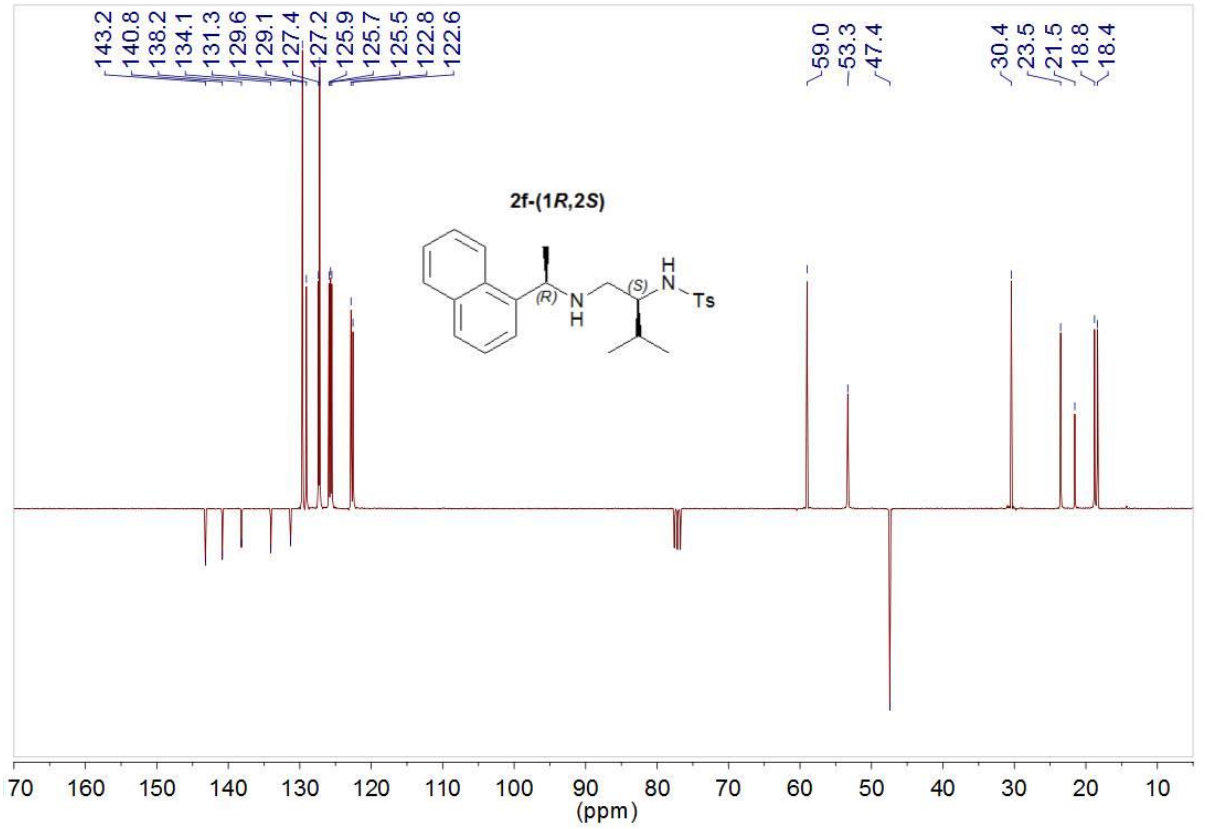
7.89
7.81
7.62
7.55
7.54
7.42
7.38
7.08
4.14
4.08
3.09
2.73
2.60
2.29
1.85
0.81
0.79
2e-(2S)
Ts
(S)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

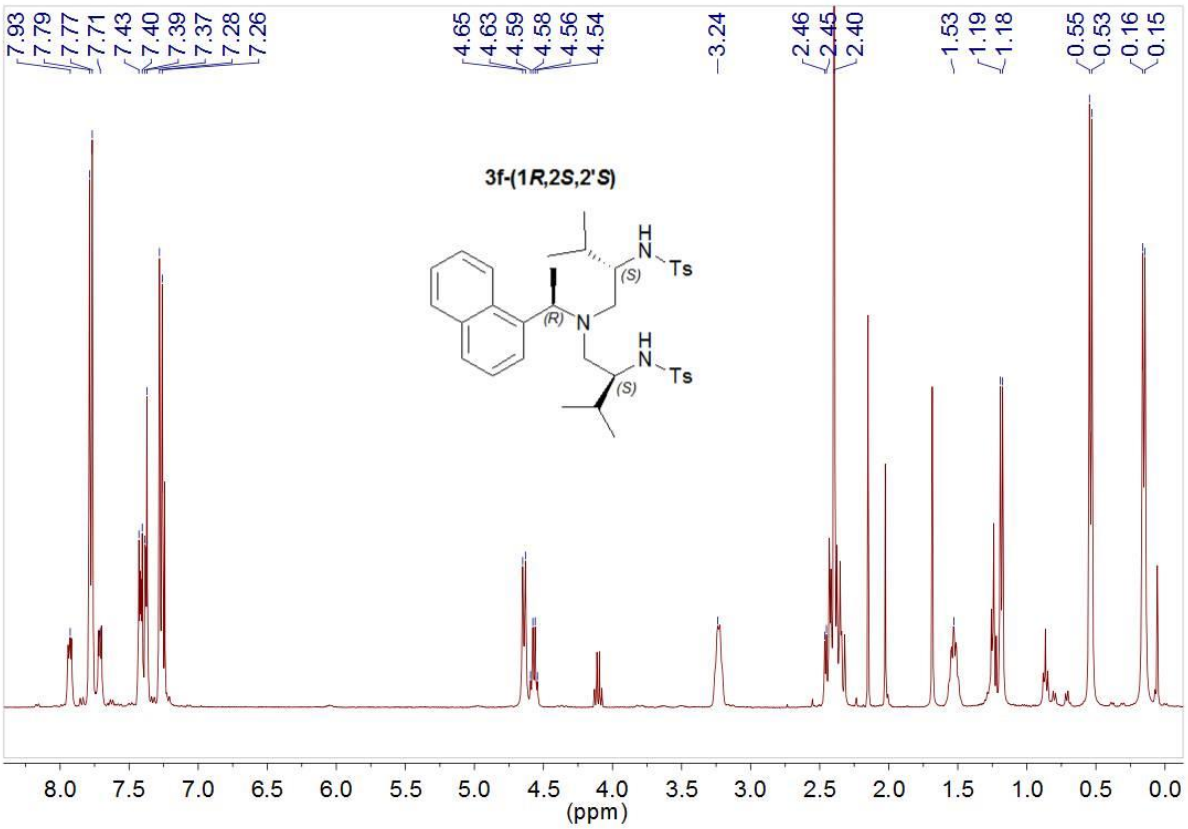

129.6
129.0
128.5
127.2
126.7
126.6
126.1
125.5
123.6
58.2
50.9
49.0
30.5
21.5
18.9
18.4
2e-(2S)
Ts
(S)
130 120 110 100 90 80 70 60 50 40 30 20
(ppm)

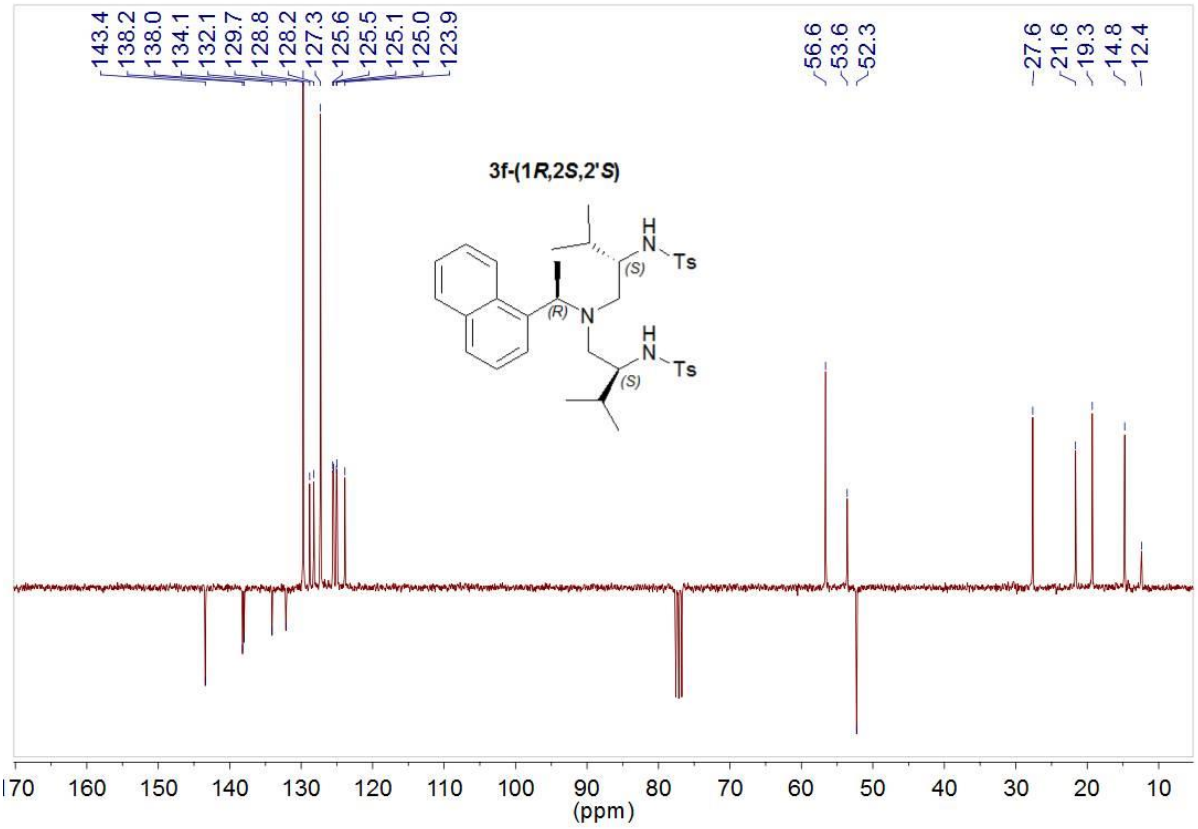

8.18
7.85
7.80
7.76
7.74
7.52
7.38
7.35
7.32
7.25
7.22
5.00
4.04
3.80
3.45
2.55
2.38
2.35
1.80
0.54
0.51
3e-(2S,2'S)
H
N
Ts
(S)
N
H
N
Ts
(S)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

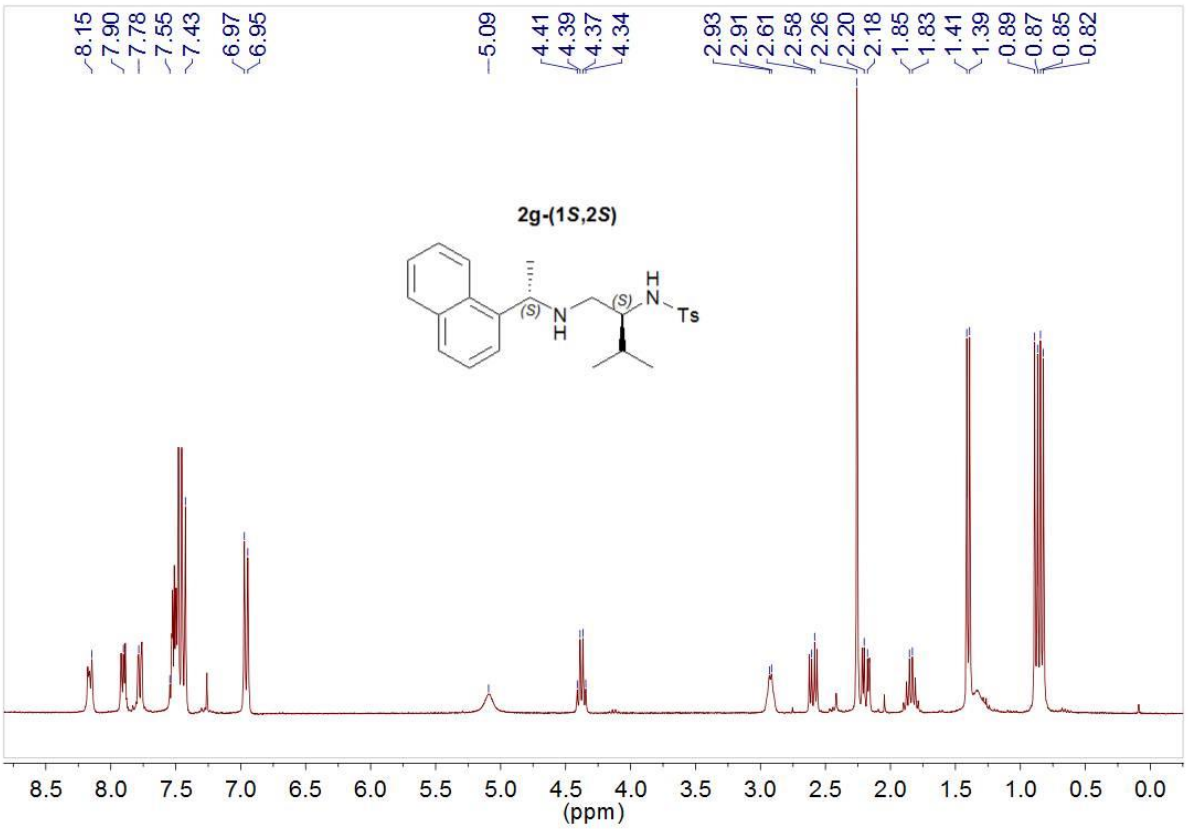

143.2
138.6
133.9
132.2
129.6
128.6
128.2
127.1
126.3
125.8
125.3
124.3
56.9
55.9
54.9
29.3
21.6
17.9
16.9
3e-(2S,2'S)
H
N
Ts
(S)
N
H
N
Ts
(S)
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

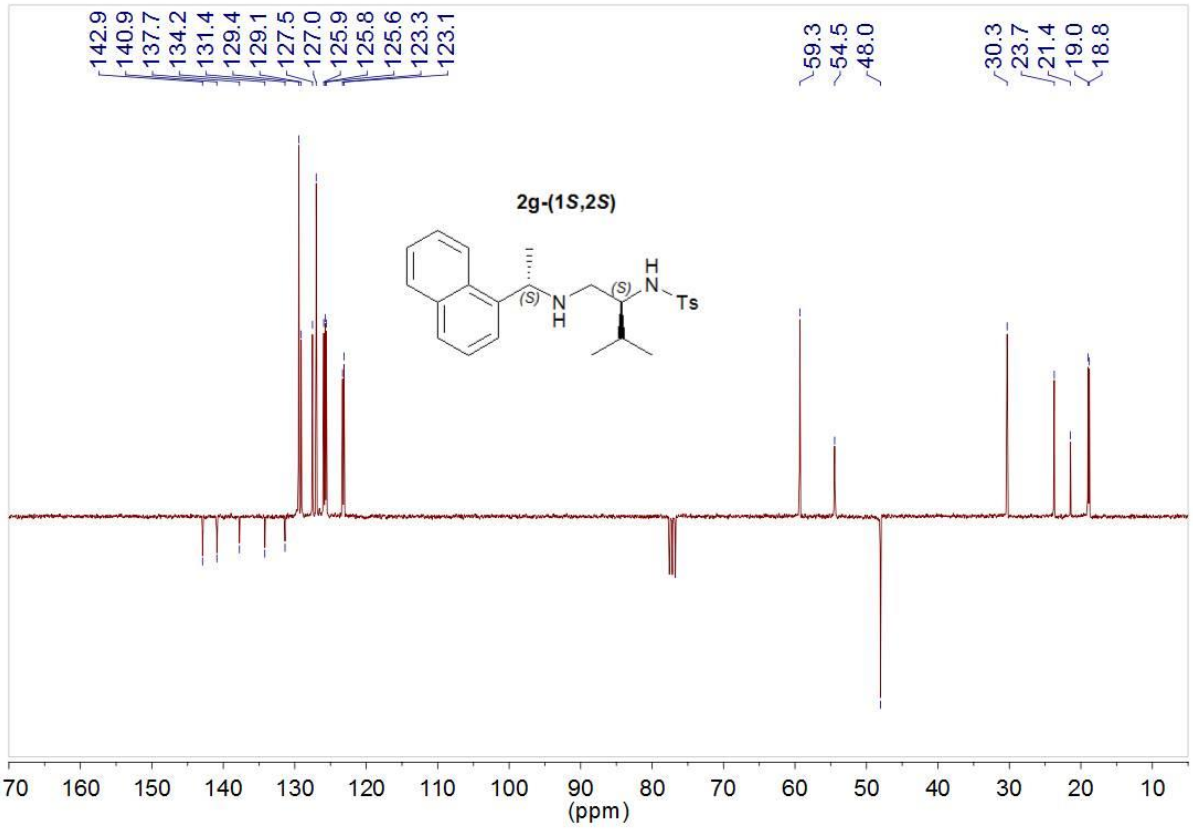

8.04
8.01
7.89
7.79
7.77
7.75
7.52
7.45
7.26
7.24
5.22
4.36
4.34
3.08
2.47
2.42
2.40
1.86
1.84
1.37
1.35
0.83
0.80
0.79
0.77
2f-(1R,2S)
(R)
(S)
H
N
Ts
(ppm)

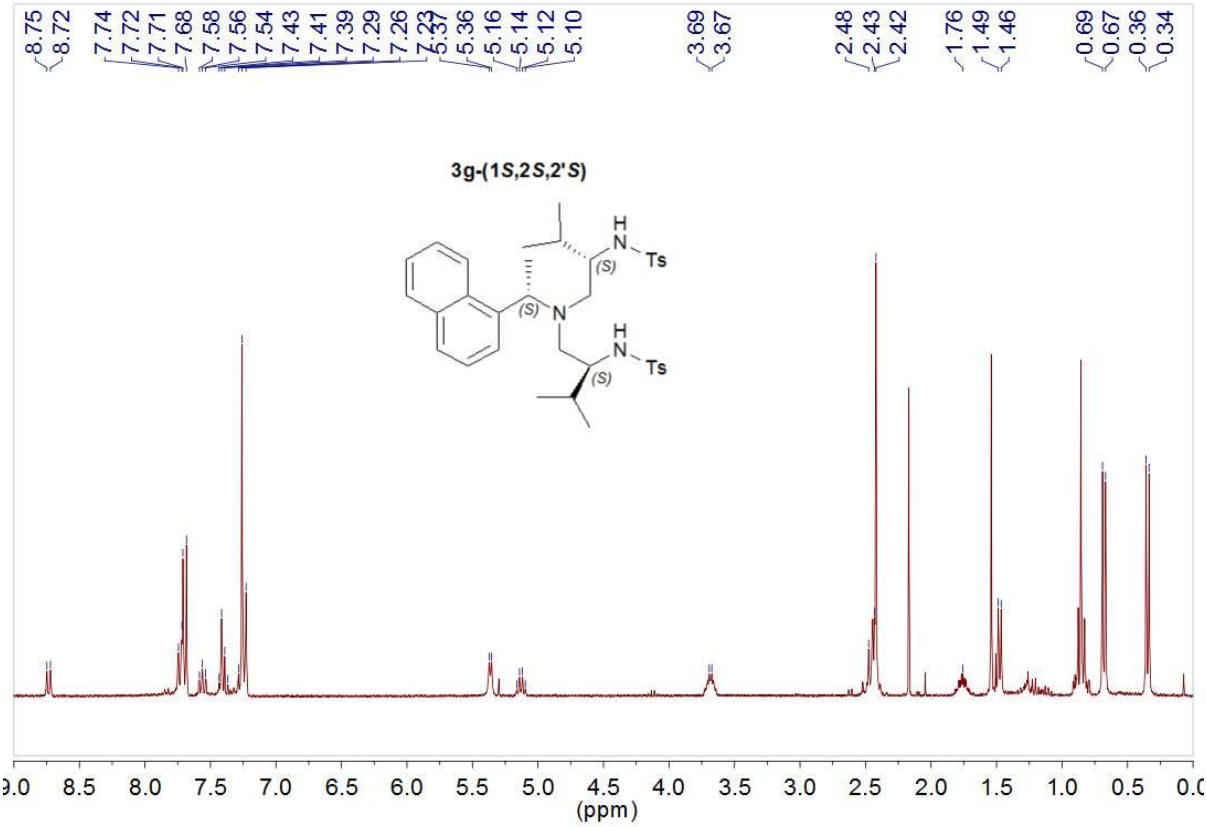

143.2
140.8
138.2
134.1
131.3
129.6
129.1
127.4
127.2
125.9
125.7
125.5
122.8
122.6
59.0
53.3
47.4
30.4
23.5
21.5
18.8
18.4
2f-(1R,2S)
(R)
(S)
H
N
Ts
(ppm)

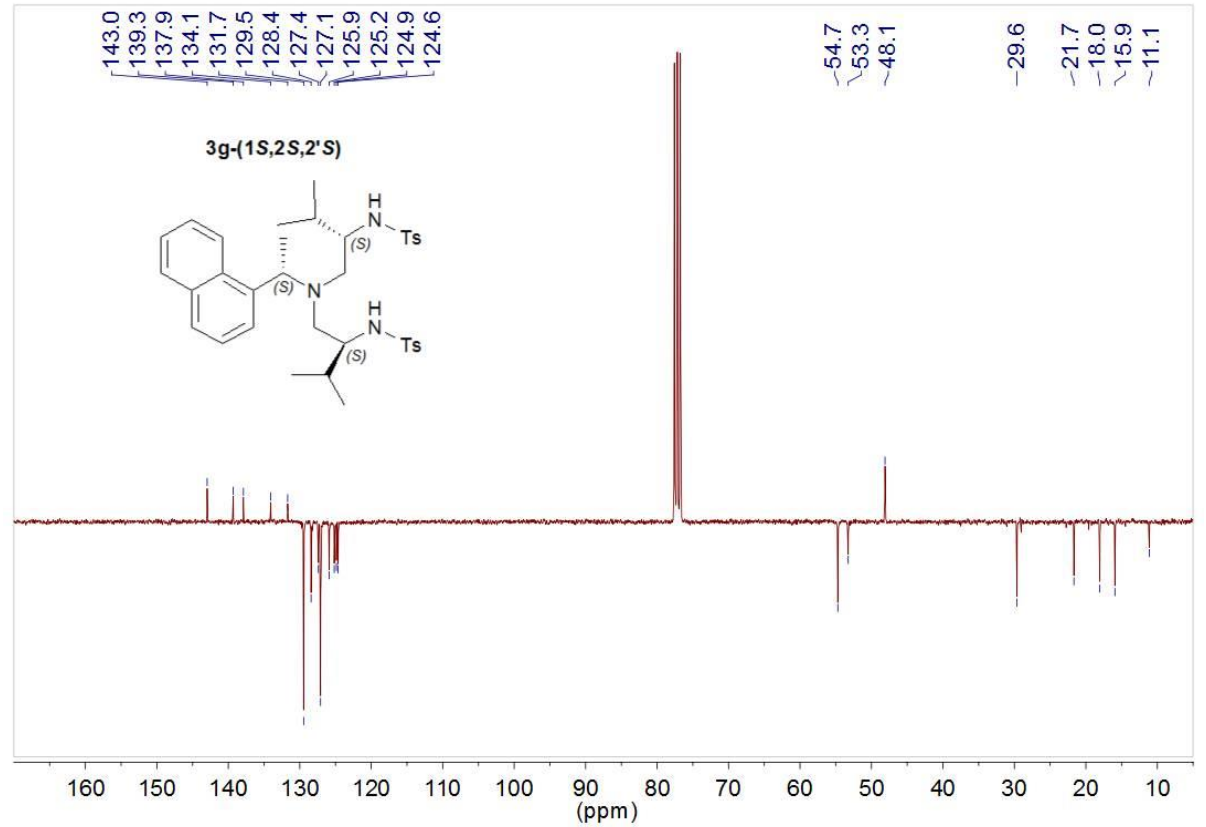

7.93
7.79
7.77
7.71
7.43
7.40
7.39
7.37
7.28
7.26
4.65
4.63
4.59
4.58
4.56
4.54
3.24
2.46
2.45
2.40
1.53
1.19
1.18
0.55
0.53
0.16
0.15
3f-(1R,2S,2'S)
H
N
Ts
(S)
(R)
N
H
N
Ts
(S)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

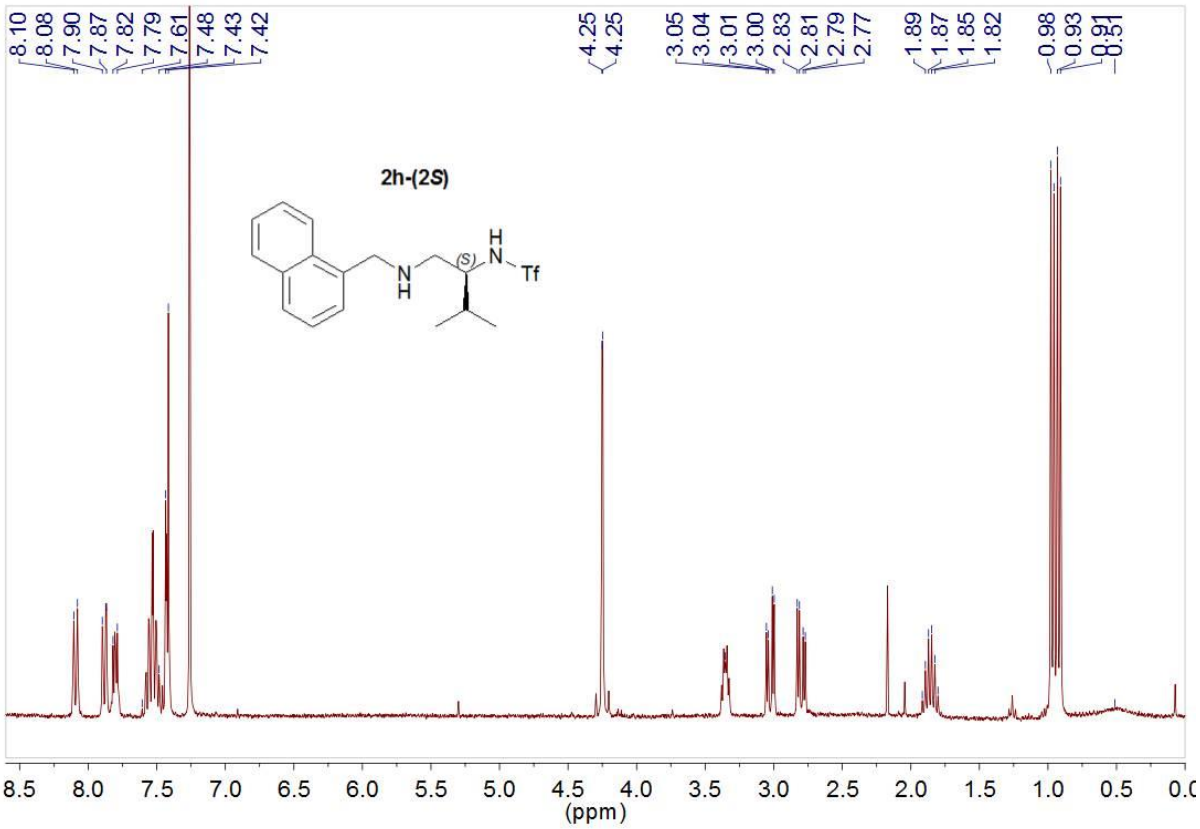

143.4
138.2
138.0
134.1
132.1
129.7
128.8
128.2
127.3
125.6
125.5
125.1
125.0
123.9
56.6
53.6
52.3
27.6
21.6
19.3
14.8
12.4
3f-(1R,2S,2'S)
H
N
Ts
(S)
(R)
N
H
N
Ts
(S)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

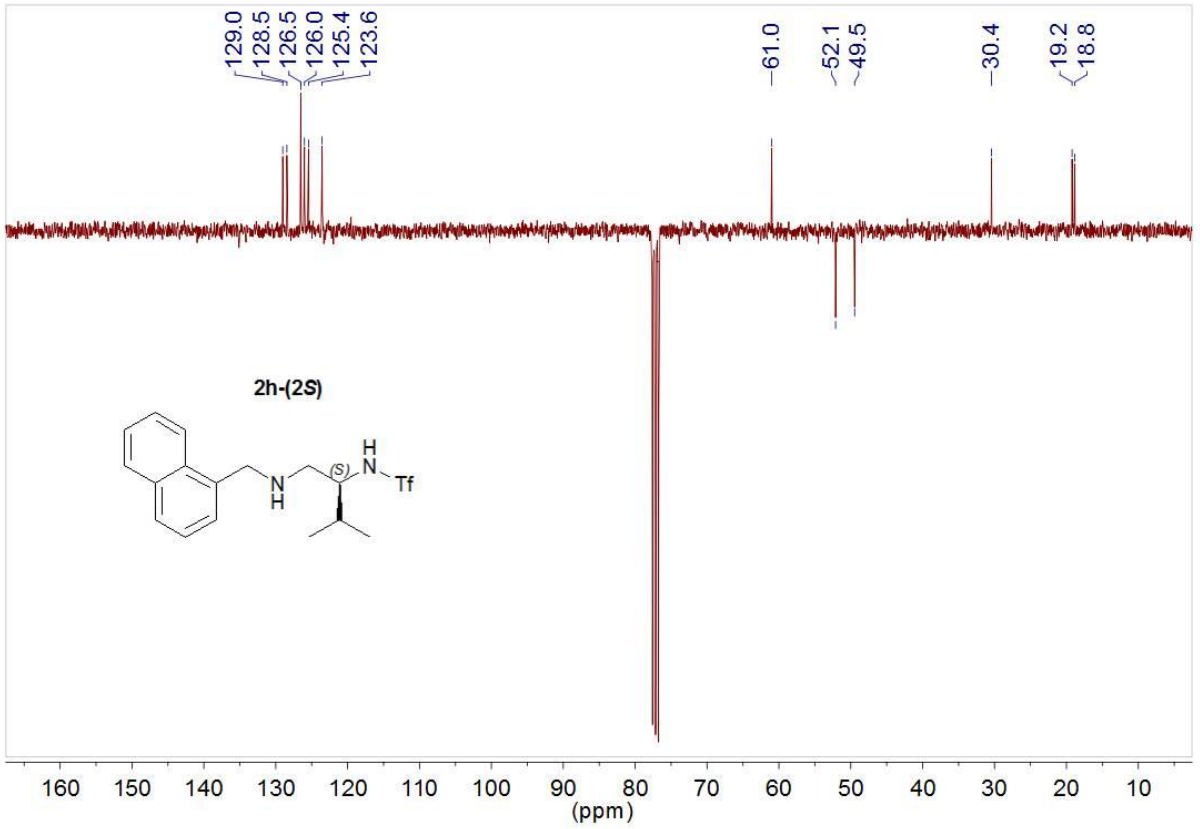

8.15
7.90
7.78
7.55
7.43
6.97
6.95
5.09
4.41
4.39
4.37
4.34
2.93
2.91
2.61
2.58
2.26
2.20
2.18
1.85
1.83
1.41
1.39
0.89
0.87
0.85
0.82
2g-(1S,2S)
(S)
N
H
(S)
H
N
Ts
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

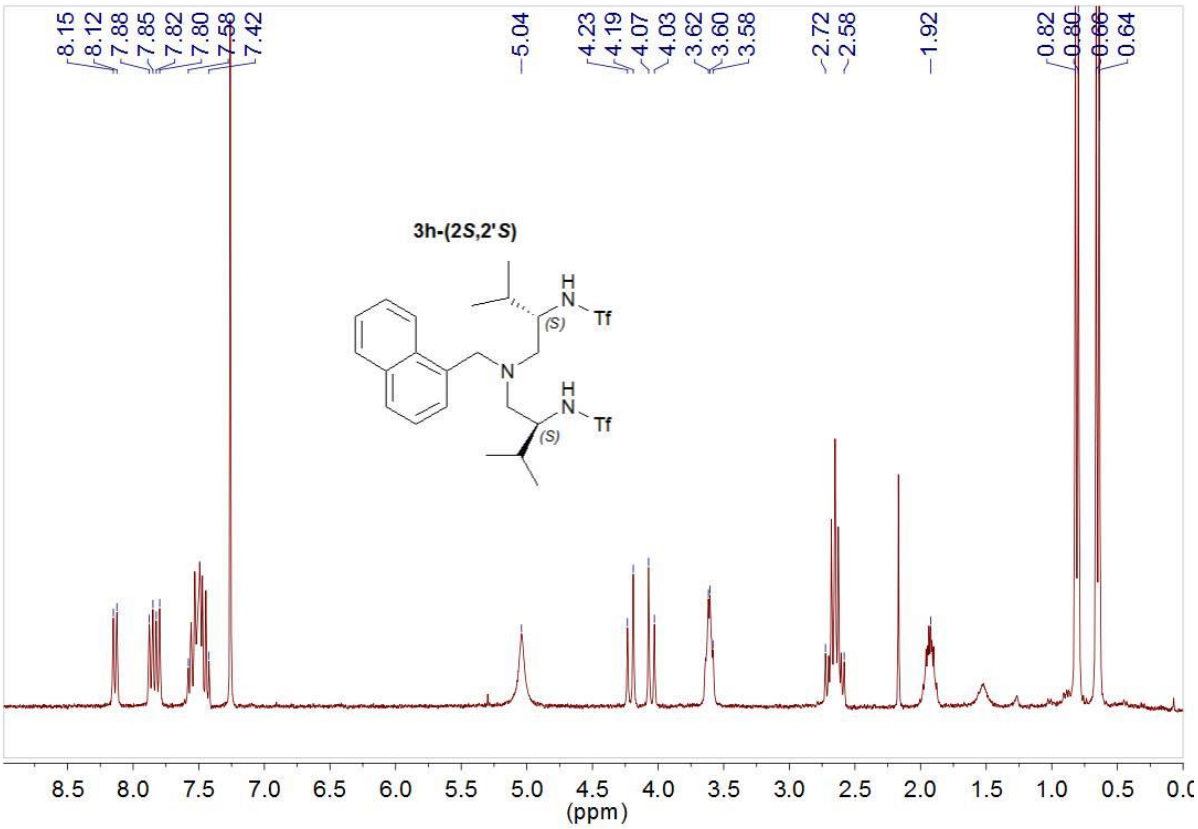

142.9
140.9
137.7
134.2
131.4
129.4
129.1
127.5
127.0
125.9
125.8
125.6
123.3
123.1
59.3
54.5
48.0
30.3
23.7
21.4
19.0
18.8
2g-(1S,2S)
(S)
N
H
(S)
H
N
Ts
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

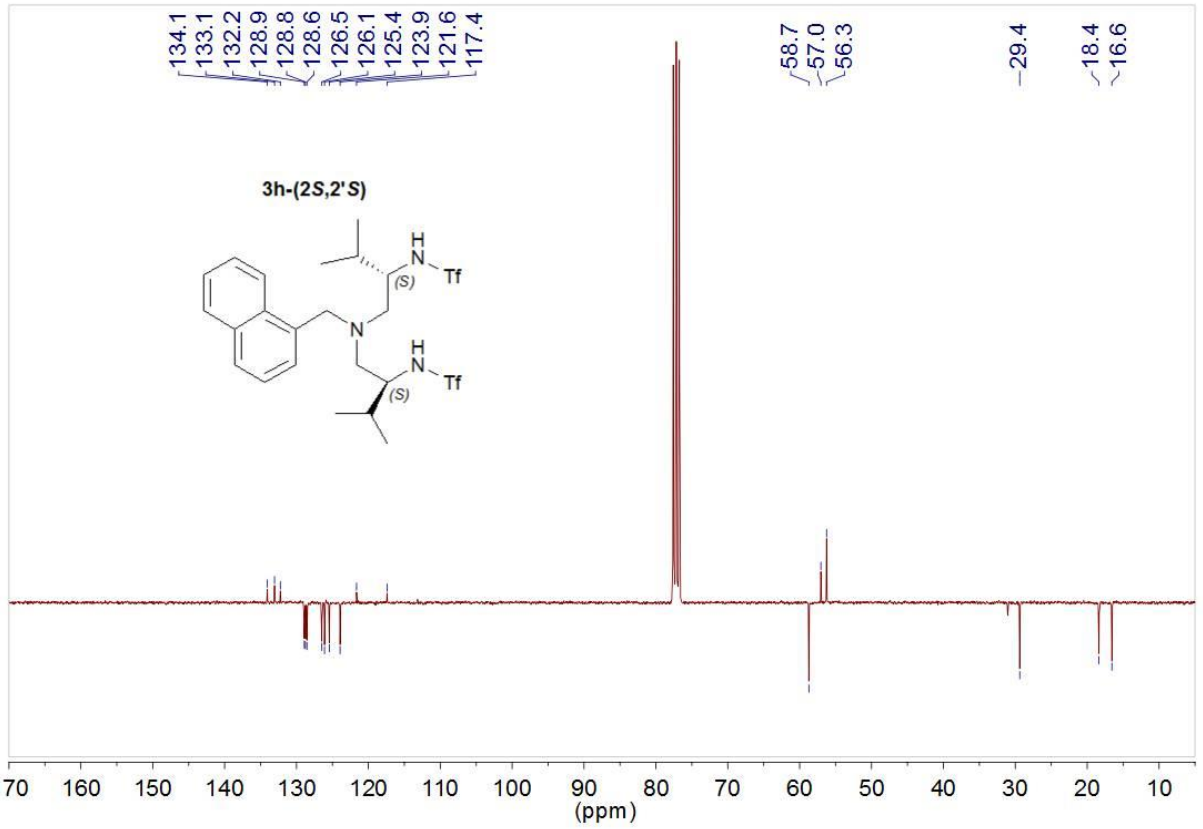

8.75
8.72
7.74
7.72
7.71
7.68
7.58
7.56
7.54
7.43
7.41
7.39
7.29
7.26
5.36
5.16
5.14
5.12
5.10
3.69
3.67
2.48
2.43
2.42
1.76
1.49
1.46
0.69
0.67
0.36
0.34
3g-(1S,2S,2'S)
H
N
Ts
(S)
(S)
N
H
N
Ts
(S)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

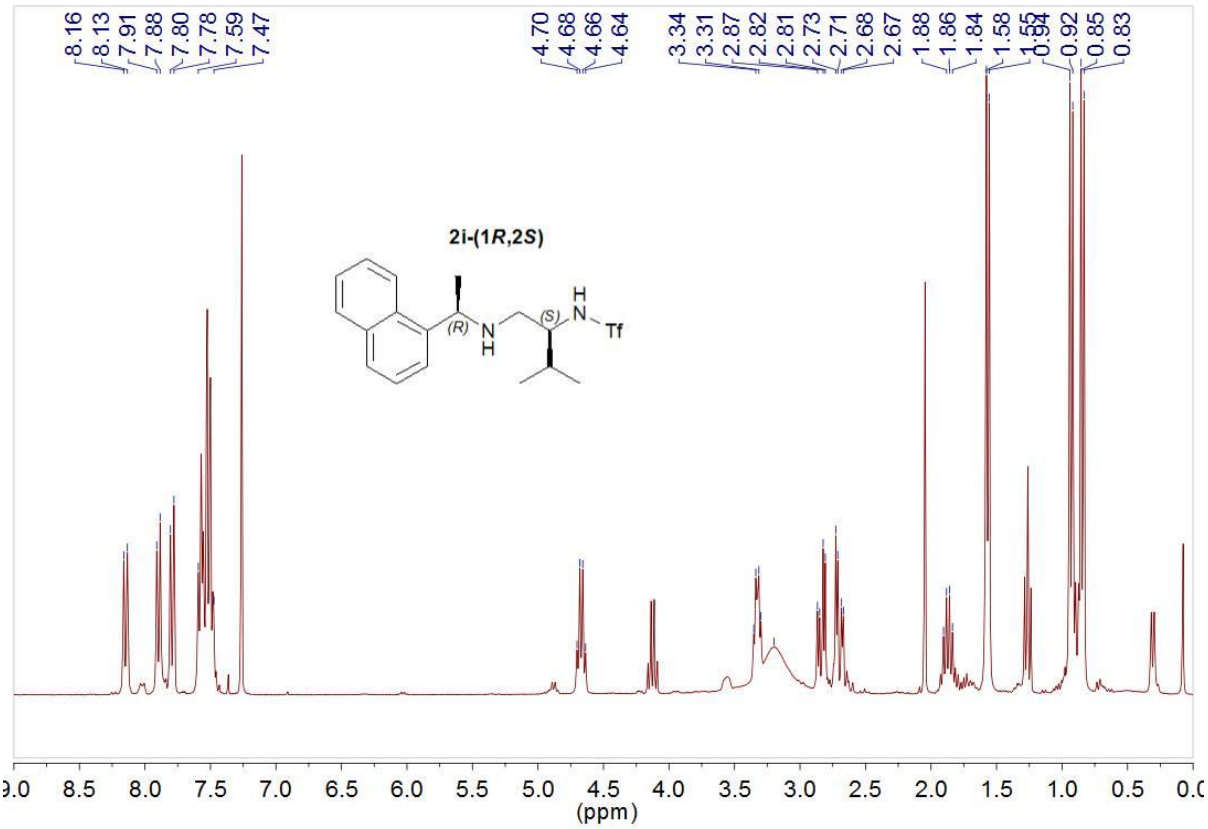

143.0
139.3
137.9
134.1
131.7
129.5
128.4
127.4
127.1
125.9
125.2
124.9
124.6
54.7
53.3
48.1
29.6
21.7
18.0
15.9
11.1
3g-(1S,2S,2'S)
H
N
Ts
(S)
(S)
N
H
N
Ts
(S)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

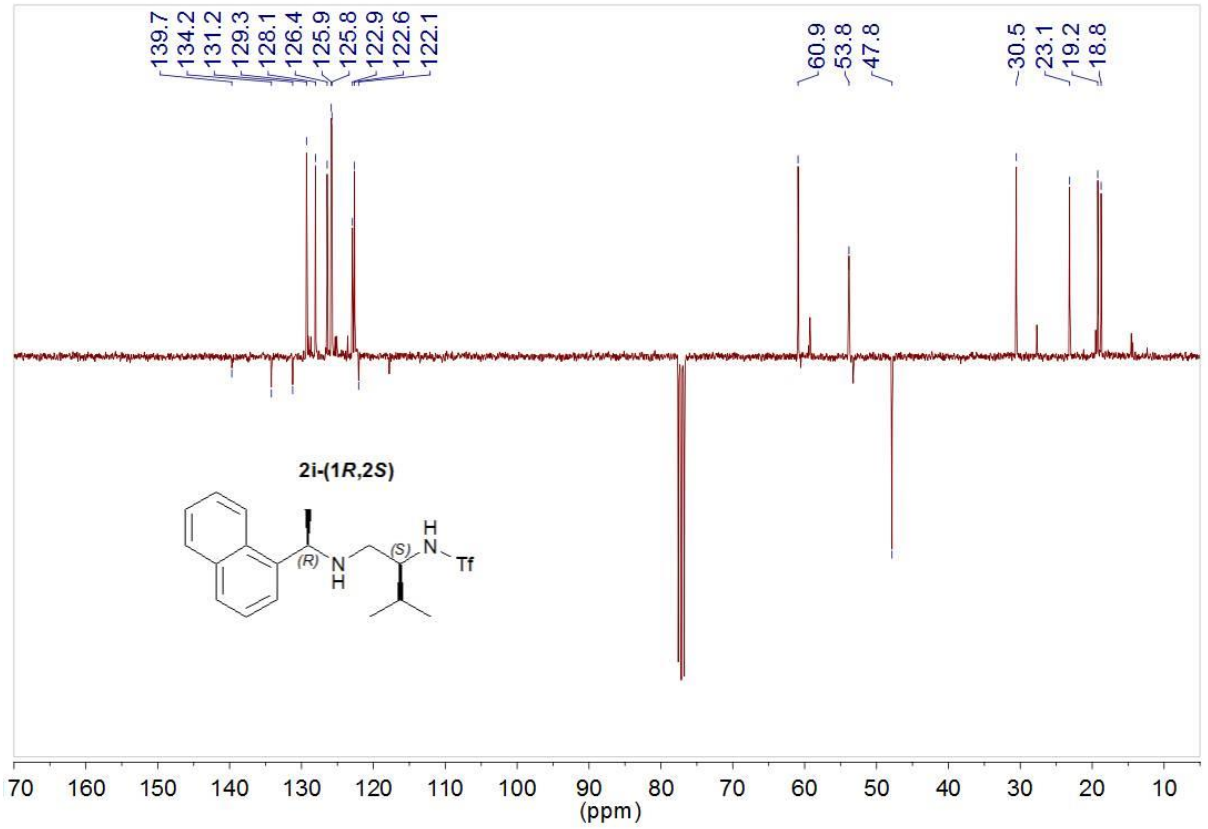

8.10
8.08
7.90
7.87
7.82
7.79
7.61
7.48
7.43
7.42
4.25
4.25
3.05
3.04
3.01
3.00
2.83
2.81
2.79
2.77
1.89
1.87
1.85
1.82
0.98
0.93
0.91
0.51
2h-(2S)
H
N
(S)
N
H
Tf
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

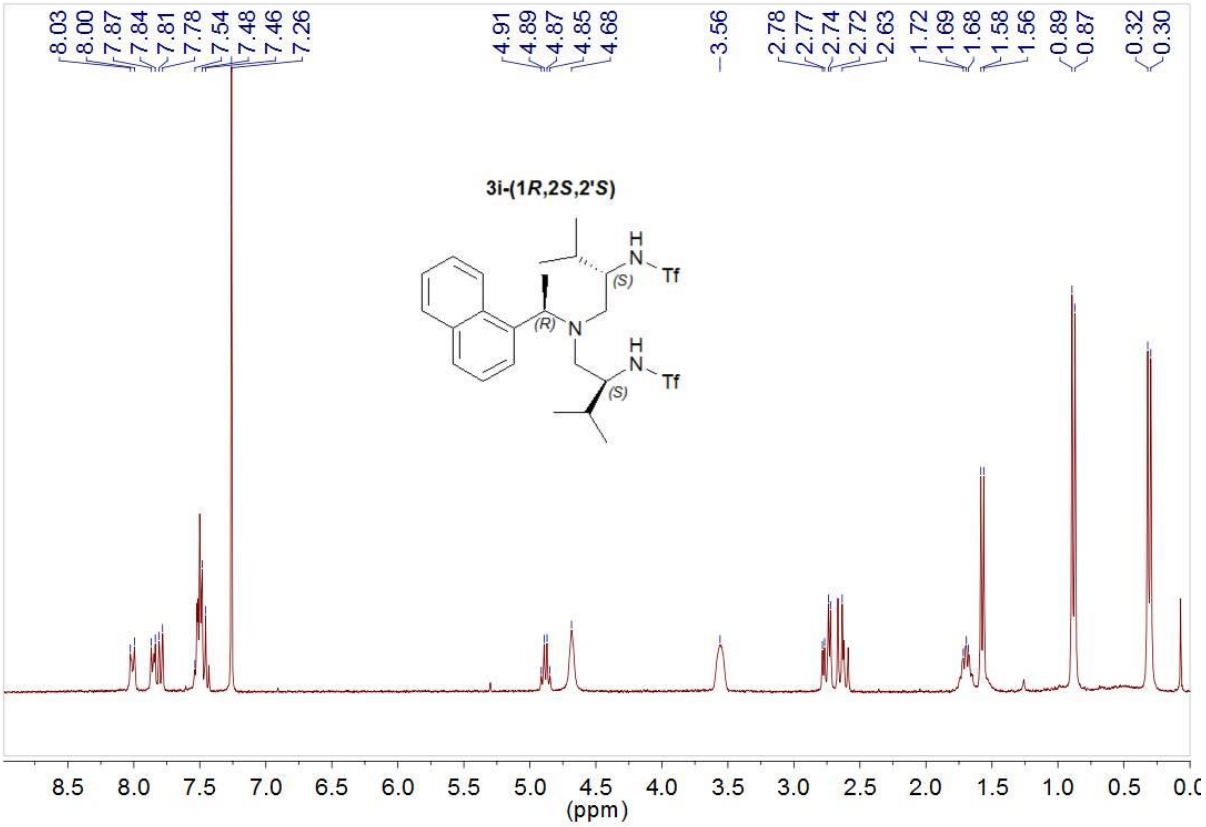

129.0
128.5
126.5
126.0
125.4
123.6
61.0
52.1
49.5
30.4
19.2
18.8
2h-(2S)
H
N
(S)
N
H
Tf
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

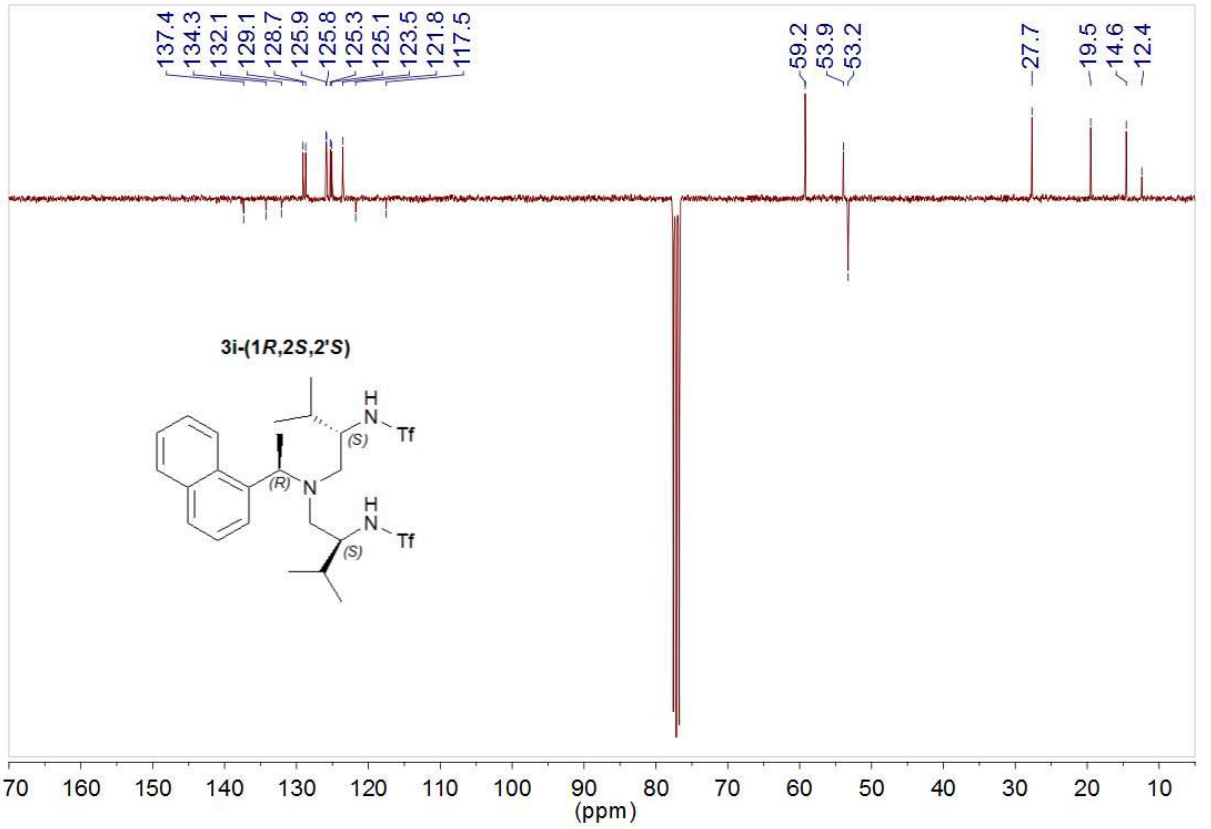

8.15
8.12
7.88
7.85
7.82
7.80
7.58
7.42
5.04
4.23
4.19
4.07
4.03
3.62
3.60
3.58
2.72
2.58
1.92
0.82
0.80
0.66
0.64
3h-(2S,2'S)
H
N
Tf
(S)
N
H
N
Tf
(S)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

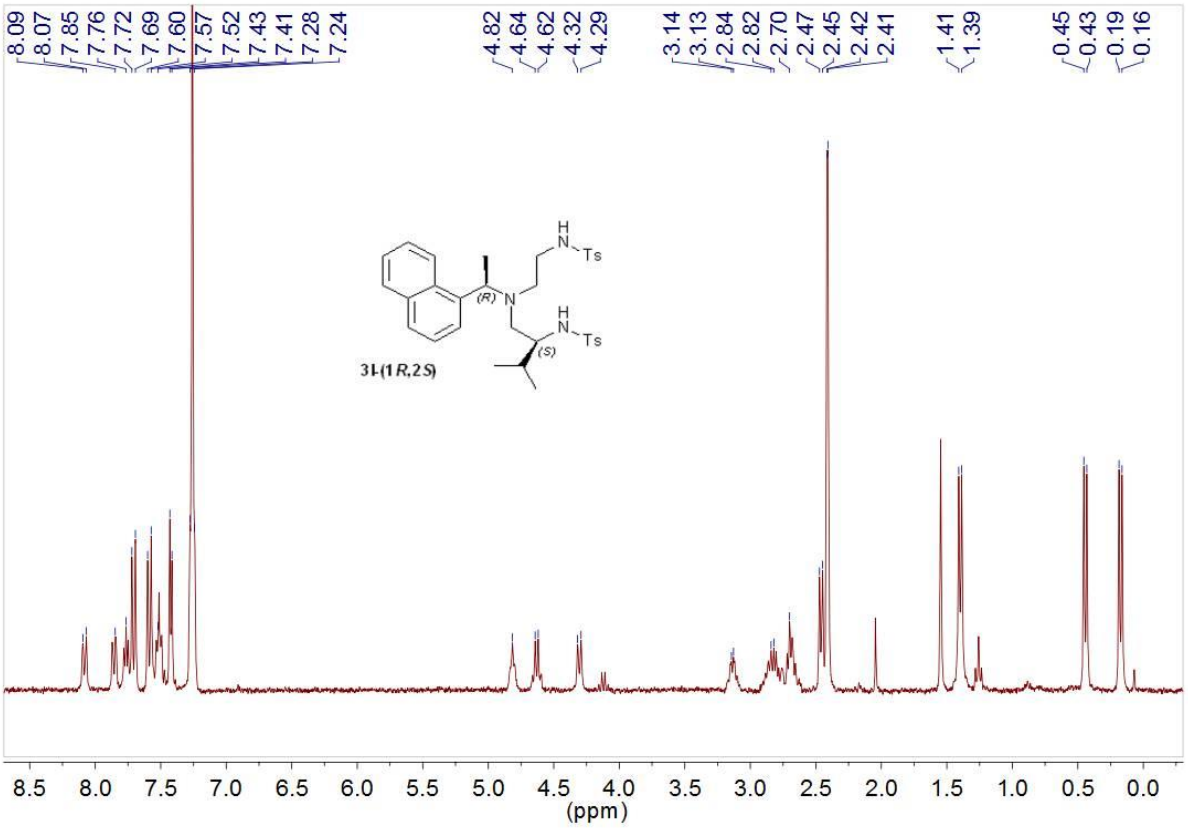

134.1
133.1
132.2
128.9
128.8
128.6
126.5
126.1
125.4
123.9
121.6
117.4
58.7
57.0
56.3
29.4
18.4
16.6
3h-(2S,2'S)
H
N
Tf
(S)
N
H
N
Tf
(S)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

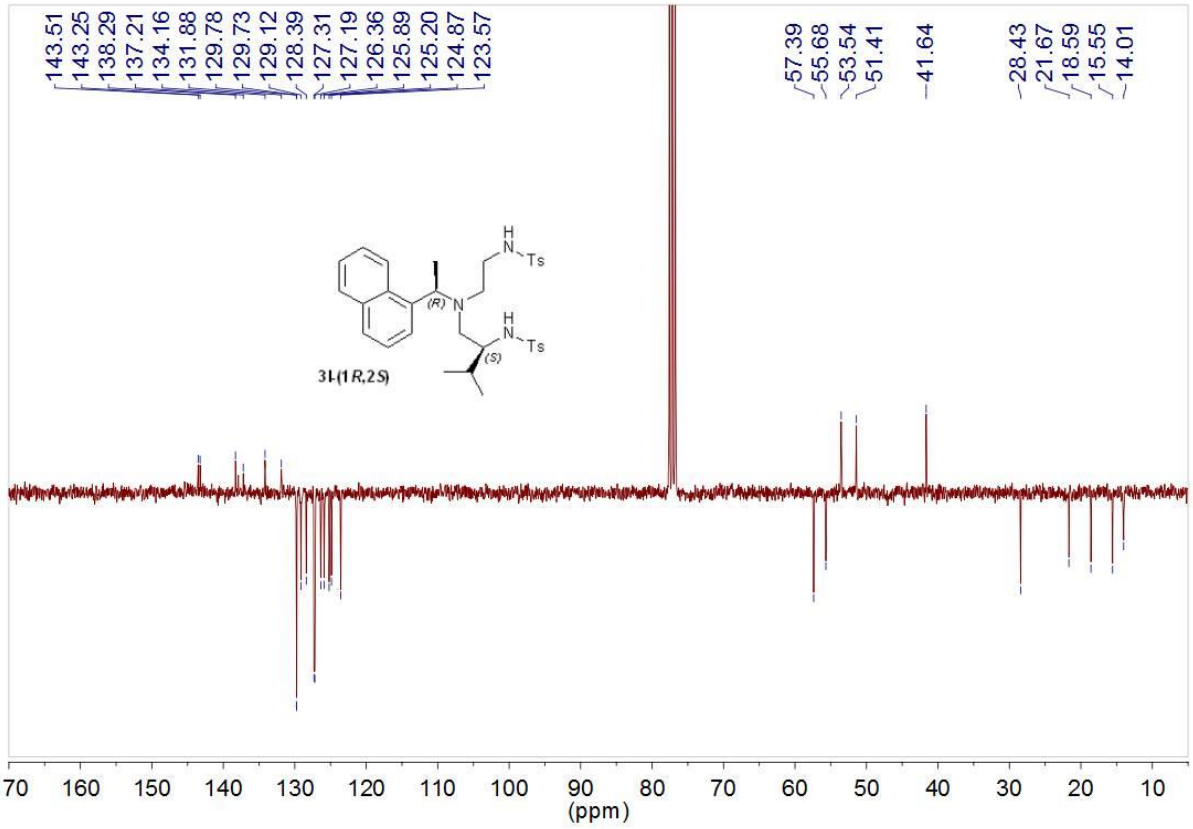

8.16
8.13
7.91
7.88
7.80
7.78
7.59
7.47
4.70
4.68
4.66
4.64
3.34
3.31
2.87
2.82
2.81
2.73
2.71
2.68
2.67
1.88
1.86
1.84
1.58
1.55
0.94
0.92
0.85
0.83
2i-(1R,2S)
(R)
(S)
Tf
(ppm)


139.7
134.2
131.2
129.3
128.1
126.4
125.9
125.8
122.9
122.6
122.1
60.9
53.8
47.8
30.5
23.1
19.2
18.8
2i-(1R,2S)
(R)
(S)
Tf
(ppm)

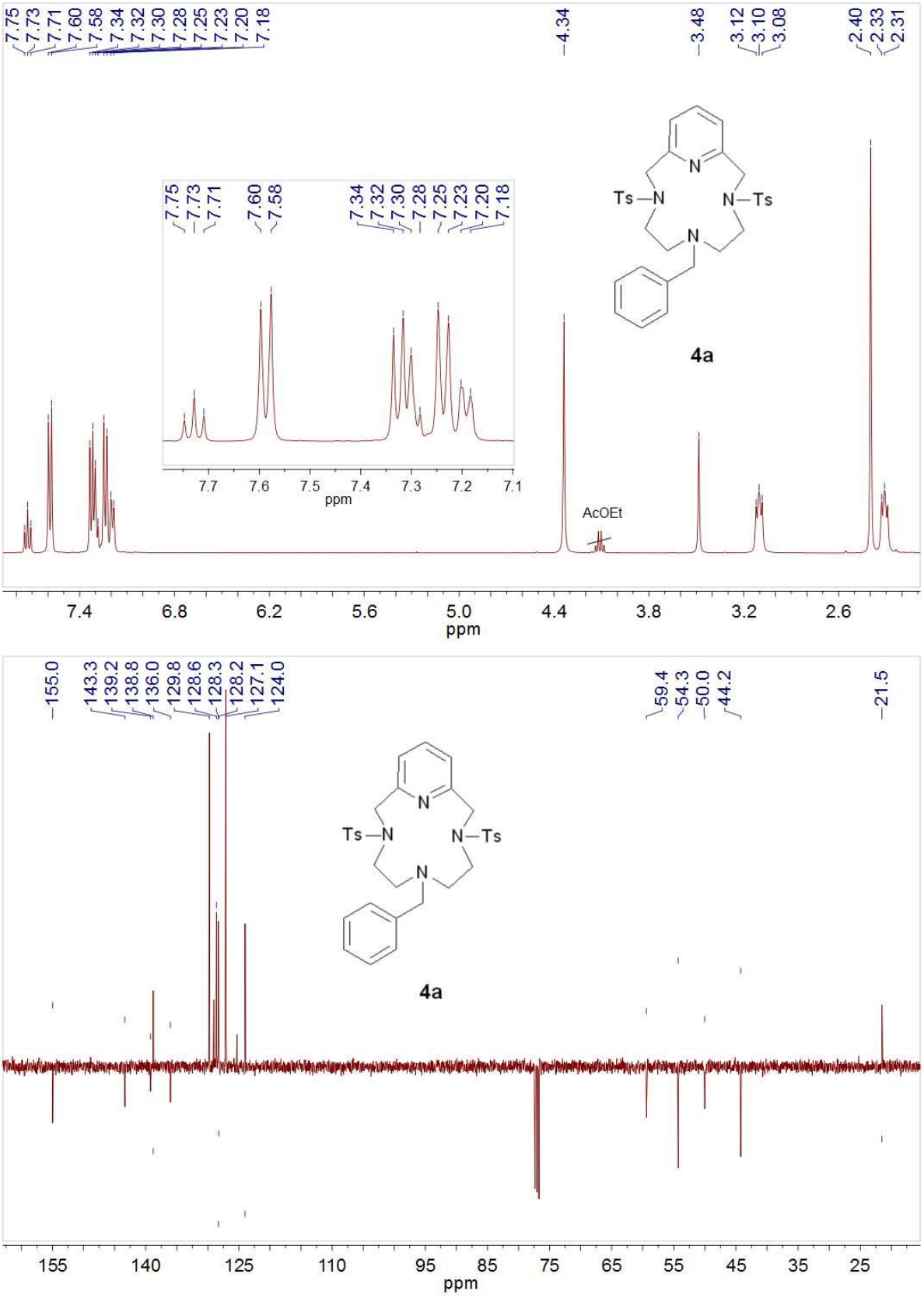

8.03
8.00
7.87
7.84
7.81
7.78
7.54
7.48
7.46
7.26
4.91
4.89
4.87
4.85
4.68
3.56
2.78
2.77
2.74
2.72
2.63
1.72
1.69
1.68
1.58
1.56
0.89
0.87
0.32
0.30
3i-(1R,2S,2'S)
H
N
Tf
(S)
(R)
N
H
N
Tf
(S)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

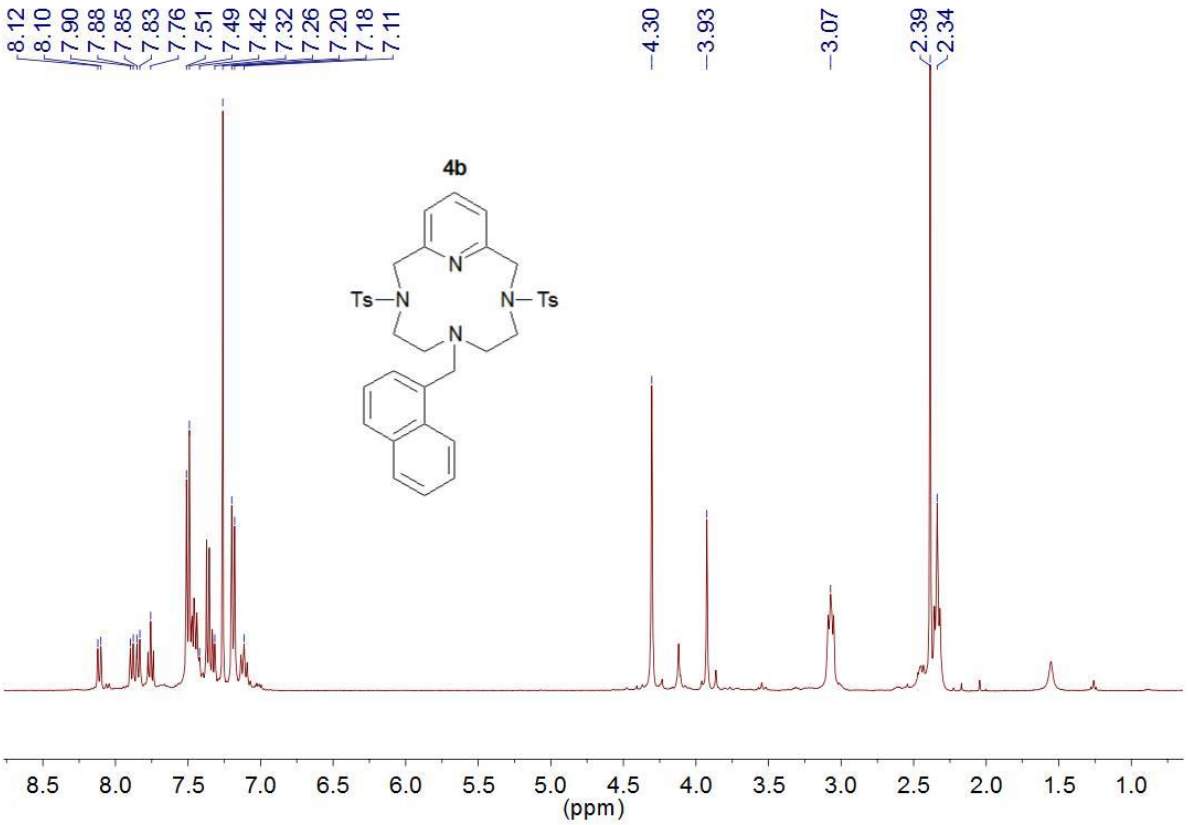

137.4
134.3
132.1
129.1
128.7
125.9
125.8
125.3
125.1
123.5
121.8
117.5
59.2
53.9
53.2
27.7
19.5
14.6
12.4
3i-(1R,2S,2'S)
H
N
Tf
(S)
(R)
N
H
N
Tf
(S)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

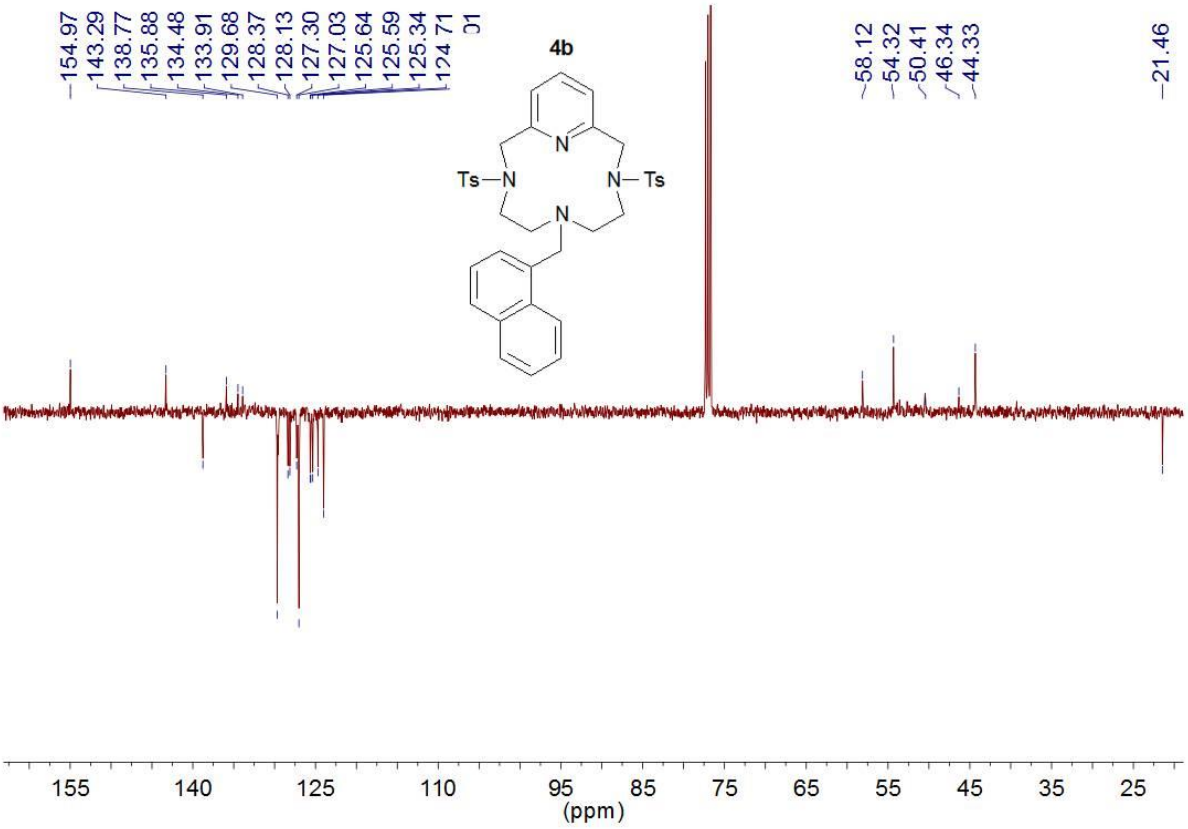

8.09
8.07
7.85
7.76
7.72
7.69
7.60
7.57
7.52
7.43
7.41
7.28
7.24
4.82
4.64
4.62
4.32
4.29
3.14
3.13
2.84
2.82
2.70
2.47
2.45
2.42
2.41
1.41
1.39
0.45
0.43
0.19
0.16
3l-(1R,2S)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

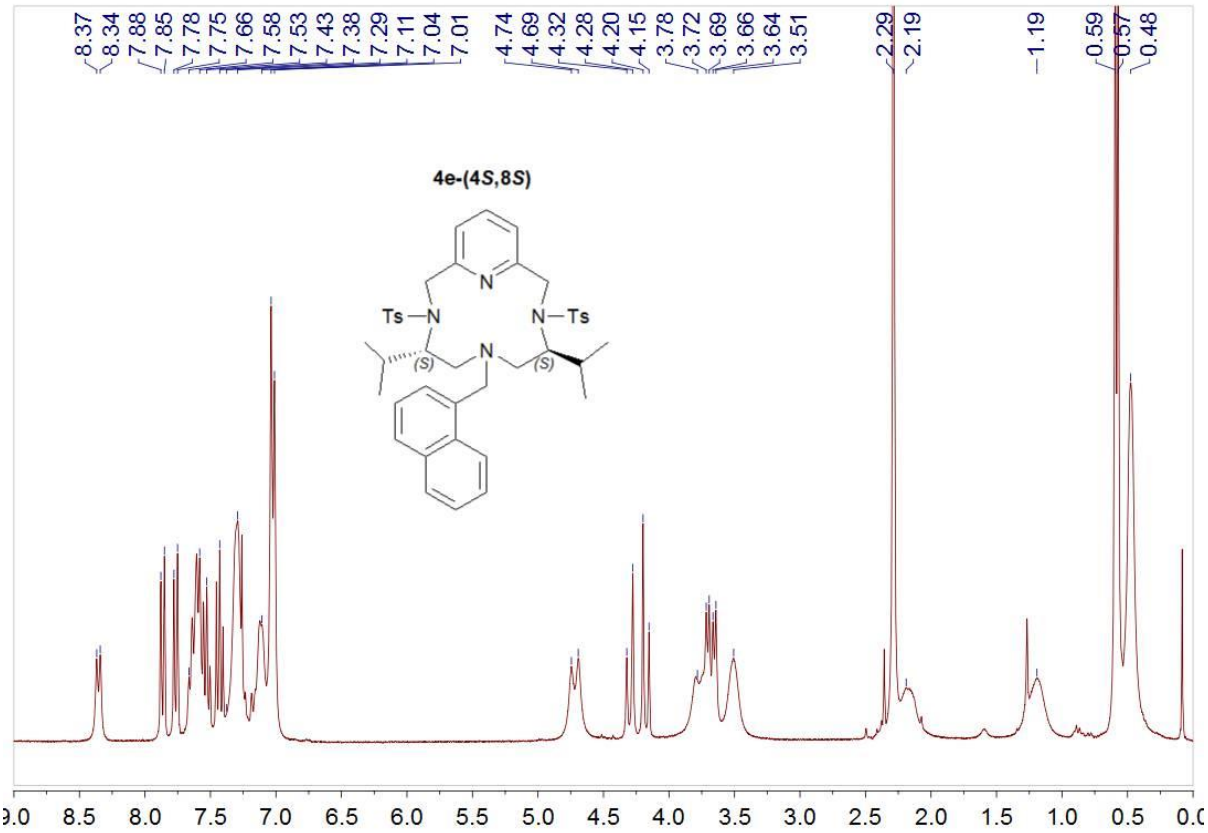

143.51
143.25
138.29
137.21
134.16
131.88
129.78
129.73
129.12
128.39
127.31
127.19
126.36
125.89
125.20
124.87
123.57
57.39
55.68
53.54
51.41
41.64
28.43
21.67
18.59
15.55
14.01
3l-(1R,2S)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

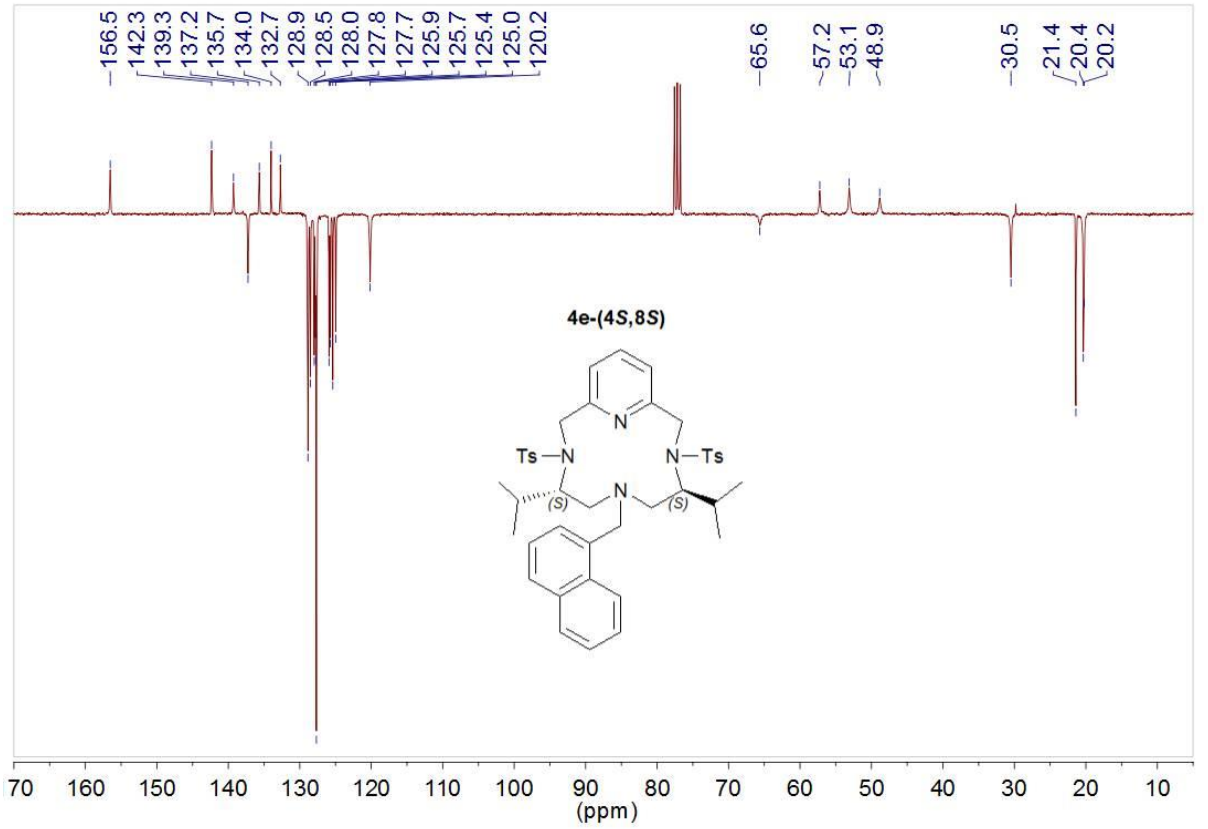
3.10.2 Ligands

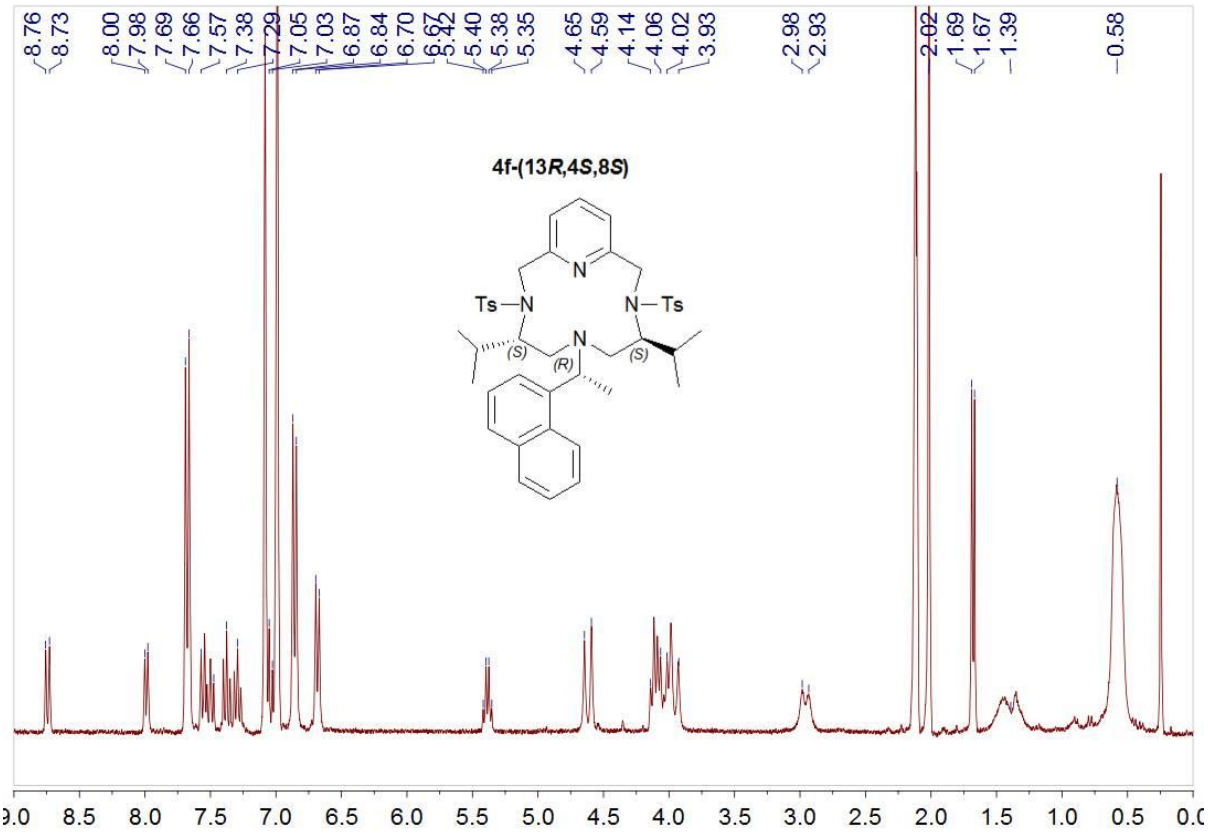


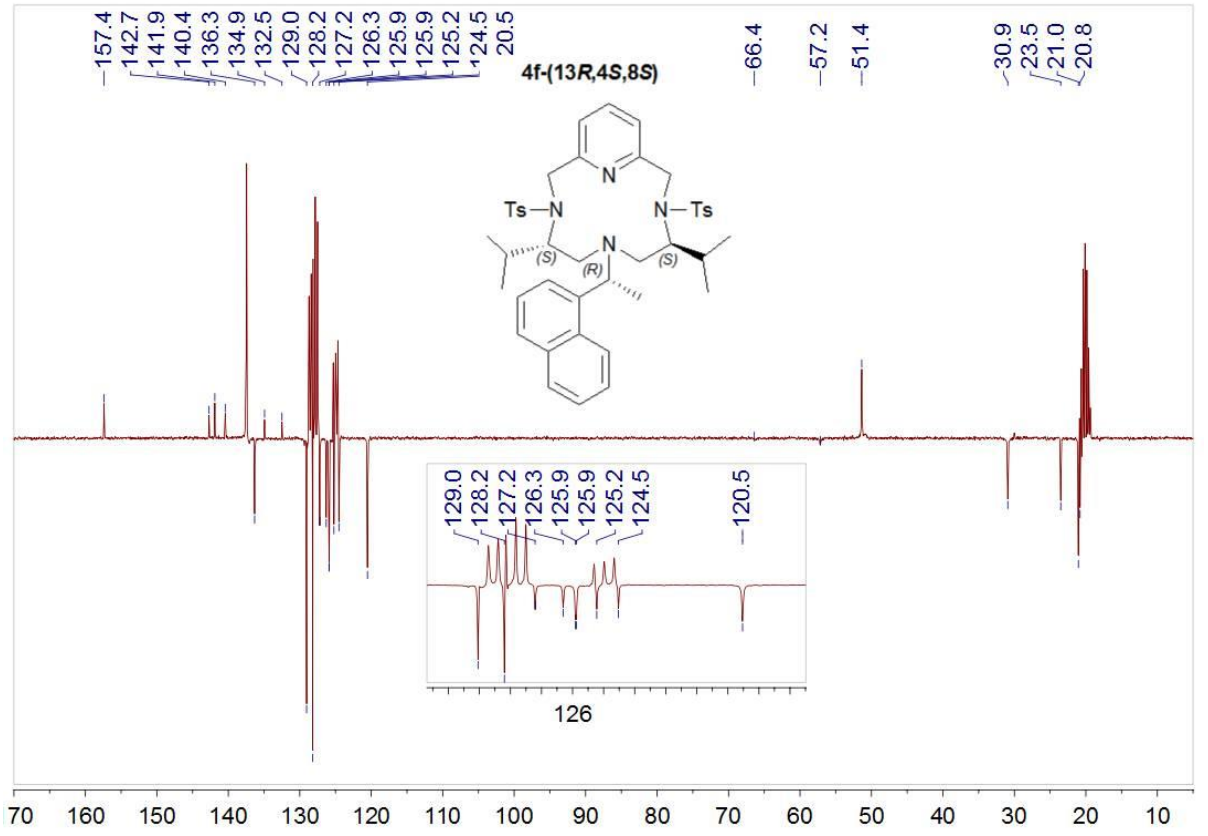

8.12
8.10
7.90
7.88
7.85
7.83
7.76
7.51
7.49
7.42
7.32
7.26
7.20
7.18
7.11
4.30
3.93
3.07
2.39
2.34
4b
Ts—N
N—Ts
N
N
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

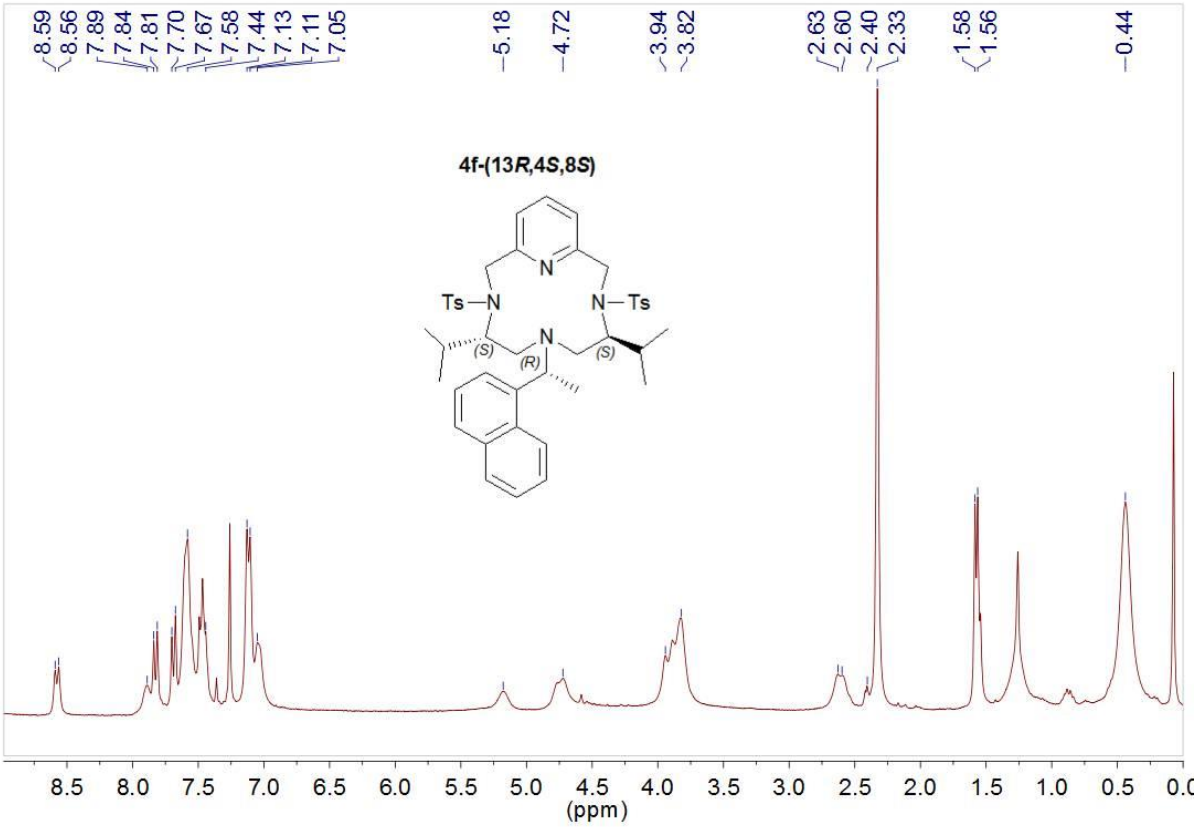

154.97
143.29
138.77
135.88
134.48
133.91
129.68
128.37
128.13
127.30
127.03
125.64
125.59
125.34
124.71
58.12
54.32
50.41
46.34
44.33
21.46
4b
Ts—N
N—Ts
N
N
155
140
125
110
95
85
75
65
55
45
35
25
(ppm)

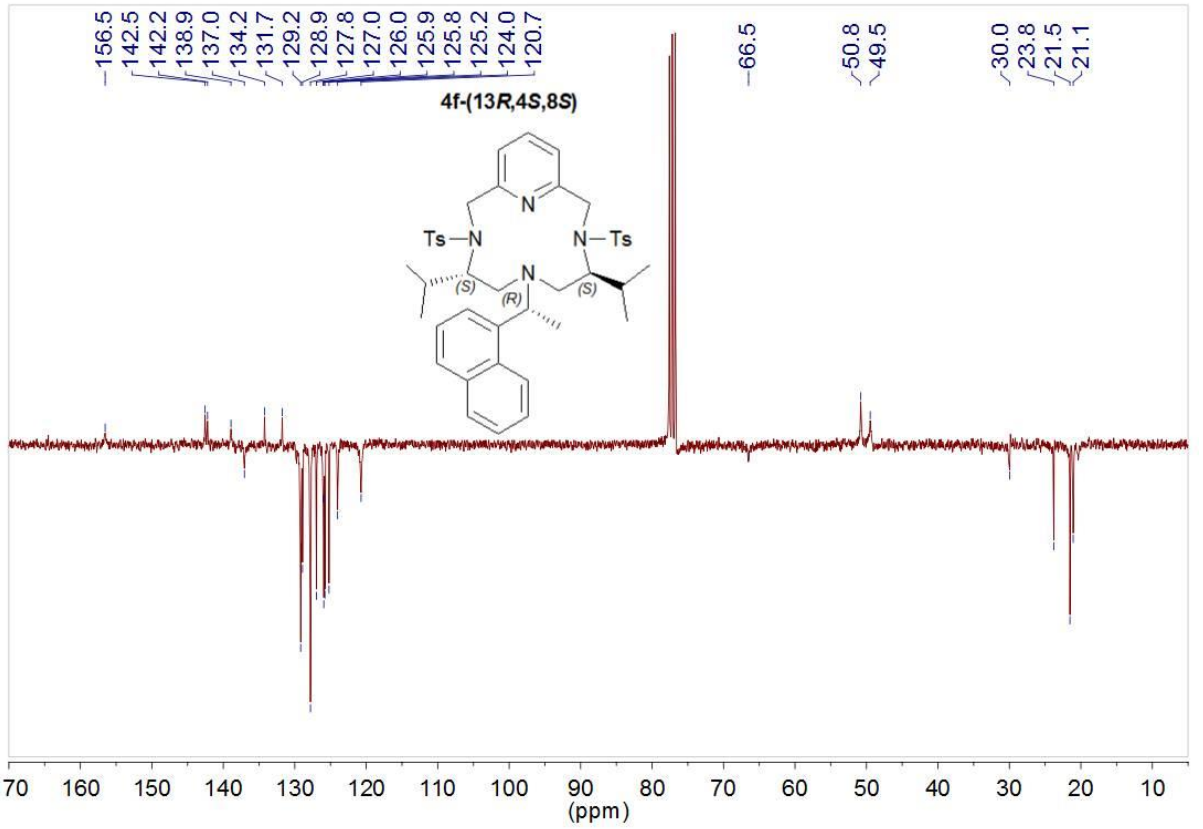

8.37
8.34
7.88
7.85
7.78
7.75
7.66
7.58
7.53
7.43
7.38
7.29
7.11
7.04
7.01
4.74
4.69
4.32
4.28
4.20
4.15
3.78
3.72
3.69
3.66
3.64
3.51
2.29
2.19
1.19
0.59
0.57
0.48
4e-(4S,8S)
Ts—N
N—Ts
N
(S)
(S)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

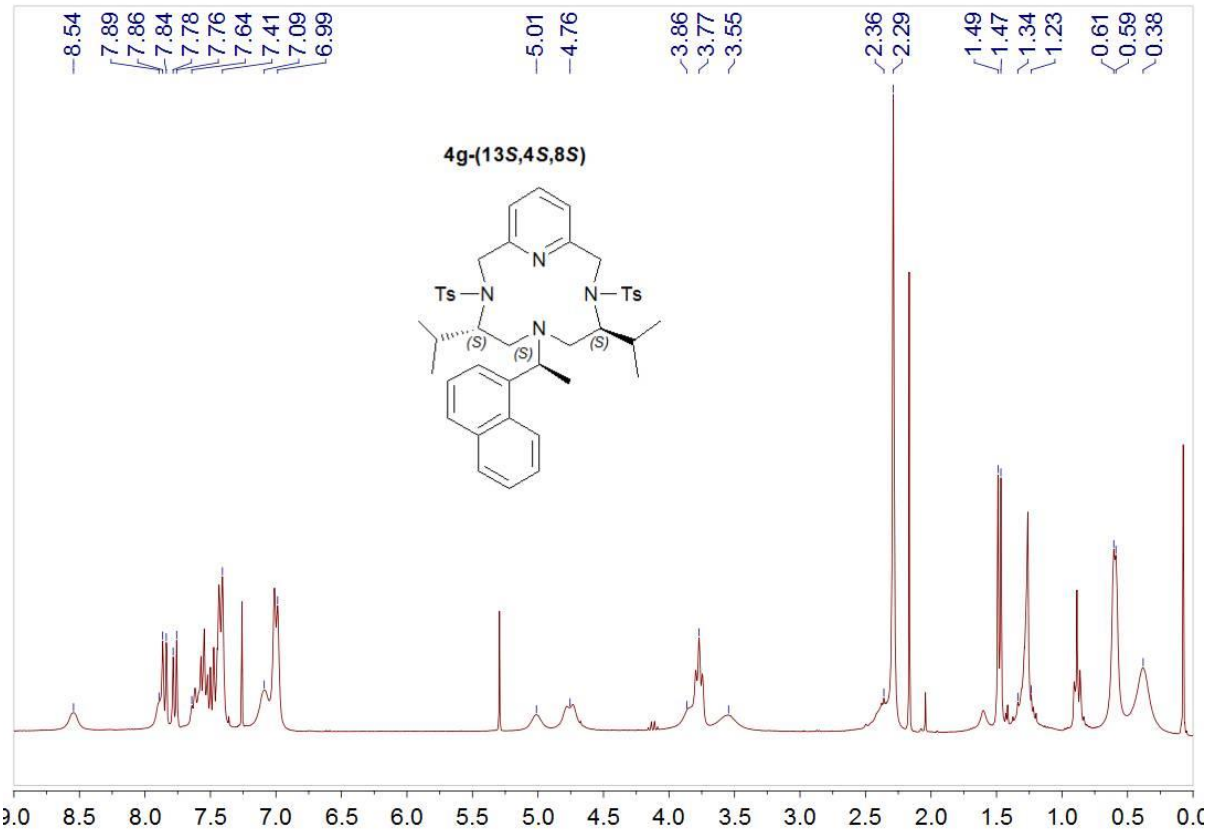

156.5
142.3
139.3
137.2
135.7
134.0
132.7
128.9
128.5
128.0
127.8
127.7
125.9
125.7
125.4
125.0
120.2
65.6
57.2
53.1
48.9
30.5
21.4
20.4
20.2
4e-(4S,8S)
Ts—N
N—Ts
N
(S)
(S)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

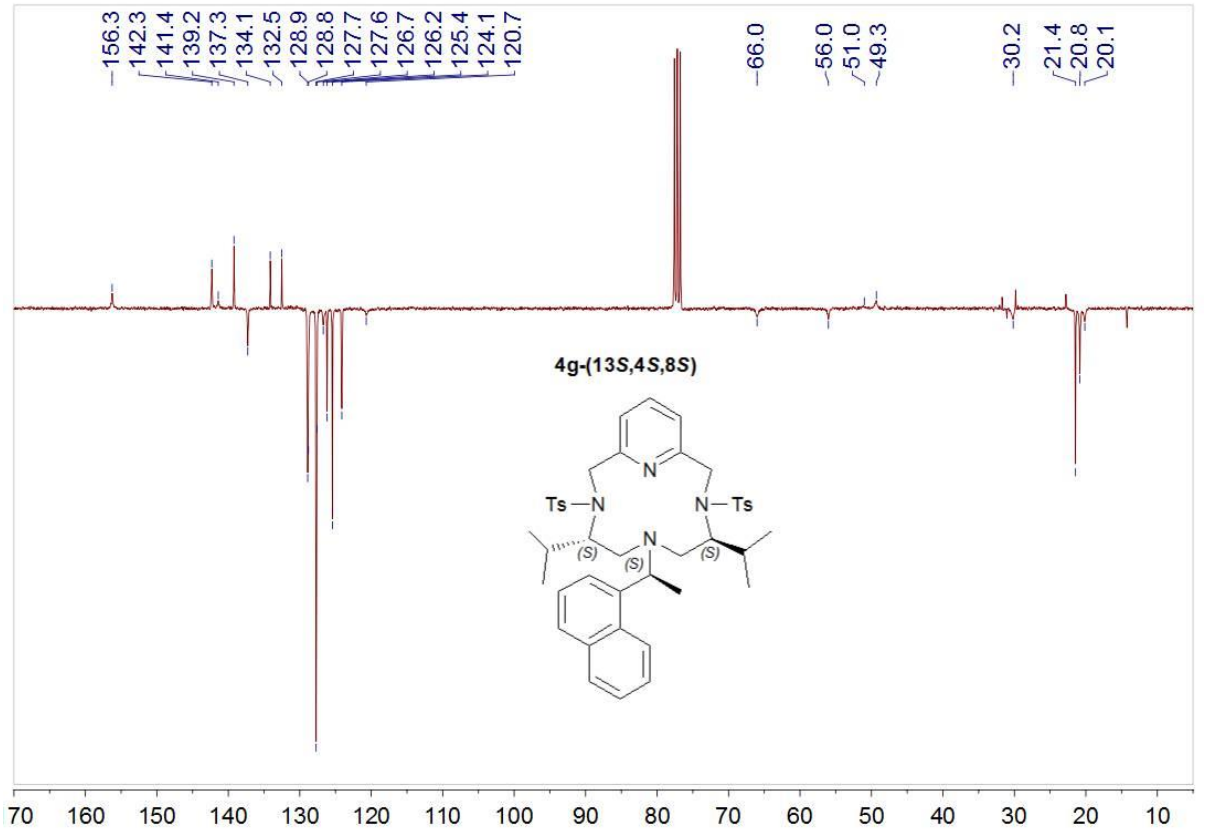

8.76
8.73
8.00
7.98
7.69
7.66
7.57
7.38
7.29
7.05
7.03
6.87
6.84
6.70
6.67
6.42
5.40
5.38
5.35
4.65
4.59
4.14
4.06
4.02
3.93
2.98
2.93
2.02
1.69
1.67
1.39
0.58
4f-(13R,4S,8S)
Ts—N
N—Ts
N
(S)
(R)
(S)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

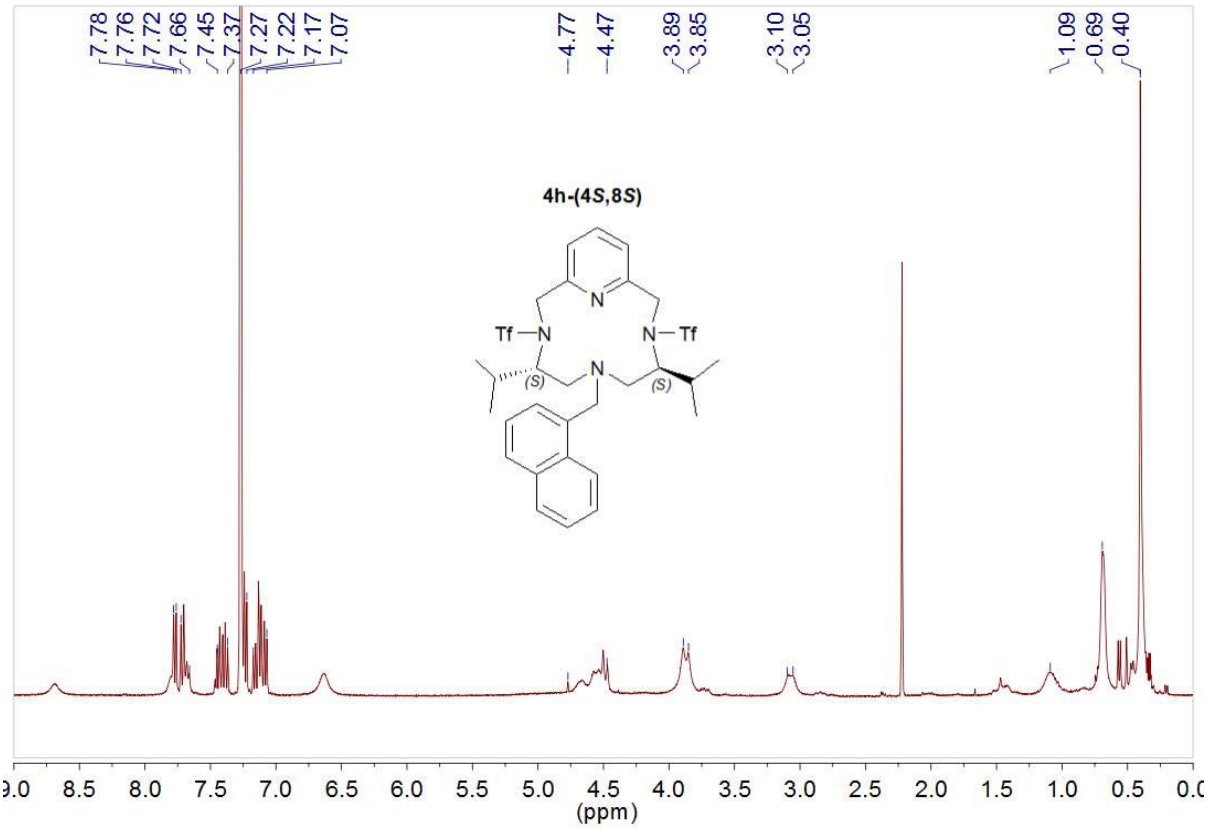

157.4
142.7
141.9
140.4
136.3
134.9
132.5
129.0
128.2
127.2
126.3
125.9
125.9
125.2
124.5
20.5
66.4
57.2
51.4
30.9
23.5
21.0
20.8
4f-(13R,4S,8S)
Ts—N
N—Ts
N
(S)
(R)
(S)
129.0
128.2
127.2
126.3
125.9
125.9
125.2
124.5
120.5
126
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

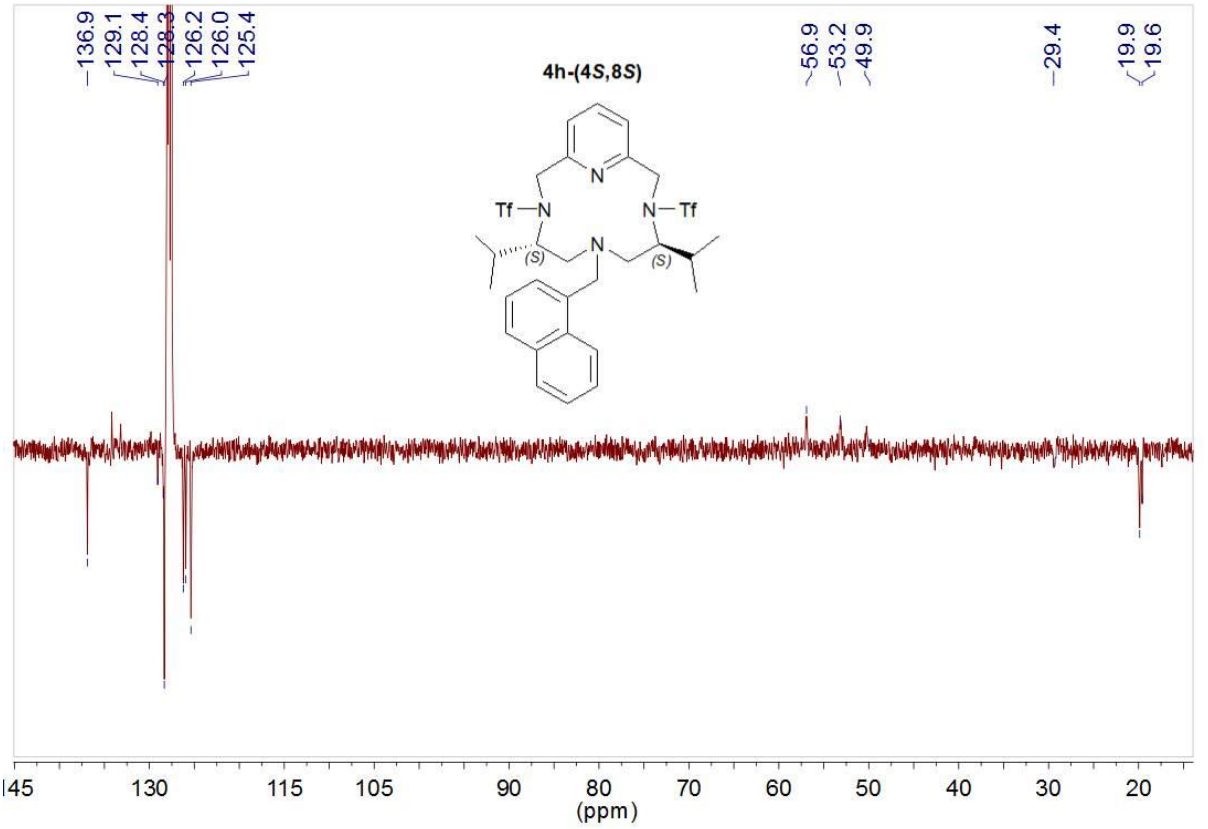

8.59
8.56
7.89
7.84
7.81
7.70
7.67
7.58
7.44
7.13
7.11
7.05
5.18
4.72
3.94
3.82
2.63
2.60
2.40
2.33
1.58
1.56
0.44
4f-(13R,4S,8S)
Ts—N
N—Ts
N
(S)
(R)
(S)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

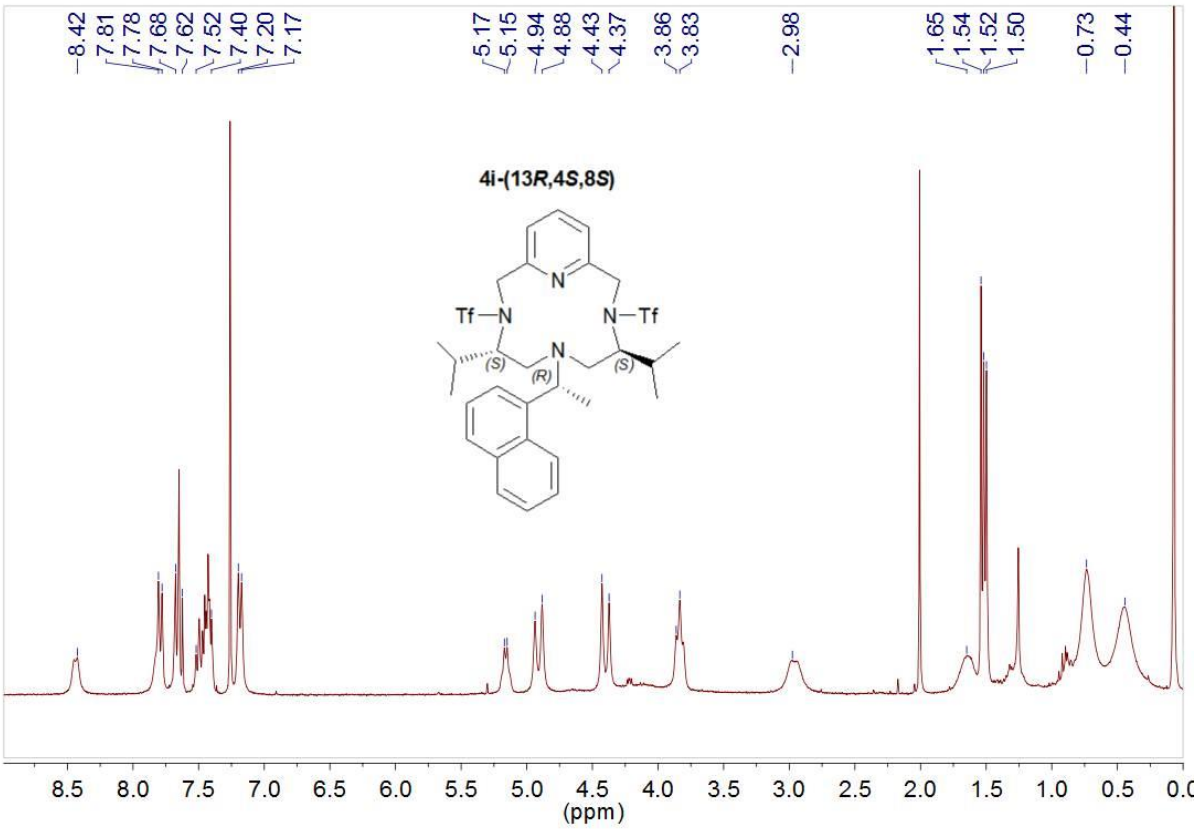

156.5
142.5
142.2
138.9
137.0
134.2
131.7
129.2
128.9
127.8
127.0
126.0
125.9
125.8
125.2
124.0
120.7
66.5
50.8
49.5
30.0
23.8
21.5
21.1
4f-(13R,4S,8S)
Ts—N
N—Ts
N
(S)
(R)
(S)
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

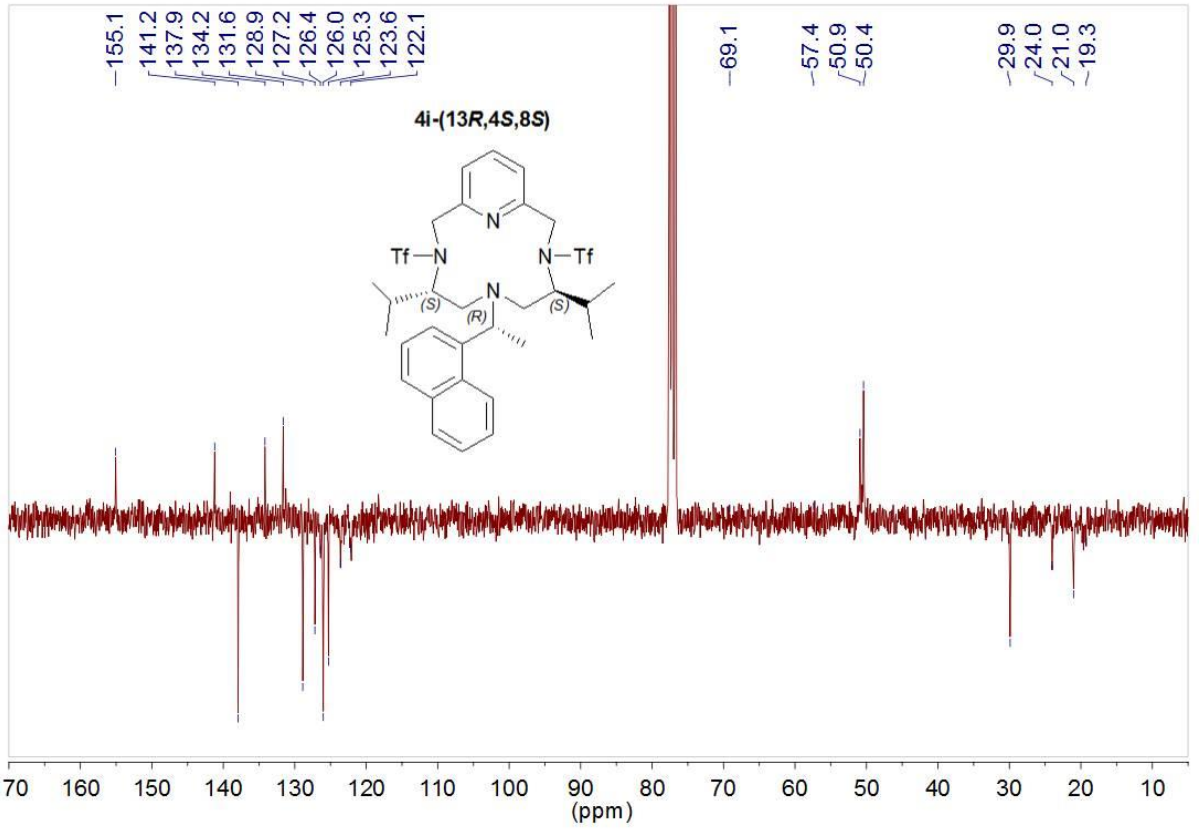

8.54
7.89
7.86
7.84
7.78
7.76
7.64
7.41
7.09
6.99
5.01
4.76
3.86
3.77
3.55
2.36
2.29
1.49
1.47
1.34
1.23
0.61
0.59
0.38
4g-(13S,4S,8S)
Ts—N
N—Ts
N
(S)
(S)
(S)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

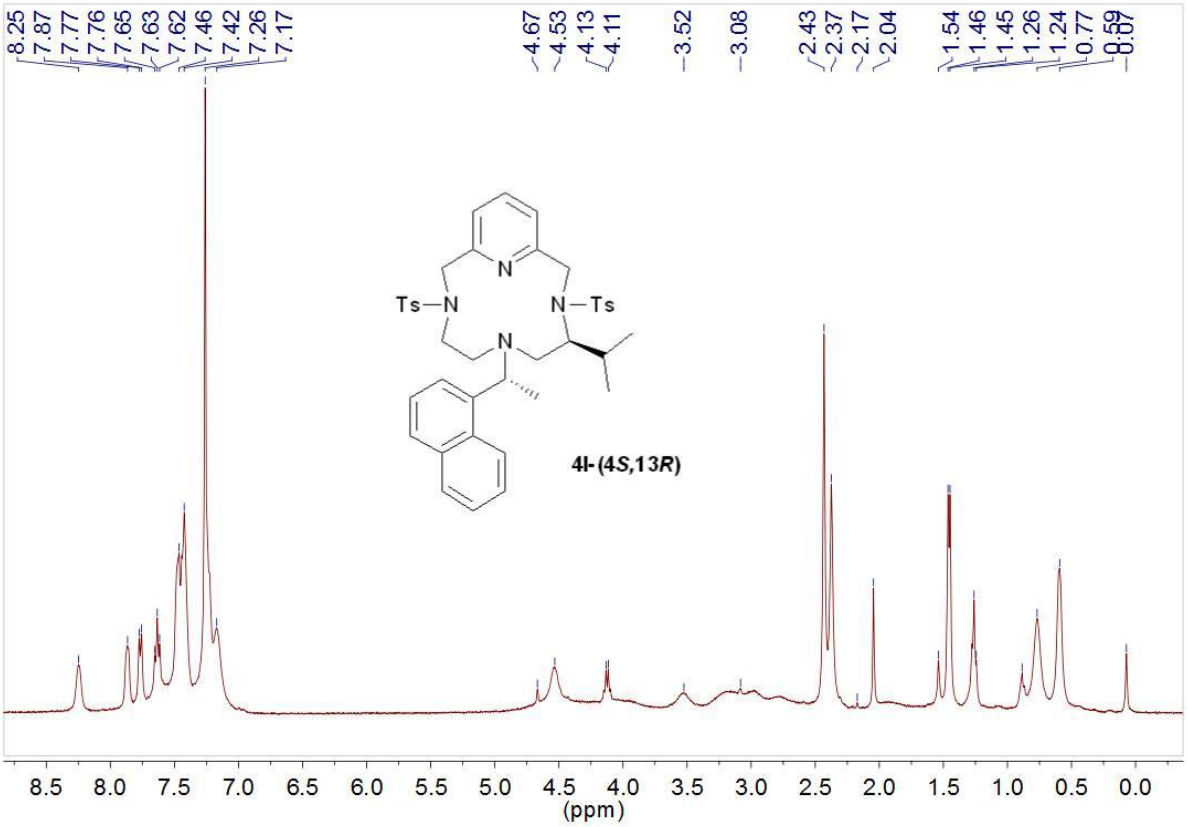

156.3
142.3
141.4
139.2
137.3
134.1
132.5
128.9
128.8
127.7
127.6
126.7
126.2
125.4
124.1
120.7
66.0
56.0
51.0
49.3
30.2
21.4
20.8
20.1
4g-(13S,4S,8S)
Ts—N
N—Ts
N
(S)
(S)
(S)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

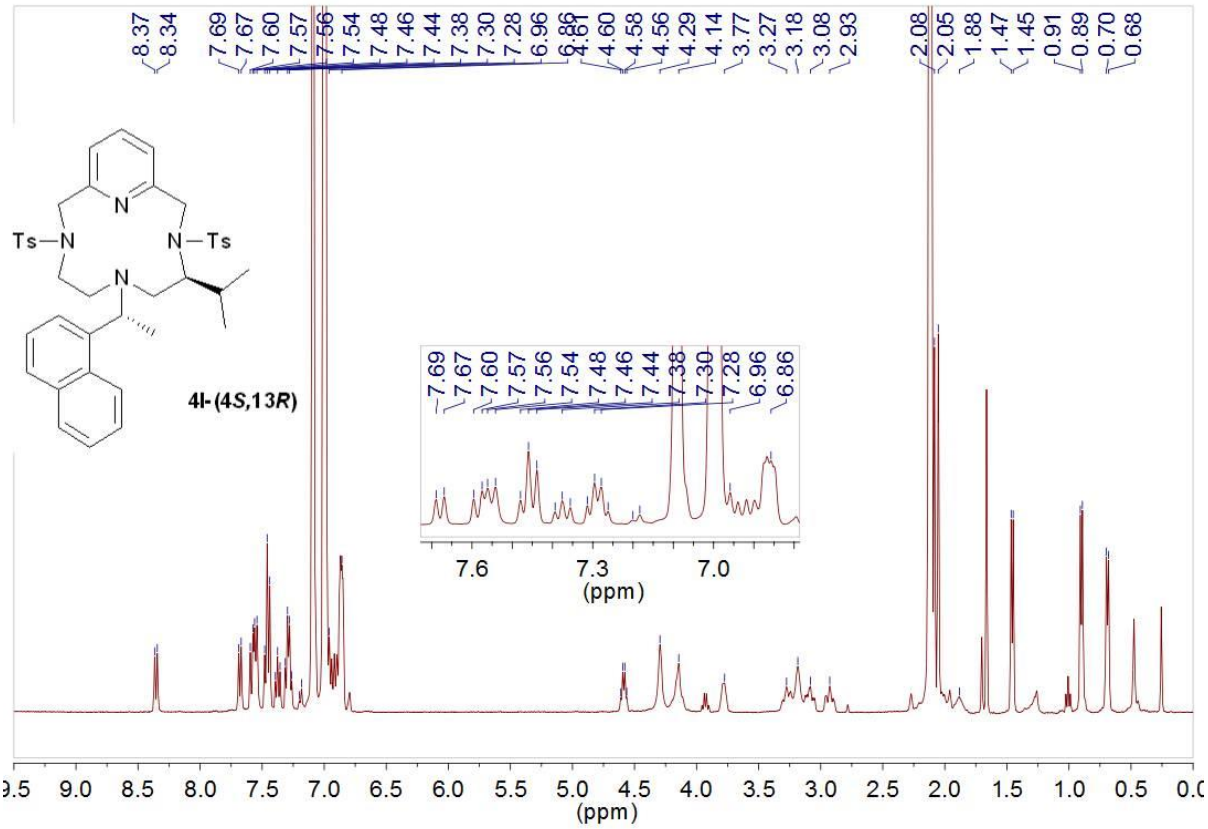

7.78
7.76
7.72
7.66
7.45
7.37
7.27
7.22
7.17
7.07
4.77
4.47
3.89
3.85
3.10
3.05
1.09
0.69
0.40
4h-(4S,8S)
Tf—N
N—Tf
N
(S)
(S)
(ppm)

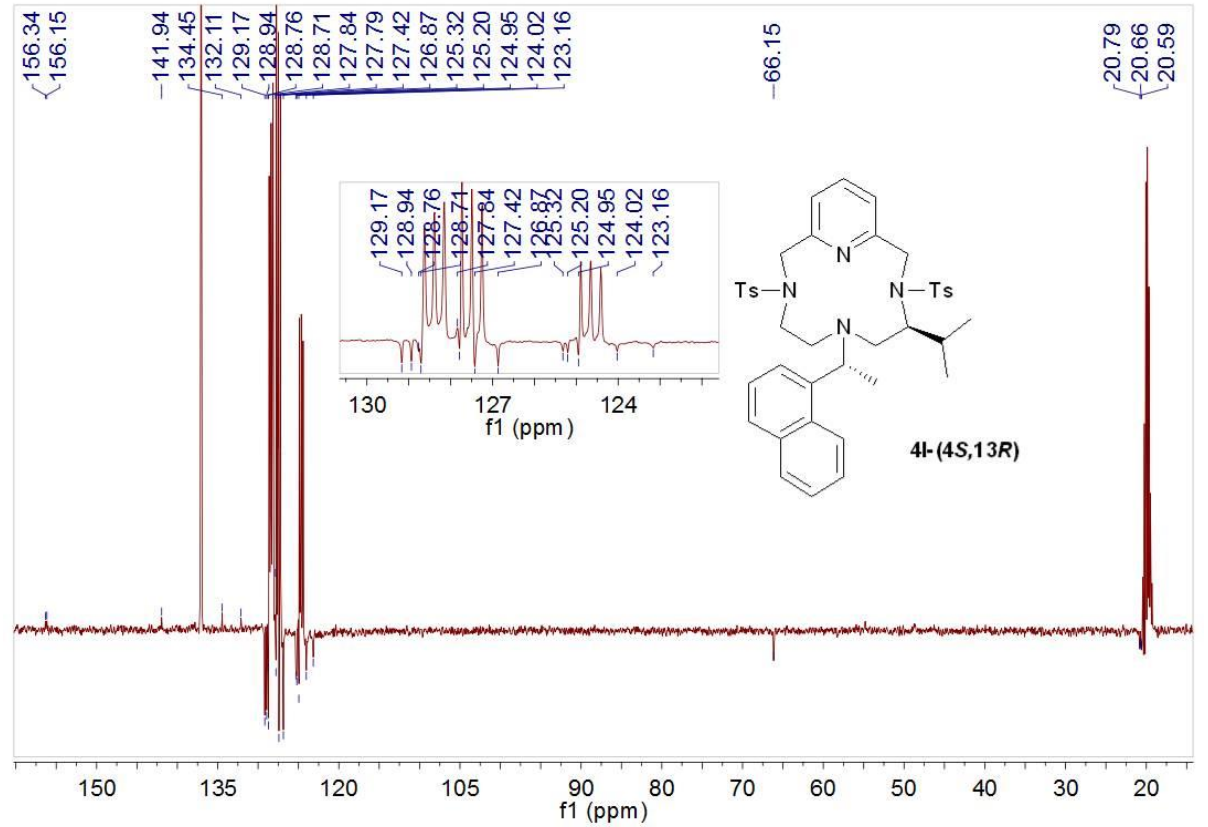

136.9
129.1
128.4
128.3
126.2
126.0
125.4
56.9
53.2
49.9
29.4
19.9
19.6
4h-(4S,8S)
Tf—N
N—Tf
N
(S)
(S)
(ppm)

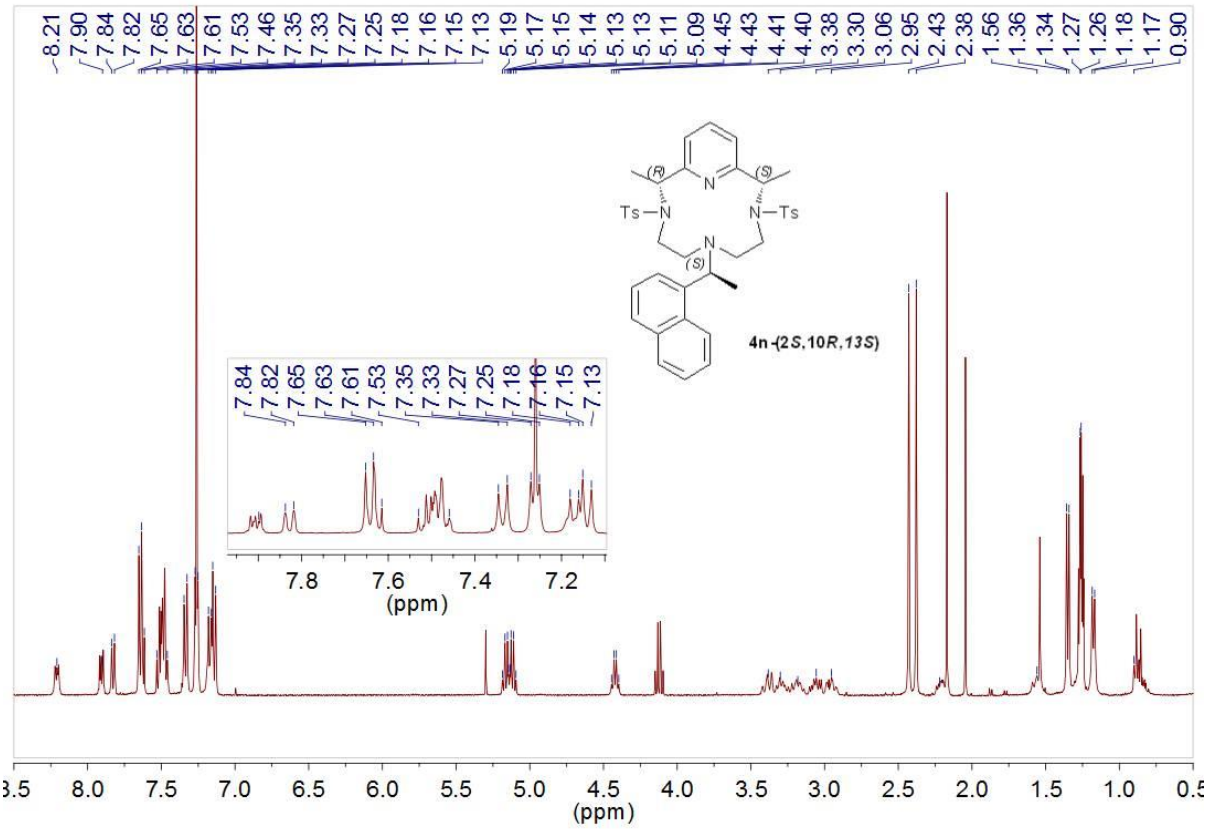

8.42
7.81
7.78
7.68
7.62
7.52
7.40
7.20
7.17
5.17
5.15
4.94
4.88
4.43
4.37
3.86
3.83
2.98
1.65
1.54
1.52
1.50
0.73
0.44
4i-(13R,4S,8S)
Tf—N
N—Tf
N
(S)
(R)
(S)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

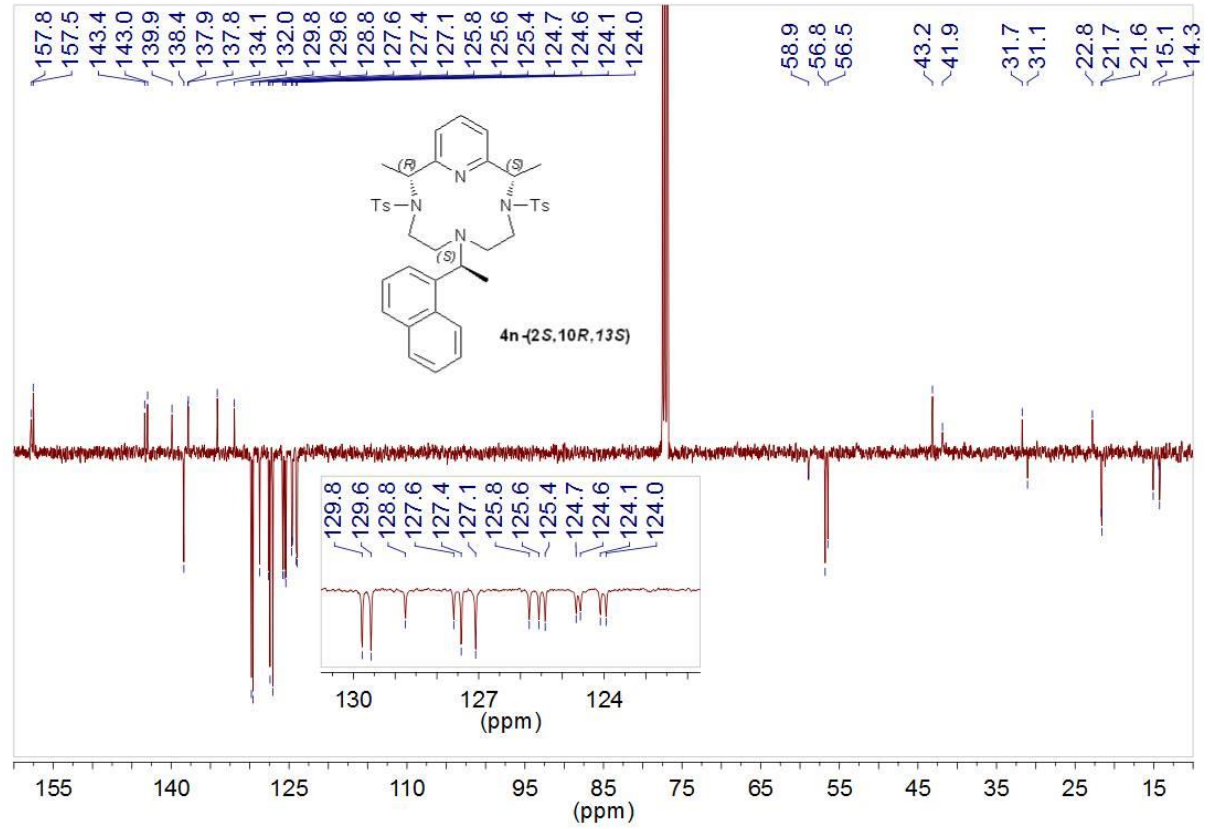

155.1
141.2
137.9
134.2
131.6
128.9
127.2
126.4
126.0
125.3
123.6
122.1
69.1
57.4
50.9
50.4
29.9
24.0
21.0
19.3
4i-(13R,4S,8S)
Tf—N
N—Tf
N
(S)
(R)
(S)
70 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
(ppm)

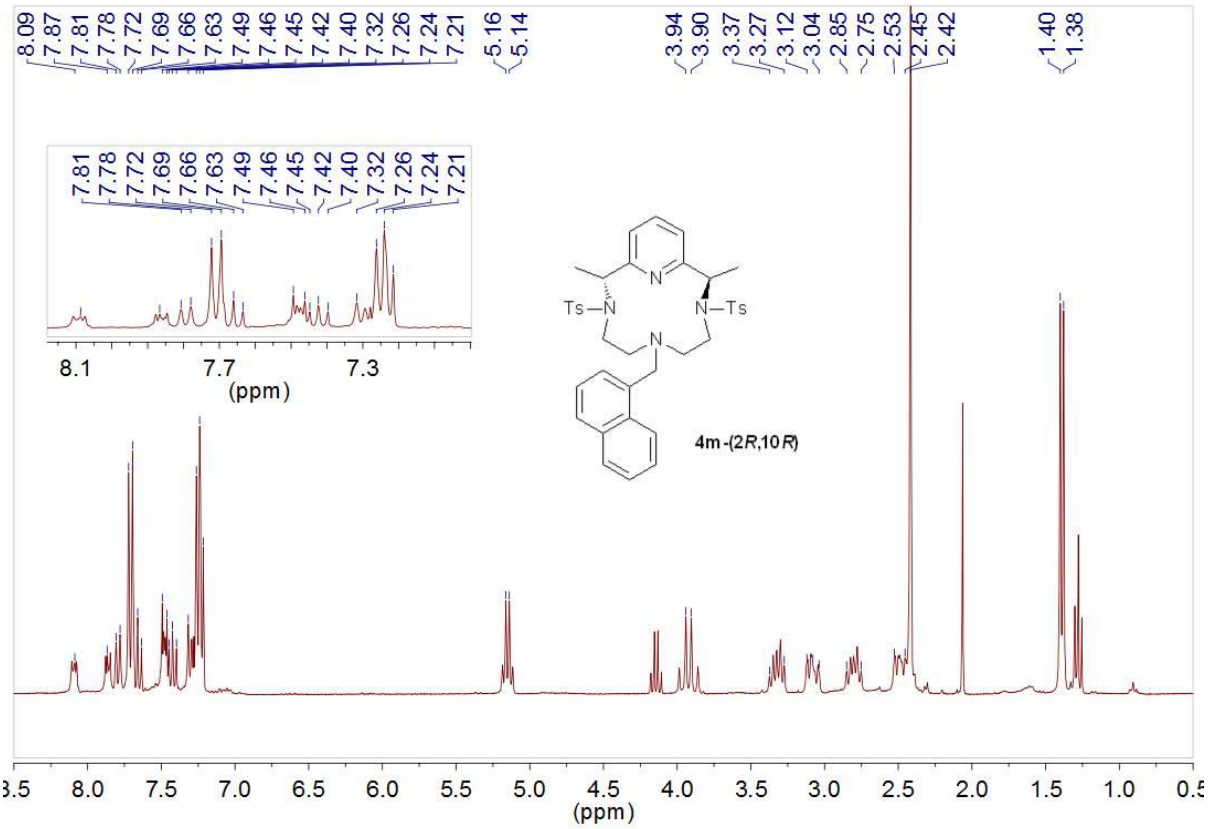

8.25
7.87
7.77
7.76
7.65
7.63
7.62
7.46
7.42
7.26
7.17
4.67
4.53
4.13
4.11
3.52
3.08
2.43
2.37
2.17
2.04
1.54
1.46
1.45
1.26
1.24
0.77
0.59
0.07
Ts—N
N—Ts
N
N
4l-(4S,13R)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

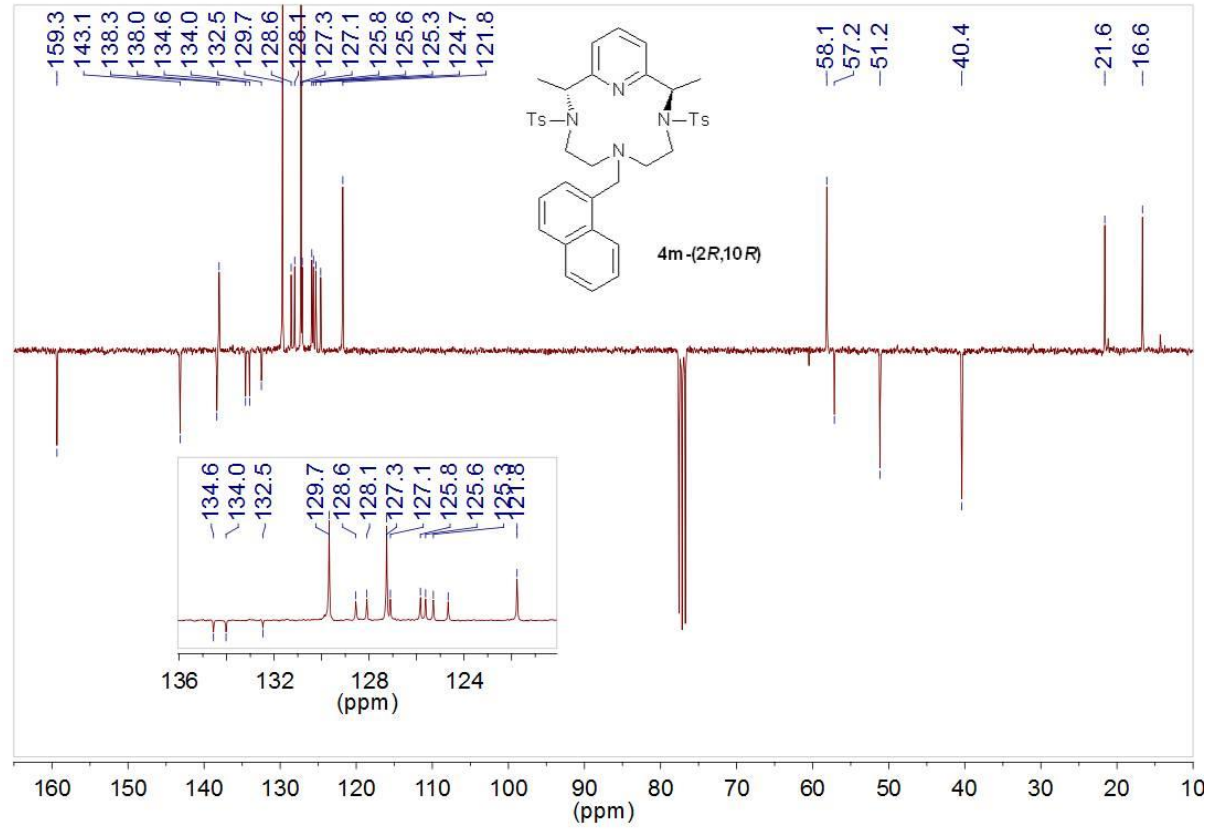

8.37
8.34
7.69
7.67
7.60
7.57
7.56
7.54
7.48
7.46
7.44
7.38
7.30
7.28
6.96
6.86
4.60
4.58
4.56
4.29
4.14
3.77
3.27
3.18
3.08
2.93
2.08
2.05
1.88
1.47
1.45
0.91
0.89
0.70
0.68
Ts—N
N—Ts
N
N
4l-(4S,13R)
7.6
7.3
7.0
(ppm)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)

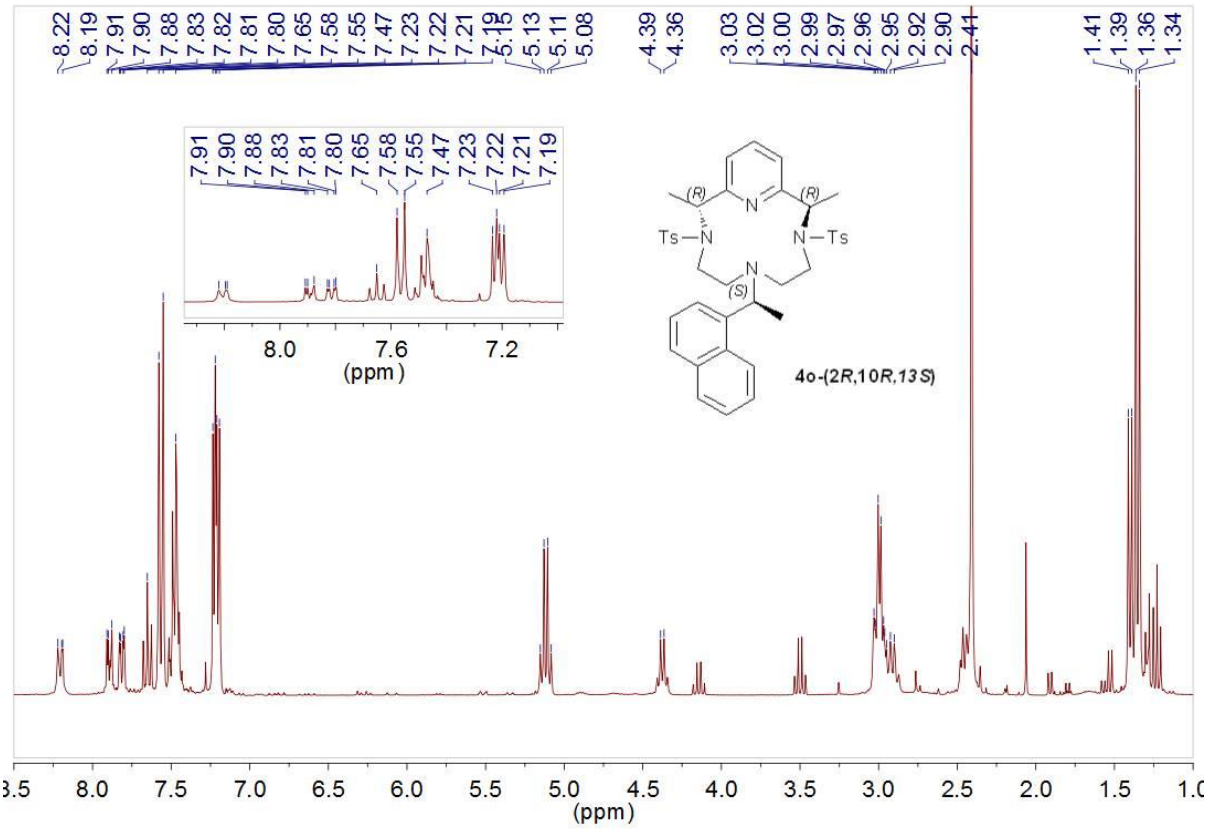

156.34
156.15
141.94
134.45
132.11
129.17
128.94
128.76
128.71
127.84
127.79
127.42
126.87
125.32
125.20
124.95
124.02
123.16
66.15
20.79
20.66
20.59
Ts—N
N—Ts
N
N
4l-(4S,13R)
130
127
124
f1 (ppm)
150 135 120 105 90 80 70 60 50 40 30 20
f1 (ppm)

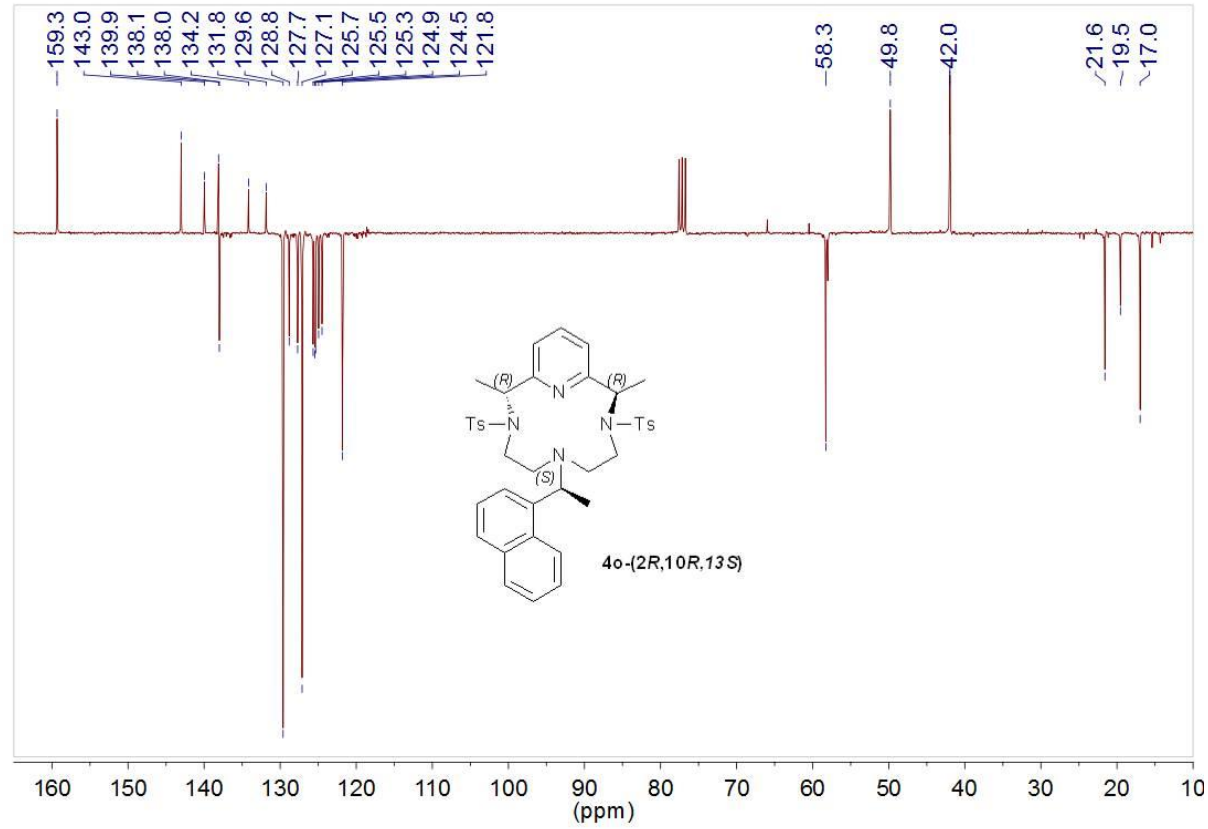

8.21
7.90
7.84
7.82
7.65
7.63
7.61
7.53
7.46
7.35
7.33
7.27
7.25
7.18
7.16
7.15
7.13
5.19
5.17
5.15
5.14
5.13
5.13
5.11
5.09
4.45
4.43
4.41
4.40
4.38
3.30
3.06
2.95
2.43
2.38
1.56
1.36
1.34
1.27
1.26
1.18
1.17
0.90
4n-(2S,10R,13S)
7.8
7.6
7.4
7.2
(ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
(ppm)

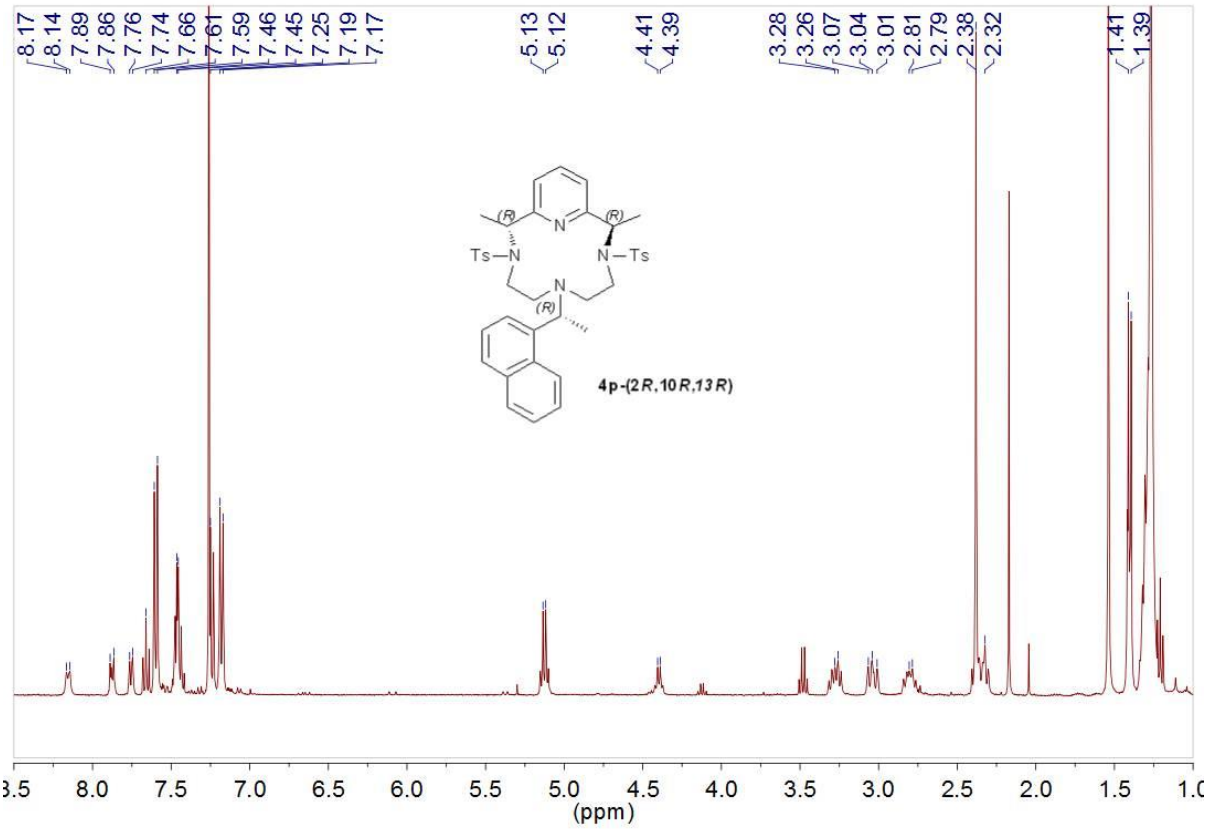

157.8
157.5
143.4
143.0
139.9
138.4
137.9
137.8
134.1
132.0
129.8
129.6
128.8
127.6
127.4
127.1
125.8
125.6
125.4
124.7
124.6
124.1
124.0
58.9
56.8
56.5
43.2
41.9
31.7
31.1
22.8
21.7
21.6
15.1
14.3
4n-(2S,10R,13S)
130
127
124
(ppm)
155
140
125
110
95
85
75
65
55
45
35
25
15
(ppm)

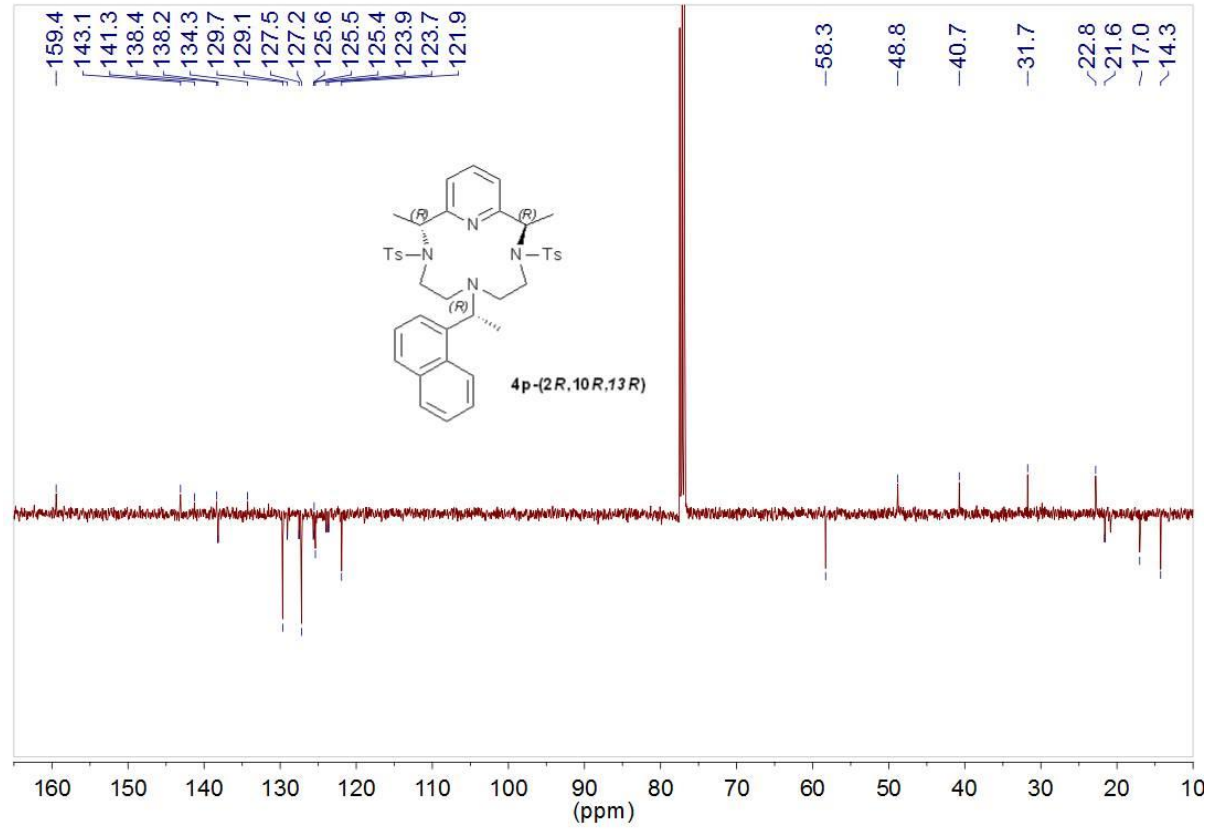

8.09
7.87
7.81
7.78
7.72
7.69
7.66
7.63
7.49
7.46
7.45
7.42
7.40
7.32
7.26
7.24
7.21
5.16
5.14
3.94
3.90
3.37
3.27
3.12
3.04
2.85
2.75
2.53
2.45
2.42
1.40
1.38
8.1
7.7
7.3
(ppm)
Ts—N
N—Ts
N
4m-(2R,10R)
3.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


159.3
143.1
138.3
138.0
134.6
134.0
132.5
129.7
128.6
128.1
127.3
127.1
125.8
125.6
125.3
124.7
121.8
58.1
57.2
51.2
40.4
21.6
16.6
Ts—N
N—Ts
N
4m-(2R,10R)
136
132
128
124
(ppm)
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)

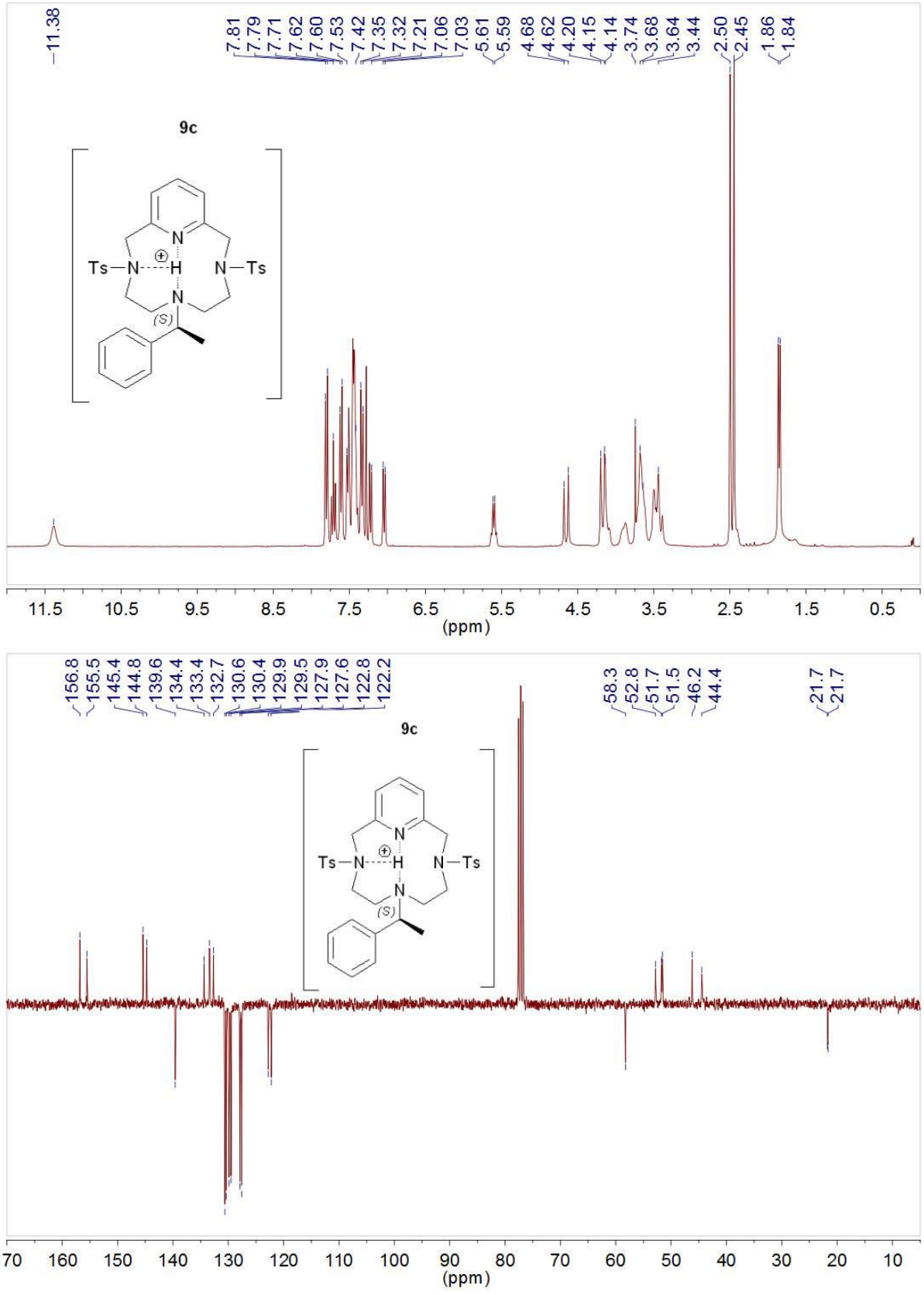

8.22
8.19
7.91
7.90
7.88
7.83
7.82
7.81
7.80
7.65
7.58
7.55
7.47
7.23
7.22
7.21
7.19
5.15
5.13
5.11
5.08
4.39
4.36
3.03
3.02
3.00
2.99
2.97
2.96
2.95
2.92
2.90
2.41
1.41
1.39
1.36
1.34
8.0
7.6
7.2
(ppm)
Ts
N
(R)
(S)
4o-(2R,10R,13S)
(ppm)

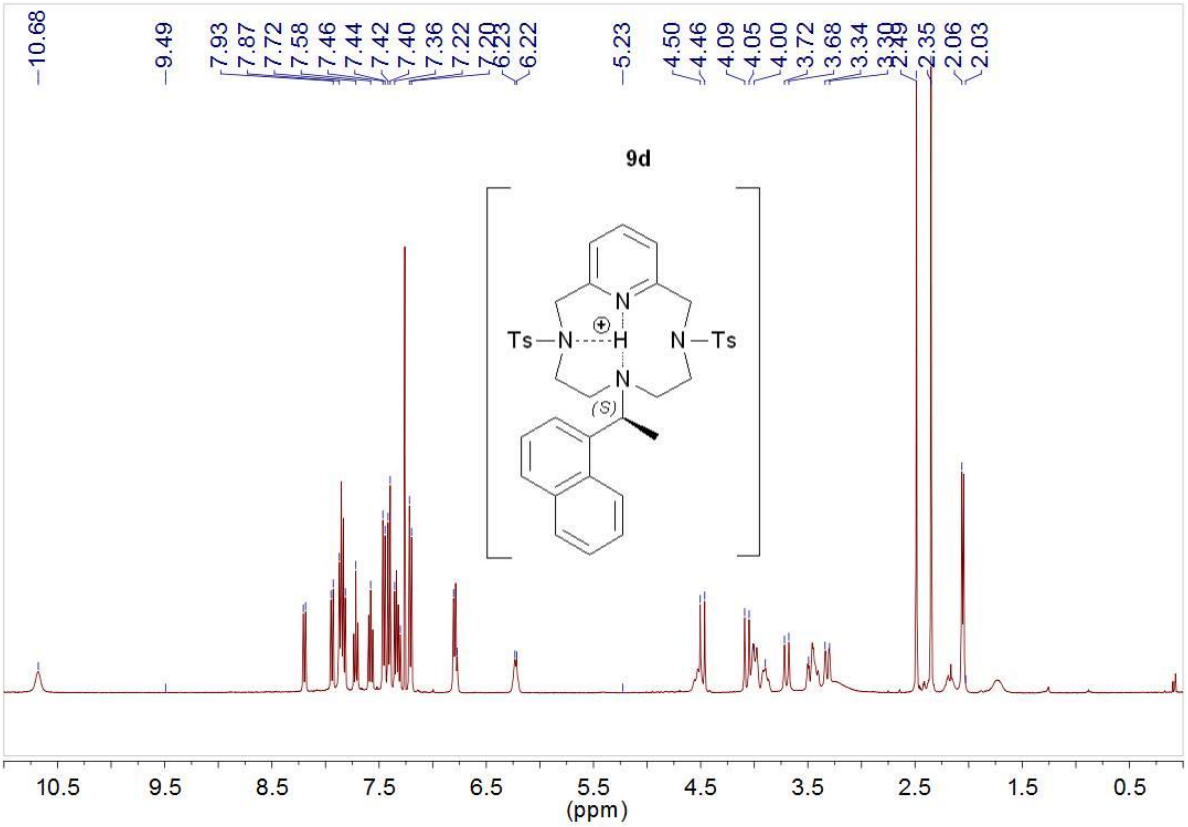

159.3
143.0
139.9
138.1
138.0
134.2
131.8
129.6
128.8
127.7
127.1
125.7
125.5
125.3
124.9
124.5
121.8
58.3
49.8
42.0
21.6
19.5
17.0
Ts
N
(R)
(S)
4o-(2R,10R,13S)
(ppm)

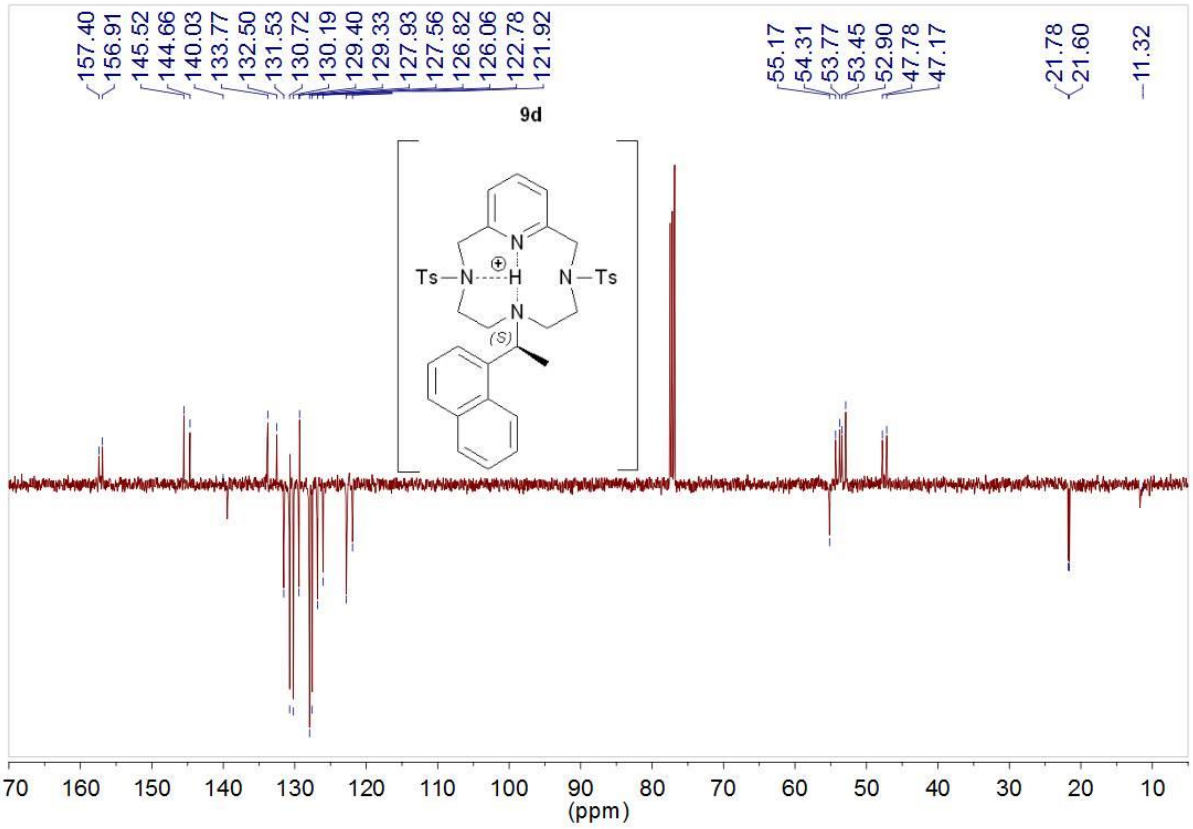

8.17
8.14
7.89
7.86
7.76
7.74
7.66
7.61
7.59
7.46
7.45
7.25
7.19
7.17
5.13
5.12
4.41
4.39
3.28
3.26
3.07
3.04
3.01
2.81
2.79
2.38
2.32
1.41
1.39
Ts—N
N—Ts
4p-(2R,10R,13R)
(ppm)

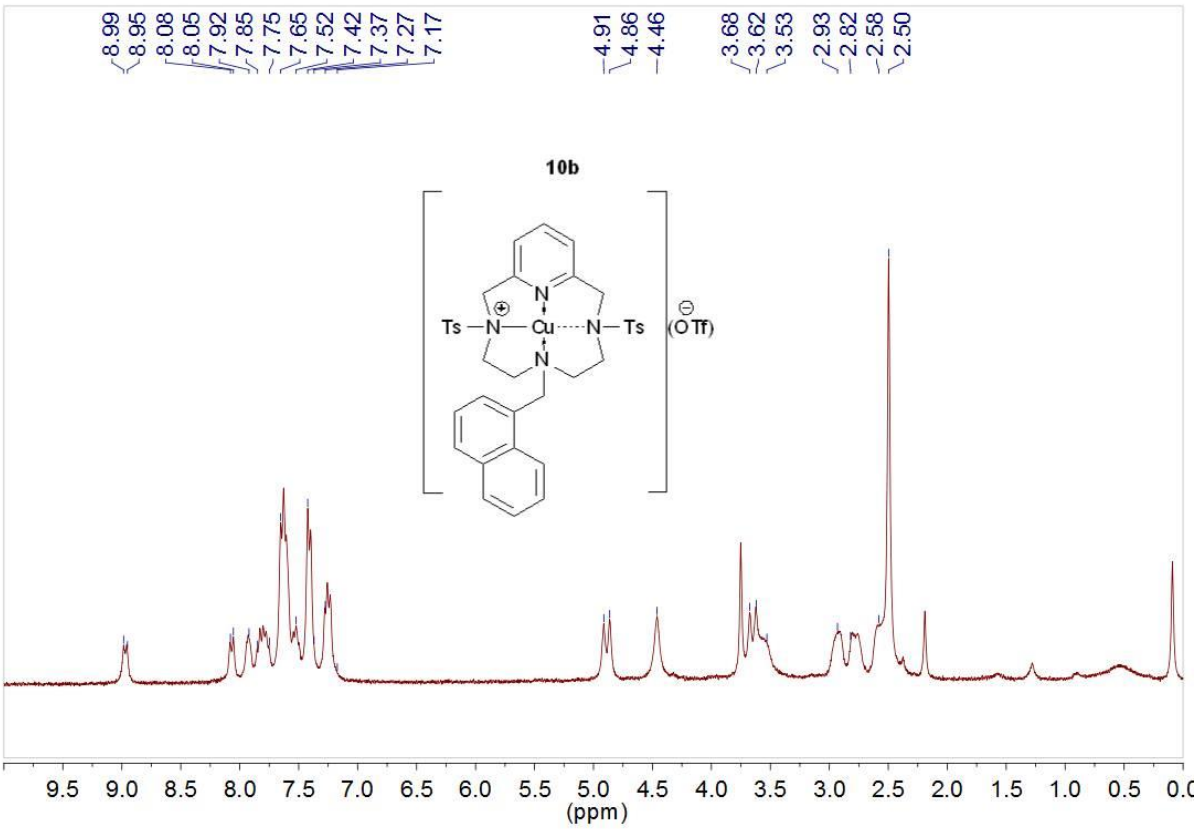

159.4
143.1
141.3
138.4
138.2
134.3
129.7
129.1
127.5
127.2
125.6
125.5
125.4
123.9
123.7
121.9
58.3
48.8
40.7
31.7
22.8
21.6
17.0
14.3
Ts—N
N—Ts
4p-(2R,10R,13R)
(ppm)

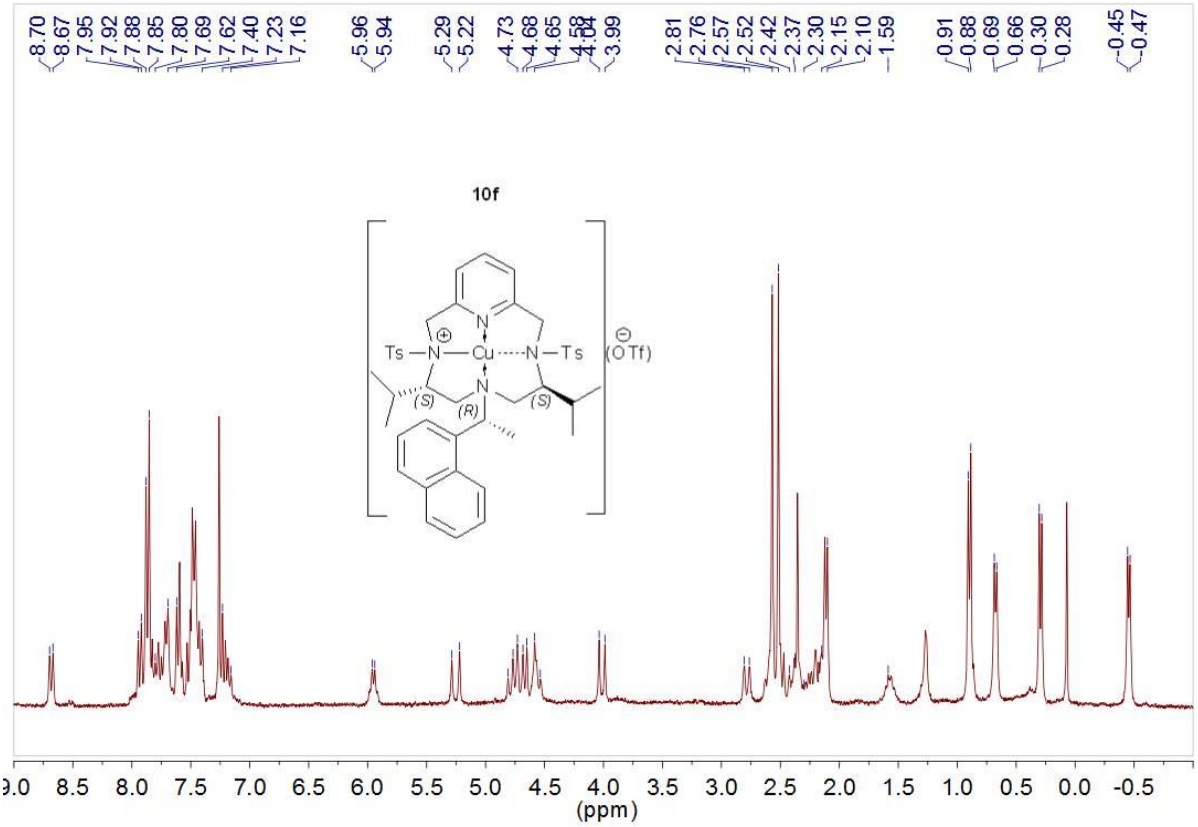
3.10.3 Protonated salts and metal complexes

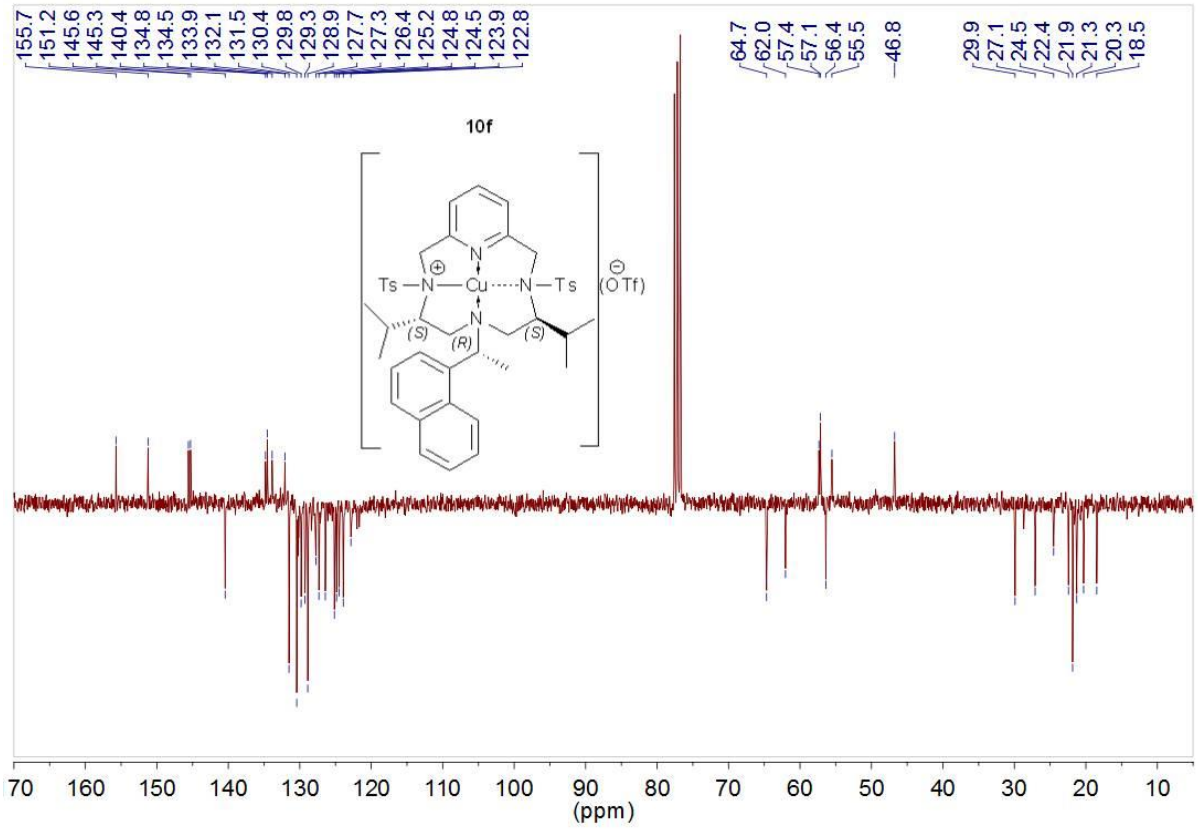



10.68
9.49
7.93
7.87
7.72
7.58
7.46
7.44
7.42
7.40
7.36
7.22
7.20
6.23
6.22
5.23
4.50
4.46
4.09
4.05
4.00
3.72
3.68
3.34
2.35
2.06
2.03
9d
Ts—N
H
N—Ts
N
(S)
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)


157.40
156.91
145.52
144.66
140.03
133.77
132.50
131.53
130.72
130.19
129.40
129.33
127.93
127.56
126.82
126.06
122.78
121.92
55.17
54.31
53.77
53.45
52.90
47.78
47.17
21.78
21.60
11.32
9d
Ts—N
H
N—Ts
N
(S)
70
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)


8.99
8.95
8.08
8.05
7.92
7.85
7.75
7.65
7.52
7.42
7.37
7.27
7.17
4.91
4.86
4.46
3.68
3.62
3.53
2.93
2.82
2.58
2.50
10b
Ts
N
Cu
N
Ts
(OTf)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)


8.70
8.67
7.95
7.92
7.88
7.85
7.80
7.69
7.62
7.40
7.23
7.16
5.96
5.94
5.29
5.22
4.73
4.68
4.65
4.58
4.04
3.99
2.81
2.76
2.57
2.52
2.42
2.37
2.30
2.15
2.10
1.59
0.91
0.88
0.69
0.66
0.30
0.28
-0.45
-0.47
10f
Ts
N
Cu
N
Ts
(OTf)
(S)
(R)
(S)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)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128.9
127.7
127.3
126.4
125.2
124.8
124.5
123.9
122.8
64.7
62.0
57.4
57.1
56.4
55.5
46.8
29.9
27.1
24.5
22.4
21.9
21.3
20.3
18.5
10f
Ts
N
Cu
N
Ts
(OTf)
(S)
(R)
(S)
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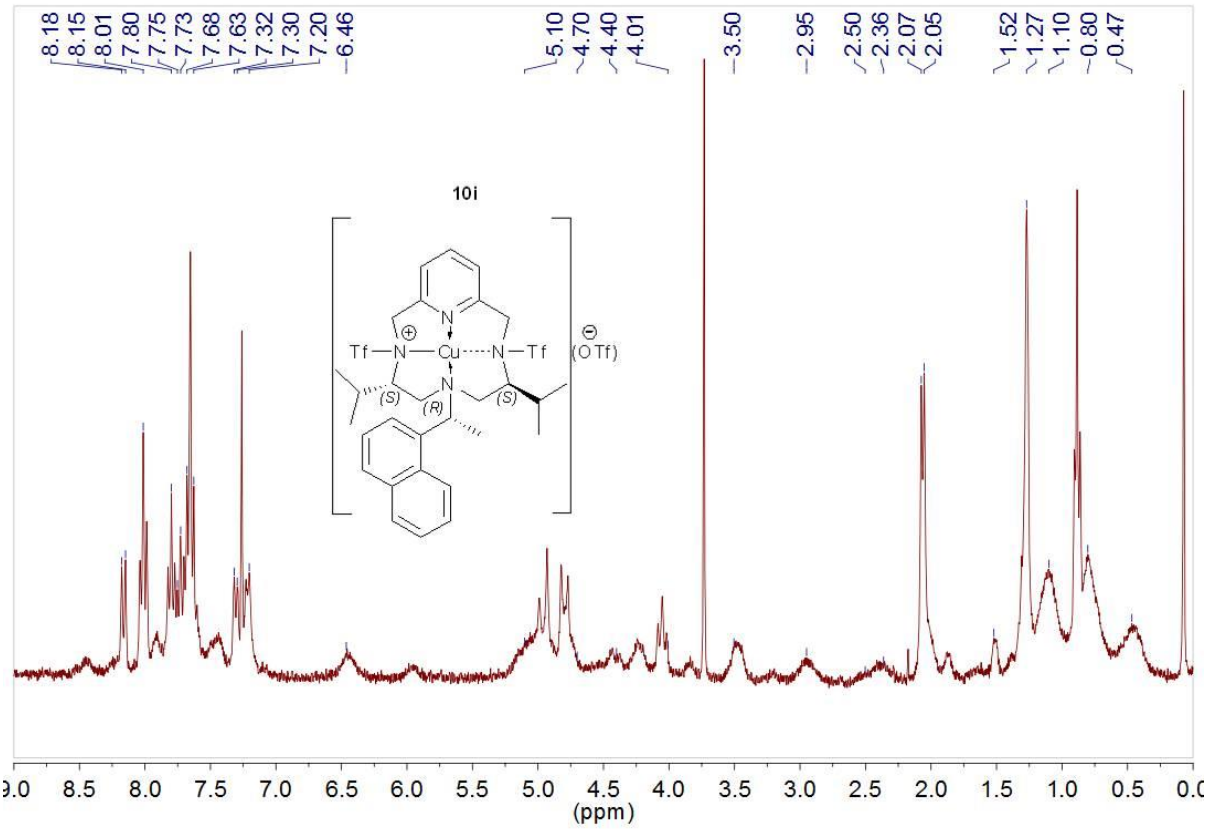
(ppm)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7.63
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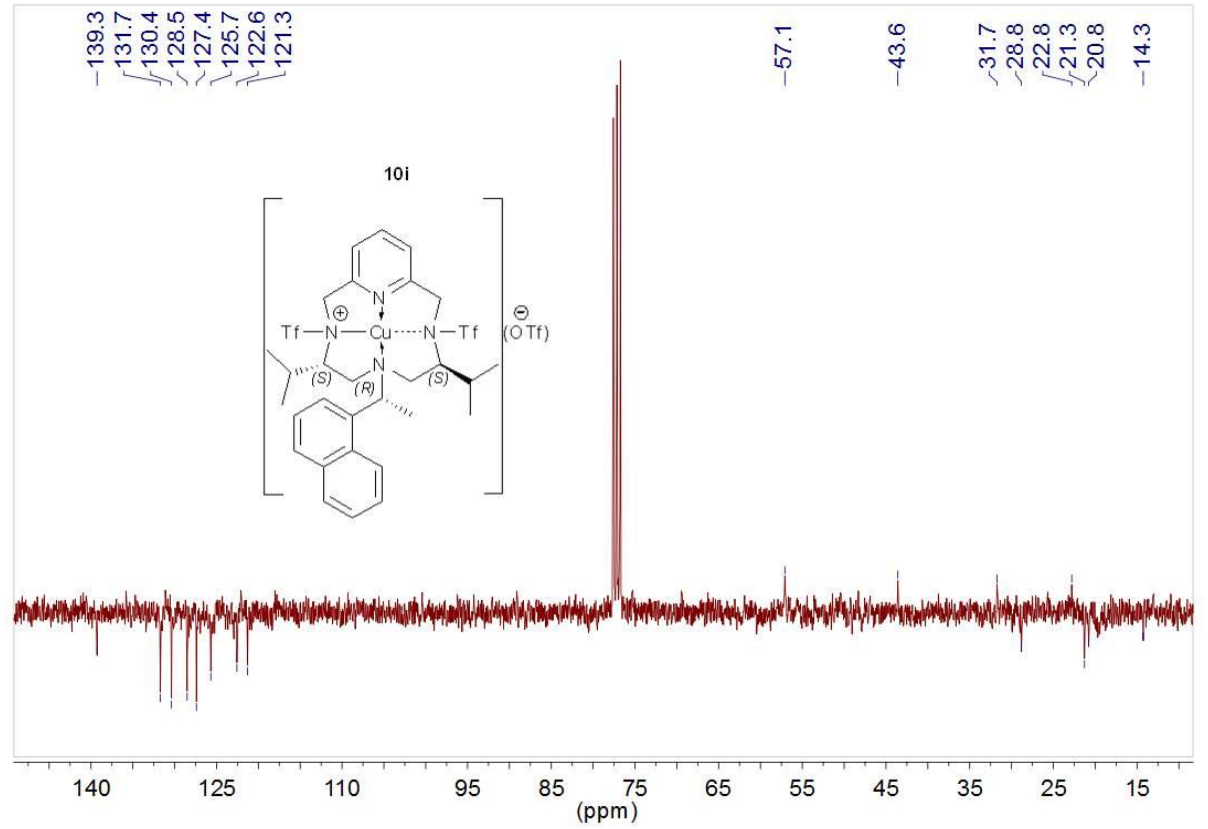
7.30
7.20
6.46
5.10
4.70
4.40
4.01
3.50
2.95
2.50
2.36
2.07
2.05
1.52
1.27
1.10
0.80
0.47
10i
Tf—N—Cu····N—Tf
(OTf)
(S)
(R)
(S)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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122.6
121.3
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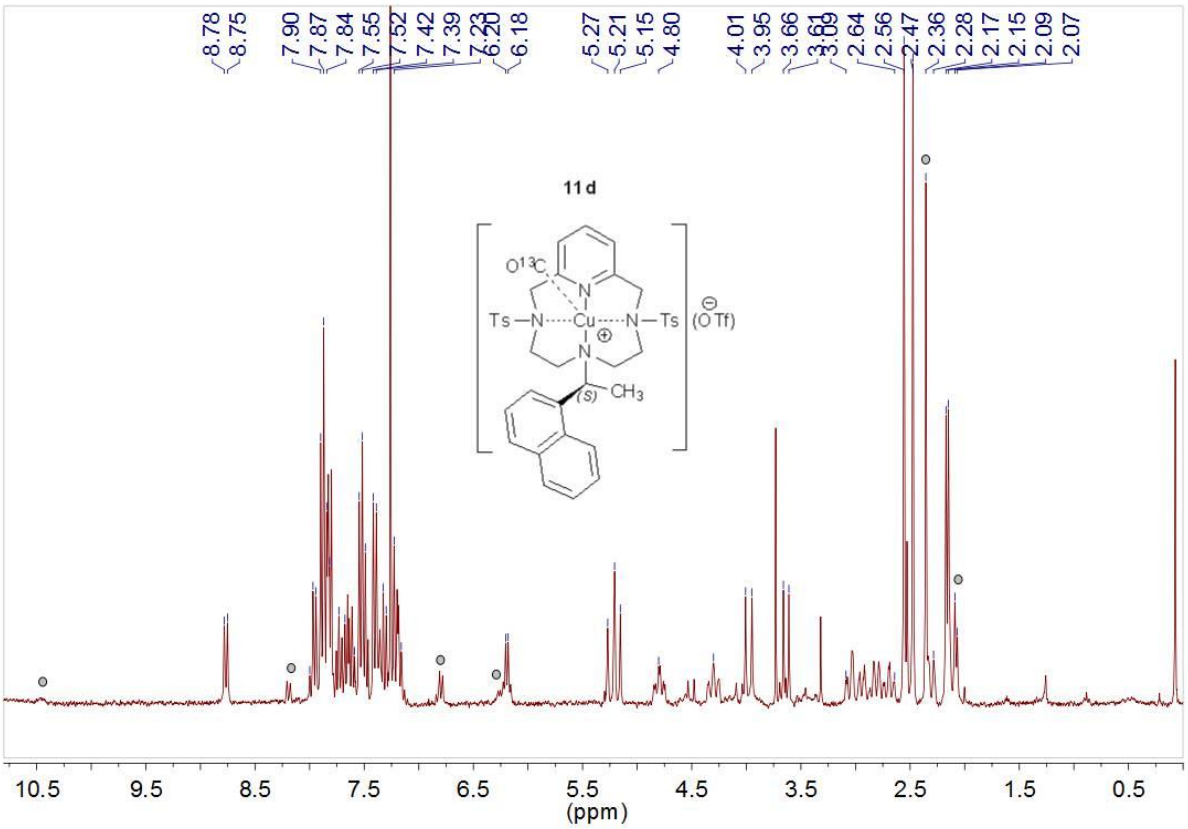
31.7
28.8
22.8
21.3
20.8
14.3
10i
Tf—N—Cu····N—Tf
(OTf)
(S)
(R)
(S)
140 125 110 95 85 75 65 55 45 35 25 15
(ppm)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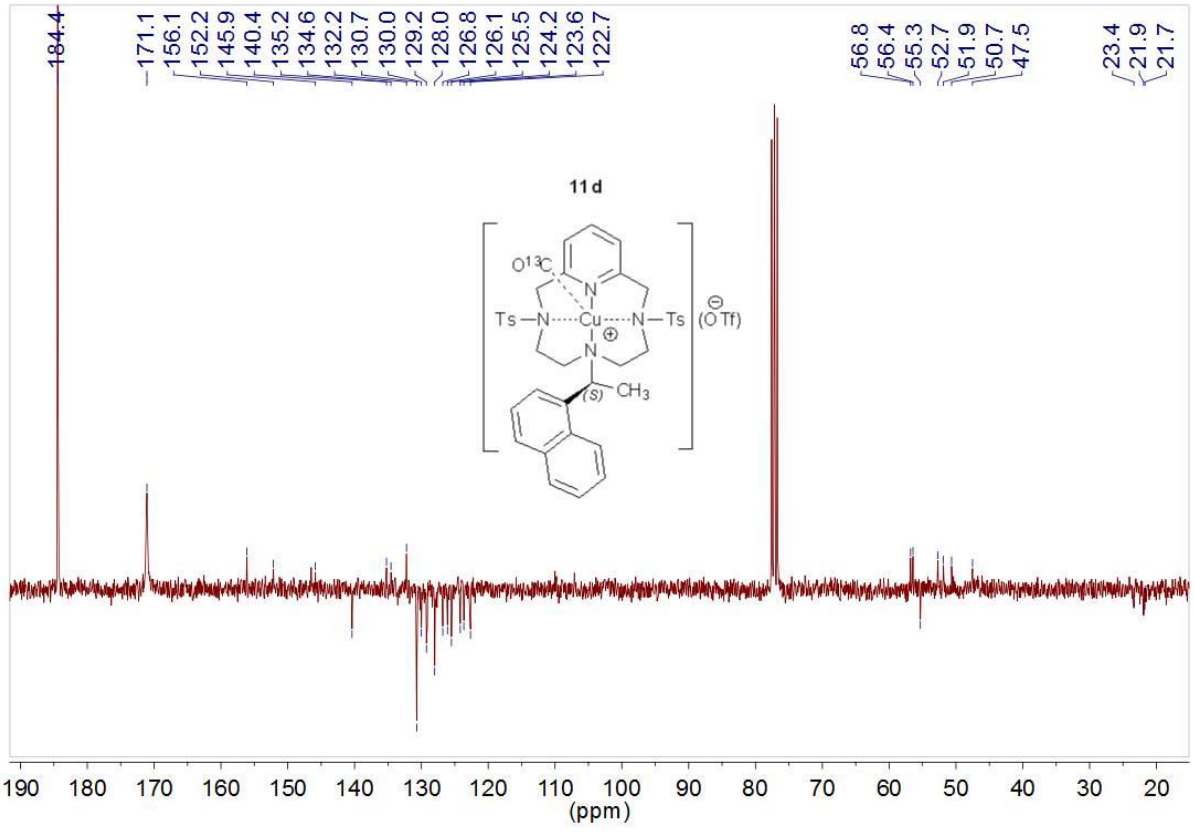
4.80
4.01
3.95
3.66
2.64
2.56
2.47
2.36
2.28
2.17
2.15
2.09
2.07
11d
Ts
Cu
Ts
(OTf)
CH3
10.5
9.5
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
(ppm)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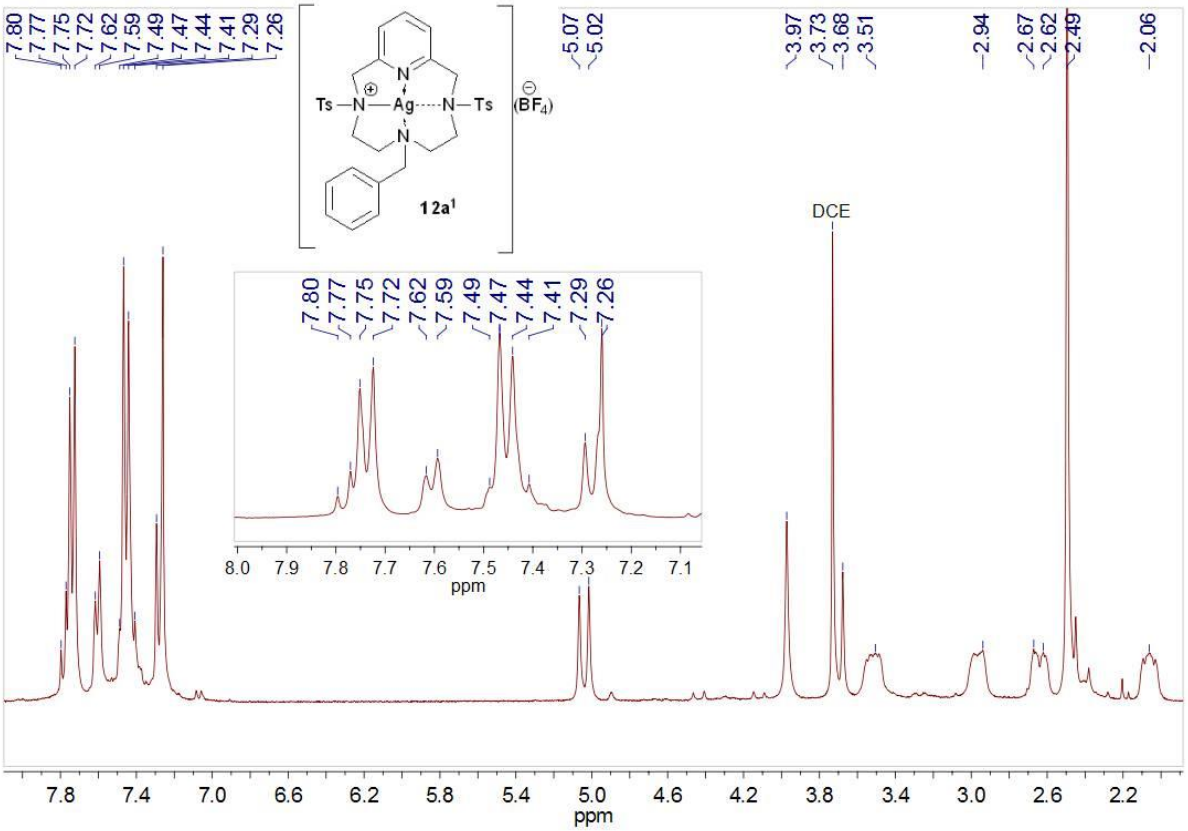
126.8
126.1
125.5
124.2
123.6
122.7
56.8
56.4
55.3
52.7
51.9
50.7
47.5
23.4
21.9
21.7
11d
Ts
Cu
Ts
(OTf)
CH3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)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7.26
5.07
5.02
3.97
3.73
3.68
3.51
2.94
2.67
2.62
2.49
2.06
DCE
Ts—N—Ag—N—Ts
(BF4)
12a1
8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1
ppm
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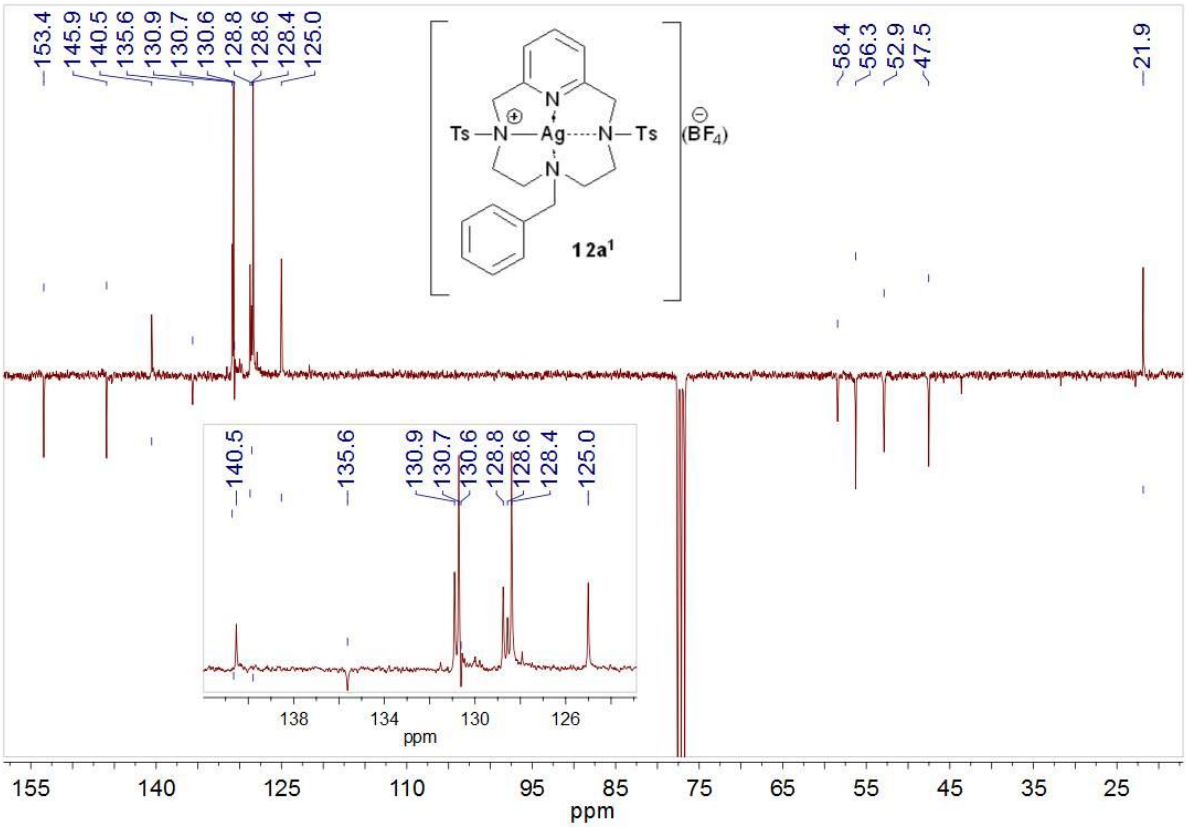
ppm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130.7
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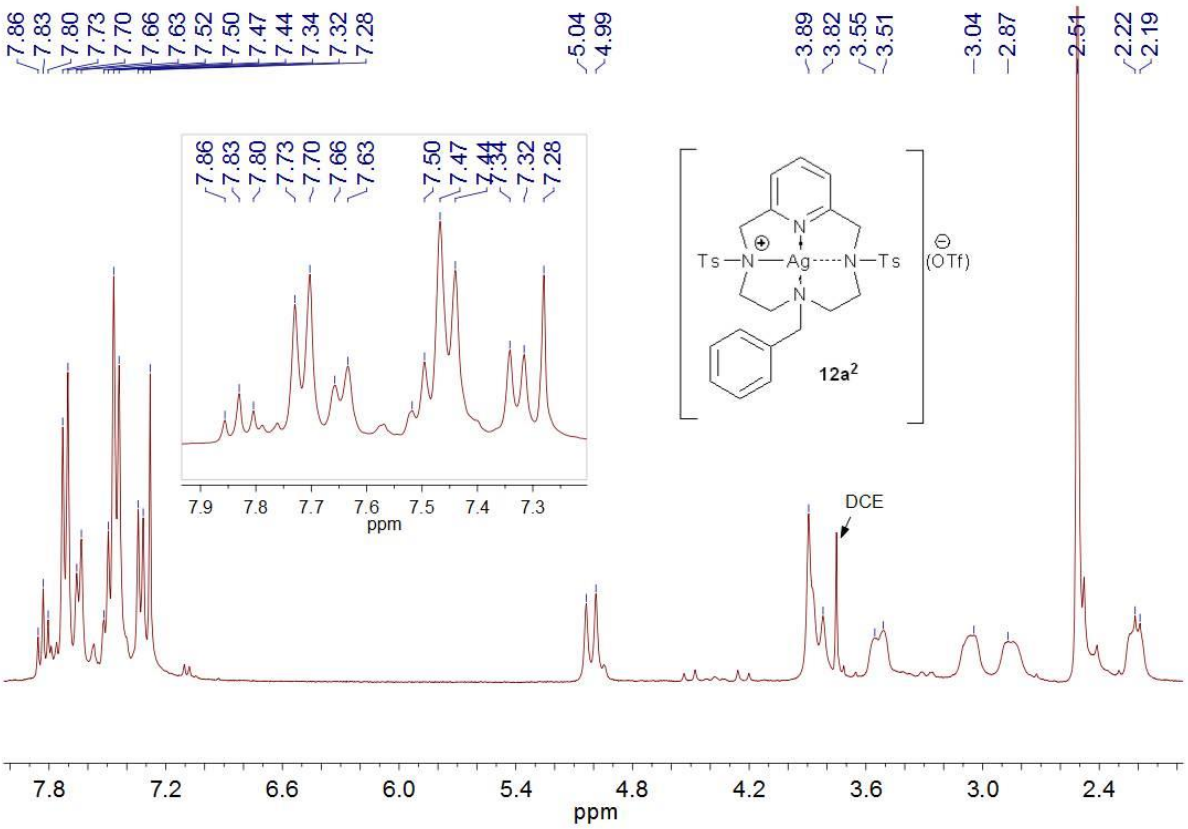
128.8
128.6
128.4
125.0
58.4
56.3
52.9
47.5
21.9
Ts—N—Ag—N—Ts
(BF4)
12a1
138 134 130 126
ppm
155 140 125 110 95 85 75 65 55 45 35 25
ppm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7.44
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7.32
7.28
5.04
4.99
3.89
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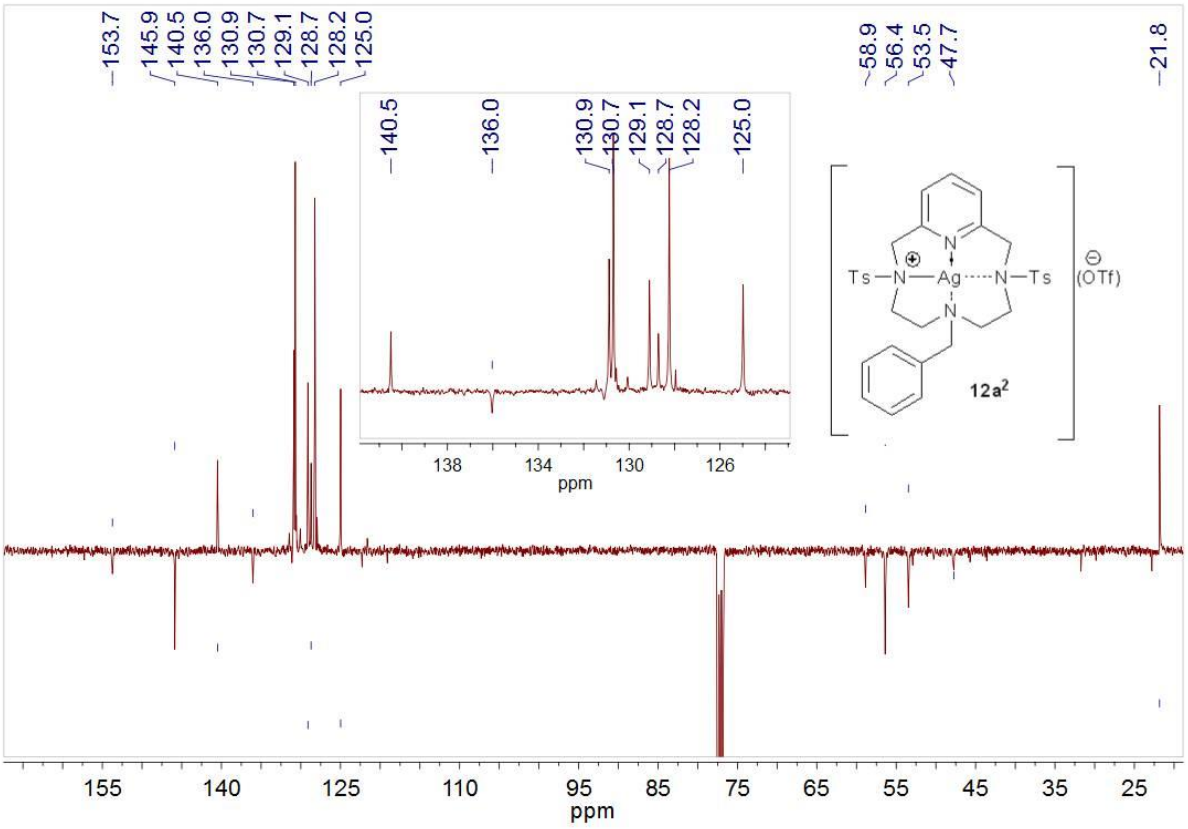
3.51
3.04
2.87
2.61
2.22
2.19
DCE
ppm
12a2
(OTf)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128.2
125.0
58.9
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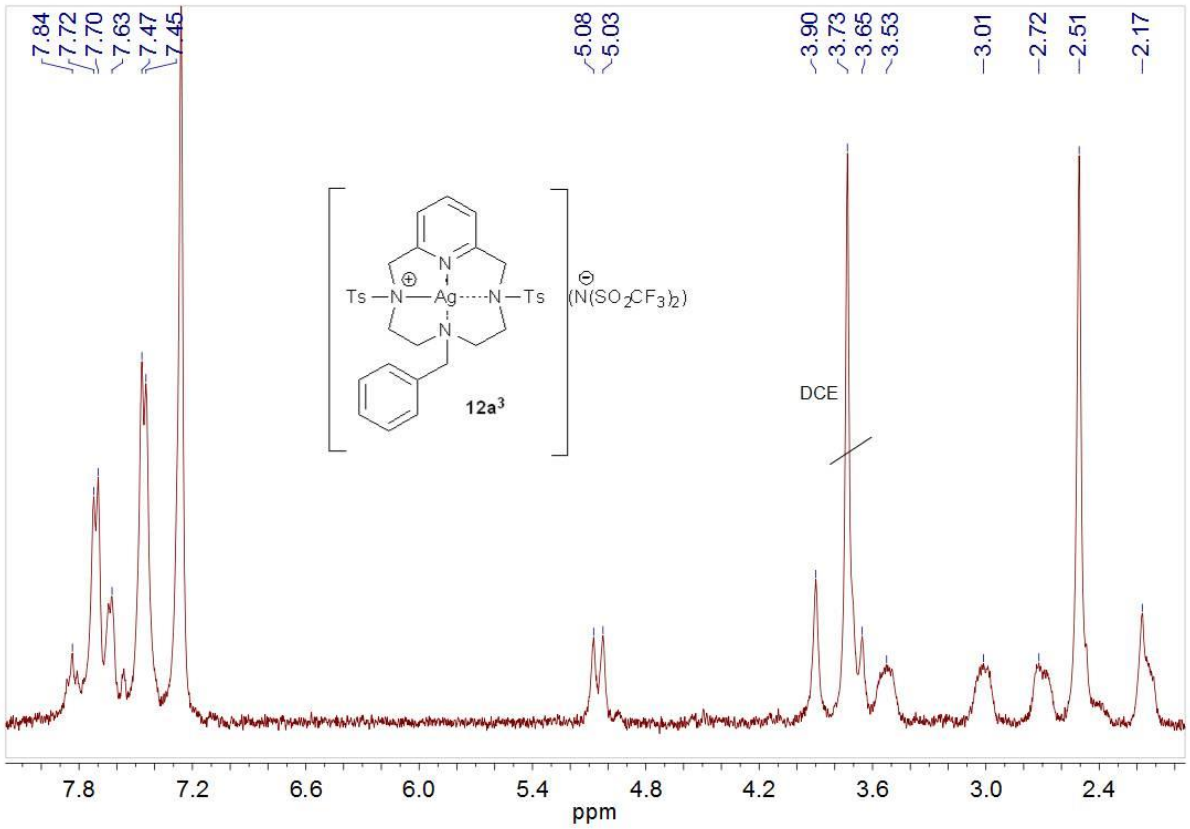
53.5
47.7
21.8
ppm
12a2
(OTf)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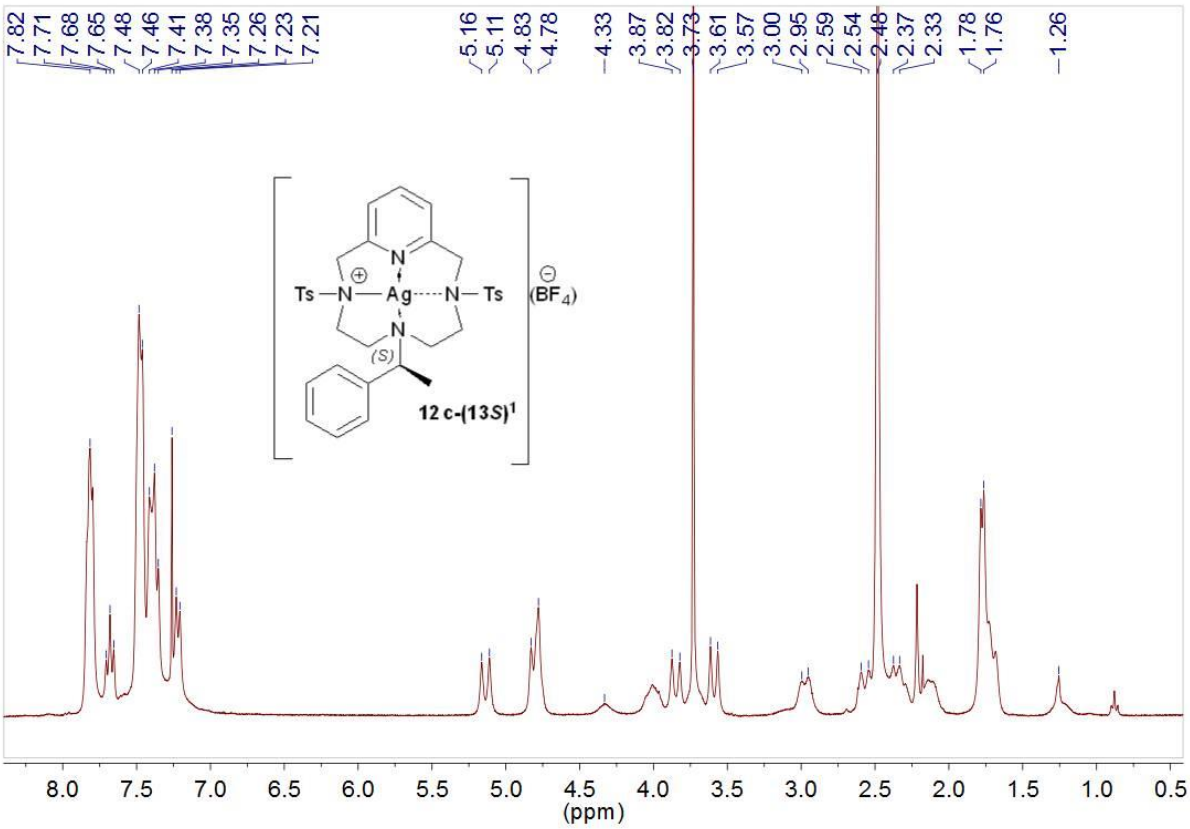
3.01
2.72
2.51
2.17
DCE
12a3
7.8
7.2
6.6
6.0
5.4
4.8
4.2
3.6
3.0
2.4
ppm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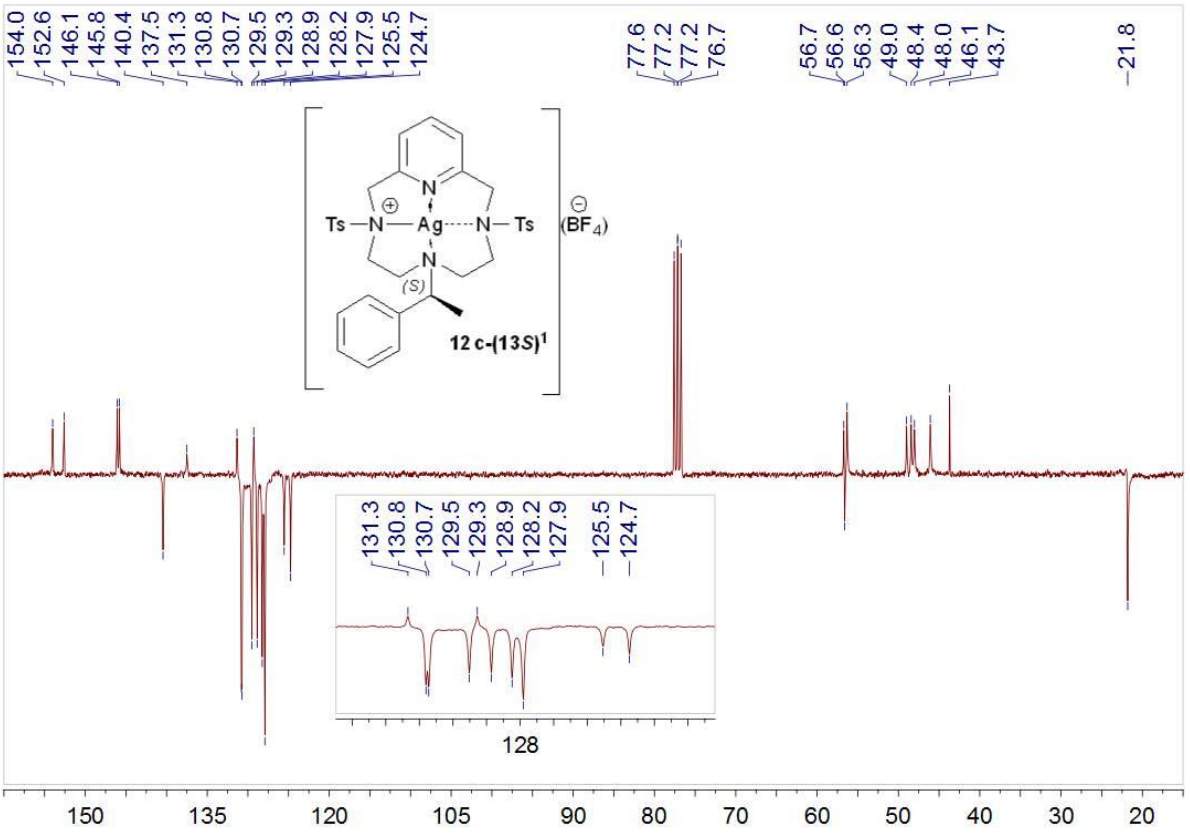
7.21
5.16
5.11
4.83
4.78
4.33
3.87
3.82
3.73
3.61
3.57
3.00
2.95
2.59
2.54
2.48
2.37
2.33
1.78
1.76
1.26
Ts—N—Ag···N—Ts
(BF4)
(S)
12 c-(13S)1
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)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145.8
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137.5
131.3
130.8
130.7
129.5
129.3
128.9
128.2
127.9
125.5
124.7
77.6
77.2
77.2
76.7
56.7
56.6
56.3
49.0
48.4
48.0
46.1
43.7
21.8
Ts—N—Ag···N—Ts
(BF4)
(S)
12 c-(13S)1
131.3
130.8
130.7
129.5
129.3
128.9
128.2
127.9
125.5
124.7
128
150
135
120
105
90
80
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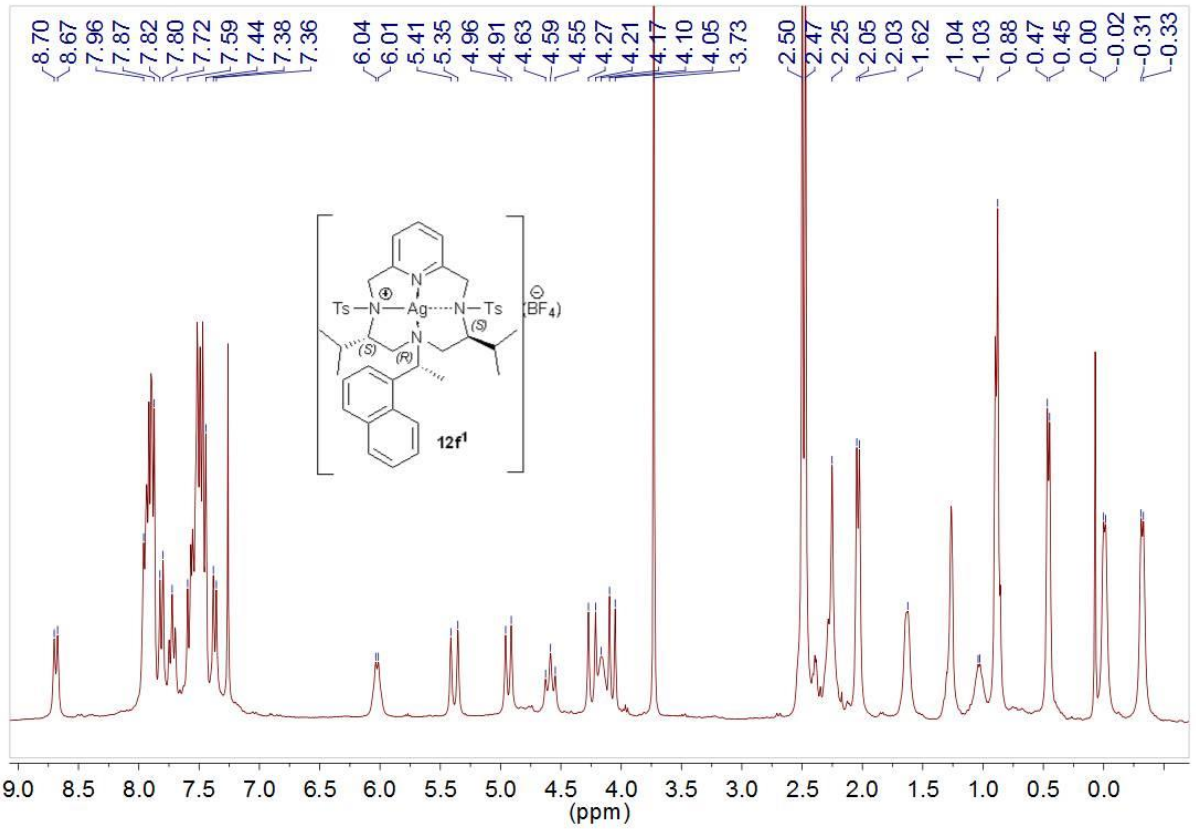
60
50
40
30
20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7.44
7.38
7.36
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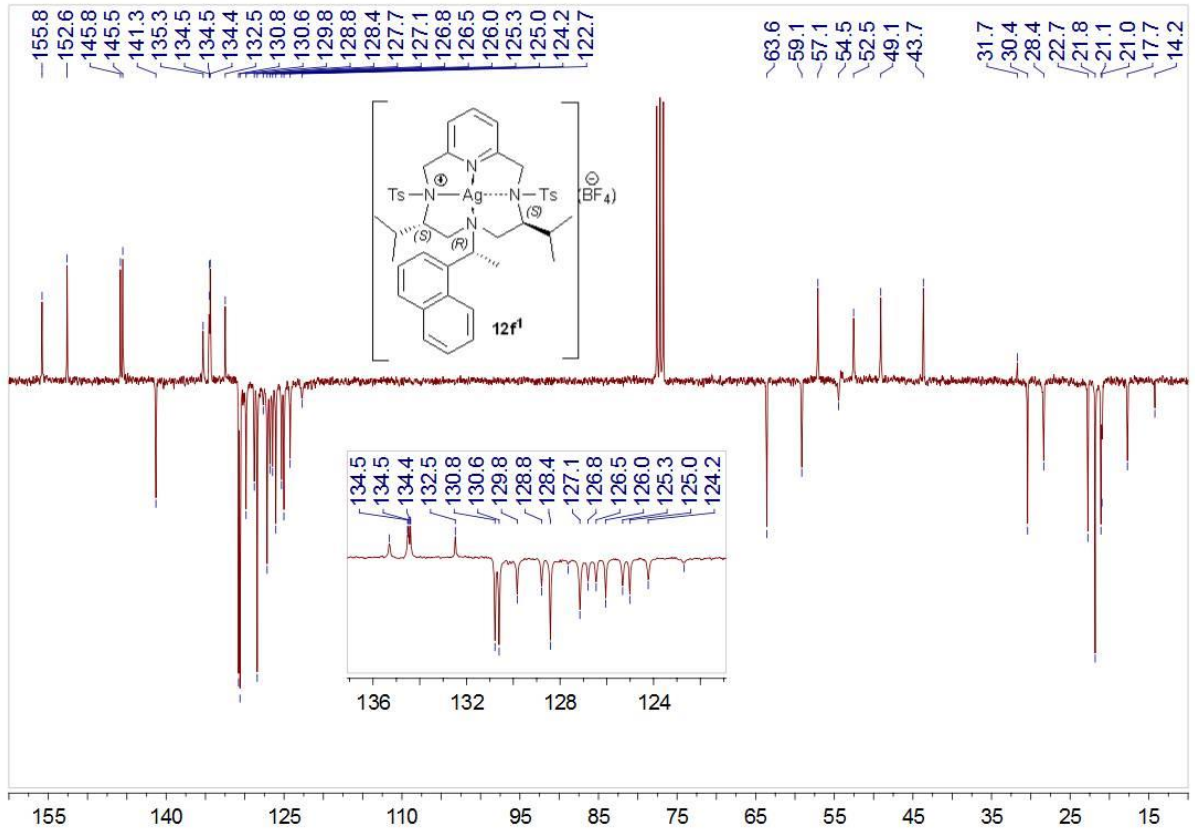
6.01
5.41
5.35
4.96
4.91
4.63
4.59
4.55
4.27
4.21
4.17
4.10
4.05
3.73
2.50
2.47
2.25
2.05
2.03
1.62
1.04
1.03
0.88
0.47
0.45
0.00
-0.02
-0.31
-0.33
Ts—N—Ag····N—Ts
(BF4)
12f1
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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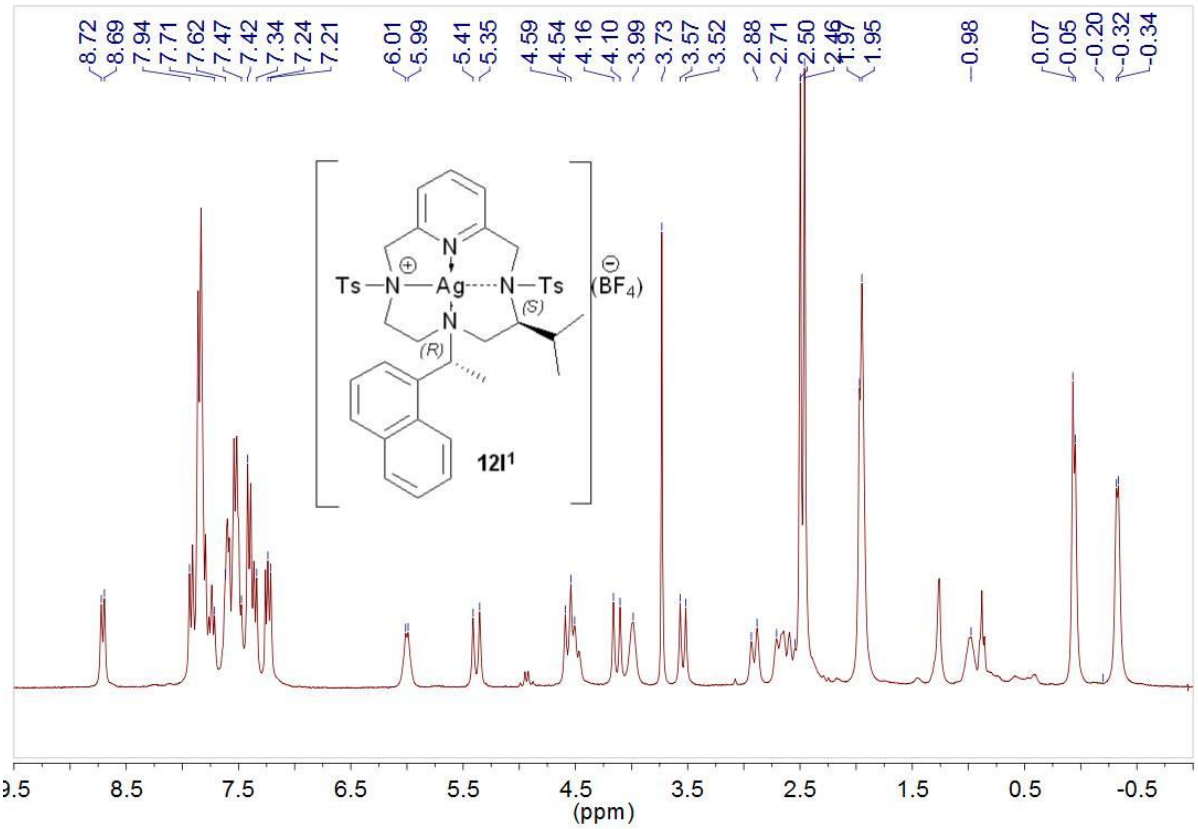
130.6
129.8
128.8
128.4
127.7
127.1
126.8
126.5
126.0
125.3
125.0
124.2
122.7
63.6
59.1
57.1
54.5
52.5
49.1
43.7
31.7
30.4
28.4
22.7
21.8
21.1
21.0
17.7
14.2
Ts—N—Ag····N—Ts
(BF4)
12f1
136 132 128 124
155 140 125 110 95 85 75 65 55 45 35 25 15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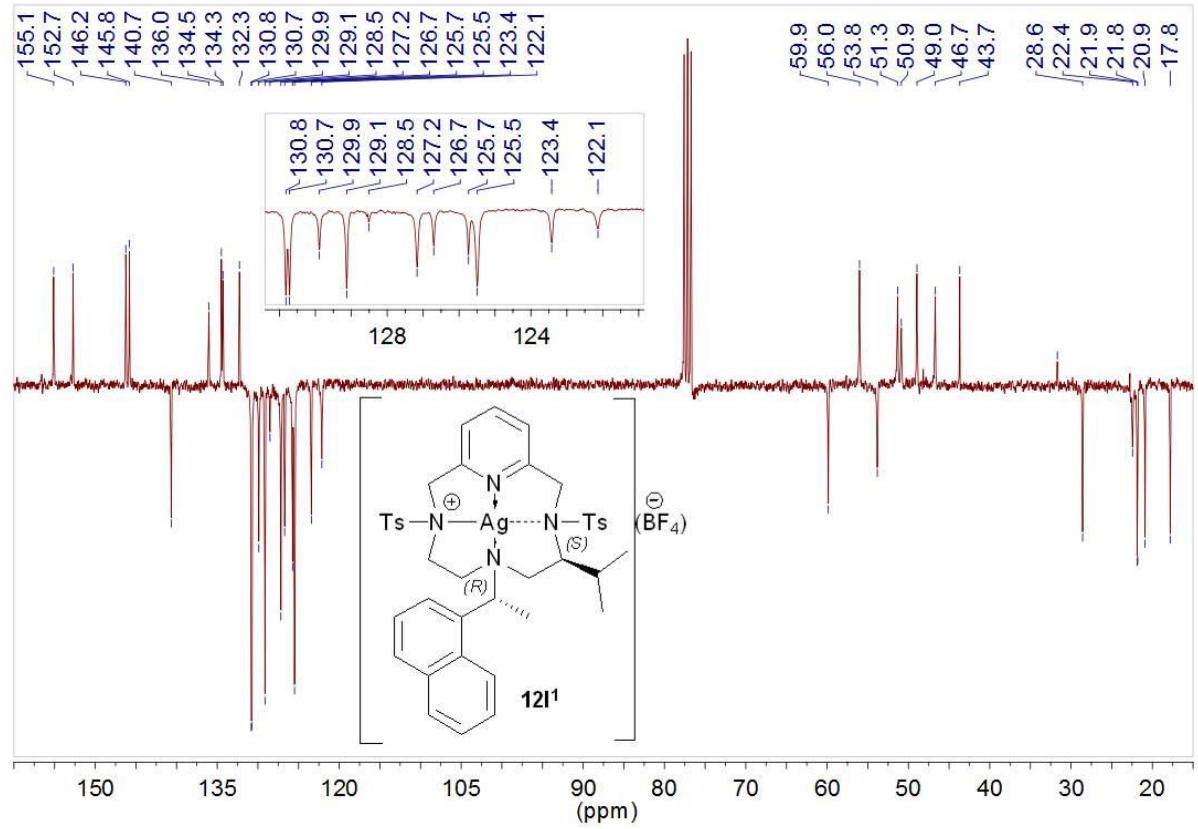
4.10
3.99
3.73
3.57
3.52
2.88
2.71
2.50
2.46
1.97
1.95
0.98
0.07
0.05
-0.20
-0.32
-0.34
Ts—N—Ag—N—Ts
(BF4)
(S)
(R)
12l1
8.5
7.5
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
(ppm)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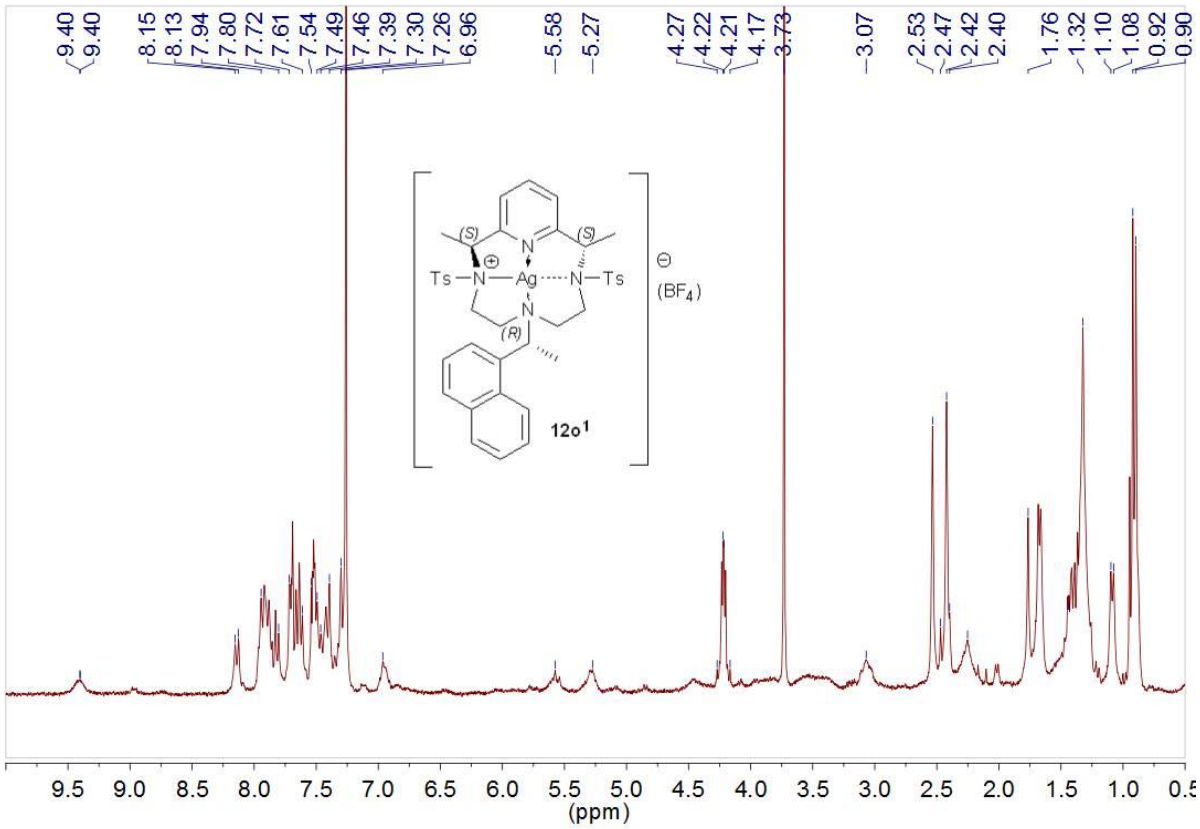
128.5
127.2
126.7
125.7
125.5
123.4
122.1
59.9
56.0
53.8
51.3
50.9
49.0
46.7
43.7
28.6
22.4
21.9
21.8
20.9
17.8
128
124
Ts—N—Ag—N—Ts
(BF4)
(S)
(R)
12l1
150
135
120
105
90
80
70
60
50
40
30
20
(ppm)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5.58
5.27
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4.22
4.21
4.17
3.73
3.07
2.53
2.47
2.42
2.40
1.76
1.32
1.10
1.08
0.92
0.90
(S)
(S)
N
Ts—N—Ag···N—Ts
(R)
N
(BF4)
12o1
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

3.11 Tiosemicarbazone complexes

3.11.1 General procedure

All the reagents employed for the preparation of the ligands and their complexes were of the highest grade available and used without further purification. Copper(II) acetate monohydrate was purchased from Aldrich and used as received. All aldehydes and thiosemicarbazide were of reagent grade and used as purchased. 2-Hydroxybenzaldehyde *N*-ethylthiosemicarbazone (**9)** was purchased from Sigma-Aldrich. Unless otherwise stated, all catalytic tests were carried out under an atmosphere of purified dinitrogen using modified Schlenk techniques. Used solvents were dried and distilled before use by standard methods. Benzene, cyclohexene and 1-octene were distilled over sodium, styrene and α-methyl styrene were distilled over calcium hydride and stored under dinitrogen. NMR spectra were recorded on an Avance 300-DRX Bruker instrument, operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. Chemical shifts (ppm) are reported relative to TMS. The ^{1}H NMR signals of compounds described in the following have been attributed by COSY and NOESY techniques. Assignments of the resonances in ^{13}C NMR were made using the APT pulse sequence, HSQC and HMQC techniques. Elemental analyses and mass spectra were recorded in the analytical laboratories of Milan University. GC analyses were performed on a Shimadzu 2010 FAST-GC equipped with an automatic sampler AOI-20i.

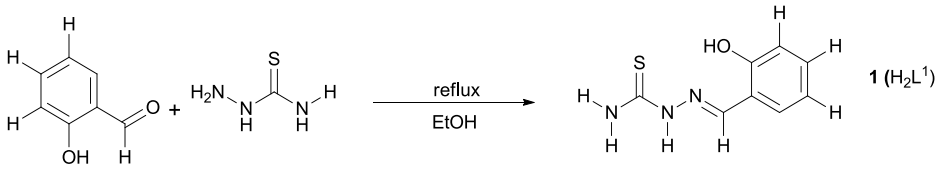
Some of the ligands and their metal complexes were analysed for C, H, N and M contents at the Microanalytical Laboratory, Faculty of Science, Cairo University, Egypt. IR spectra of the ligands and their metal complexes were measured using KBr discs with a Jasco FT/IR 300E Fourier transform infrared spectrophotometer and/or on a Varian Scimitar FTS 1000 spectrophotometer covering the range 400-4000 cm^{-1} and in the 500-100 cm^{-1} region using polyethylene-sandwiched Nujol mulls on a Perkin Elmer FT-IR 1650 spectrophotometer. The electronic spectra of the ligands and their complexes were obtained in DMSO solutions using a Agilent 8453 UV-Visible recording spectrophotometer. Molar conductivities of the metal complexes in DMSO (10^{-3} M) were measured using a dip cell and a Bibby conductimeter MC1 at room temperature. The resistance measured in ohms and the molar conductivities were calculated according to the equation: $\Lambda = V \times K \times Mw/g \times \Omega$, where Λ, molar conductivity (ohm^{-1} cm^{2} mol^{-1}); V, volume of the complex solution (mL); K, cell constant 0.92 cm^{-1}; Mw, molecular weight of the complex; g, weight of the complex; and Ω, resistance measured in ohms. Magnetic moments at 298 K were determined using the Gouy method with $Hg[Co(SCN)_4]$ as

calibrant.[236] XPS analyses were carried out using a M-probe apparatus (Surface Science Instruments).

For ligand numerations see scheme 2.20 and for complex numerations see scheme 2.21 reported in *Result and Discussion* in section **2.6.1**.

3.11.2 Synthesis of different ligands

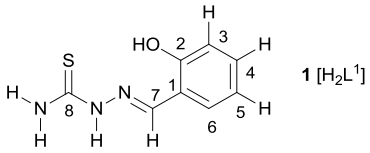
3.11.2.1 Ligand 1



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Thiosemicarbazide	91.14	0.2022	-	-	2.22	1
salicylaldehyde	122.12	0.2713	1.146	0.237	2.22	1

Thiosemicarbazide was added to a hot (75 ^{o}C) solution of salicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum (MW 195.24 g/mol).

yield = 413 mg, 2.11 mmol, 95%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ 11.33 (s, 1H, N*H*), 9.84 (s, 1H, O*H*), 8.34 (s, 1H, H^7), 8.07 (br s, 1H, NH_2), 7.90 (br s, 1H, NH_2), 7.87 (d, *J* = 7.5 Hz, 1H, H^3), 7.18 (pst, *J* = 7.5 Hz, 1H, H^4), 6.83 (d, *J* = 7.5 Hz, 1H, H^6), 6.79 (pst, *J* = 7.5 Hz, 1H, H^5).

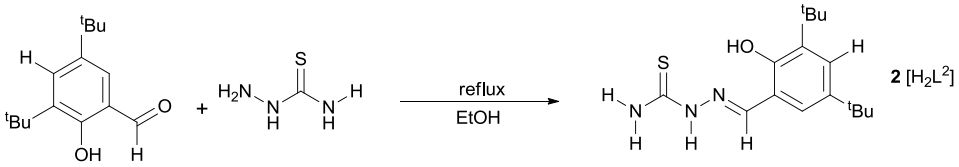
MS (EI): *m/z* = 195 (M^+).

Elemental analysis: *Calcd.* for $C_8H_9N_3OS$ (195.24 g/mol): C, 49.21; H, 4.65; N, 21.52. Found: C, 49.64; H, 4.55; N, 21.51.

IR (KBr, ν/ cm^{-1}): 3441m (ν_{OH}), 3318s-2987s (ν_{as} and ν_{sNH2}), 3172s (ν_{OH}), 1616s (δ_{NH2}), 1603s ($\nu_{C=N}$), 1539s, 1265s (ν_{CO}), 1061m ($\nu_{C=S}$), 829m (ν_{sCS}), 751s.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 276, 340.

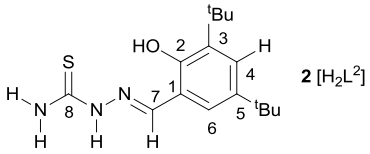
3.11.2.2 Ligand 2



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
3,5-di-tert-butylsalicylaldehyde	234.33	0.520	2.22	1

Thiosemicarbazide was added to a hot (75 °C) solution of 3,5-di-tert-butylsalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. In order to separate any trace of starting thiosemicarbazide, a further purification by column chromatography was needed (eluant *n*-hexane:EtOAc : 7/3) (MW 307.45 g/mol).

yield = 546 mg, 1.78 mmol, 80%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 11.33 (s, 1H, N*H*), 9.84 (s, 1H, O*H*), 8.26 (s, 1H, *H*^{7}), 8.02 (br s, 2H, N*H*$_2$), 7.29 (d, ^4J = 2.3 Hz, 1H, *H*^{4}), 7.16 (d, ^4J = 2.3 Hz, 1H, *H*^{6}), 1.40 (s, 9H, C*H*$_3$), 1.27 (s, 9H, C*H*$_3$).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.17 (s, 1H, N*H*), 9.93 (s, 1H, O*H*), 8.13 (s, 1H, *H*^{7}), 7.44 (s, 1H, *H*^{4}), 7.08 (s, 1H, *H*^{6}), 6.57 (br s, 2H, N*H*$_2$), 1.45 (s, 9H, C*H*$_3$), 1.32 (s, 9H, C*H*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 177.9 (*C*^{8}), 155.1 (*C*^{2}), 150.4 (*C*^{7}), 142.4 (*C*^{q}), 137.2 (*C*^{q}), 128.3 (*C*^{4}), 127.0 (*C*^{6}), 116.3 (*C*^{q}), 35.5 (*C*^{q}), 34.5 (*C*^{q}), 31.8 (*C*H$_3$), 29.8(*C*H$_3$).

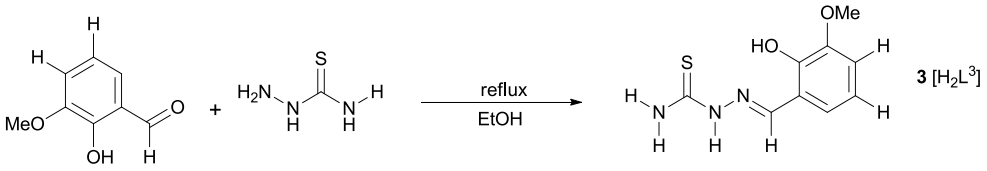
MS (EI): *m/z* = 307 (M$^+$).

Anal. Calcd. for $C_{16}H_{25}N_3OS$ (307.45 g/mol): C, 62.50; H, 8.20; N, 13.67. Found: C, 62.38; H, 8.06; N, 13.60.

IR (KBr, ν/ cm^{-1}): 3452m (ν_{OH}), 3274-2961s (ν_{as} and ν_{s}NH2), 3166s (ν_{NH}), 1715s (δ_{NH2}), 1606s ($\nu_{C=N}$), 1579m, 1538s, 1290m, 1265m (ν_{CO}), 1108m, 1067w ($\nu_{C=S}$), 826m (ν_{s}CS), 769m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 274, 340.

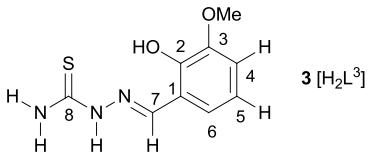
3.11.2.3 Ligand 3



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
3-Methoxysalicylaldehyde	152.15	0.338	2.22	1

Thiosemicarbazide was added to a hot (75 ^{o}C) solution of *o*-Vanillin in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 225.27 g/mol).

yield = 445 mg, 1.97 mmol, 89%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 11.36 (s, 1H, N*H*), 9.19 (s, 1H, O*H*), 8.39 (s, 1H, H^7), 8.05 (s, 1H, NH_2), 7.85 (s, 1H, NH_2), 7.51 (d, 1H, , ^{3}J = 7.5 Hz, H^6), 6.96 (dd, 1H, , ^{3}J = 7.5 Hz, ^{4}J = 1.3 Hz, H^4), 6.77 (pst, 1H, ^{3}J = 7.5 Hz, H^5), 3.80 (s, 3H, OCH_3).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 178.6 (C^8), 148.7 (C^2), 140.7 (C^3), 140.4 (C^7), 121.6 (C^1), 119.9 (C^6), 119.0 (C^5), 113.7 (C^4), 56.8 (CH$_3$).

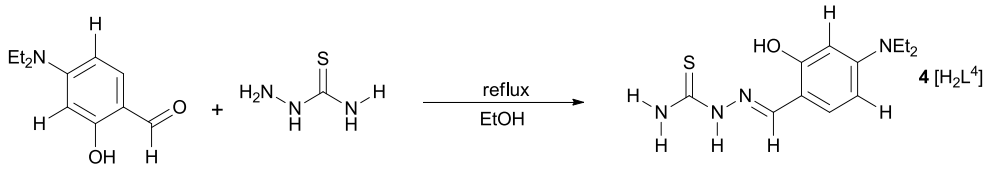
MS (EI): *m/z* = 225 (M^+).

Anal. Calcd. for $C_9H_{11}N_3O_2S$ (225.27 g/mol): C, 47.99; H, 4.92; N, 18.65. Found: C, 47.93; H, 5.02; N, 18.40.

IR (KBr, ν/ cm^{-1}): 3461s (ν_{OH}), 3343-2975m (ν_{as} and ν_{sNH2}), 3167m (ν_{NH}), 1621m (δ_{NH2}), 1598s ($\nu_{C=N}$), 1588m, 1536s, 1281m, 1263s (ν_{CO}), 1059m ($\nu_{C=S}$), 822m (ν_{sCS}), 778m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 323, 390.

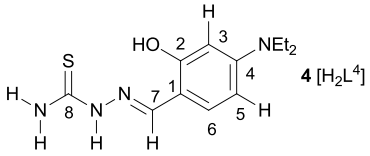
3.11.2.4 Ligand 4



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
4-(diethylamino)salicylaldehyde	193.24	0.429	2.22	1

Thiosemicarbazide was added to a hot (75 °C) solution of 4-(diethylamino)salicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 266.36 g/mol).

yield = 503 mg, 1.89 mmol, 85%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 11.04 (s, 1H, N*H*), 9.52 (s, 1H, O*H*), 8.18 (s, 1H, *H*^{7}), 7.81 (s, 1H, N*H*$_2$), 7.64 (s, 1H, N*H*$_2$), 7,50 (d, 1H, ^{3}J= 8.8 Hz, *H*^{6}), 6.20 (dd, 1H, ^{3}J= 8.8 Hz, ^{4}J= 2,2 Hz, H^{5}), 6.08 (d, 1H, ^{4}J= 2,2 Hz, *H*^{3}), 3.30 (q, 4H, ^{3}J= 6,9 Hz, N(*CH*$_2$CH$_3$)$_2$), 1.09 (t, 6H, ^{3}J = 6.9 Hz, N(CH$_2$*CH*$_3$)$_2$).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 177.3 (*C*^{8}), 159.0 (*C*^{2}), 151.0 (*C*^{4}), 143.3 (*C*^{7}), 129.9 (*C*^{6}), 108.2 (*C*^{1}), 104.8 (*C*^{5}), 98.2 (*C*^{3}), 44.7 (*C*H$_2$), 13.4 (*C*H$_3$).

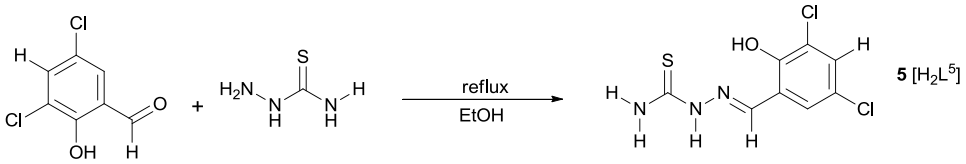
MS (EI): *m/z* = 266 (M^{+}).

Anal. Calcd. for $C_{12}H_{18}N_4OS$ (266.36 g/mol): C, 54.11; H, 6.81; N, 21.03. Found: C, 54.52; H, 6.79; N, 21.20.

IR (KBr, ν/ cm^{-1}): 3409s (ν_{OH}), 3302-2960m (ν_{as} and ν_{sNH2}), 3175m (ν_{NH}), 1630s (δ_{NH2}), 1610s ($\nu_{C=N}$), 1590s, 1553s, 1286m, 1245s (ν_{CO}), 1058m ($\nu_{C=S}$), 821m (ν_{sCS}), 787w.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 273, 364.

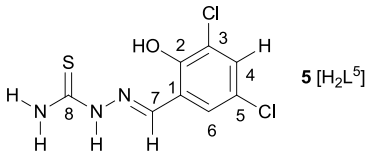
3.11.2.5 Ligand 5



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
3,5-dichlorosalicylaldehyde	191.01	0.424	2.22	1

Thiosemicarbazide was added to a hot (75 °C) solution of 3,5-dichlorosalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 264.13 g/mol).

yield = 528 mg, 2.00 mmol, 90%



^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.52 (s, 1H, N*H*), 10.06 (s, 1H, O*H*), 8.33 (s, 1H, H^7), 8.22 (br s, 2H, NH_2), 8.06 (d, ^4J = 2.6 Hz, 1H, H^4), 7.52 (d, ^4J = 2.6 Hz, 1H, H^6).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 179.0 (C^8), 151.4 (C^2), 138.5 (C^7), 130.5 (C^4), 126.0 (C^q), 125.1 (C^6), 125.0 (C^q), 123.5 (C^q).

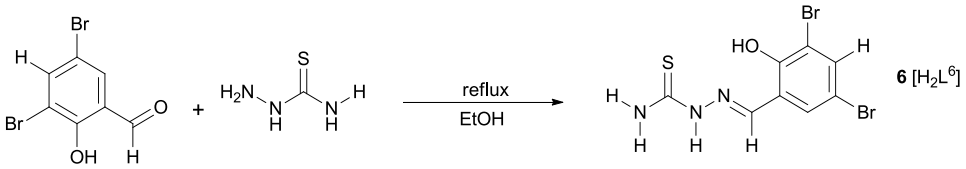
MS (EI): *m/z* = 264 (M^+).

Anal. Calcd. for $C_8H_7Cl_2N_3OS$ (263.13 g/mol): C, 36.38; H, 2.67; N, 15.91. Found: C, 36.54; H, 2.66; N, 15.75.

IR (KBr, ν/ cm^{-1}): 3464s (ν_{OH}), 3347s ($\nu_{as}NH_2$), 3154m (ν_{NH}), 1612s ($\nu_{C=N}$), 1153s, 1099m ($\nu_{C=S}$), 817m ($\nu_{s}CS$).

UV/Vis (10^{-5} M, DMSO (nm)): λ = 275, 346.

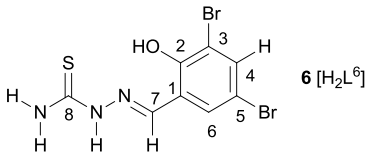
3.11.2.6 Ligand 6



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
3,5-dibromosalicylaldehyde	279.91	0.621	2.22	1

Thiosemicarbazide was added to a hot (75 ^{o}C) solution of 3,5-dibromosalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 353.03 g/mol).

yield = 392 mg, 1.11 mmol, 50%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 11.50 (s, 1H, N*H*), 10.04 (bs, 1H, O*H*), 8.29 (s, 1H, *H*^{7}), 8.20 (br s, 2H, N*H*$_2$), 8.11 (br s 1H, *H*^{4}), 7.74 (d, ^{4}J = 2.3 Hz, 1H, *H*^{6}).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 178.9 (*C*^{8}), 152.8 (*C*^{2}), 139.3 (*C*^{7}), 136.0 (*C*^{4}), 129.9 (*C*^{6}), 126.0 (*C*^{q}), 113.8 (*C*^{q}), 112.9 (*C*^{q}).

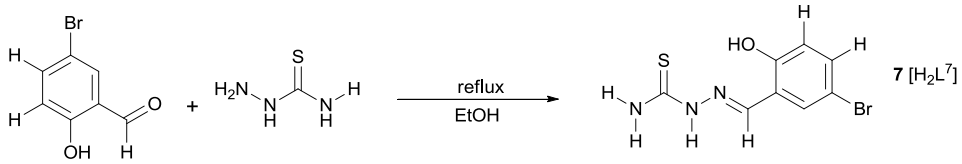
MS (EI): *m/z* = 353 (M^{+}).

Anal. Calcd. for $C_8H_7Br_2N_3OS$ (353.03 g/mol): C, 27.22; H, 2.00; N, 11.90. Found: C, 23.34; H, 2.01; N, 11.91.

IR (KBr, ν/ cm^{-1}): 3468s (ν_{OH}), 3357s-3015m (ν_{as} and ν_{sNH2}), 3155m (ν_{NH}), 1611s ($\nu_{C=N}$), 1542s, 1535s, 1288s, 1265m (ν_{CO}), 1138s, 1094m ($\nu_{C=S}$), 859w, 815w, 714w.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 321, 346, 413.

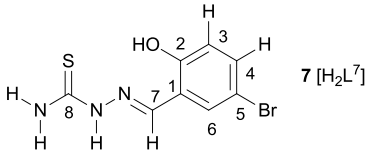
3.11.2.7 Ligand 7



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
5-bromosalicylaldehyde	201.02	0.446	2.22	1

Thiosemicarbazide was added to a hot (75 °C) solution of 5-bromosalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 274.14 g/mol).

yield = 511 mg, 1.87 mmol, 84%



^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.40 (s, 1H, N*H*), 10.21 (s, 1H, O*H*), 8.29 (s, 1H, H^7), 8.20 (d, ^4J = 2.6 Hz, 1H, H^6), 8.14 (br s, 2H, NH_2), 7.33 (dd, ^3J = 8.7 Hz, ^4J = 2.6 Hz, 1H, H^4), 6.82 (d, ^3J = 8.7 Hz, 1H, H^3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 179.0 (C^8), 156.4 (C^2), 138.1 (C^7), 134.0 (C^4), 129.2 (C^6), 123.7 (C^1), 119.0 (C^3), 112.0 (C^5).

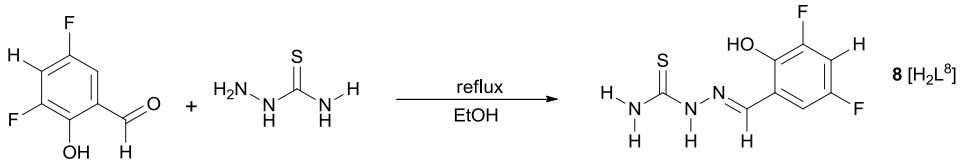
MS (EI): *m/z* = 273 (M^+).

Anal. Calcd. for $C_8H_8BrN_3OS$ (274.14 g/mol): C, 35.05; H, 2.94; N, 15.33. Found: C, 35.06; H, 2.59; N, 15.01.

IR (KBr, ν/ cm^{-1}): 3456s (ν_{OH}), 3250s-2997m (ν_{as} and ν_{sNH2}), 3162s (ν_{NH}), 1655s (δ_{NH2}), 1610s ($\nu_{C=N}$), 1601s, 1545s, 1294m, 1264m (ν_{CO}), 1064 ($\nu_{C=S}$), 819m (ν_{sCS}).

UV/Vis (10^{-5} M, DMSO (nm)): λ = 270, 347, 400.

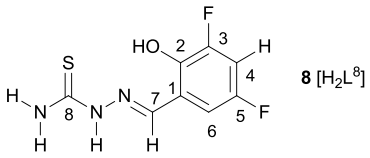
3.11.2.8 Ligand 8



Reagents	MW (g/mol)	g	mmol	EQ
Thiosemicarbazide	91.14	0.2022	2.22	1
3,5-difluorosalicylaldehyde	158.10	0.351	2.22	1

Thiosemicarbazide was added to a hot (75 °C) solution of 3,5-difluorosalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 231.22 g/mol).

yield = 159 mg, 0.688 mmol, 31%



^{1}H NMR (300 MHz, DMSO-d$_6$): δ = 11.51 (s, 1H, N*H*), 10.05 (s, 1H, O*H*), 8.34 (s, 1H, H^7), 8.19 (br s, 2H, NH_2), 7.78 (d, ^3J = 9.5 Hz, 1H, H^4), 7.22 (dt, ^3J = 9.5 Hz, ^4J = 2.9 Hz, 1H, H^6).

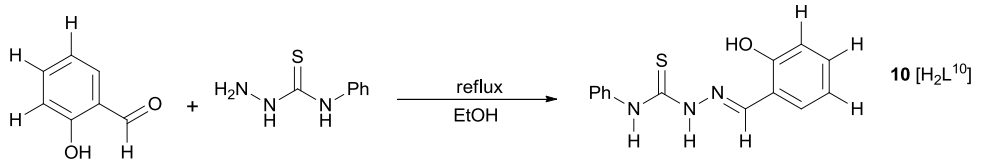
^{19}F NMR (282 MHz, DMSO-d$_6$): δ = -122.0 (pst, ^3J = 9.5 Hz, 1F, F^5), -131.1 (d, ^3J = 9.6 Hz, 1F, F^3).

MS (EI): *m/z* = 231 (M^+).

Anal. Calcd. for $C_8H_7F_2N_3OS$ (231.22 g/mol): C, 41.56; H, 3.05; N, 18.17. Found: C, 41.54; H, 3.14; N, 18.02.

IR (KBr, ν/ cm^{-1}): 3430s, 3324m, 3289s, 3176s, 1618s, 1588m, 1541s, 1485s, 1459s, 1378s, 1298m, 1226m, 1104m, 1011m, 987m, 832m.

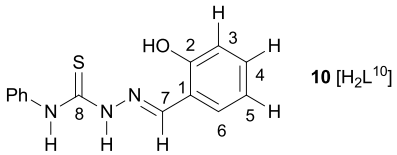
3.11.2.9 Ligand 10



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-Phenylthiosemicarbazide	167.23	0.371	-	-	2.22	1
salicylaldehyde	122.12	0.2713	1.146	0.237	2.22	1

4-Phenylthiosemicarbazide was added to a hot (75 °C) solution of salicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 271.34 g/mol).

yield = 398 mg, 1.46 mmol, 66%



^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 11.75 (s, 1H, N*H*), 10.04 (s, 1H, N*H*Ph), 9.97 (bs, 1H, O*H*), 8.50 (s, 1H, H^7), 8.08 (d, *J* = 7.6 Hz, 1H, H^6), 7.58 (d, *J* = 7.8 Hz, 2H, PhH_{ortho}), 7.37 (pst, *J* = 7.8 Hz, 2H, PhH_{meta}), 7.24 (pst, *J* = 7.6 Hz, 1H, H^4), 7.20 (pst, *J* = 7.8 Hz, 1H, PhH_{para}), 6.89 (d, *J* = 7.6 Hz, 1H, H^3), 6.84 (pst, *J* = 7.6 Hz, 1H, H^5).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 176.6 (C^8), 157.5 (C^2), 141.0 (C^7), 140.0 (C^{Ph}), 132.2 (C^4), 128.9 ($C^{Ph\text{-}meta}$), 127.9 (C^6), 126.5 ($C^{Ph\text{-}ortho}$), 126.0 ($C^{Ph\text{-}para}$), 121.1 (C^1), 120.1 (C^3), 116.9 (C^5).

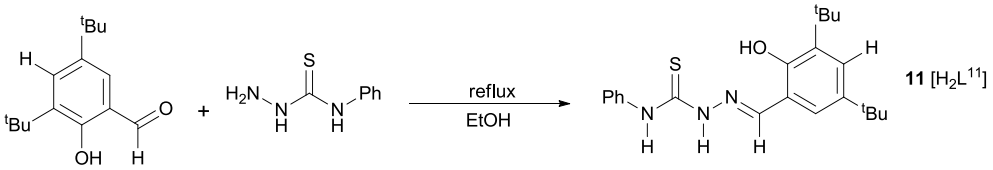
MS (EI): *m/z* = 271 (M^+).

Anal. Calcd. for $C_{14}H_{13}N_3OS$ (271.34 g/mol): C, 61.97; H, 4.83; N, 15.49. Found: C, 61.40; H, 5.15; N, 15.29.

IR (KBr, ν/ cm^{-1}): 3380m, 3150s, 2992m, 1621m, 1604m, 1593m, 1539s, 1509s, 1271s, 1260m, 1208s, 1151m, 1080m, 1033m, 794w, 755m, 742m, 692m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 283, 344.

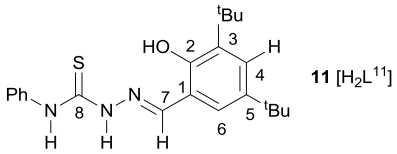
3.11.2.10 Ligand 11



Reagents	MW (g/mol)	g	mmol	EQ
4-Phenylthiosemicarbazide	167.23	0.371	2.22	1
3,5-di-tert-butylsalicylaldehyde	234.33	0.520	2.22	1

4-Phenylthiosemicarbazide was added to a hot (75 °C) solution of 3,5-di-tert-butylsalicylaldehyde in ethanol (20 mL). The reaction mixture was refluxed for 2.5 hrs. The reaction mixture was then concentrated to *ca.* 10 mL. The precipitated white product was filtered off, washed with water, methanol, recrystallized from ethanol and dried under vacuum. (MW 383.55 g/mol).

yield = 673 mg, 1.75 mmol, 79%



^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 11.66 (s, 1H, N*H*), 10.15 (s, 1H, N*H*Ph), 9.98 (br s, 1H, O*H*), 8.38 (s, 1H, *H*^{7}), 7.50 (d, *J* = 7.5 Hz, 2H, Ph*H*), 7.38 (pst, *J* = 7.5 Hz, 2H, Ph*H*), 7.32 (d, *J* = 2.1 Hz, 1H, *H*^{4}), 7.20 (m, 2H, *H*^{6} and Ph*H*), 1.41 (s, 9H, C*H*$_3$), 1.29 (s, 9H, C*H*$_3$).

^{13}C NMR (75 MHz, DMSO-d$_6$): δ = 177.1 (*C*^{8}), 154.1 (*C*^{2}), 149.1 (*C*^{7}), 141.8 (*C*^{Ph}), 140.2 (*C*^{5}), 136.9(*C*^{3}), 129.1 (*C*$^{Ph\text{-}meta}$), 126.7 (*C*$^{Ph\text{-}para}$), 126.6 (*C*^{4}), 126.4 (*C*$^{Ph\text{-}ortho}$)126.1 (*C*^{6}), 118.7 (*C*^{1}), 35.5 (*C*^{CMe3}), 34.8 (*C*^{CMe3}), 32.1 (*C*^{CH3}), 30.2 (*C*^{CH3}).

MS (EI): *m/z* = 383 (M^{+}).

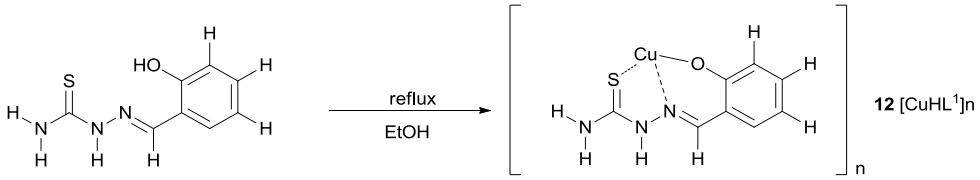
Anal. Calcd. for $C_{22}H_{29}N_3OS$ (383.55 g/mol): C, 68.89; H, 7.62; N, 10.96. Found: C, 68.58; H, 8.00; N, 10.91.

IR (KBr, ν/ cm^{-1}): 3325s, 3142s, 2956s, 1560s, 1545s, 1272s, 1210s, 1087m, 803w, 747m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 283, 345.

3.11.3 Synthesis of different complexes

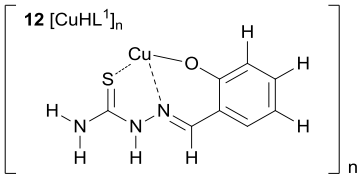
3.11.3.1 Complex 12



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^1, **1**	195.24	0.214	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^1 **1** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^1]_n$ (**12**) was collected as a light brown powder. (MW 257.78 g/mol).

yield = 234 mg, 0.909 mmol, 83%



MS (FAB^+): *m/z* = 258 (M^++1).

Anal. Calcd. for $C_8H_8CuN_3OS$: C, 37.27; H, 3.13; N, 16.30. Found: C, 37.66; H, 3.00; N, 16.14.

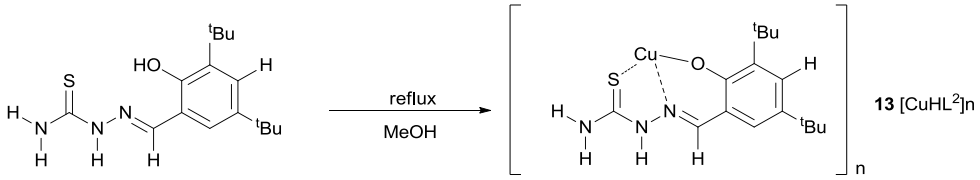
IR (KBr, ν/ cm^{-1}): 3467s, 3367s, 3352s, 3267s, 1599s, 1596m, 1511s, 1492s, 1317m, 1278m, 1210m, 1152w, 809m, 751s.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 279, 329, 396.

UV/Vis (10^{-3} M, DMSO (nm)): λ 578.

Conductance Λ_m (DMSO 10^{-3} M): 2.5 $\Omega^{-1}cm^2mol^{-1}$. $\mu_{eff.}$ (25°C) = diamagnetic.

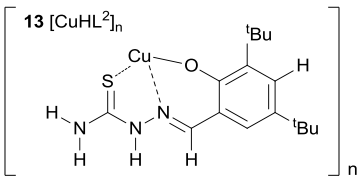
3.11.3.2 Complex 13



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^2, **2**	307.45	0.338	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^2 **2** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^2]_n$ (**13**) was collected as a brown powder. (MW 369.99 g/mol).

yield = 358 mg, 0.968 mmol, 88%



MS (FAB^+): *m/z* = 370 (M^++1), 677 $[2M\text{-}Cu + 2]^+$.

Anal. Calcd. for $C_{16}H_{24}CuN_3OS$: C, 51.94; H, 6.54; N, 11.36. Found: C, 51.90; H, 6.31; N, 11.10.

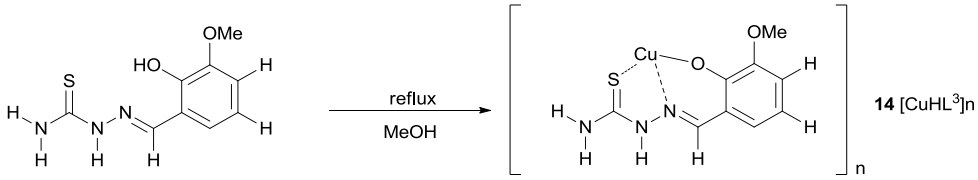
IR (KBr, ν/ cm^{-1}): 3472s, 3294s, 2960s, 1600s, 1596m, 1528m, 1432s, 1332s, 1301m, 1172s, 1026w, 839w, 784m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 275, 335, 407.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 583.

Conductance Λ_m (DMSO 10^{-3} M): 8.8 $\Omega^{-1}cm^2mol^{-1}$. $\mu_{eff.}$ (25°C) = diamagnetic.

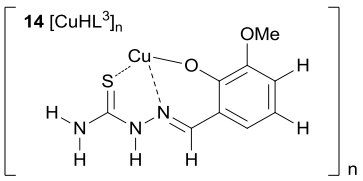
3.11.3.3 Complex 14



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^3, **3**	225.27	0.248	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^3 **3** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^3]_n$ (**14**) was collected as a green powder. (MW 287.81 g/mol).

yield = 184 mg, 0.638 mmol, 58%



MS (FAB^+): *m/z* = 288 (M^++1), 513 $[2M\text{-}Cu + 2]^+$.

Anal. Calcd. for $C_9H_{10}CuN_3O_2S$: C, 37.56; H, 3.50; N, 14.60. Found: C, 37.42; H, 3.39; N, 14.20.

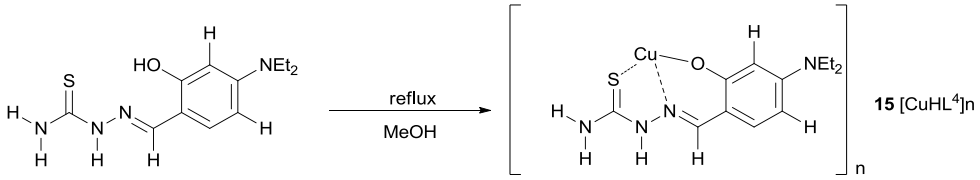
IR (KBr, ν/ cm^{-1}): 3449s, 3347m, 3303s, 3200m, 1618m, 1602s, 1336m, 1307m, 1246s, 1218s, 1085w, 968w, 857w, 775m, 734m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 260, 329, 398.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 577.

Conductance Λ_m (DMSO 10^{-3} M): 3.5 $\Omega^{-1}cm^2mol^{-1}$. $\mu_{eff.}$ (25°C) = diamagnetic.

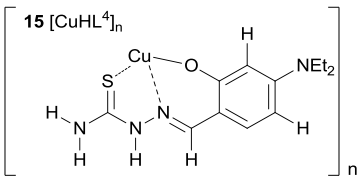
3.11.3.4 Complex 15



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^4, **4**	266.36	0.293	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^4, **4** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^4]_n$ (**15**) was collected as a light brown powder. (MW 328.90 g/mol).

yield = 326 mg, 0.990 mmol, 90%



MS (FAB^+): *m/z* = 329 (M^++1), 595 $[2M\text{-}Cu + 2]^+$.

Anal. Calcd. for $C_{12}H_{17}CuN_4OS$: C, 43.82; H, 5.21; N, 17.03. Found: C, 44,24; H, 5.07; N, 16.75.

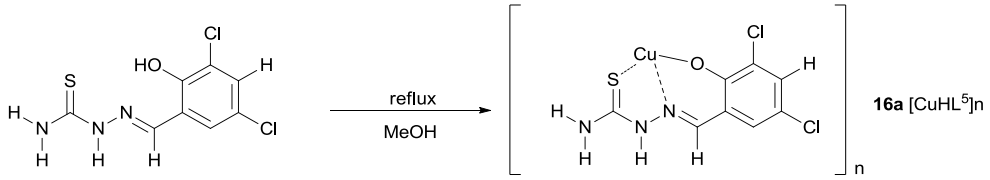
IR (KBr, ν/ cm^{-1}): 3409s, 3291m, 3103s, 2967m, 1637m, 1610s, 1587s, 1354s, 1297m, 1244s, 1134s, 1051w, 829w, 785m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 270, 388.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 573.

Conductance Λ_m (DMSO 10^{-3} M): 1.2 $\Omega^{-1}cm^2mol^{-1}$.

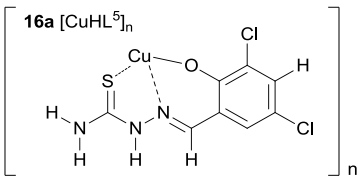
3.11.3.5 Complex 16a



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^5, **5**	264.13	0.291	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^5, **5** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^5]_n$ (**16a**) was collected as a brown powder. (MW 326.67 g/mol).

yield = 262 mg, 0.803 mmol, 73%



MS (FAB^+): *m/z* =326 (M^++1).

Anal. Calcd. for $C_8H_6Cl_2CuN_3OS$: C, 29.41; H, 1.85; N, 12.86. Found: C, 29.32; H, 1.80; N, 12.82.

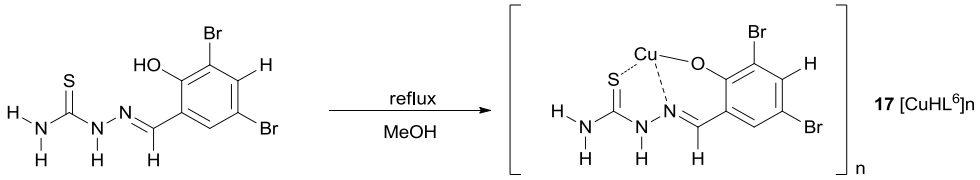
IR (KBr, ν/ cm^{-1}): 3439s, 3247m, 3154s, 1617s, 1613s, 1477s, 1441s, 1342m, 1319m, 1213m, 1182s, 866w, 772m, 760m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 274, 331, 418.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 591.

Conductance Λ_m (DMSO 10^{-3} M): 8.0 $\Omega^{-1}cm^2mol^{-1}$.

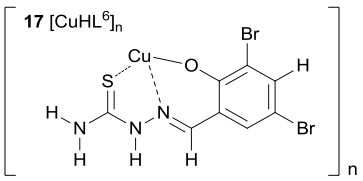
3.11.3.6 Complex 17



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^6, **6**	353.03	0.388	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^6, **6** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^6]_n$ (**17**) was collected as a brown powder. (MW 415.57 g/mol).

yield = 233 mg, 0.561 mmol, 51%



MS (FAB^+): *m/z* = 414 (M^++1), 766 $[2M\text{-}Cu + 2]^+$, 829 $[2M + 2]^+$.

Anal. Calcd. for $C_8H_6Br_2CuN_3OS$: C, 23.12; H, 1.46; N, 10.11. Found: C, 23.18; H, 1.50; N, 9.98.

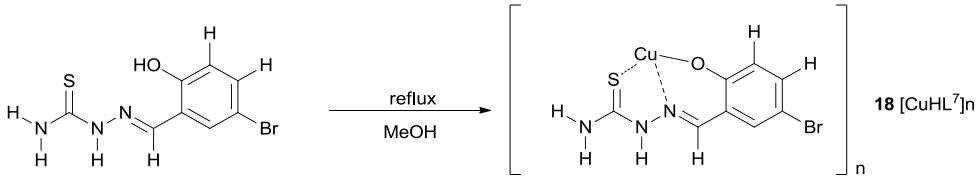
IR (KBr, ν/ cm^{-1}): 3468s, 3232m, 3135m, 3066m, 1618s, 1608m, 1596m, 1474s, 1435s, 1410m, 1340m, 1308m, 1218m, 1167m, 867w, 730m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 276, 341, 410.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 585.

Conductance Λ_m (DMSO 10^{-3} M): 4.2 $\Omega^{-1}cm^2mol^{-1}$.

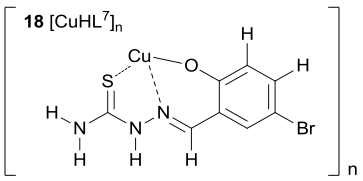
3.11.3.7 Complex 18



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^7, **7**	274.14	0.302	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^7, **7** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^7]_n$ (**18**) was collected as a brown powder. (MW 336.68 g/mol).

yield = 248 mg, 0.737 mmol, 67%



MS (FAB^+): *m/z* = 336 (M^++1).

Anal. Calcd. for $C_8H_7BrCuN_3OS$: C, 28.54; H, 2.10; N, 12.48. Found: C, 28.77; H, 2.09; N, 11.99.

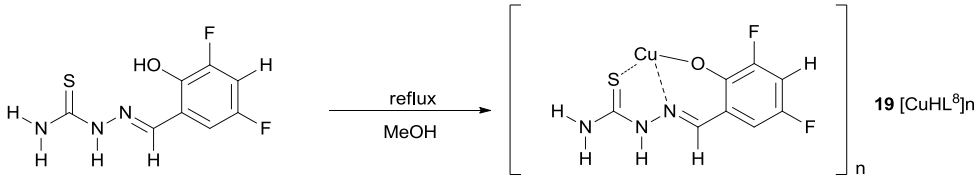
IR (KBr, ν/ cm^{-1}): 3418s, 3268m, 2999s, 1637s, 1600s, 1496s, 1464s, 1341m, 1294m, 1187s, 1038m, 869w, 809m, 751w.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 271, 335, 406.

UV/Vis (10^{-3} M, DMSO (nm)): λ = 578.

Conductance Λ_m (DMSO 10^{-3} M): 5.2 $\Omega^{-1}cm^2mol^{-1}$. $\mu_{eff.}$ (25°C) = 1.18 B.M.

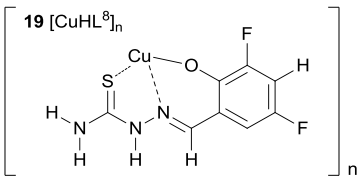
3.11.3.8 Complex 19



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^8, **8**	231.22	0.254	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^8, **8** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^8]_n$ (**19**) was collected as a dark green powder. (MW 293.76 g/mol).

yield = 107 mg, 0.363 mmol, 33%



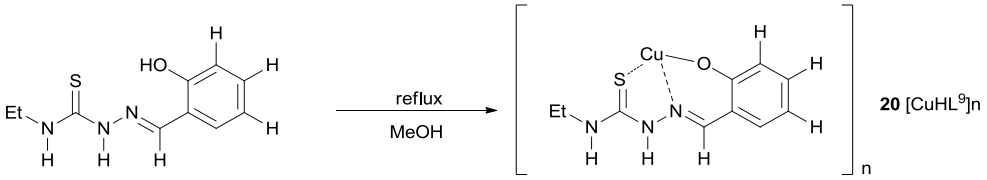
MS (FAB^+): *m/z* = 294 (M^++1).

Anal. Calcd. for $C_8H_6CuF_2N_3OS$: C, 32.71; H, 2.06; N, 14.30. Found: C, 33.11; H, 1.74; N, 14.40.

IR (KBr, ν/ cm^{-1}): 3430m, 3301s, 3154m, 2874m, 1587s, 1561m, 1465s, 1300m, 1267s, 1125s, 1069w, 997m, 849w, 832s, 745w.

Conductance Λ_m (DMSO 10^{-3} M): 1.0 $\Omega^{-1}cm^2mol^{-1}$.

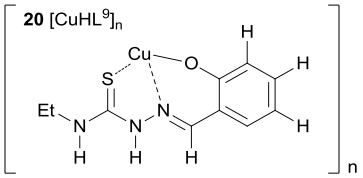
3.11.3.9 Complex 20



Reagents	MW (g/mol)	g	mmol	EQ
2-Hydroxybenzaldehyde N-ethylthiosemicarbazone, **9**	223.29	0.246	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 ^oC) solution of 2-Hydroxybenzaldehyde N-ethylthiosemicarbazone, **9** in ethanol (50 mL) at 75 ^oC. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^9]_n$ (**20**) was collected as a light brown powder. (MW 285.83 g/mol).

yield = 267 mg, 0.936 mmol, 85%



^1H NMR (300 MHz, $CDCl_3$): δ = 11.75 (bs, 1H, C*H*), 11,00 (br s, 1H, O*H* or N*H*), 8.00-7.80 (br s, 2H, Ar*H*), 5.98 (br, 2H, Ar*H*), 4.11 (br s, 1H, N*H*), 1.75 (br, 2H, CH_2), 1.58 (br, 2H, CH_3).

MS (FAB^+): *m/z* = 286 (M^++1).

Anal. Calcd. for $C_{10}H_{12}CuN_3OS$: C, 42.02; H, 4.23; N, 14.70. Found: C, 41.67; H, 4.13; N, 14.92.

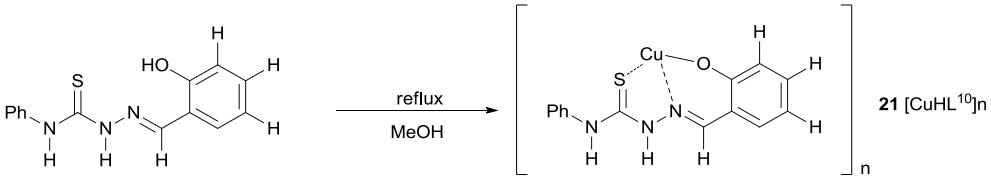
IR (KBr, ν/ cm^{-1}): 3369s, 2968m, 1596s, 1555m, 1506s, 1474s, 1438m, 1320m, 1280m, 1204s, 1156w, 1073w, 835w, 745m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 275, 332, 397.

UV/Vis (10^{-3} M, DMSO (nm)): λ 577.

Conductance Λ_m (DMSO 10^{-3} M): 3.1 $\Omega^{-1}cm^2mol^{-1}$.

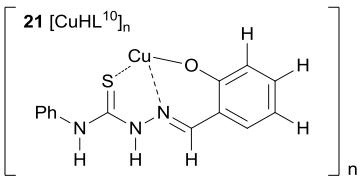
3.11.3.10 Complex 21



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^{10}, **10**	271.34	0.298	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^{10}, **10** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^{10}]_n$ (**21**) was collected as a light brown powder. (MW 333.88 g/mol).

yield = 228 mg, 0.682 mmol, 62%



MS (FAB^+): *m/z* = 334 (M^++1), 605 $[2M\text{-}Cu + 2]^+$.

Anal. Calcd. for $C_{14}H_{12}CuN_3OS$: C, 50.36; H, 3.62; N, 12.59. Found: C, 50.25; H, 3.72; N, 12.28.

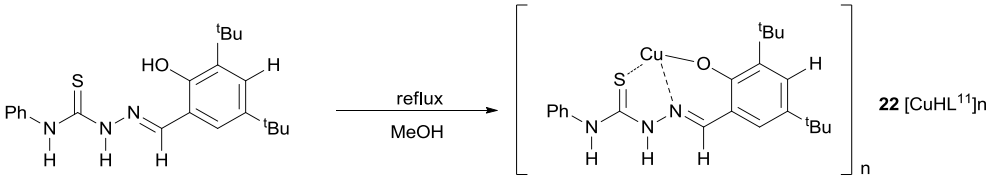
IR (KBr, ν/ cm^{-1}): 3404w, 3235m, 3024m, 2937m, 1595m, 1508m, 1498m, 1458s, 1431s, 1314m, 1251w, 1210m, 1178m, 1088w, 866w, 769m, 747m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 287, 323, 408.

UV/Vis (10^{-3} M, DMSO (nm)): no *d-d band* was detected.

Conductance Λ_m (DMSO 10^{-3} M): 3.5 $\Omega^{-1}cm^2mol^{-1}$.

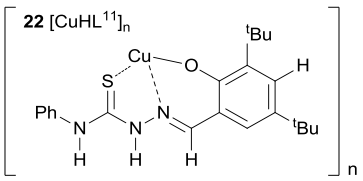
3.11.3.11 Complex 22



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^{11}, **11**	383.55	0.422	1.10	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.222	1.11	1

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (75 °C) solution of H_2L^{11}, **11** in ethanol (50 mL) at 75 °C. The reaction mixture was then refluxed for 2.5 h. The brown precipitate so formed was recovered by filtration and was recrystallized from refluxing ethanol. The collected solid was suspended in cold ethanol (3 x 10 mL), separated by centrifugation, then suspended in diethyl ether (3 x 10 mL), separated by centrifugation and dried under vacuum. $[CuHL^{11}]_n$ (**22**) was collected as a dark green powder. (MW 446.09 g/mol).

yield = 228 mg, 0.682 mmol, 77%



MS (FAB^+): *m/z* = 446 (M^++1), 829 $[2M\text{-}Cu + 2]^+$.

Anal. Calcd. for $C_{22}H_{28}CuN_3OS$: C, 59.23; H, 6.33; N, 9.42. Found: C, 58.92; H, 6.46; N, 9.33.

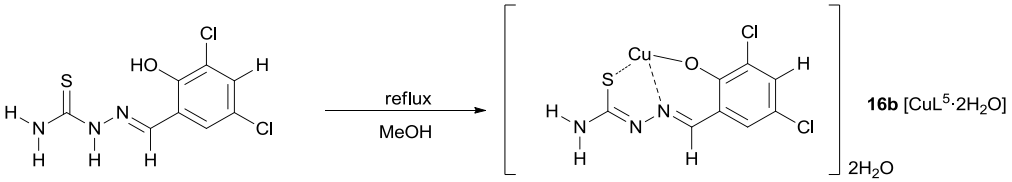
IR (KBr, ν/ cm^{-1}): 3421m, 3221m, 2955s, 2904m, 2868m, 1592s, 1541s, 1498s, 1548s, 1438s, 1314m, 1299m, 1256s, 1167s, 1065w, 832w, 745m.

UV/Vis (10^{-5} M, DMSO (nm)): λ = 324, 417.

UV/Vis (10^{-3} M, DMSO (nm)): λ 592.

Conductance Λ_m (DMSO 10^{-3} M): 2.5 $\Omega^{-1}cm^2mol^{-1}$.

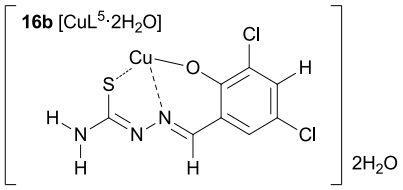
3.11.3.12 Complex 16b



Reagents	MW (g/mol)	g	mmol	EQ
H_2L^5, **5**	264.13	0.191	0.723	1
$Cu(CO_2CH_3)_2\ H_2O$	199.65	0.200	1.00	1.4

A solution of copper(II) acetate monohydrate in the minimum required amount of methanol was added dropwise to a hot (60 °C) solution of H_2L^5, **5** in methanol (50 mL). The reaction mixture was refluxed for 3 h and then concentrated to half volume. The dark green precipitate so formed was recovered by filtration, it was washed with ethanol, then with diethyl ether and dried under vacuum over anhydrous $CaCl_2$. [$CuL^5 \cdot 2H_2O$] (**16b**) was collected as a dark green powder.(MW 361.69 g/mol).

yield = 205 mg, 0.564 mmol, 78%



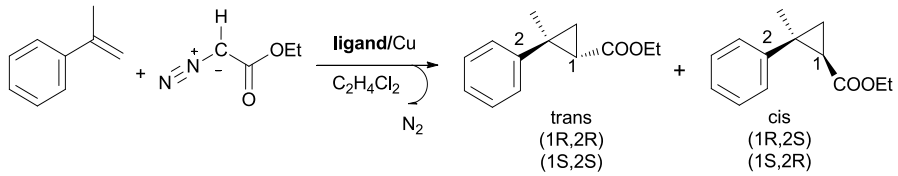
Anal. Calcd. for $C_8H_9Cl_2CuN_3O_3S$: C, 26.57; H, 2.51; N, 11.91; Cu 17.57. Found: C, 26.42; H, 2.63; N, 11.74; Cu 17.44.

IR (KBr, ν/ cm^{-1}): 3480s, 3464s, 3277s, 3182s, 1748w, 1620s, 1610m, 1601s, 1473s, 1439s, 1314s, 1212s, 1164w, 950m, 867m, 630w, 520w, 431w, 364w.

$\mu_{eff.}$ (25°C) = 1.79 B.M.

3.11.4 Cyclopropanation reactions

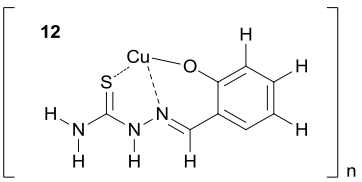
3.11.4.1 Cyclopropanation with different complexes



All the reactions carried out for this section were conducted between α-methlstyrene and ethyldiazoacetate (EDA) with different preformed complexes**.** EDA (2.52 mmol) dissolved in 1,2-dichloroetahne (DCE) (1 mL) was slowly added (100 min) with a syringe pump to a hot (70 °C) solution of catalyst (0.0051 mmol) and α-methylstyrene (5.1 mmol) in DCE (9 mL), with catalyst/EDA/ α-methylstyrene ratio 1/500/1000. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yields were determined by GC with the addition of 2,4-dinitrotoluene as internal standard. Isolated yields are reported in parentheses; in these cases the solvent was evaporated under vacuum and the crude product was purified by chromatographic column (eluant EtOAc/*n*-hexane : 0.3/10). The two diasteroisomers of the cyclopropane molecules were obtained (MW 204.26 g/mol). Fumarate and maleate accounted for the rest of the reaction mass balance.

3.11.4.1.1 Catalysis with complex 12

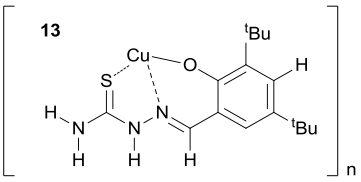
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
12	257.78	0.00131	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.411	2.01	>99%	79	56:44

3.11.4.1.2 Catalysis with complex 13

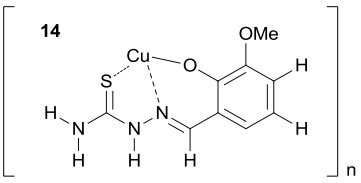
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
13	369.99	0.00189	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.406	1.99	>99%	78	56:44

3.11.4.1.3 Catalysis with complex 14

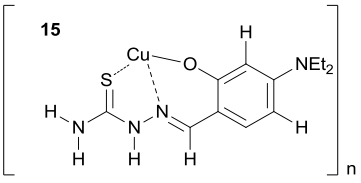
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
14	287.81	0.00147	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.3002	1.48	>99%	58	55:44

3.11.4.1.4 Catalysis with complex 15

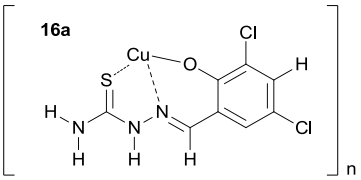
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
15	328.90	0.00168	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.323	1.58	>99%	62	56:44

3.11.4.1.5 Catalysis with complex 16a

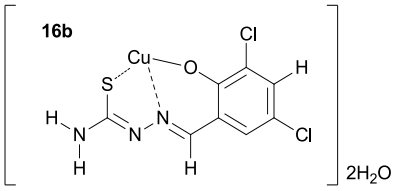
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16a	326.67	0.00167	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.505	2.47	>99%	97 (68)	57:43

3.11.4.1.6 Catalysis with complex 16b

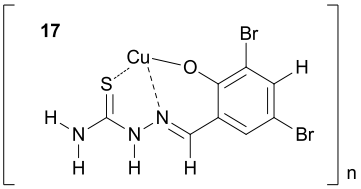
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.505	2.47	>99%	97	57:43

3.11.4.1.7 Catalysis with complex 17

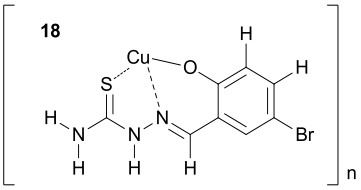
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
17	415.57	0.00212	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.484	2.37	>99%	93	55:45

3.11.4.1.8 Catalysis with complex 18

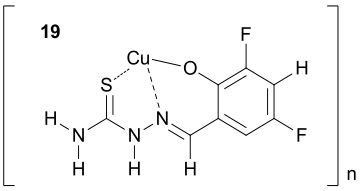
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
18	336.68	0.00172	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.479	2.35	>99%	92	56:44

3.11.4.1.9 Catalysis with complex 19

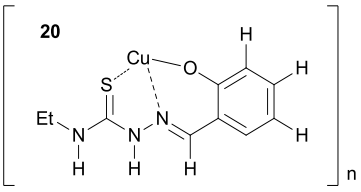
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
19	293.76	0.00172	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.281	1.38	>99%	54	54:46

3.11.4.1.10 Catalysis with complex 20

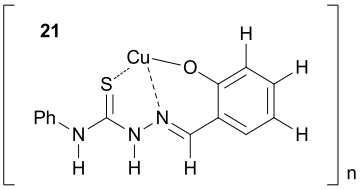
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
20	285.83	0.00146	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.421	2.06	>99%	81	56:44

3.11.4.1.11 Catalysis with complex 21

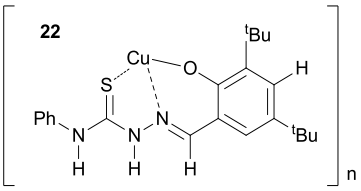
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
21	333.88	0.00170	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.453	2.22	>99%	87	57:43

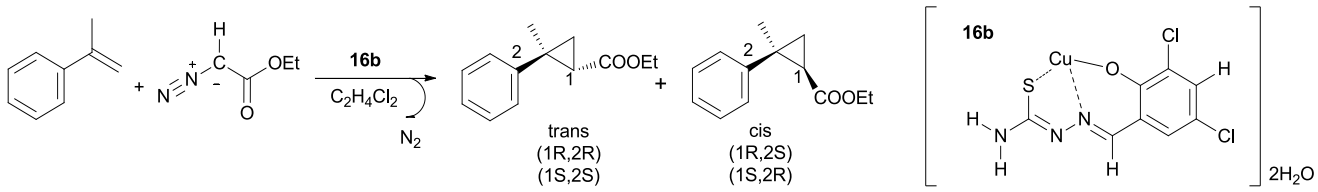
3.11.4.1.12 Catalysis with complex 22

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.602	0.909	0.662	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
22	446.09	0.00228	-	-	0.00510	1



g	mmol	conver. (%)	yield (%)	*trans:cis*
0.458	2.24	>99%	88	55:45

3.11.4.2 Optimization of the catalysed cyclopropanation reaction



All the reactions carried out for this section were conducted between α-methlstyrene and ethyldiazoacetate (EDA) with complexes **16b.** EDA was added to a hot (70 °C) solution of catalyst and α-methylstyrene in DCE. Different ratio between **16b**/EDA/ α-methylstyrene were tested. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yields were determined by GC with the addition of 2,4-dinitrotoluene as internal standard. The two diasteroisomers of the cyclopropane molecules were obtained (MW 204.26 g/mol). Fumarate and maleate accounted for the rest of the reaction mass balance.

3.11.4.2.1 Catalysis 1/500/1000

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.886	0.909	0.974	7.50	1000
EDA	114.11	0.428	1.082	0.395	3.75	500
16b	361.69	0.00273	-	-	0.00750	1

EDA was added to a solution of **16b** and α-methylstyrene in dichloroethane (10 mL) at 70 °C. After complete consumption of the starting EDA, the catalytic cycle was restored twice by addition of EDA and α-methylstyrene; global yield is reported.

time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
7/5/5	2.00	9.79	>99%	87	57:43

3.11.4.2.2 Catalysis 1/1000/1500

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.661	0.909	0.727	5.60	1500
EDA	114.11	0.427	1.082	0.394	3.73	1000
16b	361.69	0.00135	-	-	0.00373	1

EDA dissolved in DCE (1 mL) was slowly added to a solution of **16b** and α-methylstyrene in dichloroethane (9 mL) at 70 °C. After complete consumption of the starting EDA, the catalytic cycle was restored twice by addition of EDA and α-methylstyrene; global yield is reported.

time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100/100/100	2.17	10.6	>99%	95	57:43

3.11.4.2.3 Catalysis 1/10000/20000

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.881	0.909	0.969	7.46	20000
EDA	114.11	0.426	1.082	0.393	3.73	10000
16b	361.69	0.000135	-	-	0.000373	1

This solution was prepared by dissolving **16b** (1.35 mg, 0.0037 mmol) in DCE (10 mL); 1 mL of this solution was added to the solution of α-methylstyrene in 9 mL of DCE.

time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
380	0.587	2.87	92	77	56:44

3.11.4.2.4 Catalysis 1/20000/40000

Reagents	MW (g/mol)	g	d	mL	mmol	EQ
α-methylstyrene	118.08	0.874	0.909	0.961	7.40	40000
EDA	114.11	0.422	1.082	0.390	3.70	20000
16b	361.69	0.0000675	-	-	0.000185	1

This solution was prepared by dissolving **16b** (1.35 mg, 0.0037 mmol) in DCE (10 mL); 0.5 mL of this solution was added to the solution of α-methylstyrene in 9.5 mL of DCE.

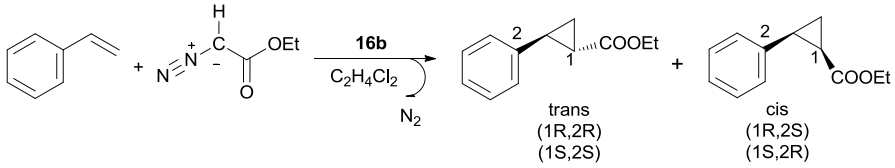
time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
420	0.559	2.74	92	74	55:45

3.11.4.3 Reaction scope with different ligands

General procedure for the catalytic cyclopropanation reactions

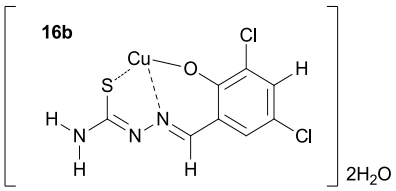
In a typical experiment, EDA was added to a solution of catalyst (0.0051 mmol) and olefin in dichloroethane (10 mL) at 70 °C with a catalyst/EDA/olefin ratio of 1/500/1000. The reaction was monitored by IR, following the disappearance of the band due to the stretching of N_2 moiety at 2114 cm^{-1}. The reaction was considered to be finished when the absorbance of the EDA was below 0.03 (by using a 0.1 mm thick 10 cell). All the reported yields were determined by GC with the addiction of 2,4-dinitrotoluene as internal standard. Isolated yields are reported in parentheses. Fumarate and maleate accounted for the rest of the reaction mass balance.

3.11.4.3.1 Styrene with 16b



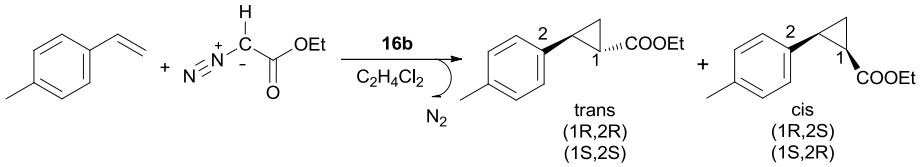
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
styrene	104.15		0.906		5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

(MW 190.24 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
12	0.330	1.73	> 99	68	72:28

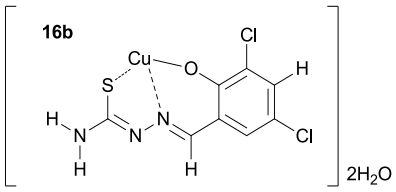
3.11.4.3.2 4-methylstyrene with 16b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(Me)styrene	104.15	0.531	0.906	0.586	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

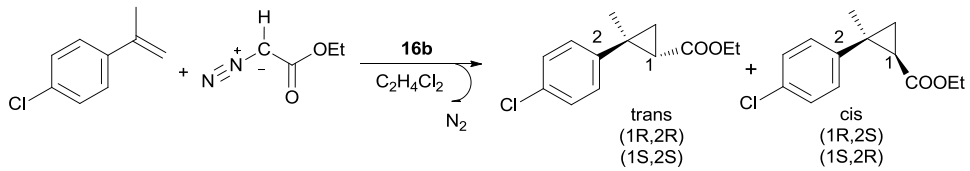
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 204.26 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.516	2.52	> 99	99(90)	92:8

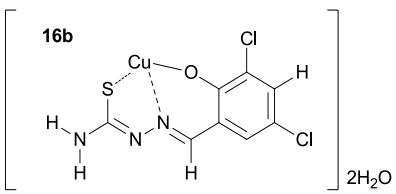
3.11.4.3.3 4-chloro-α-methylstyrene with 16b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
4-(Cl)-α-(Me)styrene	152.62	0.778	1.065	0.731	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

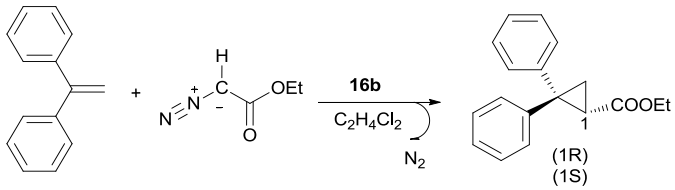
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 238.71 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.499	2.09	> 99	82(68)	57:43

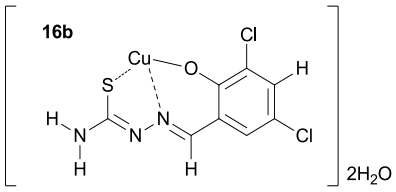
3.11.4.3.4 1,1-diphenylethylene with 16b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1,1-(diPh)ethylene	180.25	0.919	1.021	0.900	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

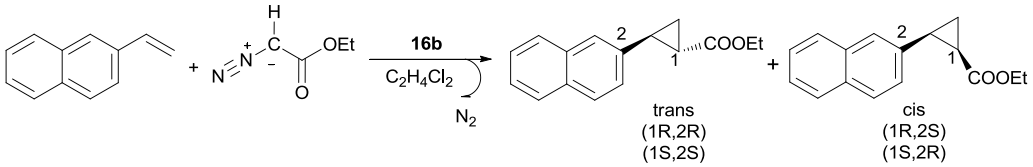
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 266.13 g/mol).



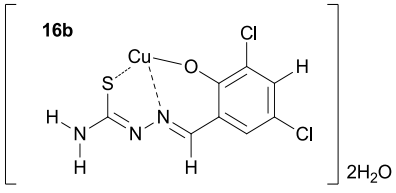
time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.610	2.30	> 99	90(63)	-

3.11.4.3.5 2-vinylnaphthalene with 16b



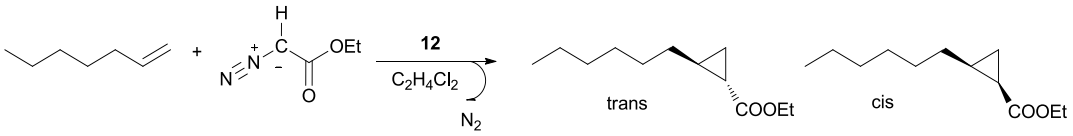
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
2-Vinylnaphthalene	154.21	0.786	-	-	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

(MW 240.30 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
31	0.466	1.94	> 99	76	71:29

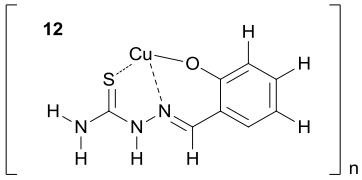
3.11.4.3.6 1-octene with 12



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	0.623	0.715	0.872	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
12	257.78	0.00131	-	-	0.00510	1

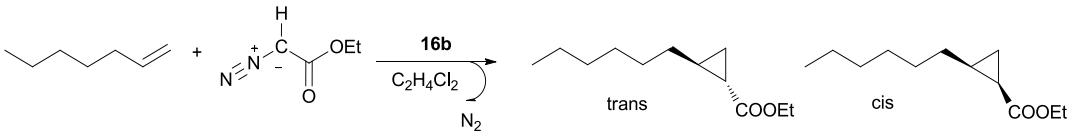
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 198.30 g/mol).



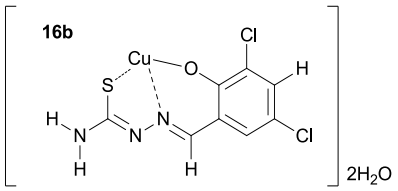
time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.319	1.61	> 99	63	68:32

3.11.4.3.7 1-octene with 16b



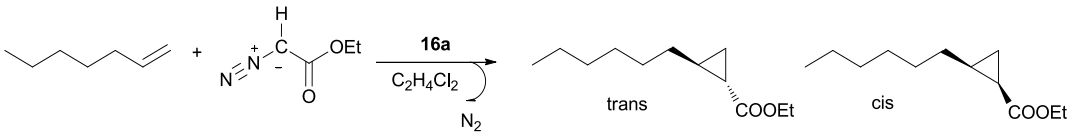
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	0.623	0.715	0.872	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

(MW 198.30 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
19	0.329	1.66	> 99	65	69:31

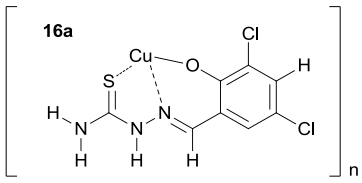
3.11.4.3.8 1-octene with 16a



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	0.623	0.715	0.872	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16a	326.67	0.00167	-	-	0.00510	1

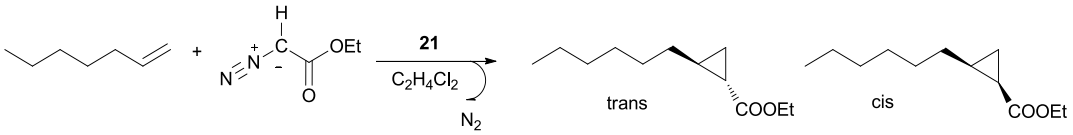
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 198.30 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.379	1.91	> 99	75	80:20

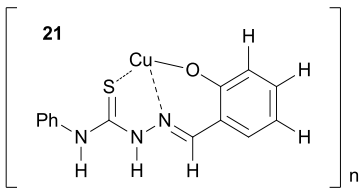
3.11.4.3.9 1-octene with 21



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	0.623	0.715	0.872	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
21	333.88	0.00170	-	-	0.00510	1

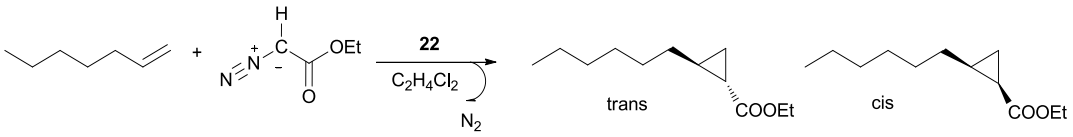
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 198.30 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.384	1.94	> 99	76	73:27

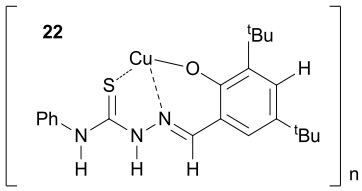
3.11.4.3.10 1-octene with 22



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
1-octene	122.22	0.623	0.715	0.872	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
22	446.09	0.00228	-	-	0.00510	1

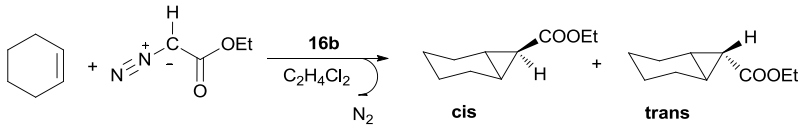
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 198.30 g/mol).



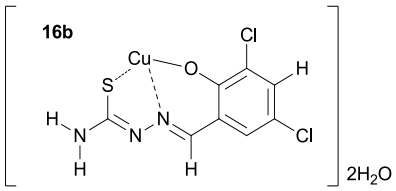
time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.394	1.99	> 99	78	66:44

3.11.4.3.11 Cyclohexene with 16b



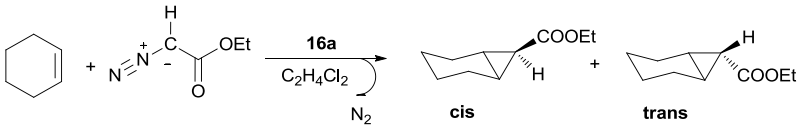
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
cyclohexene	82.14	0.419	0.811	0.516	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

(MW 168.23 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
11	0.287	1.71	> 99	67	91:9

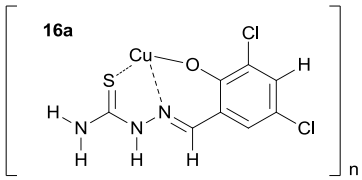
3.11.4.3.12 Cyclohexene with 16a



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
cyclohexene	82.14	0.419	0.811	0.516	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16a	326.67	0.00167	-	-	0.00510	1

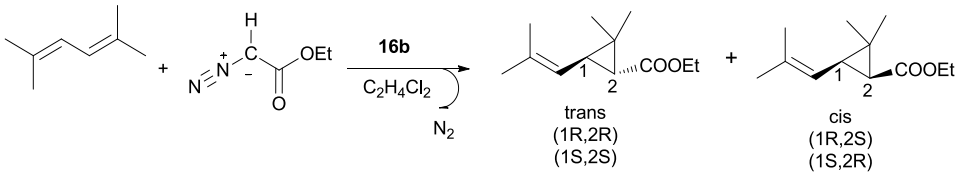
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 198.30 g/mol).



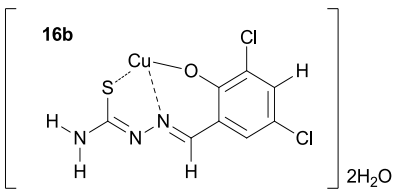
time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.395	2.35	> 99	92	91:9

3.11.4.3.13 2,5-dimethyl-2,4-hexdiene with 16b



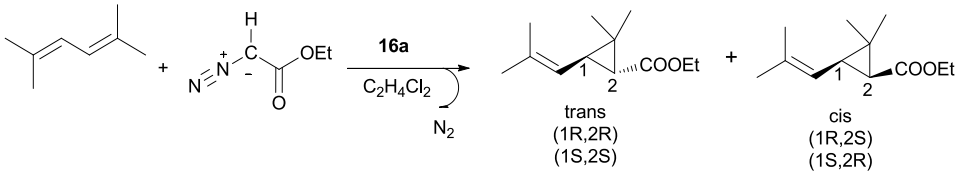
Reagents	MW (g/mol)	g	d	mL	mmol	EQ
2,5-dimethyl-2,4-hexdiene	110.20	0.562	0.773	0.727	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

(MW 196.29 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
32	0.410	2.09	> 99	82	64:36

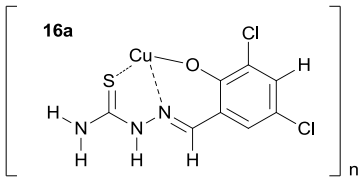
3.11.4.3.14 2,5-dimethyl-2,4-hexdiene with 16a



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
2,5-dimethyl-2,4-hexdiene	110.20	0.562	0.773	0.727	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16a	326.67	0.00167	-	-	0.00510	1

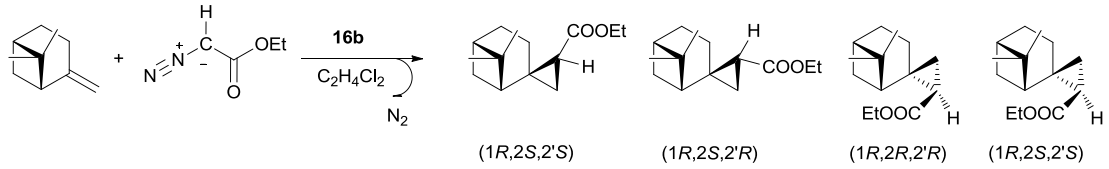
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL).

(MW 196.29 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	*trans:cis*
100	0.490	2.50	> 99	98	50:50

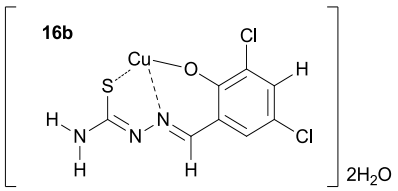
3.11.4.3.15 (-)β-pinene with 16b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
(-)β-pinene	136.23	0.695	0.866	0.802	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

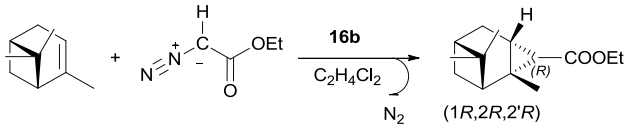
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL). The two major products were determined to be (1R,2R,2'R) and (1R,2R,2'S).[230] The fourth possible diastereoisomer was not detected.

(MW 222.32 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	-
100	0.482	2.17	> 99	85(51)	58:41:1:0

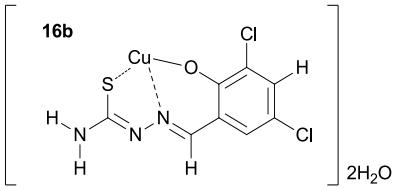
3.11.4.3.16 (-)α-pinene with 16b



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
(-)α-pinene	136.23	0.695	0.858	0.810	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
16b	361.69	0.00184	-	-	0.00510	1

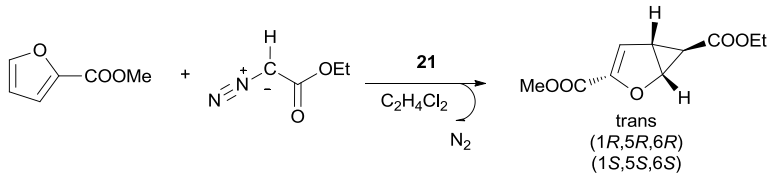
EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL). Only one diasteroeisomer (1R, 2R, 2'R) was isolated (*n*-hexane:EtOAC / 8:2).[230]

(MW 222.32 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	-
100	0.510	2.30	> 99	90 (84)	> 99

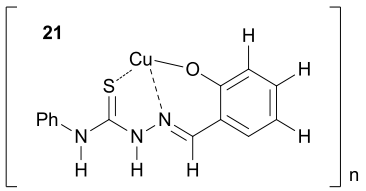
3.11.4.3.17 Methyl-2-furoate with 21



Reagents	MW (g/mol)	g	d	mL	mmol	EQ
Methyl-2-furoate	126.11	0.643	1.179	0.546	5.10	1000
EDA	114.11	0.291	1.082	0.269	2.55	500
21	333.88	0.00170	-	-	0.00510	1

EDA dissolved in DCE (1 mL) was slowly added to the solution containing the catalyst and the olefin in dichloroethane (9 mL). Only one diasteroeisomer (1R, 2R, 2'R) was isolated.[230]

(MW 210.20 g/mol).



time (min)	g	mmol	conver. (%)	yield (%)	-
100	0.0812	0.382	> 99	15	> 99

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