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Modular approach to chiral pyridine containing macrocycles: synthesis, characterization, reactivity and catalytic activity of their metal complexes

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1. INTRODUCTION

1.1 Overview on macrocycles

The history of macrocyclic compounds could be really long, since, in a certain way, they are ancients as life: porphyrins, corrins, chlorins are natural compounds with biological and vital roles both in animal (*i.e.* hemoglobin) and in vegetal world (*i.e.* chlorophyll). Anyway, while the first synthesized porphyrin is dated to 1926, thanks to the works of Fisher and Walach[1], the first non-natural macrocycle came to life "only" in 1960, when N. F. Curtis synthesized a nickel (II) complex from tris-ethylenediamine nickel (II) perchlorate and acetone.[2]

The strong importance of the biological occurring macrocycles directed the development of this branch of the metallorganic chemistry to the mimicking of those species. The natural ligands have been taken as model in the synthesis, causing an initial predominance of nitrogen containing ligands with respect to macrocycles bearing other heteroatoms. Regardless of their nature, the role of these heteroatoms was always to act as donating moiety and coordination site.
The interest around oxygen containing ligands grown with the design of molecules that could act as receptors for recognition in modeling biological processes (i.e. ion transport). The studies of Pedersen, in 1967,[3] led to the synthesis of a large and versatile class of ligands able to strongly coordinate alkali and alkaline earth metals. These macrocycles had been called cyclic polyethers or crown ethers. A couple of years later, Lehn synthesized the mixed oxygen-nitrogen cryptands[4] and a few more years after, Cram obtained the first examples of cavitands.[5] These studies allowed the three chemists to be awarded of the Nobel Prize in chemistry in 1987.

[1] H. Fisher, B. Walach, *Justus Liebigs Ann. Chem.*, **1926**, 450, 164-181
[2] N. Curtis, *Journal of the Chemical Society* **1960,** 4409-4413
[3] C. J . Pedersen, *J. Am. Chem. Soc.* **1967,** *89,* 7017-7036
[4] B. Dietrich, J. M. Lehn, J. P. Sauvage, *Tetrahedron Lett.* **1969,** *10,* 2889-2892
[5] D. J. Cram, *Science (Washington D.C.)* **1983,** 1177-1183

1.2 Macrocyclic versus acyclic chelators

Even if the first macrocycles were synthesized in 1960, it was only in 1969 that in literature was introduced the concept of "macrocyclic effect".[6] With this name, it is described the notable enhancement of the complex stability constants of ligands with cyclic structure with respect to the acyclic analogues. The thermodynamic stabilities of macrocycles and acyclic compounds have been determined to be comparable, but there is a great difference for what concern the kinetic liability, since macrocycles, generally speaking, are drastically more inert than acyclic ligands.[7,8,9,10] Is well known that the presence of more than one coordination atom increases the stability of the complexes (chelating effect); at the same time, the cyclic structure imposes a reduced structural freedom to the ligands, determining a constrained geometry and, consequently, a preorganized binding site. On the contrary, acyclic chelators, must undergo to a heavy change of geometry to organize the binding atoms in the right orientation to coordinate the metal ion: for this reason, the entropy drastically decreases, making the coordination unfavorable with respect to macrocyclic ligands.[11]

In this way they can complex only those metal ions with the correct ion radius (ring size effect). For this reason, the structure of the macrocycles and their chemical and electronic properties strongly affect their affinity for one or another metal.

1.3 Aza-Macrocycles

As mentioned above, the polyaza macrocycles are a common class of macrocyclic compounds, because their similarity with natural and fundamental molecules and because their ability to form stable complexes with metals from the later transition series, more than with alkali or alkaline earth metal ions. This important difference with respect to polyethers makes polyaza macrocycles more suitable for application in organometallics.

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[6] D. K. Cabbiness, D. W. Margerum, *J. Am. Chem. Soc.* **1969**, *91*, 6540-6541
[7] J. Byegård, G. Skarnemark and M. Skålberg, *J. Radioanal. Nucl. Chem.*, **1999,** *241*, 281-290
[8] J. B. Stimmel and F. C. Kull Jr., *Nucl. Med. Biol.*, **1998,** *25*, 117-125
[9] J. B. Stimmel, M. E. Stockstill and F. C. Kull, *Bioconjugate Chem.*, **1995,** *6*, 219-225
[10] L. Camera, S. Kinuya, K. Garmestani, C. Wu, M. W. Brechbiel, L. H. Pai, T. J. McMurrym, O. A. Gansow, I. Pastan, C. H. Paik and J. A. Carrasquillo, *J. Nucl. Med.*, **1994,** *35*, 882-889
[11] R. D. Hancock, *J. Chem. Educ.*, **1992,** *69*, 615-621

The similarity to porphyrins and corrins made **Cyclam** (1, 4, 8, 11-tetraazacyclotetradecane) and related ligands the most investigated among the polyaza compounds. They have been mostly applied in stabilizing high oxidation state metal catalysts and in forming bifunctional chelators. This kind of molecules is used for the attachment of radioisotopes to biological targets (antibodies, peptides...).

Tetramethylcyclam is frequently employed as stabilizer of reactive high valent iron oxo compounds, since it forms stable oxoiron(IV) complexes with a wide range of anions trans-coordinated to the oxo ligand.[12]

Delgado and co-workers reported the monopicolinate cyclam derivatives **I** (**figure 1.1**); they formed stable copper(II) complexes **II** demonstrating preference for Cu(II) complexation over other metal ions.[13]

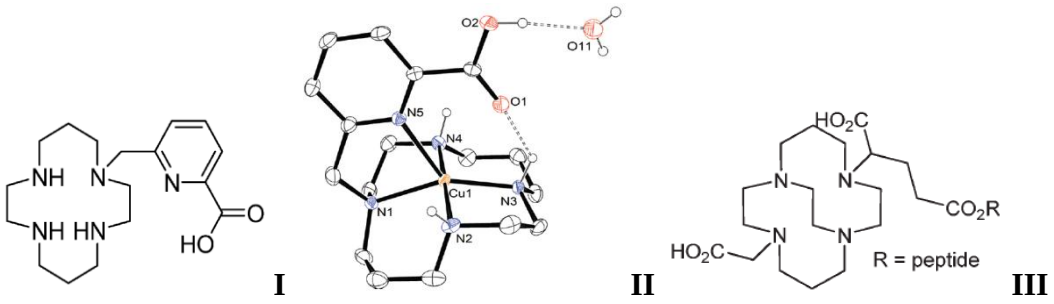


Figure 1.1 – Cyclam derivatives (**I**) and ORTEP view of [Cu(**A**)]$(ClO_4)_2 \cdot H_2O$ (**II**) - perchlorate anions and hydrogen atoms bound to carbon atoms are omitted for clarity. Cyclam ligand grafted on peptide (**III**)

^{64}Cu complexes of molecules like the compounds **III (figure 1.1),** formed by cyclam units grafted on biomolecules, are unsymmetrical N-functionalized chelators that were deeply studied with regards to their application as imaging agents for PET.[14]

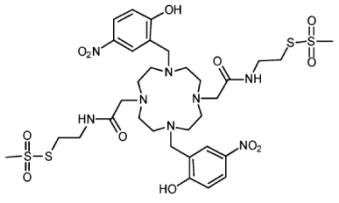
As analogue of the crown ether 12-crown-4, also the **Cyclen** (1,4,7,10-tetraazacyclododecane) was studied for long time, as were its derivatives. One of the most interesting applications of such

[12] T. A. Jackson, J. U. Rohde, M. S. Seo, C. V. Sastri, R. DeHont, A. Stubna, T. Ohta, T. Kitagawa, E. Munck, W. Nam, L. Que, *J. Am. Chem. Soc*., **2008**, 130, 12394

[13] L. M. P. Lima, D. Esteban-Gómez, R. Delgado, C. Platas-Iglesias, R. Tripier, *Inorg. Chem.* **2012**, *51*, 6916-6927

[14] C. A. Boswell, C. A. S. Regino, K. E. Baidoo, K. J. Wong, A. Bumb, H. Xu, D. E. Milenic, J. A. Kelley, C. C. Lai, M. W. Brechbiel, *Bioconjugate Chem*., **2008**, 19, 1476

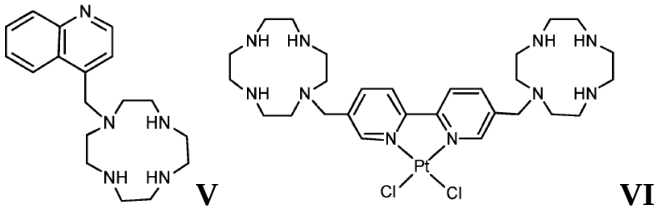
compounds was in the biological NMR field, like the paramagnetic lanthanide(III) chelating protein probe **IV (figure 1.2),** that shows different properties depending on the pH.[15]



IV

Figure 1.2 – Example of cyclen derivative

As was for cyclam, Delgado and coworkers developed cyclen analogues of macrocycles with pinacolate arms and tested their reactivity toward copper(II).[12] Also in that case, the coordination of the cyclen derivative switched between the carboxylate and the nitrogen donors depending on the pH. They reported also an example of a macrocycles with two trans-*N*-acetate arms, very selective for Cu(II).[16] Anyway, not only Cu(II) is employed with these ligand: zinc(II) complex of compound **V** is able to bind selectively the thymine bulges in DNA with micromolar affinity,[17] while bismacrocyclic chelators containing a platinum bipyridyl linking unit **VI** have been designed to target the amyloid β-peptide, a known Alzheimer's marker **(figure 1.3)**[18]



V **VI**

Figure 1.3 – Structural formulae of selected cyclam.

It is common to find in literature some tetraaza macrocycles described as "cyclen derivatives", especially in the last years, due to their ability to form very stable complexes with a range of important metal cations. In 2012, twelve-membered pyridine-based macrocycles with quinoline as

[15] W. M. Liu, P. H. J. Keizers, M. A. S. Hass, A. Blok, M. Tirnmer, A. J. C. Sarris, M. Overhand, M. Ubbink, *J. Am. Chem. Soc.*, **2012**, 134, 17306.
[16] C. V. Esteves, P. Lamosa, R. Delgado, J. Costa, P. Désogère, Y. Rousselin, C. Goze, F. Denat, *Inorg. Chem.* **2013**, *52*, 5138-5153.
[17] I. M. A. Del Mundo, K. E. Siters, M. A. Fountain, J. R. Morrow, *Inorg. Chem.*, **2012**, *51*, 5444-5457
[18] X. Wang, X. Wang, C. Zhang, Y. Jiao, Z. Guo, *Chem. Sc.*, **2012**, *3*, 1304-1312

pendant arms were reported (**figure 1.4**, **VII**). The copper(II) complexes of these ligands showed that the reaction kinetics and the stability of the complexes are affected by the N-substitution pattern of the quinoline.[19]

These compounds give to their complexes with relevant isotopes a plethora of important chemical properties as high kinetic inertness, high thermodynamic stability and mild complex formation. These features, together with appropriate pharmacokinetics and the possibility of coupling with targeting biomolecules, are necessary to make complexes applicable for medical uses.[20] For these reasons, Cooper and co-workers employed this pyridine-based twelve-membered pattern for ^{64}Cu complexes for labeling of antibodies[21] and the same did Ferreira for the study of pharmacokinetic properties with several radionuclides (**figure 1.4**, **VIII** and **IX**).[22]

In order to complex a more bulky ion as iron(IV), also the fourteen-membered pyridine containing cyclam derivative **X** was synthesized and studied as mediator for catalytic epoxidations of cyclooctene and other olefins.[23]

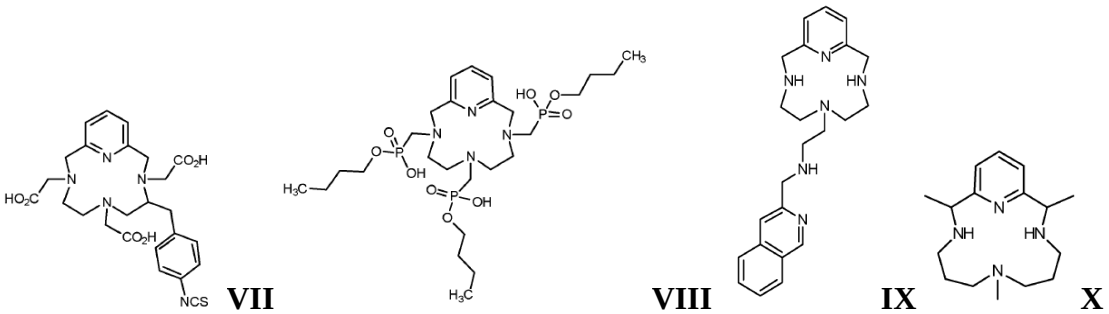


Figure 1.4 – Structural formulae of selected examples of 'cyclam derivatives'.

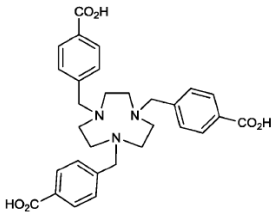
The ligands synthesized by our group, described in **section 1.1.5**, are part of this category, since they are twelve-membered tetraaza macrocycles and they include a pyridine ring in their structure.

Another interesting class of polyaza macrocycles are **Cyclidenes** (1,4,7-triazacyclononane). They are lacunar ligands synthesized and extensively studied by D. H. Busch. They are able to coordinate

[19] C. E. Castillo, M. A. Manez, M. G. Basallote, M. P. Clares, S. Blasco, E. Garcia-Espana, *Dalton Trans.*, **2012**, 41, 5617.
[20] R. Delgado, V. Félix, L. M. P. Lima, D. W. Price, *Dalton Trans.*, **2007**, 2734-2743
[21] M. S. Cooper, M. T. Ma, K. Sunassee, K. P. Shaw, J. D. Williams, R. L. Paul, P. S. Donnelly, P. J. Blower, *Bioconjugate Chem*., **2012**, 23, 1029.
[22] C. L. Ferreira, I. Holley, C. Bensimon, P. Jurek and G. E. Kiefer, *Mol. Pharmacol*., **2012**, 9, 2180
[23] W. H. Ye, D. M. Ho, S. Friedle, T. D. Palluccio and E. V. Rybak-Akimova, *Inorg. Chem*., **2012**, 51, 5006

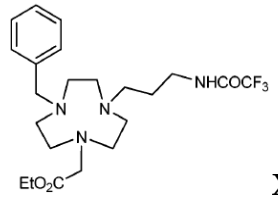
a single metal ion and to maintain a 'persistent void' which allows access to small molecules within the vaulted cavity. For this reason, they are still studied and their complexes are applied in many different field as catalysis (as example for oxidation[24,25]), biological target,[26] RNA cleavage,[27] *etc.*

This kind of compounds was also employed in building metallorganic framework structure for the absorption of CO_2.[28] The zinc(II) complex of ligand **XI** (**figure 1.5**) is able to form a framework with a surface area of 1350 m^2/g and shows a good selectivity for CO_2 over other gases similar in dimension as CO, CH_4 and N_2. Finally, recently introduced synthetic methodologies opened the way for synthesizing unsymmetrical compounds as **XII** (**figure 1.6**) in high yields.[29]



XI

Figure 1.5 – Structural formulae of symmetrical cyclidene.



XII

Figure 1.6 – Structural formulae of asymmetrical cyclidene.

Finally it is important to cite also **larger polyaza** macrocycles. They can be classified by increasing macrocyclic ring size and number of donor atoms. The application for this kind of compounds is often the chelation of metal ions, as for what concern the macrocyclic pentaaza ligands **XIII** and **XIV** (**figure 1.7**) that were synthesized and evaluated as novel chelating agents in copper(II) and nickel(II).[30] In some cases, anyway, larger polyaza macrocycles can have interesting features, as for the two novel copper(II) complexes of ligand **XV** (**figure 1.7**), synthesized by a one-pot metal

[24] N. J. Schoenfeldt, A. W. Korinda, J. M. Notestein, *Chem. Commun*., **2010**, 46, 1640
[25] I. Garcia-Bosch, Z. Codola, I. Prat, X. Ribas, J. Lloret-Fillol, M. Costas, *Chem.–Eur. J*., **2012**, 18, 13269
[26] F. Zobi, R. Alberto, *Chem.–Eur. J*., **2010**, 16, 2710
[27] D. R. Edwards, W. Y. Tsang, A. A. Neverov and R. S. Brown, *Org. Biomol. Chem*., **2010**, 8, 822
[28] G. Ortiz, S. Brandes, Y. Rousselin, R. Guilard, *Chem.–Eur. J*., **2011**, 17, 6689
[29] T. D. Sobiesciak, P. Zielenkiewicz, *J. Org. Chem*., **2010**, 75, 2069
[30] A. S. Fernandes, M. F. Cabral, J. Costa, M. Castro, R. Delgado, M. G. B. Drew, V. Félix, *Journal of Inorganic Biochemistry* **2011**, *105*, 410-419

template Mannich reaction. They have been shown to produce cleavage of DNA in the presence of H_2O_2 potentially via a hydroxyl radical mediated process.[31]

Increasing the number of coordination site to even more extended systems, an octaaza macrocycle (**figure 1.7**, **XVI**) has been functionalized with methyl-naphthyl groups for the detection of zinc(II) using chelation enhanced fluorescence.[32] The derived fluorescence by complexation was not switched on by other biologically relevant ions, enhancing its potential as a sensor for biological systems.

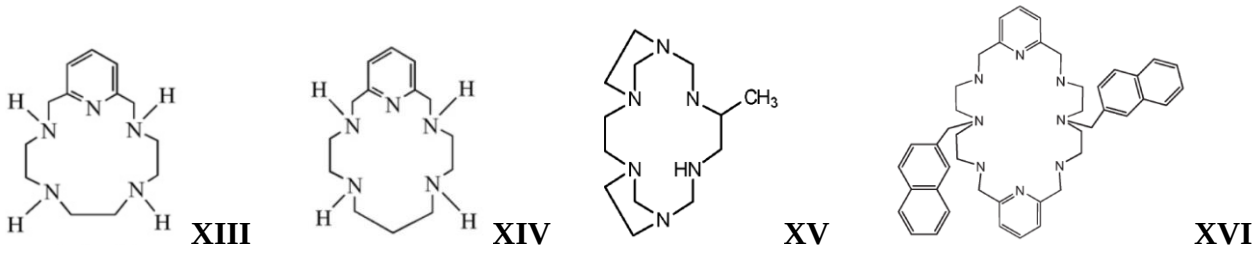


Figure 1.7 – Structural formulae of selected examples of penta, hexa and octaaza macrocycles.

1.4 Porphyrins

As particular tetraaza macrocycles, porphyrins deserve a dedicated section. The general structure of this molecule is made by four pyrrolic units, connected by methinic bonds (**figure 1.8, XVII**). Depending on the position, carbon atoms could be known as meso-carbon (5, 10, 15 and 20) or β-pyrrolic. Meso-carbons are involved in methinic bonds.

The importance of porphyrins is due, above all, to their abundance in nature, where they play crucial roles in the metabolism of living beings, often associated to metal ions in metalloporphyrins. After the removal of two internal protons, porphyrins act as tetradentate dianionic ligand and they are able to coordinate nearly every metal ion in their central cavity. Porphyrin complexes are known for all the transition metals, all the lanthanides, several of the actinides and even some of the main group metals.[33] The reason of such a kind of versatility is due to the high electron density and to the high electron stabilization of the porphyrin ring.

[31] B. P. Burke, S. J. Archibald *Annu. Rep. Prog. Chem., Sect. A: Inorg. Chem*., **2013**, *109*, 232-253
[32] J. Alarcon, M. T. Albelda, R. Belda, M. P. Clares, E. Delgado-Pinar, J. C. Frias, E. Garcia-Espana, J. Gonzalez,C. Soriano, *Dalton Trans*., **2008**, 6530
[33] Brothers, P. J., Organoelement chemistry of main-group porphyrin complexes. In Advances in Organometallic chemistry, Academic Press: **2001**; Vol. Volume 48, pp 289-342

Among the metalloporphyrins, one of the most known is iron protoporphyrin IX, named as heme, that is the cofactor of the hemoglobin, responsive of the O_2/CO_2 transportation in blood and pigment of the red blood cells (**figure 1.8**, **XVIII**)

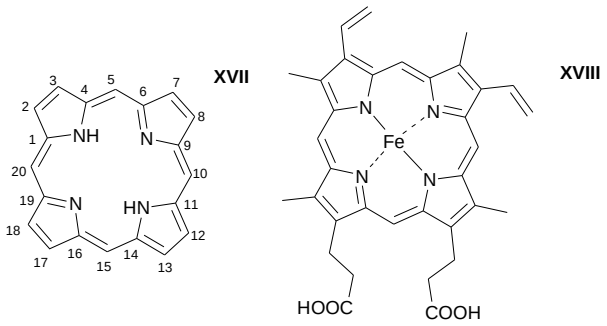
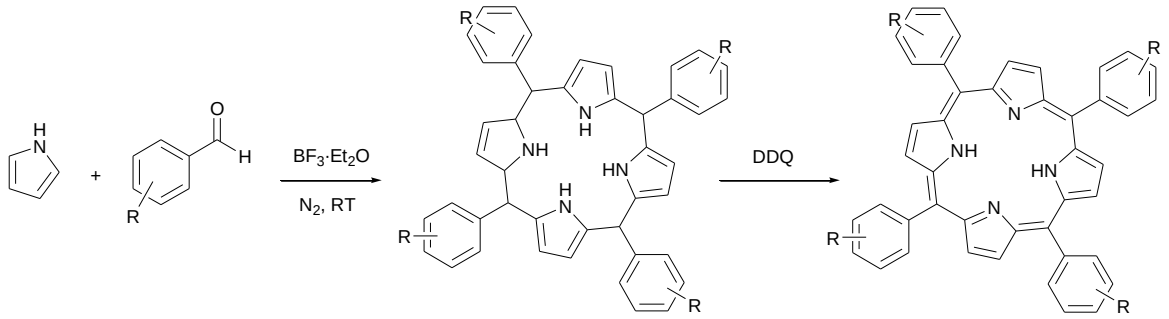


Figure 1.8 – Porphine (**XVII**) with numbering scheme adopted; Heme B (**XVIII**)

In 1926 Hans Fisher and Bruno Walach described the first synthesis of a porphyrin,[1] setting the stage for the different and increasingly optimized routes reported between 1930s and 1950s, in particular by Rothermund.[34] These new works, despite the limitations in the number of aldehydes used and the low yields, paved the way for the studies by Adler and Longo, who published a one pot procedure for the reaction of different benzaldehydes and pyrrole in presence of propionic acid. The yield of this synthetic pathway is up to 20%.[35] This method is still used nowadays, when large amounts of non-symmetrical porphyrins are needed. Higher yields (55%) and milder conditions are reported in the work of Lindsey and co-workers, who proposed a way of synthesis via porphyrinogen (**scheme 1.1**).[36]



Scheme 1.1 – Synthetic method reported by Linsdey. The porphyrinogen intermediate can be directly aromatized by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

[34] a) P. Rothemund, *J. Am. Chem. Soc*., **1935**, 57, 2010-2011. b) P. Rothemund, *J. Am. Chem. Soc*., **1936**, 58, 625-627. c) P. Rothemund, *J. Am. Chem. Soc*., **1939**, 61, 2912-2915. d) P. Rothemund and A. R. Menotti, *J. Am. Chem. Soc*., **1941**, 63, 267-270.
[35] (a) A. D. Adler, F. R. Longo, W. Shergalis, *J. Am. Chem. Soc*., **1964**, 86 (15), 3145-3149; (b) A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, L. Korsakoff, *J. Org. Chem.*, **1967**, 32 (2), 476-476; (c) J. B. A., Kim, Longo, F. R., Academic Press: New York. The Porphyrins **1978/79**, vols. 1-7.
[36] J. S. Lindsey, I. C. Schreiman, H.C. Hsu, P.C. Kearney, A. M. Marguerettaz, *J. Org. Chem*., **1987**, 52 (5), 827-836.

Synthetic chiral porphyrin derivatives have been developed over the years, to extend the application of metalloporphyrins also to enantioselective applications. Chiral derivatives have been mainly prepared by the approach of Groves and Meyers that involves the attachment of chiral units to preformed porphyrins.[37] Then O'Malley and Kodadek demonstrated that it is possible to insert chiral substituent on the porphyrin by using the classical Lindsey procedure with chiral aldehydes.[38] Since then, the number of chiral porphyrins appeared in literature is still growing.

A significant example of chiral porphyrin is the single-face protected picket fence and picnic basked compounds (**figure 1.9**), synthesized by Collman in 1993 and used as ligands for iron(III)-chloride complexes in enantioselective epoxidation of styrene by Rose and colleagues.[39] Important works in asymmetric catalysis mediated by chiral porphyrines are those by Che and Berkessel, who employed ruthenium and manganese complexes of the simplest D_4-symmetric double faced porphyrins for stoichiometric and catalytic oxidation,[40] cyclopropanation,[41] and amination[42]reactions of unfunctionalized hydrocarbons, always reaching good to very good results in term of yields.

It is important to mention also the family of the "bis-strapped" porphyrins, characterized by the presence of a chiral binaphthyl (BINAP) moiety, that produce a significant steric hindrance in the proximity of the active cavity. In this way, the catalytic activity and, in particular, the selectivity are drastically enhanced. Collman and Rose reported the synthesis of C_2-symmetric bis-binaphthyl chiral porphyrin and the corresponding Fe(III) complex (figure 1.18, **F**) that gave TON of 16000 in the epoxidation of some terminal olefins.[43]

[37] J.T. Groves, R.S. Myers, *J. Am. Chem. Soc*. **1983**, 105 (18), 5791-5796
[38] S. O'Malley, T. Kodadek, *J. Am. Chem. Soc.*, **1989**, 111 (25), 9116-9117
[39] E. Rose, B. Andrioletti,S. Zrig, M. Quelquejeu-Etheve, *Chem. Soc. Rev*. **2005**, 34 (7), 573-583
[40] (a) T.-S. Lai, H.-L. Kwong, R. Zhang, C.-M. Che, *Dalton Trans 1998*, (21), 3559-3564; (b) T.-S. Lai, R. Zhang, C.-M. Che, H.-L. Kwong, *Chem. Commun*. **1998**, (15), 1583-1584; (c) R. Zhang, W.-Y. Yu, T.-S. Lai, C.-M. Che, *Chem. Commun*.**1999**, (18), 1791-1792; (d) R. Zhang, W.-Y. Yu, H.-Z. Sun, W.-S. Liu,C.-M. Che, *Chem. Eur. J.* **2002**, 8 (11), 2495-2507;
[41] (a) A. Berkessel, P. Kaiser, J. Lex, *Chem. Eur. J.* **2003**, 9 (19), 4746-4756; (b) M. Frauenkron, A. Berkessel, *Tetrahedron Letters* **1997**, 38 (41), 7175-7176; (c) W.-C. Lo, C.-M Che, K.-F. Cheng, C. W. Mak, *Chem. Commun*.**1997**, (13), 1205-1206; (d) C.-M. Che, J.-S. Huang, F.-W. Lee, Y. Li, T.-S. Lai, H.-L. Kwong, P.-F. Teng, W.-S. Lee, W.-C. Lo, S.-M. Peng, Z.-Y. Zhou, *J. Am. Chem. Soc*. **2001**, 123 (18), 4119-4129.
[42] (a) T.-S. Lai, C.-M. Che, H.-L. Kwong, S.-M. Peng, *Chem. Commun*. **1997**, (24), 2373-2374; (b) X.-G. Zhou, X.-Q. Yu, J.-S. Huang, C.-M. Che, *Chem. Commun*.**1999**, (23), 2377-2378; (c) J.-L. Liang, J.-S. Huang, X.-Q. Yu, N. Zhu, C.-M. Che, *Chem. Eur. J*., **2002**, 8 (7), 1563-1572
[43] E. Rose,Q.-Z. Ren, B. Andrioletti, *Chemistry – A European Journal*, **2004**, 10 (1), 224-230.

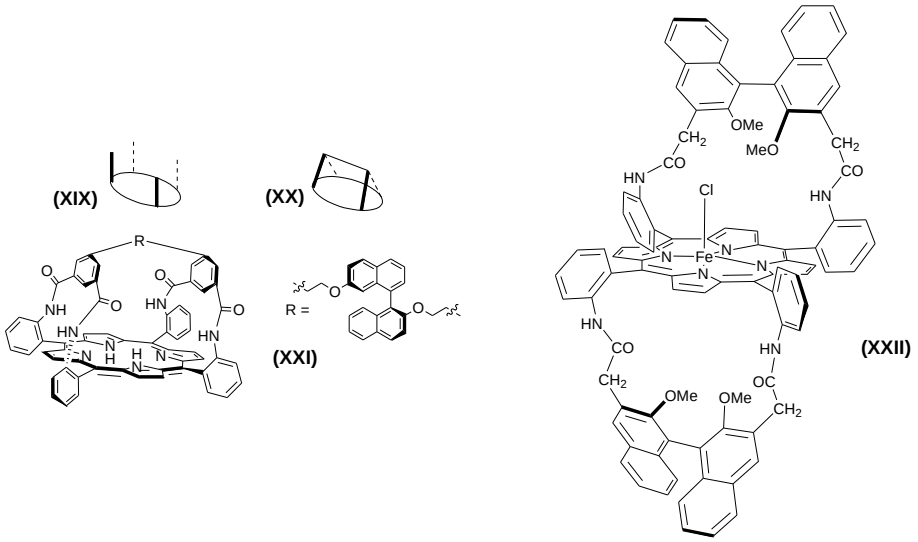


Figure 1.9 – Schematic representation of the single-face protected picket fence (**XIX**) and picnic basket (**XX**); picnic basket porphyrin bearing isophthalate amide loops and a binaphthyl dieter linkers (**XXI**); iron (II) complex of the C_2 bis-strapped porphyrin (**XXII**).

Expanded porphyrins are macrocycles based on the pyrrolic backbone of porphyrins, but they are modified in size in order to achieve a larger cavity (**XXIII**) or to create a second coordination site (**XXIV**). A review of expanded porphyrin ligands has been published in 1991.[44] The cadmium complex of the texaphyrins (figure 1.10, **XXIII**) is found to be planar with a pentadentate coordination of the ligand 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 1.10**, B) is a more flexible expanded porphyrin.[45]

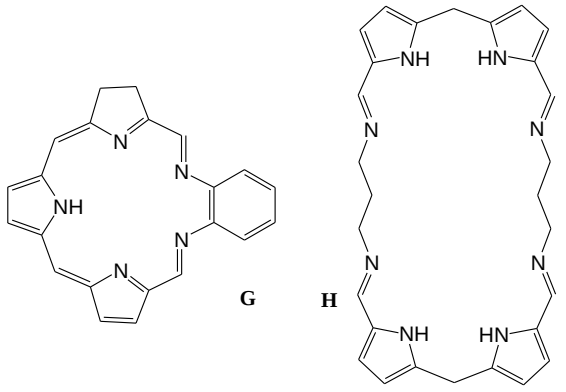
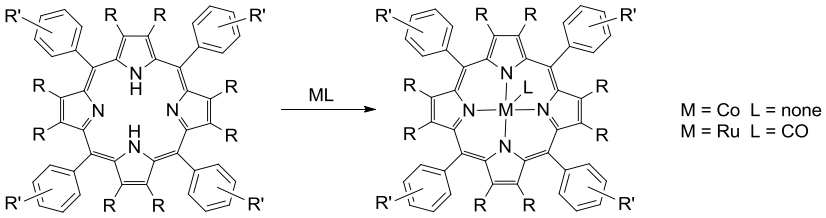


Figure 1.10 – Texaphyrins (**XXIII**) and expanded porphyrin (**XXIV**)

[44] J. L. Sessler and A. K. Burrell, *Top. Curr. Chem.*, **1991**, 161, 177
[45] W. A. Reiter, A. Gerges, S. Lee, T. Deffo, T. Clifford, A. Danby, K. Bowman-James, *Coord. Chem. Rev.*, **1998**, *174*, 343-359

1.5 Tetra-aza macrocycles

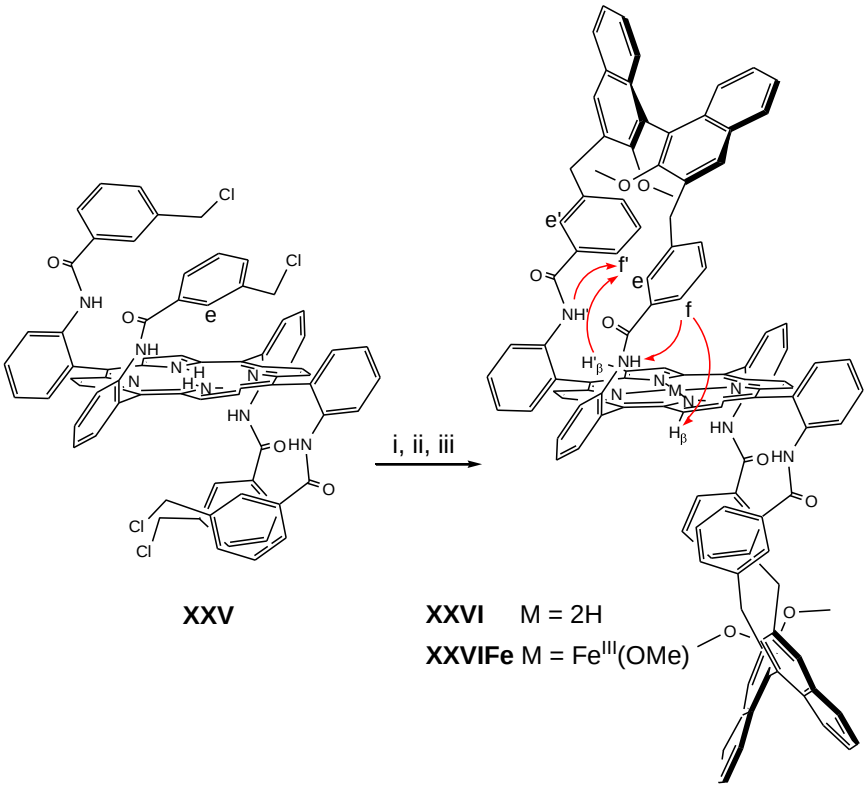
The group in which I conducted my PhD thesis is interested in the use of nitrogen containing ligands, in particular tetra-aza macrocyclic compounds, and on the studies of their reactivity and their catalytic activity as metal complexes. Several years ago, Cenini and co-workers reported the synthesis of Co^{II}-porphyrin complexes that catalyzed the amination of benzyl compounds[46] and the cyclopropanation of alkenes.[47] Since then, other interesting reaction were exploited, such as the amination of 1,2-dihydronaphthalene derivatives, demonstrating an unusual reactivity of dihydronaphthalene towards several aryl azides.[48] Using another porphyrin [Ru-(CO)(TPP)] (TPP = dianion of tetraphenylporphyrin) as catalyst we catalyzed the aziridination of olefins using aryl azides as nitrogen source.[49] 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.[50] 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).[51]



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, **XXVI**), obtaining cyclopropanes with excellent yields (up to 99%), enantio- and diastereoselectivities (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).[52]

[46] F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. Li Gotti, M. Lapadula, E. Mangioni, S. Cenini, *Chem. Eur. J.* **2003**, *9*, 249-259
[47] A. Penoni, R. Wanke, S. Tollari, E. Gallo, D. Musella, F. Ragaini, F. Demartin, S. Cenini, *Eur. J. Inorg. Chem.* **2003**, *7*, 1452-1460
[48] P. Zardi, D. Intrieri, A. Caselli, E. Gallo, *J. Organomet. Chem.* **2012**, *716*, 269-274
[49] S. Fantauzzi, E. Gallo, A. Caselli, C. Piangiolino, F. Ragaini, S. Cenini, *Eur. J. Org. Chem.* **2007**, 6053-6059
[50] C. Piangiolino, E. Gallo, A. Caselli, S. Fantauzzi, F. Ragaini, S. Cenini, *Eur. J. Org. Chem.* **2007**, 743-750
[51] D. Intrieri, A. Caselli, F. Ragaini, S. Cenini, E. Gallo, *J. Porphyrins Phthalocyanines* **2010**, *14*, 732-740
[52] D. Intrieri, S. Le Gac, A. Caselli, E. Rose, B. Boitrel, E. Gallo, *Chem. Commun.*, **2014**, *50*, 1811-1813



Scheme 1.3 – Synthesis of C_2-symmetrical binap-*bis*-strapped porphyrin **XXVI** 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 coordinate the metal in one way only. For example, chiral porphyrin complexes of cobalt(II) and ruthenium(II) were tested in catalytic cyclopropanation[53] and amination reactions.[54]

On the other hand the synthesis of this class of compound generates several problems, especially if some functional groups are introduced on the framework or if the optical pure form is synthesized. Also the synthetic methodologies reported in literature concerning chiral porphyrins require laborious procedures, expensive reagents and carry to very low overall yields. For this reason, our attention turned to the development of synthetic pathways that allow to obtain a class of tetraaza macrocyclic ligands easy to functionalized in few synthetic steps, in good yield and with economic and commercially available starting materials. In collaboration with Prof. Sisti of Università dell'Insubria, we synthesized a new type of tetraaza macrocycle containing a pyridinic ring. Sisti

[53] S. Fantauzzi, E. Gallo, E. Rose, N. Raoul, A. Caselli, S. Issa, F. Ragaini, S. Cenini, *Organometallics* **2008**, *27*, 6143-6151
[54] A. Caselli, E. Gallo, F. Ragaini, F. Ricatto, G. Abbiati, S. Cenini, *Inorg. Chim. Acta* **2006**, *359*, 2924-2932

and co-workers studied these classes of compounds and their use as ligand for gadolinium(III)[55] since their complexes are useful contrast agents for magnetic-resonance images (MRI) **(figure 1.11)**.

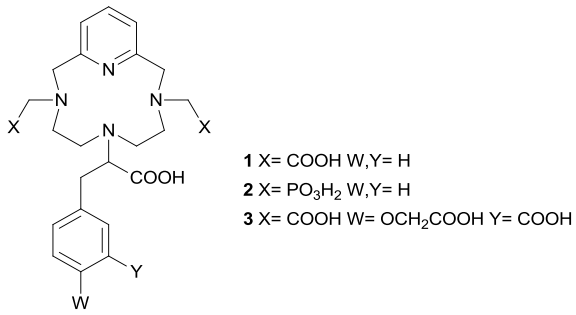
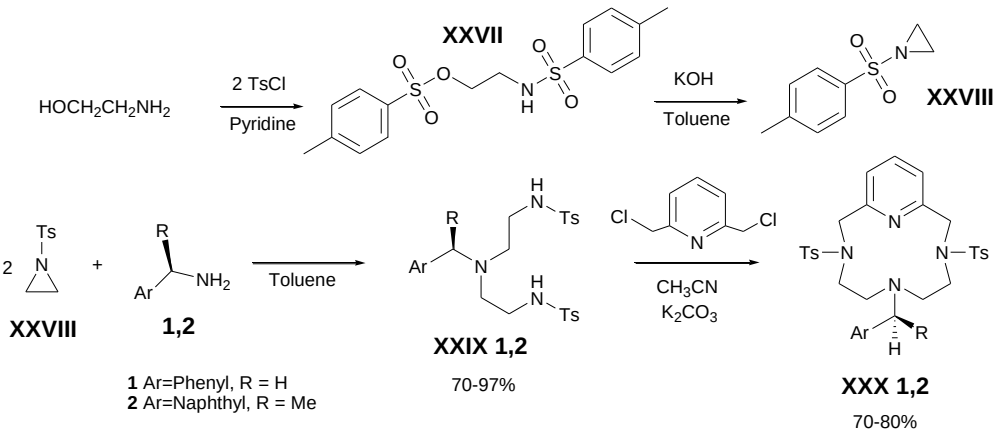


Figure 1.11 – Structure of the PC-type ligand.

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.[56] The synthetic approach employed to synthesize these macrocyclic ligands, is reported in **scheme 1.4**.



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

The synthesis of the macrocycle is simple and it involves three main steps. Firstly ethanolamine is reacted with tosyl chloride and the obtained *N,O*-ditosylethanolamine **XXVII** undergoes to a ring closure reaction after treatment with a base to obtain the tosyl-aziridine **XXVIII**. Then a solution of **XXVIII** (2 equivalents) is added to commercially available chiral aryl-amine **1** or **2** to yield a

[55] S. Aime, E. Gianolio, D. Corpillo, C. Cavallotti, G. Palmisano, M. Sisti, G. B. Giovenzana, R. Pagliarin, *Helv. Chim. Acta* **2003**, *86*, 615-632.
[56] A. Caselli, F. Cesana, E. Gallo, N. Casati, P. Macchi, M. Sisti, G. Celentano, S. Cenini, *Dalton Trans.*, **2008**, 4202-4205

substituted bis-sulfonamide **XXIX**. Finally, compound **XXIX** is made to react with 2,6-bis(chloromethyl)pyridine, yielding the desired macrocycle **XXX**. It should be underlined that the crucial step of macrocyclization, is conducted under heterogeneous conditions as a modification of Richman-Atkins protocol (NaH/DMF). This synthetic strategy allows to avoid high dilution techniques and to obtain the 12 membered macrocycle **XXX** in 70–80% yields, without any racemization at the asymmetric carbon. Moreover, it is worth of note that, even conducting this step in concentrated condition, we never observed any polymerization side-reaction. The presence of different types of variously substituted nitrogen atoms (one sp^2 and three sp^3) makes this class of compounds of great interest.

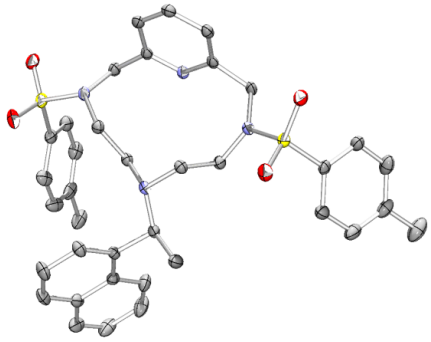
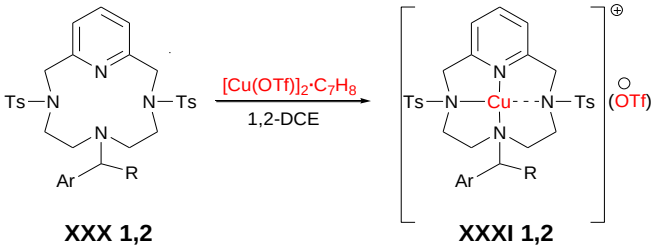


Figure 1.12 – Ortep view of compound **XXX2.** The ORTEP view shows the good conformational degree of freedom of the macrocyclic cavity.

This synthetic methodology is simple and allows to apply different functionalizations on the macrocyclic framework, in order to change the steric hindrance and to create stereocenters on the backbone. It is possible to develop a modular design of the ligand by varying – for example – the structure of the amine nucleophile, starting from different commercially available chiral or non chiral amines. Furthermore the tosyl groups can be removed and replaced with others protecting group. All this aspect will be deeply treated in the result and discussion section of this thesis.

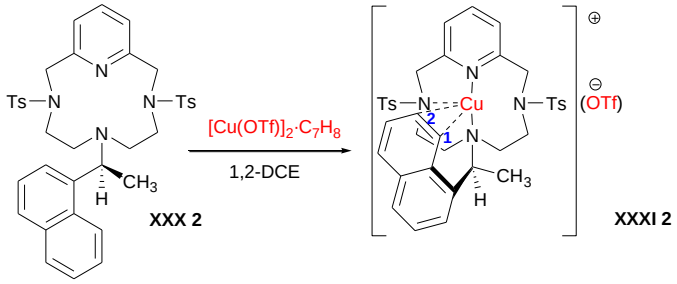
Metal complex formation with ligands **XXX 1,2** was investigated with copper(I) triflate toluene complex ($[Cu(OTf)]_2 \cdot C_7H_8$) as copper(I) source (**scheme 1.5**).[56]



XXX 1,2 **XXXI 1,2**

Scheme 1.5 – Synthesis of the copper(I) complexes **XXXI 1,2**.

Treating ligand **XXX 1** with $[Cu(OTf)]_2 \cdot C_7H_8$, a pale yellow Cu(I) complex **XXXI 1** was obtained and it undergoes to oxidation quite readily. On the other hand, by layering with benzene a 1,2-dichloroethane (DCE) solution of ligand **XXX 2,** after treatment with an equimolar amount of $[Cu(OTf)]_2 \cdot C_7H_8$, a colorless crystalline solid was obtained (**scheme 1.6**).



Scheme 1.6 – Cu(I) complex formation from ligand **XXX 2**, 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) with formula [Cu**XXX 2**]·(OTf), **XXXI 2,** which did not readily oxidize to Cu(II). This complex has been isolated and fully characterized. The ^{1}H-NMRspectrum of complex **XXXI 2** in $CDCl_3$ displays a very low symmetry: in particular, in the ^{1}H-NMR (**figure 1.13**) spectrum, the proton directly bound to carbon **1** shifted to higher frequencies, 8.93 ppm compared to 8.16 ppm for the free ligand **XXX 2**.

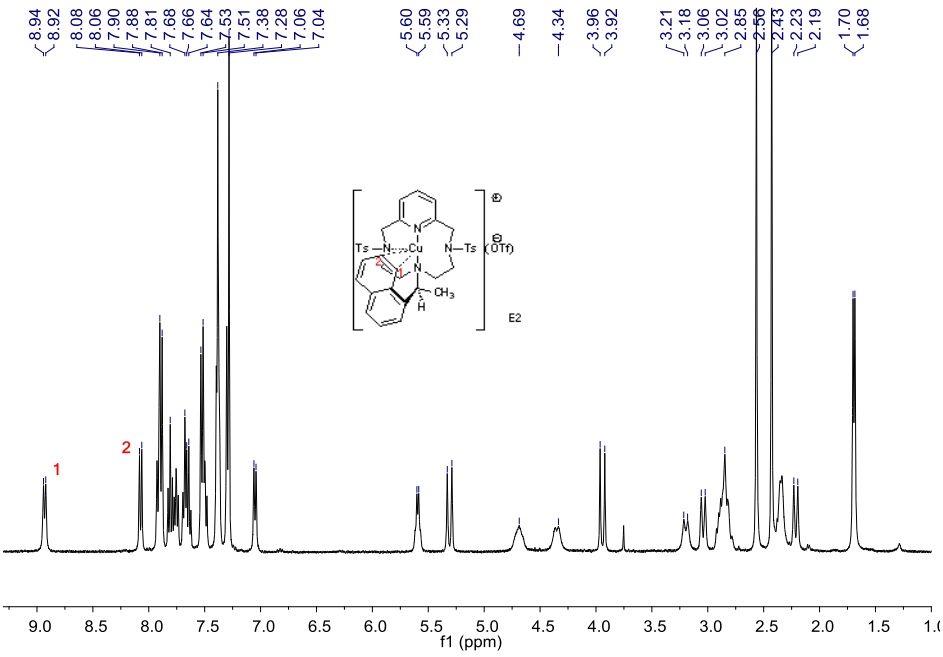


Figure 1.13 – ^{1}H-NMRspectrum of complex **XXXI 2** in $CDCl_3$

Moreover, two sets of signals are observed for the sulfonamide moieties and this can be due only to very low symmetry of the molecule, retained also in solution. Indeed, the solid state structure of complex **XXXI 2** 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 1.14**).

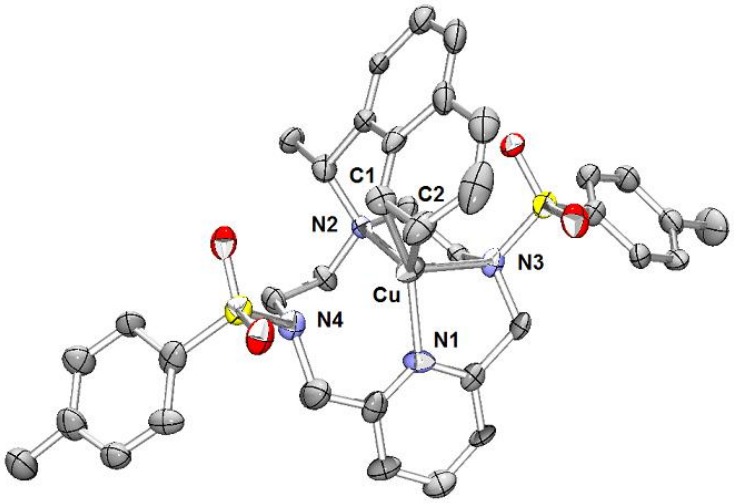


Figure 1.14 – Ortep view of the cation of **XXXI 2**. Selected bond distances: Cu–N1 1.980 Å, Cu–N2 2.151Å, Cu–N3 2.346 Å, Cu–N4 2.820 Å, Cu–C1 2.017 Å, Cu–C2 2.428 Å.

To be precise, in this complex the copper is tetra-coordinated since for steric reasons it is shifted toward 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-NMRstudies in $CDCl_3$ solution. The signal of naphthyl carbon **1** involved in the η^2 bond with copper shifts from 124.5 ppm in the free ligand, to 94.2 ppm in the complex (see **figure 1.14** for labeling of the carbon atoms **1** and **2**). Conversely, 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, ^{1}H) of 149 Hz for carbon **1** provides hints of a partial re-hybridization state from sp^2 to sp^3. Since carbon **2**, instead, is less affected a predictable ^1J (^{13}C, ^{1}H) of 163 Hz is observed.[57]

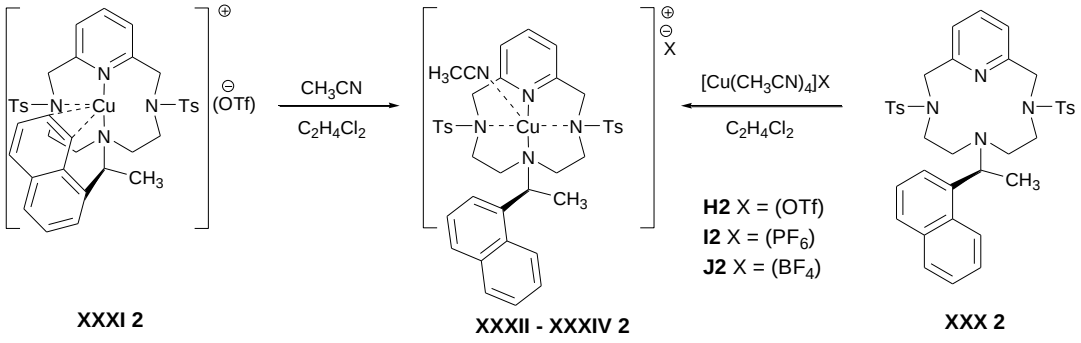
The effect of the copper complexation to the ligand was shown also by the ^{15}N-NMRchemical shifts observed in $CDCl_3$ solution. The ^{15}N-NMRspectrum shows a marked shift for the pyridinic nitrogen atom (from 313 to 245 ppm), while the sp^3 nitrogen atom bonded to the asymmetric carbon is

[57] -Molina, A. Locati, E. Alvarez, F. Maseras, T. s. R. Belderrain, P. J. , *Organometallics* **2010**, *29*, 3481-3489.

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 **XXX 2** with respect to **XXX 1**, but also the higher performances in term of enantioselection observed in the catalysis.[56]

The reactivity of complex **XXXI 2** was then tested with acetonitrile (**scheme 1.7**).



XXXI 2 **XXXII - XXXIV 2** **XXX 2**

Scheme 1.7 – Reaction of complex **XXXI 2** with CH_3CN. Synthesis of complexes **XXXII-XXXIV2**.

The reaction was conducted by stirring a dichloroethane solution of **XXXI 2** in the presence of excess of acetonitrile (5 equivalents). The ^{1}H-NMRspectrum shows a marked shift of all the signals, especially in the aliphatic region. The ^{15}N-NMRspectrum 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)**XXX2**]·(OTf), **XXXII 2**, containing only one coordinated acetonitrile molecule (ν_{CN} = 2250 cm^{-1}), as shown by integration of the CH_3CN signal in the ^{1}H-NMRspectrum.

The same product, with different counter anions, can also be synthesized by treating the free ligand **XXX 2** with copper salts containing acetonitrile, as [Cu(CH_3CN)$_4$]·(PF_6) or [Cu(CH_3CN)$_4$]·(BF_4), to yield complexes **XXXIII 2** and **XXXIV 2**, respectively (**scheme 1.7**). Both complexes show the same chemical shifts as **XXXII 2** for the cation in the ^{1}H-NMRspectra, 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 **XXXIV 2** crystals suitable for an X-ray structural determination were obtained by crystallization from dichloroethane/*n*-hexane.[56] The structure of complex **XXXIV 2**, (**figure 1.15**) shows the copper atom placed in the middle of the macrocyclic cavity, in a real fivefold coordination site consisting

in the four ligand nitrogens and the acetonitrile. At variance from copper complex **XXXI 2**, in **XXXIV 2** 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 predictable, 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)).

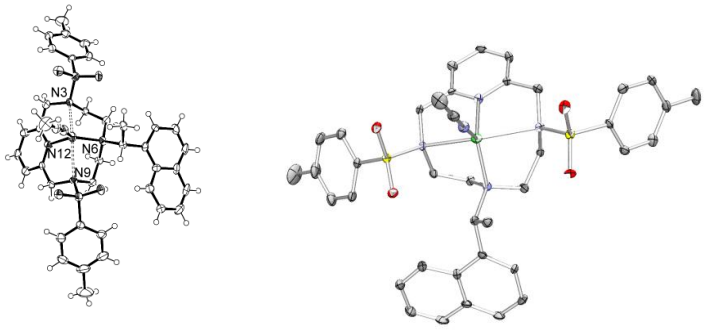


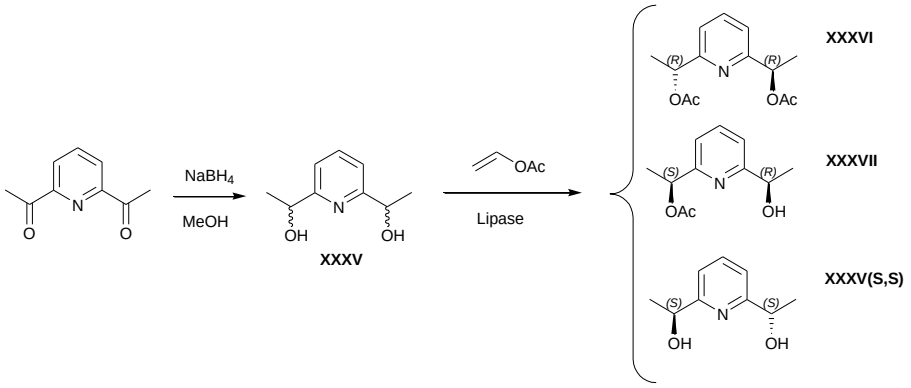
Figure 1.15 – Structure of compound **XXXIV 2** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°): Cu-N12 2.058(4), Cu-N6 2.111(5), Cu-N3 2.567(4), Cu-N9 2.549(5), Cu-N(CH_3C*N*) 1.898(5), N3-Cu-N9 139.1(1). For sake of comparison with **F2** and **G2**, N6---N12 is 3.306(5) and N3---N9 is 4.793(6).

1.6 Structural modifications

As it will be discussed in the next chapter (result and discussion), it is easy to insert new substituents, and hence new stereocenters, on the backbone of the ligand, just by changing one or more of the starting reagent.

The easiest and cheapest way to modify the final outlook of the ligands is to use an enantiomerically pure aminoalcohol instead of the 1,2 – ethanolamine. Since they are derivatives of naturally available aminoacids, L-aminoalcohols are perfect to be used as starting material in the synthesis of our ligands. As first test, we used L-valinol for the synthesis of a chiral ligand, bearing two isopropyl substituents on the backbone. While the synthesis of the corresponding aziridine is simple and quite fast, the ring opening reaction is slower and it could be stopped after the addition of 1 equiv. of the aziridine. Hence, the mono-adducts could be isolated, although in moderate yields (13-50%).

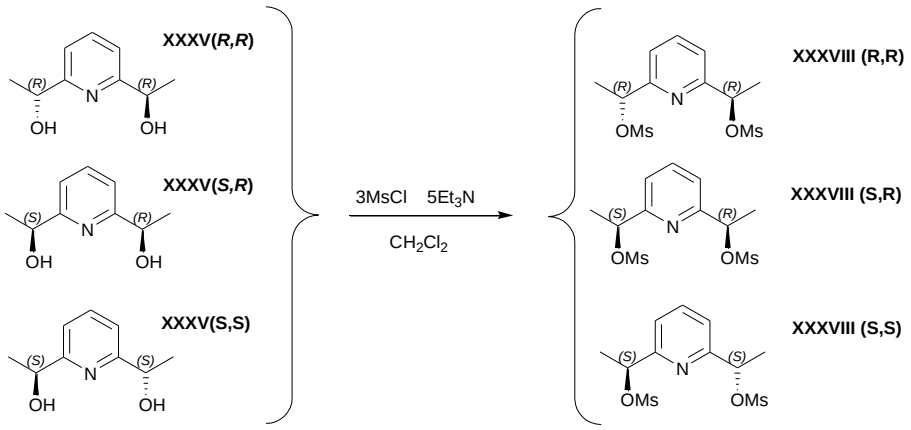
At the same time we made some modifications to the pyridine moieties,[58a] in order to insert two new stereocenters in position 2 and 10 (figure 2.1). Following a well described procedure,[58b] we started from the reduction of the commercially available 2,6-diacetylpyridine with $NaBH_4$ to give the 2,6-bis(1-hydroxy-ethyl)pyridine **XXXV** as mixture of the two enantiomers and the *meso*-form. A kinetic acetylation of the mixture of **XXXV** with vinyl acetate in the presence of *Candida antarctica* lipase gave three different products: diacetate **XXXVI** in 19% yield, monoacetate **XXXVII** in 40% yield and the unacetylated products **XXXV (*S,S*)** in 19% yield. This enzyme acts selectively on the stereocenters in *R* conformation. The three chiral pyridines are separated by silica gel chromatography (**scheme 1.8**).



Scheme 1.8 – General procedure for the reduction and acetylation of the mixture of **XXXV**.

Then, potassium carbonate promoted deacetylation of **XXXVI** gave diol **XXXV-(*R,R*)** and diol **XXXV-(*S,R*)** from **7.** Each form is then mesylated, by treating a solution of **XXXV** pyridine in CH_2Cl_2 with methanesulfonyl chloride and triethylamine, obtaining the corresponding products **XXXVIII** in high yields (**scheme 1.9**).

[58] a) B. Castano, "Synthesis, charachterization and catalytitc activity of chiral tetraazamacrocycle – PcL – Cu(I) and Ag (I) complexes", **2013** - PhD thesis. b) J. I. Uenishi, S. Aburatani, T. Takami, *J. Org. Chem.,* **2007,** *72,* 132-138



Scheme 1.9 – General procedure for mesylation of **XXXV**.

The pure mesylated pyridines are made to react with the various bis-sulfonamides to get a new class of macrocycles of C_1 symmetry (from chiral amines) and C_{2v} symmetry (from achiral amines and chiral optical active pyridines). Treating the amines with the mesylated pyridines **XXXVIII** in refluxing anhydrous acetonitrile in presence of K_2CO_3, we isolated 12 member ligands **XXXIX 1-7** in yields between 12 and 76% (**figure 1.16**).

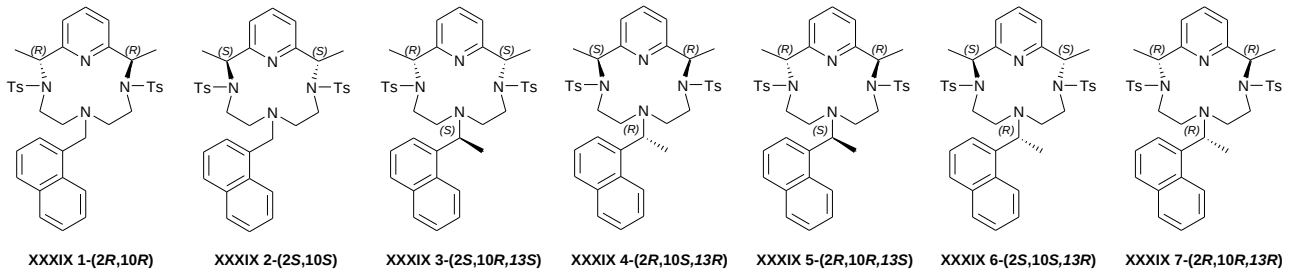


Figure 1.16 – Macrocyclic ligands (Pc-L*) **XXXIX 1-7.**

The nucleophilic attack of the bis-sulfonamides on the pyridine **XXXVIII** occurs with SN_2 mechanism and thus the inversion of configuration of the stereocenter present on the pyridine is involved. These new synthesized ligands have been completely characterized, including, ^1H, ^{13}C - NMR analysis, MS and specific optical rotation. Moreover crystals suitable for X-ray structural determination were obtained by crystallization of macrocycle **XXXIX 5-(2*R*,10*R*,13*S*)** from a dichloromethane–toluene solution, proving the involved SN_2 mechanism. Crystals of macrocycle **XXXIX 3-(2*S*,10*R*,13*S*),** suitable for X-ray structural determination, were also obtained (**figure 1.17**).

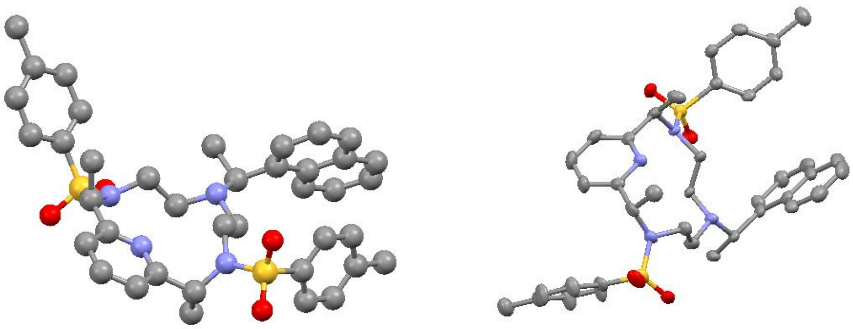


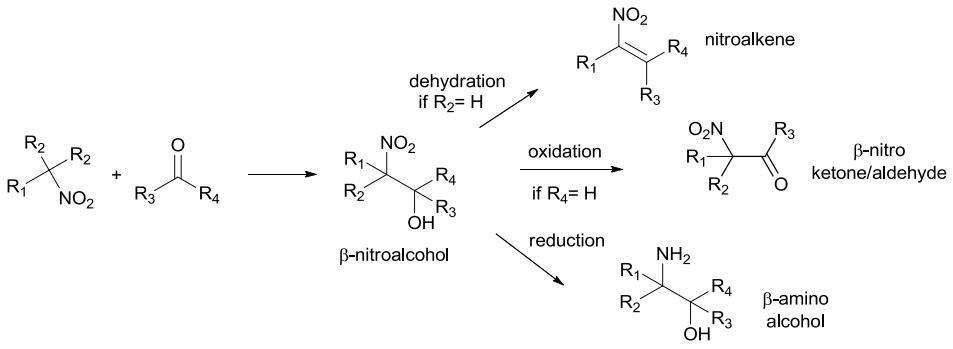
Figure 1.17 – X-ray structures of macrocycles **XXXIX 5-(2*R*,10*R*,13*S*)** and **XXXIX 3-(2*S*,10*R*,13*S*)** respectively.

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

1.7 Catalytic applications

1.7.1 Henry reaction

The nitroaldol or Henry reaction is a valuable way for the formation of C-C bonds, through the base-mediated coupling of carbonyl compounds and nitroalkanes. The β-nitroalcohols formed in this reaction are important building blocks for pharmaceutical synthesis of molecules as (S)-propanolol and (S)-pindolol, amino sugars and alkaloids.[59] A careful control of the conditions used to carry on the reaction is required, since some competitive base catalyzed side-reactions such as aldol condensation (with aliphatic aldehydes), Cannizzaro reaction or water elimination could occur (**scheme 1.10**).[60]



Scheme 1.10 – Henry reaction and the other possible collateral reactions.

[59] Y. Xiong, F. Wang, X. Huang, Y. Wen, X. Feng, *Chem. Eur. J.* **2007**, *13*, 829-833
[60] R. Ballini, G. Bosica, *J. Org. Chem.* **1997**, *62*, 425-427

A wide variety of promoters, basic catalysts and reaction conditions for simple nitroaldol reactions were reported in the excellent review of Luzzio.[61] Worth of note is the study of Ballini[60] and coworkers, which described 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.

The first application of metal ion complexes as Lewis acid catalysts for the Henry reaction were described in 1992 by Shibasaki *et al*.[62] 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,[63] mainly devoted to the asymmetric version of the reaction.

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[64] and co-workers in 2001 with bisoxazoline ligands. Many studies inspired to the work of Jørgensen have been published, employing the ligands collected in **figure 1.18**. [65]

[61] F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915-945
[62] H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc*. **1992**, 114, 4418–4420
[63] Selected references (a) A. Noole, K. Lippur, A. Metsala, M. Lopp, T. Kanger, *J. Org. Chem*. **2010**, 75, 1313–1316; (b) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.*, **2010**, 16, 6761–6765; (c) M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J*. **2009**, 15, 12764–12769; (d) G. Zhang, E. Yashima, W.-D. Woggon, *Adv. Synth. Catal*. **2009**, 351, 1255–1262; (e) G. Blay, L. R. Domingo, V. Hernández-Olmo, J. R. Pedro, *Chem. Eur. J*. **2008**, 14, 4725–4730; (f) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem*. **2007**, 2561–2574; (g) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymm*. **2006**, 17, 3315–3326; (h) A. Kumar, S. S. Pawar, *J. Mol. Catal. A: Chem*. **2005**, 235, 244–248; (i) C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem. Int. Ed*. **2004**, 43, 5442–5444; (l) G. Klein, S. Pandiaraju, O. Reiser, *Tetrahedron Lett*. **2002**, 43, 7503–7506
[64] C. Christensen, K. Juhl, K.A. Jørgensen, *Chem. Commun*. **2001**, 2222–2223
[65] (a) D. A. Evans, D. Seidel, M. Rueping, H.W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc*. **2003**, 125, 12692 – 12693; (b) K. Ma, J. You, *Chem. Eur. J.*, **2007**, 13(6), 1863-1871; (c) A. Gualandi, L. Cerisoli, H. Stoeckli-Evans, D. Savoia, *J. Org. Chem.* **2011**, *76*, 3399-3408; (d) B. V. S. Reddy, S. M. Reddy, S. Manisha, C. Madan, *Tetrahedron: Asymmetry* **2011**, *22*, 530-535; (e) J. Mao, X. Nie, M. Wang, Q. Wang, B. Zheng, Q. Bian, J. Zhong, *Tetrahedron: Asymmetry* **2012**, *23*, 965-971; (f) M. Solinas, B. Sechi, S. Baldino, G. Chelucci, *J. Mol. Catal. A: Chem.* **2013**, *378*, 206-212; (g) E. Wolińska, *Tetrahedron* **2013**, *69*, 7269-7278

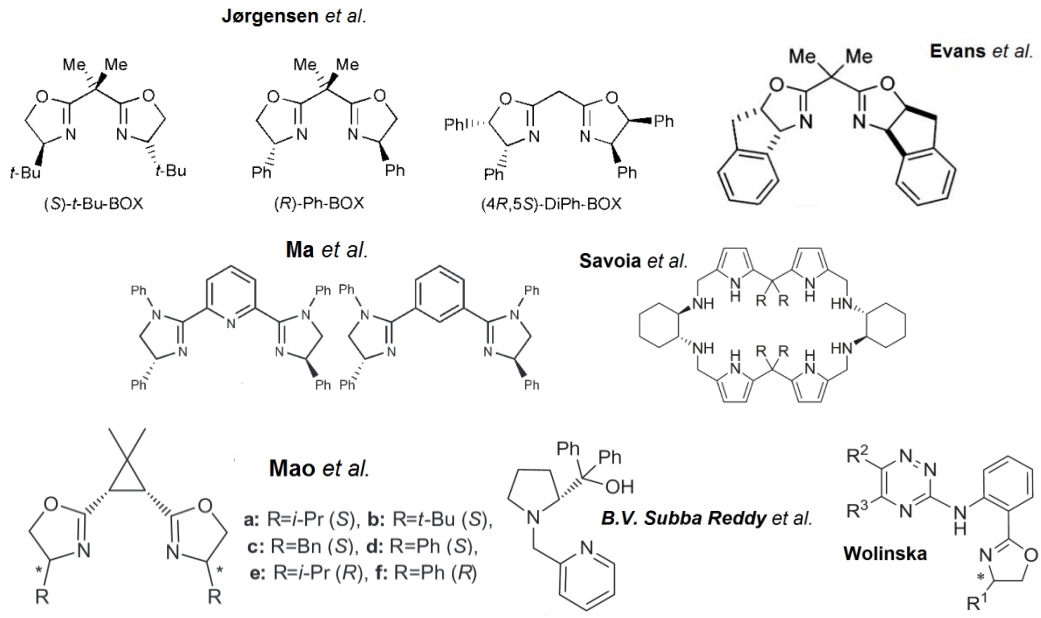
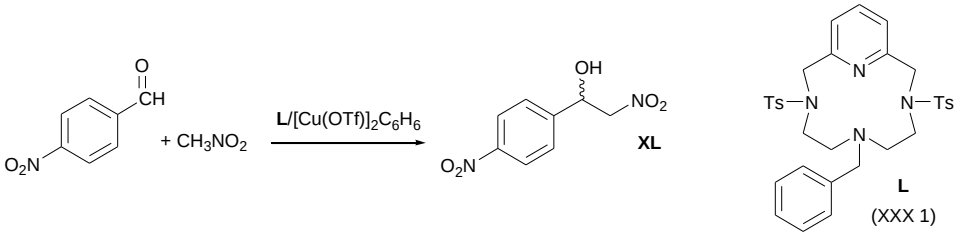


Figure 1.18 - Selected examples of polydentate ligands as catalysts for Henry reaction.

In 2011, during my master degree thesis, we applied the copper(I) complexes of ligand **XXX 1** described in the **section 1.5** as catalyst for the Henry reaction.[66] Feasibility studies were initially carried out on 4-nitrobenzaldehyde and nitromethane (**scheme 1.11**).



Scheme 1.11 – Henry reaction on *p*-NO_2-benzaldehyde

Since identical results were obtained with both the isolated preformed and the *in situ* formed complexes, for practical reasons, all the experiments were run with the *in situ* generated complex, using $[Cu(OTf)]_2 \cdot C_6H_6$ as copper source.

In aromatic hydrocarbons such as benzene and toluene, the reaction did not take place. Dichloromethane at room temperature was hence proved to be the best solvent in which conduct the reaction, while in more polar and coordinating solvents the yields are lower. The ratio between catalyst, aldehyde and nitromethane was set to 1:10:560; since every step of the process is

[66] B. Castano, T. Pedrazzini, M. Sisti, E. Gallo, F. Ragaini, N. Casati, A. Caselli, *App. Organomet. Chem.* **2011**, *25*, 824-829

reversible, a large excess of nitroalkane is generally required to carry the reaction to completion. Finally, we fixed to 24 hours the time of the reaction. Under these conditions, the catalytic cycle can be restored just upon addition of both aldehyde and nitromethane, without any loss of catalytic activity after three cycles: the global isolated yield was 91%.
Temperature was observed not to affect the outcome of the reaction, while the nature of the copper source influenced the rate of the process: 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. It is important to underline that in the absence of ligand copper(I) triflate was unable to promote the reaction.

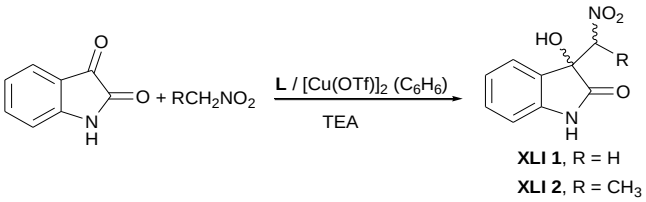
As a prior step to the nucleophilic attack on the carbonyl group of an aldehyde, generation of the activated nitronate species is needed. Nitroalkane activation by base promoted hydrogen transfer must necessarily be part of the catalytic cycle, together with the activation of the acceptor carbonyl through coordination to the copper atom. To study the beneficial effect of a basic co-catalyst, which is well documented in the literature,[67] we added a substoichiometric amount (fivefold excess with respect to the catalyst) of triethylamine (TEA) to the reaction mixture. The TEA drastically increased the reaction rate, since we could reduce the excess of nitromethane from 56 to 5 equivalents with respect to the aldehyde without significant loss of yields. Furthermore, the catalyst loading could be reduced to 1%, even if, in this case, longer reaction times are needed.

We conducted a screening on several aromatic and aliphatic aldehydes, proving that the system allows the synthesis of a wide range of β-aminoalcohols. Best results in term of yields were obtained when an electron withdrawing group was present on the aryl ring and 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, probably because the less pronounced electrophilic character of the aldehyde displaces the reaction equilibrium towards the reagents. Bulky aliphatic aldehydes such as pivalaldehyde were less reactive but in the case of cyclohexanecarbaldehyde acceptable yields have been obtained. Noteworthy, no trace of the product derived from water elimination was ever detected and in all cases selectivities of >99% were observed.

[67] K. Lang, J. Park, S. Hong, *J. Org. Chem.* **2010**, *75*, 6424-6435

Furthermore, we conducted the reaction with nitroethane,[68] in order to test the diastereoselectivity of our system, obtaining the desired nitroalcohol in good yields, although the observed *syn/anti* ratio was very modest.

Finally, taking into account that the indole nucleus is present in a large number of compounds of biological and/or pharmaceutical interest, we extended the system to isatine (**scheme 1.12**).



Scheme 1.12 – Reaction with isatine.

The reaction with nitromethane gave the desired 3-hydroxy-3-(nitromethyl)-1,3-dihydro-2H-indol-2-one in 75% yield.[69] Encouraged by this result, isatine was reacted with nitroethane and a mixture of the diastereoisomers **XLI 2** in the ratio 5:1 (**figure 1.19**) was obtained with an overall yield up to 80%.[70]

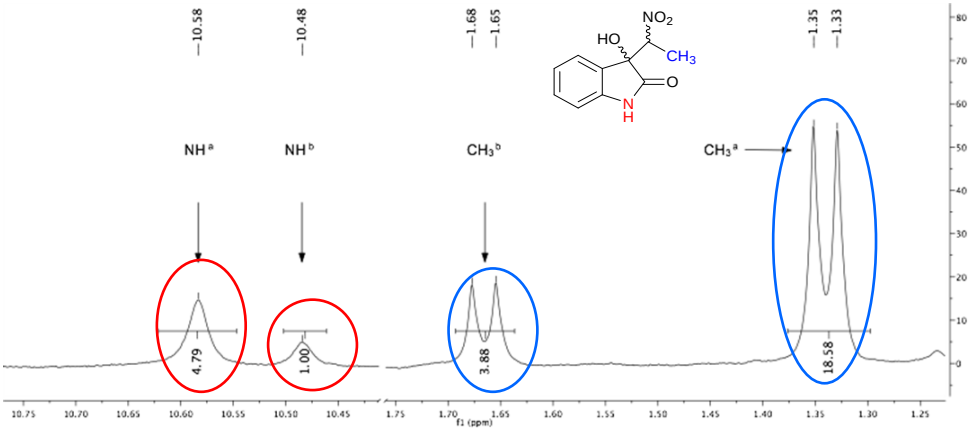


Figure 1.19 – Selected part of ^{1}H-NMR spectrum of reaction with isatine and nitroethane

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

[68] C. Pettinari, F. Marchetti, A. Cerquetella, R. Pettinari, M. Monari, T. C. O. Mac Leod, L. Martins, A. J. L. Pombeiro, *Organometallics* **2011**, *30*, 1616-1626
[69] M. N. Elinson, A. I. Ilovaisky, V. M. Merkulova, F. Barba, B. Batanero, *Tetrahedron* **2008**, *64*, 5915-5919
[70] W. R. Conn, H. G. Lindwall, *J. Am. Chem. Soc.* **1936**, *58*, 1236-1239

subject has been published.[71]

Preliminary studies were conducted employing the chiral ligands in the presented 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.

1.7.2 Cyclopropanation

These catalysts were also preliminarily tested in cyclopropanation, using the cyclopropanation of α-methyl styrene with EDA (EDA = ethyl diazoacetate) as model reaction. Optimization studies were made with different copper sources, temperature and modality of addition of the EDA solution. A Cu/PC-L/EDA/olefin ratio 1 : 1 : 35 : 170 was used in all the experiment conducted. The best results in terms of yield were obtained at 0 °C by slow addition of EDA by a syringe pump employing $[Cu(OTf)]_2 \bullet C_6H_6$ as the copper source (same results are obtained with the more expensive toluene complex).

An introduction about the cyclopropanation reaction and the extended study of feasibility of this catalytic system with different ligands and on different substrate – that was object of this thesis - will be given in the next chapter (**section 2.2.3**).

[71] L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, W. Duan, W. Wang, *Chem. Eur. J.* **2011**, *17*, 7791-7795

1.8 Heterogenization

Homogenous catalysis presents some inherent problem, if compared to its heterogeneous 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.[72] The Heterogenization of the known homogenous catalyst on solid support is the ideal combination in order to achieve the advantages of both heterogeneous and homogeneous catalysis.[73]

There are several solid supports suitable for heterogeneous catalysis or for Heterogenization of homogeneous catalysts. For example, molecular sieves present a porous structure combined with high adsorption capacity and these peculiar proprieties have prompted their application in heterogeneous catalysis as solid support for catalyst. The most widely used supporting materials in industry are the zeolites: they are microporous aluminosilicate minerals with a crystalline structure, characterized by channels and cavities in the range of 5-12 Å and very high surface area. Their intricate channel structure allows the zeolites to be very shape selective for products, reactants, or transition state. For this reason, they can be used to direct a given catalytic reaction toward the desired product avoiding undesired side reactions.

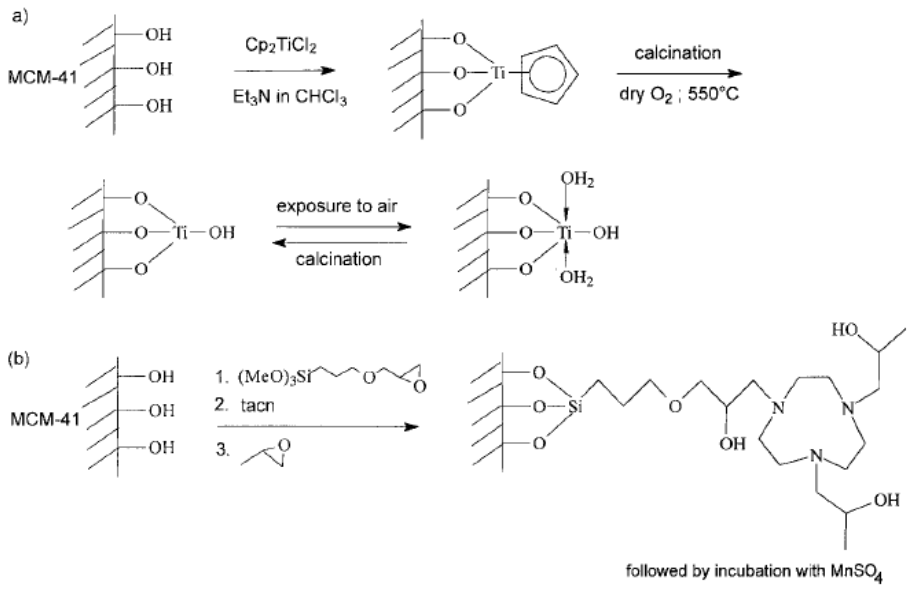
Despite these catalytically desirable properties of zeolites, they become inadequate when reactants with sizes above the dimensions of the pores are involved in the reaction. In this case a rational approach to overcome such a limitation would be to maintain the porous structure, which is responsible for the benefits described above, but to increase their diameter to bring them into the mesoporous region (2.0-50.0 nm). In this field, is well know a family of materials generally called M41S, represented by mesoporous silicate and aluminosilicate molecular sieves, synthesized with LCT (*Liquid Crystal Templating*) technique. These mesoporous silica have surface areas above 700

[72] P. B. Webb, M. F. Sellin, T. E. Kunene, S. Williamson, A. M. Z. Slawin, D. J. Cole-Hamilton, *J. Am. Chem. Soc.* **2003**, *125*, 15577-15588
[73] Cotton F. A.; Wilkinson G.; Murillo C. A.; Bochmann M. Advance Inorganic Chemistry, 6th ed.; Wiley-nterscience: New York, **1999**; Chapter 22

m^2 g^{-1}, large channels from 1.5 to 10.0 nm, ordered in a hexagonal (MCM-41), cubic (MCM-48), and laminar (MCM-50) array.[74]

Recently, other supports such as ionic liquids or polymers are employed and researches have been devoted towards the design of inorganic or polymer-based monoliths as supports. For example, our research group reported Schiff base complexes of cobalt (II) heterogeneized in polymeric membranes. These supported complexes were tested as catalysts in the asymmetric cyclopropanation of olefins by EDA.[75]

The development of mesoporous molecular sieves extended the scope to much larger substrates and guest and metal complexes can be grafted or tethered (via a spacer ligand) to the internal surface (**scheme 1.13**).



Scheme 1.13 – 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 modifications onto the catalytic behavior of the supported species. Especially for what concern chiral catalysts, when they are immobilized onto solid surfaces, the interaction between the active metal complex and the surface could reduce the obtained stereoselectivities,[76] and has often a detrimental effect on the observed

[74] A. Corma, *Chem. Rev.* **1997**, *97*, 2373-2419
[75] A . Caselli, M. G. Buonomenna, F. de Baldironi, L. Laera, S. Fantauzzi, F. Ragaini, E. Gallo, G. Golemme, S. Cenini, E. Drioli, *J. Mol. Catal. A: Chem.* **2010**, *317*, 72-80
[76] D. Rechavi, M. Lemaire, *Chem. Rev.* **2002**, *102*, 3467-3494

enantioselectivities.[77] Few years ago an innovative technique called **Supported Hydrogen-Bonded** (**SHB**), based only on weak interactions, was developed. This technique links the silanol groups of the support via hydrogen bonding to the sulfonate tail of the Rh(I) catalyst (**figure 1.20**).

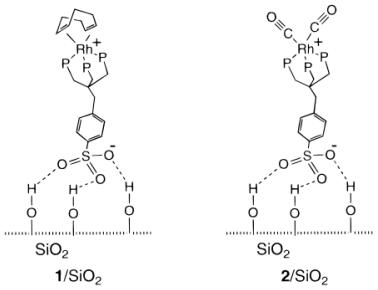
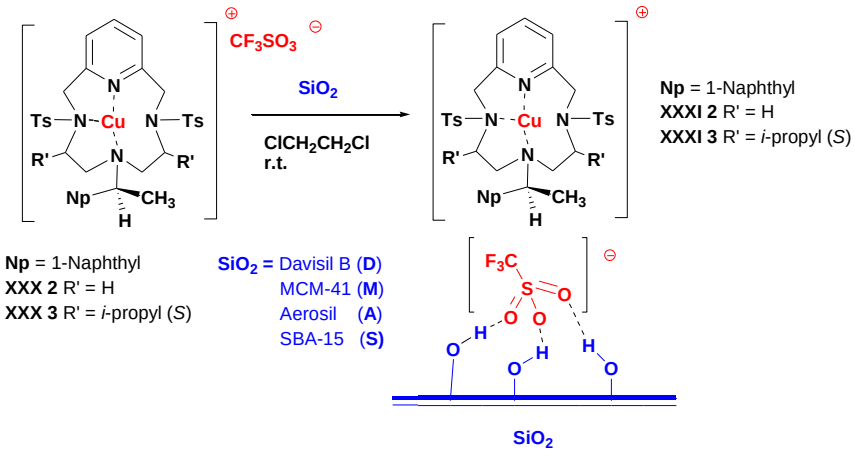


Figure 1.20 – Rh(I) catalysts supported on silica with SHB method

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.[78] 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.[(e quella precedente)79] 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.[80]

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 Milano (**scheme 1.14**).

[77] F. Fakhfakh, L. Baraket, A. Ghorbel, J. M. Fraile, C. I. Herrerías, J. A. Mayoral, *J. Mol. Catal. A: Chem.* **2010**, *329*, 21-26
[78] C. Bianchini, D. G. Burnaby, J. Evans, P. Frediani, A. Meli, W. Oberhauser, R. Psaro, L. Sordelli, F. Vizza, *J. Am. Chem. Soc.* **1999**, *121*, 5961-5971
[79] V. Dal Santo, M. Guidotti, R. Psaro, L. Marchese, F. Carniato, C. Bisio, *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences* **2012**, *468*, 1904-1926
[80] C. Bianchini, V. Dal Santo, A. Meli, W. Oberhauser, R. Psaro, F. Vizza, *Organometallics* **2000**, *19*, 2433-2444



Scheme 1.14 – General synthesis of supported Cu(I) complexes of **Pc-L*** ligands.

These grafted preformed Pc-L* copper(I) complexes on four different ordered and non-ordered silicas were tested under heterogeneous batch conditions for the olefin cyclopropanation.[81] The adopted SHB methodology allowed the easy and very mild preparation of the supported catalyst.

Copper complex **XXXI 3** 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. 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 1.21**).

[81] B. Castano, P. Zardi, Y. C. Honemann, A. Galarneau, E. Gallo, R. Psaro, A. Caselli, V. D. Santo, *RSC Advances* **2013**, *3*, 22199-22205

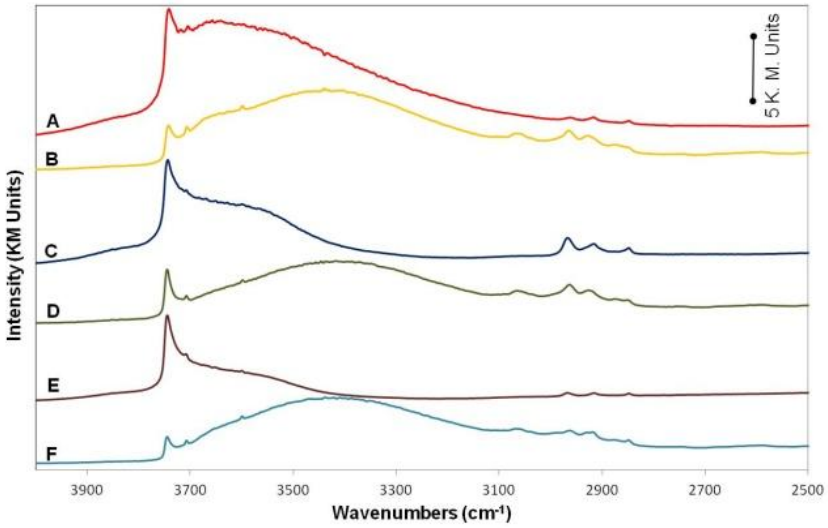


Figure 1.21 - DRIFT spectra showing the interaction via H-bonding.

A: bare Davisil, **B**: **XXXI**/D; **C:** bare MCM-41 (6124), **D: XXXI**/M1; **E:** bare SBA-15 (MFDC061), **F: XXXI**/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 **XXXI 2**, nor in location, nor in intensity (**figure 1.22**).

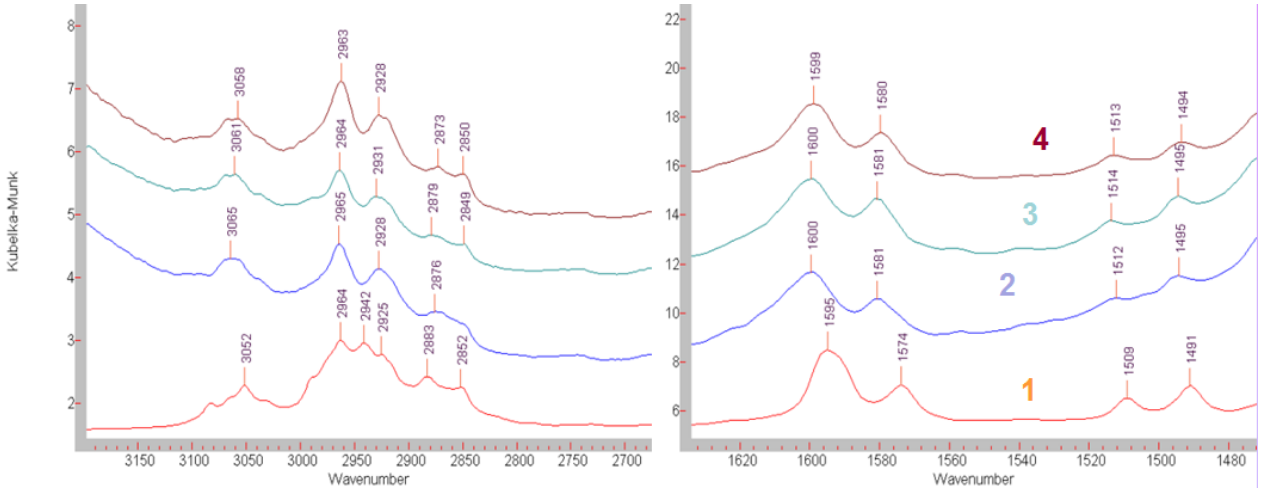


Figure 1.22 - DRIFT spectra of $[Cu^{I}(Pc\text{-}L^{*})]CF_3SO_3$ pure complex **XXXI 2** in solid state (mixed with KBr), trace 1; with Davisil LC150 sample, trace 2; with SBA-15 (MFDC065) sample, trace 3; with MCM-41 (6124) sample, trace 4.

SHB copper catalysts were hence applied in cyclopropanations by using *n*-hexane as reaction solvent in place of the less desirable halogeno-alkanes. The copper(I) complex **XXXI 2** was chosen

as a model to be supported on different silica and the cyclopropanation of α-methylstyrene by EDA was elected as standard reaction, in conditions very similar to those used in homogeneous phase,[56] allowing a direct comparison of the obtained results. Experimental data show only a very weak dependence of the reaction efficiency from the surface area characteristics of the employed silica. In particular, almost indistinguishable diastereo- and enantio-selectivities were used using either commercial Davisil or Aerosil 380 and 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.

The catalyst activity was almost unchanged in the heterogeneous phase with respect to the homogeneous one, although in some cases 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. Actually, in selected cases, reaction yields in cyclopropane products increase in the second run and this can be explained with a better release of the formed product from the silica. As often observed for heterogeneized catalysts, the *ees* were in any case slightly lower if compared to the homogeneous system, especially for the *trans* isomer. [82]

Concerning the catalyst, the Sheldon test [82] showed that it 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. Furthermore, after the catalytic run, the filtrate solution was analyzed 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.

Compared to the homogeneous reaction better diastereomeric excesses in favor of the *cis* isomer were obtained in *n*-hexane, a fact that is in agreement with those reported for clay-immobilized copper complexes.[83] 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 favor the preferential formation of the *cis* isomer.[84] It should be pointed out that the complex used 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. This may well be due to the enhancement of the polarity of the medium that

[82] R. A. Sheldon, M. Wallau, I. W. C. E. Arends, U. Schuchardt, *Acc. Chem. Res.* **1998**, *31*, 485-493
[83] A. I. Fernández, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, L. Salvatella, *Catalysis Communications* **2001**, *2*, 165-170
[84] J. M. Fraile, J. I. García, G. Jiménez-Osés, J. A. Mayoral, M. Roldán, *Organometallics* **2008**, *27*, 2246-2251

will affect the strength of ion pairs and ions-silica interactions,[85] finally leading to the observed differences in enantioselectivity. However, in this last solvent, some leached catalyst could be active in solution, as shown by the Sheldon test performed in 1,2-dichloroethane and this may explain the higher enantiomeric excesses obtained in the second and third run of the reaction when employing Aerosil 380 as a support, while *ee* obtained in *n*-hexane remains constant during all the consecutive runs. Also in this case the filtered reaction mixture after catalysis was analyzed by ICP-OES, showing Cu concentrations below 12.4 ppm, corresponding to a maximum leaching of 4.3% of copper present in the catalyst.

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 some cases the reaction was repeated for several consecutive runs and only after the seventh recycle (two days) a decrease in activity was observed.

Finally, since the Cu(I) complex **XXXI 3** of a more sterically hindered ligand gave the best results in term of enantioselectivity in the homogeneous phase (see **section 2.2.3**), 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. Remarkably the new catalyst gave cyclopropane products in very similar yields to that used before. It should be pointed out that complex **XXXI 3** 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 catalyzed cyclopropanation reactions. Enantioselectivities obtained for the *cis* cyclopropane products with those substrates were higher than those observed in the homogeneous reactions.[56] Low yields and enantioselectivities were obtained with diphenylethylene. Interestingly, benzophenone (less than 10% with respect to starting diphenylethylene) was found in this case amongst the reaction products.

[85] J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, M. A. Harmer, *J. Catal.* **1999**, *186*, 214-221

Catalysts were analyzed by DRIFT spectra and by CO-DRIFT spectroscopy. In general the analyses showed very robust catalysts, stable under the reaction conditions. Moreover the catalysts were investigated at the end of the catalysis by IR spectroscopy which confirmed the intact Cu complex structure, showing the presence of all the bands in the typical skeletal range of the spectrum. 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 1.23**) probably due to by-products by-products[85] (diethyl maleate and fumarate) and formation of diazoacetate polymers.[86]

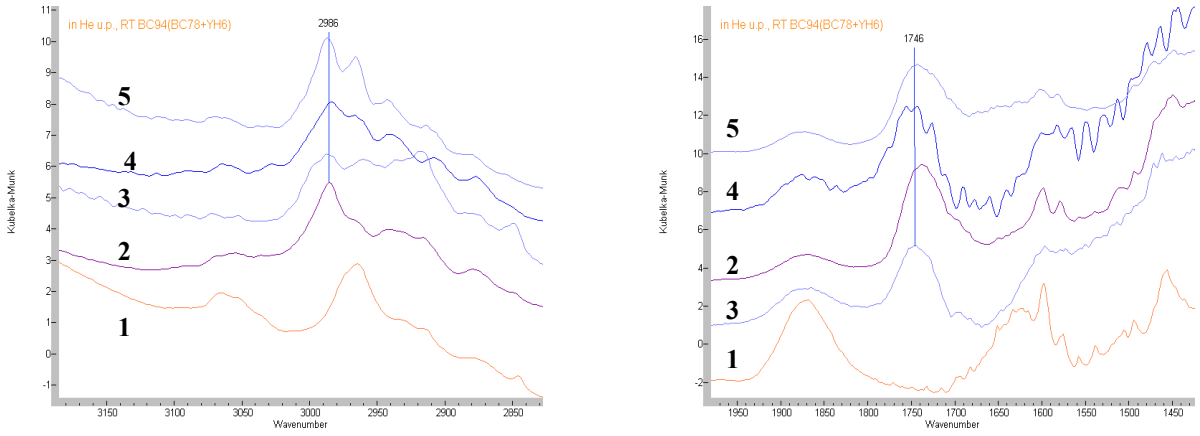


Figure 1.23 DRIFT spectra of $[Cu^{I}(Pc\text{-}L^{*})]CF_3SO_3$/Davisil samples before (**1**) and after catalysis: **2**, 4-chloro styrene + EDA; **3**, 4-methyl styrene + EDA; **4**, α-methyl styrene + EDA; **5**, α-methyl styrene + EDA (after 3 cycles and washing in 1,2-dichloroethane); characteristic bands of cyclopropanation products (pure cyclopropanes) at 2980 and 1730 cm^{-1}.

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 1.24**).

[86] L. J. Liu, Y. Song, H. Li, *Polymer International* **2002**, *51*, 1047-1049

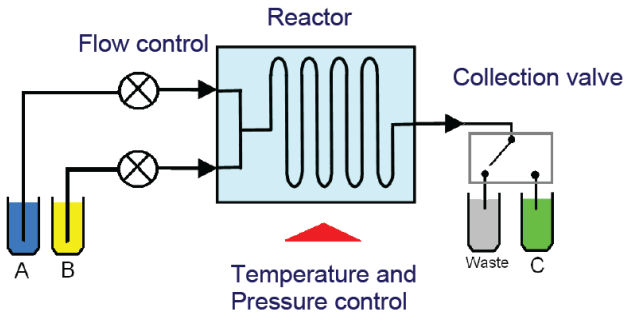


Figure 1.24 - General scheme of a flow reactor where reactants A and B are pumped continuously in the reactor.

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 supercritical CO_2 is an attractive solvent as it is safe and an ideal substitute for many hazardous and toxic solvents.[87] These kind of catalytic systems have been used for a wide range of reaction such as cyclopropanation reactions,[88] hydroformilation,[72] alkene methatesis.[89]

In a very recent work, we reported 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

[87] a) P. g. Jessop, W. Leitner, Editors, *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, **1999**; (b) W. Leitner, in *Modern Solvents in Organic Synthesis, Vol. 206* (Ed.: P. Knochel), Springer Berlin Heidelberg, **1999**, pp. 107-132; (c) D. J. Cole-Hamilton, *Adv. Synth. Catal.* **2006**, *348*, 1341-1351; dB. S. Sekhon, *International Journal of PharmTech Research* **2010**, *2*, 810-826

[88] M. I. Burguete, A. Cornejo, E. García-Verdugo, M. J. Gil, S. V. Luis, J. A. Mayoral, V. Martínez-Merino, M. Sokolova, *J. Org. Chem.* **2007**, *72*, 4344-4350

[89] R. Duque, E. Ochsner, H. Clavier, F. Caijo, S. P. Nolan, M. Mauduit, D. J. Cole-Hamilton, *Green Chemistry* **2011**, *13*, 1187-1195

(UK).[90] All these results obtained with the Cu complexes of the first generation Pc-Ls synthesized in our research group will pave the way to further studies by employing both the new ligands and the silver complexes described in the following chapter.

[90] B. Castano, E. Gallo, D. J. Cole-Hamilton, V. Dal Santo, R. Psaro, A. Caselli, *Green Chem.*, **2014,** *16*, 3202-3209

2 - RESULTS AND DISCUSSION

2.1 - Ligands

The first aim of this PhD work was the development of a synthetic strategy for obtaining an increased number of ligands different by substituents and protecting groups, with a general structure as the one showed in **figure 2.1**. Particular attention has been addressed to the optimization of any single step, in order to maximize the yields and to reduce the time of reaction.

The major part of the ligands are protected by tosyl groups, since they are the most used and studied by us thanks to the easiness of synthesis, their excellent stability in standard conditions, their ability in forming copper(I) complexes and the low cost of tosyl source (tosyl chloride) with respect to other protecting groups. Some triflyl protected macrocycles were synthesized and studied in order to understand how the change of the protecting group affects the catalytic activity.

Finally, since both the tosyl and triflyl protected compounds demonstrated not to be responsive to deprotection reaction, we developed a new class of *ortho*-nosyl protected ligands. We used them to achieve unprotected macrocycles bearing two -NH moieties.

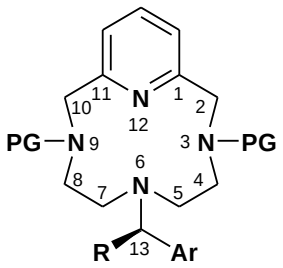


Figure 2.1 – General structure of PcL ligands

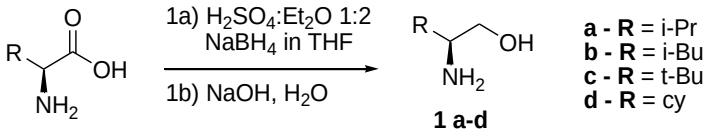
Every subchapter is devoted to a single step of the general pathway, from the aminoacids to the complexes. Whenever the nature of the protecting group affects the synthetic conditions of a step, the subchapter is further divided in order to enhance the differences.

2.1.1 – Synthesis of aminoalcohols

As mentioned in the introduction (**section 1.6**), one of the easiest modification that could be made on the structure of the ligands, is to change the starting aminoalcohol in order to insert substituents and stereocenters (if the alcohol is chiral) on the backbone of the molecule. Enantiomerically pure

aminoalcohols are widely available on commerce and the prices are not too high. Anyway, the cost of directly synthesizing them from the corresponding aminoacids is significantly lower, especially if non natural aminoacids are taken in account.

The classical procedure consists in the esterification of the carboxylic group, followed by the reduction of the ester with $LiAlH_4$. This pathway allowed us to obtain the products in good yields (75-90%), but it was expensive in terms of time. Furthermore, the double work-up enhanced the risk of product losses. We found in literature only one direct synthesis of aminoalcohols from aminoacids, reported by Cozzi et al.,[91] involving $NaBH_4$ and H_2SO_4 **(scheme 2.1)**. The procedure worked very well and enabled us to recover the aminoalcohols **1a-d** in excellent yields (90-99%) with complete retention of configuration.

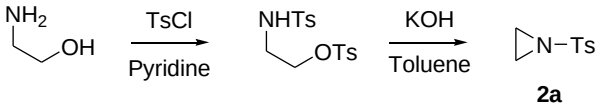


Scheme 2.1 – Reduction of aminoacids

2.1.2 – Synthesis of aziridines

2.1.2.1 – Synthesis of tosyl protected aziridines

The synthetic approach we used to convert aminoalcohols to tosyl protected aziridines depended on the nature of the substituents. The simpler reaction is the one with ethanolamine that involves a first tosylation of both the nitrogen and the oxygen atoms and the ring closure driven by NaOH **(scheme 2.2).**

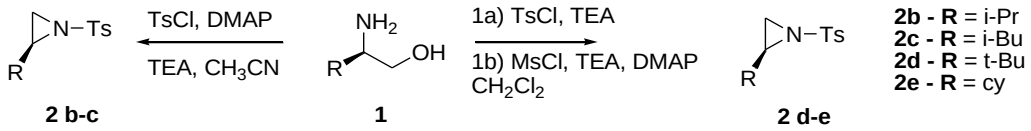


Scheme 2.2 – Synthesis of N-Ts-aziridine

For L-valinol and L-isoleucinol, we simply made the alcohol to react with tosylchloride in presence of DMAP for 20 hours **(scheme 2.3).**[92] Following this procedure, we met some difficulties in obtaining the aziridine from the L-cyclohexylglycinol and the L-isoleucinol since these hindering aliphatic groups seemed to prevent the reaction; so we looked in literature for a different pathway involving the tosylation of the nitrogen atom, followed by the mesylation of the oxygen and the

[91] P.G. Cozzi, E. Solari, C. Floriani, A. Chiesa-Villa, C. Rizzoli, *Chem. Ber.* **1996,** *129*, 1361-1368
[92] M. B. Barry, D. Craig, *Synlett* **1992**, 42.

subsequent ring closure. Surprisingly, this two steps one pot reaction allowed us not just to obtain the desired products, but also to achieve high yields (about 80%) without expensive chromatographic purifications **(scheme 2.3)**.[93] We decided, therefore, to apply this synthetic pathway also to the other aminoalcohols we used.



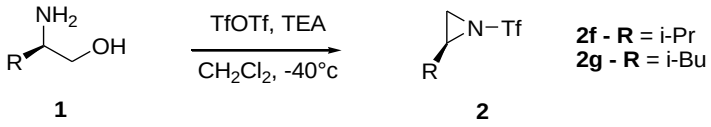
2 b-c **1** **2 d-e**

Scheme 2.3 – Synthesis of substituted N-Ts-aziridines

2.1.2.2 – Synthesis of triflyl protected aziridines

The synthesis of triflyl protected aziridines is slightly more sensitive with respect to the previous one, because of their major reactivity towards nucleophile. Hence, the reaction between the aminoalcohols and the triflic anhydride was conducted at -40°C, following a procedure described in literature **(scheme 2.4)**.[94]

We conducted this reaction only on L-valinol and L-leucinol, obtaining the products in high yields (80-90%) and sufficiently pure after work-up to be used in subsequent steps.



1 **2**

Scheme 2.4 – Synthesis of N-Tf-aziridines

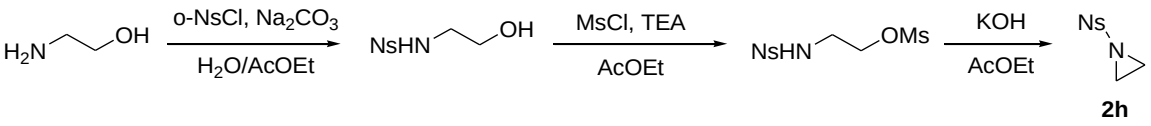
2.1.2.3 – Synthesis of o-nosyl protected aziridines

The synthesis of *ortho*-nosyl protected aziridines was simple and fast. Up to now, we synthesized only the aziridines deriving from ethanolamine and L-valinol and we adopted two different strategies depending on the starting material.

For aminoethanol, the pathway consists in a three step reaction, where the first two steps are the protection of the nitrogen and oxygen atoms respectively with *ortho*-nosyl and mesyl groups. The last step is the base-catalyzed ring-closure reaction that yields the *ortho*-nosyl protected aziridine **(scheme 2.5)**. Particular attention was given to temperature in the second step (protection of oxygen atom), in order to avoid a double mesylation of both the oxygen and the nitrogen atoms. The

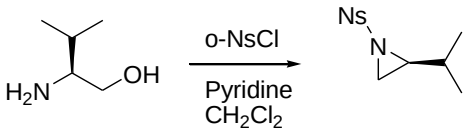
[93] W. Ye, D. Leow, S. L. M. Goh, C.-T. Tan, C.-H. Chian, C. H. Tan, *Tetrahedron Lett.*, **2006**, *47*, 1007-1010
[94] M. Cernerud, A. Skrinning, I. Bérgère, C. Moberg, *Tetrahedron Asymm.*, **1997,** *8*, 3437-3443

aziridine, if needed, is purified by precipitation of the impurities, and the overall yield of the three steps is very high (90%).



Scheme 2.5 – Synthesis of N-Ns-aziridine

On the other hand, the pathway for L-valinol is simpler and it involves a one pot reaction **(scheme 2.6)**.[95] Even if faster, this reaction allowed us to obtain the aziridine only in 60% yields after necessary chromatographic purification.



Scheme 2.6 – Synthesis of 2-isopropyl-N-Ns-aziridine

2.1.3 – Synthesis of 1,4,7-triazaheptanes

The general procedure for this step involves the ring opening reaction of one or two aziridines by a primary aromatic amine: we used benzylamine, 1-R- and 1-S-methyl benzylamine, naphthylmethylamine and both the isomers of 1-(*)-naphthylethylamine. In addition to the low price of these compounds, we chose them because of the availability of the pure enantiomers and their stability to the racemization. It is important to underline that, for every amine used, the attack at the terminal position of the aziridines is highly regioselective, we never observed a competing ring opening reaction at the substituted carbon and the absolute configuration of the stereocenters was always maintained.

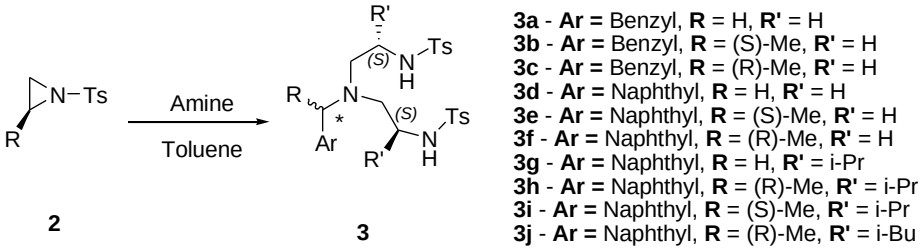
2.1.3.1 – Synthesis of "Disubstituted" 1,4,7-triazaheptane

The procedure for this step consisted in refluxing two equivalents of aziridine and one of amine in the appropriate solvent until the reaction was complete.

For tosyl protected aziridines, the solvent we initially chose was toluene: it allowed us to carry the reaction at high temperature and avoided the formation of any byproduct. Anyway, while the

[95] J. Farràs, X. Ginesta, P. W. Sutton, J. Taltavull, F. Egeler, P. Romea, F. Urpì, J. Vilarrasa, *Tetrahedron*, **2001**, *57*, 7665-7674

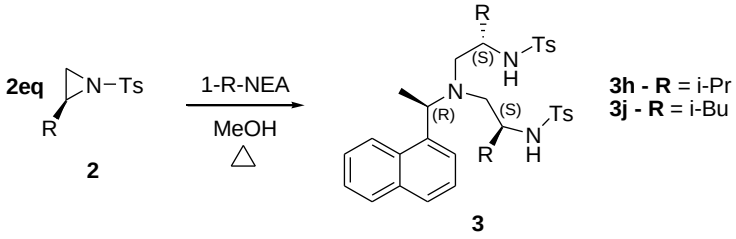
reaction takes only few hours for unsubstituted aziridines, it takes prolonged times (more than one week) for substituted aziridines (we used this strategy for compounds **2a-b**) **(scheme 2.7)**. We usually obtained a mean of 60% yield, depending on how much time we spend for the reaction: thanks to some kinetic studies, we realized that over 800h of reflux were necessary to obtain the product in a >95% yield for compound **3h**. This is the reason why we studied an alternative.



Scheme 2.7 – Synthesis of tosyl protected sulfonamides

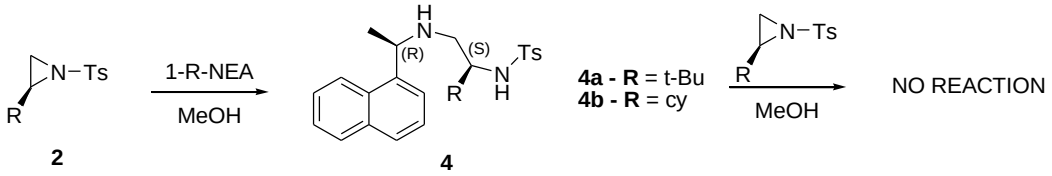
We conducted some reaction in solvents more suitable for nucleophilic substitutions and, in order to reduce the reaction time and to prevent the formation of undesired compounds, we increase the concentration of the reactants as much as possible.

In this way, we found that MeOH (3M solution with respect to the starting aziridine) is the best solvent in which carry the reaction: in just 24 hours of reflux, we obtained the target triazaheptane (bis-sulfonamide from now) **3h-j** in 70% overall yield after chromatographic purification **(Scheme 2.8)**. Using CH_3CN as solvent, the reaction was slower, but it was easier to recover the pure products.



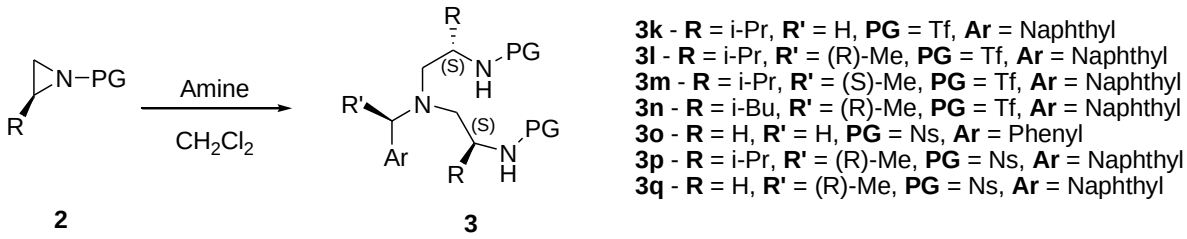
Scheme 2.8 – Synthesis of tosyl protected bis-sulfonamides with bulkier substituents.

Both the classical and the new pathways did not allowed us to obtain the bis-sulfonamides deriving from aziridines **2d-e**. Even by increasing the reaction time, we never recognized any trace of the desired products. The reaction always stopped at the first attack, giving the sulfonamides **4**. We isolated the sulfonamides **4a-b** (over 90% yield), in order to purify and use them in a step by step reaction, but it did not changed the final outcome **(scheme 2.9)**. As reported in the next section, we used the sulfonamides to form monosubstituted compounds.



Scheme 2.9 – Step by step synthesis of tosyl protected bis-sulfonamides

On the other hand, the reactions between the triflyl and nosyl protected aziridines and the amines were drastically shorter thanks to the activating effect of the protecting groups. So, it was possible to conduct these reactions in milder conditions **(scheme 2.10).**



Scheme 2.10 – Synthesis of triflyl and nosyl protected bis-sulfonamides

For bis-sulfonamide **3k -** as for the monoaddition compound **4k –** we obtained crystals suitable for X-ray determination **(figure 2.2).** As it possible to see from the figure, the monoamine **4k** showed a zwitterionic formula, where one of the nitrogen atoms bears two hydrogens instead of one. This structure is responsive of the low solubility of compound **4k** in organic solvent, but does not affect the stereochemistry of the molecule.

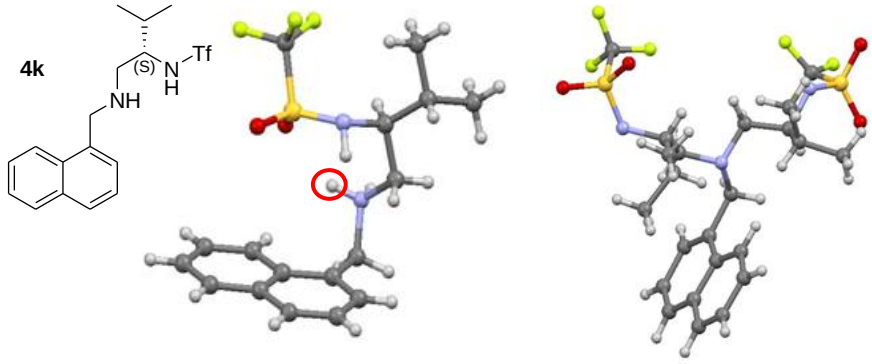
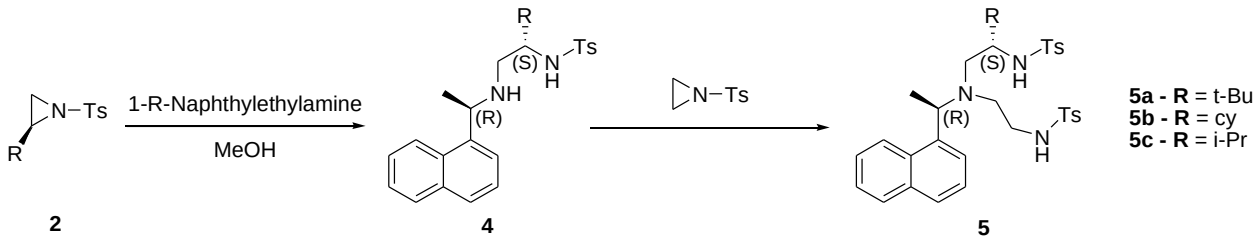


Figure 2.2 – Structure of sulfonamide **4k**, the hydrogen highlighted in red is a disordered proton, coming from the presence of a zwitterionic formula (70%) equilibrating with the neutral molecule; and bis-sulfonamide **3k** (NH hydrogens omitted)

2.1.3.1 – Synthesis of "Monosubstituted" triazaheptanes

Necessity is the mother of invention and we decided to use the monoaddition products **4** as starting material for a monosubstituted class of bis-sulfonamides. Hence, we conducted the reaction step by step, using a substituted aziridine in the first and, in the second, an aziridine bearing no substituent on the ring. Also in this case, MeOH was the best solvent with regards to the yield, while CH_3CN avoided the formation of byproducts **(Scheme 2.11)**.

We easily obtained in this way the bis-sulfonamides **5a-c**, in really high yield (80-85%) after chromatographic purification.



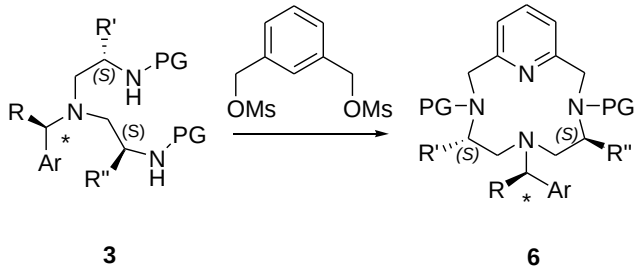
2 **4** **5**

Scheme 2.11 – Synthesis of monosubstituted bis-sulfonamides

2.1.4 – Synthesis of macrocycles

All the bis-sulfonamides we obtained were used to form the corresponding macrocycles, by reacting with a suitably 2,6 substituted pyridine. This step was conducted in heterogeneous conditions, employing K_2CO_3 as base, in order to avoid high dilution techniques.[96] The reaction allows to obtain the desired macrocycles in yields from 50 to 85% after chromatographic purification **(scheme 2.12)**.

[96] S. Aime, M. Botta, S. G. Crich, G. B. Giovenzana, G. Jommi, R. Pagliarin, M. Sisti, *Inorg. Chem.* **1997**, *36*, 2992-3000

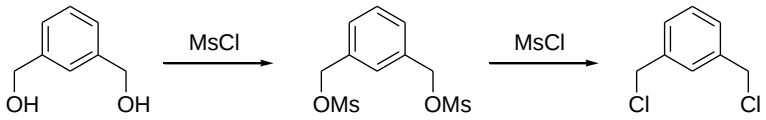


3 6

6a - **Ar =** Benzyl, **R** = **R'** = **R''** = H, **PG** = Ts
6b - **Ar =** Benzyl, **R** = (S)-Me, **R'** = **R''** = H, **PG** = Ts
6c - **Ar =** Benzyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = Ts
6d - **Ar =** Naphthyl, **R** = **R'** = **R''** = H, **PG** = Ts
6e - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R''** = H, **PG** = Ts
6f - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = Ts
6g - **Ar =** Naphthyl, **R** = H, **R'** = **R''** = i-Pr, **PG** = Ts
6h - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Pr, **PG** = Ts
6i - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R'' =** i-Pr, **PG** = Ts
6j - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Bu, **PG** = Ts
6k - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = cy, **R'' =** H, **PG** = Ts
6l - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = t-Bu, **R'' =** H, **PG** = Ts
6m - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = i-Pr, **R'' =** H, **PG** = Ts
6n - **Ar =** Naphthyl, **R** = H, **R'** = **R''** = i-Pr, **PG** = Tf
6o - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Pr, **PG** = Tf
6p - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R''** = i-Pr, **PG** = Tf
6q - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Bu, **PG** = Tf
6r - **Ar =** Benzyl, **R** = **R'** = **R''** = H, **PG** = oNs
6s - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = oNs
6t - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Pr, **PG** = oNs

Scheme 2.12 – Synthesis of macrocycles

Concerning the substituted pyridine, initially, we used the commercially available 2,6-bis(chloromethyl)pyridine,[97] afterwards we discovered that 2,6-bis(mesylmethyl)pyridine is more reactive (and cheap) with respect to the previous one. We synthesized it by reacting 2,6-bis(methanol)pyridine with mesylchloride; the great advantage of this reaction is that the only byproduct we observed was the 2,6-bis(chloromethyl)pyridine **(scheme 2.13)**.[98]



Scheme 2.13 – Synthesis of 2,6-bis(OMs-methyl)-pyridine

Although the employed conditions allowed the synthesis of all the target ligands, 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 started focusing on the synthesis of compound **6o**, that under conventional heating required 110 hours of reflux to give the macrocycle in 40% yield after purification. We maintained the same stoichiometry and concentration of the reactants and we conducted the reaction at 130°C for 2 hours (20% yield) and 150°C for 3 hours (50% yield). Anyway, even by increasing the reaction time, no further beneficial effect was observed with respect to the yield.

[97] B. Castano, T. Pedrazzini, M. Sisti, E. Gallo, F. Ragaini, N. Casati, A. Caselli, *App. Organomet. Chem* **2011,** *25*, 824-829
[98] O. Meth-Cohn, H. Hiang, *J. Chem. Soc., Perkin Trans.* 1, **1998,** 3737-3742

Surprisingly, the same procedure failed to yield the desired compound when applied to tosyl protected species.

2.1.5 - Characterization of the ligands

All products have been fully characterized by ^{1}H and ^{13}C-NMR, EA and MS. For some of them we also obtained crystals suitable for X-Ray analysis.

Ligand **6a** was crystallized from dichloromethane/toluene. In the absence of chirality, this compound crystallizes in centrosymmetric P-1 **(figures 2.3)**.

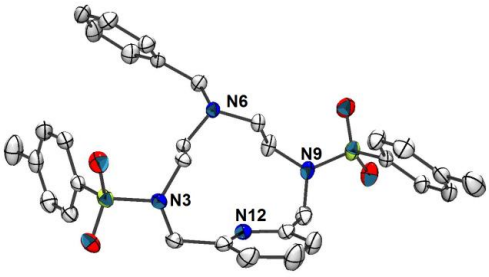


Figure 2.3 – Structure of **Pc-L** tetraazamacrocyclic ligand **6a**. Distances within the coordination pocket are: **N12-N6** 3.933 Å and **N3-N9** 5.741 Å, the asymmetric unit includes the entire molecule

A crystal structure for **6h** 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.

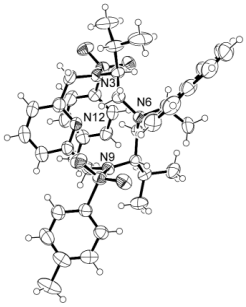


Figure 2.4 – Structure of compound **6h** (thermal ellipsoids are shown at 50% probability level). Distances within the coordination pocket are: **N6-N12** 3.629(5) Å and **N3-N9** 4.910(6) Å

In **6h** the bonds C2-N3 and C10-N9 (see **figure 2.1** for labeling 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 **6a (figure 2.3)**. 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 **6h** which is in agreement with expectations.

For what concern the characterization of the other highly substituted ligands, we met difficulties in assigning the peaks in the NMR spectra of the ligands **6j-l,** because of the presence of too many and broad signals. Since both EA and MS analyses confirmed the purity of the compounds, we hypothesized the presence of two (or more) conformers.

By increasing the acquiring temperature, we generally observed a slight sharpening of the signals **(figure 2.5)** that gave us some evidence of the presence of two major conformers.

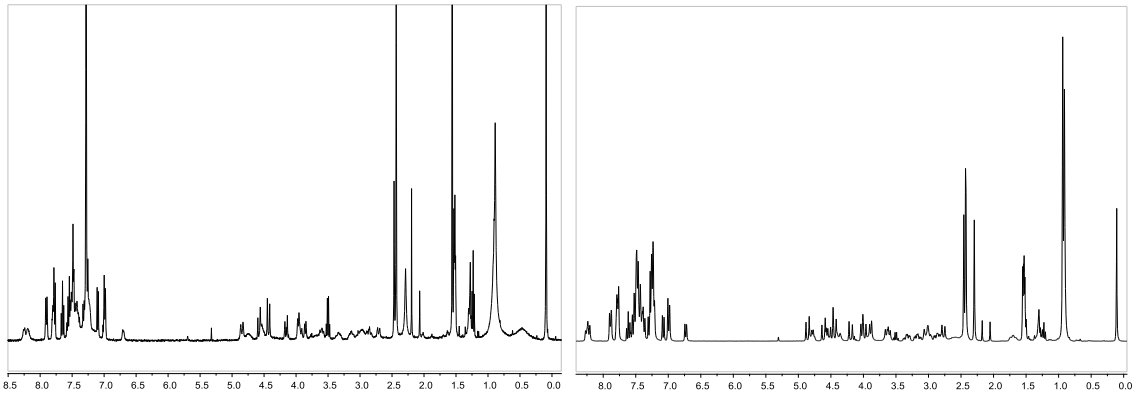
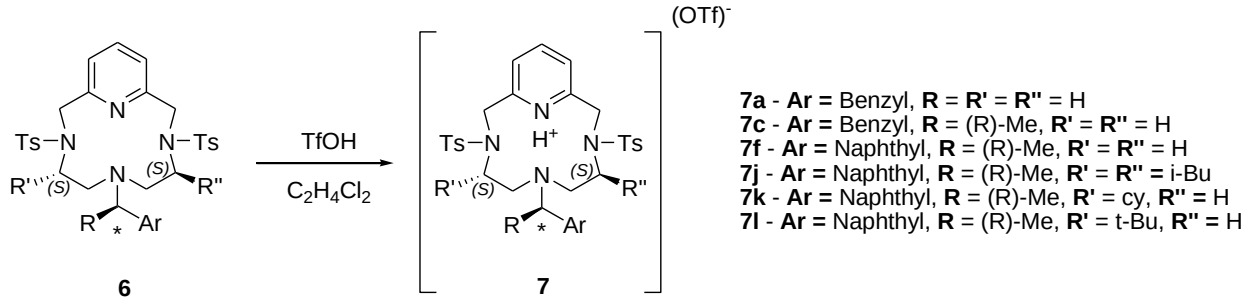


Figure 2.5 – *^{1}H-NMR spectrum of **6l** at 298K (left) and 333K (right)*

In order to investigate the basicity of the four nitrogen atoms, we synthesized and characterized the protonated salts of some of the macrocycles, by treating the compounds with the properly chosen triflic acid: this acid is soluble in organic solvent and the counter ion OTf^- is the common anion of our copper(I) complexes (see **section 2.2**). At the same time, we used this method to see if a weak coordination could simplify the spectra of the ligands **6j-l**, by avoiding the presence of conformers. We hence isolated the compounds **7**, arising from ligands **6a,c,f,j-l (scheme 2.14).**



Scheme 2.14 – Synthesis of protonated ligands

The reaction was fast and quantitative and the pure protonated salts could be isolated in high yields (90%). The products have been fully characterized, including a X-Ray structure of the complex **7f** (**figure 2.6**). As expected for an ammonium salt, the proton was located at high frequencies in the ^{1}H-NMR spectrum (11.82 ppm for **7a**, 11.24 ppm for **7c**, 10.66 ppm for **7f**, 9.25 ppm for **7j** and **7k** and 8.59 ppm for **7l** in $CDCl_3$ at room temperature). In almost all cases, the NMR spectra of the protonated ligands were clearer and easier to read than the spectra of the free macrocycles.

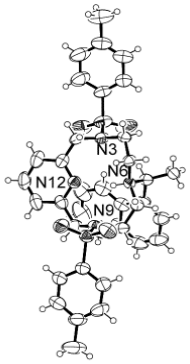


Figure 2.6 – Structure of compound **7f** (thermal ellipsoids are shown at 50% probability level; the $[CF_3SO_3]^-$ counter ion is omitted for clarity). Selected bond distances (Å) and angle (°) : **N6-H2** is fixed at 0.91 , **N6-H2-N12** 153. For sake of comparison with **6h**, **N6-N12** is 2.916(5) and **N3-N9** 5.090(5)

In the case of complex **7j**, the ^{1}H-NMR spectrum was – as also for the free ligand – very hard to analyze **(figure 2.7).** Probably, the large freedom of the *i*-Bu arms prevents the ligand to take a stable conformation.

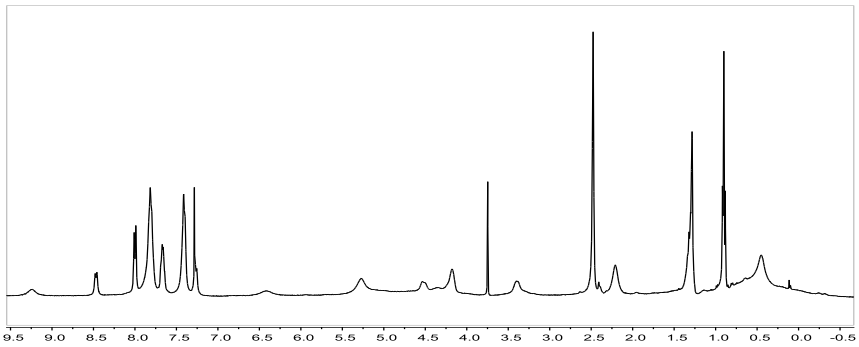


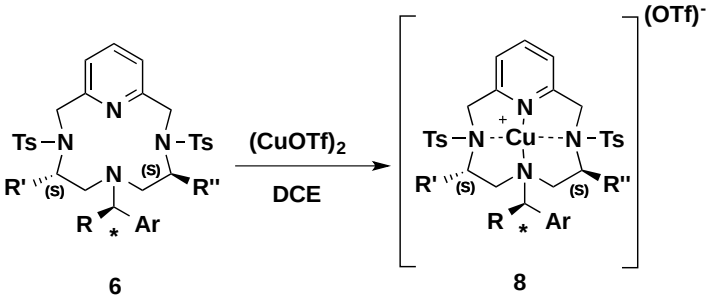
Figure 2.7 – 7j ^{1}H-NMR spectrum

As mentioned above, we obtained crystals suitable for an X-Ray structural determination of **7f**, by crystallization from a dichloroethane solution **(figure 2.6).** The species crystallized as salt of $[CF_3SO_3]^-$ in chiral $P2_12_12_1$. **7f** and free ligand **6h** have some similarities in the conformation of the cycle: the bonds C2-N3 and C10-N9 are associated with *anti-clinal* conformations that make 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))

2.2 - Copper

2.2.1 - Synthesis

As already reported in the introduction (**section 1.5**), the treatment of ligand **6c** with $[Cu(OTf)]_2 \cdot C_7H_8$ gave yellow Cu(I) complex (**8c**) that undergo oxidation quite readily. The same behavior was observed for Cu(I) complex **8a** derived from free ligand **6a**.[66] This complex has been isolated and fully characterized. The process consists in treating a suspension of the copper salt in 1,2-dichloroethane (DCE) at room temperature with toluene, the precipitation of complex as a white powder, in good yields. Complex **8a** was characterized by NMR spectroscopy.
The corresponding copper(I) complexes were synthesized also for the other ligands.



8a - Ar = Benzyl, R = R' = R'' = H cede
8c - Ar = Benzyl, R = (R)-Me, R' = R'' = H
8d - Ar = Naphthyl, R = R' = R'' = H
8f - Ar = Naphthyl, R = (R)-Me, R' = R'' = H
8g - Ar = Naphthyl, R = H, R' = R'' = i-Pr
8h - Ar = Naphthyl, R = (R)-Me, R' = R'' = i-Pr
8j - Ar = Naphthyl, R = (R)-Me, R' = R'' = i-Bu
8k - Ar = Naphthyl, R = (R)-Me, R' = cy, R'' = H
8l - Ar = Naphthyl, R = (R)-Me, R' = t-Bu, R'' = H
8m - Ar = Naphthyl, R = (R)-Me, R' = i-Pr, R'' = H

Scheme 2.15 – Synthesis of Cu complexes

As previously reported, the effect of the copper complexation to the ligands was shown also by the shift of the signals in ^{1}H, ^{13}C and ^{15}N-NMR spectra. Moreover, although the synthesis is performed under protecting atmosphere to maximize the yield, complexes **8d-m** could be manipulated in air without decomposition. The reason of this major stability is due to the presence of the naphthyl group that acts as a further coordination site for the metal. In these cases low symmetry is retained in solution, as shown by NMR studies (see **figure 2.8** as example for complex **8h**). 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 characterized.

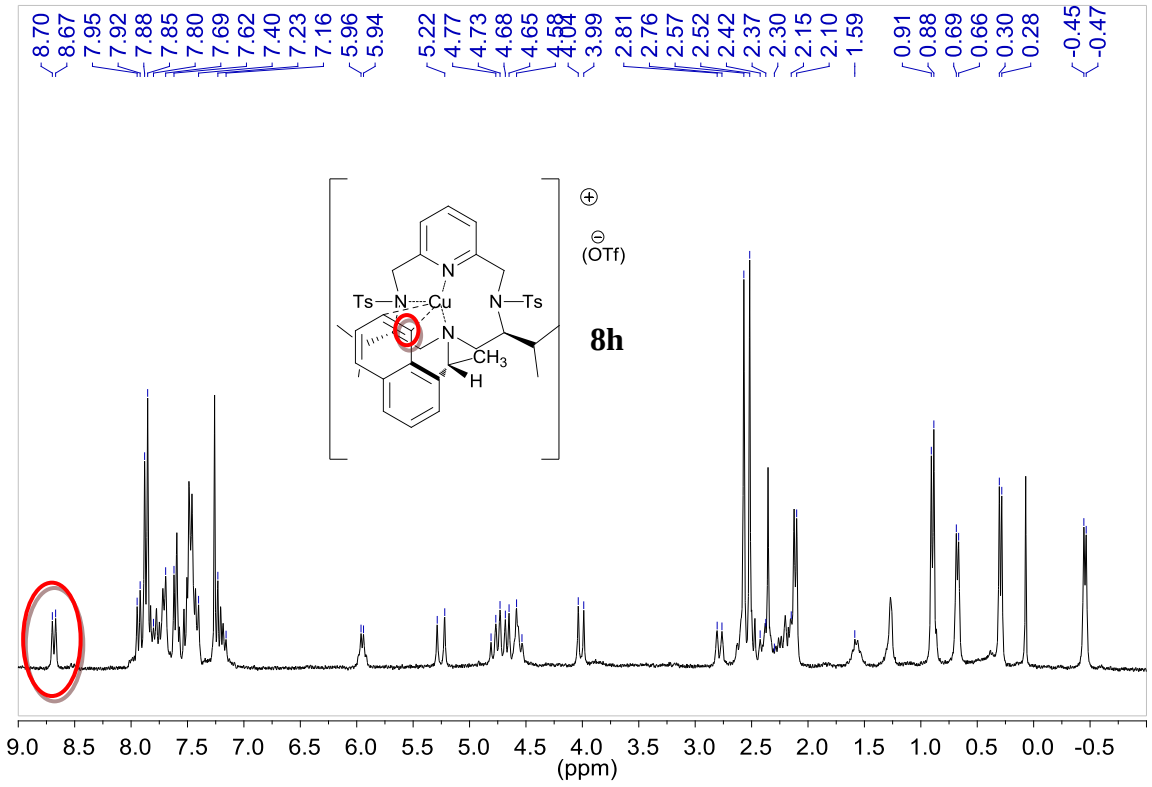
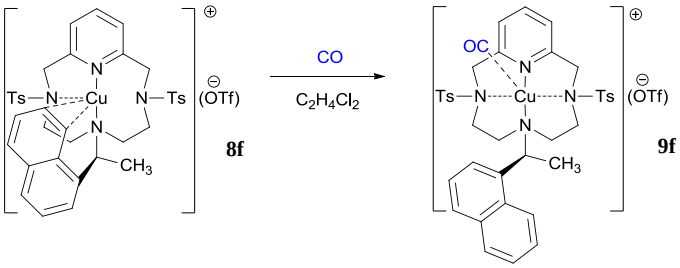


Figure 2.8 – ^{1}H-NMR relative to complex **8h.** In the ^{1}H-NMR the proton directly bound to the highlighted carbon shifted to higher frequencies 8.68 ppm compared to 8.58 ppm for the free ligand **6h**

2.2.2 - Reactivity

To better understand the behavior of the naphthyl group, we studied the complexes in the presence of added ligands. For this scope we fluxed CO in a dichloroethane solution of the complex **8f** and we analyzed the product (**scheme 2.16).**



Scheme 2.16 – Complexation of CO

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 **9f** is higher than those reported in the case of tetracoordinated copper(I) CO complexes of [bis(2pyridylmethyl)amine],[99] 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 **9f** in an NMR tube to ^{13}C doped carbon monoxide atmosphere. As reported in **figure 2.9**, beyond a clear signal at 184.1 ppm related to the free CO, a sharp signal at 171.3 ppm was observed, in a typical range for CO coordinated to copper(I).[100]

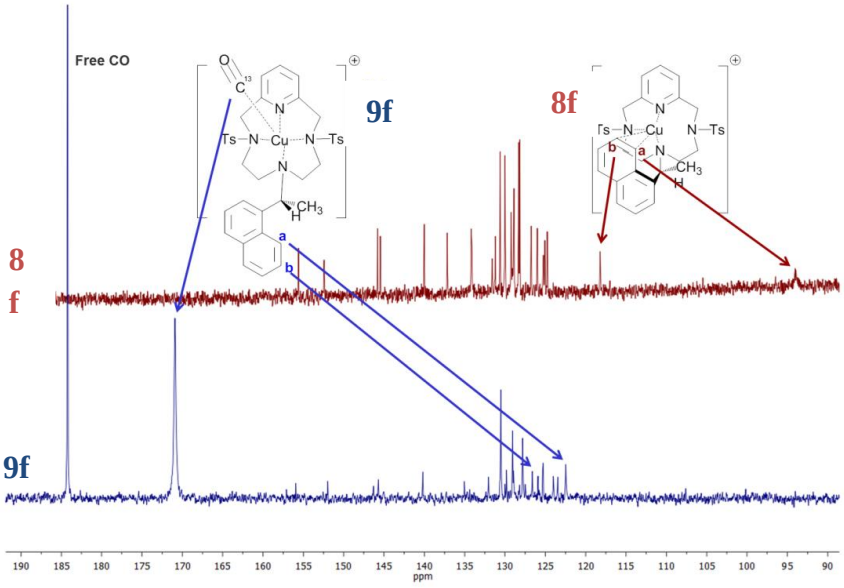


Figure 2.9 - ^{13}C-NMR spectra of complexes **8f** (upper red line) and **9f** (lower blue line) in $CDCl_3$

[99] H. R. Lucas, G. J. Meyer, K. D. Karlin, *J. Am. Chem. Soc.* **2010**, *132*, 12927-12940.
[100] M. Kujime, T. Kurahashi, M. Tomura, H. Fujii, *Inorg. Chem.* **2007**, *46*, 541-551

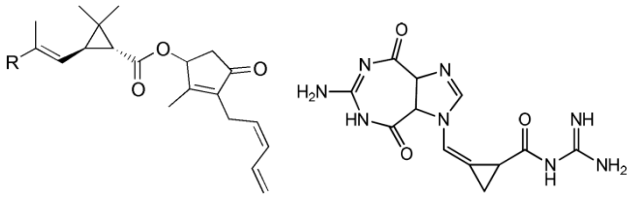
On the other hand, signals relative to carbon **a** and **b** were located at 122.9 and 127.0 ppm respectively, clearly indicating that the naphthyl group is no more coordinated to the copper atom after the CO uptake. This result, that is consistent with the complexation study with CH_3CN (see introduction, **section 1.5**), is of particular relevance to catalysis, since it is reasonable to assume that the naphthyl moiety can stabilize the coordination sphere of the copper atom, but can be easily displaced by incoming substrates. Anyway, in absence of competitors of the CO molecule, the complex is stable under inert atmosphere; this behavior is different from the analogous complex of silver(I), where the coordination with CO is weak and the molecule is coordinated only under flux of gas (*vide infra* **section 2.3.2**).

2.2.3 – Catalysis: cyclopropanation

2.2.3.1 – Introduction

Cyclopropanes are the simplest cyclic compounds in organic chemistry and, perhaps for this very reason, they are widely spread in nature. Thanks to their importance in natural – and hence biological and pharmaceutical – products,[101] they are attracting ever greater interest in the recent years. They are versatile intermediates in the synthesis of more complex molecules of any field of application: cyclopropanes have been found to exhibit diverse biological proprieties and applications ranging from enzyme inhibitions to antibacterial,[102] insecticidal (figure **2.10a**),[103] antifungal, herbicidal, antimicrobial,[104] antibiotic, antibacterial, anticancer and antitumor activities. For example, Betulins and their derivative containing a cyclopropane moiety were synthesized and proven to be the most cytotoxic toward human melanoma of the *Colo 38* and *Bro lines* and human ovarian carcinoma of the *CaOv line*.[105] Cyclopropanes also have antiestrogenic, anti-HIV[106] and antiviral activities like the nucleoside analogue reported in **figure 2.10b**.

[101] C. J. Suckling, *Angew. Chem. Int. Ed. Engl*., **1998**, 27, 537
[102] Kirk-Othmer in Encyclopedia of Chem Tech. Insecticides **1965**, Vol 2, p 685
[103] (a) K. Naumann, Synthetic Pyrethroid Insecticides: Chemistryand Patents. In Chemistry of Plant Protection, Synthetic Pyrethroid Insecticides; Haug, G., Hoffmann, H., Eds.; Springer-Verlag: Heidelberg, **1990**; Vol. 5, p 63. (b) D. Arlt, M. Jautelat, R. Lantzsch, *Angew. Chem., Int. Ed*. **1981**, 20, 703.
[104] K. V. Toraskar MP, Kulkarni VM, *Int J Pharm and Pharma Sci 2*, 132-133.
[105] V. N. Symon AV, Kaplun AP, Vlasenkova NK, Fedorova, GA, Liutik AI, Gerasimova GK, Shvrts VI, *Bioorg Khim* **2005**, *31*, 320-325.
[106] T. R. Liu L, Liu S, Chen X, Guo L, Che Y, Pestaloficiols A-E,, *Bioorg and Med Chem* **2008**, *16*, 6021-6026

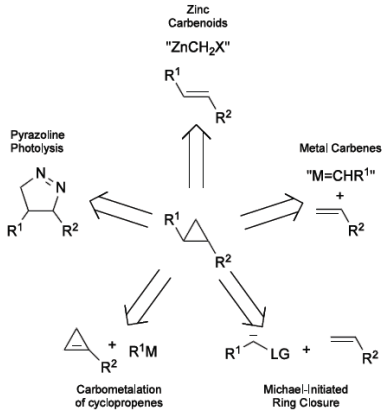


a **b**

Figure 2.10 - **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 are present also in molecules produced in industrial scale as antidepressants[107] and drugs for the treatment of sleep disorders.[108]

Many different methods have been reported up to now for the synthesis of cyclopropane derivatives from various achiral substrates **(scheme 2.17)**.

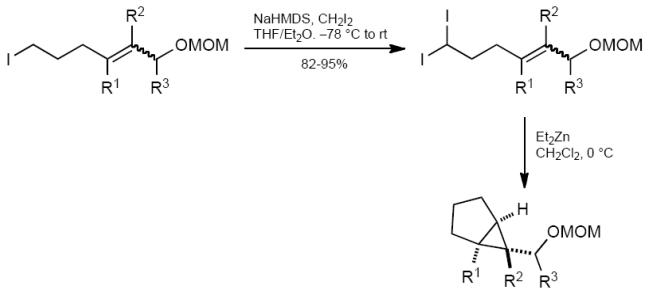


Scheme 2.17 – Various approaches to cyclopropane derivatives

From the historical point of view, after the first work of Emschwiller[109] in 1929, the conversion of alkenes to cyclopropane derivatives was discovered by Simmons and Smith only in 1958, using zinc carbenoids[110] and, still today, this method remains one of the most important for the synthesis of cyclopropanes. Several zinc carbenoid reagents have been prepared shortly after Simmons and Smith, Wittig,[111] and Furukawa publications.[112] Recently, several new zinc carbenoids have been prepared to tailor their reactivities and properties to specific applications.[113,114]

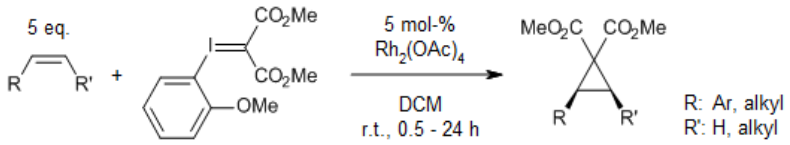
[107] R. Csuk, M. J. Schabel, Y. Von Scholz, *Tetrahedron: Asymm*, **1996**, 7, 3505
[108] H. U. Blaser, E. Shmidt, *Asymmetric Catalysis on Industrial Scale*, **2004**, 6, 335.
[109] G. Emschwiller, *Compt. Rend*. **1929**, 188, 1555
[110] (a) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc*. **1958**, 80, 5323. (b) H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc*., **1959**, 81, 4256
[111] G. Wittig, K. Schwarzenbach, *Angew. Chem*. **1959**, 71, 652
[112] J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett*. **1966**, 7, 3353
[113] A. Voituriez, L. E. Zimmer, A. B. Charette, *J. Org. Chem*., **2010**, 75, 1244

Various synthetic strategies have appeared via intramolecular Simmons-Smith cyclopropanation. 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 2.18)**.[115]



Scheme 2.18 – Intramolecular Simmons-Smith cyclopropanation leading to bicyclo[3.1.0]hexanes

Different alternative routes have been proposed to obtain 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-catalyzed cyclopropanation under homogeneous conditions (**scheme 2.19**).[116]



Scheme 2.19 – Synthesis of functionalized cyclopropane molecules proposed by Zhu and co-workers

One of the most useful method to obtain the cyclopropane ring involves the transition metal catalyzed decomposition of a carbene precursor, such as a diazoalkane, an iodonium ylide, or a 1,2,3-triazole, to form a reactive specie (**figure 2.11**, **a b, c** respectively).

[114] J. C. Lorenz, J. Long, Z. Q. Yang, S. Xue, Y. Xie, Y. J. Shi, *J. Org. Chem*., **2004**, 69, 327
[115] J.A. Bull, A.B. Charette, *J. Am. Chem. Soc*., **2010**, 132, 895
[116] C. Zhu, A. Yoshimura, L. Ji, Y. Wei, V. N. Nemykin, V. V. Zhdankin, *Org. Lett*., **2012**, 14, 3170-3173

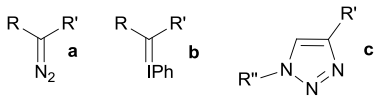
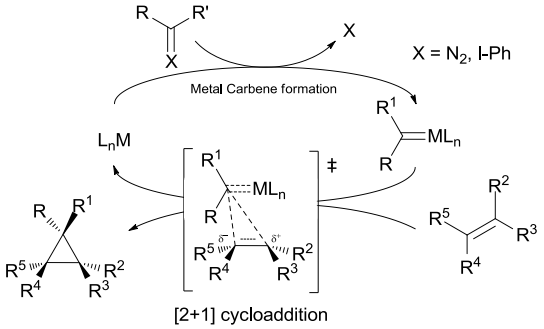


Figure 2.11 – Most commonly used types of carbene precursors in asymmetric cyclopropanation

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 2.20**).



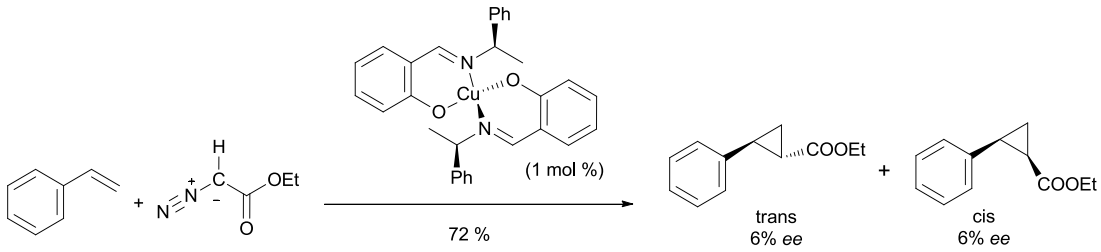
Scheme 2.20 General mechanism of the intermolecular cyclopropanation using metal carbenes

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.[117]

The reaction of unsubstituted diazocarbonyl compounds 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. Ethyl diazoacetate (EDA),[118] which is one of the rare commercially

[117] H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977-1050
[118] 2-diazoacetic acid ethyl ester CAS. 623-73-4

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.[119] 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 2.21**).



Scheme 2.21 Nozaki's copper catalyzed cyclopropanation

Although the enantiomeric ratios were modest, this catalyst defined the basis for further ligand optimization. In particular the copper-catalyzed enantioselective version of the reaction is now well established, and chiral C_2 symmetric bidentate ligands such as bisoxazolines[120, 121, 122] are the most widely used, also with EDA as carbene source.[123] 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 2.12**).[124]

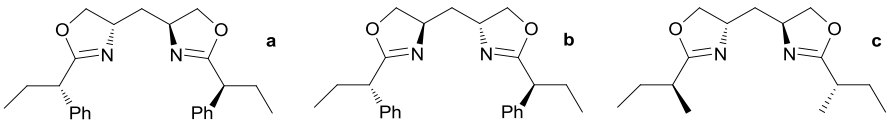


Figure 2.12 Two different PhPrAraBOX (**a** and **b**) and MePrArBOX (**c**) synthesized by Kellehan *et al.*

Also porphyrines are widely employed as ligands in cyclopropanation reactions,[125] very recently, S.

[119] H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239-5244
[120] H. Pellissier, *Tetrahedron* **2008**, *64*, 7041-7095
[121] T. Matsumoto; K. Masumoto; A. Tanaka, , PCT Int. Appl., **2013**, WO 2013073596 A1 20130523
[122] T. Sawada, M. Nakada, *Tetrahedron: Asymmetry*, **2012**, 23(5),350-356
[123] A. R. Silva, V. Guimarães, L. Carneiro, N. Nunes, S. Borges, J. Pires, Â. Martins, A. P. Carvalho, *Microporous and Mesoporous Materials* **2013**, *179*, 231-241
[124] D. Kellehan, F. Kirby, D. Frain, A. M. Rodríguez-García, J. I. García, P. O'Leary, *Tetrahedron: Asymmetry* **2013**, *24*, 750-757
[125] D. Intrieri, A. Caselli, E. Gallo, *Eur. J. Inorg. Chem.*, **2011**, 5071-5081

Gharaati[126] *et al.* 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.

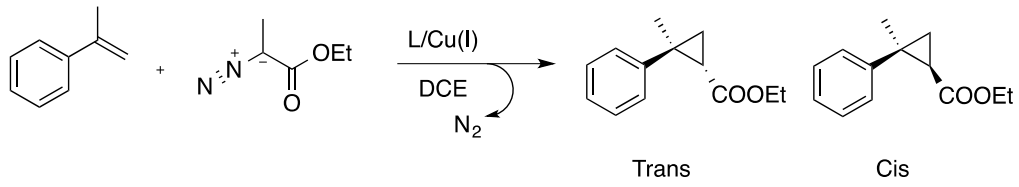
The literature concerning the cyclopropanation reaction is continuously expanding:[127] new and more efficient methods for the preparation of these functionalities in enantiomerically pure form are still evolving. Few years ago, our group reported the synthesis and characterization of copper(I) complexes of the previously described (*vide supra*) ligands (Pc-L) and preliminary results on their use as catalysts in asymmetric cyclopropanation reactions.[56] Here we report our new findings concerning the asymmetric cyclopropanation reaction of alkenes exploring the catalytic performances of copper(I) complexes derived from the new synthesized tetraazamacrocyclic ligands (**Pc-L**).[128]

2.2.3.2 – Catalysis

All the complexes **8** of the ligands **6** were tested in cyclopropanation reaction, applying the optimized conditions described in our previous work and in the introduction (**section 1.7.2**): EDA was slowly added to a solution containing the olefin, the ligand and the Cu salt (Cu/Ligand/EDA/Olefin ratio 1:1:35:170) at 0°C and the reaction was followed by monitoring the disappearance of the band due to the stretching of the N_2 moiety of EDA. We already found $[Cu(OTf)]_2 \bullet C_6H_6$ to be the best copper source and dichloroethane the best solvent. The reaction proceeds equally well either using preformed isolated complexes or synthesizing the catalysts in situ, by mixing equimolar amounts of the copper(I) salt and the ligand.

The test reaction was the cyclopropanation of the double bond of α-methylstyrene, as reported in **scheme 2.22**

[126] S. Gharaati, M. Moghadam, S. Tangestaninejad, V. Mirkhani, I. Mohammadpoor-Baltork, B. Barati, F. Sadegh, *J. Organomet. Chem.* **2013**, *741–742*, 78-82
[127] G. Bartoli, G. Bencivenni, R. Dal Pozzo, *Synthesis*, **2014**, *48*, 979-1029
[128] B. Castano, S. Guidone, E. Gallo, F. Ragaini, N. Casati, P. Macchi, M. Sisti, A. Caselli, *Dalton Trans.* **2013**, *42*, 2451-2462



Scheme 2.22 – Catalysis of cyclopropanation reaction

We studied the effect of the different ligands in these conditions and we reported the results in **table 2.1** and **2.2**. The yields were determined by GC, using 2,4-dinitrotoluene as internal standard and were then confirmed by ^{1}H-NMR quantitative analysis of the reaction mixture. The cyclopropanes were always obtained in good to excellent yields, in selected cases after column chromatography, and fumarate and maleate were the only noticed byproducts.

It is important to underline that the naphthyl moiety, although confers a better stability to the complexes, does not alter the reaction outgoing, so that the results obtained with these compounds are comparable to those obtained with benzyl-containing ligands. Furthermore, the presence of the naphthyl moiety seemed to be positive for the enantioselectivity, since, for example, results obtained with ligand **6f** are slightly better than those obtained with ligand **6c** (**table 2.1**, entries 6-7 versus 3-4). In order to maximize the enantioselectivity, we lowered the temperature to -20°C, but we did not observe any significant improvement.

Finally, the best results in terms of enantioselectivity were obtained with ligand **6h**, that is the more sterically hindered (**table 2.1**, entry 9); ligands with the same structure, but different chirality have mismatching effects on the enantioselectivity of the reaction (**table 2.1**, **6f** entry 6 and **6g** entry 8).

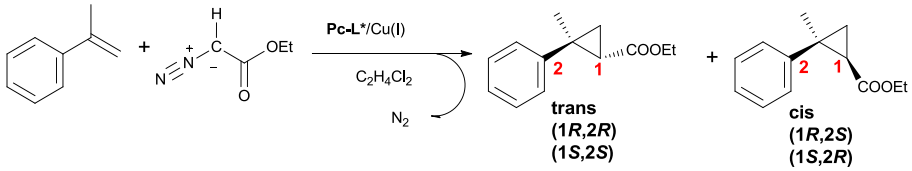
On the other hand, we observed a mismatching diasteroselection: ligand **6d** gave preferentially the *cis* isomer, on the contrary ligand **6g** the *trans.* Ligand **6h** did not lead to any preferential isomer, as well as its diastereoisomer **6i** but their effect on enantioselectivity are opposite, as it was logical to suppose (**table 2.1**, entries 9-10). Another key factor to increase the enantioselectivity is the presence of a stereocenter in position 13 (**figure 2.1**), as well as the presence of bulky substituents on the backbone (as told before). Anyway, these substituents reduce the amount of *cis* isomer as it is possible to see by the comparison of the results in diastereoselectivity among ligand **6f, 6m** and **6h** (with zero, one and two i-Pr moieties each) (**table 2.1,** entries 6, 15 and 9).

Results with ligands **6n, 6o** and **6p** showed that the triflyl moiety has an effect very hard to rationalize. Ligand **6n**, having no stereocenter in position 13, brought to a lower and opposite enantioselectivity with respect to the analogous tosyl-protected **6g.** Anyway, ligands **6o** and **6p** – that have a methyl substituent in 13, with different chirality – induced an effect, even if really

lower, in the same direction as they tosyl-protected analogous**.** We supposed that both the triflyl moiety and the substituent in 13 affects the possible conformation of the ligand, generating different conformers and thus different transition states during the catalysis. It would be not possible, then, to talk precisely about match or mismatch effect, because the role of the single moiety is depending also on either the presence or the absence of the other. For what concern the diastereoselectivity we observed that, in opposition to what we noticed from tosyl-ligands, the substituent on the backbone enhanced the *cis* product, while the methyl in 13 (specially in R-conformation) promote the formation of the *trans* isomer. Anyway, the results obtained with the triflyl-protected ligands were definitely worse than those obtained with the corresponding tosyl-protected macrocycles and we decided to focus on this second class of compounds.

The results obtained with the monosubstituted ligands **6k, 6l** and **6m** (**table 2.1**, entries 16, 17 and 15) are quite interesting: we confirmed that even just one substituent on the backbone (and so a cheaper ligand) is enough to obtain very good results in terms of enantioselectivity and we were prompted to find (in vain for now) a way to synthesize the disubstituted analogues. Complex **6l**/$[Cu(OTf)]_2 \cdot C_6H_6$ was then applied to other substrates (see, next, **table 2.3**) and demonstrated to be a versatile catalyst for different types of olefins.

Table 2.1 Cu(I)/**6** complexes for asymmetric cyclopropanation of α-methylstyrene [a]



Entry	**Pc-L*** / Cu	T	Yield (%)[b]	*cis* : *trans*[c]	ee (%)[d]	
					cis	*trans*
1	**6d** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	86	43 : 57	-	-
2[e]	**6b** / $[Cu(OTf)]_2 \cdot C_6H_6$	r.t.	75(53)	55 : 45	-44	-35
3[e]	**6b** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	90(70)	65 : 35	-50	-38
4	**6c** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	91(72)	65 : 35	50	38
5	**6c** / $[Cu(OTf)]_2 \cdot C_6H_6$	-20 °C	80(59)	64 : 36	53	38
6	**6f** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(83)	60 : 40	53	65
7[e]	**6e** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(83)	60 : 40	-53	-65
8	**6g** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	99(88)	33 : 67	30	50
9	**6h** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	98(57)	50 : 50	88	99
10[e]	**6i** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	66	35 : 65	57	52
11[e]	**6n** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	91	52 : 48	-21	-16
12	**6o** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	95	42 : 58	25	33
13	**6p** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	85	49:51	4	5
14	**6j** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	85	50:50	71	94
15	**6m** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	48	60:40	74	79
16	**6k** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	77	44:56	65	81
17	**6l** / $[Cu(OTf)]_2 \cdot C_6H_6$	0 °C	83	47:53	74	90

[a] Reactions were performed with equimolar amounts of Cu(I) salt (3.0×10^{-2} mmol) in dichloroethane (5 mL). Cu/**4a**/EDA/α-methylstyrene 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*).

Identical results were obtained whether preformed **8f** or **6f**/$[Cu(OTf)]_2 \cdot C_6H_6$ were used (comparing **table 2.2**, 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 2.2**,

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 **8f** whilst [**8f**/CH_3CN][OTf], [**8f**/CH_3CN][PF_6] and [**8f**/CH_3CN][BF_4] are inactive. The inhibiting effect was observed also upon addition of external acetonitrile (**table 2.2**, entry 8).

Noticeably, the reaction with **6h**/$Cu(OTf)_2$ (**table 2.2**, entry 3) gave still very good yields with respect to **6h**/$[Cu(OTf)]_2 \cdot C_6H_6$ (**table 2.1**, entry 9), but a significant drop in the enantioselection. The activity is due to the well known reduction from Cu(II) to Cu(I) due the action of EDA.[129]

Table 2.2 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	**6c** / $[Cu(CH_3CN)_4] \cdot BF_4$	0 °C	78(65)	57 : 43	33	36
2	**6f** / $[Cu(CH_3CN)_4] \cdot BF_4$	0 °C	70(56)	55 : 45	45	44
3	**6h** / $Cu(OTf)_2$	0 °C	96	52 : 48	70	77
4	**8f**	0 °C	98(82)	57 : 43	55	66
5	[**8f**/CH_3CN][OTf]	0 °C	80(72)	58 : 42	49	63
6	[**8f**/CH_3CN][PF_6]	0 °C	75(65)	57 : 43	45	62
7	[**8f**/CH_3CN][BF_4]	0 °C	85(73)	55 : 45	54	62
8[e]	**6f** / $[Cu(OTf)]_2 \cdot C_6H_6$	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-methylstyrene 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, we used other alkenes to test the efficiency of our macrocyclic **Pc-Ls*** and $[Cu(OTf)]_2 \cdot C_6H_6$ system in dichloroethane (**table 2.3**).

The absence of α-substituents on the styrene affected the diastereoselectivity of the reaction (**table 2.3**, entries 1-10) yielding preferentially to the *trans* isomer (up to a 4 fold excess in the case of 4-Cl-styrene, entry 8). Steric hindrance at the α position does not prevent the reaction and good yields were generally obtained even with 1,1-diphenyl ethylene (**table 2.3**, entries 11-14). The catalytic

[129] R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.*, **1973**, *95*, 3300-3310

activity is not confined to styrenic double bonds. With 2,5-dimethyl-2,4-hexadiene, an important precursor to the chrysanthemic acid synthesis,[130] the catalytic reaction yielded the desired cyclopropanes (cyclopropanation of only one double bond was observed)[131] and with reasonable diastereoselectivities, if a large excess of the olefin is employed (**table 2.3**, entry 15). We obtained good yields (attack only at the non-substituted double bond) and excellent diastereoselectivities in favor of the *trans* isomer (> 99%) with 2-methylfuroate, (**table 2.3**, entries 16-19). From this precursor, some years ago Reiser reported a very elegant synthesis of roccellaric acid.[132]

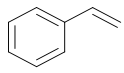
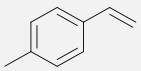
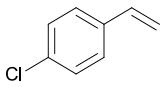
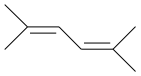
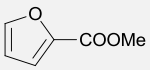
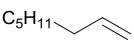
Non-activated aliphatic alkenes are known to be less reactive in comparison with aromatic or activated alkenes towards copper mediated cyclopropanations.[133] Anyway, when 1-octene was reacted with EDA in the presence of Cu(I)/**6h** or **6l** the corresponding cyclopropane derivative was obtained in 73% yield, extending the scope of **Pc-L*** copper(I) complexes to aliphatic double bonds (**table 2.3**, entry 20-21).

Worth to note is the fact that, among the various ligands, **6l** was found to give the highest enantiomeric excess for the trans isomer in selected case (entries 3, 6 and 10, **table 2.3**). As previously mentioned, ligand **6l** has only one substituent on the backbone, instead of two as **6f**, **g** and **h**. This pave the way to the employ of a new class of ligands that are easier to obtain since the pathway involves the use of a unprotected and more reactive aziridine and, since derive from half the amount of chiral aminoalcohol precursors, cheaper to synthesize.

On the other hand, if we discover how to synthesize a macrocycle bearing two hindering substituent as t-butyl for ligand **6l**, it is possible to suppose that we could obtain even better results.

[130] M. Itagaki, K. Suenobu, *Org. Process Res. Dev.* **2007**, *11*, 509-518.
[131] A. G. M. Barrett, D. C. Braddock, I. Lenoir, H. Tone, *J. Org. Chem.* **2001**, *66*, 8260-8263
[132] C. Bohm, O. Reiser, *Org. Lett.* **2001**, *3*, 1315-1318
[133] N. S. Youssef, A. M. A. El-Seidy, M. Schiavoni, B. Castano, F. Ragaini, E. Gallo, A. Caselli, *J. Organomet. Chem.* **2012**, *714*, 94-103.

Table 2.3 Asymmetric cyclopropanation of alkenes by Cu(I)/**Pc-L*** [a]

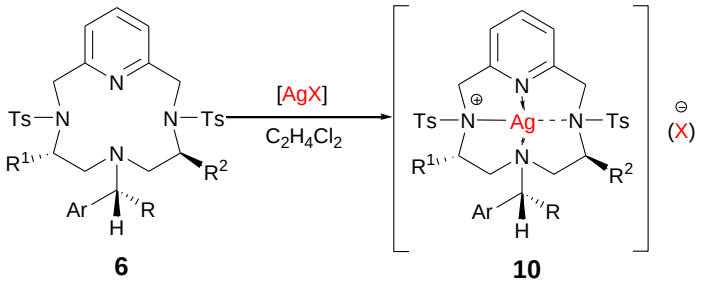
Entry	**Pc-L*** / Cu	T	Yield (%)[b]	*cis* : *trans*[c]	ee (%)[d]	
					cis	*trans*
1	**6f**		72(51)	50 : 50	33	50
2	**6h**		97	38 : 62	99	87
3	**6l**		86	44 : 56	53	91
4	**6f**		66(45)	53 : 47	34	45
5	**6g**		79	25 : 75	33	40
6	**6l**		61	36 : 64	57	80
7	**6f**		88(68)	47 : 53	36	50
8	**6g**		88	19 :81	42	53
9	**6h**		86	42 : 58	66	78
10	**6l**		76	40 : 60	57	87
11	**6f**		64(56)	-	50	
12	**6g**		85	-	62	
13	**6h**		45	-	88	
14	**6l**		15	-	82	
15[e]	**6f**		81(54)	67 : 33	30	15
16	**6f**		54(45)	> 1 : 99	n.d.	57
17	**6g**		55	> 1 : 99	n.d.	28
18	**6h**		74	> 1 : 99	n.d	76
19	**6l**		82	> 1 : 99	n.d	94
20[f]	**6h**		73	38 : 62	75	55
21	**6l**		83	45 : 55	69	46

[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)/**6f**/EDA/olefin = 1:1:35:1750. [f] Cu(I)/**6h**/EDA/olefin = 1:1:35:330.

2.3 - Silver

2.3.1 - Synthesis

As just reported, our ligands are particularly able to complex and stabilize copper (I) salts; for this reason we decided to extend our research on the complexation of another metal of the group: silver. We have prepared silver(I) complexes **10** of our macrocycle from different sources, respectively silver tetrafluoroborate ([1]), silver triflate ([2]) and silver *bis*-triflimidate ([3]) (**scheme 2.23**).



6 **10**

6a, 10a: R=H, Ar=Ph, R^1=R^2= H
6b, 10b: R=CH_3, Ar=Ph, R^1=R^2= H
6d, 10d: R = R^1=R^2= H, Ar = Naphthyl
6h, 10h: R=CH_3, Ar=Naphthyl, R^1=R^2=^{i}Pr
6l, 10l: R=CH_3, Ar=Naphthyl, R^1= H, R^2=*cy-Hex*
6l, 10l: R=CH_3, Ar=Naphthyl, R^1= H, R^2=^{t}Bu
6m, 10m: R=CH_3, Ar=Naphthyl, R^1= H, R^2=^{i}Pr

X^1 = BF_4, **10a^1**
X^2 = OTf, **10a^2**
X^3 = $N(Tf)_2$ **10a^3**

Scheme 2.23 Synthesis of silver(I) complexes **10** with different anions

We added the silver salt to the solution of the ligand **6** in DCE and we stirred the solution for one hour, keeping the mixture in the dark until we isolated the final product. Silver complexes **10** are easily obtained by precipitation, concentrating the solvent and adding *n*-hexane. We filtered and collected the white precipitated in yields up to 91%.

When we tried to synthesize a complex with a chloride as counter-ion we did not obtained the desired product. We conducted the direct reaction between ligand **6a** and silver chloride with no results, as well as an anion-exchange between complex **10a^1** and tetrabutylammonium chloride, leading to the immediate formation of silver chloride precipitated. This fact showed us that our silver complexes **10** could be sensitive to any halogenide source present in the environment, so to the chlorinated solvents if not carefully passed over basic alumina and distilled. All the obtained silver complexes **10** have been fully characterized by ^{1}H and ^{13}C-NMR, ESI-MS, IR and UV-Vis spectroscopy.

As the Cu(I) complexes **8**, Ag(I) complexes **10** are stable to air oxidation and can be used under

open-air atmosphere without any problem. Anyway, they are more sensitive to the atmospheric moisture and tend to form monoaquo species, as confirmed by X-ray determination of single crystals obtained from complex **10a**[1] (**figure 2.13**).

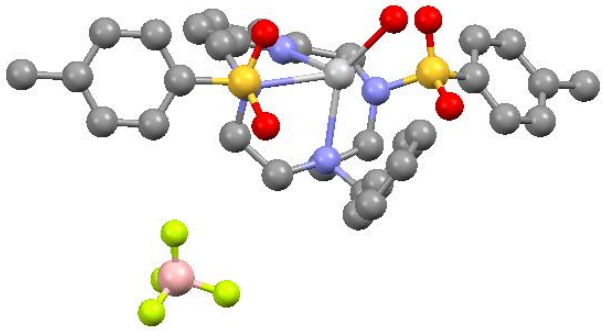


Figure 2.13 Structure of **10a**[1] with a molecule of water coordinated to the metal centre (hydrogen atoms omitted)

As previously reported for copper(I) complexes, the effect of the metal complexation to the ligand was revealed also by the ^{1}H and ^{13}C NMR. The ^{1}H-NMR spectrum of complex **10h**[1], for example, in $CDCl_3$ has a very low symmetry: the proton directly bound to carbon **a** (**figure 2.14**) shifts to higher frequencies 8.69 ppm compared to 8.58 ppm for the free ligand **6h**.

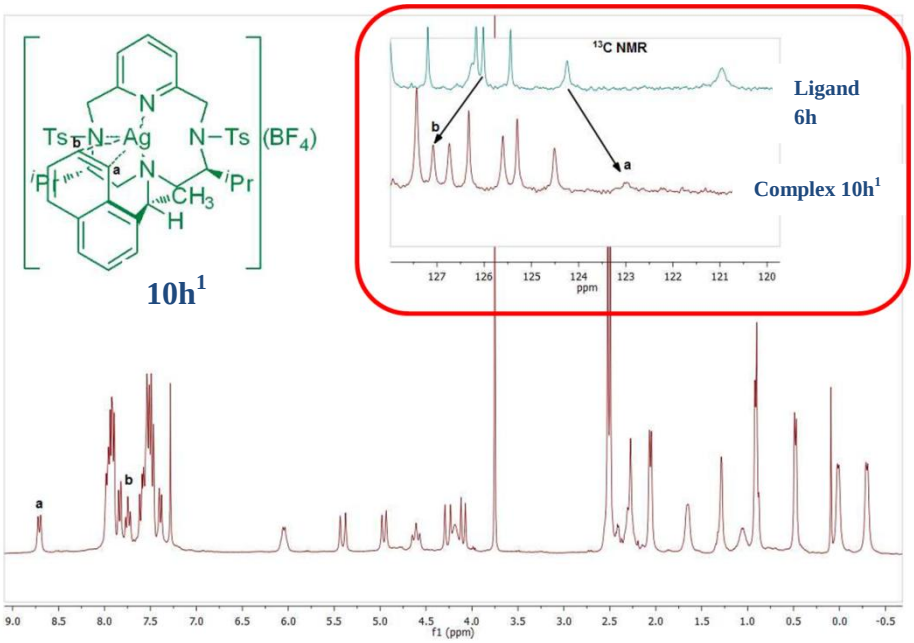


Figure 2.14 ^{1}H-NMR of complex **10h**[1] with carbons **a** and **b** involved in η^2 coordination of the naphthyl on silver(I). In the red box ^{13}C-NMR spectra of ligand **6h** and complex **10h**[1], respectively, are reported

Also in this case the η^2 coordination of the naphthyl on silver(I) in solution has been proposed from ^{13}C-NMR studies in $CDCl_3$. We observed a shift to low frequencies of the naphthyl 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 **6h** to 127.1 ppm in complex **10h**[1]. Unsymmetrical shift of the η^2-carbon bond atoms is common for strongly distorted double bonds coordinated to a metal atom.[134] Carbon **a** is held in close proximity to the silver atom by steric requirements and as a result carbon **b** is less strongly coordinated. In the absence of a crystal X-ray structure determination, we can not rule out the presence of a weak η^1-binding mode.[135] In any case, the presence of an agostic interaction is excluded by the proton shift (a shift to lower frequencies would be expected), the J, which remained almost unchanged, and the absence of any interaction between proton and silver in both ^{1}H and ^{109}Ag spectra. Furthermore, no typical agostic interaction band in the region 2700-2300 cm^{-1} in the IR spectra was observed.

For complexes **10a**[1-3] we observed the same signals in the ^{1}H-NMR, ^{13}C-NMR and ^{15}N-NMR spectra, without dependence from the counter ion. These complexes 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 **10a**[1] has proximity interactions mainly with the pyridine ring of the ligand (**figure 2.15**).

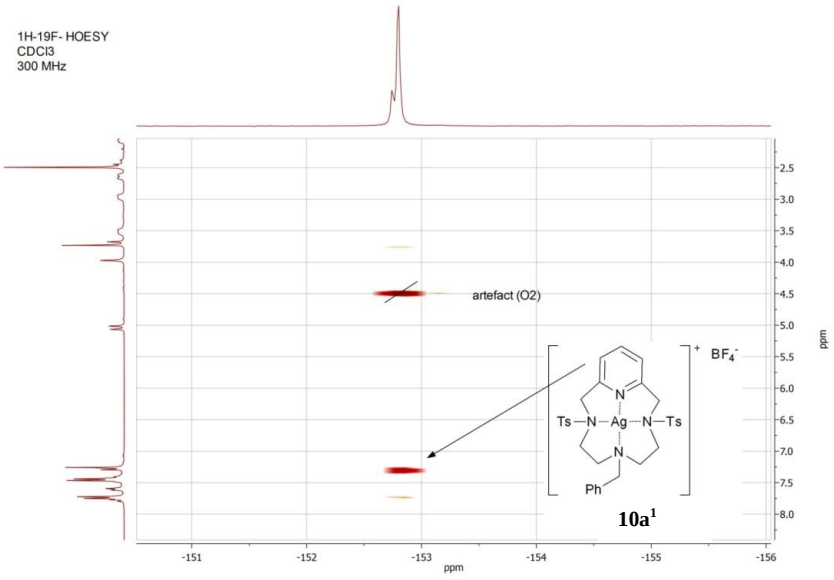


Figure 2.15 – ^{1}H-^{19}F HOESY experiment in $CDCl_3$ for complex **10a**[1]

[134] C. Martin, J. M. Munoz-Molina, A. Locati, E. Alvarez, F. Maseras, T. R. Belderrain, P. J. Perez, *Organometallics*, **2010**, *29*, 3481-3489
[135] P. G. A. Kumar, P. Dotta, R. Hermtschweiler, P. S. Pregosin, *Organometallics*, **2005**, *24*, 1306-1314

Unfortunately, no crystal without additional ligands was obtained to confirm our thesis.

The UV-vis spectra of complex **10a**^{1} and **10a**^{2} in chloroform showed the absence of absorption bands at wavelength higher than 290 nm, which is consistent with the observed absence of color and the d^{10} electronic configuration for the metal - no *d-d* transitions allowed (**figure 2.15**). The shape of the UV-vis spectra of ligand **6a** does not vary due to complexation, while the intensities of the absorptions are slightly different; for this reason, the bands recorded in the near UV region can be related to ligand-centered transition (**figure 2.16**).

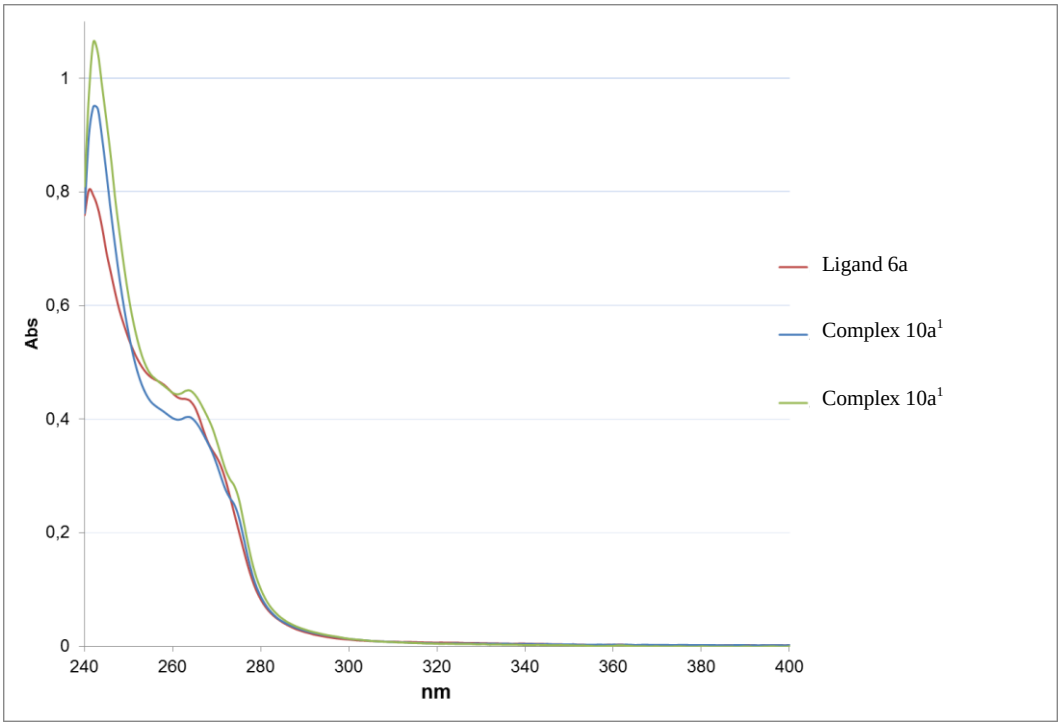


Figure 2.16 – UV spectra of ligand **6a** and Ag(I) complexes **10a** with different anions (10^{-5} M in $CHCl_3$)

2.3.2 - Reactivity

By exposing a dichloroethane/hexane solution of complex **10d** to CH_3CN vapour, we obtained and crystallized the [(**10d**)(CH_3CN)]BF_4 complex. The X-Ray structure of this complex, confirmed the tendency of these species to bind an additional ligand and showed that the metal is located in a very low symmetry site; it is pentacoordinated in a highly distorted trigonal bipiramid geometry, with the two non-equivalent sulfonamidic nitrogens as the apices. Anyway, the N-Ag-N angle is 124°, quite smaller than a plane angle **(figure 2.17).**

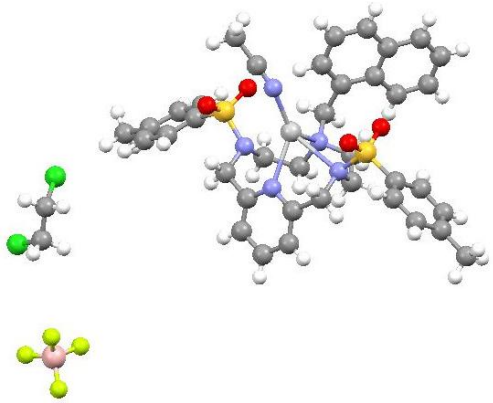


Figure 2.17 – Crystal structure of [(**10d**)(CH_3CN)]BF_4

Besides resolving the crystal structure of the complex [(**10d**)(CH3CN)]BF_4 (**figure 2.17**), we also studied the coordination of acetonitrile in solution via IR spectroscopy. After the addition of two equivalents of CH_3CN to a DCE solution of [(**10d**)(CH3CN)]BF_4, four absorption bands were observed in the 2400 to 2200 cm^{-1} region of the spectrum (**figure 2.19**). Those at 2256 and 2294 cm^{-1}, correspond to the vibration modes of free acetonitrile (**figure 2.18**), specifically C≡N triple bond stretching for the former and a combination of C-H bending and C-C stretching for the latter. The two new bands at 2279 and 2308 cm^{-1} are due to the coordinated nitrile, and their shift at higher energies is a common occurrence in metal-acetonitrile complexes. It has been explained by noting that the nitrogen atom's lone pair resides in an orbital with partial antibonding character, so that following donation to the metal the C≡N bond is strengthened and with it the force constant of the vibrational mode increases.[136]

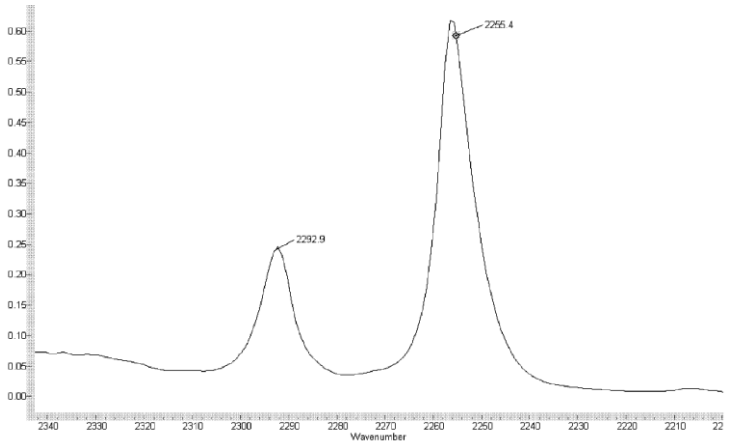


Figure 2.18 – IR spectrum of acetonitrile

[136] D. Jamroz, M. Wojcik, J. Lindgren *Spectrochim. Acta Mol. Biomol. Spectros.* **2000**, *56*, 1939–1948.

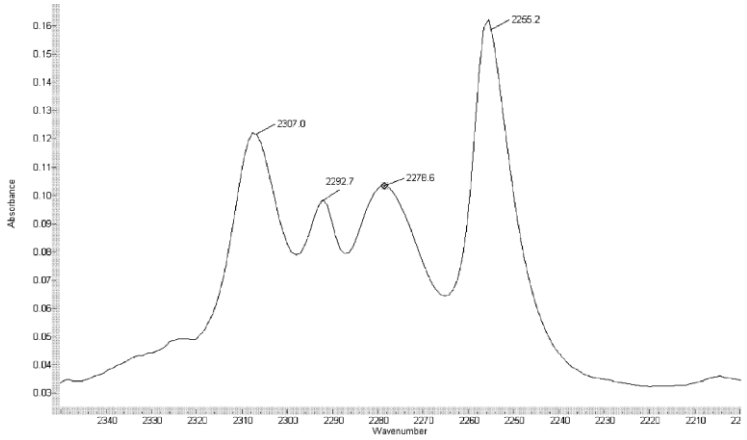


Figure 2.19 – IR spectrum of [(**10d**)(CH_3CN)]BF_4

The complex [(**10d**)(CH_3CN)]BF_4, which partially precipitated from solution, was recovered by filtration and characterized by NMR spectroscopy. The ^1H spectrum shows the presence of exatctly one equivalent of CH_3CN, with a CH_3 signal at 2.08 ppm, shifted only of a small amount from its position for the uncoordinated molecule (2.10 ppm).

The complexes are also capable of coordinating carbon monoxide, albeit in a weak manner. When we exposed a solution of [(**10d**)]BF_4 to a 1 bar CO atmosphere and recorded its IR spectrum, an absorption band at 2156 cm^{-1} was observed (**figure 2.20**). This is at higher energies than free CO's band at 2143 cm^{-1}, making the adduct a non-classical metal carbonyl,[137] meaning that back-donation from the metal to the antibonding CO orbital is scarce or null. This is not unexpected for a d^{10} closed-shell ion. A brief exposure to vacuum and flushing with nitrogen caused the CO band to disappear.

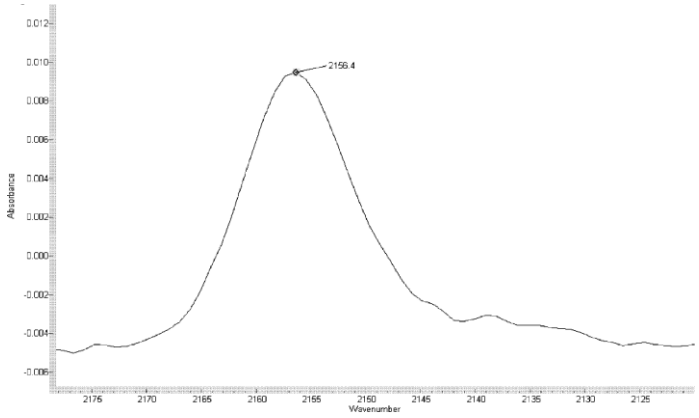


Figure 2.20 – IR spectrum of [(**10d**)(CO)]BF_4

[137] McIntosh, D. F.; Ozin, G. A.; Messmer, R. P. *Inorg. Chem.* **1981**, *20*, 3640–3650

We prepared the analogous complex using isotopically enriched carbon monoxide and [(**10d**)]OTf in deuterated chloroform solution, in order to easily detect the signal of the species [(**10d**)(^{13}CO)]OTf. The CO resonance is found at 177.3 ppm (**figure 2.21**), shifted at lower frequencies when compared to non-coordinated CO (181.3 ppm). The latter, though, was not detected, despite the presence of a ^{13}CO atmosphere in the sample tube and, consequently, of dissolved carbon monoxide. This can be justified by the existence of a fast equilibrium on the NMR timescale, between solution CO and metal-coordinated CO, so that the observed signal is due to CO experiencing an averaged environment. This is in contrast with the analogous copper complexes, which instead exhibit two different signals for CO, suggesting a stronger coordination (section 2.2.2).

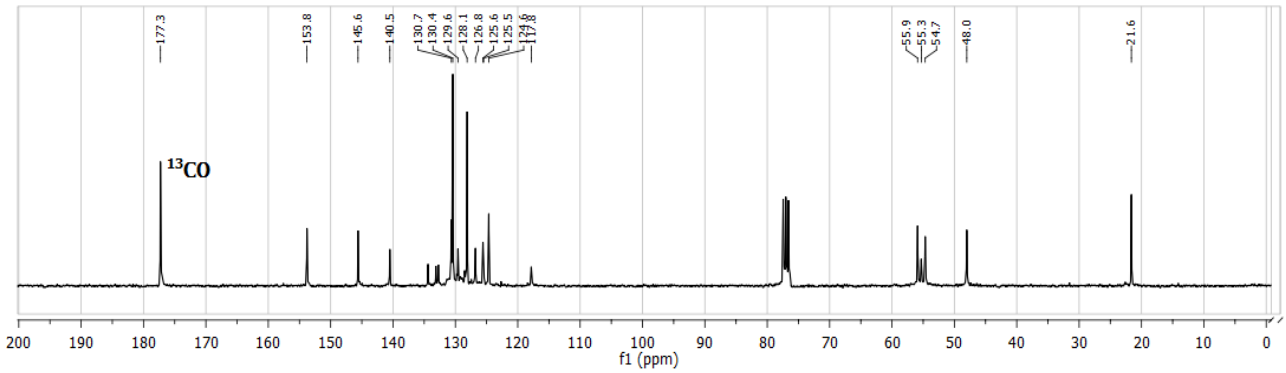
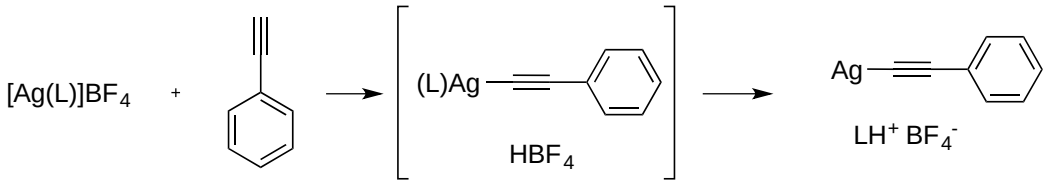


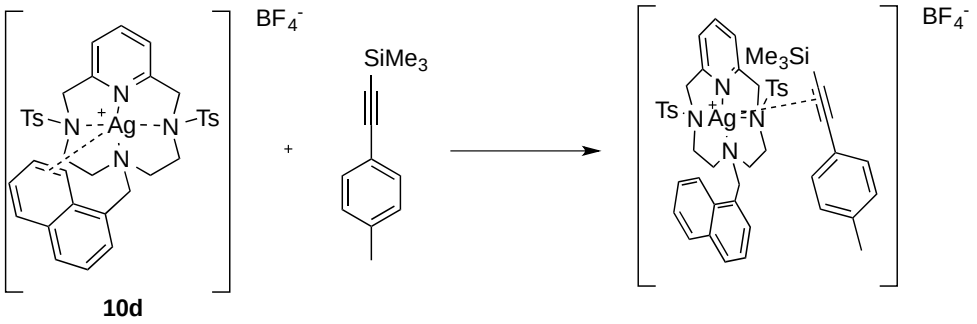
Figure 2.21 – ^{13}C-NMR spectrum of [(**10d**)(CO)]BF_4 in $CDCl_3$

Concerning the catalytic applications envisaged for these compounds, the interactions with alkynes are those of greatest interest. Unfortunately we found out that **10d**[1] reacts very easily with a terminal alkyne such as phenylacetylene, to give the silver acetylide. This liberates acid, which protonates the ligand causing the decomplexation and partial precipitation of the salt (**scheme 2.24**).



Scheme 2.24 – Reaction of silver complexes with terminal alkynes

If, on the other hand, an internal alkyne is used, η^2 coordination occurs without unwanted decompostion reactions. We characterized via NMR spectroscopy the coordination of ((4-methylphenyl)ethynyl)trimethylsilane (**scheme 2.25**).



Scheme 2.25 – Coordination of an internal alkyne

Evidence of the complexation, on adding 3 equivalents of alkyne to [(**10d**)]BF_4, was gathered from the ^{1}H, ^{13}C and ^{29}Si spectra. The shifts for the alkyne are fairly small: -17.08 vs -17.29 ppm for the ^{29}Si signal (detected via HMBC experiment, **figure 2.22**), 2.36 vs 2.33 ppm for the tolyl group CH_3 (figure 24), 91.3 vs 93.2 ppm and 105.5 vs 105.4 ppm for the two quaternary alkyne carbons (also detected only via HMBC). This is likely due to the presence of an excess of uncoordinated alkyne in equilibrium with the complex, and the remoteness of the methyl groups from the coordinating moiety. The effects on the ligand are instead quite dramatic, with the H^h signal shifted at 7.93 ppm, more than observed in any other species, and H^7 and $H^{7'}$ at 3.09/1.91 ppm from 2.85/2.25 ppm.

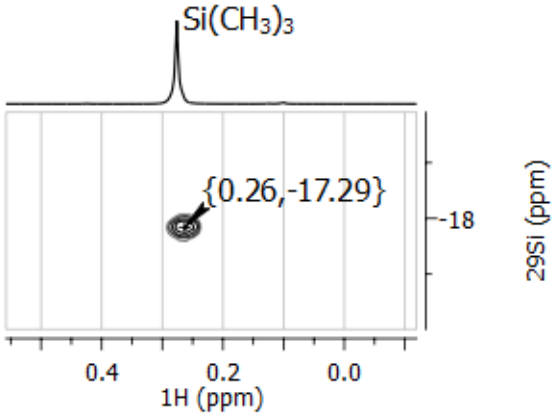
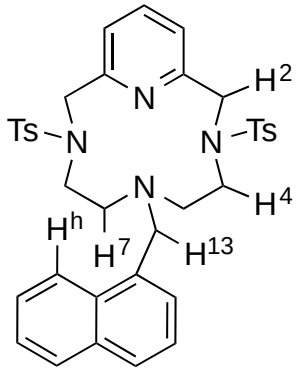


Figure 2.22 – ^{1}H-^{29}Si HMBC spectrum of [(**10d**)]BF_4 + 4-(methylphenyl)ethynyl)trimethylsilane

The shift of H^h signal to lower frequencies, towards the position observed in the free ligand, is a common feature of all the species with an additional ligand besides the macrocycle. The displacement of the η^2-coordinated naphthyl group from the metal is the likely cause of this feature. Smaller shifts are observed for the corresponding ^{13}C signal, as well as for other protons (**table 2.4**).

Table 2.4 – Chemical shift of the signals in ligand **10d** and its complexes



Ligand	H^h	C^h	H^2	H^4	H^7	H^{13}
6d	8.13	125.1	4.30	3.07	2.34	3.92
7d	8.13	*a*	5.38	*b*	*b*	*b*
Complex in presence of						
- (**10d**)	9.16	111.8	4.87/3.59	3.54/2.73	2.85/2.25	4.36
CO	8.94	114.4	4.93/3.59	3.49/2.63	2.88/2.17	4.36
CH_3CN	8.79	117.0	4.99/3.59	3.49/2.63	2.90/2.21	4.39
CH_3COCH_3	8.73	117.3	4.97/3.55	3.48/2.62	2.87/2.21	4.37
TolC≡CTMS	7.93	124.9	4.93/3.59	3.45/2.59	3.09/1.91	4.31

a = spectrum not recorded, *b* = signals could be not assigned

The entity of these shifts varies with the added external ligand, and could in principle be taken as a measure of the strength of coordination of weak ligands which are in equilibrium with the solution. The larger is the fraction of complex that is bound to an auxiliary ligand, the larger is this shift. The η^2 alkyne coordinated complex shows the biggest effects, with H^h at 7.93 ppm that is even lower than that of the free ligand; this probably depends on the different conformations that are accessible to the naphthyl moiety in the free ligand to relieve steric crowding.

We also prepared an alcohol-coordinated complex of a different, chiral ligand, **6b**, which does not possess a naphthyl group, by suspending [Ag(**6b)**)]BF_4 in refluxing 2-propanol. We used an alcoholic solvent in order to protect the complex from absorbing atmospheric water: because alcohols are reagents in the catalytic synthesis of isochromenes, we supposed that the iPrOH complex could be an intermediate of the reaction and, hence, have no deactivating effect if applied to the system, in contrast to H_2O complexes. Its structure was determined from a crystal obtained from a 2-propanol/hexane solution (**figure 2.23**). The structure shows a strongly distorted trigonal bipyramidal conformation, where the axial ligands are the tosyl protected nitrogens.

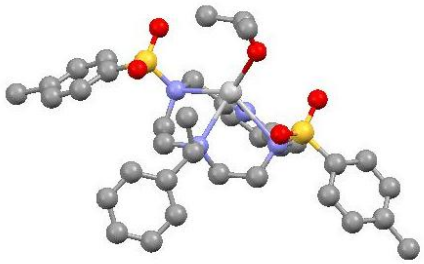


Figure 2.23 – Crystal structure of [Ag(**6b**)(2-PrOH)]BF_4

2.3.3 - Catalysis

2.3.3.1 - Domino

Silver complexes **10a**[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.[138]

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[139] 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.[140] Moreover, the structure of isochromane is the skeleton of a diterpene from *Antarctic sponge Dendrilla Membranosa* called membranolide B[141] (**figure 2.24**). All these compounds are characterized by a cyclic-acetal framework, due to the presence of a methoxy group on C1.

[138] M. Dell'Acqua, B. Castano, C. Cecchini, T. Pedrazzini, V. Pirovano, E. Rossi, A. Caselli, G.Abbiati *J. Org.Chem.* **2014**, *79*, 3494-3505
[139] G. Attardo, W. Wang, T. Breining, T. Li, Y. St-Denis, J.-L. Kraus, Int. Patent WO 9 512 588, **1995**
[140] W.Wang, T. Li, R. Milbum, J. Yates, E. Hinnant, M. J. Luzzio, S. A. Noble, G. Attardo, *Bioorg. Med. Chem. Lett.* **1998**, 8, 1579-1584
[141] S. Ankisetty, C. D. Amsler, J. B. Clintock, B. J. Baker, *J. Nat. Prod.* **2004**, 67, 1172-1174

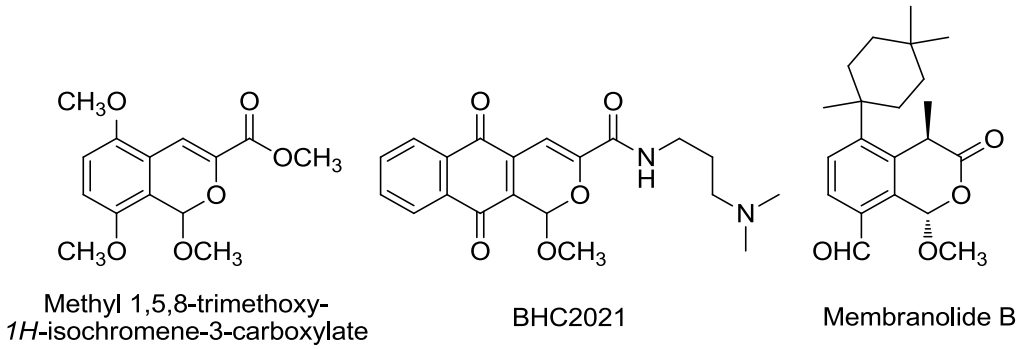
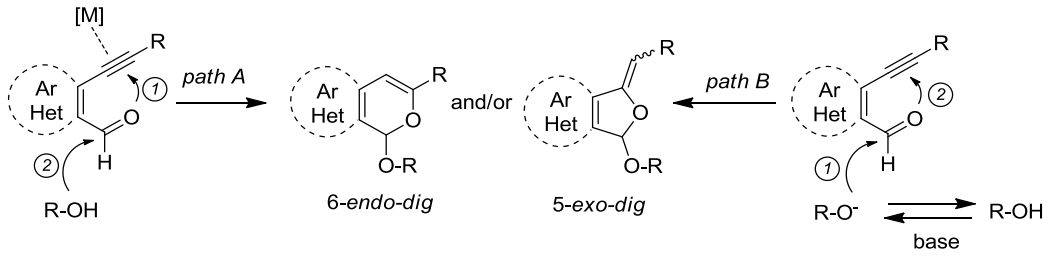


Figure 2.24 – Examples of 1-alkoxy-isochromene/ane-containing bioactive molecules.

An efficient method to build-up 4-unsubstituted-1-alkoxyisochromenes and related heteroaryl compounds (dihydropyranoquinolines among the other species) is the regioselective domino addition/cycloisomerization of a properly substituted 2-alkynyl(hetero)arylaldehyde with an alcohol.[142] These reactions are usually catalyzed 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* cyclization) in not always easy to rationalize[143] (**scheme 2.26**). In general the reaction promoted by bases lead preferentially to the 5-*exo-dig* cyclizations products (i.e., dihydroisobenzofurans, dihydrofuroquinolines or dihydrofuropyrimidines) via an addition/annulation sequence that probably involves the formation of a hemiacetal anion (**scheme 2.26**, path B).[144] Conversely, the metal catalyzed 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. Usually, 6-*endo-dig* cyclization 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 2.26**, path A).

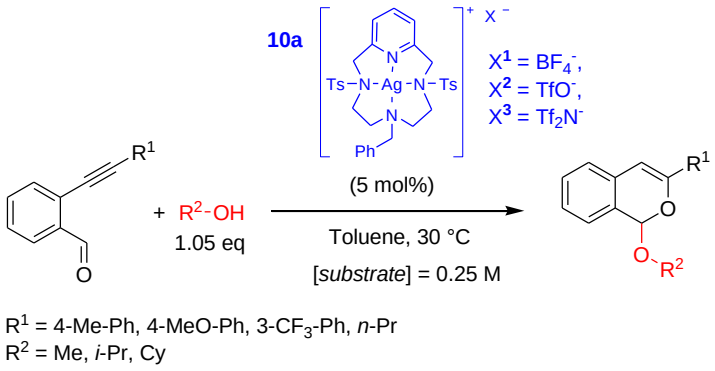
[142] General reviwes: (a) I. Nakamura, Y. Yamamoto, *Chem. Rev*. **2004**, 104, 2127-2198. (b) G. Zeni, ; R. C. Larock, *Chem. Rev*. **2004**, 104, 2285-2310. (c) F. Alonso, ; I. P. Beletskaya, ; M. Yus, *Chem. Rev*. **2004**, 104, 3079-3160.
[143] For a more extensive discussion see: M. Dell'Acqua, D. Facoetti, G. Abbiati, E. Rossi, *Synthesis* **2010**, 2367-2378 and references cited therein
[144] (a) T. Godet, J. Bosson, P. Belmont, *Synlett* **2005**, 2786-2790. (b) I. Cikotiene, M. Morkunas, D. Motiejaitis, A. Brukstus, *Synlett* **2008**, 1693-1967. (c)C. Kanazawa, A. Ito, M. Terada, *Synlett* **2009**, 638-642



Scheme 2.26 – 5-*exo-dig* vs 6-*endo-dig* cyclization mode of 2-alkynyl(hetero)arylaldehydes and alcohols.

Several metal ions, i.e., Pd(II),[145] Cu(I),[146] Ag(I),[147] Au(I)[148] and In(III)[149] salts, have been used as catalysts for the synthesis of isochromenes and analogues following this approach. An enantioselective version of this reaction, catalyzed by chiral gold acyclic diaminocarbene (ADC) complexes has been also recently reported.[150]

In 2010, Dr. Giorgio Abbiati and co-workers reported a regioselective synthesis of substituted 1-methoxy-3-methylen-1,3-dihydroisobenzofurans domino addition/cycloisomerization reaction of 2-alkynylbenzaldehydes and methanol enhanced by microwave in the presence of a suitable base.[145] The approach was also successfully transformed in an advantageous multicomponent process.[151] As prosecution of these studies, in collaboration with Dr. G. Abbiati of the Universtity of Milano we focused our attention to the selective synthesis of regioisomeric 1-alkoxyisochromenes starting from 2-alkynylbenzaldehydes **14 (scheme 2.27)**.



Scheme 2.27 – General synthesis for the isocromenes species promoted by silver(I) complexes **10a**[1-3].

[145] N. Asao, T. Nogami, K. Takahashi, Y. Yamamoto, *J. Am. Chem. Soc*. **2002**, 124, 764-765
[146] N. T. Patil, Y. Yamamoto, *J. Org. Chem*. **2004**, 69, 5139-5142
[147] (a) T. Godet, C. Vaxelaire, ; C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.* **2007**, 13, 5632-5641. (b) S. Rudys, I. Cikotiene, C.Rios-Luci, E. Perez-Roth, J. M. Padron, *Bioorg. Med. Chem. Lett*. **2010**, 20, 1504-1506. (c) I. Cikotiene, R. Buksnaitiene, S. Rudys, M. Morkunas, D. Motiejaitis, *Tetrahedron* **2010**, 66, 251–258.
[148] Enomoto, T.; Girard, A.-L.; Takemoto, Y.; Yasui, Y. *J. Org. Chem*. **2009**, 74, 9158-9164
[149] S. Obika, H. Kono, Y. Yasui, R. Yanada, Y. Takemoto, *J. Org. Chem*. **2007**, 72, 4462 – 4468
[150] S. Handa, L. M. Slaughter, *Angew. Chem. Int. Ed.* **2012**, 51, 2912–2915
[151] (a) M. Dell'Acqua, D. Facoetti, G. Abbiati, E. Rossi, *Tetrahedron* **2011**, 1552-1556; (b) Facoetti, D.; Abbiati, G.; Dell'Acqua, M.; Rossi, E. *Tetrahedron* **2011**, *67*, 6833–6837. (c) Dell'Acqua, M.; Facoetti, D.; A. Arcadi, G. Abbiati, E. Rossi, *Synlett*, **2010**, 2672–2676

We conducted the first studies using on 2-[(4-methoxyphenyl)ethynyl]benzaldehyde **11a** using methanol as reagent/solvent under non-optimized conditions (**table 2.5**, entry 1). With this test we revealed that the silver complex **10a[1]** (5 mol%) was able to promote the addition/cycloisomerization of **11a** with methanol yielding regioselectively the corresponding isochromene **12a** in very good yield (83%) in 5h. A small amount of the dimethyl acetal **18a** was the only by-product detected by ^{1}H-NMR of reaction crude, and accounted for the mass balance of the reaction (**table 2.5**, entry 1).

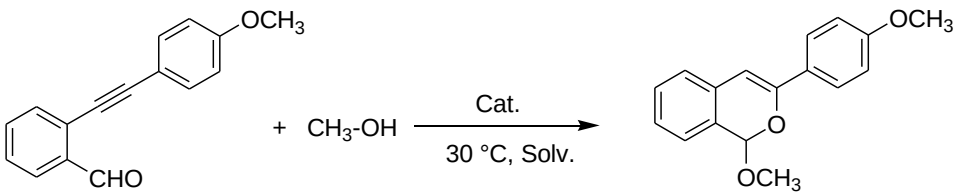
We performed a series of new experiments, to improve the reaction conditions. In order to find a proper medium to be used with alcohols different from methanol and in order to suppress the formation of the acetal **18a**, we used different solvents with decreasing relative polarity (**table 2.5**, entries 2-4), in the presence of 3 equivalents of methanol. All the solvents tested gave excellent results and the formation of dimethyl acetal **18a** was strongly reduced (**table 2.5**, entry 3) or completely avoided (**table 2.5**, entries 2 and 4). Even though the reaction in DCE seems to be a little faster (**table 2.5**, entry 3), the best yield and chemoselectivity of the reaction were obtained in toluene (**table 2.5**, entry 4).

The effect of the substrate's concentration on the reaction seems to be little (**table 2.5**, entries 5 and 6), whereas the yield of the reaction is lowered by Ag(I) complexes **10a[2]** and **10a[3]**, characterized respectively by the presence of a slightly more coordinating counter ion such as triflate[152] or a more bulky and charge delocalized anion as triflimidate,[153] (**table 2.5**, entries 7, 8). Methanol has an inhibiting effect to the reaction, as quantitative yields are obtained in 2 and 2.5 hours when 1.05 and 1.5 equivalents of MeOH respectively are used in toluene, while only 83% of yield in 5 hours is achieved when the reaction is performed in neat (**table 2.5**, entries 1, 9-10). At the same time, the catalyst loading is a critical factor and amounts of catalysts lower than 5 mol% results in extended reaction times and lower reaction yields (**table 2.5**, entries 11, 12).

Finally, we conducted two control experiments in the presence of simple silver salts such as AgOTf (5 mol%) and $AgBF_4$ (5 mol%) as catalysts. These tests demonstrated the superiority of our Ag complexes (**table 2.5**, entries 13 and 14) in increasing the yield and in reducing the amount of byproducts.

[152] R. Díaz-Torres, S. Alvarez, *Dalton Trans*. **2011**, 40, 10742-10750
[153] S. Antoniotti, V. Dalla, E. Duñach, *Angew. Chem. Int. Ed.* **2010**, 49, 7860-7888

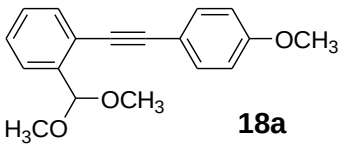
Table 2.5 – Optimization of the reaction conditions



11a **12a**

Entry	Solv.	equiv. MeOH	[**11a**] M	t (h)	Cat.	Cat. loading (mol%)	**12a** (Yield %)
1	MeOH	-	0.25	5	**10a**[1]	5	83[a]
2	Dioxane	3	0.25	5	**10a**[1]	5	88
3	DCE	3	0.25	1	**10a**[1]	5	94[b]
4	**Toluene**	3	**0.25**	2.5	**10a**[1]	5	99
5	Toluene	3	0.125	4	**10a**[1]	5	98
6	Toluene	3	0.50	2.5	**10a**[1]	5	98
7	Toluene	3	0.25	22	**10a**[2]	5	92
8	Toluene	3	0.25	24	**10a**[3]	5	93
9	Toluene	1.5	0.25	2.5	**10a**[1]	5	99
10	Toluene	**1.05**	0.25	2	**10a**[1]	5	99
11	Toluene	1.05	0.25	8	**10a**[1]	2.5	82
12	Toluene	1.05	0.25	36	**10a**[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 **18a** in 15% yield. [b] Beside traces of acetal **18a.**[c] Yields calculated via ^{1}H-NMR using dimethyl terephthalate (DMT) as internal standard.



18a

It is important to underline that the absence of byproducts allows, in many cases, the isolation of the pure product through a simple work-up, i.e., washing of the crude with $NaHCO_3$ saturated solution followed by an extraction with dichloromethane. The ease of the purification step represents an

outstanding peculiarity of our approach: it is well known that the purification of 1-alkoxyisochromenes and related compounds could be quite troublesome.

Furthermore, we tested scope and limitation of the approach, employing the optimized reaction conditions. 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 **11a-d** were synthesized in good to excellent yields starting from commercially available 2-bromobenzaldheyde and a selection of terminal acetylenes through a typical Sonogashira coupling,[154] and their reactivity was tested with four alcohols with increasing steric hindrance. The results are reported in Table **2.6**.

All alkynylbenzaldehydes bearing aryl or alkyl substituent on alkynyl moiety (**11a-d**) reacted with methanol to give the corresponding isochromenes **12a-d** in excellent yields, and the presence of groups on the phenyl substituent was well tolerated (**table 2.6**, entries 1-6). Surprisingly in the presence of the trimethylsilyl group on alkynyl moiety no reaction occurred and the starting material **11e** was recovered unreacted also after prolonged reaction time (**table 2.6**, entry 7) or under higher temperatures (**table 2.6**, entries 8-9).

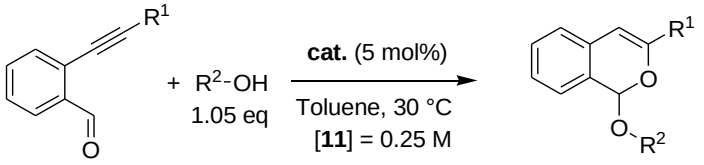
The reaction worked well also with more hindered secondary alcohols, i.e., isopropanol and cyclohexanol, that smoothly reacted with alkynylbenzaldehydes **11a-d,** to give the desired isochromenes **12e-l** in very high yields (**table 2.6**, entries 10-20). Anyway, all the attempts to react **11a** with highly sterically demanding tertiary alcohol such as *tert*-butanol failed, giving rise to a unidentified breakdown products (**table 2.6**, entries 21-22). Finally, catalysts **10a**^{2}and **10a**^{3} gave results comparable to **10a**^{1} (**table 2.6**, entries 3, 6, 12, 15 and 20).

In some cases the products obtained after the standard work-up were not sufficiently pure and needed purification by flash column chromatography (**table 2.6**, entries 5, 14 and 16). In these cases the resulted yields are lowered because of the low stability of 1-alkoxyisochromenes, that underwent to partial decomposition during the purification. We supposed that the acidic character of silica was the main responsible of this degradation due to the acetal nature of the products. We made two experiments to test the stability of 1-alkoxyisochromenes, treating a 0.25 M solution of **12a** in ethyl acetate under alkaline and acidic conditions. We observed that in the presence of a base (TEA, 0.2 equiv) the product remains unmodified even after 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

[154] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett*. **1975**, 50, 4467-4469. For a recent review see: R. Chinchilla, C. Nájera, *Chem. Rev*. **2007**, 107, 874-922.

unidentified byproducts. 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[155] (maybe in equilibrium with its *cis/trans* enol forms) resulting from hydrolysis of **12a**. Nevertheless, even performing the chromatographic purification of new synthetized isochromenes **12** with a basified eluent mixture a slight reduction of yields due to partial decomposition of product was observed.

Table 2.6 – Scope and limitation of the approach.



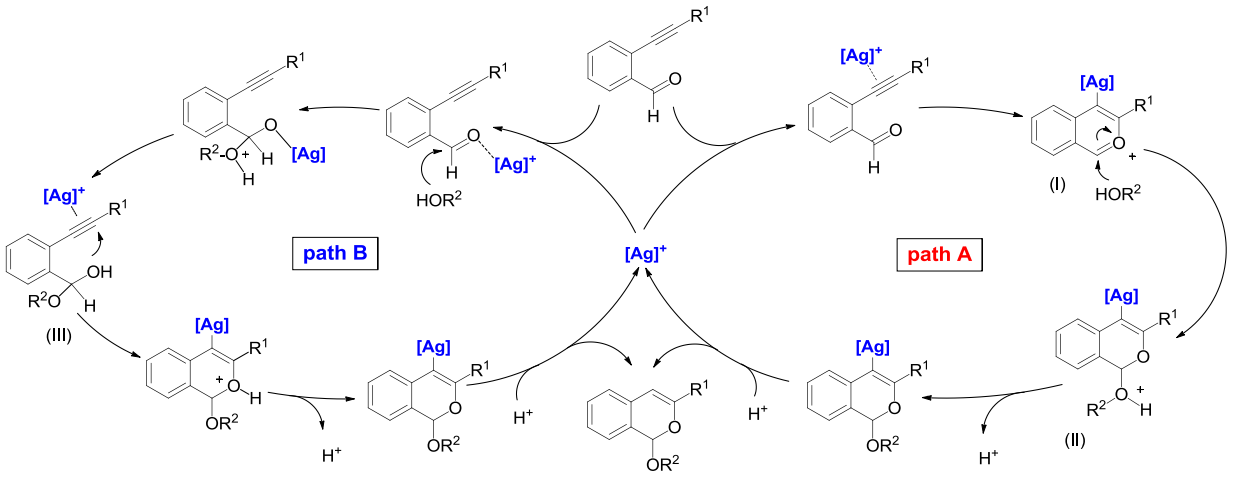
11 a-e **12 a-l**

Entry	sub.	cat.	R^1	R^2	t (h)	Product	yield[a] (%)
1	**11a**	**10a^1**	*p*-MeO-Ph-	Me	2	**12a**	99
2	**11b**	**10a^1**	*p*-Me-Ph-	Me	22	**12b**	97
3	**11b**	**10a^3**	*p*-Me-Ph-	Me	24	**12b**	94
4	**11c**	**10a^1**	*m*-F-Ph-	Me	24	**12c**	98
5	**11d**	**10a^1**	CH_3-CH_2-CH_2-	Me	2	**12d**	96 (76)[b]
6	**11d**	**10a^2**	CH_3-CH_2-CH_2-	Me	2	**12d**	95
7	**11e**	**10a^1**	$(CH_3)_3$Si-	Me	24	**12e**	-
8	**11e**	**10a^1**	$(CH_3)_3$Si-	Me	4[d]	**12e**	-
9	**11e**	**10a^1**	$(CH_3)_3$Si-	Me	18[c]	**12e**	-
10	**11a**	**10a^1**	*p*-MeO-Ph-	*i*-Pr	6	**12f**	99
11	**11b**	**10a^1**	*p*-Me-Ph-	*i*-Pr	26	**12g**	97
12	**11b**	**10a^3**	*p*-Me-Ph-	*i*-Pr	22	**12g**	93
13	**11c**	**10a^1**	*m*-F-Ph-	*i*-Pr	24	**12h**	97
14	**11d**	**10a$_1$**	CH_3-CH_2-CH_2-	*i*-Pr	2	**12i**	89 (62)[b]
15	**11d**	**10a^3**	CH_3-CH_2-CH_2-	*i*-Pr	4	**12i**	88
16	**11a**	**10a^1**	*p*-MeO-Ph-	Cy	24	**12j**	92 (67)[b]
17	**11b**	**10a^1**	*p*-Me-Ph-	Cy	24	**12k**	94
18	**11c**	**10a^1**	*m*-F-Ph-	Cy	48	**12l**	96
19	**11d**	**10a^1**	CH_3-CH_2-CH_2-	Cy	2	**12m**	94
20	**11d**	**10a^2**	CH_3-CH_2-CH_2-	Cy	2	**12m**	86
21	**11a**	**10a^1**	*p*-MeO-Ph-	*t*-Bu	27	**12n**	-
22	**11a**	**10a^1**	*p*-MeO-Ph-	*t*-Bu	72[d]	**12n**	-

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

[155] The spectrum was compared with the spectrum of pure 2-(2-(4-methoxyphenyl)-2-oxoethyl) benzaldehyde reported in the literature: S. Zhu, R. Liang, H. Jiang, W. Wu, *Angew. Chem. Int. Ed*. **2012**, 51, 10861-10865.

As previously mentioned, the most accepted mechanism to describe synthesis of isochromenes catalyzed by silver(I) involves the formation of a isochromenilium intermediate (**I**) (metal ate complex) stabilized by resonance, as result of the direct nucleophilic attack of the aldehyde oxygen to the activated triple bond (**scheme 2.28**, path A).[156] It follows the attack of the alcohol to the activate isochromenilium intermediate (**I**) to give the intermediate (**II**). A fast demetallation leads to the isochromene and restore the catalyst. Alternatively, since the ambivalence of silver salts and complexes, i.e., σ-philic *vs* π-philic character,[157] has been repeatedly established,[158] a possible path could involve the direct nucleophilic attack of the alcohol to the aldehyde activated by the metal to give a hemiacetal intermediate (**III**), which is able to react with the metal activated triple bond (**scheme 2.28**, path B). Also in this case, the following demetallation is the final step and leads to the formation of the isochromene, restoring the catalyst.



Scheme 2.28 – Plausible reaction mechanisms.

We have done some ^{1}H-NMR experiments to gain insight into the mechanism. In the first experiment, we repurposed the preliminary reaction conditions (see **table 2.5**, entry 1) reacting **11a** at 30 °C in deuterated methanol in a NMR test tube (**figure 2.25**).

[156] P. Belmont, in Silver in Organic Chemistry (Ed. M. Harmata), John Wiley and Sons, Inc., Hoboken, **2010**, pp 143-165; Chapter 5
[157] For a recent review on electrophilic Lewis acids see: Y. Yamamoto, *J. Org. Chem*., **2007**, 72, 7817-7831
[158] T. Godet, C. Vaxelaire, ; C. Michel, A. Milet, P. Belmont, *Chem. Eur. J.* **2007**, 13, 5632-5641

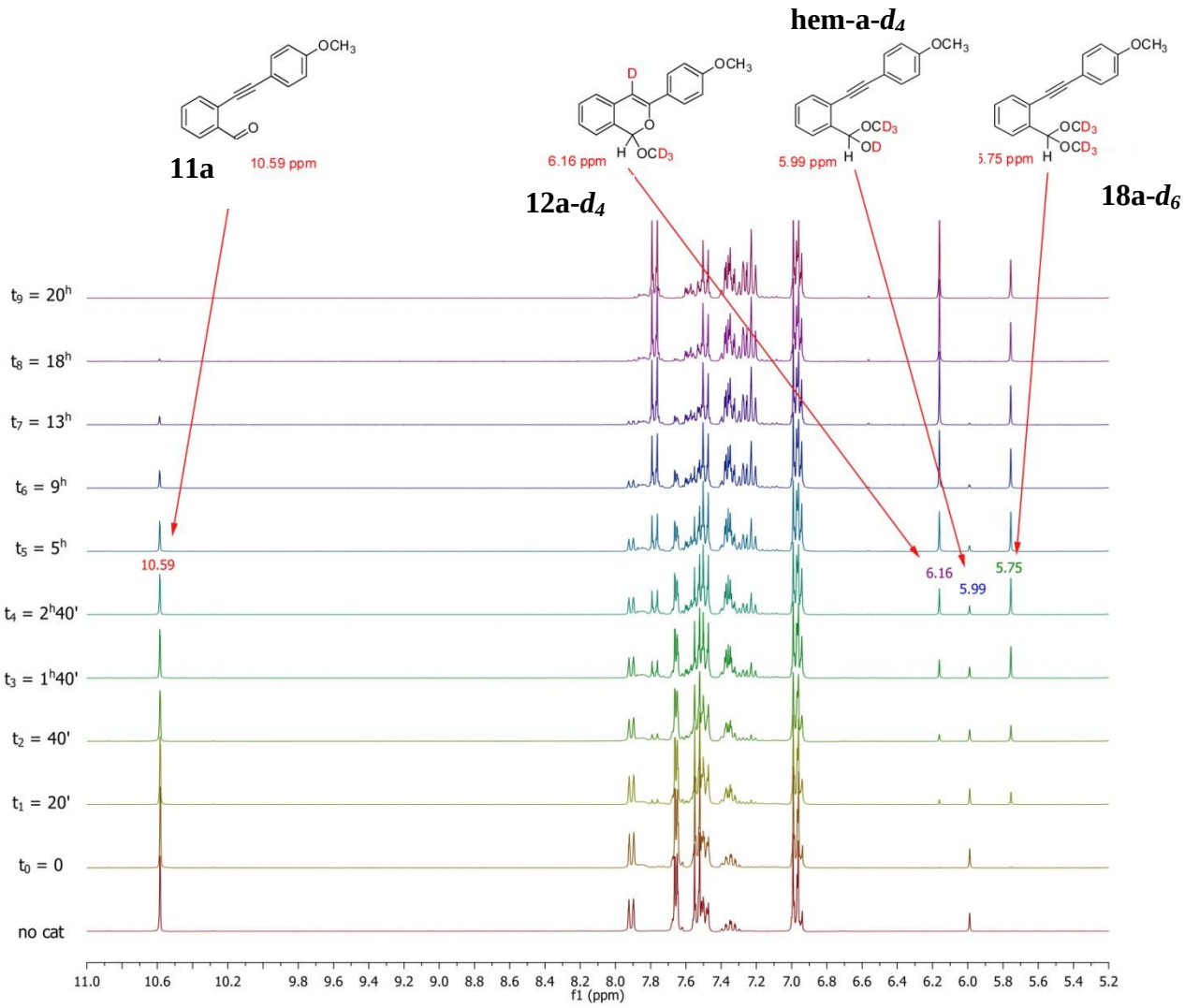


Figure 2.25 – Kinetic ^{1}H-NMR experiment of **11a** in CD_3OD in the presence of **10a**[1] (5 mol%), T = 30 °C.

In the absence of the catalyst (**figure 2.25**, no cat spectrum) we observed only the formation of a little amount (≈18%) of the deuteromethyl-hemiacetal **hem-a-***d*$_4$ (5.99 ppm). We calculated the amount of **hem-a-***d*$_4$ on the basis of relative integration of the hemiacetal proton signal at 5.99 ppm and the aldehydic one at 10.59 ppm.

Then, **10a**[1] (5 mol%) was added (**figure 2.25**, T^0 spectrum). After 20 minutes (**figure 2.25**, T^1 spectrum) two new signals at 5.75 ppm and 6.16 ppm were detected, relative to the deuterodimethyl-acetal **18a-***d*$_6$ and the isochromene **12a-***d*$_4$, respectively. The spectra appeared very clean, and then the reaction proceeded with complete disappearance of the signals relative to aldehyde **11a** (10.59 ppm) and methyl-hemiacetal **hem-a-***d*$_4$ (5.99 ppm). The spectrum shape and the ratio between aldehyde **11a** and hemiacetal **hem-a-***d*$_4$ do not change in time (20 h), showing that it exists an equilibrium between the two compounds.

The reaction was complete in 20 h (**figure 2.25**, T^9 spectrum) when only the signals relative to isochromene **12a**-d_4 and the acetal **18a**-d_6 were detectable. We attributed the signal relative to acetal **18a**-d_6 at 5.75 ppm by comparison with those observed in the spectrum of a pure sample of the dimethyl-acetal **18a**. It is interesting to note that in all spectra we never detected any signal around 10.1 ppm, attributable to a possible isochromenilium intermediate.[159]

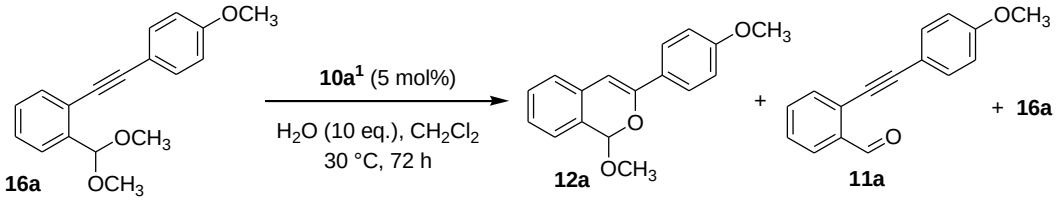
Moreover the analysis of the integrals at different times of the signals relative to deuterodimethyl-acetal **18a**-d_6 (5.75 ppm) with respect to those relative to CH_3 of 4-methoxyphenyl moieties chosen as reference (all these signals fall around 3.84-3.85 ppm and their overall integral is invariable), revealed that under these reaction conditions the hydrolysis of deuterodimethyl-acetal **18a**-d_6 to give the methyl-hemiacetal **hem-a**-d_4 is a very slow process (**table 2.7**).

This statement was confirmed by an additional experiment: the reaction of a pure sample of the dimethyl-acetal **18a** in CH_2Cl_2 in the presence of **10a**[1] (5 mol%) and 10 equiv of water gave a mixture of isochromene **12a**, aldehyde **11a** and unreacted starting material **18a** 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 2.29**).

Table 2.7 – Integrals of selected signals of kinetic ^{1}H-NMR experiment.

Time	ref. (**11a+12a+18a+hem-a**) (3.84-3.85 ppm) $C\underline{H}_3O$-Ph-	Aldehyde **11a** (10.5 ppm) -C<u>H</u>O	Hemiacetal **hem-a** (5.99 ppm) -C<u>H</u>(OD)OCH_3	Acetal **18a** (5.75 ppm) -C<u>H</u>$(OCH_3)_2$	Isochromene **12a** (6.16 ppm) -C<u>H</u>(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

[159] Related isochromenilium TfO^- salts have been isolated and characterized, see: J. D. Tovar, T. M. Swager, *J. Org. Chem*. **1999**, 64, 6499-6504



Scheme 2.29 – Reactivity of acetal **18a**

We made some consideration starting from these results:

1) The formation of dimethyl-acetal **18a**-d_6 in the reaction performed in deutero-methanol in the presence of complex **10a**[1] confirmed its oxo-philic character (as yet previously observed for Ag(I) salts),[160] and its ability to promote the acetalization of methyl-hemiacetal **hem-a**-d_4.

2) This 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 **12a** (**scheme 2.28,** path **B**). Conversely, the absence in ^{1}H-NMR spectra of any signal referable to a isochromenilium intermediate (**scheme 2.28**, path **A**) 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 **10a**[1] (5 mol%) and only 2 equivalents of methanol, no traces of hemiacetal **hem-a**, acetal **18a** neither isochromenilium intermediates were observed, but only a slow direct conversion of aldehyde **11a** in the desired product **12a** was detected (**figure 2.26**).

[160] M. Dell'Acqua, G. Abbiati, A. Arcadi, E. Rossi, *Org. Biomol. Chem.* **2011**, 7836-7848

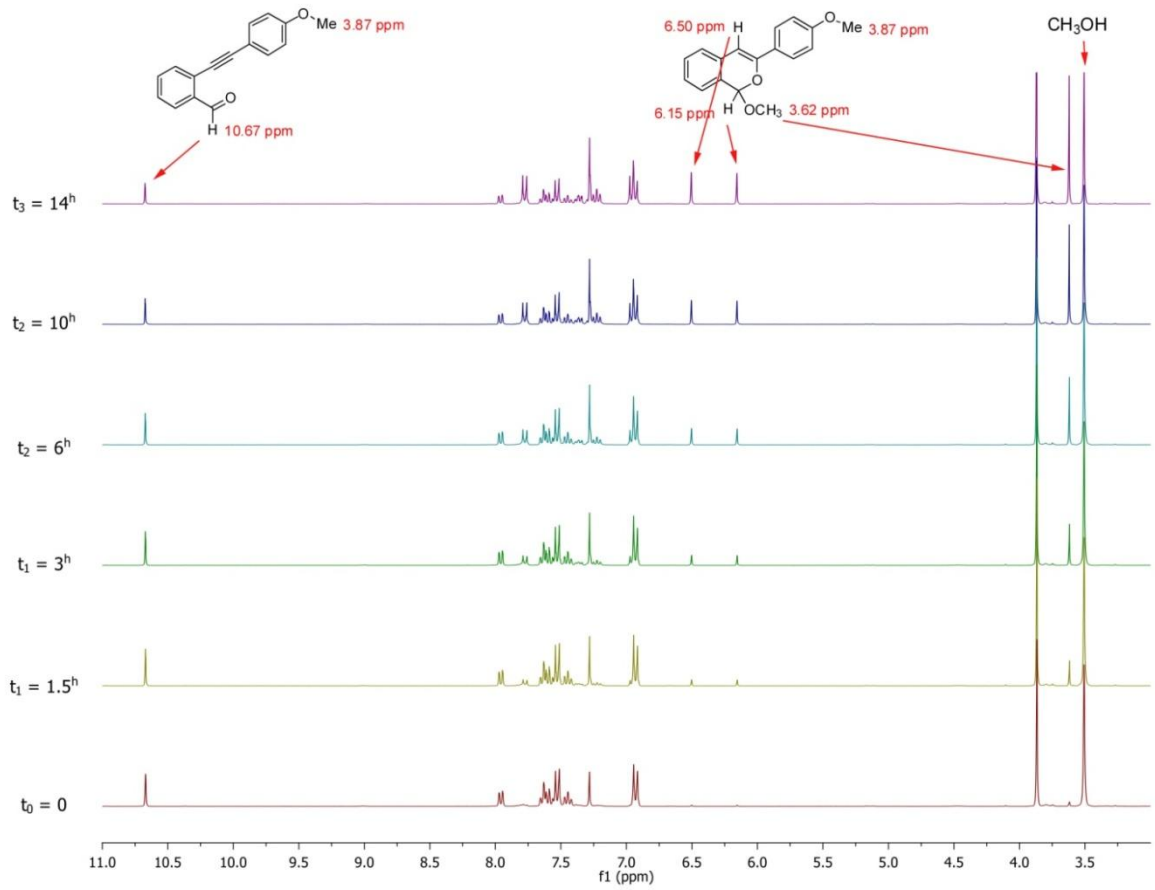
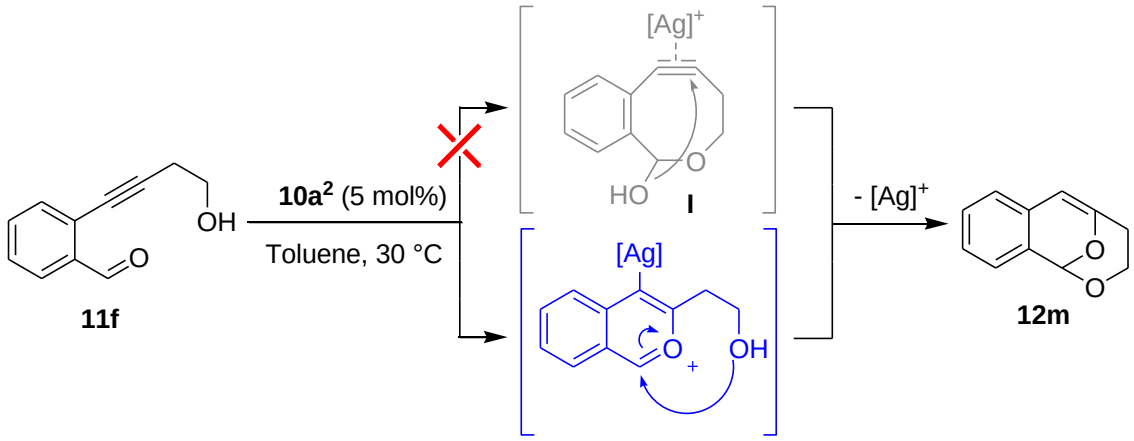


Figure 2.26 – Kinetic ^{1}H-NMR experiment of **11a** in $CDCl_3$ in the presence of 2 equivalents of methanol and **10a**[1] (5 mol%), T = 30 °C.

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 synthesized alkyne **11f**, characterized by the presence of a hydroxyethyl pendant at alkyne terminus, under standard condition in the absence of any other alcohol (**scheme 2.30**). Due to geometric requirements, the hypothetical formation of the corresponding tricyclic isochromene derivative **12m** can only occur by formation of an isochromenilium intermediate, because an alternative oxa-benzocyclooctyne hemiacetal (**I**) is a strongly improbable intermediate and, at the time of our studies, such oxa-benzocyclooctyne bicyclic structures were never observed in the literature.[161]

[161] To the best of our knowledge, the most similar oxa-cycloalkyne reported in the literature is the oxa-dibenzocyclooctyne prepared by photochemical decarbonylation of corresponding cyclopropenones: C. D. McNitt, V. V. Popik, *Org. Biomol. Chem*. **2012**, 10, 8200-8202.

Moreover, the feasibility of the synthesis of **12m** was yet verified independently by the group of Wu and Hammond by AgOTf[162] and triazole-Au[163] catalyzed processes, respectively.



Scheme 2.30 – Intramolecular addition/cycloisomerization of alkyne **11f**.

We were pleased to find that the reaction in the presence of Ag(I) complex **10a²** gave the attained product **12m** in 5h (50 % yield), thus confirming that an isochromenilium ion is presumably the main intermediate involved in the reaction mechanism.

[162] X. Yu, Q. Ding, W. Wang, J. Wu, *Tetrahedron Lett.*, **2008**, 49, 4390-4393
[163] L.-P. Liu, G. B. Hammond, *Org. Lett*. **2010**, 12, 4640-4643

2.3.3.2 - A^3 Coupling

We tested our Ag(I) complexes also in a multicomponent reaction such as the A^3-coupling. Multicomponent reactions (MCR'S) are the way for the synthesis of complex molecules starting from more than two simple building blocks in a single operative step.[164] This kind of procedure allows to reduce the overall time required to obtain the desired product, beside a valuable solvents and energy saving and the reduction of waste production. The advantages from the ecological and economic point of view, hence, are significant. In this context, the transition-metal catalyzed three-component reaction of an aldehyde, an amine and an alkyne, better known as A^3-coupling,[165] represents the most convenient method to access propargylamines, which are recurrent moieties in biologically active compounds and valuable intermediates for the synthesis of more complex nitrogen-containing molecules. Starting from the pioneering works of Dax[166] and Dyatkin,[167] the most popular procedures for A^3-coupling are based on copper(I) catalysis[168], even if the other coinage metals, silver[169] and gold,[170] gave valuable results[171] too and some other metals such as iron,[172] indium,[173] zinc,[174] nickel,[175] cobalt[176] and mercury[177] demonstrated their skill to catalyze this transformation. Silver based catalysts, it is worth to note that the catalytic systems most frequently used are simple silver(I) salts (e.g., AgX,[169, 178] Ag_2O,[179] or $Ag_3PW_{12}O_{40}$[180]), just

[164] (a) J. Zhu, Eds. H. Bienaymé, *Wiley-WCH: Weinheim*, **2006;** (b) B. Ganem, *Acc. Chem. Res.* **2009,** *42*, 463-472
[165] (a) V. A. Peshkov, O. P. Pereshivko, E.V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790–3807. (b) W.-Y. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta*, **2011**, *44*, 43–51. (c) C. Wei, Z. Li, C.-J. Li, *Synlett*, **2004**, 1472–1483.
[166] J. J. McNally, M. Youngman, S. L. Dax *Tetrahedron Lett.* **1998**, *39*, 967-970
[167] A. B. Dyatkin, R. A. Rivero *Tetrahedron Lett.* **1998**, *39*, 3647–3650
[168] Selected examples: (a) S. B. Park, H. Alper, *Chem. Commun.* **2005**, 1315–1317. (b) B. Sreedhar, P. S. Reddy, B. V. Prakash, A. Ravindra, *Tetrahedron Lett.* **2005**, 46, 7019–7022. (c) C. E. Meyet, C. J. Pierce, C. H. Larsen, *Org. Lett.* **2012**, 14, 964–967
[169] The first example: C. Wei, Z. Li, C.-J. Li, *Org. Lett.* **2003**, *5*, 4473–4475
[170] Selected examples: (a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584–9585. (b) V. K.-Y. Lo, Y. Liu, M.-K. Wong, C.-M. Che, *Org. Lett.* **2006**, *8*, 1529–1532. (c) M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.* **2007**, *9*, 742–745. (d) X. Zhang, A. Corma, *Angew. Chem., Int. Ed.* **2008**, *47*, 4358–4361
[171] G. Abbiati, E. Rossi, *Beilstein J. Org. Chem.* **2014,** *10*, 481–513
[172] (a) P. Li, Y. Zhang, L. Wang, L. *Chem. Eur. J.* **2009**, *15*, 2045–2049. (b) W.-W. Chen, R. V. Nguyen, C.-J. Li, *Tetrahedron Lett.*, **2009**, *50*, 2895–2898
[173] (a) Y. Zhang, P. Li, M. Wang and L. Wang, *J. Org. Chem.*, **2009**, *74*, 4364–4367. (b) J. S. Yadav, B. V. Subba Reddy, A. V. Hara Gopal, K. S. Patil, *Tetrahedron Lett.* **2009**, 50, 3493–3496
[174] (a) E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, Tetrahedron Lett., 2007, 48, 7184–7190; (b) M. L. Kantam, V. Balasubrahmanyam, K. B. S. Kumar, G. T. Venkanna, Tetrahedron Lett. 2007, 48, 7332–7334
[175] S. Samai, G. C. Nandi, M. S. Singh, *Tetrahedron Lett.*, **2010**, *51*, 5555–5558
[176] W.-W. Chen, H.-P. Bi, C.-J. Li, *Synlett* **2010**, 475–479
[177] P. Li, L. Wang, *Chin. J. Chem.*, **2005**, *23*, 1076–1080
[178] B. Huang, X. Yao, C.-J. Li, *Adv. Synth. Catal.* **2006,** *348*, 1528–1532
[179] Q. Liu, Y. Lu, W.-Y. Sun, L.-L. Zhai, Y. Zhao, X. Zhou, *RSC Adv.* **2013** , *3*, 1732–1734
[180] K. M. Reddy, N. S. Babu, I. Suryanarayana, P. S. S. Prasad, N. Lingaiah, *Tetrahedron Lett.* **2006,** *47*, 7563–7566

occasionally as acetonitrile complexes[181] or (*N*-heterocyclic carbene)Ag(I) complexes (**figure 2.27**).[182]

Interestingly, when this MCR was endeavored in the presence of phosphine-based Ag(I) complexes, a switch of activity was observed and the simple propargyl alcohol originated from aldehyde-alkyne coupling was obtained.[183]

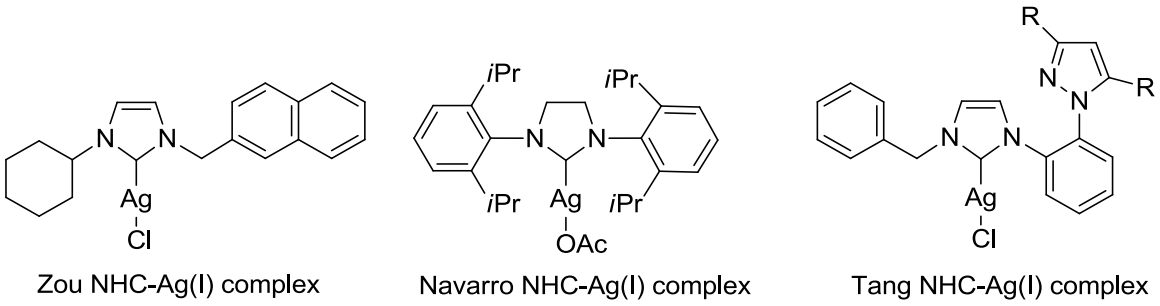


Figure 2.27 – Some NHC-Ag(I) complexes used as catalysts for A^3-coupling

In first example of Ag(I) catalyzed A^3-coupling, by Li et. al,[75] a simple silver(I) halide demonstrated to be able to catalyze the reaction in water at 100°C. The system worked well for alkyl aldehydes, while aryl aldehydes and secondary acyclic amines were not well tolerated. In any case, this procedure avoids the undesired aldehyde trimerization, that is usually observed in Cu(I) and Au(I) catalysis.

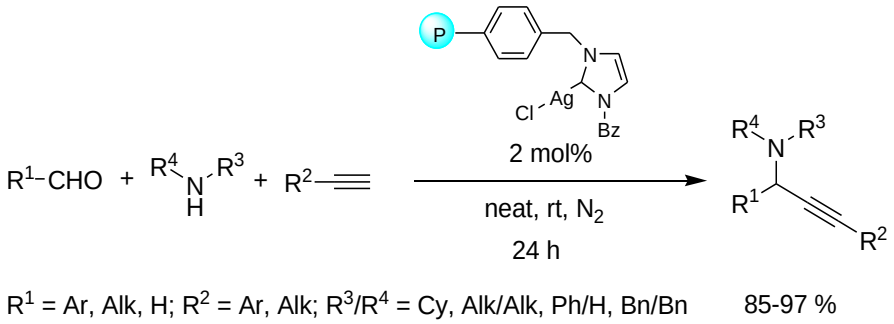
The Ag(I)-acetonitrile complexes, stabilized by bulky anions (i.e. BF_4^-), catalyze in good yield the coupling between secondary cyclic amines, phenylacetylene and various substituted aldehydes.

Finally, the (*N*-heterocyclic carbene)Ag(I) complexes[88] came out as valuable catalysts for this reaction: they are able to efficiently catalyze the coupling (even in solvent-free conditions and at room temperature) with an enhanced activity with respect to Ag(I) halides. This kind of complexes allowed the use of aromatic and aliphatic aldehydes, a wide range of secondary amines and both aromatic and aliphatic alkynes (**scheme 2.31**). Even formaldehyde, *o*-substituted benzaldehydes and secondary aromatic amines have been demonstrated to be suitable substrates.

[181] Y. Zhang, A. M. Santos, E. Herdtweck, J. Mink, F. E. Kühn, *New J. Chem.* **2005**, *29*, 366–370

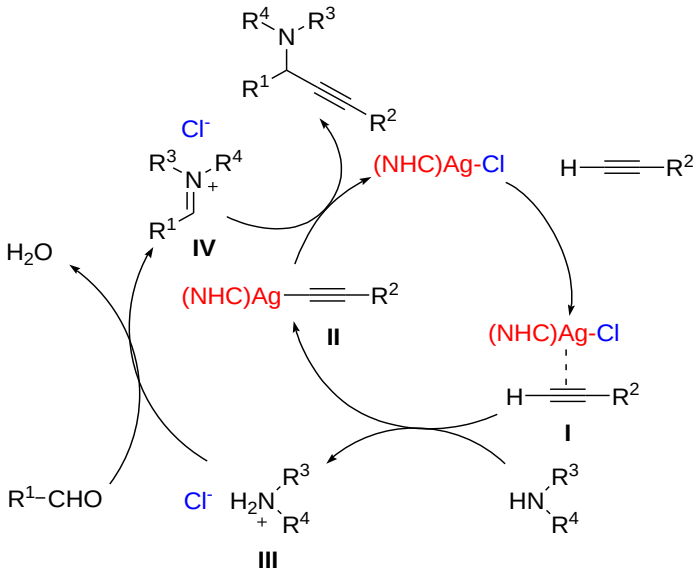
[182] (a) P. Li, L. Wang, Y. Zhang, M. Wang, *Tetrahedron Lett.* **2008,** *49*, 6650–6654. (b) Y. He, M.-F. Lv, C. Cai, *Dalton Trans.* **2012,** *41*, 12428–12433. (c) Y. Li, X. Chen, Y. Song, L. Fang, G. Zou, *Dalton Trans.* **2011**, *40*, 2046–2052. (d) M.-T. Chen, B. Landers, O. Navarro, *Org. Biomol. Chem.* **2012**, *10*, 2206–2208. (e) C.-H. Cheng, D.-F. Chen, H.-B. Song, L.-F. Tang, *J. Organomet. Chem.* **2013,** *726*, 1–8

[183] X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395–4398



Scheme 2.31 – A^3-coupling reaction catalyzed by polystyrene-supported NHC-silver halides

Zou and co-workers reported structurally well-defined N-heterocyclic-carbene silver halides of 1-cyclohexyl-3-arylmethyl imidazolylidene as effective catalyst in a model reaction among 3-phenylpropionaldehyde, phenylacetylene and piperidine, in dioxane at 100 °C in open air.[184] Although the scope was not investigated, the authors observed that the activity of the catalyst was notably affected by the nature of the anion in the order Cl > Br > I. They argued that the true catalytic species would be a structurally stable and coordinatively unsaturated N-heterocyclic carbene silver halide (NHC)AgX rather than a silver cation. Thus, a more detailed mechanism was proposed, in which firstly the π-complex of the catalyst with the alkyne **I** reacts with an amine to form the silver acetylide **II** and the amine hydrohalide **III**. The latter then condenses with the aldehyde to generate the iminium halide **IV**, which reacts with the previously generated silver acetylide **II** to afford the desired product and regenerate the catalyst (**Scheme 2.32**).

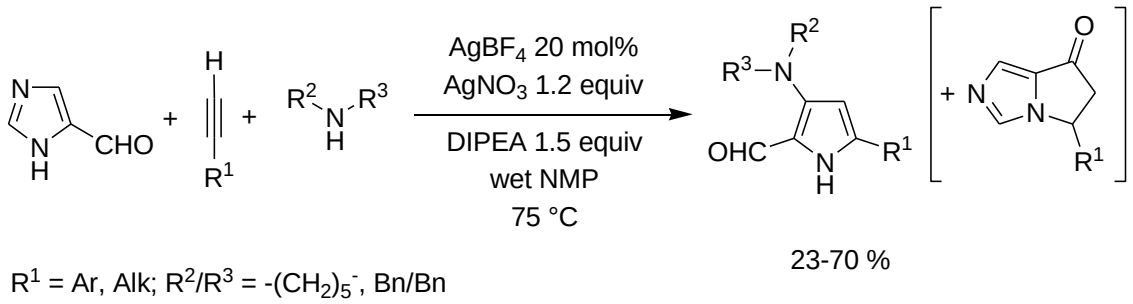


Scheme 2.32 – Proposed reaction mechanism for (NHC)AgCl catalyzed A^3-coupling reactions

[184] C.-H. Cheng, D.-F. Chen, H.-B. Song, L.-F. Tang, *J. Organomet. Chem.*, **2013**, *726*, 1-8

Prompted by the discovery about the role of the counter ion in the Ag complex, Navarro and co-workers developed a new saturated 1,3-*bis*(2,6-diisopropylphenyl)imidazolium (SIPr) silver complex, characterized by the presence of a less bulky acetoxy anion.[185] The new NHC-Ag(I) complex demonstrated to be a versatile catalyst in A^3-coupling reaction, tolerating alkyl, aryl aldehydes (even inactivated), cyclic and linear secondary amines, and alkyl/aryl terminal alkynes. Noteworthy, the reactions occurred under mild conditions with a low catalyst loading. They used methanol (technical grade) as solvent but the reaction ran well also in acetonitrile and other alcohols, whereas yields were very low in toluene.

The interest around A^3-coupling reaction is high also because it can be a MCR step of a more complex cascade transformation.[186] For example, in 2011 Liu reported an interesting Ag promoted cascade synthesis of pyrrole-2-carboxyaldehydes involving an A^3-coupling followed by an unusual imidazole ring opening.[187] The authors discovered that the propargylamines derived from the $AgBF_4$ catalyzed coupling of imidazole-4-carboxyaldehydes, differently substituted alkynes and secondary amines were susceptible of a further *in situ* transformation to give 3,5-substituted pyrrole-2-carboxyaldehydes in moderate to good yields beside variable amounts of 5-substituted-5*H*-pyrrolo[1,2-c]imidazol-7(6*H*)-one (**Scheme 2.33**). In order to obtain the best results and to reduce the formation of the pyrroloimidazolone**,** the reactions were performed in the presence of 20 mol% of $AgBF_4$, 1.2 equiv of $AgNO_3$ and 1.5 equiv of DIPEA in wet NMP.

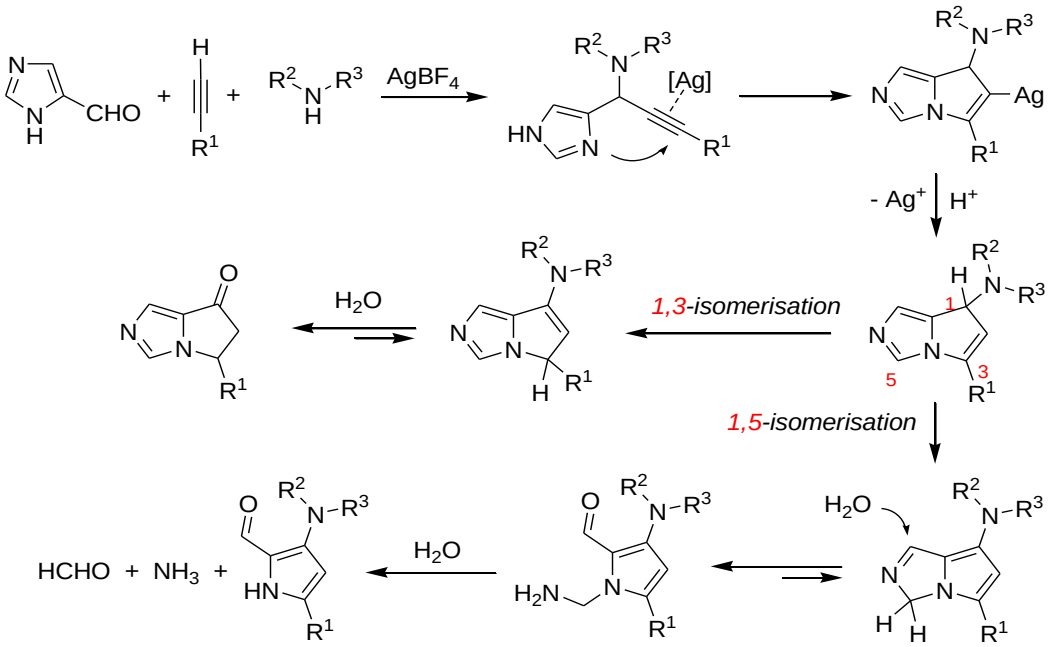


Scheme 2.33 – Liu's synthesis of pyrrole-2-carboxyaldehydes

It is important to underline that the yields drop by employing alkyl alkynes. Water was proven to be necessary in the reaction system; to clarify its role and the mechanism of pyrrole-2-carboxyaldehydes (and by-product) formation, Liu et co-workers performed a series of experiments

[185] M.-T. Chen, B. Landers, O. Navarro, *Org. Biomol. Chem.*, **2012**, *10*, 2206-2208
[186] Y. Liu, *Arkivoc*, **2014**, 1-20.
[187] J. Zeng, Y. Bai, S. Cai, J. Ma, X.-W. Liu, *Chem. Commun.*, **2011**, *47*, 12855-12857.

with 1-or 2- or 5-substituted imidazole aldehydes and some control reactions on the isolated propargylamine intermediate, also in the presence of D_2O or $H_2{}^{18}O$. They found that the key steps of the process are the silver catalyzed intramolecular cyclization of propargylamine followed by competitive 1,3- or 1,5-isomerization and subsequent hydrolysis, yielding respectively the pyrroloimidazolone or the pyrrole (**Scheme 2.34**). The 1,5-isomerization path leads to formaldehyde and ammonia, so in the presence of silver salt the well-known silver mirror reaction could take place, thus justifying the need of at least one equiv of $AgNO_3$



Scheme 2.34 – Proposed reaction mechanism for Liu's synthesis of pyrrole-2-carboxyaldehydes

On the other hand, the asymmetric version of the A^3-coupling (the so-called AA^3-coupling) is absolutely dominated by Cu-based complexes,[188] and to the best of our knowledge no examples have been already reported with any other transition metal.[189]

[188] Selected examples: (a) C. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639. (b) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766. (c) P. Aschwanden, C. R. J. Stephenson, E. M. Carreira, *Org. Lett.* **2006**, *8*, 2437–2440. (d) A. Bisai, V.K. Singh, *Org. Lett.* **2006**, *8*, 2405–2408. (e) S. Nakamura, Y. Nakamura, M. Ohara, N. Shibata, T. Toru, *Chem. Eur. J.* **2010**, *16*, 2360–2362. (f) A. Bisai, V. K. Singh, *Tetrahedron* **2012**, *68*, 3480–3486

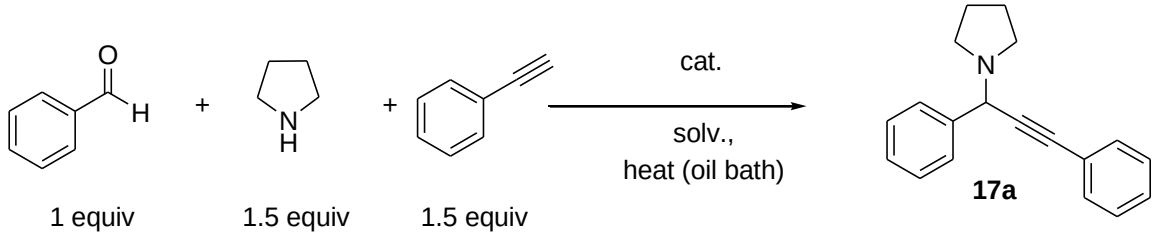
[189] Some related examples of silver and gold catalyzed enantioselective addition of acetylenes on preformed imines have been recently reported, see for example: with a gold phosphine catalyst: M. J. Campbell, D. Toste, *Chem. Sci.* **2011**, *2*, 1369–1378; with a silver phosphine catalyst: Y. Su, M. Lu, B. Dong, H. Chen, X. Shi, *Adv. Synth. Catal.* **2014**, *356*, 692–696.

In connection with our ongoing interest in the just described study of metal catalyzed domino and multicomponent[151] processes involving alkynes, carbonyl compounds and ammonia/amines, we set to point a microwave enhanced synthesis of propargylamines, catalyzed by our Ag(I) complexes.

As testing reaction we chose the coupling between benzaldehyde, pyrrolidine and phenylacetylene and we use as catalyst the **10d[1]** complex. We set as the initial conditions – ratio among reagents, temperature and catalyst loading – the more frequently reported in the literature for this kind of reactions (i.e., ratio aldehyde/amine/alkyne = 1 : 1.5 : 1.5, T = 100 °C, cat. 3 mol%). Under these conditions, we explored the effect of different solvents with decreasing relative polarity[190] (**Table 2.8**, entries 1-5). We found that complex **10d[1]** is able to catalyze the reaction in all the solvent tested, anyway the best results were obtained performing the reaction in methanol and in toluene (**Table 2.8**, entries 2, 5). It is interesting to note that despite the low solubility of the complex and of the reactants, the reaction however occurs in water (**Table 2.8**, entry 1), although at the end of the reaction a great amount of free silver(0) was observed in the test tube. Since a similar behavior was observed when the reaction was performed in methanol, we chose toluene as solvent for further tests. In order to avoid a negative effect from the H_2O traces in the system, we added a small amount of 3 Å molecular sieves, but it did not improve significantly the reaction yields in both methanol and toluene (**Table 2.8**, entries 6 and 7). Decreasing the temperature to room temperature, the reaction become extremely slow and the yield is scarce (**Table 2.8**, entry 8). Conversely, increasing the catalyst loading to 6 mol% we observed an improvement in yield up to 87 % (**Table 2.8**, entry 9). Moreover, also changing the counter ion of the complex from BF_4^- to TfO^- induces an additional rise in yield (**Table 2.8**, entry 10).

[190] C. Reichardt, Solvents and Solvent Effects in Organic Chemistry, 3rd ed., Wiley-VCH, Weinheim, **2003**.

Table 2.8 – Exploring the best reaction conditions under conventional heating



Entry	Catal. mol%	Solvent	Mol. sieves 3 Å	T (°C)	t (h)	Yield (%)[a]
1	3	Water	no	100	4	65
2	3	MeOH	no	100	4	62
3	3	DMF	no	100	4	26
4	3	DCE	no	100	4	22
5	3	Ph-Me	no	100	4	60
6	3	MeOH	yes	100	3	57
7	3	Ph-Me	yes	100	3	54
8	3	Ph-Me	yes	r.t.	90	31
9	6	Ph-Me	no	100	5	87
10[b]	6	Ph-Me	no	100	5	96

[a] Yields of pure isolated product. [b] **10d**[2] was used as catalyst

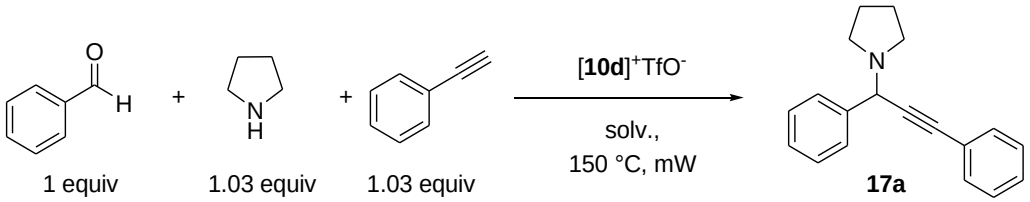
Among the many remarkable results obtained, we noticed some drawbacks of our approach, as the long reaction times and the high catalyst loading. To overcome these difficulties we decide to change the energy source.

The ability of dielectric heating to promote different type of Cu(I) catalyzed A^3-coupling has been well established and described by Leadbeater,[191] Tu[192] and Van der Eycken[193] so we decided to continue our study under microwave irradiation (**Table 2.9**). It is well known that the efficiency of dielectric heating is strongly related to the nature and the polarity of the solvent,[194] For this reason we repeated the solvent screening (**Table 2.9**, entries 1-6) and we found that, also under microwave heating, toluene demonstrated to be the best solvent (**Table 2.9**, entry 3); the reaction was complete

[191] N. E. Leadbeater, H. M. Torenius, H. Tye *Molec. Divers.*, **2003**, *7*, 135-144
[192] L. Shi, Y. Q. Tu, M. Wang; F. M. Zhang, C. A. Fan, *Org. Lett*., **2004**, *6*, 1001–1003.
[193] J. B. Bariwal, D. S. Ermolat'ev, E. V. Van der Eycken, *Chem.–Eur. J.*, **2010**, *16*, 3281–3284.
[194] AA.VV., Microwaves in Organic Synthesis, ed. A. Loupy, Wiley VCH, Weinheim, **2002**.

in 15 minutes with excellent yield. Moreover we reduced the ratio among reaction partner to 1:1.03:1.03 and the catalyst loading (**Table 2.9**, entry 7) to 3 mol% without loss of efficiency, whereas in the presence of 1 mol% of catalyst the yield drop-out to 68% (**Table 2.9**, entry 8). Finally, we discovered that the reaction time can be reduced to 10 minutes without appreciable loss of efficiency (**Table 2.9**, entry 9). Shorter times (5 minutes) resulted in lower yield (**Table 2.9**, entry 10).

Table 2.9 – Exploring the best reaction conditions under microwave heating.



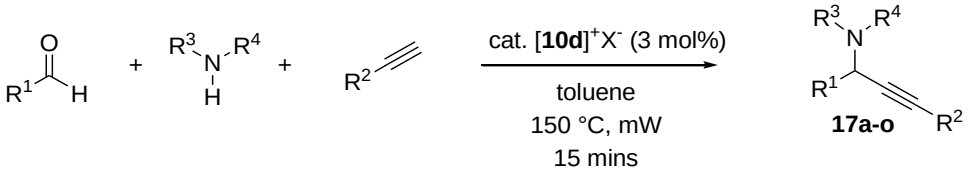
Entry	Catalyst [a] mol%	Solvent	t (min)	Yield (%)[b]
1	6	Cyclohexane	15	63
2	6	MeOH	15	47
3	6	Ph-Me	15	96
4	6	Dioxane	15	9
5	6	DCE	15	64
6	6	Me-CN	15	66
7	3	Ph-Me	15	96
8	1	Ph-Me	15	68
9	3	Ph-Me	10	95
10	3	Ph-Me	5	93

[a] **10d**[2] [b] Yields calculated via ^{1}H-NMR using dimethyl terephthalate (DMT) as internal standard.

With the best conditions in hands, we explored scope and limitations of the reaction. In particular, our target was to verify the ability of our catalysts to promote the reaction among partners of different nature, such as substituted aliphatic and aromatic aldehydes, alkynes substituted with alkyl or aryl moieties bearing EWG or EDG, and secondary amines. EWGs and EDGs on arylalkyne

partner were in general well-tolerated (**Table 2.10**, entries 2, 3, 11), except for strongest EWG such as nitro group (**Table 2.10,** entry 4). Conversely, the presence of an alkyl group on alkyne partner gave low reaction yield (**Table 2.10**, entry 5). Benzaldehydes derivatives bearing EWGs or EDGs in any position of the ring gave satisfying results (**Table 2.10**, entries 6-8) as well as cyclohexanecarbaldehyde (**Table 2.10**, entries 9 and 11). Nevertheless, also in this case lower yields were observed when the aldehyde was characterized by an acyclic alkyl substitution (**Table 2.10**, entry 10). The nature of the amine was the more critical feature: cyclic secondary amines such as pyrrolidine and piperidine gave best results (**Table 2.10**, entries 1-3, 6-9, 11-13), whereas acyclic secondary amines (**Table 2.10**, entries 15, 16), and less basic cyclic amines (i.e., morpholine, **Table 2.10**, entry 14) gave only fair to good reaction yields.

Table 2.10 – Scope of (Pc-L)-Ag(I) catalyzed A^3-coupling with secondary amines

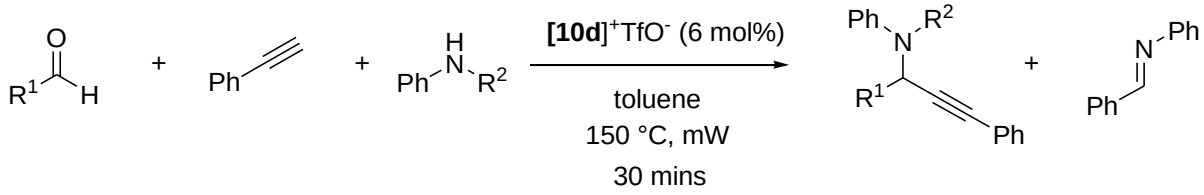


Entry	Product	X	Aldehyde R^1	Amine R^3	Amine R^4	Alkyne R^2	Product Yield %[b]
1	**17a**	TfO^-	Ph-	-$(CH_2)_4$-		Ph-	96
2	**17b**	TfO^-	Ph-	-$(CH_2)_4$-		*p*-MeO-Ph-	75
3	**17c**	TfO^-	Ph-	-$(CH_2)_4$-		*m*-F-Ph-	83
4	**-**	TfO^-	Ph-	-$(CH_2)_4$-		*p*-NO_2-Ph-	-
5	**17d**	TfO^-	Ph-	-$(CH_2)_4$-		C_3H_7-	53[c]
6	**17e**	TfO^-	*p*-MeO-Ph-	-$(CH_2)_4$-		Ph-	78[c]
7	**17f**	BF_4^-	*m*-Cl-Ph-	-$(CH_2)_4$-		Ph-	79
8	**17g**	TfO^-	*o*-OH-Ph-	-$(CH_2)_4$-		Ph-	83
9	**17h**	TfO^-	Cy-	-$(CH_2)_4$-		Ph-	98
10	**17i**	BF_4^-	C_4H_9-	-$(CH_2)_4$-		Ph-	61 (62)[d]
11	**17j**	TfO^-	Cy-	-$(CH_2)_4$-		*p*-MeO-Ph-	89
12	**17k**	TfO^-	Ph-	-$(CH_2)_5$-		*p*-MeO-Ph-	91
13	**17l**	TfO^-	Cy-	-$(CH_2)_5$-		*m*-F-Ph-	96
14	**17m**	TfO^-	Ph-	-$(CH_2)_2O(CH_2)_2$-		Ph-	59[c]
15	**17n**	TfO^-	Ph-	Et-	Et-	Ph-	57[c] (61)[d]
16	**17o**	TfO^-	Ph-	Bz-	Bz-	Ph-	61[c]

[a] Unless other stated, the reactions were performed in toluene by dielectric heating at 150°C, with 3 mol% of catalyst, a ratio aldehyde/amine/alkyne = 1 : 1.03 : 1.03 for 15 min. [b] Yields of pure isolated products. [c] reaction time: 20 min. [d] Yields calculated via ^{1}H-NMR using dimethyl terephthalate (DMT) as internal standard.

Subsequently, we applied our Ag(I)(Pc-L)-based catalytic system to challenging substrates such as primary and secondary aromatic amines. A number of example of A^3-coupling reaction with anilines or *N*,*N*-diarylamines as amine partners have been reported in the literature, mainly catalyzed by Cu(I) salts and complexes,[195, 196]
Ru(III)-Cu(I),[197] $AuCl_3$-CuBr,[198] and $InBr_3$,[173b] but only a single reaction catalyzed by a silver salt (AgI) was published.[199]

Table 2.11 – Study of A^3-coupling with aniline



Entry	R^1	R^2	Ratio **Ald:Alk:Amm**	Additive	Yield %[a]	Yield imine %[a]
1	Ph-	H-	1 : 1.1 : 1.1	-	28	68
2	Ph-	H-	1.1 : 1.1 : 1	mol. sieve	24	74
3	Ph-	H-	1.1 : 2 : 1	-	34	58
4	Ph-	H-	1 : 3 : 1.1	-	42	55
5	Ph-	H-	3 : 1 : 3	-	30	74[b]
6	Ph-	Ph-	1 : 1.03 : 1.03	-	-	-
7	Cy-	Ph-	1 : 1.03 : 1.03	-	-	-

[a] Yields calculated via ^{1}H-NMR using dimethyl terephthalate (DMT) as internal standard with respect to limiting reagent. [b] With respect to aniline.

[195] (a) K. Nagaiah, V. Naveenkumar, R. S. Rao, B. V. Subba Reddy, J. S. Yadav, *New. J. Chem.*, **2004**, *28*, 335–337. (b) M. Mirzaei, A. Sharifi, M. R. Naimi-Jamal, *J. Chem. Res.*, **2007**, 129-132.
[196] (a) B. Alakesh, S. K. Vinod, *Org. Lett.,* **2006,** *8*, 2405-2408; (b) N. Shuichi, O. Mutsuyo, N. Yuko, S. Norio, T. Takeshi, *Chem. Eur. J.* **2010,** *16*, 2360-2362
[197] C.-J. Li, C. Wei, *Chem. Commun.*, **2002**, 268-269.
[198] Y. Chen, Y. Liu, J. Wang, F. Xiao, *Tetrahedron*, **2008**, *64*, 2755-2761.
[199] L. Chen, C.-J. Li, Z. Li, C. Wei, R. S. Varma, Chao-Jun Li, *Tetrahedron Lett.*, **2004**, *45*, 2443-2446.

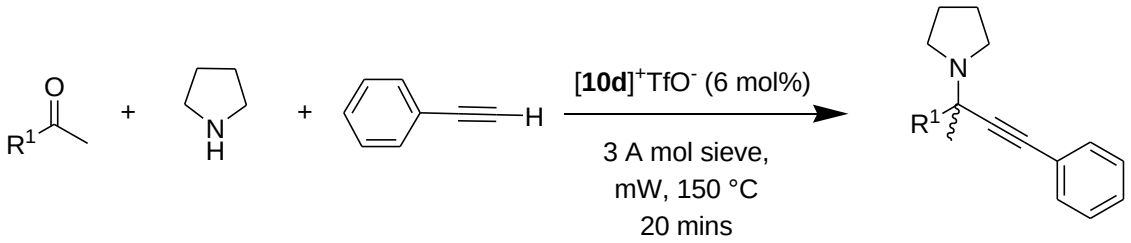
The first attempt was performed with benzaldehyde, phenylacetylene and aniline. The reaction conditions were slightly modified: the catalyst loading and the reaction time were increased to 6 mol% and 30 min, respectively (**Table 2.11**, entry 1). Under these conditions, the corresponding propargylamine was obtained in a modest 28% yield, beside a 68% yield of the imine. Also in this case, the addition of molecular sieves did not improve the yield of the desired product (**Table 2.11**, entry 2). Slightly better results were obtained by increasing the amount of alkyne, but also in these cases the imine remained the main product (**Table 2.11**, entries 3-4). The use of a three-fold excess of amine and aldehyde partners was unsuccessful (**Table 2.11**, entry 5), whereas the reactions with diphenylamine as secondary aromatic amines did never give the desired products (**Table 2.11** entries 6-7). We supposed that the low yields observed are most probably related to the weak basicity of arylamines.

In the literature some examples of a variant of A^3-coupling called KA^2-coupling that involves the use of a ketone instead of an aldehyde to yield propargylamines bearing a quaternary carbon are reported. In most cases this reactions were performed using copper(I/II)[200] salts as catalysts, but also examples catalyzed by gold(III) bromide[201] and Ti(IV)/Cu(II)[202] were reported. However, to the best of our knowledge, no example of Ag catalyzed KA^2-coupling has already been reported.

We were intrigued to test if our Ag catalyst [**6d**Ag]$^+$TfO$^-$ was able to catalyze this kind of challenging reaction. In table **2.12** are reported the results of our preliminary screening by using 2-pentanone, pyrrolidine and phenylacethylene as reactants. Following the methodology optimized for A^3-coupling, the reactions were performed under microwave heating at 150°C for 20 minutes by changing only the molar ratio between reactants. 3Å molecular sieves were added to promote the formation of iminium ion. The reaction do not seemed to be dependent by this parameter, as depicted in table **2.12**, yields ranging from 30 to 40%. Probably, the reaction yield is modest due to the intrinsic lower reactivity of ketones, more hindered and less electrophilic than aldehydes. This hypothesis is supported by the complete failure of the reaction with the more deactivated acetophenone (**table 2.12**, entry 5).

[200] (a) X. Tang, J. Kuang, S. Ma *Chem. Commun.*, **2013**, *49*, 8976-8978. (b) C. J. Pierce, C. H. Larsen *Green Chem.*, **2012**, *14*, 2672-2676. (c) O. P. Pereshivko, V. A. Peshkov, E. V. Van der Eycken *Org. Lett.*, **2010**, *12*, 2638-2641.
[201] M. Cheng, Q. Zhang, X.-Y. Hu, B.-G. Li, J. X. Ji, A. S. C. Chan *Adv. Synth. Cat.*, **2011**, *353*, 1274-1278.
[202] C. J. Pierce, M. Nguyen, C. H. Larsen *Ange. Chem. Int. Ed.*, **2012**, *51*, 12289-12292.

Table 2.12 – Preliminary test on KA^2-coupling



Entry	R^1	Ratio **Ket:Amm:Alk**	Yield%[a]
1	*n*-Pr	1 : 1.1 : 1.1	30
2	*n*-Pr	2 : 2 : 1	32
3	*n*-Pr	1 : 1 : 2	36
4	*n*-Pr	1.1 : 1.1 :1	41[b]
5	Ph	1.1 : 1.1 :1	-

[a] Yields calculated via ^{1}H-NMR using dimethyl terephthalate (DMT) as internal standard. [b] reaction performed using procedure 2 (conventional heating)

Finally we performed also some preliminary tests to screen if our chiral Ag complexes **10h**[1] and **10k**[1] were able to promote the asymmetric A^3-coupling (AA^3). As reported above, this reaction was reported in literature with great results using especially copper catalyst and, to the best of our knowledge, no examples have been reported with silver based catalysts.

Firstly, we tried to perform the reaction with catalyst **10h**[1] at room temperature, to test if our catalysts are able to promote the reaction under milder conditions with respect to those used in the achiral protocol, since milder conditions generally favor the achievement of optically enriched products. Unfortunately the reaction didn't start after 48 h under stirring at r.t.. So we conducted the reaction at 100°C and this allowed us to obtain the desired product, even if raceme. Similar results were observed in the reaction catalyzed by **10k**[1]**.**

We also performed the reaction with chiral catalysts under microwave irradiation, investigating if a reduced reaction time could avoid the contingent racemization processes. Also in this case, the reaction gives the desired product in good yields, but we never observed any appreciable enantiomeric excess.

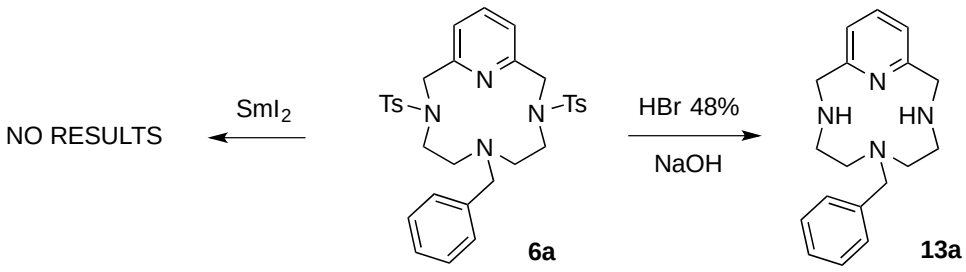
2.4 - Other metals

2.4.1 - Synthesis of free base ligands

In the previous sections we have discussed the coordinative behavior of the PcL* ligands with the coinage metals copper and silver in +1 oxidation state. Some trials made up to now with gold(I) salts met with failure, probably due to the size of the macrocyclic ligands. The good catalytic activities observed for Cu(I) and Ag(I) complexes are due to the weak coordinative ability of the sulfonyl protected nitrogen atoms, possessing a very low basicity. In order to extend the range of metals suitable for complexation, we decided to deprotect the N-sulfonilated atoms. This transformation should increase the basicity of the two nitrogens and give access to dianionic complexes with different catalytic features.

First of all, we tried to remove the tosyl moieties from the ligand **6a**. The classical procedures involve strong acids, strong bases[203] or powerful reactants.[204] Aime et al.[205] used concentrated sulphuric acid to deprotect similar ligands, without aryl arm. An alternative method involves the use of SmI_2 under various condition; Anker and Hilmersson optimized this reaction for many tosylamides, tosylaziridines and tosylesters.[206]

The route that we chose involves the use of an HBr solution (48% w/w in water). The reaction worked well and we obtained the product in 60%, whereas we did not obtain appreciable results by employing the Anker-Hilmersson procedure (**scheme 2.35**).



Scheme 2.35 – Deprotection of ligand **6a**

We also managed to collect crystals of **13a** as hydrochloride salt suitable for X-Ray analysis (**figure 2.28**).

[203] B. Hu, Q. Song, Y. Xu, *Org. Process Res. Dev.* **2012**, *16*, 1552–1557
[204] H. Rubin, J. Cockrell, J. B. Morgan, *J. Org. Chem.* **2013**, 130827114305001
[205] S. Aime, M. Botta, L. Frullano, S. Geninatti Crich, G. Giovenzana, R. Pagliarin, G. Palmisano, F. R. Sirtori, M. Sisti, *J. Med. Chem.* **2000**, *43*, 4017–4024
[206] T. Ankner, G. Hilmersson, *Org. Lett.* **2009**, *11*, 503–506

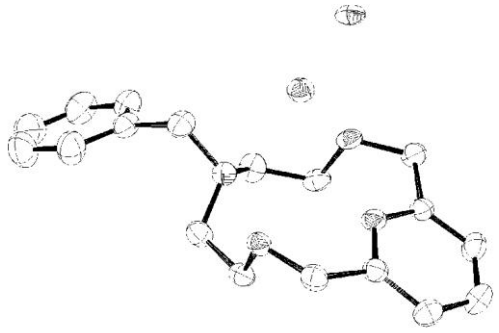
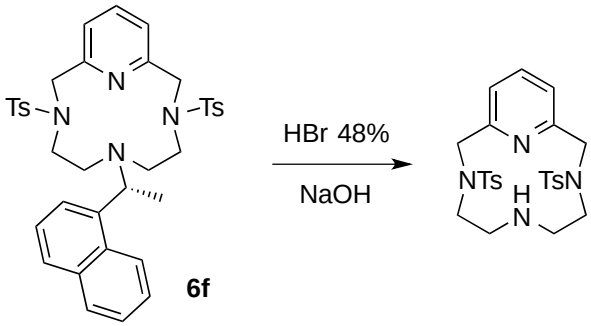


Figure 2.28 – X-Ray structure of ligand **13a·2HCl**

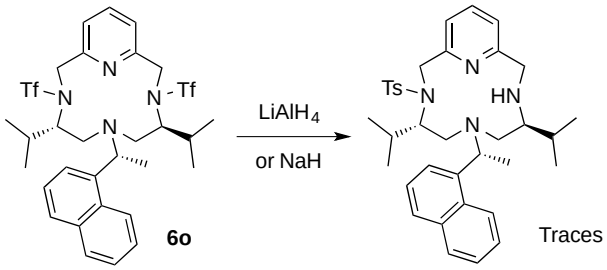
However, the same method turned out to be effective just on the simplest macrocycle **6a**, bearing a benzyl substituent in position 6, while employing the macrocycles with a naphthyl pendant arm, the same conditions caused the cleavage of the sole aryl moiety (**Scheme 2.36**), without affecting the tosyl groups.



Scheme 2.36 – Deprotection of ligand **6f**

We moved our attention to the triflyl protected macrocycles, whose deprotection requires harsh conditions as well.[207,208] We followed two among the various procedures described in literature,[209,210] but they revealed to be ineffective on our target ligand **6o**: we allowed the macrocycle to reflux with $LiAlH_4$, as well as NaH in THF, but we never saw any results except for traces of monoprotected ligand (**scheme 2.37**).

[207] D. F. Taber, Y. Wang, *J. Am. Chem. Soc.* **1997**, *119*, 22–26
[208] S. Bozec-Ogor, V. Salou-Guiziou, J. J. Yaouanc, H. Handel, *Tetrahedron Lett.* **1995**, *36*, 6063–6066
[209] A.-M. Bàlint, A. Bodor, Á. Gömöry, K. Vékey, D. Szabò, J. Ràbai, *J. Fluor. Chem.* **2005**, *126*, 1524–1530
[210] M. C. De la Fuente, S. E. Pullan, I. Biesmans, D. Domìnguez, *J. Org. Chem.* **2006**, *71*, 3963–3966



Scheme 2.37 – Deprotection of ligand **6o**

These failures were the reason that prompted us to develop a new class of o-Nosyl protected macrocycles, as described in **section 2.1**.

We successfully synthesized and characterized ligands **6r, 6s** and **6t** (**figure 2.29**) in excellent overall yields.

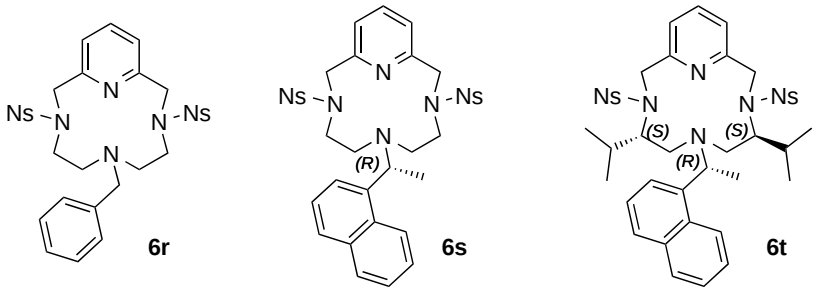
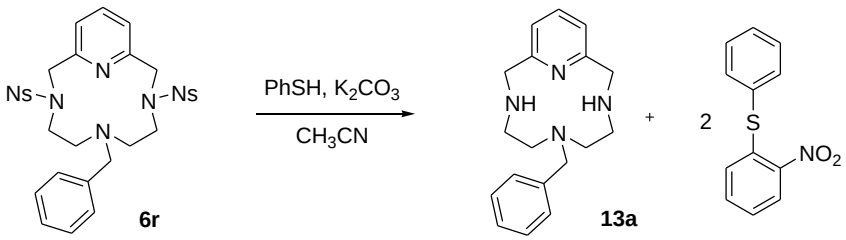


Figure 2.29 – Nosyl protected ligands

Concerning the deprotection of these ligands, we profitably employed the conditions reported by Fukayama:[211] we allowed our ligands to react with thiophenol in acetonitrile in the presence of K_2CO_3 as base. The base generates a thiolate anion that attacks the nosyl aromatic ring, forming a thioether and SO_2 as byproducts (**scheme 2.38**). It is important to notice that both the base and the solvent employed for this step are the same used for the macrocyclization reaction, it means that it could be possible to conduct the two steps in one pot.



Scheme 2.38 – Deprotection of ligand **6r**

[211] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374

By following the reaction course by TLC, we never observed the formation of other species different from the desired product and the thioether: the two nosyl moieties are removed with the same rate and it was impossible to isolate a monoprotected product under these conditions. The absence of starting material after the workup confirmed that the reaction proceeds quantitatively.

The purification of the crude revealed to be a crucial point, especially because the two -NH_2 moieties made chromatographic column unattractive.

As first purification method, we formed the hydrochloride of the ligands and we separated them from the impurities by precipitation, employing acetone as added solvent. The procedure worked well, but with a significant loss of yield due to the non-complete precipitation of the salt.

Better results were obtained by employing HOTf, that is soluble in the organic phase and it could cause the precipitation of the protonated ligand directly from dichloroethane solution.

The precipitated hydrochloride was then washed with dichloroethane, separated by centrifugation and, finally, deprotonated with a solution of NaOH 2M.

The final product was extracted from the aqueous solution through multiple washing with dichloromethane, in yield from 40 to 60%.

In this way, we obtained the ligands **13a, 13f** and **13h** (**figure 2.30**).

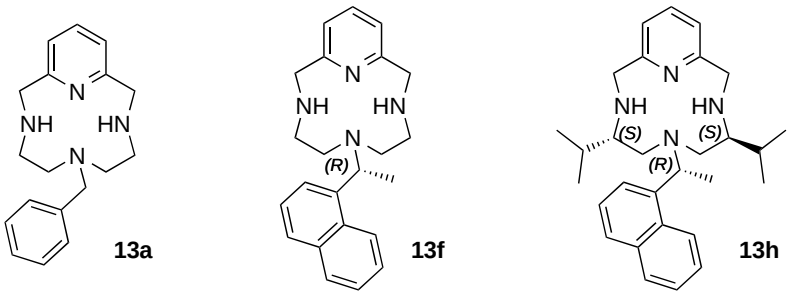


Figure 2.30 – Deprotected ligands

2.4.2 - Group 11 metals

2.4.2.1 - Copper

Since our best results were obtained with copper(I) complexes and the major part of our investigations were devoted to this metal ion, we started our studies of complexation of the new ligands, by reacting them with copper(I) salts. These studies have as primary task the comparison of the features between the protected and the deprotected ligands. The coordinative properties of the

two classes of compounds should be drastically affected by the difference of basicity between ligands **6** and ligands **13.**

We studied through ^{1}H-NMR spectroscopy the reactivity of **13a** with $[Cu(CH_3CN)_4]PF_6$ and $[Cu(OTf)]_2 \cdot C_6H_6$ salts. In order to prevent oxidation due to the contact with the air oxygen, the spectra of both the ligand and the complexes were registered under inert atmosphere.

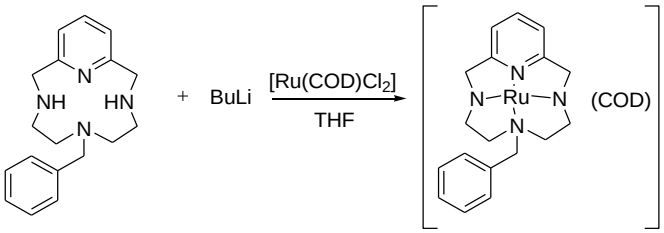
When we added the Cu(I) precursor to the solution of **13a** in $CDCl_3$, suddenly we noticed the change of the color of the solution from pale yellow to light blue in concert with the formation of a dark powder. We associated the color to the presence of Cu(II) ions – that made the NMR spectra totally unreadable – while the dark powder was doubtless Cu(0). The same behavior was shown with each copper(I) source. Also the experiments conducted with ligands **13f** and **13h** gave the same results. Hence, we understood that these ligands promote the disproportion of Cu(I), which confirm that its features are very different from those of the N-protected macrocycles.

We decided, therefore, to exploit the different coordination skills of these compounds, by focus our attention on metal ions from different groups.

2.4.3 - Group 8 metals

2.4.3.1 - Ruthenium

Our group has some experience for what concern the ruthenium chemistry,[212] for this reason we first investigated the reactivity between ligand **13a** and ruthenium(II), using $[Ru(COD)Cl_2]$ as metal source (**scheme 2.39**). We employed BuLi in order to obtain a lithium salt of the deprotonated ligand **13a**, to be reacted with the ruthenium source as dianionic ligand.



13a **14a**

Scheme 2.39 – Synthesis of Ru complex **14a**

[212] Recent advances: a) P. Zardi, A. Caselli, P. Macchi, F. Ferretti, E. Gallo, *Organometallics*, **2014**, *33*, 2210-2218; b) P. Zardi, A. Savoldelli, D. Carminati, A. Caselli, F. Ragaini, E. Gallo, *ACS Catalysis*, **2014**, *4*, 3820-3823

Bidimensional and coupled NMR experiments revealed the presence of two hydrogen atoms, not carbon bounded, coupling with protons of the ligand skeleton (**figures 2.31-32)**. The complex, hence, seemed to be the **14b** rather than **14a** (**figure 2.31**).

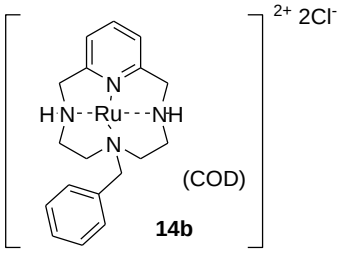
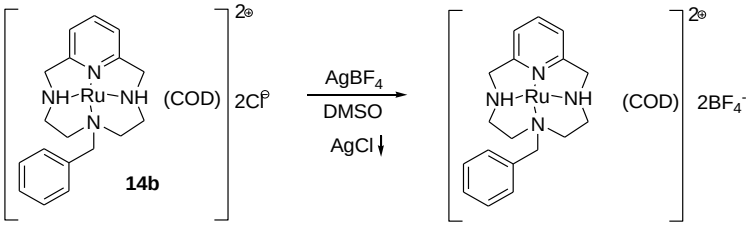


Figure 2.31 – Effective structure of Ru complex **14a**

This explanation rationalized the solubility of the complex that is extremely poor in organic solvent, while it is good in water and DMSO. Again, the molar conductivity of a 10^{-3}M solution of the complex in DMSO is a typical conductance of an ionic compound.

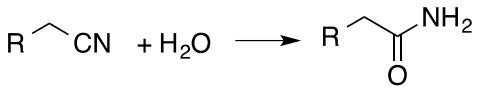
Finally, both the mass spectrum (MS-FAB) and the elemental analysis, confirmed the supposed structure. To verify the nature of the anion, we conducted an exchange reaction with $AgBF_4$ that conduced to the precipitation of silver chloride (**scheme 2.40**).



Scheme 2.40 – Exchange reaction between **14b** and $AgBF_4$

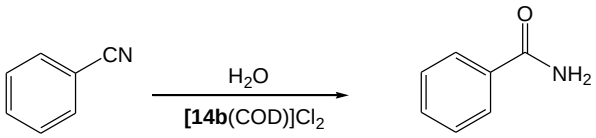
Because of the low solubility of the complex, no crystals suitable for X-Ray analysis were obtained, so we could not have the final evidence of our suppositions. Anyway, the reasons of such a behavior are still unknown: we confirmed the purity of the BuLi used and, by conducing the reaction in absence of the base, we noticed that it was possible to recover only the unreacted starting complex. This fact demonstrated that BuLi is anyway involved in the reaction mechanism, even if the ligand remains protonated. Studies, to understand this reactivity are still on course.

We started, then, to investigate the catalytic activity of complex **14b**, using this catalyst in the reaction of hydration of nitriles (**scheme 2.41**). Cadierno and co-workers developed a protocol that involves arene-Ru(II) complexes of P-donor ligands as catalyst and water as solvent and reactant, overcoming the use of organic solvent.[213] Subsequently, Ferrer et al. highlighted the activity of some ruthenium(II) complexes with N-donor ligand in the same reaction[214] and this discover inspired us in using our complex in this way.



Scheme 2.41 – Hydration of nitriles

We conducted, up to now, only a preliminary test on benzonitrile (**scheme 2.42**), using complex **14b** as catalyst. After 24 hours of reaction at 80°C in water, only a small amount of hydrated product was revealed by ^{1}H-NMR spectroscopy, suggesting a low activity of the catalyst.



Scheme 2.42 – Hydration of benzonitrile

2.4.3.2 - Iron

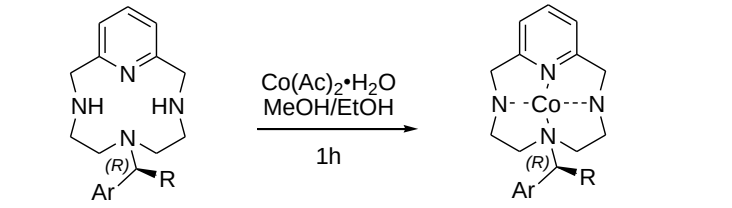
In collaboration with professor Grassi of the *Università degli Studi di Salerno*, we synthesize also iron(II) complexes. The solubility of these compounds, anyway, is so low that their characterization is really hard and their nature remains still uncertain.

[213] R. Garcia-Alvarez, M. Zabloka, P. Crochet, C. Duhayon, J.-P. Majoral, V. Cadierno, *Green Chem.*, **2013**, *15*, 2447-2456
[214] I. Ferrer, J. Rich, X. Fontrodona, M. Rodriguez, I. Romero, *Dalton Trans.*, **2013,** *42*, 13461-13469

2.4.4 - Group 9 metals

2.4.4.1 - Cobalt

At the same time, we moved our attention on another metal that our group is used to employ: cobalt.[48, 215] We conducted some studies on the affinity of ligands **13a** and **13f** with cobalt(II) ions, deriving from $Co(OAc)_2 \cdot 4H_2O$. We dissolved the ligands in EtOH and we added dropwise a solution of Co(II) salt in MeOH, then we allowed the reaction to reflux for one hour (**scheme 2.43**).



13a - Ar = Ph, R = H
13f - Ar = Naphthyl, R = Me

15a - Ar = Ph, R = H
15b - Ar = Naphthyl, R = Me

Scheme 2.43 – Synthesis of cobalt complexes of ligand **13a** and **13f**

The complexes **15a** and **15b** were recovered by crystallization in good yields. Crystals of complex **15a** suitable for X-Ray analysis (**figure 2.32**) were grown from a saturated alcoholic solution. The structure showed that the ligand binds the ion as cobalt acetate, forming hydrogen bonds with the NH moieties, leading to a distorted octahedral conformation. Mass spectrometry and elemental analysis confirmed the structure depicted by X-Ray, while, as easy to predict, the complex is highly paramagnetic and it is impossible to characterize it by NMR.

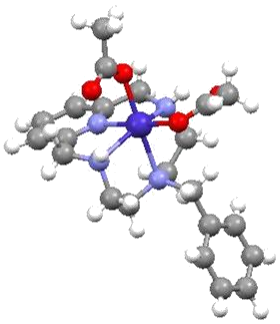
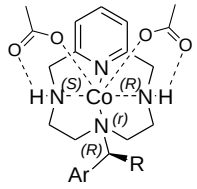


Figure 2.32 – X-Ray structure of complex **15a**

On the base of the results collected, we proposed an analogue structure for complex **15b (figure 2.33).**

[215] A. Caselli, E. Gallo, S. Fantauzzi, S. Morlacchi, F. Ragaini, S. Cenini, *Eur. J. Inorg. Chem.*, **2008**, 3009-3019



16a - Ar = Ph, R = H
16b - Ar = Naphthyl, R = Me

Figure 2.33 – Proposed structure for complexes **15a** and **15b**

Any trial to remove acetic acid from the molecule in solid failed. We kept the complex **16a** in vacuum at 110°C for 8 hours without any loss of weight and even a termogravimetric analysis (TGA) confirmed the stability of this specie, until the starting of a complete decomposition at very high temperature.

We made some conductivity test on 10^{-3}M solutions of **16a** in DMSO and water. The pH of the water solution resulted to be 4.5 and showed a conductivity of 8.2 μS, that is typical for ionic compounds; we supposed that, in water, a partial hydrolysis to give acetic acid occurs. For this reason, we treated the complex **16a** with a Na_2CO_3 solution in water to promote the removal of the acid, but we still did not manage to obtain a neutral cobalt(II) complex.

2.4.5 - Group 4 metals

2.4.4.1 - Zirconium

In collaboration with doctor Giambastiani from the Università degli Studi di Firenze, we obtained a structure of a Zr(IV) complex of ligand **13a** (**figure 2.34**). The complex was obtained starting from $Zr(NMe_2)_4$, the reaction was conducted in THF and allowed to obtain the product in quantitative yield. Unlike the previous complexes, in this zirconium complex the ligand is effectively a dianionic compound and no counterions are present. The macrocycle is strongly bent in order to let the zirconium assume a distorted octahedral conformation.

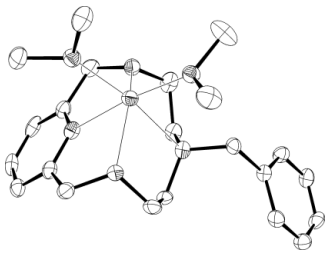
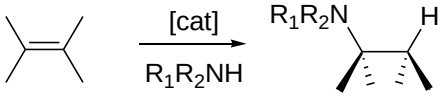


Figure 2.34 – Structure of Zr(IV) complex of ligand **13a**

This complex will be used as catalyst in hydroamination reaction, that represents a process of primary importance for the sustainable production of intermediates of synthetic and pharmacological interest. Such process, formally an addition of an N-H bond to an unsaturated substrate (**scheme 2.44**), represents a fundamental synthetic avenue to the intra- and intermolecular functionalization of inactivated molecules.



Scheme 2.44 – Hydroamination of alkene

Up to now, rare earth metal complexes are known to play a fundamental role in promoting the process. The scarcity of rare earths in commerce, the consequent high prices and the typically severe reaction conditions required have paved the way to the development of efficient catalytic systems based on group 4 metals.[216,217]

However , all these catalytic protocols do not yet exhibit the sustainability character (process and atom economy, catalyst efficiency, chemo-, region- and stereoselectivity) which a process of broad synthetic application should have.

[216] T. E. Muller, K. C. Hultzsch, M. Yus, F. Foubelo, M. Tada, *Chem. Rev.*, **2008,** *108,* 3795-3892
[217] L. Luconi, A. Rossin, A. Motta, G. Tuci, G. Giambastiani, *Chem.-Eur. J.*, **2013,** *19,* 4906-4921

2.5 Concluding Remarks

In conclusion, we synthesized and fully characterized a library of both non-chiral and chiral macrocycles bearing four nitrogen atoms with same donor properties, but having different symmetries (C_1, C_2 or C_{2v}). The adopted synthetic pathway is versatile and allows easy structural modifications in almost every part of the ligand. The steric and electronic features of these compounds could be easily modulated by employing different non expensive reactants. In particular, the starting aminoacids generally are easily available and naturally enantiopure. It is worth to note that their optical purity is maintained after every step of the synthetic route.

We formed copper and silver complexes with every ligand we synthesized, obtaining, with simple procedures, pure complexes in high yields. These compounds demonstrated to be stable and, at the same time, to readily react with other molecules, whereby they were evaluated to be suitable as catalysts.

Copper complexes were used as catalysts for asymmetric cyclopropanation reaction. We developed a catalytic protocol that allowed us to obtain the desired products from a wide range of substrates in mild condition, in good to excellent yields and with enantiomeric excesses up to 99%. Excellent results were also obtained when compounds bearing only a chiral substituent on the backbone were used as ligands. This class of ligands are easier to obtain and cheaper to synthesize. Further studies are devoted to optimize the ligand design so to increase the diastereoselection of the system.

At the same time, silver complexes were applied in the synthesis of iscromenes starting from propargylaldehydes and different primary and secondary alcohols. The catalytic system is characterized by absolute regioselectivity, very mild reaction conditions, excellent yields on different substrates and by the remarkable cleanness of the reaction, that allowed us to recover the products with reduced purification steps. We also investigated the reaction mechanism, by NMR studies and by trapping experiments, proposing with confidence a pathway that involves the formation of an isochromenilium intermediate.

We also used silver complexes as catalysts for A^3-coupling reaction, under both conventional and microwave heating. In both cases we demonstrated that our catalysts were effective, even if dielectric heating allowed a lower catalyst loading, reduced ratio among the reaction partners and shorter reaction times. The system showed a wide applicability on different secondary amines and some unprecedented propargylamines have been synthesized. The catalysts have been proven to

work also on more challenging substrates (as aromatic amines and ketones), although the results were only modest. However, this study represented the first example of A^3-coupling reaction catalyzed by tetra-aza marcocycle silver complexes.

For both the synthesis of isochromenes and the A^3-coupling reaction, we are working on the development of an enantioselective procedure.

Finally, a new class of deprotected ligands has been synthesized, starting from ortho-nosyl protected macrocycles. The synthetic pathway allowed us to easily obtain both achiral and chiral compounds in very high overall yields. In preliminary studies, these compounds have being used as ligands for ruthenium, cobalt, copper, iron and zirconium complexes, demonstrating to be very versatile towards a wide range of metals with very different electronic properties. X-ray structures showed that, depending on the metal ion used, our macrocycles act as both neutral and dianionic ligands. This features will be exploited for drastically expand the applicability of our ligands in the catalysis of organic reaction.

3. EXPERIMENTAL PART

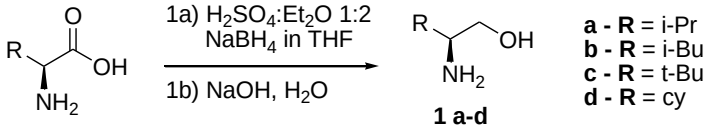
3.1 General procedures

NMR spectra were recorded on *Bruker Avance 300-DRX* and *Bruker Avance 400-DRX* spectrometers. The chemical shifts are reported in ppm relatively to TMS. The ^{1}H-NMR signals of the compounds have been assigned employing COSY and NOESY experiments. Assignments of the resonance in ^{13}C-NMR were made using APT pulse sequence and HSQC and HMBC experiments. Infrared spectra were recorded on a *BIO-RAD FTS-7* spectrophotometer. Elemental analyses and mass spectra were recorded in the analytical laboratories of Università degli Studi di Milano. GC-MS analyses were performed on a *Shimadzu GCMS-QP5050A* instrument. Data collections for the crystal structure determinations were carried out using a *Bruker Apex II* diffractometer with an *Agilent SuperNova* Mo microsource, Al[218] filtered and working at 50kV and 0.8 mA. All crystal structures were solved by direct methods using SHELXS97 and refined with SHELX97,[219] within the wings suite of programs.[220] H atoms were rigidly modeled on the riding C or N atoms. Optical rotations 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. HPLC analyses were performed on a *Hewlett-Packard 1050* instrument equipped with *DAICEL CHIRALCEL IB, OJ* and *AD* chiral columns. Unless otherwise specified, all the reactions were carried out in a N_2 atmosphere employing standard Schlenk techniques and magnetic stirring. Solvents were dried prior use by standard procedures and stored under N_2. α-Methylstyrene was distilled over CaH_2 and stored under N2. Copper(I) triflate benzene complex was synthesized following literature methods.[221] All other starting materials were commercial products and were used as received.

[218] P. Macchi, H.-B. Buergi, A. S. Chimpri, J. Hauser and Z. Gal, *Journal of Applied Crystallography*, **2011**, *44*, 763-771
[219] G. M. Sheldrick, *Acta Crystallographyca Section A; Foundations of Crystallography*, **2008,** *64*, 112-122
[220] L. J. Farrugia, *Journal of Applied Crystallography*, **1999**, *32*, 837-838
[221] K. M. Gillespie, C. J. Sanders, P. O'Shaughnessy, J. Westmoreland, C. P. Thickitt, P. Scott, *J. Org. Chem.* **2002**, *67*, 3450-3458

3.2 Synthesis

3.2.1 Aminoalcohols

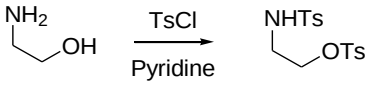


Aminoacid (100mmol) was added to a suspension of $NaBH_4$ (220mmol) in THF (100ml), at a temperature between 10 and 15°C. A chilled solution of H_2SO_4 conc. (6.6ml, 125mmol) and Et_2O (13.3ml) was carefully added monitoring the temperature. The solution was allowed to react overnight at room temperature, then MeOH (20ml) was carefully added drop by drop to destroy the unreacted $NaBH_4$ and the solution was concentrated to half the volume. The solution was diluted in 100mL of a 5N solution of NaOH in water and the volatile solvents were distilled away. Finally, the solution was allowed to reflux for three hours. The water layer was separated and the aminoalcohol was recovered as uncolored oil, concentrated in vacuum, and used without further purifications. The products were characterized by ^{1}H-NMR spectroscopy and the results are according with the tabulated data.

Yields	**L-valinol**	94%
	L-leucinol	97%
	L-t-leucinol	98%
	L-cycloexylglicinol	95%

3.2.2 Tosyl protected aziridines

2-tosyl ammine ethyl toluene sulfonate

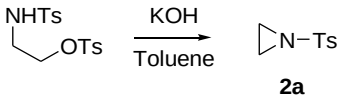


A solution of ethanolamine (12.1mL, 200.0 mmol) in pyridine (20 mL) was added dropwise to a suspension of tosyl chloride (80.26g, 421.0 mmol) in pyridine (50 mL) at -40 C°. The suspension was vigorously stirred for 2 hours at -10 C° then transferred in an ice bath. Ice was added to the suspension, the solid was filtered and washed with water, than it was dissolved in chloroform and washed again with water. The product obtained was recrystallized from ethanol as a yellow solid.

Yield 55%

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

N-tosyl ariziridine



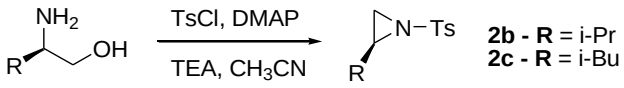
2a

The reaction was carried out in air. A solution of KOH (5.516g, 98.3 mmol) in water (30 mL) was added dropwise to a suspension of 2-tosyl ammine ethyl toluene sulfonate (10.651g, 28.8 mmol) in toluene (80 mL). 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 **2a**. (MW 197.25 g/mol).

Yield 88%

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

2-substituted N-tosyl ariziridine 2c-e

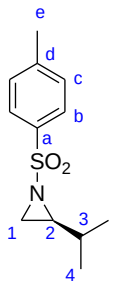


1 **2 b-c**

Aminoalcohol (30 mmol) was dissolved in CH_3CN dist. (125 ml) and TEA (120 mmol, 16.5 ml) was added. The solution was cooled to 0°C and tosylchloride (66 mmol) was added in four parts over one hour, followed by DMAP (3 mmol). The solution was allowed to react 20 hours at room temperature, then was concentrated, diluted with AcOEt and washed with brine (6x). The organic layer was anhydrified with Na_2SO_4, filtered, concentrated in vacuum to give the pure products as white powder. The products were characterized by ^{1}H-NMR spectroscopy and the results are according with the tabulated data.

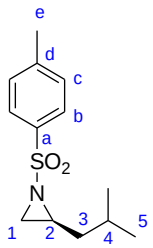
Yields **2b:** 97%

2c: 92%



2b

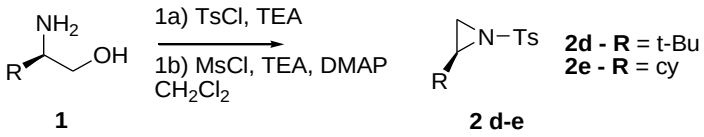
^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 7.83 (d, J = 8.6 Hz, 2H, H_b), 7.33 (d, J = 8.6 Hz, 2H, H_c), 2.61 (d, J = 7.0 Hz, 1H, H_1), 2.55-2.49 (m, 1H, H_2), 2.45 (s, 3H, H_e), 2.10 (d, J = 4.8 Hz, 1H, H_1), 1.42 (m, J = 7.0 Hz, 1H, H_3), 0.90 (d, J = 6.8 Hz, 3H, H_4), 0.80 (d, J = 7.0 Hz, 3H, H_4).



2c

^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 7.83 (d, J = 8.6 Hz, 2H, H_b), 7.33 (d, J = 8.6 Hz, 2H, H_c), 2.82-2.80 (m, 1H, H_2), 2.65 (d, J = 7.0 Hz, 1H, H_1), 2.46 (s, 3H, H_e), 2.05 (d, J = 4.6 Hz, 1H, H_1), 1.42 (hep, J = 6.6 Hz, 1H, H_4), 1.42-1.30 (m, 2H, H_3), 0.91 (d, J = 6.6 Hz, 3H, H_5), 0.90 (d, J = 6.6 Hz, 3H, H_5).

Aziridines 2d-e

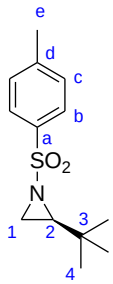


1 **2 d-e**

Aminoalcohol (26 mmol) and TEA (103 mmol) were dissolved in CH_2Cl_2 (75 ml) and the solution was cooled to 0°C then tosylchloride (28 mmol) was added. The solution was allowed to react at 0°C for 20 minutes, then for one hour at room temperature. The solvent was evaporated and AcOEt (100ml) was added. The solid residuals were filtered and solvent was evaporated. CH_2Cl_2 (75ml), TEA (103 mmol) and DMAP (26 mmol) were added and mesylchloride (52 mmol) was added dropwise. The solution became ever darker. After 2h30', the solvent was evaporated and AcOEt (150 ml) was added. The insoluble residuals were filtered and the product was obtained by concentrating the solution in vacuum. The products were characterized by ^{1}H-NMR spectroscopy.

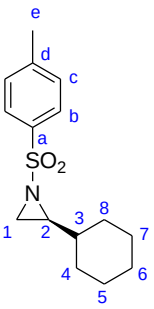
Yields **2d:** 88%

2e: 87%



2d

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 7.82 (d, J = 8.2 Hz, 2H, H_b), 7.32 (d, J 8.2, 2H, H_c), 2.55 (dd, J = 7.6 Hz, 4.4 Hz, 1H, H_2), 2.51 (d, J = 7.6 Hz, 1H, H_1), 2.44 (s, 3H, H_e), 2.16 (d, J = 4.4 Hz, 1H, H_1), 1.36 (1 H, s), 0.78 (s, 9H, H_4).



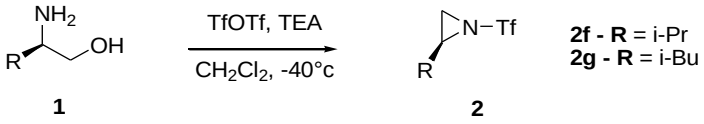
2e

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 7.85 (d, *J* = 8.1 Hz, 2H, H_b), 7.36 (d, *J* = 8.1 Hz, 2H, H_c), 2.62 (d, *J* = 7.0 Hz, 1H, H_1), 2.56 (ddd, *J* = 11.8, 6.0 Hz, 1H, H_2), 2.47 (s, 3H, H_e), 2.12 (d, *J* = 4.5 Hz, 1H, $H_{1'}$), 1.75-1.50 (b, 5H, H_{cy}), 1.25-0.90 (b, 6H, H_{cy})

^{13}C-NMR (75 MHz; $CDCl_3$) δ 144.78 (C_b), 135.52 (C_d), 129.97 (C_a), 128.46 (C_c), 45.52 (C_2), 37.74 (C_3), 33.01 (C_1), 30.55 (C_{cy}), 30.00 (C_{cy}), 26.40 (C_{cy}), 25.94 (C_{cy}), 25.75 (C_{cy}), 22.01 (C_e)

3.2.3 - Triflyl protected aziridines

Triflyl protected aziridines 2f-g

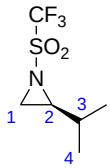


1 **2**

Triflic anhydride (35.3 mmol) was added dropwise to a solution of L-valinol (17.7 mmol) and distilled TEA (5 mL) 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.

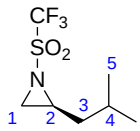
Yields **2f:** 67%

2g: 71%



2f

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 2.88 (m, 2H, $H_{1\text{-}2}$), 2.47 (d, J = 4.7 Hz, 1H, $H_{1'}$), 1.78 (m, 1H, H_3), 1.08 (d, J = 7.0 Hz, 3H, H_4), 1.05 (d, J = 7.1 Hz, 3H, H_4).

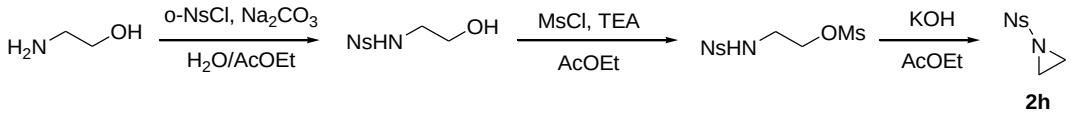


2g

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 3.11 (m, 1H, H_2), 2.92 (d, J = 7.0 Hz, 1H, $H_{1'}$), 2.41 (d, J = 5.8, 1H, H_1), 1.84 (m, 2H, H_3), 1.46 (m, 1H, H_4), 1.01 (d, J = 6.7 Hz, 3H, H_5), 1.00 (d, J = 6.6 Hz, 3H, H_5).

3.2.4 – Nosyl protected aziridines

o-Nosyl Aziridine



2h

Step 1

Ethanolamine (3 mL, 49.7 mmol) was added to a mixture of ethyl acetate (80 mL) and a solution of Na_2CO_3 (149.1 mmol) in water (200 mL). A solution of nosyl chloride (49.7 mmol) in ethyl acetate (40 mL) was added dropwise at 0°C. The reaction was left at room temperature for 4 hours and the product formation was evaluated with TLC chromatography (hexane:ethyl acetate = 4:6). The two layers were then separated, the organic phase was washed with brine, dried and evaporated. A slightly yellowish solid was obtained.

Yield 92%

^{1}H-NMR (300 MHz, $CDCl_3$, T = 300K) δ 8.17 (m, 1H), 7.80 (m, 1H), 7.89 (m, 2H), 5.80 (s, 1H), 3.78 (m, 2H), 3.28 (dd, J = 10.4, 5.8 Hz, 2H), 1.90 (s, 1H).

Step 2

Triethylamine (69.0 mmol) was added to a solution of 2-nosyl amino ethanol (34.6 mmol) in ethyl acetate (94 mL) and the reaction mixture was cooled to 15°C. Keeping the temperature between 15 and 18°C, a solution of mesyl chloride (34.6 mmol) in ethyl acetate (2.7 mL) was added dropwise, leading to the formation of abundant white precipitate. After the addition the flask was left at room temperature for 4 hours and the product formation was evaluated with TLC chromatography (hexane:ethylacetate = 6:4). The precipitate was then filtered away and the solvent was washed with brine, dried and evaporated. A white solid was obtained.

Yield: 95%

^{1}H-NMR (400 MHz, $CDCl_3$, T = 300K) δ 8.17 (dd, J = 5.8, 3.4 Hz, 1H), 7.96-7.86 (m, 1H), 7.86-7.72 (m, 2H), 5.89 (t, J = 5.7 Hz, 1H), 4.32 (t, J = 5.2 Hz, 2H), 3.52 (m, 2H), 3.04 (s, 3H).

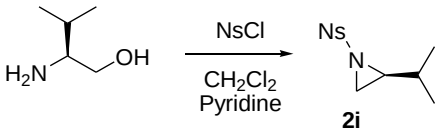
Step 3

KOH (28.5 mmol) in water (90 mL) was added to a solution of methanesulfonic acid 2-(2-nitrobenzenesulfonylamino) ethyl ester (28.5 mmol) in toluene (180 mL). The mixture was stirred for one hour, concentrated, diluted with ethyl acetate and the organic phase was washed with water and brine and dried over Na_2SO_4. The organic layer was concentrated and the crude was isolated as white solid.

Yield 80%.

^{1}H-NMR (400 MHz, $CDCl_3$, T = 300K) δ 8.20-8.19 (m, 1H), 8.18-8.17 (m, 3H), 7.83-7.81 (m, 1H), 2.61 (s, 4H)

Nosyl protected (S)-isopropyl aziridine

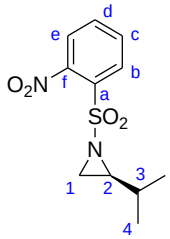


2i

L-Valinol (576.1 mg, 5.6 mmol) was added to a solution of dichloromethane (35 mL) and pyridine (14 mL) at 0°C. A solution of ortho-nosyl chloride (727.0 mg, 12.3 mmol) in dichloromethane (35 mL) was dropwise and the solution is allowed to react at 0°C for 4 hours.

The mixture is diluted with 70 mL of dichloromethane and then washed three times 2M HCl (3 x 25 mL). The aqueous layers were washed again with dichloromethane (3 x 25 mL) and the collected organic phases were washed with aqueous KOH (3 x 50 mL), treated with Na_2SO_4 and concentrated *in vacuo*.

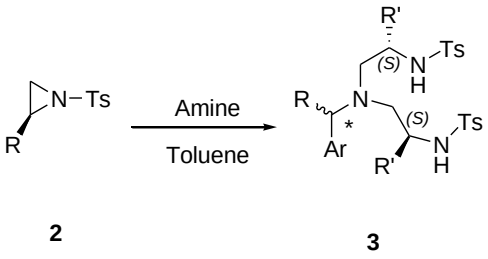
The crude was dissolved in dichloromethane (3 mL) and the pure product was obtained by precipitation, layering n-hexane on the solution. (**Yield:** 84%)



^{1}H-NMR (400 MHz, $CDCl_3$, T = 300K) δ 8.22 (d, J = 5.3 Hz, 1H, H_{Ar}), 7.79 – 7.74 (m, 3H, H_{Ar}), 2.85-2.84 (m, 2H, H_1), 2.35-2.34 (m, 1H, H_2), 1.61-1.59 (m, 1H, H_3), 0.99 (d, J = 6.7, 3H, H_4), 0.93 (d, J = 6.7, 3H, H_4)

3.2.5 – Bis-sulfonamides

Triazaheptanes 3a-j in toluene



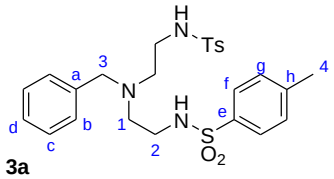
2 **3**

3a - **Ar =** Benzyl, **R** = H, **R'** = H
3b - **Ar =** Benzyl, **R** = (S)-Me, **R'** = H
3c - **Ar =** Benzyl, **R** = (R)-Me, **R'** = H
3d - **Ar =** Naphthyl, **R** = H, **R'** = H
3e - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = H
3f - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = H
3g - **Ar =** Naphthyl, **R** = H, **R'** = i-Pr
3h - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = i-Pr
3i - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = i-Pr
3j - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = i-Bu

A solution of **2** (7.3 mmol) and amine (3.3 mmol – see **table 3.1**) in toluene (20 mL) was stirred and refluxed for (see **table 3.1**). The mixture was dried and purified by column chromatography on silica using ethyl acetate:hexane = (see **table 3.1**) as eluant. Yields are reported in the **table 3.1**.

Table 3.1 – Reaction conditions for compounds 3a-j

Product	Amine	Reaction time	AcOEt:Hexane	Yield
3a	Benzylamine	4 hours	1:1	97%
3b	S-Benzylamine	4 hours	1:1	70%
3c	R-Benzylamine	4 hours	1:1	72%
3d	1- Naphthylmethylamine	5 hours	2:3	75%
3e	1-(S)-Napthylethylamine	10 hours	2:3	97%
3f	1-(R)-Napthylethylamine	10 hours	2:3	96%
3g	1- Naphthylmethylamine	5 hours	3:7	30%
3h	1-(R)-Napthylethylamine	220 hours	3:7	40%
3i	1-(S)-Napthylethylamine	220 hours	3:7	41%
3j	1-(R)-Napthylethylamine	220 hours	3:7	43%



3a

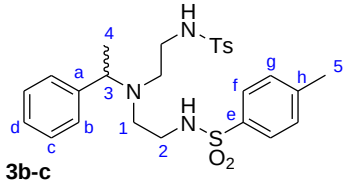
^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 7.73 (d, J = 8.0 Hz, 4H, H_f), 7.29 (d, J = 8.0 Hz, 4H, H_g), 7.27-7.25 (m, 3H, H_{Ar}), 7.13 (m, 2H, H_{Ar}), 5.17 (br s, 2H, NH), 3.44 (s, 2H, H_3), 2.95 (m, 4H, H_1), 2.57 (m, 4H, H_2), 2.42 (s, 6H, H_4)

^{13}C-NMR (100 MHz; $CDCl_3$; T = 300K) δ 143.8 (C_h), 138.2 (C_e), 137.1 (C_a), 130.2 (C_f), 129.3 (C_b), 128.9 (C_c), 127.8 (C_d), 127.5 (C_g), 58.8 (C_3), 53.6 (C_1), 41.0 (C_2), 21.9 (C_4)

Elem. an. found: C, 60.0; H, 6.2; N, 8.6%

calculated: C, 59.9; H, 6.2; N, 8.4%

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

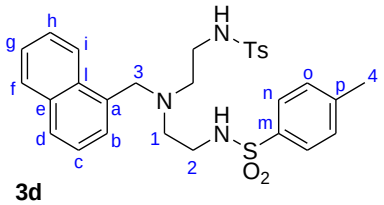


3b-c

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K): δ 7.72 (d, J = 8.4 Hz, 4H, H_f), 7.34–7.28 (m, 7H, H_g, H_b, H_c), 7.18–7.16 (m, 2H, $H_{b'}$, $H_{c'}$), 4.85 (brs, 2H, NH), 3.73 (q, J = 6.9 Hz, 1H, H_3), 2.88 (m, 4H, H_2), 2.61 (m, 2H, $H_{1'}$), 2.43 (m, 6H, H_5), 2.42 (m, 2H, H_1), 1.30 (d, J = 6.9 Hz, 3H, H_4).

^{13}C-NMR (100 MHz; $CDCl_3$; T = 300K): δ 143.9 (C), 137.2 (C), 136.7 (C), 130.3 (C_g), 128.8 (C_b), 128.4 (C_c), 127.8 (C_d), 127.55 (C_f), 58.8 (C_3), 50.5 (C_1), 41.6 (C_2), 21.9 (C_5), 21.5 (C_4).

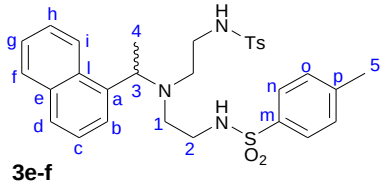
MS m/z 516.4 (M^+1), 538.4 (90 + Na), 1053.1 (100 2M + Na).



3d

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.14 (d, J = 8.3 Hz, 1H, H_i), 7.86 (d, J = 8.3 Hz, 1H, H_{Ar}), 7.78 (m, 1H, H_{Ar}), 7.54 (d, J = 8.0 Hz, 4H, H_n) overlapping with 7.61-7.49 (m, 2H, H_{Ar}), 7.42-7.32 (m, 2H, H_{Ar}), 7.19 (d, J = 8.0 Hz, 4H, H_o), 4.83 (bs, 2H, NH), 4.00 (br, 2H, H_3), 2.90 (m, 4H, H_1), 2.66 (m, 4H, H_2), 2.38 (s, 6H, H_4).

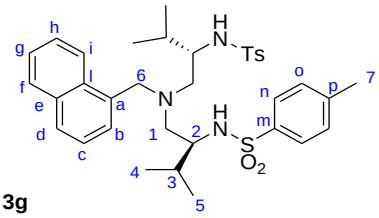
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 143.5 (C), 136.7 (C), 134.0 (C), 132.0 (C), 129.8 (CH), 129.0 (C_o), 127.1 (C_n), 126.3 (CH), 125.4 (CH), 123.7 (C_i), 54.2(CH_2), 40.8 (C_3), 21.6 (C_4). Signals relative to a quaternary carbon, three aromatic *C*H and a couple of CH_2 were not detected.



3e-f

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K): δ 8.36 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.86 (d, J = 7.5 Hz, 1H, H_n), 7.76 (m, 1H, H_c), 7.67 (m, 1H, H_{Ar}), 7.54 (m, 1H, H_{Ar}), 7.50 (d, J = 8.0 Hz, 4H, H_o), 7.41–7.40 (m, 2H, H_b), 7.24 (d, J = 8.0, 4H, H_{Ar}), 4.69 (q, J = 6.7, 1H, H_3), 4.63 (brs, 2H, NH), 2.82–2.71 (m, 2H, $H_{1'}$), 2.69 (m, 4H, H_2), 2.56 (m, 2H, H_1), 2.42 (s, 6H, H_5), 1.46 (d, J = 6.7 Hz, 3H, H_4).

^{13}C-NMR (100 MHz; $CDCl_3$; T = 300K) δ 143.2 (CH), 138.3 (C_h), 136.7 (C_a), 134.9 (CH), 133.9 (C_i), 131.6 (C_p), 129.7 (CH), 128.3 (C_c), 126.6 (C_o), 124.2 (CH), 57.1 (CH), 51.1 (C_3), 41.8 (C_i), 21.5 (C_5), 12.7 (C_4).



3g

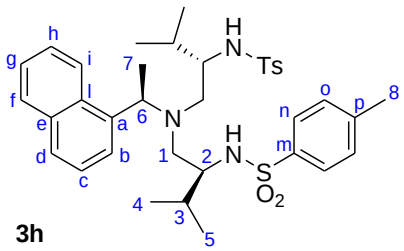
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.18 (d, J = 8.0 Hz, 1H, H_i), 7.85-7.76 (m, 2H, H_d, H_f), 7.75 (d, J = 8.2 Hz, 4H, H_n), 7.51-7.38 (m, 3H, H_c, H_h, H_g), 7.34 (d, J = 8.0 Hz, 1H, H_b), 7.23 (d, J = 8.2 Hz, 4H, H_o), 4.99 (d, J = 6.0 Hz, 2H, NH), 4.04 (d, J = 13.1, 1H, H_6), 3.80 (d, J = 13.1 Hz, 1H, $H_{6'}$), 3.45 (m, 2H, H_2), 2.55-2.35 (m, 4H, H_1), overlapping with 2.38 (s, 6H, CH_7), 1.79 (m, 2H, H_3), 0.53 (d, J = 6.9 Hz, 6H, CH_4), 0.52 (J = 6.9 Hz, 6H, CH_5).

^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 143.2 (C), 138.6 (C), 133.9 (C), 132.2 (C), 129.6 (C_n), 128.6 (CH), 128.2 (CH), 127.1 (C_o), 126.3 (CH), 125.8 (CH), 125.3 (CH), 124.3 (C_i), 56.9 (C_6), 55.9 (C_2), 54.9 (C_1), 29.3 (C_3), 21.6 (C_7), 17.9 (C_4), 16.9 (C_5). A signal relative to a quaternary carbon was not detected.

Elem. An. Found: C, 66.3; H, 7.2; N, 6.3%
Calculated: 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 $CHCl_3$)



3h

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 7.94 (m, 1H, H_i) 7.79(d, J = 8.0 Hz, 4H, H_n) overlapping with 7.79 (m, 1H, H_{Ar}), 7.73 (dd, J = 5.8 Hz, J = 3.4 Hz, 1H, H_{Ar}), 7.45-7.42 (m, 2H, H_{Ar}), 7.40-7.39 (m, 2H, H_{Ar}), 7.29 (d, J = 8.0 Hz, 4H, H_o), 4.66 (d, J = 7.9 Hz, 2H, NH), 4.59 (q, J = 6.6 Hz, 1H, H_6), 3.26 (m, 1H, H_2), 2.46 (dd, J = 13.4 Hz, J = 5.1 Hz, 2H, H_1), 2.41 (s, 6H, H_8), 1.55 (m, 2H, H_3), 1.20 (d, J = 6.6 Hz, 3H, H_7) 0.56 (d, J = 6.9 Hz, 6H, H_4), 0.19 (d, J = 6.8 Hz, 6H, H_5).

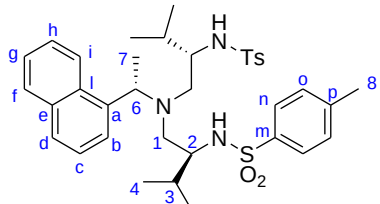
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 143.4 (C), 138.2 (C), 138.0 (C), 134.1 (C), 132.1 (C), 129.7 (C_n), 128.8 (CH), 128.2 (CH), 127.3 (C_o), 125.6 (CH), 125.5 (CH), 125.1 (CH), 125.0 (CH), 123.9 (CH), 56.6 (C_2), 53.6 (C_6), 52.3 (C_1), 27.6 (C_3), 21.6 (C_8), 19.3 (C_4), 14.8 (C_5), 12.4 (C_7).

^{15}N-NMR (40 MHz; $CDCl_3$; T = 300K) δ 94.0 (*N*HTs), 38.3 (*N*HC_6).

Elem. An. Found: C, 66.6; H, 7.6; N, 6.5%

Calculated: C, 66.5; H, 7.3; N, 6.5%

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



3i

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.73 (d, J = 8.2 Hz, 1H, H_i), 7.73 (d, J = 7.8 Hz, 2H, H_{Ar}), 7.70 (d, J = 8.3 Hz, 4H, H_n), 7.56 (pt, J = 8.2 Hz, 1H, H_{Ar}), 7.43-7.37 (m, 2H, H_{Ar}), 7.29 (m, 1H, H_{Ar}), 7.24 (d, J = 8.3 Hz, 4H, H_o), 5.36 (d, J = 5.4 Hz, 2H, NH), 5.13 (q, J = 6.5 Hz, 1H, H_6), 3.68 (m, 2H, H_2), 2.48-2.42 (m, 4H, H_1), overlapping with 2.42 (s, 6H, H_8), 1.76 (m, 2H, H_3), 1.48 (d, J = 6.5 Hz, 3H, H_7), 0.68 (d, J = 7.0 Hz, 6H, H_4), 0.35 (d, J = 7.0 Hz, 6H, H_5)

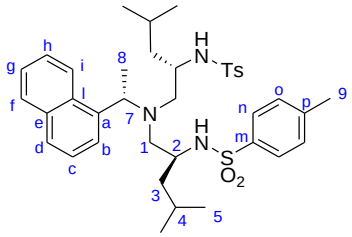
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 143.0 (C_p), 139.3 (C), 137.9 (C), 134.1 (C), 131.7 (C), 129.5 (C_n), 128.4 (CH), 127.4 (CH), 127.1 (C_o), 125.9 (CH), 125.2 (CH), 124.9 (CH), 124.6 (CH), 54.7 (C_2), 53.3 (C_6), 48.1 (C_1), 29.6 (C_3), 21.7 (C_8), 18.0 (C_4), 15.9 (C_5), 11.1 (C_7). A signal relative to an aromatic carbon was not detected.

Elem. An. Found: C, 66.4; H, 7.3; N, 6.7%

Calculated: 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 $CHCl_3$).



3j

^{1}H-NMR (300 M*Hz*; $CDCl_3$) 8.02 (dd, *J* = 6.1, 3.4 Hz, 1H, H_h), 7.84-7.82 (m, 1H, H_{Ar}), 7.81 (d, *J* = 8.1 Hz, 4H, H_m), 7.77–7.74 (m, 1H, H_{Ar}), 7.46 (dd, *J* = 6.3, 3.2 Hz, 2H, H_{Ar}), 7.44 – 7.41 (m, 2H, H_{Ar}), 7.32 (d, *J* = 8.1 Hz, 4H, H_o), 4.70 (q, *J* = 6.6 Hz, 1H, H_7) 4.65-4.61 (m, 2H, NH), 3.29 (b, 2H, H_2), 2.70 (dd, *J* = 13.4, 5.3 Hz, 2H, H_1), 2.44 (s, 6H, H_9), 2.36 (dd, *J* = 13.4, 8.0 Hz, 2H, $H_{1'}$), 1.33 (d, *J* = 6.6 Hz, 3H, H_8), 1.28 (m, 2H, H_4), 0.93 (ddd, J = 13.8, 9.2, 4.6 Hz, 2H, H_3), 0.70 (ddd, *J* = 14.1, 9.1, 4.8 Hz, 2H, $H_{3'}$), 0.51 (d, J = 6.3 Hz, 6H, $H_{5,6}$), 0.50 (d, J = 6.4 Hz, 6H, $H_{5',6'}$).

^{13}C-NMR (75 MHz; CDCl3) δ 143.66 (C_p), 138.67 (C_m), 138.58 (C_a), 134.30 (C_l), 132.60 (C_e), 129.99 (C_o), 129.19 (CH), 128.32 (CH), 127.56 (C_n), 126.26 (CH), 125.80 (C_h), 125.31 (CH), 125.24 (CH), 124.08 (CH), 57.52 (C_1), 54.25 (C_7), 51.05 (C_2), 43.28 (C_3), 24.57 (C_4), 23.31 ($C_{5,6}$), 21.96 ($C_{5',6'}$), 21.89 (C_9), 14.46 (C_8).

Synthesis of bis-sulfonamides 3h and 3j in methanol

Aziridine **2** (2.7mmol) was dissolved in MeOH (0.9 mL) and 1-(R)-Naphthylethylamine was added. The solution was allowed to react to reflux for 24 hours. The crude was obtained by concentrating the solution in vacuo and purified by chromatographic column (Hexane:AcOEt = 7:3).

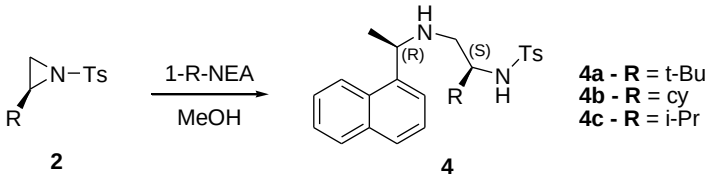
Yield **3h:** 82%

3j: 79%

NMR are according with those registered for compounds **3h** and **3j** synthesized with the previous procedure.

3.2.6 – Mono-sulfonamides

Synthesis of sulfonamides 4a-c

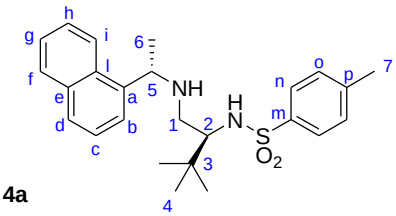


Aziridine **2** (12.9 mmol) was dissolved in MeOH (4.2 ml) and 1-(R)-naphthylethylamine (13.2 mmol) is added. The solution was allowed to react to reflux for 8 hours. The crude was is obtained by concentrating the solution in vacuum and was purified, if needed, by chromatographic column (Hexane:AcOEt = 7:3).

Yields **4a:** 95%

4b: 93%

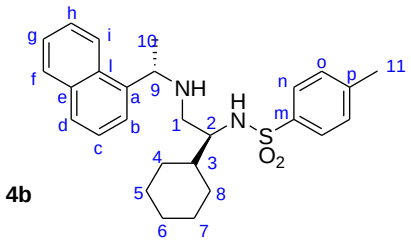
4c: 71%



4a

^{1}H-NMR (400 M*Hz*; $CDCl_3$, 300 K) δ 8.02 (d, *J* = 7.9 Hz, 1H, H_h), 7.89-7.87 (m, 1H, H_{Ar}), 7.84 (d, *J* = 8.2 Hz, 2H, H_n), 7.76 (d, *J* = 8.1 Hz, 1H, H_{Ar}), 7.55-7.46 (m, 2H, H_{Ar}), 7.41 (d, *J* = 6.9 Hz, 1H, H_{Ar}), 7.29 (d, *J* = 8.1 Hz, 2H, H_o), 5.05 (b, 1H, NH), 4.37 (b, 1H, H_5), 3.16 (dd, *J* = 4.8 Hz, 5.7 Hz, 1H, H_2), 2.52-2.43 (m, 2H, H_1), 2.41 (s, 3H, H_7), 1.37 (d, *J* = 6.3 Hz, 3H, H_6), 0.79 (s, 9H, H_4). One NH signal is too broad to be detected.

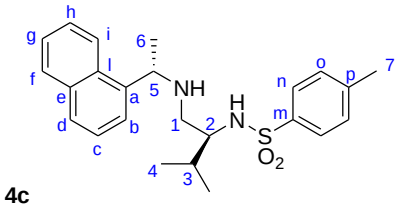
^{13}C-NMR (100 MHz; $CDCl_3$, 300 K) δ 143.27 (C_p), 138.43 (C_m), 133.95 (C_{Ar}), 131.12 (C_{Ar}), 129.62 (C_n), 129.04 (C_{Ar}), 127.44 (C_{Ar}), 127.19 (C_o), 125.95 (C_{Ar}), 125.66 (C_{Ar}), 125.50 ($C_{naphthyl}$), 122.58 (C_h), 122.44 (C_{Ar}), 61.78 (C_2), 53.72 (C_5), 47.59 (C_1), 34.61 (C_3), 26.98 (C_4), 23.52 (C_6), 21.49 (C_7).



4b

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) 8.03-8.00 (m, 1H, H_h), 7.89 (m, 1H, H_{Ar}), 7.78-7.75 (m, 3H, H_n and H_{Ar}), 7.52 (m, 4H, H_{Ar}), 7.27 (2H, d, J = 8.2 Hz, H_o), 5.09 (b, 1H, NH), 4.38 (pd, 1H, *J* = 6.4 Hz, H_9), 3.07 (pd, *J* = 4.5 Hz, 1H, NH), 2.51-2.37 (m, 3H, H_1 and H_2), 2.42 (3H, s, H_{11}), 1.68-1.58 (5H, m), 1.51-1.47 (m, 1H), 1.38 (3H, d, J = 6.5 Hz, H_{10}), 1.14-1.01 (m, 3H), 0.85-0.76 (m, 2H)

^{13}C-NMR (100 M*Hz*; $CDCl_3$) δ 143.18 (C_p), 140.18 (C_a), 137.98 (C_m), 133.97 (C_l), 131.13 (C_e), 129.56 (C_n), 129.03 (C_{Ar}), 127.49 (C_{Ar}), 127.16 (C_o), 125.93 (C_{Ar}), 125.59 (C_{Ar}), 125.52 (C_{Ar}), 122.66 (C_h), 122.55 (C_{Ar}), 58.17 (C_2), 53.35 (C_9), 47.31 (C_1), 40.14 (C_3), 29.24 (C_{cy}), 28.85 (C_{cy}), 26.19 (C_{cy}), 26.09 (C_{cy}), 26.03 (C_{cy}), 23.24 (C_{10}), 21.49 (C_{11})

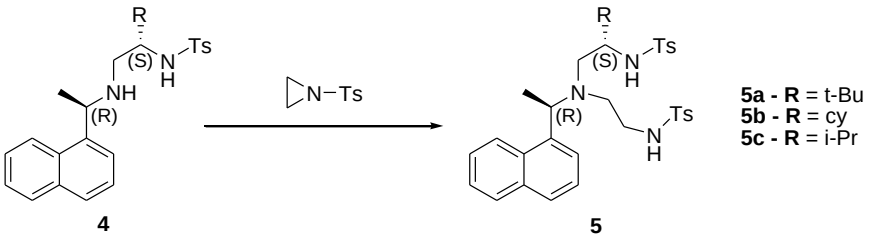


4c

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.03 (m, 1H, H_i), 7.89 (m, 1H, H_{Aryl}), 7.78 (d, J = 8.4 Hz, 2H, H_n) overlapping with 7.79-7.75 (m, 1H, H_{Aryl}) 7.52-7.45 (m, 4H, H_{Aryl}), 7.25 (d, J = 8.4 Hz, 2H, H_o), 5.22 (br, 1H, NH), 4.35 (q, J = 6.6 Hz, 1H, H_5), 3.08 (m, 1H, H_2), 2.46-2.42 (m, 2H, H_1), 2.40 (s, 3H, H_7), 1.85 (dh, J = 13.4 Hz, J = 6.8 Hz, 1H, H_3), 1.36 (d, J = 6.6 Hz, 3H, H_6), 0.81 (d, J = 6.8 Hz, 3H, H_4), 0.78 (d, J = 6.8 Hz, 3H, H_4) One NH signal is too broad to be detected.

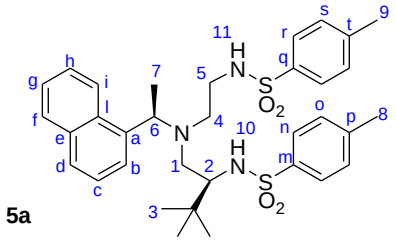
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 143.2 (C_{Aryl}), 140.8 (C_{Aryl}), 138.2 (C_{Aryl}), 134.1 (C_{Aryl}),131.3 (C_{Aryl}),129.6 (C_o), 129.1 (C_{Aryl}),127.4 (C_{Aryl}), 127.2 (C_{Aryl}), 125.9 (C_{Aryl}), 125.7 (C_{Aryl}), 125.5 (C_{Aryl}), 122.8 (C_i),122.6 (C_{Aryl}), 59.0 (C_2), 53.3 (C_6), 47.4 (C_1), 30.4 (C_3), 23.5 (C_7), 21.5 (C_8), 18.8 (C_4), 18.4 (C_5).

3.2.7 – Monosubstituted bis-sulfonamides



4 5

Monoamine **4** (0.33mmol) was dissolved in MeOH (1ml) and N-Ts aziridine (0.33mmol) was added. The solution was allowed to react to reflux for 16 hours. The crude was obtained by concentrating the solution *in vacuo* and purified by chromatographic column (Hexane:AcOEt = 7:3).



5a

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.18 (d, *J* = 8.4 Hz, 1H, H_h), 7.87-7.82 (m, 5 H, H_n, H_r, H_{Ar}), 7.76 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.56-7.51 (m, 2H, H_{Ar}), 7.51-7.45 (m, 2H, H_{Ar}), 7.33-7.27 (m, 4H, H_o, H_s), 6.31 (b, 1H, NH_{11}), 4.84 (q, *J* = 6.8 Hz, 1H, H_6), 4.45 (d, *J* = 8.1 Hz, 1H, NH_{10}), 3.42-3.38 (m, 1H, H_2), 3.07-3.02 (m, 1H, H_5), 2.99-2.91 (m, 2H, H_5, H_4), 2.75-2.68 (m, 2H, H_4, H_1), 2.44 (s, 6H, H_8, H_9), 2.42-2.39 (m, 1H, H_1), 1.52 (d, *J* = 6.8 Hz, 3H, H_7), 0.54 (s, 9H, H_3).

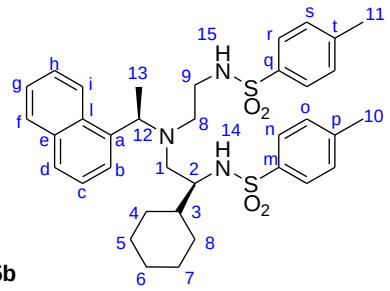
^{13}C-NMR (75 M*Hz*; C_6D_6; T = 300K) δ 143.32 (C_p, C_t), 139.55 (C_m), 139.46 (C_a), 137.84 (C_q), 134.24 (C_l), 132.33 (C_e), 129.92 (C_o), 129.83 (C_s), 129.21 (CH), 127.93 (CH), 127.59 (C_n), 127.43 (C_r), 126.56 (CH), 125.90 (CH), 125.64 (CH), 124.93 (CH), 123.82 (C_h), 62.41 (C_2), 55.17 (C_6), 54.20 (C_1), 51.27 (C_4), 42.11 (C_5), 34.90 (C), 27.81 (C_3), 27.33 (C_3), 27.01 (C_3), 21.90 (C_8, C_9), 20.00 (C_7)

Elem. An. Found: C, 65.41; H, 7.10; N, 6.71%

Calculated: C, 65.67; H, 6.97; N, 6.76%

$[\alpha]_D^{20}$ -15.41 (in $CHCl_3$)

MS m/z 725.4 (M^+1), 747.5 (M^+Na)



5b

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 8.13 (d, *J* = 8.3 Hz, 1H, H_h), 7.86 (d, *J* = 7.3 Hz, 1H, H_{Ar}), 7.77 (dd, *J* = 5.5 Hz, 3.9 Hz, 1H, H_{Ar}), 7.73 (d, *J* = 8.2 Hz, 2H, H_n), 7.64 (d, *J* = 8.2 Hz, 2H, H_r), 7.57-7.52 (m, 1H, H_{Ar}), 7.53-7.48 (m, 1H, H_{Ar}), 7.42-7.40 (m, 1H, H_{Ar}), 7.41 (s, 1H, H_{Ar}), 7.28 (m, 4H, H_o, H_s), 4.93 (t, *J* = 5.5 Hz, 1H, H_{15}), 4.63 (q, *J* = 6.6 Hz, 1H, H_{12}), 4.46 (d, *J* = 7.9 Hz, 1H, H_{14}), 3.07 (m, 1H, H_2), 3.03-2.98 (m, 1H, H_9), 2.91-2.83 (m, 1H, H_9), 2.83-2.76 (m, 1H, H_8), 2.70-2.64 (m, 1H, H_8), 2.53 (dd, *J* = 13.3, 8.4 Hz, 1H, H_1), 2.43 (s, 6H, H_{10}, H_{11}), 2.38 (dd, *J* = 13.3, 5.8 Hz, 1H, H_1), 1.39 (d, *J* = 6.6 Hz, 3H, H_{13}), 1.44 (m, 1H, H_7), 1.36 (m, 1H, H_6), 1.23 (m, 1H, H_5), 1.05 (m, 1H, H_8), 0.99 (m, 1H, H_3), 0.77-0.73 (m, 2H, H_7, H_6), 0.63 (m, 1H H_8), 0.56 (m, 1H, H_4), 0.39 (ddd, *J* = 3.1, 12.1 Hz, 1H, H_4), 0.19 (m, 1H, H_5)

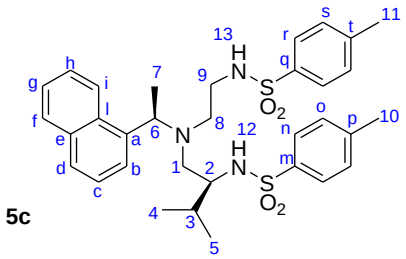
^{13}C-NMR (100 MHz; $CDCl_3$, T = 300K) δ 143.28 (C_p), 143.14 (C_t), 138.01 (C_a), 137.86 (C_m), 137.15 (C_q), 134.07 (C_l), 131.84 (C_e), 129.60 (C_o), 129.57 (C_s), 128.97 (CH), 128.20 (CH), 127.18 (C_m), 127.03 (C_r), 126.23 (CH), 125.71 (CH), 124.94 (CH), 124.75 (CH), 123.60 (C_h), 57.23 (C_2), 55.51 (C_{12}), 52.58 (C_1), 51.55 (C_8), 41.45 (C_9), 38.09 (C_3), 29.41 (C_{cy}), 26.17 (C_{cy}), 28.08 (C_{cy}), 25.97 (C_{cy}), 25.66 (C_{cy}), 21.50 (C_{10}, C_{11}), 12.92 (C_{13})

Elem. An. Found: C, 66.91; H, 6.88; N, 6.37%

Calculated: C, 66.74; H, 7.00; N, 6.49%

$[\alpha]_D^{20}$ -13.18 (in $CHCl_3$)

MS m/z 670.6 (M^+Na)



5c

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.08 (d, J = 8.2 Hz, 1H, H_i) 7.85 (m, 1H, H_f), 7.77 (m, 1H, H_c), 7.71 (d, J = 8.2 Hz, 2H, H_n),7.59 (d, J = 8.2 Hz, 2H, H_r),7.52 (m, 2H, H_g, H_h), 7.42 (m, 2H, H_b, H_d) 7.28-7.24 (m, 4H, H_o, H_s), 4.82 (m, 1H, NH_{13}), 4.63 (q, J = 6.6 Hz, 1H, H_6), 4.30 (d, J = 7.5 Hz, 1H, NH_{12}), 3.14 (m, 1H, H_2), 2.83 (m, 2H, H_9, $H_{9'}$), 2.70 (m, 2H, H_8, $H_{8'}$), 2.46 (m, 2H, H_1, $H_{1'}$), 2.42 (br, 6H, H_{10}, H_{11}), 1.40 (d, J = 6.6 Hz, 3H, H_7) overlapping with 1.41-1.39 (m, 1H, H_3), 0.44 (d, J = 6.9 Hz, 6H, H_4), 0.17 (d, J = 6.8 Hz, 6H, H_5).

^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) 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), 129.7 (C_o), 129.1 (C_f), 128.4 (CH), 127.3 (C_r), 127.2 (C_n), 126.4 (CH), 125.9 (CH), 125.2 (CH), 124.9 (CH), 123.7 (C_i), 57.4 (C_2), 55.7 (C_6), 53.5 (C_1), 51.4 (C_8), 41.6 (C_9), 28.4 (C_3), 21.7 ($C_{11,10}$), 18.6 (C_4), 15.6 (C_5), 14.0 (C_7).

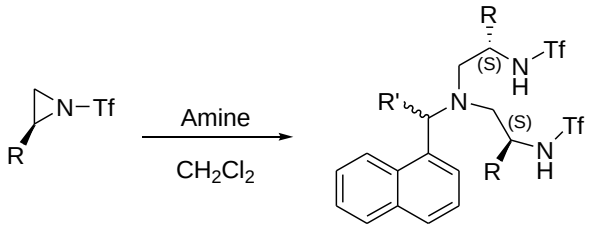
Elem. An. Found: C, 65.61; H, 7.02; N, 6.58%

Calculated: 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)

3.2.8 - Tf-protected bis-sulfonamides

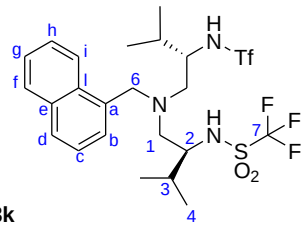


2 **3**

3k - **R** = i-Pr, **R'** = H, **PG** = Tf
3l - **R** = i-Pr, **R'** = (R)-Me, **PG** = Tf
3m - **R** = i-Pr, **R'** = (S)-Me, **PG** = Tf
3n - **R** = i-Bu, **R'** = (R)-Me, **PG** = Tf

A solution of amine (4.0 mmol – see **table 3.2**) in distilled CH_2Cl_2 (10 mL) was added dropwise to a solution of aziridine **2** in distilled CH_2Cl_2 (20 mL) at -40°C. After 30 minutes the solution was carried to room temperature. A white suspension immediately formed. The reaction was allowed to stir for (**see table 3.2**) and was followed by TLC. When the reaction was completed, the suspension was filtered off, the crude was recovered by concentrating the solution and was purified by (**see table 3.2**).

Product	Amine	Reaction time	Purification	Yield
3k	1- Naphthylmethylamine	48 hours	Crystallization	55%
3l	1-(R)-Naphthylethylamine	90 hours	Column (Hexane:AcOEt = 7:3)	89%
3m	1-(S)-Naphthylethylamine	90 hours	Column (Hexane:AcOEt = 7:3)	87%
3n	1-(R)-Naphthylethylamine	90 hours	Column (Hexane:AcOEt = 7:3)	82%



3k

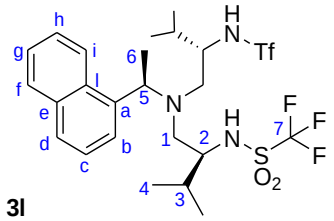
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.14 (d, J = 8.1 Hz, 1H, H_i), 7.86 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.81 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.58-7.42 (m, 4H, H_{Ar}), 5.04 (br, 2H, NH), 4.21 (d, J = 13.2 Hz, 1H, H_6), 4.05 (d, J = 13.2 Hz, 1H, $H_{6'}$), 3.61 (m, 2H, H_2), 2.72-2.58 (m, 4H, H_1), 1.92 (m, 2H, H_3), 0.81 (d, J = 6.9 Hz, 6H, H_4), 0.65 (d, J = 6.9 Hz, 6H, H_5).

^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 134.1 (C), 133.1 (C), 132.2 (C), 128.9 (CH), 128.8 (CH), 128.6 (CH), 126.5 (CH), 126.1 (CH), 125.4 (CH), 123.9 (C_i), 119.5 (C_7, q, J = 321 Hz), 58.7 (C_2), 57.0 (C_6), 56.2 (C_1), 29.4 (C_3), 18.4 (C_4), 16.6 (C_5).

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

Elem. An. Found: C, 46.6; H, 5.4; N, 7.1%

Calculated: C, 46.7; H, 5.3; N, 7.1%.



3l

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.01 (d, J = 9.4 Hz, 1H, H_i), 7.85 (d, J = 9.4 Hz, 1H, H_{Ar}), 7.80 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.54-7.48 (m, 3H, H_{Ar}), 7.46 (pst, J = 7.4 Hz, 1H, H_{Ar}), 4.88 (q, J = 6.5 Hz, 1H, H_6), 4.68 (br, 2H, NH), 3.56 (m, 2H, H_2), 2.75 (dd, J = 13.5 Hz, J = 4.9 Hz, 2H, H_1), 2.63 (dd, J = 13.5 Hz, J = 9.7 Hz, 2H, $H_{1'}$), 1.70 (m, 2H, H_3), 1.57 (d, J = 6.7 Hz, 3H, H_7) 0.88 (d, J = 6.9 Hz, 6H, H_4), 0.31 (d, J = 6.8 Hz, 6H, H_5).

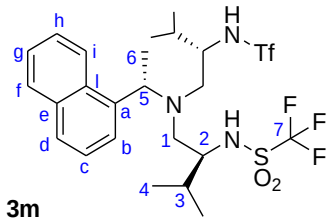
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 137.4 (C), 134.3 (C), 132.1 (C), 129.1 (CH), 128.7(CH), 125.9 (CH), 125.8 (CH), 125.3 (CH), 125.1 (CH), 123.5 (C_i), 119.6 (C_8, q, J = 321 Hz), 59.2 (C_2), 53.9 (C_6), 53.2(C_1), 27.7 (C_3), 19.5 (C_4), 14.6 (C_5), 12.4 (C_7).

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

Elem. An. Found: C, 47.4; H, 5.8; N, 6.6%

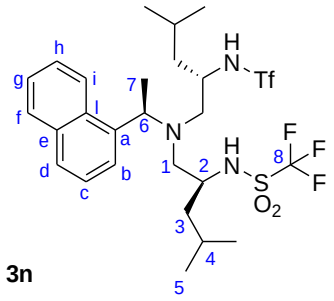
Calculated: C, 47.6; H, 5.5; N, 6.9%.

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



3m

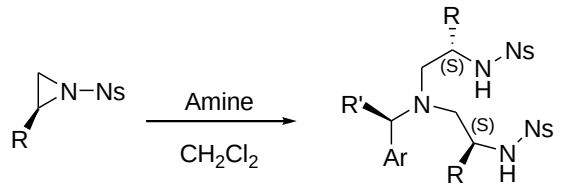
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.34 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.88 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.84 (d, J = 7.8 Hz, 1H, H_{Ar}), 7.65 (dd, J = 7.0 Hz, 1H, H_{Ar}), 7.56 – 7.47 (m, 3H, H_{Ar}), 4.95 (q, J = 6.6 Hz, 1H, H_5), 4.92 (br, 1H, NH), 3.55 (m, 2H, H_2), 2.71-2.58 (m, 4H, H_1), 2.06-2.02 (m, 2H, NH), 1.57 (d, J = 6.6 Hz, 3H, H_6), 1.03 (m, 2H, H_3), 0.82 (d, J = 6.9 Hz, 6H, H_4), 0.56 (d, J = 6.8, 6H, H_4)



3n

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.12 (d, J = 7.77 Hz, 1H, H_{Ar}), 7.90-7.87 (m, 1H, H_{Ar}), 7.82 (d, J = 7.1 Hz, H_{Ar}), 7.55-7.47 (m, 4H, H_{Ar}), 4.94 (q, J = 6.8 Hz, 1H, H_6), 3.67-3.60 (m, 2H, H_2), 2.88 (dd, J = 13.5, 4.7 Hz, 2H, H_1), 2.57 (dd, J = 13.6, 8.4 Hz, 2H, H_1), 1.61-1.54 (m, 4H, H_3), 1.59 (d, J = 6.8 Hz, 3H, H_7), 1.13 (m, 2H, H_4), 0.85 (d, J = 6.5 Hz, 6H, H_5), 0.67 (d, J = 6.6 Hz, 4H, H_5), 0.11 (d, J = 6.6 Hz, 2H, $H_{5'}$)

3.2.9 - Synthesis of Ns-protected bis-sulfonamides

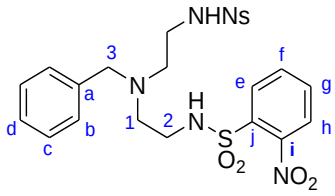


2 **3**

3o - **R** = H, **R'** = H, **PG** = Ns, **Ar** = Phenyl
3p - **R** = i-Pr, **R'** = (R)-Me, **PG** = Ns, **Ar** = Naphthyl
3q - **R** = H, **R'** = (R)-Me, **PG** = Ns, **Ar** = Naphthyl

Amine (4.0 mmol – see **table 3.2**) was added to a solution of aziridine **2** (8.0 mmol) in distilled toluene (20 mL). The solution was allowed to reflux for (**see table 3.2**) and was monitored by TLC. The crude was recovered by concentrating the solution and was purified by chromatographic column (**see table 3.2**).

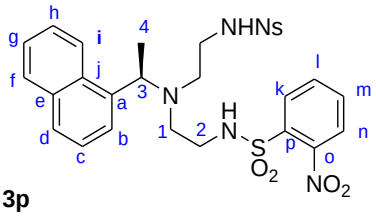
Product	Amine	Reaction time	AcOEt:Hexane	Yield
3o	Benzylamine	6 hours	7:3	70%
3p	1-(R)-Naphthylethylamine	40 hours	6:4	58%
3q	1-(R)-Naphthylethylamine	6 hours	8:2	60%



3o

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.04 (m, 2H, H_5), 7.83 (m, 2H, H_6), 7.79-7.66 (m, 4H, H_{Ar}), 7.37-7.04 (m, 5H, H_{Ar}), 5.63 (s, 2H, NH), 3.07 (t, J = 6.0 Hz, H_2), 2.63 (t, J = 6.0 Hz, H_1)

^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 148.46 (C_i), 138.15 (C_a), 134.14 (C_g), 133.50 (C_j), 133.25 (C_f), 131.26 (C_h), 129.29 (CH), 129.02 (CH), 127.95 (CH), 125.91 (C_e), 59.4 (C_3), 54.02 (C_1), 41.79 (C_2)



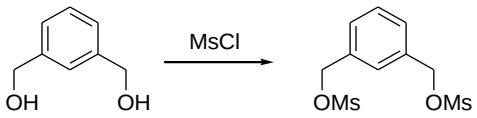
3p

^{1}H-NMR (300 MHz, $CDCl_3$, T = 300K) δ 8.24 (d, J = 8.5 Hz, 1H), 8.07 – 7.32 (m, 14H), 5.40 (s, 2H, NH), 4.69 (q, J = 6.4 Hz, 1H, H_3), 3,04 – 2,50 (m, 8H, H_1, H_2), 1.49 (d, J = 6.4 Hz, 3H, H_4).

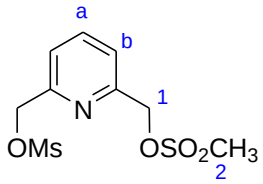
^{13}C-NMR (300 MHz, $CDCl_3$, T = 300K) δ 148.35 (C) 138.59 (C), 134.15 (C), 133.86 (CH), 133.45 (C), 133.09, 132.04 (C), 131.33 (CH), 129.19 (CH), 128.57 (CH), 127.18 (CH), 126.28 (CH), 125.78 (CH), 125.39 (CH), 124.61 (CH), 123.89 (CH), 57.84 (CH), 52.08 (CH_2), 43.00 (CH), 14.61(CH_3)

3.2.10 – Synthesis of macrocycles

Synthesis of 2,6-bis (OMs-methyl)-pyridine

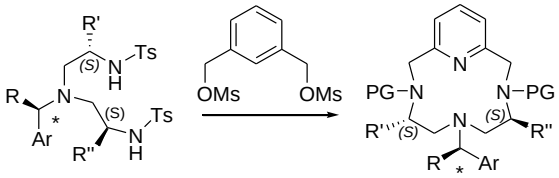


2,6-bismethanolpyridine (15.6 mmol) was suspended in AcOEt (45 mL) and TEA (10.9 mL, 78.0 mmol) was added. The temperature was set to 0°C and MsCl (3.6 mL, 46.7 mmol) was added dropwise. After 15', the reaction was quenched with a saturated $NaHCO_3$ (50 mL) solution in water and the product was extracted with AcOEt (3x40 mL). The organic layers were treated with Na_2SO_4 and concentrated in vacuum giving the final product as white powder (13.2 mmol, 85%).



^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 7.88 (t, J = 7.8 Hz, 1H, H_a), 7.52 (d, J = 7.8 Hz, 2H, H_b), 5.36 (s, 4H, H_1), 3.13 (s, 6H, H_2).

Synthesis of macrocycles 6a-t

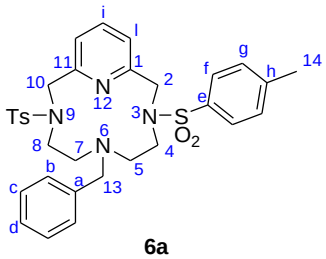


3 **6**

6a - **Ar =** Benzyl, **R** = **R'** = **R''** = H, **PG** = Ts
6b - **Ar =** Benzyl, **R** = (S)-Me, **R'** = **R''** = H, **PG** = Ts
6c - **Ar =** Benzyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = Ts
6d - **Ar =** Naphthyl, **R** = **R'** = **R''** = H, **PG** = Ts
6e - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R''** = H, **PG** = Ts
6f - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = Ts
6g - **Ar =** Naphthyl, **R** = H, **R'** = **R''** = i-Pr, **PG** = Ts
6h - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Pr, **PG** = Ts
6i - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R'' =** i-Pr, **PG** = Ts
6j - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Bu, **PG** = Ts
6k - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = cy, **R'' =** H, **PG** = Ts
6l - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = t-Bu, **R'' =** H, **PG** = Ts
6m - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = i-Pr, **R'' =** H, **PG** = Ts
6n - **Ar =** Naphthyl, **R** = H, **R'** = **R''** = i-Pr, **PG** = Tf
6o - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Pr, **PG** = Tf
6p - **Ar =** Naphthyl, **R** = (S)-Me, **R'** = **R''** = i-Pr, **PG** = Tf
6q - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Bu, **PG** = Tf
6r - **Ar =** Benzyl, **R** = **R'** = **R''** = H, **PG** = oNs
6s - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R''** = H, **PG** = oNs
6t - **Ar =** Naphthyl, **R** = (R)-Me, **R'** = **R'' =** i-Pr, **PG** = oNs

2,6-(bis-mesylmethyl)pyridine (1.5 mmol) in distilled CH_3CN (9 mL) was added dropwise to a suspension of K2CO3 (3.7 mmol) and amine **3** (1.5 mmol) in distilled CH_3CN (24 mL). The reaction was allowed to react to reflux for (see table for reaction time). The reaction mixture was then quenched with water (25 mL) and washed with AcOEt (3 x 25 mL). The organic phases were concentrated in vacuum and the crude was purified by (see table).

Product	Reaction time	Purification	Yield	Product	Reaction time	Purification	Yield
6a	11 hours	Crystallization by layering n-hexane to a solution in warm AcOEt	88%	6k	35 hours	Column (n-hexane : AcOEt = 7:3)	47%
6b	11 hours		72%	6l	70 hours	As 6k	48%
6c	11 hours		73%	6m	22 hours	As 6k	55%
6d	45 hours	Column (Toluene : CH_2Cl_2 : iPrOH = 90:10:5)	51%	6n	28 hours	Column (Toluene : CH_2Cl_2 : iPrOH = 85:10:5)	53%
6e	10 hours	As 6a	80%	6o	36 hours	As 6n	39%
6f	10 hours	As 6a	78%	6p	30 hours	As 6n	34%
6g	45 hours	As 6d	56%	6q	26 hours	As 6n	36%
6h	40 hours	Column (n-hexane : AcOEt = 6:4)	47%	6r	5 hours	Column (CH_2Cl_2 : MeOH 10:0.3)	80%
6i	53 hours	Column (n-hexane : CH_2Cl_2 : iPrOH = 80:17.5:2.5)	50%	6s	5 hours	As 6r	58%
6j	24 hours	As 6h	67%	6t	32 hours	-	50%



6a

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.78 (t, J = 7.7 Hz, 1H, H_i), 7.61 (d, J = 8.0 Hz, 4H, H_f), 7.38 (d, J = 7.7 Hz, 2H, H_l), 7.34–7.32 (m, 3H, H_{Ph}), 7.27 (d, J= 8.0 Hz, 4H, H_g), 7.20 (m, 2H, H_{Ph}), 4.37 (m, 4H, H_{10} and H_2), 3.52 (s, 2H, H_{13}), 3.13 (m, 4H, H_4 and H_8), 2.45 (s, 6H, H_{14}), 2.32 (m, 4H, H_5 and H_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), 136.0 (C_a), 129.7 (C_g), 128.6 (C_{Ph}), 128.3 (C_{Ph}), 128.2 (C_{Ph}), 127.1 (C_f), 124.0 (C_l), 59.4 (C_{13}), 54.3 (C_5), 50.0 (C_2), 44.2 (C_4), 21.5 (C_{14}).

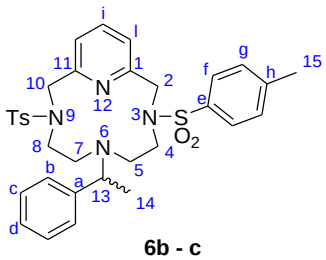
^{15}N-NMR (40 MHz; $CDCl_3$; T = 300 K): δ 312 (N_{12}), 94 (N-Ts), 32 (N_6).

Elem. an. Found: C, 63.6; H, 6.2; N, 9.2%

Calculated: C, 63.6; H, 6.0; N, 9.3%

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

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



6b - c

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.78 (t, J = 7.7 Hz, 1H, H_n), 7.57 (d, J = 8.1 Hz, 4H, H_h), 7.40 (d, J = 7.7 Hz, 2H, H_o), 7.34–7.32 (m, 3H, H_{Ar}), 7.26 (d, J = 8.1 Hz, 4H, H_{Ar}), 7.20 (m, 2H, H_{Ar}), 4.32 (m, 4H, H_2 and H_{10}), 3.58 (q, J= 6.6 Hz, 1H, H_{13}), 3.13 (m, 2H, H_5), 3.00–2.92 (m, 2H, H_7), 2.44 (s, 6H, H_{15}), 2.23–2.19 (m, 4H, H_4 and H_8), 1.24 (d, J = 6.6 Hz, 3H, H_{14}).

^{13}C-NMR (75 MHz, $CDCl_3$; T = 300 K) δ 155.3 (C), 145.4 (C), 139.2 (C_n), 136.2 (CH), 130.1 (CH), 128.7 (CH), 127.6 (C_i), 127.5 (C_f), 127.3 (C_h), 124.6 (C_o), 61.7 (CH), 54.8 (C_2), 50.1 (C_4), 45.7 (C_5), 21.9 (C_{15}), 20.5 (C_{14}). 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).

Elem. An. Found: C, 64.0; H, 6.2; N, 9.1%

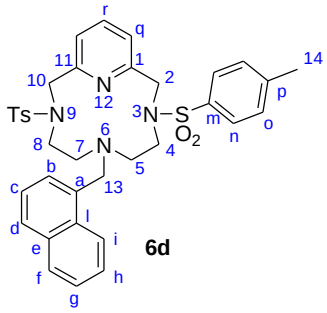
Calculated: C, 64.05; H, 6.2; N, 9.05%.

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 $CHCl_3$) (ligand **6b**).

50 (*c* 1 in $CHCl_3$) (ligand **6c**).



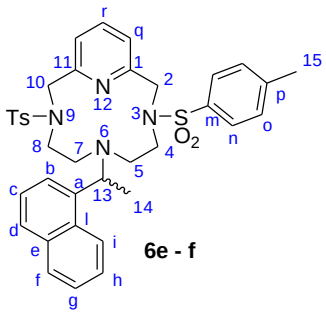
6d

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.11 (d, J = 8.1 Hz, 1H, H_i), 7.90-7.83 (m, 2H, H_{Ar}), 7.76 (pst, J = 7.8 Hz, 1H, H_r), 7.50 (d, J = 8.2 Hz, 4H, H_n), overlapping with 7.52-7.23 (m, 6H, H_{Ar}), 7.19 (d, J = 8.2 Hz, 4H, H_o), 4.31 (br, 4H, H_2), 3.93 (br, 2H, H_{13}), 3.07 (m, 4H, H_4), 2.39 (s, 6H, H_{14}) overlapping with 2.36 (m, 4H, H_5).

^{13}C-NMR (75 MHz, $CDCl_3$; T = 400 K) δ 155.0 (C), 143.3 (C), 138.8 (C_r), 135.9 (C), 134.5 (C), 133.9 (C), 129.7 (C_o), 128.4 (C), 128.1 (C), 127.0 (C_n), 125.6 (C), 125.6 (C), 125.3 (C), 124.7 (C_i), 124.0 (C), 58.1 (C_{13}), 54.3 (C_2), 50.4 (C_5), 44.3 (C_4), 21.5 (C_{14}). A signal relative to an aromatic quaternary carbon and an aliphatic carbon were not detected.

Elem. An. Found: C, 66.2; H, 5.8; N, 8.4%

Calculated: C, 66.0; H, 5.8; N, 8.6%.



6e - f

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K): δ 8.16 (d, J = 8.4 Hz, 1H, H_i), 7.94 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.87-7.77 (m, 2H, H_{Ar}), 7.56–7.54 (m, 4H, H_{Ar}), 7.43 (d, J = 7.5 Hz, 2H, H_{Ar}), 7.41 (d, J = 8.1 Hz, 4H, H_n), 7.13 (d, J = 8.1, 4H, H_o), 4.37 (q, J = 6.5 Hz, 1H, H_{13}), 4.27 (m, 4H, H_2 and CH_{10}), 3.09 (m, 2H, H_7), 2.82-2.85 (m, 2H, H_5), 2.37 (s, 6H, H_{15}), 2.28-2.32 (m, 4H, H_4 and H_8), 1.34 (d, J = 6.5 Hz, 3H, H_{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), 129.1 (CH), 127.9 (CH), 127.4 (C_o), 126.1 (CH), 125.8 (CH), 125.7 (CH), 124.8 (CH), 124.6 (CH), 124.5 (CH), 58.2 (C_{13}), 54.8 (C_2), 50.2 (C_4), 45.6 (C_5), 21.8 (C_{15}), 14.5 (C_{14}).

^{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.

Elem. An. Found: C, 66.2; H, 6.2; N, 8.3%

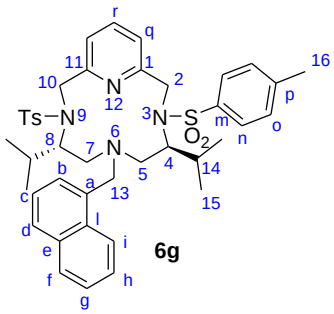
Calculated: C, 66.4; H, 6.0; N, 8.4%.

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 $CHCl_3$) (ligand **6e**)

+43 (c 1 in $CHCl_3$) (ligand **6f**)



6g

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.35 (d, J = 8.0 Hz, 1H, H_i), 7.86 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.76 (d, J = 8.0 Hz, 1H, H_{Ar}) 7.66-7.58 (m, 3H, H_{Ar}), 7.53 (pt, J = 7.6 Hz, 1H, H_{Ar}), 7.43 (pt, J = 7.6 Hz, 1H, H_{Ar}), 7.29-7.11 (m, 6H, H_{Ar}), 7.02 (d, J = 7.8 Hz, 4H, H_o), 4.72 (d, J = 15.6 Hz, 2H, H_2 and H_{10}), 4.30 (d, J = 13.5 Hz, 1H, H_{13}), 4.18 (d, J = 13.5 Hz, 1H, H_{13}), 3.78 (d, J = 15.6 Hz, 2H, H_2 and H_{10}), 3.68 (dd, J = 15.6 Hz J = 6.9 Hz, 2H, H_5 and H_7), 3.51 (m, 2H, H_4 and H_8), 2.29 (s, 6H, CH_{16}), 2.19 (m, 2H, H_5 and H_7), 1.19 (m, 2H, H_{14}), 0.58 (d, J = 6.9 Hz, 6H, H_{15}), 0.48 (br, 6H, H_{15}).

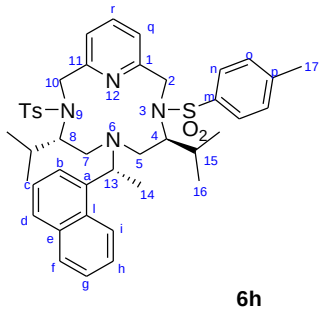
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300 K) δ 156.5 (C), 142.3 (C), 139.3 (C), 137.2 (CH), 135.7 (C), 134.0 (C), 132.7 (C), 128.9 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 125.9 (CH), 125.7 (CH), 125.4 (CH), 125.0 (CH), 120.2 (CH), 65.6 (C_4), 57.2 (C_{13}), 53.1 (C_5), 48.9 (C_2), 30.5 (C_{14}), 21.4 (C_{16}), 20.4 (C_{15}), 20.2 (C_{15}).

Elem. An. Found: C, 68.4; H, 6.8; N, 7.4%

Calculated: 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 $CHCl_3$).



6h

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.58 (d, J = 8.1 Hz, 1H, H_i), 7.89 (m, 1H, H_{Ar}), 7.83 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.69 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.64-7.42 (m, 8H, H_{Ar}), 7.12 (d, J = 7.8 Hz, 4H, H_o), 7.05 (m, 2H, H_{Ar}), 5.18 (m, 1H, H_{13}), 4.72 (m, 2H, H_2), 3.94-3.82 (m, 6H, H), 2.63-2.60 (m, 2H, H), 2.40 (m, 2H, H) overlapping with 2.33 (s, 6H, CH_{17}), 1.57 (d, J = 6.5 Hz, 3H, H_{14}), 0.44 (m, 12H, H_{16}).

^{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 (CH), 134.2 (C), 131.7 (C), 129.2 (C_o), 128.9 (CH), 127.8 (C_n), 127.0 (CH), 126.0 (CH), 125.9 (CH), 125.8 (C_h), 125.2 (CH), 124.0 (C_i), 120.7 (CH), 66.5 (CH), 50.8 (CH_2), 49.5 (CH_2), 30.0 (CH), 23.8 (C_{14}), 21.5 (C_{18}), 21.1 (C_{16}). 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 (d, J = 8.8 Hz, 1H, H_i), 7.99 (d, J = 7.2 Hz, 1H, H_b), 7.68 (pst, J = 8.0 Hz, 4H, H_n) overlapping with 7.69-7.66 (m, 1H, H_g), 7.57-7.47 (m, 2H, H_d and H_h), 7.38 (pst, J = 7.5 Hz, 1H, H_c), 7.29 (pst, J = 7.5 Hz, 1H, H_f), 7.05-7.03 (m, 1H, H_r), 6.86 (d, J = 8.0 Hz, 4H, H_o), 6.68 (d, J = 7.8 Hz, 2H, H_q), 5.39 (q, J = 6.6 Hz, 1H, H_{13}), 4.62 (d, J = 15.9 Hz, 2H, H_2), 4.14-4.06 (m, 4H, H_4 and H_5), 4.02-3.93 (m, 2H, $H_{2'}$), 2.96 (d, J = 15.0 Hz, 2H, $H_{5'}$), 2.02 (s, 6H, H_{17}), 1.68 (d, J = 6.6 Hz, 3H, H_{14}), 1.39 (m, 2H, H_{15}), 0.58 (m, 12H, H_{16}).

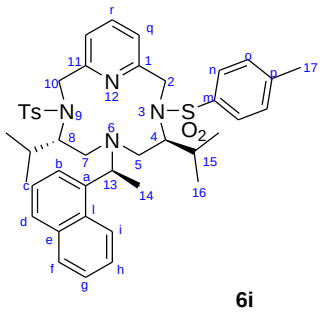
^{13}C-NMR (75 MHz; $C_6D_5CD_3$; T = 300 K) δ 157.4 (C), 142.7 (C), 141.9 (C), 140.4 (C), 136.3 (C_r), 134.9 (C), 132.5 (C), 129.0 (C_o), 128.2 (C_n), 127.2 (C_d), 126.3 (C_b), 125.9 (C_d) overlapping with 125.9 (C_h), 125.2 (C_f), 124.5 (C_i), 120.5 (C_q), 66.4 (C_4), 57.2 (C_{13}),

51.4 ($C_{2\text{-}5}$), 30.9 (C_{15}), 23.5 (C_{14}), 21.0 (C_{16}), 20.8 (C_{18}). A signal relative to an aromatic carbon was not detected.

Elem. An. Found: C, 68.4; H, 7.4; N, 7.1%

Calculated: C, 68.6; H, 7.0; N, 7.4%.

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



6i

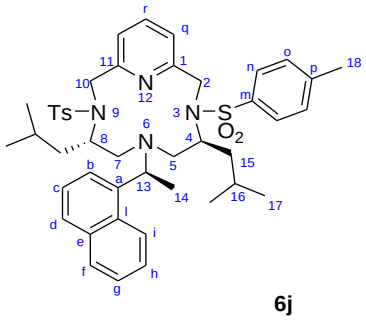
^{1}H-NMR (300 MHz; $CDCl_3$;T = 300 K) δ 8.54 (m, 1H, H_i), 7.89 (m, 1H, H_{Ar}), 7.85 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.77 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.64-7.41 (m, 8H, H_{Ar}), 7.09-6.99 (m, 6H, H_{Ar}), 5.01 (m, 1H, H_{13}), 4.76 (m, 2H, H_2), 3.86 (m, 2H, $H_{2'}$), 3.77 (m, 2H, H_4), 3.55 (m, 2H, H_5), 2.36 (m, 2H, $H_{5'}$), 2.29 (s, 6H, CH_{17}), 1.48 (d, J = 6.6 Hz, 3H, CH_{14}), 1.34-1.23 (m, 2H, H_{15}), 0.60 (m, 6H, CH_{16}), 0.38 (m, 6H, CH_{16}).

^{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 (CH), 134.1 (C), 132.5 (C), 128.9 (C_n), 128.8 (CH), 127.7 (C_o), 127.6 (CH), 126.7 (CH), 126.2 (CH), 125.4 (CH), 124.1 (CH), 120.7 (CH), 66.0 (C_4), 56.0 (C_{13}), 51.0 (C_5), 49.3 (C_2), 30.2 (C_{15}), 21.4 (C_{17}), 20.8 (C_{14}), 20.1 (C_{16}) overlapping with 20.1 (C_{16}).

Elem. An. Found: C, 68.6; H, 7.2; N, 7.4%

Calculated: C, 68.6; H, 7.0; N, 7.4%.

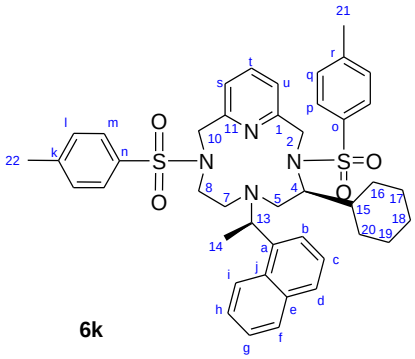
MS (FAB) m/z 753 (M^++1).



6j

[1]H-NMR (300 MHz; $CDCl_3$;T = 300 K) δ 8.29 (m, 1H, H_{Ar}), 7.85-7.84 (m, 1H, H_{Ar}), 7.79-7.69 (m, 3H, H_{Ar}), 7.58-7.43 (m, 6H, H_{Ar}), 7.38 (m, 1H, H_{Ar}), 7.30-7.25 (m, 4H, H_{Ar}), 4.90-4.88 (m, 1H, H_{13}), 4.79-4.74 (m, 1H, H_2), 4.45 (br, 1H, H_{10}), 3.99-3.94 (m, 1H, H_2), 3.86-3.81 (m, 1H, H_5), 3.65 (br, 1H, H_{10}), 3.50 (m, 1H, H_7), 3.05 (m, 1H, H_7), 2.94 (m, 1H, H_5), 2.43 (s, 6H, H_{18}), 1.43 (d, J = 6.2 Hz, 3H, H_{14}), 1.37-1.25 (m, 6H, H_{15} and H_{16}), 0.76-0.21 (widespread, 12H, H_{17})

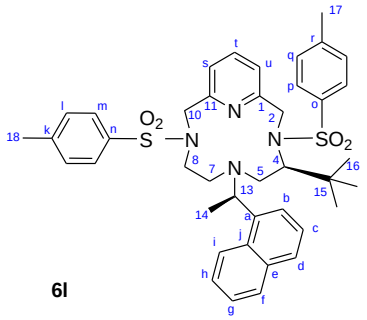
[13]C-NMR (75 MHz, $CDCl_3$) δ 143.07 (C), 140.68 (C), 138.56 (CH), 134.65 (C), 132.16 (C), 129.72 (CH), 129.05 (CH), 127.68 (CH), 127.63 (CH), 126.03 (CH), 125.74 (CH), 125.52 (CH), 124.89 (CH) 58.30 (C_{13}), 31.88 (C_2), 23.81 (C_{18}), 24.80 (C_4), 24.72 (C_{16}), 22.93 (C_5), 21.68 (C_{17}), 14.31 (C_{14}).



6k

[1]H-NMR (300 M*Hz*; $CDCl_3$, 300 K) δ 8.57 (d, *J* = 8.6 Hz, 1H - H_h), 7.83-7.71 (m, 6H – H_{Ar}), 7.58-7.53 (m, 2H – H_{Ar}), 7.45-7.37 (m, 2H – H_{Ar}), 7.16-7.12 (m, 2H – H_{Ar}), 6.94 – 6.89 (m, 4H – H_{Ar}), 5.00-2.50 (m, 10H), 2.04 (s, 6H, H_{21} and H_{22}), 1.70-0.65 (m, 16H).

[13]C-NMR (75 M*Hz*; $CDCl_3$, 300 K) δ 142.86 ($C_{k\text{-}r}$), 140.56 (C_{11}), 137.82 (C_{Ar}), 134.89 (C_{Ar}), 132.88 (C_{Ar}), 129.95 ($4C_{Ts}$), 129.55 (C_{Py}), 129.34 (C_{Ar}), 127.50 (C_{Ar}), 125.84 (C_{Ar}), 125.54 (C_{Ar}), 124.79 (C_h), 124.04 (C_{Ar}), 65.75, 31.51, 26.75, 26.63, 21.29 ($C_{21\text{-}22}$)



6l

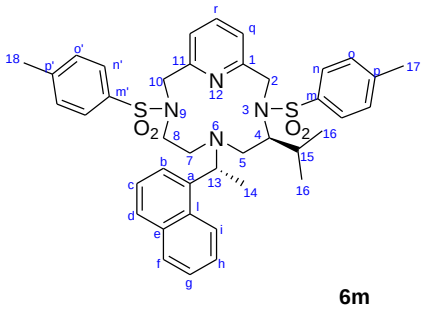
*Two major conformers (1:1). Signals of the second conformer are reported as marked by *.*

^{1}H-NMR (300 M*Hz*; $CDCl_3$, 300 K) δ 8.29-8.25 (m, 1H, H_h), 8.27-8.19 (m, 1H, H_{h*}), 7.91-7.86 (m, 2H, H_{Ar}), 7.79-7.76 (m, 4H, H_{Ar}), 7.64-7.59 (m, 1H, H_{Ar}), 7.55-7.36 (m, 13H, H_{Ar}), 7.31-7.20 (m, 10H, H_{Ar}), 7.08 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 6.99 (d, *J* = 8.1, 2H, H_{Ar}), 6.73 (d, *J* = 7.6 Hz, 1H, H_{Ar}), 4.85 (d, *J* = 14.5, 2H, $H_{2\text{-}2*}$), 4.78 (q, *J* = 6.5 Hz, 1H, H_{13}), 4.62 (d, *J* = 15.2 Hz, 1H, H_{10}), 4.57 (q, *J* = 6.7 Hz, 1H, H_{13*}), 4.48 (d, *J* = 12.1 Hz, 1H, H_{10*}), 4.44 (d, *J* = 14.5 Hz, 1H, H_2), 4.43-4.35 (m, 1H, H_{2*}), 4.19 (d, *J* = 15.2 Hz, 1H, H_{10}), 4.03 (d, *J* = 9.1 Hz, 1H, H_4), 3.99 (d, *J* = 12.1 Hz, 1H, H_{10*}), 4.03 (d, *J* = 8.9 Hz, 1H, H_{4*}), 3.63 (dd, *J* = 13.4, 9.1 Hz, 2H, $H_{5,\ 5*}$), 3.39-3.27 (m, 1H, H_8), 3.24-3.11 (m, 1H, H_{8*}), 3.08-2.95 (m, 2H, $H_{5,\ 7}$), 2.93 – 2.82 (m, 2H, $H_{8,\ 8*}$), 2.77 (d, *J* = 13.4 Hz, 1H, H_{5*}), 2.69-2.41 (m, 2H, H_{7*}), 2.46-2.30 (m, 12H, $H_{17\text{-}18}$ and $H_{17*\text{-}18*}$), 1.77-1.65 (m, 1H, H_7), 1.53 (d, *J* = 6.5 Hz, 3H, H_{14}), 1.52 (d, *J* = 6.7 Hz, 3H, H_{14*}), 0.94 (s, 9H, H_{16}), 0.91 (s, 9H, H_{16})

^{13}C-NMR (75 M*Hz*; $CDCl_3$, 300 K) δ 156.48 ($C_{2,2*}$), 155.96 (C_{10}), 155.58 (C_{10*}), 143.22 (C_k), 143.21 (C_{k*}), 143.05 (C_r), 142.96 (C_{r*}), 140.74 (C_a), 139.69 (C_{a*}), 139.58 (C_n), 139.57 (C_{n*}), 138.19 (C_t), 137.38 (C_{t*}), 137.17 (C_o), 136.94 (C_{o*}), 134.50 (C_j), 134.49 (C_{j*}), 132.19 (C_e), 131.99 (C_{e*}), 129.83 ($2C_{Ts}$), 129.70 ($2C_{Ts}$), 129.51 ($2C_{Ts}$), 129.18 ($2C_{Ts}$), 129.06 ($2C_{Ts}$), 128.36 ($2C_{Ts}$), 127.82 (C_{Ar}), 127.60 ($2C_{Ar}$), 127.45 (C_{Ar}), 127.14 ($2C_{Ts}$), 127.12 ($2C_{Ts}$), 125.97 (C_{Ar}), 125.64 (C_{Ar}), 125.48 (C_{Ar}), 125.46 (C_{Ar}), 125.42 (C_{Ar}), 125.33 (C_{Ar}), 125.29 (C_{Ar}), 124.46 (C_{Ar}), 124.18 (C_{Ar}), 123.91 (C_{Ar}), 123.75 (C_{Ar}), 123.49 (C_{Ar}), 123.17 (C_{Ar}), 121.53 (C_{Ar}), 69.03 (C_4), 68.02 (C_{4*}), 59.34 (C_{13}), 55.98 (C_{10}), 55.18 (C_{10*}), 54.92 (C_8), 52.81 (C_7), 50.65 ($C_{2,2*}$), 49.51 (C_{7*}), 47.62 (C_{8*}), 38.42 (C_{15}), 36.45 (C_{15*}), 29.26 (C_{16}), 29.05 (C_{16*}), 22.31 (C_{14}), 21.59 (C_{18}), 21.54 (C_{18*}), 21.51 (C_{17}), 21.47 (C_{17*}), 17.97 (C_{14}).

MS (FAB) m/z 751.5 (M^+1), 773.5 (M^+Na).

$[\alpha]_D^{20}$ - 64.3 (in $CHCl_3$).



6m

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.25 (m, 1H, H_i), 7.87 (m, 1H, H_{Ar}), 7.77 (d, J = 7.6 Hz, 1H, H_{Ar}) 7.65-7.62 (m, 2H, H_{Ar}), 7.50-7.40 (m, 7H, H_{Ar}), 7.26 (4H, covered by solvent residual peak), 7.17 (m, 2H, H_{Ar}), 4.80-4.20 (m, 4H, CH_2), 3.80-2.60 (m, 4H, CH_2), 2.43 (s, 3H, H_{18}), 2.37 (s, 3H, H_{17}), 2.00-1.76 (m, 1H, CH_2), 1.46 (d, J = 6.2 Hz, 3H, CH_{14}), 0.77 (m, 3H, CH_{16}), 0.59 (m, 3H, H_{16}). Some signals were too broad to be detected.

^{1}H-NMR (400 MHz; $C_6D_5CD_3$; T = 373 K) δ 8.36 (d, J = 8.6 Hz, 1H, H_i), 7.68 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.60-7.54 (m, 3H, H_{Ar}), 7.48-7.44 (m, 3H, H_{Ar}), 7.38 (pst, J = 7.5 Hz, 1H, H_{Ar}), 7.31 (d, J = 7.0 Hz, 1H, H_{Ar}), 7.27 (d, J = 7.0 Hz, 1H, H_{Ar}), 7.10-6.80 (m, 7H, H_{Ar} overlapped with toluene), 4.59 (q, J = 6.1 Hz, 1H, H_{13}), 4.29-4.14 (m, 4H, H_2 and H_{10}), 3.77 (m, 1H, H_8), 3.28-3.08 (m, 4H, H_4 and H_7), 2.93 (m, 1H, H_5), 2.08 (s, 3H, H_{18}), 2.05 (s, 3H, H_{17}), 2.01 (m, 1H, H_5), 1.88 (m, 1H, H_{15}),1.46 (d, J = 6.6 Hz, 3H, H_{14}), 0.90 (d, J = 6.7 Hz, 3H, H_{16}), 0.69 (d, J = 6.7 Hz, 3H, H_{16}).

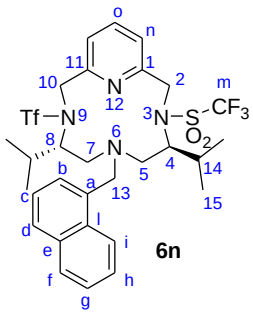
^{13}C-NMR (75 MHz; $C_6D_5CD_3$; T = 300 K) δ 156.3 (C), 156.2 (C), 141.9 (C), 134.5 (C), 132.1 (C),129.2 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 127.8 (C), 127.8 (CH), 127.4 (CH), 126.9 (CH) 125.3 (CH), 125.2 (CH), 125.0 (CH), 124.0 (C_i), 123.2 (CH), 20.8 (CH), 20.7 (CH), 20.6 (CH). Signals relative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

Elem. An. Found: C, 67.1; H, 6.9; N, 7.6%

Calculated: 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 $CHCl_3$).



6n

^{1}H-NMR (400 MHz; C_6D_6; T = 300 K) δ 7.78-7.76 (m, 2H, H_{Ar}), 7.72-7.66 (m, 2H, H_{Ar}), 7.45-7.37 (m, 2H, H_{Ar}), 7.27-7.22 (m, 1H, H_{Ar}),7.17-7.07 (m, 3H, H_{Ar}), 4.77-4.47 (m, 4H, CH), 3.89-3.85 (m, 4H, H), 3.10-3.05 (m, 2H, H), 1.09 (m, 2H, H_{14}), 0.69 (bs, 6H, H_{15}), 0.40 (bs, 6H, H_{15}). Two CH 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 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 126.2 (CH), 126.0 (CH), 125.4 (CH), 56.9 (C_2), 53.2 (C_{13}), 49.9 (CH_2), 29.4 (C_{14}), 19.9 (C_{15}), 19.6 (C_{15}). Signals relative to quaternary carbons and aromatic CH were not detected.

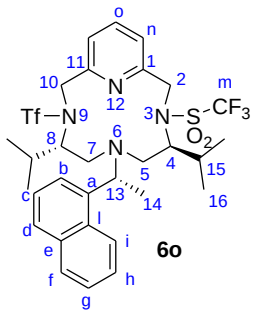
^{19}F-NMR (376 MHz; C_6D_6; T = 300 K) δ - 74.5 (bs).

Elem. An. Found: C, 51.8; H, 5.4; N, 8.0%

Calculated: 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 $CHCl_3$).



6o

^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.42 (m, 1H, H_i), 7.81-7.78 (m, 2H, H_{Ar}), 7.68-7.62 (m, 2H, H_{Ar}), 7.52-7.40 (m, 3H, H_{Ar}), 7.20-7.17 (m, 2H, H_{Ar}), 5.16 (q, J = 6.3 Hz, 1H, H_{13}), 4.91 (d, J = 16.0 Hz, 2H, H_2), 4.40 (d, J = 16.0 Hz, 2H, $H_{2'}$), 3.82 (m, 2H,

H_5), 2.98 (m, 2H, $H_{5'}$), 1.65 (m, 2H, H_4), 1.51 (d, J = 6.3 Hz, 3H, CH_{14}), 0.73 (bs, 6H, CH_{16}), 0.44 (bs, 6H, CH_{16}). 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 (CH), 127.2 (CH), 126.4 (CH), 126.0 (CH), 125.3 (CH), 123.6 (CH), 122.1 (CH), 69.1 (C_4), 57.4 (C_{13}), 50.9 (C_2), 50.4 (C_5),29.9 (C_{15}), 24.0 (C_{14}), 21.0 (C_{16}), 19.3 (C_{17}).

^{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.

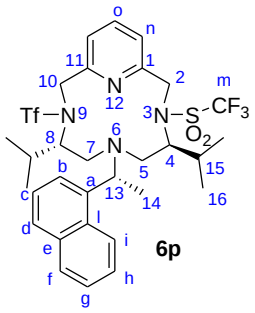
^{19}F-NMR (282 MHz; $CDCl_3$; T = 300 K) δ - 74.15 (s).

Elem. An. Found: C, 52.4; H, 5.3; N, 8.0%

Calculated: C, 52.5; H, 5.4; N, 7.9%.

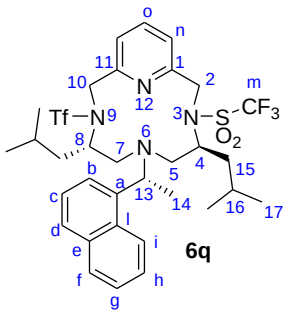
MS (FAB) m/z 709 (M^++1), 575 (M^+-133).

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

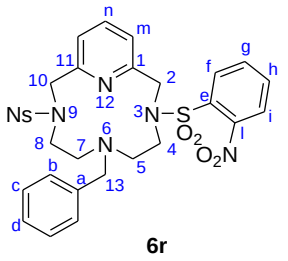


6p

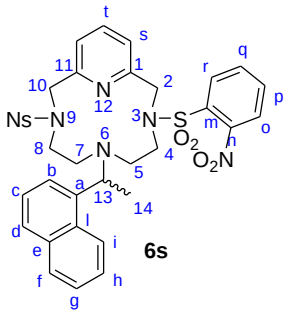
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.55 (m, 1H, H_i), 7.91-7.88 (m, 1H, H_{Ar}), 7.83 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.75 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.70-7.66 (m, 1H, H_{Ar}), 7.56-7.52 (m, 1H, H_{Ar}), 7.50-7.45 (m, 2H, H_{Ar}), 7.22-7.18 (m, 2H, H_{Ar}), 5.30-5.22 (m, 1H, H_{13}), 4.89 (br, 2H, H_2 and H_{10}), 4.44-4.40 (m, 2H, H_5 and H_7), 3.81 (br, 2H, H_2 and H_{10}), 3.01-2.98 (m, 2H, H_5 and H_7), 1.63-1.56 (m, 2H, H_4 and H_8), 1.47-1.45 (d, J = 6.33 Hz, 3H, H_{14}), 0.81-8.76 (m, 12H, H_{16})



^{1}H-NMR (300 MHz; C_7D_8; T = 300 K) δ 8.23-8.06 (m, 1H, H_{Ar}), 7.63 (d, J = 7.98 Hz, 1H, H_{Ar}), 7.52 (d, J = 8.32 Hz, 1H, H_{Ar}), 7.39-7.34 (m, 2H, H_{Ar}), 7.28-7.18 (m, 3H, H_{Ar}), 1.33-1.23 (m, 4H, H_{15}), 0.97-0.93 (m, 2H, H_{16}), 0.79 (d, J = 6.00 Hz, 6H, H_{17}), 0.77 (d, J = 5.99, 6H, H_{17}). Two signals relative to aromatic protons could not be detected because of the overlapping with the solvent signals. The signals relative to the backbone protons are too broad to be distinguished and are spread in the range between 5.5 and 2.5 ppm.



^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 7.80 (m, 3H, H_{Ar}), 7.72-7.57 (m, 6H, H_{Ar}), 7.46 (d, J = 7.7 Hz, 2H, H_{Ar}), 7.34-7.15 (m, 5H, H_{Ar}), 4.58 (s, 4H, H_2 and H_{10}), 3.54 (s, 2H, H_{13}), 3.38-3.15 (m, 4H, H_4 and H_8), 2.58-2.41 (m, 4H, H_5 and H_7)

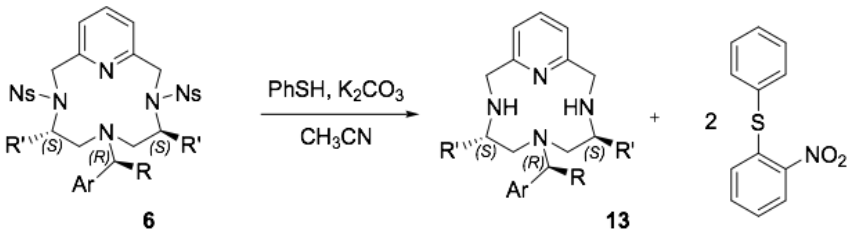


6s

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 8.21-8.19 (s, 1H, H_{Ar}), 7.88-7.41 (m, 17H, H_{Ar}), 4.52 (s, 4H, H_2 and H_{10}), 4.41 (q, 1H, H_{13}), 3.22 (ddd, 2H, H_4), 2.98 (ddd, 2H, H_8), 2.51 (ddd, 2H, H_5), 2.38 (ddd, 2H, H_7), 1.38 (d, 3H, H_{14})

3.2.11 – Free base ligands

Deprotection of macrocycles



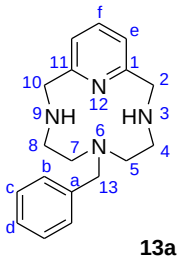
6

6r - **Ar** = Benzyl, **R** = **R'** = **R''** = H
6s - **Ar** = Naphthyl, **R** = (R)-Me, **R'** = **R''** = H
6t - **Ar** = Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Pr
6u - **Ar** = Naphthyl, **R** = H, **R'** = **R''** = H

13

13a - **Ar** = Benzyl, **R** = **R'** = **R''** = H
13b - **Ar** = Naphthyl, **R** = (R)-Me, **R'** = **R''** = H
13c - **Ar** = Naphthyl, **R** = (R)-Me, **R'** = **R''** = i-Pr
13d - **Ar** = Naphthyl, **R** = H, **R'** = **R''** = H

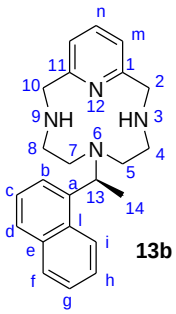
A solution of **6** (0.68 mmol), micronized potassium carbonate (2.72 mmol) and thiophenol (2.04 mmol) in distilled CH_3CN (17 mL) was allowed to react at 50°C for 5 hours. Then CH_2Cl_2 (10 mL) is added. The mixture was extracted with a 1M solution of HCl (3 x 10 mL) and the aqueous phases were basified with NaOH. The suspension was extracted with CH_2Cl_2 (3 x 10 mL) and the organic phases were then treated with Na_2SO_4 and concentrated in vacuo. A yellowish powder was obtained.



13a

Yield: 84%

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 7.57 (t, J = 7.5 Hz, 1H, H_{Ar}), 7.40-7.35 (m, 3H, H_{Ar}), 7.32-7.24 (m, 2H, H_{Ar}), 7.02 (d, J = 7.5 Hz, 1H, H_{Ar}), 3.96 (s, 4H, $H_{2\text{-}10}$), 3.68 (s, 2H, H_{13} overlapped with br, 2H, NH), 2.64 (m, 4H, $H_{4\text{-}8}$), 2.41 (m, 4H, $H_{5\text{-}7}$)

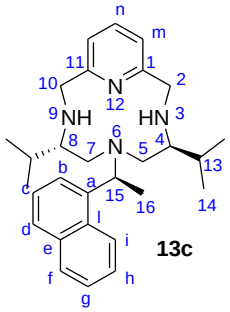


13b

Yield 78%

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300K) δ 8.59-8.56 (d, J = 8.61 Hz, 1H, H_h), 7.86 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.82 (m, 1H, H_{Ar}), 7.56-7.41 (m, 5H, H_{Ar}), 6.91 (d, J = 7.6, 2H, H_{Ar}), 4.95 (q, J = 6.8, 1H, H_{13}), 3.88 (d, J = 16.8, 2H, $H_{2\text{-}10}$), 2.88-2.84 (m, 6H, $H_{4\text{-}8}$ and NH), 2.53-2.43 (m, 2H, H_5), 2.38-2.30 (m, 2H, H_7), 1.57 (d, J = 6.8, 3H, H_{14})

^{13}C-NMR (100 MHz; $CDCl_3$; T = 300K) δ 158.04 (C_{Ar}), 139.31 (C_{Ar}), 136.24 (CH_{Ar}), 134.07 (C_{Ar}), 132.14 (C_{Ar}), 128.73 (CH_{Ar}), 128.01 (CH_{Ar}), 125.73 (CH_{Ar}), 125.32 (CH_{Ar}), 124.65 (CH_{Ar}), 119.76 (CH_{Ar}), 77.34 (C_2), 77.02 (C_{10}), 76.70 (C_4), 59.34 (C_{13}), 54.62 (C_8), 52.51 (C_5), 48.05 (C_7), 12.48 (C_{14})



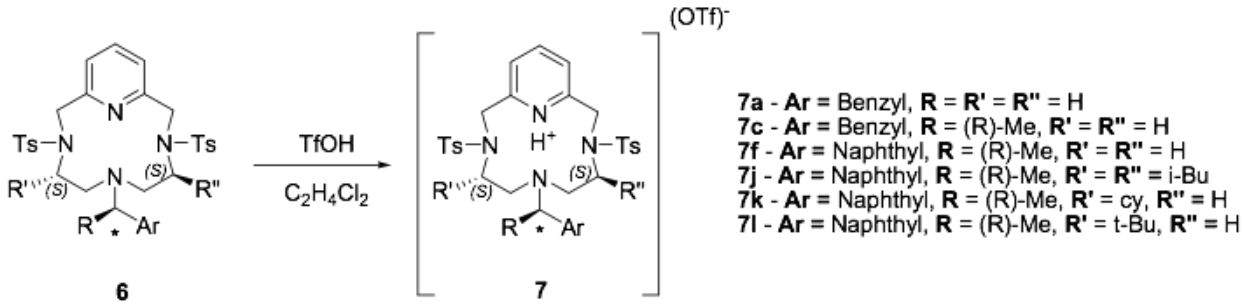
13c

Yield 74%

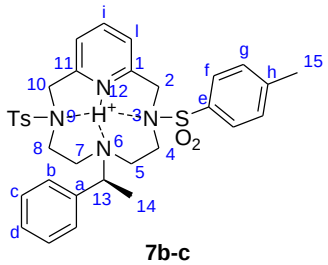
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 8.21 (d, J = 8.7 Hz, 1H, H_h), 7.80 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.77-7.68 (m, 1H, H_{Ar}), 7.54 (t, J = 7.6 Hz, 1H, H_a), 7.41-7.39 (m, 2H, H_{Ar}), 7.39-7.29 (m, 1H, H_{Ar}), 7.11-7.03 (m, 1H, H_{ar}), 6.94 (d, J = 7.6 Hz, 2H, H_b), 4.85 (q, J = 6.6 Hz, 1H, H_{15}), 3.94 (d, J = 15.6 Hz, 2H, $H_{2\text{-}10}$), 3.49 (d, J = 15.6, 2H, $H_{2\text{-}10}$), 2.65-2.61 (m, 4H, $H_{4\text{-}8}$), 2.44-2.41 (m, 4H, $H_{5\text{-}7}$), 1.59 (d, J = 6.6, 3H, H_{16}) overlapped with (br, 2H, NH), 1.31-1.19 (m, 1H, H_{13}), 0.84 (d, J = 6.8 Hz, H_{14}), 0.76 (d, J = 6.8 Hz, H_{14})

3.2.12 – Protonated ligands

Synthesis of protonated ligands



Ligand **6** (0.32 mmol) was dissolved in distilled dichloroethane (5 mL). Triflic acid (0.35 mmol) was added and the solution stirred for 2 hours. The solution was dried, then *n*-hexane (10 mL) was added and the solid **7** filtered in air.



7b-c

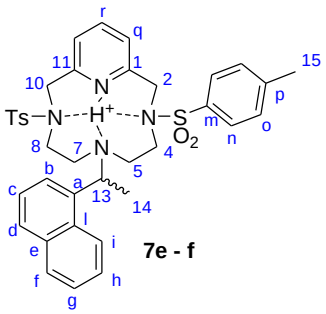
^{1}H-NMR (300 MHz; $CDCl_3$; T = 300K) δ 11.38 (s, 1H, NH), 7.80 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.71 (pt, J = 7.7 Hz, 1H, H_{Ar}), 7.61 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.52 (m, 2H, H_{Ar}), 7.45-7.39 (m, 5H, H_{Ar}), 7.34 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.22 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.04 (d, J = 7.7 Hz, 1H, H_{Ar}), 5.60 (q, J = 7.0 Hz, 1H, H_{13}), 4.65 (d, J = 17.1 Hz, 1H, CH_2), 4.17 (d, J = 17.1 Hz, 1H, CH_2), 4.16-4.09 (m, 2H, CH_2), 3.88 (m, 1H, CH_2), 3.74-3.64 (m, 3H, CH_2), 3.50-3.39 (m, 2H, CH_2), 2.50 (s, 3H, H_{15}), 2.45 (s, 3H, H_{15}) overlapping with 2.45-2.40 (m, 1H, CH_2), 1.85 (d, J = 7.0 Hz, 3H, H_{14}) overlapping with 1.85-1.80 (m, 1H, CH_2).

^{13}C-NMR (75 MHz; $CDCl_3$; T = 300K) δ 156.8 (C), 155.5 (C), 145.4 (C), 144.8 (C), 139.6 (CH), 134.4 (C), 133.4 (C), 132.7 (C), 130.7 (CH), 130.6 (CH), 130.4 (CH), 129.9 (CH), 129.5 (CH), 127.9 (CH), 127.6 (CH), 122.8 (CH), 122.2 (CH), 58.3 (C_{13}), 52.8 (CH_2), 51.7 (CH_2), 51.5 (CH_2), 46.2 (CH_2), 44.4 (CH_2), 21.8 (C_{15}), 21.7 (C_{15}). One CH_2 and C_{14} signals were not detected.

Elem. An. **Found**: C, 52.9; H, 5.1; N, 7.6%

Calculated: C, 53.1; H, 5.1; N, 7.3%.

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



^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 10.68 (s, 1H, NH), 8.20 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.94 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.87-7.81 (m, 4H, H_{Ar}), 7.72 (pt, J = 7.7 Hz, 1H, H_{Ar}), 7.58 (pt, J = 7.7 Hz, 1H, H_{Ar}), 7.45 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.41 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.36-7.30 (m, 2H, H_{Ar}), 7.21 (d, J = 8.1 Hz, 2H, H_{Ar}), 6.81-6.77 (m, 2H, H_{Ar}), 6.22 (q, J = 6.6 Hz, 1H, H_{13}), 4.53 (m, 1H, CH_2) overlapping with 4.48 (d, J = 16.6 Hz, 1H, CH_2), 4.07 (d, J = 16.6 Hz, 1H, CH_2), 4.00-3.86 (m, 3H, CH_2), 3.70 (d, J = 16.3 Hz, 1H, CH_2), 3.52-3.30 (m, 3H, CH_2), 2.49 (s, 3H, H_{15}), 2.35 (s, 3H, H_{15}), 2.20 (m, 1H, CH_2), 2.06 (d, J = 6.6 Hz, 3H, H_{14}), 1.73 (m, 1H, CH_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 (CH), 133.9 (C), 133.8 (C), 132.5 (C), 131.5 (CH), 130.7 (CH), 130.7 (C), 130.1 (CH), 129.4 (CH), 129.3 (C), 128.0 (CH), 127.9 (CH), 127.5 (CH), 126.9 (CH), 126.8 (CH), 126.1 (CH), 122.8 (CH), 122.7 (CH), 121.9 (CH), 55.2 (C_{13}), 54.3 (CH_2), 53.8 (CH_2), 53.5 (CH_2), 52.9 (CH_2), 47.8 (CH_2), 47.2 (CH_2), 21.8 (H_{15}), 21.6 (H_{15}), 11.3 (C_{14}).

^{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.

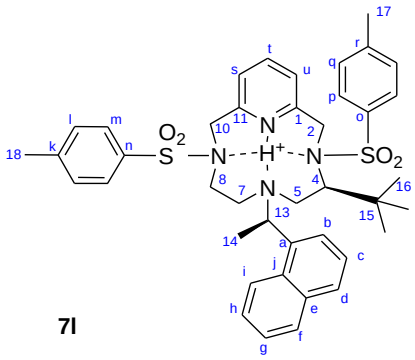
Elem. An. Found: C, 55.4; H, 5.2; N, 6.4%

Calculated: 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) (complex **7f**)

+ 168 (*c* 0.5 in CH_2Cl_2) (complex **7e**)



7l

^{1}H-NMR (400 M*Hz*; $CDCl_3$, T = 300 K) δ 9.06 (bs, 1H, H^+), 8.48 (d, *J* = 8.6 Hz, 1H, H_h), 8.01 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 8.00 (d, *J* = 7.9 Hz, 1H, H_{Ar}), 7.88 (d, *J* = 7.3 Hz, 1H, H_{Ar}), 7.71 (d, *J* = 7.8 Hz, 2H, H_{Ar}), 7.79-7.63 (m, 4H, H_{Ar}, H_t), 7.54 (b, 2H, H_{Ar}), 7.37 (d, *J* = 7.5 Hz, H_{Ar}), 7.32 (d, *J* = 7.8 Hz, 2H, H_{Ar}), 7.25 (bd, *J* = 7.2 Hz, 1H, H_s), 7.12 (b, 1H, H_u), 6.27 (b, 1H, H_{13}), 4.79 (d, *J* = 15.5 Hz, 1H, H_2), 4.76 (d, *J* = 17.1 Hz, 1H, H_{10}), 4.62 (d, *J* = 17.1 Hz, 1H, $H_{10'}$), 4.38 (b, 1H, H_5), 4.21 (d, *J* = 10.4 Hz, 1H, H_4), 3.92 (d, *J* = 15.5 Hz, 1H, $H_{2'}$), 3.79-3.69 (b, 2H, $H_{5',8}$), 3.46 (m, 1H, $H_{8'}$), 2.76 (m, 2H, $H_{7,7'}$), 2.49 (s, 3H, H_{18}), 2.47 (s, 3H, H_{17}), 2.19 (d, *J* = 5.8 Hz, 3H, H_{14}), 0.60 (s, 9H, H_{16}).

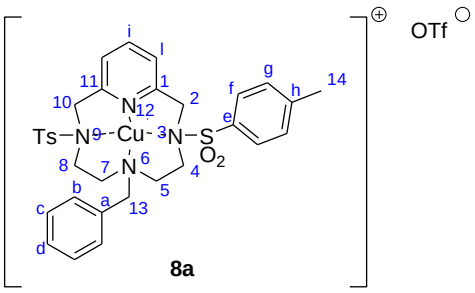
^{13}C-NMR (100 M*Hz*; $CDCl_3$) δ 156.01 (C_{Ar}), 154.39 (C_{Ar}), 146.19 (C_{Ar}), 145.03 (C_{Ar}), 144.94 (C_{Ar}), 142.24 (C_{Ar}), 139.56 (C_t), 134.31 (C_{Ar}), 130.68 (C_{Ar}), 130.59 (C_{Ar}), 130.53 (C_{Ar}), 130.27 (C_{Ts}), 129.94 (C_{Ts}), 129.56 (C_{Ar}), 127.90 (C_{Ar}), 127.88 (C_{Ts}), 126.78 (C_{Ar}), 125.59 (C_{Ar}), 124.93 (C_{Ar}), 122.35 ($C_{2,11}$), 122.33 (C_h), 62.23* (C_4), 58.88* (C_{13}), 55.75 (C_5), 53.63 (C_2), 49.50 (C_{10}), 47.10 (C_7), 44.51 (C_8), 36.27 (C_{15}), 27.95 (C_{16}), 21.56 (C_{17}, C_{18}), 21.29 (C_{14})

3.2.13 – Copper complexes

Synthesis of copper complexes a, d-f

Copper(I) triflate benzene complex (40 mg, 0.08 mmol) was added to a solution of **6** (0.16 mmol) in dichloroethane (5 mL). The solution was stirred at room temperature for 1 hour, toluene (10 mL) was layered. After standing at room temperature for 16 hours, the white precipitated was filtered and dried in vacuo under nitrogen atmosphere.

Yield a – 44% d – 98%
e – 97% f – 98%



8a

^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K): δ 7.79 (m, 4H, H_{Ts}), 7.74 (m, 1H, H_{Ar}), 7.64 (m, 1H, H_{Ar}), 7.58–7.53 (m, 2H, H_{Ar}), 7.46 (m, 2H, H_{Ar}), 7.42–7.40 (m, 4H, H_{Ts}), 7.34 (m, 1H, H_{Ar}), 7.09 (m, 1H, H_{Ar}), 5.14 (m, 1H, CH_2), 4.94 (m, 2H, H_{13}), 4.50 (d, J = 17.2 Hz, 1H, CH_2), 4.39 (m, 1H, CH_2), 4.23 (d, J = 17.2 Hz, 1H, CH_2), 4.07 (m, 1H, CH_2), 3.82 (m, 2H, CH_2), 3.40 (m, 1H, CH_2), 3.26–3.10 (m, 3H, CH_2), 2.51 (s, 3H, H_{14}), 2.48 (s, 3H, H_{14}), 2.28 (m, 1H, CH_2).

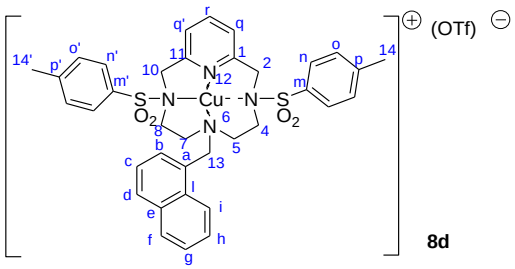
^{13}C-NMR (100 MHz; $CDCl_3$; T = 300 K) δ 157.1 (C), 139.4 (C), 139.0 (C), 131.3 (CH), 130.6 (CH), 130.4 (CH), 130.3 (C), 130.0 (CH), 128.7 (CH), 127.8 (CH), 125.9 (CH), 124.1 (CH), 121.5 (CH), 58.7 (CH_2), 56.1 (CH_2), 53.9 (CH_2), 52.8 (CH_2), 50.1 (CH_2), 48.4 (C_{13}), 45.6 (CH_2), 21.6 (C_{14}).

^{15}N-NMR (40 MHz; $CDCl_3$; T = 300 K): δ 278 (N_{12}), 92 (NTs), 46 (N_6).

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

Elem. an. **Found**: C, 48.6; H, 4.6; N, 6.7%;

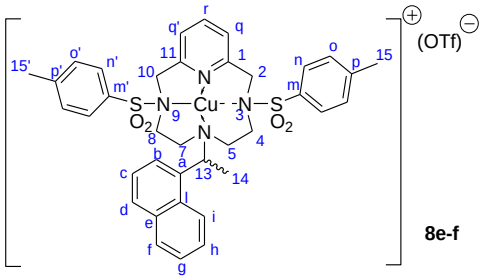
Calculated: C, 48.5; H, 4.4; N, 6.9%.



^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.97 (d, J = 7.8 Hz, 1H, H_i), 8.08-8.05 (m, 2H, H_{Ar}), 7.92 (m, 1H, H_{Ar}), 7.85-7.75 (m, 2H, H_r) 7.65-7.52 (m, 7H, H_{Ar}), 7.42-7.37 (m, 4H, H_{Ar}), 7.27-7.17 (m, 2H, H_{Ar}), 4.89 (d, J = 14.7 Hz, 2H, H_2 and H_{10}), 4.46 (m, 2H, H_{13}), 3.68 (d, J = 14.7 Hz, 2H, H_2 and H_{10}), 3.53 (m, 2H, H_4 and H_8), 2.93 (m, 2H, H_4 and H_8), 2.82 (m, 2H, H_5 and H_7), 2.50 (s, 6H, H_{14}), overlapping with 2.58-2.50 (m, 2H, H_5 and H_7).

Elem. An. **Found**: C, 51.4; H, 4.3; N, 6.1%

Calculated: C, 51.2; H, 4.4; N, 6.6%.



^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 8.93 (d, J = 8.1 Hz, 1H, H_i), 8.07 (d, J = 8.3 Hz, 1H, H_f), 7.92–7.88 (m, 3H, H_{Ar}), 7.82–7.74 (m, 2H, H_{Ar}), 7.69–7.62 (m, 2H, H_b and H_c), 7.53–7.48 (m, 3H, H_{Ar}), 7.39–7.36 (m, 3H, H_{Ar}), 7.29 (m, 2H, H_o), 7.05 (d, J = 7.5 Hz, 1H, H_q), 5.59 (q, J = 6.5 Hz, 1H, H_{13}), 5.31 (d, J = 16.4 Hz, 1H, H_{10}), 4.69 (m, 1H, H_7), 4.35 (m, 1H, H_2), 3.94 (d, J = 16.6 Hz, 1H, $H_{10'}$), 3.18 (m, 1H, $H_{2'}$), 3.04 (d, J = 14.2 Hz, 1H, H_8), 2.88–2.82 (m, 3H, CH_2), 2.56 (s, 3H, H_{15}), 2.42 (s, 3H, H_{15}), 2.34 (m, 2H, CH_2), 2.21 (d, J = 14.2 Hz, 1H, H_5), 1.69 (d, J = 6.5 Hz, 3H, H_{14}).

^{13}C-NMR (100 MHz; $CDCl_3$; T = 300 K) δ 156.2 (C_{11}), 152.9 (C_2), 146.2 (CH), 145.9 (CH), 140.0 (C_r), 137.2 (C_a), 134.1 (C_f), 131.9 (CH), 131.5 (CH), 130.6 ($C_{o'}$), 130.0 (C_o),

129.2 (C_n), 128.9 (CH), 128.3 (CH), 128.2 (CH), 126.7 (C_b), 126.0 (C_c), 125.2 ($C_{q'}$), 124.7 (C_g), 124.6 (CH), 124.1 (CH), 118.2 (C_h), 94.2 (C_i), 56.5 (C_2), 56.1 (C_{10}), 53.1 (C_{13}), 51.0 (C_5), 48.9 (C_7), 45.9 (C_4), 21.7 ($C_{15'}$), 21.5 (C_{15}), 12.9 (C_{14}).

^{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).

Elem. An.: Found: C, 51.6; H, 4.9; N, 6.7%;

Calculated: C, 51.9; H, 4.6; N, 6.4%.

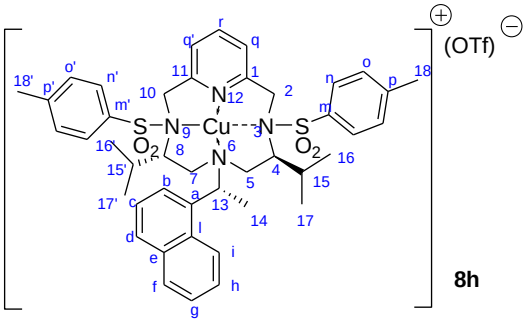
$[\alpha]_D^{20}$ - 115 (*c* 0.5 in $CHCl_3$) (complex **8e**)

115 (*c* 0.5 in $CHCl_3$) (complex **8f**)

Synthesis of copper complexes h, o, j, k, l

Copper(I) triflate benzene complex (30 mg, 0.06 mmol) was added to a solution of **6** (0.12 mmol) in dichloroethane (10 mL). The solution was stirred at room temperature for 1 hour, then was concentrated to half volume and hexane was layered until the product precipitates as white powder. The white precipitated was filtered and dried in vacuo under nitrogen atmosphere.

Yield h – 97%
k – 97%
l – 98%
o – 97%



^{1}H-NMR (300 MHz; $CDCl_3$; T = 300 K) δ 8.68 (d, J = 8.7 Hz, 1H, H_i), 7.93 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.87 (d, J = 8.1 Hz, 4H, H_n), 7.80-7.69 (m, 3H, H_{Ar}), 7.62-7.40 (m, 7H, H_{Ar}), 7.23-7.16 (m, 2H, H_{Ar}), 5.95 (q, J = 6.6 Hz, 1H, H_{14}), 5.25 (d, J = 20 Hz, 1H, H_2), 4.79 (d, J = 12.7 Hz, 1H, H_7), 4.71 (d, J = 14.6 Hz, 1H, H_{10}), 4.62 (d, J = 20 Hz, 1H, $H_{2'}$), overlapping with 4.61 (m, 1H, H_8), 4.01 (d, J = 14.6 Hz, 1H, $H_{10'}$), 2.78 (d, J = 12.7 Hz, 1H, $H_{7'}$), 2.57 (s, 3H, CH_{18}), overlapping with 2.57 (m, 1H, H_4), 2.52 (s, 3H, $H_{18'}$), 2.42-2.37 (m, 1H, H_5), 2.30-2.15 (m, 2H, $H_{5'}$ and $H_{15'}$), 2.10 (d, J = 6.8 Hz, 3H, H_{14}), 1.59 (m, 1H, H_{15}), 0.90 (d, J = 6.7 Hz, 3H, $CH_{16'}$), 0.68 (d, J = 6.2 Hz, 3H, H_{17}), 0.29 (d, J = 6.5 Hz, 3H, H_{17}), -0.49 (d, J = 6.2 Hz, 3H, H_{16}).

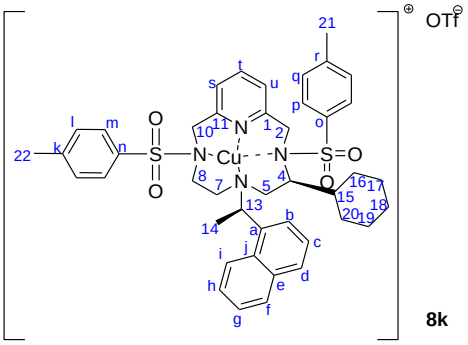
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300 K) δ 155.7 (C_{11}), 151.2 (C_1), 145.6 ($C_{p'}$), 145.3 (C_p), 140.4 (CH), 134.8 (C_a), 134.5 (C_l), 133.9 (C), 132.1 (C), 131.5 (CH), 130.4 (C_o), 129.8 (CH), 129.3 (CH), 128.9 (CH), 127.7 (CH_h), 127.3 (CH), 126.4 (CH), 125.2 (CH), 124.8 (CH), 124.5 (CH), 123.9 (CH), 122.8 (C_i), 64.7 (C_4), 62.0 (C_8), 57.4 (C_5), 57.1

(C_{10}), 56.4 (C_{13}), 55.5 (C_7), 46.8 (C_2), 29.9 ($C_{15'}$), 27.1 (C_{15}), 24.5 (C_{14}), 22.4 ($C_{16'}$), 21.9 ($C_{18 \text{ and } 18'}$), 21.3 ($C_{17'}$), 20.3 (C_{17}), 18.5 (C_{16}).

^{19}F-NMR (282 MHz; $CDCl_3$; T = 300 K) δ - 78.58 (s).

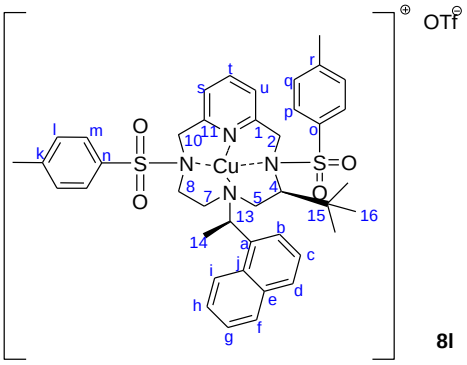
Elem. An. Found: C, 54.7; H, 5.2; N, 5.7%

Calculated: C, 54.7; H, 5.4; N, 5.8%.



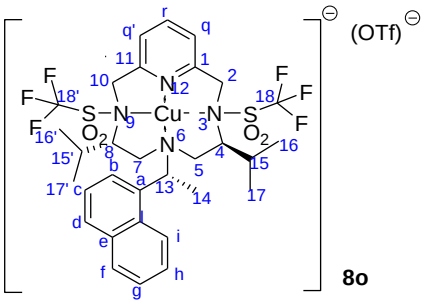
^{1}H-NMR (300 M*Hz*; $CDCl_3$, T = 300 K) δ 8.67 (d, *J* = 8.7 Hz, 1H, H_h), 7.95 (d, *J* = 8.0 Hz, 1H, H_{Ar}), 7.88-7.78 (m, 6H, H_{Ar}), 7.67-7.58 (m, 4H), 7.54-7.52 (m, 4H, H_l, H_q), 7.29 (d, *J* = 4.9 Hz, 1H - H_s), 7.16 (d, *J* = 7.4 Hz, 1H – H_u), 5.96 (d, *J* = 6.9 Hz, 1H - H_{13}), 5.17 (d, *J* = 19.5 Hz, 1H - H_2), 4.75-4.66 (m, 1H – H_7), 4.70 (d, *J* = 15.6 Hz, 1H – H_{10}), 4.58 (m, 1H – H_4), 4.44 (d, *J* = 19.5 Hz, 1H – $H_{2'}$), 3.56 (d, *J* = 15.6 Hz, 1H – $H_{10'}$), 3.00-2.76 (m, 3H, $H_{7'}$, $H_{8\text{-}8'}$), 2.55 (s, 3H, H_{21}), 2.54 (s, 3H, H_{22}), 2.54-2.47 (m, 1H, H_5), 2.34 (d, *J* = 6.5 Hz, 1H – $H_{5'}$), 1.66-1.54 (m, 2H, H_{20} – H_{17}), 1.40-1.36 (m, 1H, H_{18}), 1.16-1.10 (m, 1H, H_{15}), 1.05-0.96 (m, 2H, H_{19} - H_{17}), 0.77-0.70 (m, 2H, $H_{20'}$ - $H_{19'}$), 0.68-0.56 (m, 1H, $H_{18'}$), 0.17 (d, *J* = 11.6 Hz, 1H – H_{16}), -1.22 (d, *J* = 11.6 Hz, 1H – $H_{16'}$)

^{13}C-NMR (75 M*Hz*; $CDCl_3$, T = 300 K) δ 155.23 (C_{11}), 152.26 (C_1), 147.07 (C_r), 145.52 (C_k), 140.06 (C_t), 135.62 (C_a), 134.77 (C_j), 133.29 (C_n), 132.17 (C_e), 131.05 (C_{Ts}), 129.88 (C_{Ar}), 129.77 (C_{Ar}), 129.21 (C_m), 128.72 (C_{Ar}), 128.54 (C_o), 127.55 (C_{Ar}), 126.43 (C_{Ar}), 125.63 (C_{Ts}), 125.04 (C_{Ts}), 123.31 (C_u), 123.09 (C_s), 123.04 (C_h), 61.74 (C_4), 56.32 (C_5 - C_{10}), 56.00 (C_{13}), 51.81 (C_7), 49.20 (C_2), 46.80 (C_8), 36.48 (C_{15}), 30.30 (C_{16}), 29.35 (C_{17}), 29.06-25.96 (C_{20} – C_{18} – C_{19}), 24.27 (C_{14}), 22.13 (C_{21}), 22.08 (C_{22})



^{1}H-NMR (300 M*Hz*; $CDCl_3$, T = 300 K) δ 8.59 (d, *J* = 7.3 Hz, 1H, H_h), 8.06-7.12 (m, 17H), 6.00 (m, 1H, H_{14}), 5.25 (d, *J* = 18.9 Hz, 1H, H_2), 4.81-4.64 (m, 3H, $H_{2'}$, H_8 and H_{10}), 4.60-4.55 (m, 1H, H_4), 3.63 (d, *J* = 15.4 Hz, 1H, $H_{10'}$), 3.14 (d, *J* = 13.2 Hz, 1H, $H_{8'}$), 2.96 (m, 1H, $H_{7,7'}$), 2.79-2.36 (m, 2H, $H_{5,5'}$), 2.57-2.55 (m, 6H, H_{17} and H_{18}), 2.15 (m, 3H, H_{14}), 0.35 (s, 9H, H_{16}).

^{13}C-NMR (75 M*Hz*; $CDCl_3$, T = 300 K) δ 154.59 (C_2), 152.91 (C_{10}), 147.18 (C_r), 145.81 (C_k), 140.38 (C_t), 136.25 (C_a), 134.78 (C_{Ar}), 133.71 (C_{Ar}), 132.07 (C_{Ar}), 131.13 (C_{Ar}), 132.07 (C_{Ar}), 131.13 (C_{Ar}), 130.63 (C_{Ar}), 130.29 (C_{Ar}), 129.89 (C_{Ar}), 129.82 (C_{Ar}), 129.11 (C_{Ar}), 128.72 (C_{Ar}), 128.28 (C_{Ar}), 128.17 (C_{Ar}), 127.66 (C_{Ar}), 126.52 (C_{Ar}), 125.71 (C_{Ar}), 124.60 (C_{Ar}), 123.85 (C_{Ar}), 122.70 (C_{Ar}), 62.40 (C_4), 56.47 (C_{13}), 56.35 (C_{10}), 55.69 (C_5), 52.49 (C_8), 49.68 (C_7), 48.46 (C_2), 35.10 (C_{15}), 27.65 (C_{16}), 24.92 (C_{14}), 22.11 (C_{17} and C_{18})



^{1}H-NMR (300 MHz; $CDCl_3$; Me_4Si; T = 300 K) δ 8.16 (d, J = 8.9 Hz, 1H, H_i), 8.01 (pst, J = 7.5 Hz, 2H, H_{Ar}), 7.80 (pst, J = 7.7 Hz, 1H, H_{Ar}), 7.73 (m, 1H, H_{Ar}), 7.68-7.63 (m, 3H, H_{Ar}), 7.31 (m, 1H, H_{Ar}), 7.20 (m, 1H, H_{Ar}), 6.46 (m, 1H, H_{13}), 5.10-4.70 (m, 5H, H), 4.40-4.01 (m, 3H, H), 3.50 (m, 1H, H), 2.95 (m, 1H, H), 2.50-2.36 (m, 1H, H),

2.06 (d, J = 6.8 Hz, 3H, H_{14}), 1.52 (m, 1H, H), 1.27 (bs, 3H, H_{16}), 1.10 (bs, 3H, H_{17}), 0.80 (bs, 3H, $H_{16'}$), 0.47 (bs, 3H, $H_{17'}$).

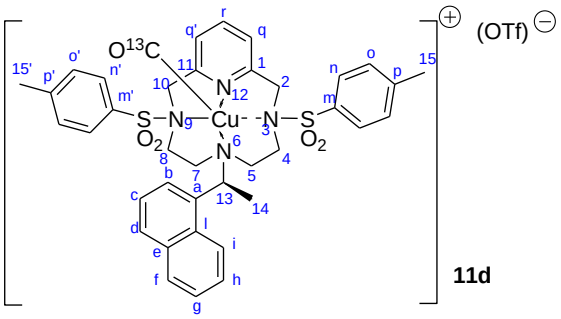
^{13}C-NMR (75 MHz; $CDCl_3$; T = 300 K) δ 139.3 (CH), 131.7 (CH), 130.4 (CH), 128.5 (CH), 127.4 (CH), 125.7 (CH), 122.6 (CH), 121.3 (C_i), 57.1 (CH_2), 43.6 (CH_2), 31.7 (CH_2), 28.8 (CH), 22.8 (CH_2), 21.3 (C_{14}), 20.8 (H_{16}), 14.3 (H_{17}). Signals relative to quaternary carbons, aromatic CH, aliphatic CH and CH_3 were not detected.

Elem. An. Found: C, 41.8; H, 3.7; N, 5.8%

Calculated: C, 41.7; H, 4.2; N, 6.1%.

Synthesis of ^{13}CO Cu complex

Copper complex **f** (20 mg) was added to anhydrous and degassed $CDCl_3$ in a NMR tube and the solution was saturated with ^{13}CO.



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, H_{Ar}), 7.88 (2H, d, J = 8.5 Hz, $H_{n \text{ or } n'}$), 7.84-7.82 (1H, m, H_{Ar}) 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, H_{Ar}), 7.53 (2H, d, J = 8.5 Hz, $H_{o \text{ or } o'}$), 7.49 (1H, m, H_{Ar}), 7.40 (2H, d, J = 8.2 Hz, $H_{o' \text{ or } o}$), 7.31 (1H, m, H_{Ar}), 7.23-7.16 (2H, m, H_{Ar}), 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, H), 2.56 (3H, s, $H_{15 \text{ or } 15'}$), 2.47 (3H, s, $H_{15' \text{ or } 15}$), 2.36-2.28 (1H, m, $H_{7 \text{ or } 5}$), 2.16 (3H, J = 6.8 Hz, H_{14}) overlapping with 2.15-2.07 (1H, m, $H_{8 \text{ or } 4}$).

^{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 (CH), 129.2 (CH_{Ts}), 129.2 (CH), 128.0 (CH_{Ts}), 126.8 (C_h), 126.1 (CH), 125.5 (2 CH), 124.2 (CH), 123.6 (CH), 122.7 (C_i), 56.8 (C_2), 56.4 ($C_{2'}$), 55.3 (C_{13}), 52.7 (C_8), 51.9 (C_5), 50.7 (C_7), 47.5 (C_4), 23.4 (C_{14}), 21.9 (C_{15}), 21.7 (C_{15}).

^{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 ν_{CO} = 2111 cm^{-1}. (CH_2Cl_2 solution)

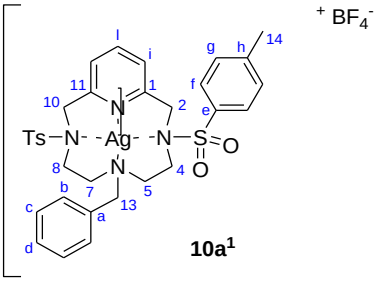
3.2.14 – Silver complexes

Synthesis of silver BF_4 complexes

Silver tetrafluoroborate (165.0 mg, 0.85 mmol) was added to a solution of 6 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 to 5 mL and distilled *n*-hexane was added causing the precipitation of the product. The precipitate was recovered by filtration and dried *in vacuo*.

Yield

a – 91%	b – 43%
d – 90%	h – 48%
k – 82%	m – 43%



10a[1]

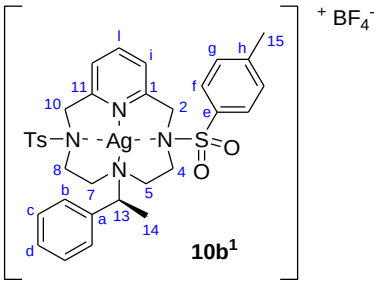
^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K): δ = 7.77 (t, J = 7.7 Hz, 1H) overlapping with 7.74 (d, J = 8.0 Hz, 4H), 7.60 (d, J = 6.9 Hz, 2H), 7.45 (d, J = 8.0 Hz, 4H) overlapping with 7.42 (m, 3H), 7.28 (d, J = 7.7 Hz, 2H), 5.04 (d, J = 15.2 Hz, 2H), 3.97 (s, 2H), 3.70 (d, J = 15.2 Hz, 2H), 3.51 (m, 2H), 2.94 (m, 2H), 2.65 (m, 2H), 2.49 (s, 6H), 2.06 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$, T = 300 K) δ 153.4, 145.9, 140.5, 135.6, 130.9, 130.7, 130.6, 128.8, 128.6, 128.4, 125.0, 58.4, 56.3, 52.9, 47.5, 21.9

^{19}F-NMR (282 MHz, $CDCl_3$, T = 300 K): δ = -152.8 .

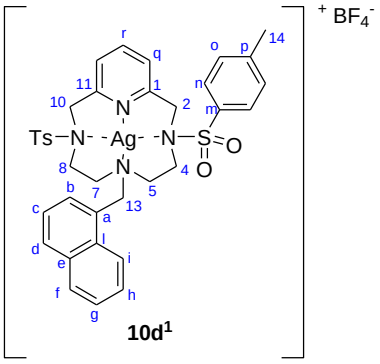
MS (FAB) m/z (%) = 711 m/z (100) $[M^+ – BF_4]$, 605 (94) $[MH – AgBF_4]^+$

UV/vis (5.2 10-5 mol L-1, CHCl3 in 1-cm cuvettes): λmax [nm], (log ε) = 243 (4.26); 263 (3.89) nm.



^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 7.82 (m, 5H, H_{Ar}), 7.51 (m, 4H, H_{Ar}), 7.46 (m, 4H, H_{Ar}), 7.39 (m, 2H, H_{Ar}), 7.26 (m, 1H, H_{Ar}), 5.10 (d, J = 16.1 Hz, 1H, H_2), 4.99 (d, J = 14.8 Hz, 1H, H_{10}), 4.82 (q, J = 6.7 Hz, 1H, H_{13}), 4.33 (br, 1H), 3.96 (br, 1H), 3.87 (d, J = 16.1 Hz, 1H, H_2), 3.65 (d, J = 14.8 Hz, 1H, H_{10}), 3.64 (br, 1H), 3.15 (br, 1H), 2.76 (m, 1H), 2.54 (s, 3H, H_{15}), 2.53 (s, 1H, H_{15}), 2.45 (br, 1H), 1.95 (br, 1H), 1.86 (br, 1H), 1.80 (d, J = 6.7 Hz, 3H, H_{14}).

^{19}F NMR (225 MHz, $CDCl_3$, T = 300 K) δ = -152.85 ($^{10}BF_4$), -152.90 ($^{11}BF_4$).



^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K): δ 9.16 (d, J = 8.1 Hz, 1H, H_i), 8.12 (d, J = 8.1 Hz, 1H, H_f), 7.99 (d, J =8.1 Hz, 1H, H_d), 7.90 (m, 1H, H_h), 7.81 (t, J = 7.9 Hz, 1H, H_r), 7.72 (m, 1H, H_b), 7.67-7.59 (m, 2H, H_c and H_g) overlapping with 7.59 (d, J = 7.8 Hz, 4H, H_n), 7.41 (d, J = 7.8 Hz, 4H, H_o), 7.24 (d, J = 7.9 Hz, 2H, H_q), 4.89 (d, J = 15.0 Hz, 2H, H^2 and H_{10}), 4.35 (br s, 2H, H_{13}), 3.50 (d, J = 15.0 Hz, 2H, $H_{2'}$ and $H_{10'}$) overlapping with 3.51-3.48 (m, 2H, CH_2), 2.81 (m, 2H, CH_2), 2.59 (m, 2H, CH_2), 2.49 (s, 6H, H_{14}), 2.13 (m, 2H, CH_2).

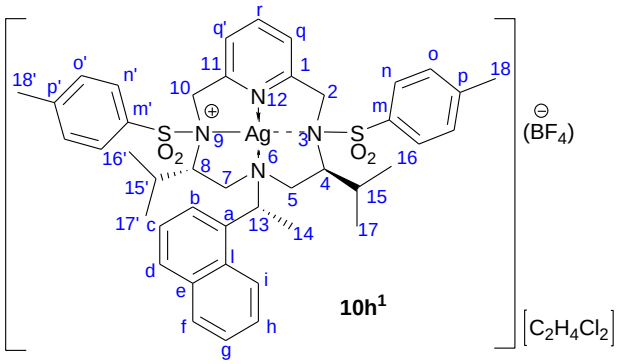
^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K): δ 154.0 (C_1), 146.0 (C_p), 141.0 (C_r), 135.3 (C_m), 133.8 (C), 133.2 (C), 132.5 (C_f), 131.1 (C), 130.8 (C_o), 130.7 (C_b), 130.0 (C_d), 128.6 (C_n), 127.1 (C_h), 126.4 (CH), 125.8 (CH), 125.3 (C_q), 112.3 (C_i), 56.4 (C_{13}), 56.3 (C_2 and C_{10}), 54.7 (CH_2), 48.3 (CH_2), 22.1 (C_{14}).

^{19}F-NMR (282 MHz, $CDCl_3$, T = 300 K): δ -152.8

MS (FAB) m/z (%) = 761/763 (90/100) $[M - BF4]^+$, 655 (37) $[MH - AgBF4]^+$

Elem. An. Found: C, 50.75; H, 4.61; N, 6.43%

Calculated: C, 50.90; H, 4.51; N, 6.60%.

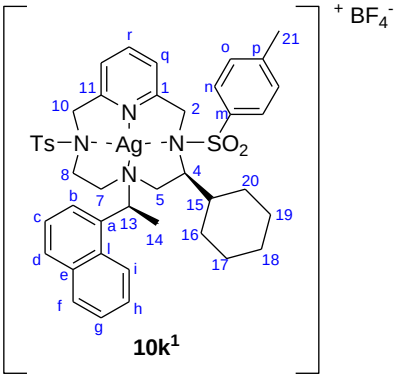


10h^1

^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K) δ 8.69 (d, J = 8.4 Hz, 1H, H_i), 7.96 – 7.87 (m, 6H, H_{Ar}), 7.81 (d, J = 7.6 Hz, 1H, H_{Ar}), 7.72 (m, 1H, H_{Ar}), 7.59 -7.44 (m, 8H, H_{Ar}), 7.37 (d, J = 7.5 Hz, 1H, H_{Ar}), 6.02 (q, J = 6.5 Hz, 1H, H_{13}), 5.38 (d, J = 17.5 Hz, 1H, H_2), 4.93 (d, J = 14.0 Hz, 1H, CH_{10}), 4.59 (pt, J = 12.1 Hz, 1H, CH_5), 4.24 (d, J = 17.5 Hz, 1H, H_2), 4.17 (m, 1H, H_8) 4.07 (d, J = 14.0 Hz, 1H, H_{10}), 3.73 (3.5H, DCE), 2.50 (s, 3H, H_{18}), 2.47 (s, 3H, $H_{18'}$) overlapping with 2.49 (m, 1H, H_7), 2.25 (m, 2H, CH_{15} and H_4), 2.04 (d, J = 6.5 Hz, 3H, H_{14}), 1.62 (m, 2H, CH_2), 1.03 (m, 1H, $H_{15'}$), 0.88 (m, 3H, H_{16}), 0.46 (d, J = 5.6 Hz, 3H, H_{17}), -0.02 (d, J = 5.0 Hz, 3H, $H_{16'}$), -0.32 (d, J = 5.6 Hz, 3H, $H_{17'}$).

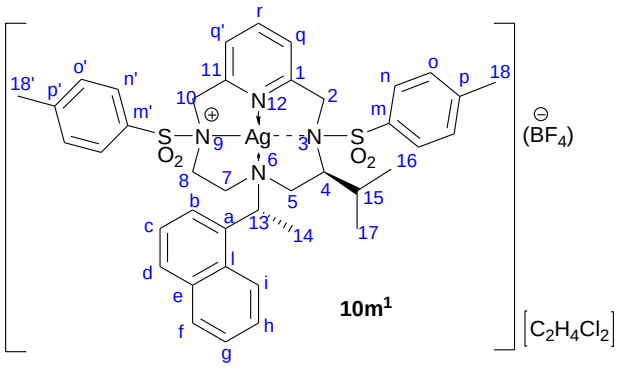
^{13}C-NMR (75 MHz, $CDCl_3$) δ 155.8 (C), 152.6 (C), 145.8 (C), 145.5 (C), 141.3 (CH), 135.3 (C), 134.5 (C), 134.5 (C), 134.4 (C), 132.5 (C), 130.8 (CH), 130.6 (CH), 129.8 (CH), 128.8 (CH), 128.4 (CH), 127.7 (CH), 127.2 (CH), 126.8 (C_h), 126.5 (CH), 126.0 (CH), 125.3 (CH), 125.0 (CH), 124.2 (CH), 122. (C_i), 63.6 (C_{15}), 59.1 (C_8), 57.1 (C_{10}), 54.4 (C_{13}), 52.5 (CH_2), 49.1 (C_2), 43.7 (DCE), 31.7 (C_4), 28.4 ($C_{15'}$), 22.7 (C_{17}), 21.8 (C_{18}), 21.1 (C_{16}), 21.0 ($C_{17'}$), 17.7 ($C_{16'}$).

^{19}F-NMR (225MHz, CDCl3, T = 300 K) δ = -153.13



^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K): δ 8.78 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.98 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.92-7.19 (m, 16H, HAr), 5.88 (q, J = 6.2 Hz, 1H, H_{13}), 5.22 (d, J = 17.7 Hz, 1H, H_2), 4.72 (d, J = 14.9 Hz, 1H, H_{10}), 4.38 (pt, J = 12.0 Hz, 1H, H_8), 4.09 (d, J = 17.7 Hz, 1H, $H_{2'}$), 3.91-3.80 (m, 1H, H_4), 3.62 (d, J = 14.9 Hz, 1H, $H_{10'}$), 3.12-3.02 (m, 2H, $H_{8'}$ and H_7), 2.72-2.59 (m, 1H, $H_{7'}$), 2.54 (s, 3H, H_{21}), 2.49 (s, 3H, $H_{21'}$), 2.72-2.59 (m, 1H, H_5), 1.97 (d, J = 6.2 Hz, 3H, H_{14}) overlapping with 2.10-1.95 (m, 1H, $H_{5'}$), 1.57-0.28 (m, 11H, H_{cy})

^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K) δ 155.28 (C_{Ar}), 153.37 (C_{Ar}), 146.57 (C_{Ar}), 145.90 (C_{Ar}), 140.82 (CH_{Ar}), 136.30 (C_{Ar}), 135.10 (C_{Ar}), 134.90 (C_{Ar}), 132.59 (C_{Ar}), 131.09 (CH_{Ar}), 130.90 (CH_{Ar}), 130.50 (CH_{Ar}), 130.12 (CH_{Ar}), 129.72 (CH_{Ar}), 129.30 (CH_{Ar}), 129.18 (CH_{Ar}), 129.08 (CH_{Ar}), 127.81 (CH_{Ar}), 127.34 (CH_{Ar}), 126.71 (CH_{Ar}), 126.11 (CH_{Ar}), 125.79 (CH_{Ar}), 125.44 (CH_{Ar}), 123.36 (CH_{Ar}), 121.49 (CH_{Ar}), 60.95 (C_4), 56.19 (C_{10}), 54.30 (C_{13}), 52.22 (C_8 and C_5), 49.19 (C_2), 47.60 (C_7), 39.53 (C_{15}), 31.86 (CH_{2cy}), 29.11 (CH_{2cy}), 26.69 (CH_{2cy}), 26.03 (CH_{2cy}), 25.80 (CH_{2cy}), 22.15 (C_{21}), 22.03 ($C_{21'}$), 21.09 (C_{14}).



10m[1]

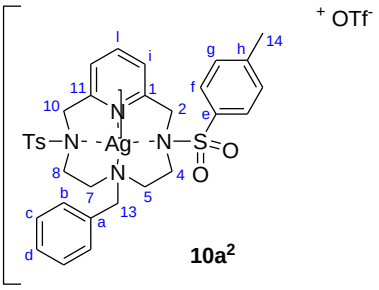
[1]H-NMR (300 MHz, $CDCl_3$, T = 300 K) δ 8.71 (d, J = 8.5 Hz, 1H, H_i), 7.94 – 7.71 (m, 8H, H_{Ar}), 7.62–7.47 (m, 5H, H_{Ar}), 7.42–7.34 (m, 3H, H_{Ar}), 7.23 (d, J = 7.6 Hz, 1H, H_q), 6.00 (q, J = 6.7 Hz, 1H, H_{13}), 5.58 (d, J = 17.7 Hz, 1H, H_2), 4.55 (m, 2H), 4.13 (d, J = 17.7 Hz, 1H, H_2), 3.99 (m, 1H, CH_2), 3.54 (d, J = 15.0 Hz, 1H, H_{10}), 2.91 (m, 1H), 2.71-2.54 (m, 2H), 2.46 (s, 3H, H_{18}), 2.48 (s, 3H, $H_{18'}$), 1.96 (d, J = 6.7 Hz, 3H, H_{14}) overlapping with 1.96 (m, 2H), 0.98 (m, 1H), 0.06 (d, J = 6.7 Hz, 3H, H_{17}), -0.33 (d, J = 5.4 Hz, 3H, H_{16}).

[13]C-NMR (75 MHz, $CDCl_3$, T = 300 K) δ 155.1 (C), 152.7 (C), 146.2 (C), 145.8 (C), 140.7 (CH), 136.0 (C), 134.5 (C), 134.3 (C), 132.3 (C), 130.8 (CH), 130.7 (CH), 129.9 (CH), 129.1 (CH), 128.5 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 125.5 (CH), 123.4 (CH), 122.1 (C_i), 59.9 (C_4), 56.0 (CH_2), 53.8 (C_{13}), 51.3 (CH_2), 50.9 (CH_2), 49.0 (CH_2), 46.7 (CH_2), 43.7 (DCE), 31.7 (CH_2), 28.6 (C_{15}), 22.4 (C_{14}), 21.9 (C_{18}), 21.8 ($C_{18'}$), 20.9 (C_{16}), 17.8 (C_{17}).

Synthesis of silver OTf complexes

Silver triflate (88.7 mg, 0.34 mmol) was added to a solution of **6** 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 to 5 mL and distilled *n*-hexane was added causing the precipitation of the product. The precipitate was recovered by filtration and dried *in vacuo*.

Yield a – 73%
b – 43%
d – 89%
l – 90%



10a[2]

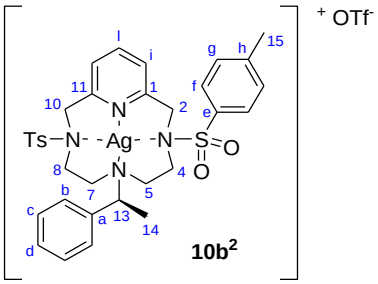
^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K): δ 7.83 (t, J = 7.7 Hz, 1H), 7.72 (d, J = 8.0 Hz, 4H), 7.65 (d, J = 7.1 Hz, 2H), 7.50 (m, 3H) overlapping with 7.45 (d, J = 8.0 Hz, 4H), 7.33 (d, J = 7.7 Hz, 2H), 5.01 (d, J = 14.9 Hz, 2H), 3.89 (s, 2H) overlapping with 3.85 (m, 2H), 3.53 (m, 2H), 3.04 (m, 2H), 2.87 (m, 2H), 2.51 (s, 6H), 2.22 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K): δ 153.7, 145.9, 140.5, 136.0, 130.9, 130.7, 130.6, 129.1, 128.7, 128.2, 125.0, 58.9, 56.4, 53.5, 47.7, 21.8

^{19}F-NMR (282 MHz, $CDCl_3$, T = 300 K): δ -78.7 .

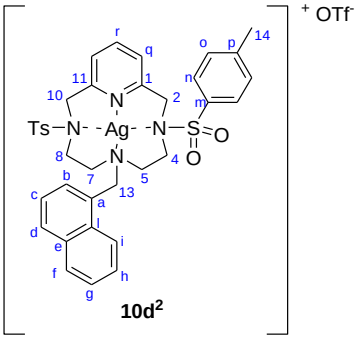
MS (FAB) m/z (%) = 711 m/z (100) $[M^+ - CF_3SO_3]$, 605 (90) $[MH - AgCF_3SO_3]^+$

UV/vis (5.1 10-5 mol L-1, CHCl3 in 1-cm cuvettes): λmax [nm], (log ε) = 242 (4.32); 263 (3.94) nm.



^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 7.80 (m, 5H, H_{Ar}), 7.43 (m, 10H, H_{Ar}), 7.29 (m, 1H, H_{Ar}), 5.07 (d, J = 15.2 Hz, 1H, H_2), 4.92 (d, J = 14.6 Hz, 1H, H_2), 4.69 (br, 1H, H_{13}), 3.98 (br, 2H), 3.69 (m, 2H), 3.11 (br, 1H), 2.83 (br, 1H), 2.62 (m, 1H), 2.51 (s, 6H, H_{15}), 2.44 (m, 1H), 1.97 (m, 1H), 1.84 (m, 1H), 1.77 (d, J = 6.8 Hz, 3H, H_{14}).

^{19}F NMR (225 MHz, $CDCl_3$, T = 300 K) δ = -78.37 (CF_3).



^{1}H NMR (300 MHz, $CDCl_3$, T = 300 K): δ 9.18 (d, J = 8.4 Hz, 1H, H_i), 8.12 (d, J = 8.4 Hz, 1H, H_f), 8.00 (d, J =8.1 Hz, 1H, H_d), 7.92 (m, 1H, H_h), 7.84 (t, J = 7.7 Hz, 1H, H_r), 7.73 (m, 1H,H_b), 7.69-7.62 (m, 2H, H_c and H_g), 7.59 (d, J = 8.2 Hz, 4H, H_n), 7.41 (d, J = 8.2 Hz, 4H, H_o), 7.26 (d, J = 7.7 Hz, 2H, H_q), 4.88 (d, J = 15.0 Hz, 2H, H_2 and H_{10}), 4.36 (br s, 2H, H_{13}), 3.59 (d, J = 15.0 Hz, 2H, $H_{2'}$ and $H_{10'}$) overlapping with 3.57-3.49 (m, 2H, CH_2), 2.84 (m, 2H, CH_2), 2.74 (m, 2H, CH_2), 2.50 (s, 6H, H_{14}), 2.26 (m, 2H, CH_2).

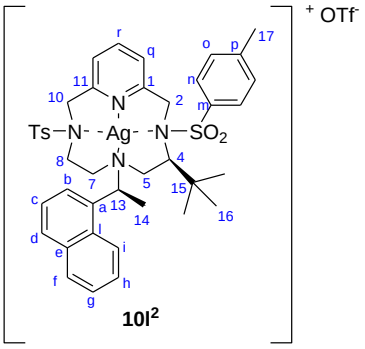
^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K): δ 154.1 (C_1), 146.0 (C_p), 141.0 (C_r), 135.3 (C_m), 133.7 (C), 133.2 (C), 132.7 (C_f), 131.2 (C), 130.8 (C_o) overlapping with 130.8 (C_b), 130.1 (C_d), 128.6 (C_n), 127.1 (C_h), 126.5 (C_H), 125.9 (C_H), 125.4 (C_q), 112.4 (C_i, J^1H-^{13}C = 156.8 Hz), 56.6 (C_{13}), 56.4 (C_2 and C_{10}), 54.8 (CH_2), 48.3 (CH_2), 22.1 (C_{14}).

^{19}F-NMR (282 MHz, $CDCl_3$, T = 300 K): δ -78.5.

MS (FAB) m/z (%) = 761/763 (90/100) $[M - CF_3SO_3]^+$, 655 (35) $[MH - AgCF_3SO_3]^+$

Elem. An. Found: C, 48.41; H, 4.52; N, 6.02%

Calculated: C, 48.74; H, 4.20; N, 6.14%.



10l²

^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K): δ 8.77 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.93-7.49 (m, 13H), 7.42-7.32 (m, 2H), 7.24 (d, J = 7.7 Hz, 1H), 5.88 (q, J = 6.9 Hz, 1H, H_{13}), 5.06 (d, J = 18.0 Hz, 1H, H_2), 4.81 (d, J = 15.4 Hz, 1H, H_{10}), 4.49 (d, J = 18.0 Hz, 1H, $H_{2'}$), 4.04 (d, J = 10.9 Hz, 1H, H_4), 3.74 (d, J = 15.4 Hz, 1H, $H_{10'}$), 3.28 (m, 1H, H_8), 2.99-2.74 (m, 2H, $H_{8'}$ and H_7), 2.54 (s, 3H, H_{17}) overlapping with 2.53-2.48 (m, 2H, H_5 and $H_{7'}$), 2.49 (s, 3H, H_{17}), 2.02 (m, 1H, $H_{5'}$) overlapping with 1.99 (d, J = 6.9, 3H, H_{14}), 0.34 (s, 9H, H_{16})

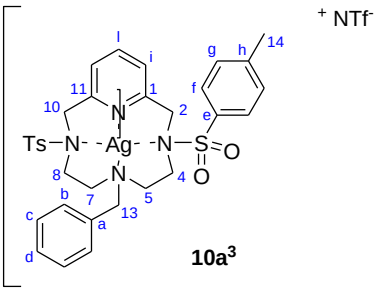
^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K): δ 155.38 (C_{Ar}), 154.25 (C_{Ar}), 146.69 (C_{Ar}), 145.81 (C_{Ar}), 140.49 (CH_{Ar}), 136.72 (C_{Ar}), 136.52 (C_{Ar}), 134.98 (C_{Ar}), 132.36 (C_{Ar}), 131.08 (CH_{Ar}), 131.00 (CH_{Ar}), 130.63 (CH_{Ar}), 129.25 (CH_{Ar}), 128.57 (CH_{Ar}), 127.59 (CH_{Ar}), 126.26 (CH_{Ar}), 125.87 (CH_{Ar}), 125.77 (CH_{Ar}), 125.02 (CH_{Ar}), 123.14 (CH_{Ar}), 63.37 (C_4), 55.96 (C_{10}), 54.95 (C_{13}), 53.34 (C_5) 53.30 (C_7), 49.78 (C_2), 48.80 (C_8), 36.21 (C_{15}), 29.02 (C_{14}), 28.52(C_{16}), 22.13 (C_{17}), 22.00 (C_{17}).

Synthesis of silver NTf complexes

Silver triflimide (116.0 mg, 0.30 mmol) was added to a solution of 6 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 to 5 mL and distilled *n*-hexane was added causing the precipitation of the product. The precipitate was recovered by filtration and dried *in vacuo*.

Yield a – 54%

h – 67%

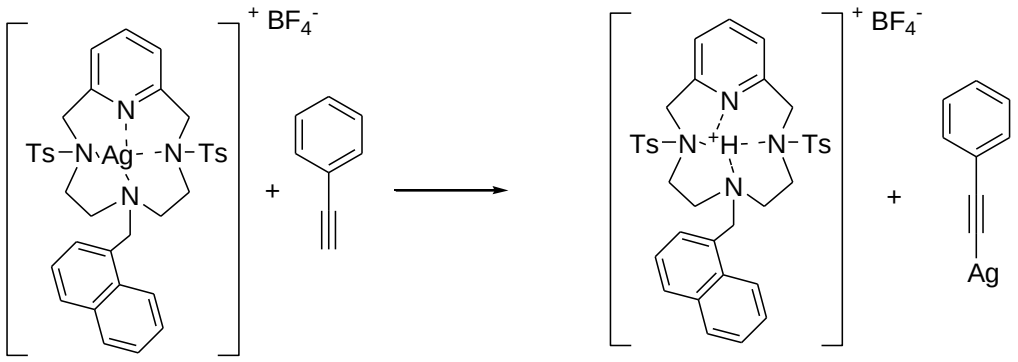


10a[3]

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.84 (t, J = 7.7 Hz, 1H), 7.71 (d, J = 8.0 Hz, 4H), 7.65 (d, J = 7.1 Hz, 2H), 7.50 (m, 3H) overlapping with 7.47 (d, J = 8.0 Hz, 4H), 7.28 (m, 2H), 5.05 (d, J = 14.9 Hz, 2H), 3.90 (s, 2H), 3.70 (m, 2H), 3.53 (m, 2H), 3.01 (m, 2H), 2.72 (m, 2H), 2.51 (s, 6H), 2.17 (m, 2H)

Spectroscopic results for complex **10a**[3] have the same pattern reported for **10a**[1] in this section.

Reaction of 10d[1] with phenylacetate



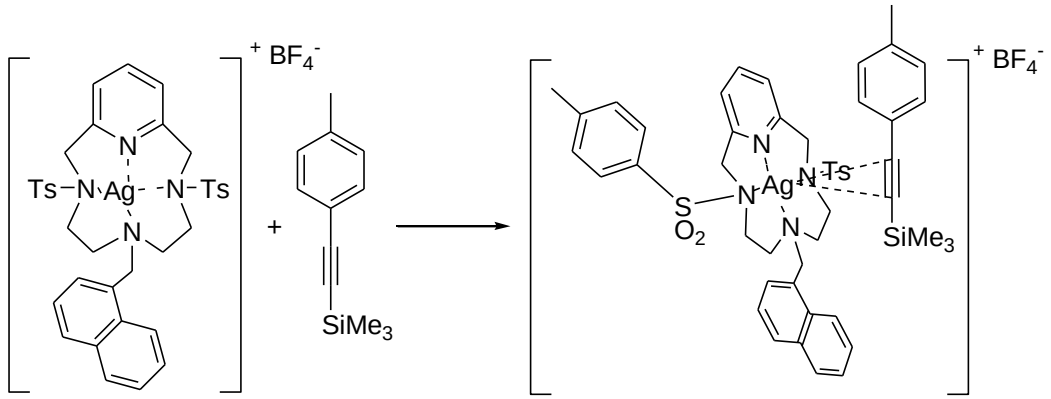
10d[1]

10d[1] (131 mg, 0.154 mmol) was dissolved in CH_2Cl_2 (5 mL), then phenylacetylene (15.8 mg, 0.155 mmol), dissolved in CH_2Cl_2 (1 mL) is added to the solution. After one hour, noticeable formation of precipitate was observed. The mixture was concentrated and hexane was layered on it; the solids was recovered by filtration.

^{1}H-NMR analysis of the crude demonstrated the formation of the protonated ligand.

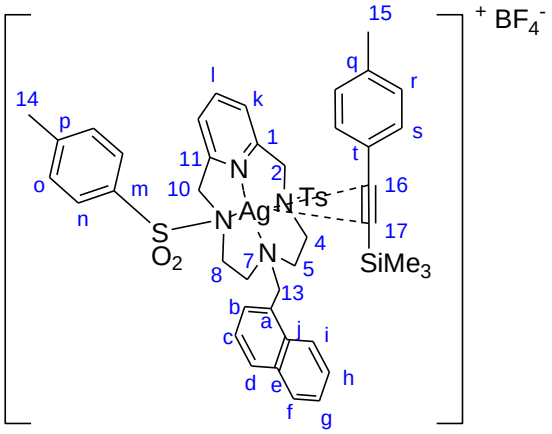
MS (FAB+) m/z 655 (LH^+)

Reaction of 10d[1] with 4-((methylphenyl)-ethynyl)trimethylsilane



10d[1]

10d[1] (18 mg, 0.021 mmol) was dissolved in $CDCl_3$ (0.7 mL), then the alkyne (12.4 mg, 0.064 mmol), was added to the solution. After one hour, noticeable formation of precipitate was observed. The mixture was concentrated and hexane was layered on it; the solids were recovered by filtration.

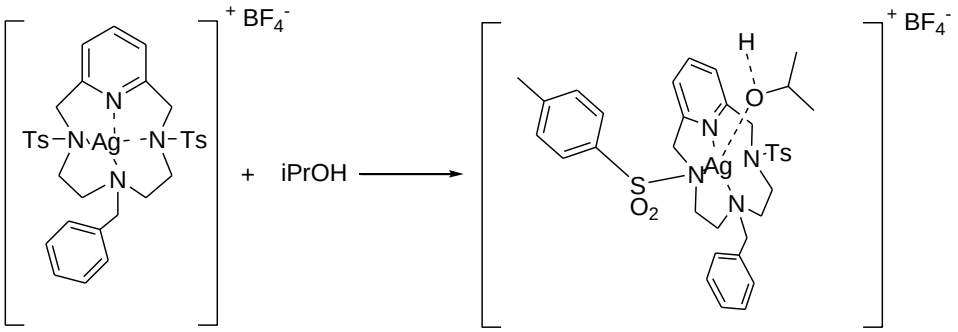


[1]H NMR (400 MHz, $CDCl_3$, T = 300 K) δ = 8.07 (s, 1H, H_i), 7.92 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.84 (d, J = 8.1 Hz, 2H, H_{Ar}), 7.76 (d, J = 7.6 Hz, 3H, H_{Ar}), 7.63 (m, 2H, H_{Ar}), 7.55 (t, J = 8.0 Hz, 1H, H_n), 7.45 (m, 16H, H_o and H_r), 7.35 (m, 1H, H_{Ar}), 7.30 (m, 3H, H_{Ar}), 7.13 (d, J = 7.8 Hz, 12H, H_s), 5.17 (d, J = 15.0 Hz, 2H, H_2), 4.31 (s, 2H, H_{13}), 3.73 (d, J = 15.0 Hz, 2H, H_2), 3.45 (m, 2H, H_4), 3.09 (s, 2H, H_5), 2.59 (d, 2H, H_8), 2.51 (s, 6H, CH_3), 2.33 (s, 12H, H_{14}), 1.91 (m, 2H, H_7'), 0.28 (s, 27H, $Si(CH_3)_3$).

[13]C NMR (100 MHz, $CDCl_3$, T = 300 K) δ = 145.4 (C_m), 138.9 (C_q), 132.1 (C_s), 130.43 (C_o), 129.0 (C_r), 128.2 (C_n), 126.2 (CH), 125.3 (CH), 105.5 (C_{16}), 91.3 (C_{17}), 47.3 (H_{14}), 21.5 (H_{15}), 0.0 ($Si(CH_3)_3$).

[29]Si NMR (80 MHz, $CDCl_3$, T = 300 K) δ = -17.08 ($Si(CH_3)_3$).

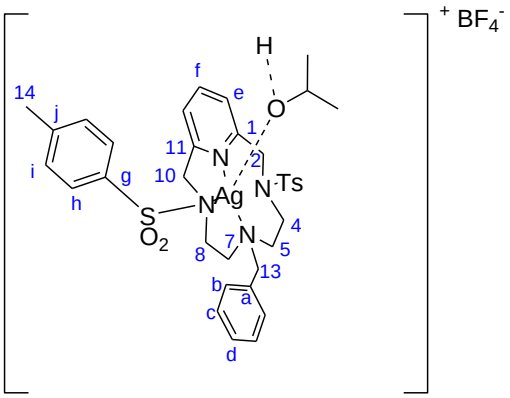
Reaction of 10b[1] with 2-propanol



10b[1]

10b[1] (219.0 mg, 0.27 mmol) was suspended in 2-propanol (20 mL) and allowed to reflux for one hour. The mixture was concentrated and the solid recovered by filtration.

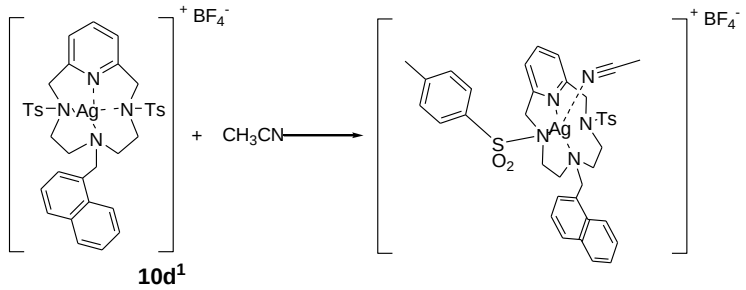
A single crystal suitable for diffraction was obtained from a solution of complex in 2-propanol by layering hexane.



[1]H-NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 7.81 (m, 5H, H_{Ar}), 7.49 (m, 4H, H_{Ar}), 7.40 (m, 5H, H_{Ar}), 7.27 (m, 1H, H_{Ar}), 5.11 (d, J = 15.3 Hz, 1H, H_2), 4.98 (d, J = 14.6 Hz, 1H, H_{10}), 4.83 (q, J = 6.4 Hz, 1H, H_{13}), 4.08 (h, J = 6.1 Hz, 1H, $(CH_3)_2CHOH$), 3.98 (br, 1H, H_5), 3.87 (d, J = 15.4 Hz, 1H, H_2), 3.69 (br, 1H, H_7), 3.64 (d, J = 14.5 Hz, 1H, CH_{10}), 3.13 (br, 1H, H_4), 2.72 (m, 1H, H_8), 2.54 (s, 3H, CH_{15}), 2.51 (s, 3H, CH_{15}), 2.42 (m, 2H, H_7 and H_5), 1.94 (m, 1H, H_4), 1.82 (t, J = 6.4 Hz, 3H, H_{14}), 1.60 (m, 1H, H_8), 1.25 (d, J = 6.1 Hz, 6H, $(CH_3)_2CHOH$).

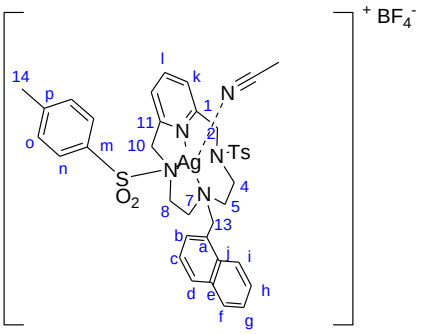
[19]F-NMR (225 MHz, $CDCl_3$, T = 300 K) δ = -152.92 ($^{10}BF_4$), -152.87 ($^{11}BF_4$).

Reaction of 10d[1] with acetonitrile



10d[1]

10d[1] (41.2 mg, 0.048 mmol) was dissolved in DCE (0.5 mL), and acetonitrile (0.1 mL of a solution in DCE, prepared in a 10 ml volumetric flask) was added. Some white precipitate formed, and the solution was analysed by IR spectroscopy, focusing on the C≡N stretching bands. The solid was then recovered by filtration. A single crystal suitable for diffraction was obtained from a solution of the complex in DCE and hexane, exposed to acetonitrile vapours.

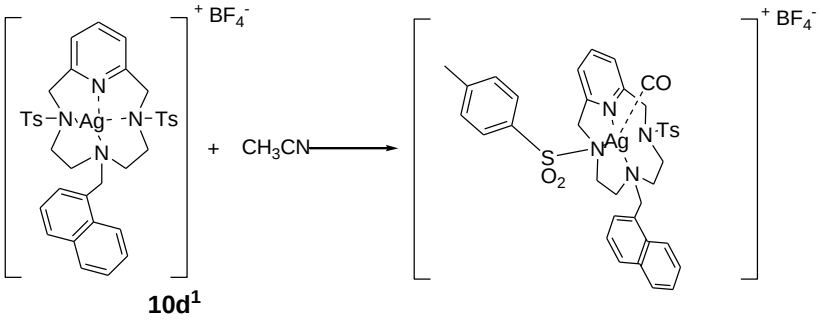


IR 2307, 2293, 2279, 2255 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 8.79 (d, J = 8.7 Hz, 1H, H_i), 8.05 (d, J = 8.1 Hz, 1H, H_{Ar}), 7.97 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.92 (d, J = 6.8 Hz, 1H, H_{Ar}), 7.84 (d, J = 7.9 Hz, 1H, H_{Ar}), 7.79 (d, J = 9.5 Hz, 1H, H_{Ar}), 7.60 (m, 2H, H_{Ar}), 7.58 (d, J = 8.1 Hz, 4H, H_o), 7.40 (d, J = 8.1 Hz, 4H, H_n), 7.25 (d, J = 7.8 Hz, 2H, H_k), 4.99 (d, J = 15.0 Hz, 2H, H_2), 4.39 (s, 2H, H_{13}), 3.59 (d, J = 15.0 Hz, 2H, H_{10}'), 3.49 (br, 2H, H_4), 2.90 (m, 2H, H_5), 2.63 (m, 2H, H_8), 2.49 (s, 6H, H_{14}), 2.21 (m, 2H, H_7), 2.12 (s, 3H, CH_3CN).

^{13}C NMR (75 MHz, $CDCl_3$, T = 300 K) δ = 154.1 (C_2), 145.8 (C_m), 140.8 (CH), 134.8 (C), 133.5 (C_{13}), 133.2 (C), 131.3 (CH), 131.2 (C), 130.8 (C_o), 129.9 (CH), 128.5 (C_n), 127.0 (CH), 126.2 (CH), 125.9 (CH), 125.1 (CH), 117.8 (CH_3CN), 117.0 (C_i); 56.4 (C_{10}), 55.5 (C_8), 54.6 (C_5 and C_7), 48.1 (C_4), 22.1 (H_{14}), 2.59 (CH_3CN).

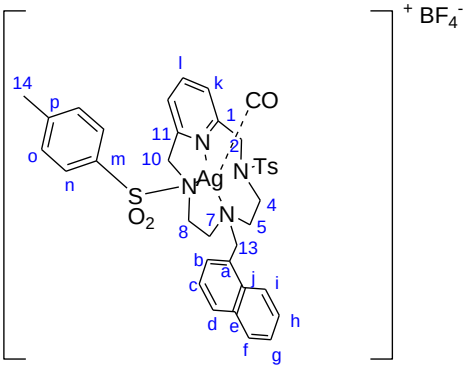
Reaction of 10d[1] with CO



10d[1]

10d[1] (15.1 mg, 0.018 mmol) was dissolved in DCE (1 mL), and the mixture was stirred for 1 hour under a CO atmosphere. The mixture was analysed by IR, showing a band at 2156 cm^{-1} (vs. 2143 cm^{-1} for uncoordinated CO). After exposure to vacuum and flushing with nitrogen, the band was no longer visible.

In an NMR tube, **10d[1]** was dissolved in $CDCl_3$ and exposed first to a CO atmosphere and then to an enriched ^{13}CO atmosphere. ^{1}H and ^{13}C NMR spectra were recorded, and then the solution was twice freezed and the atmosphere replaced with nitrogen. NMR analyses were performed again.

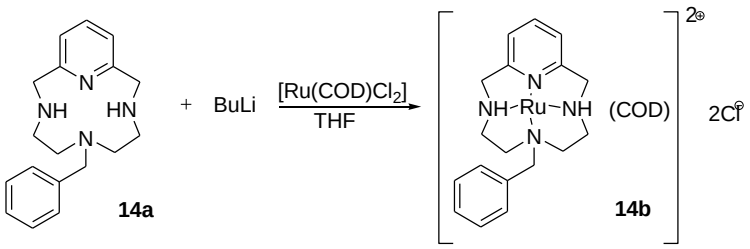


^{1}H-NMR (300 MHz, $CDCl_3$, T = 300 K) δ = 8.89 (d, J = 8.3 Hz, 1H, H_i), 8.07 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.98 (d, J = 8.2 Hz, 1H, H_{Ar}), 7.83 (m, 2H), 7.63 (m, 2H, H_{Ar}), 7.56 (d, J = 8.1 Hz, 4H, H_n), 7.39 (d, J = 8.1 Hz, 4H, H_o), 7.34 (m, 1H, H_{Ar}), 7.25 (d, J = 7.8 Hz, 2H, H_k), 4.93 (d, J = 15.2 Hz, 2H, H_2), 4.36 (s, 2H, H_{13}), 3.59 (d, J = 15.2 Hz, 2H, H_{10}), 3.49 (m, 2H, H_4), 2.88 (m, 2H, H_5), 2.63 (m, 2H, H_8), 2.45 (s, 6H, CH_{14}), 2.17 (m, 2H, H_7).

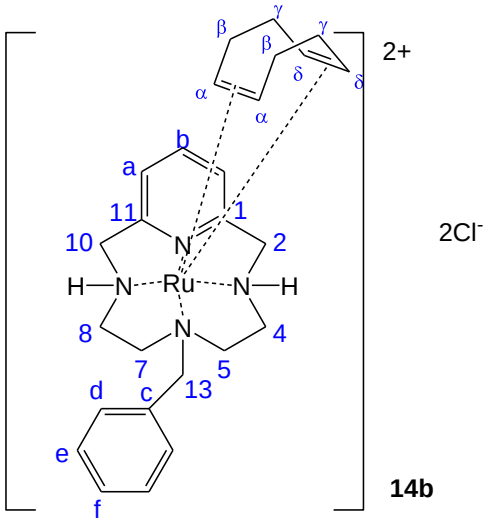
^{13}C-NMR (75 MHz, $CDCl_3$, T = 300 K) δ = 176.8 (CO), 153.7 (C_2), 145.6 (C_m), 140.5 (C), 134.6 (C), 132.9 (C), 131.5 (C), 130.7 (CH) 130.4 (C_o), 129.8 (CH), 129.4 (CH), 128.1 (C_n), 127.9 (CH), 126.8 (CH), 125.6 (CH), 125.5 (CH), 124.8 (CH), 114.4 (C_i), 55.8 (C_{10}), 54.5 (C_4 and C_8), 47.9 (C_5 and C_7), 21.6 (CH_{14}).

3.2.15 – Ruthenium complexes

Synthesis of ruthenium COD 2Cl⁻ complex



To a solution of **13a** (271.6 mg; 0.9 mmol) in distilled THF (14mL), was added of BuLi (0.8 mL, 1.8 mmol) in hexane (5 mL) solution. During the addition the mixture change its color from yellow to dark red, of $Ru(COD)Cl_2$ (260.2 mg, 0.9 mmol) were then added. The reaction is left to react to reflux for half an hour and then filtered. The precipitated was then extracted for 15 hours using the filtrated solution. The precipitated over the extractor was then collected giving the complex as brownish poweder in 45% yield.

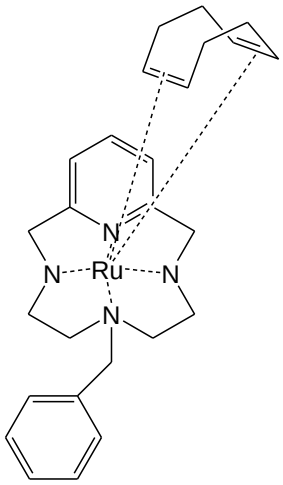


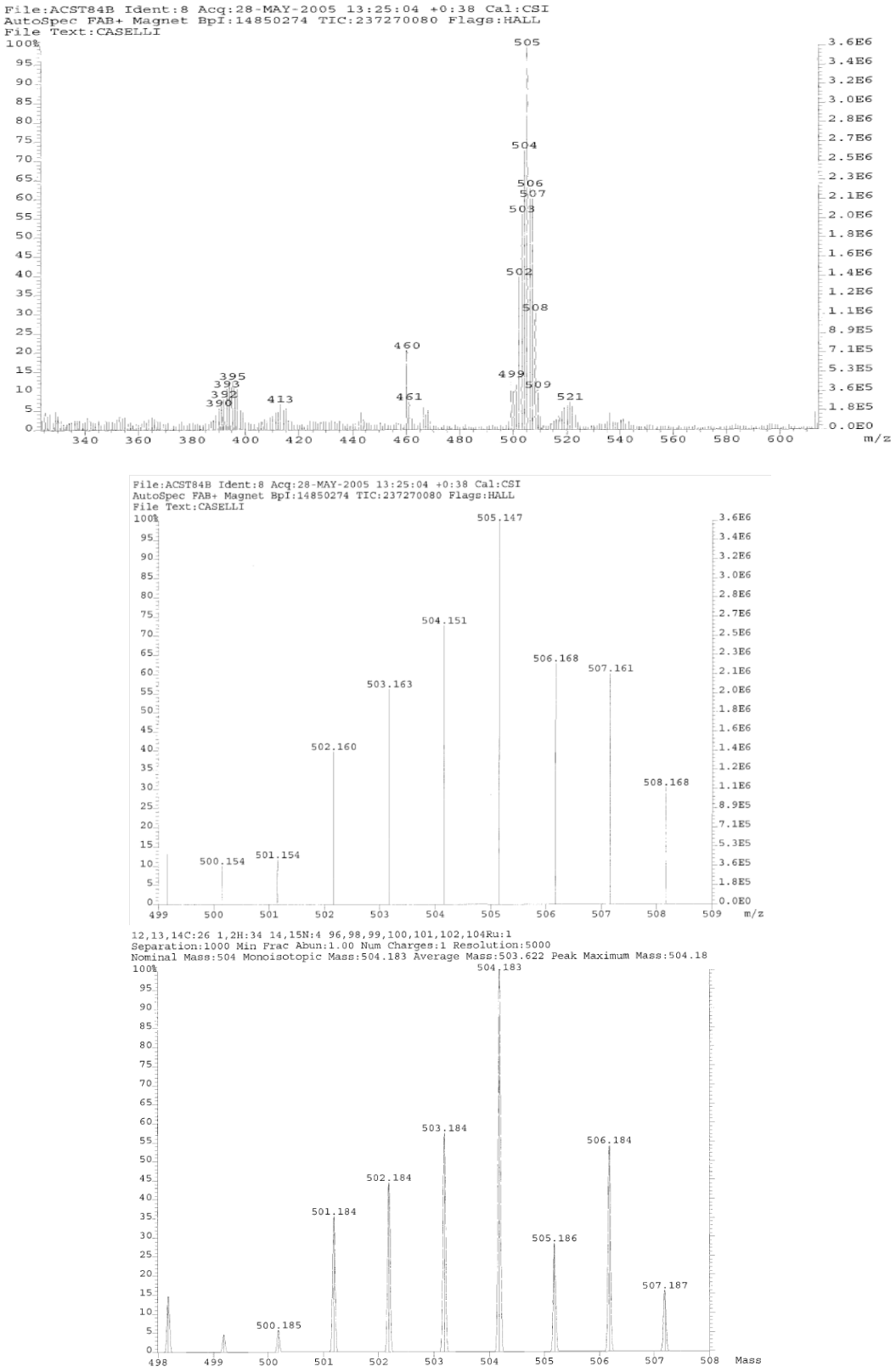
^{1}H-NMR (400 MHz, DMSO, T = 300 K) δ 7.93 (t, *J* = 7.9 Hz, 1H, H_b), 7.69 (s, 2H, NH), 7.57 (d, *J* = 7.9 Hz, 2H, H_a), 7.41 – 7.37 (m, 3H, H_{Ar}), 7.30 – 7.22 (m, 2H, H_{Ar}), 5.30 (dd, *J* = 18.6, 6.4 Hz, 2H, $H_{2,10}$), 4.60 (d, *J* = 18.6 Hz, 2H, $H_{2,10}$), 4.54 (s, 2H, $H_δ$), 4.23 (t, *J* = 13.9 Hz, 2H, $H_{4,8}$), 3.98 (s, 2H, H_{13}), 3.48 (s, 2H, $H_α$), 3.35 (s, 2H, $H_{4,8}$), 2.85 –

2,61 (m, 4H,H_{γ}), overlapped 2.72 (d, *J* = 13.9 Hz, 2H,$H_{5,7}$), 2.37 – 2.14 (m, 4H,H_{β}), 2.00 (t, *J* = 13.9 Hz, 2H, $H_{5,7}$).

^{13}C-NMR (300 MHz, DMSO, T = 300 K) δ 160.26($C_{1,11}$), 138.61(C_a), 133.83(CH), 131.07(C), 128.79 (CH), 120.39 (CH_b), 86.67 (C_{α}), 85.09 (C_{δ}), 64.95 (C_2 and C_{11}), 59.17(C_4 and C_8), 52.41(C_5 and C_7), 51.77(C_{13}), 29.53(C_{β}), 28.97(C_{γ}).

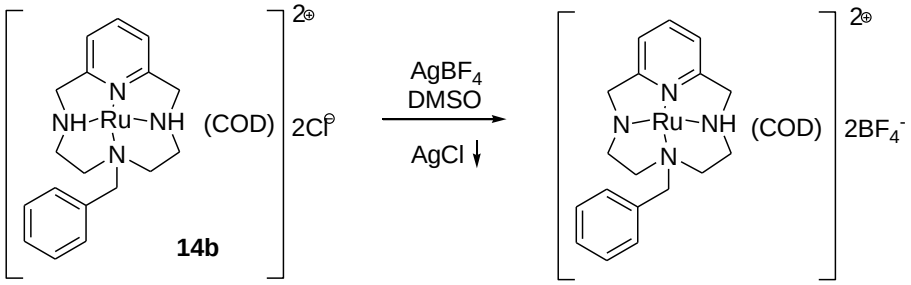
MS (FAB+) m/z 505 (M+) related to the following structure





Experimental and simulated mass spectra for complex **14b**

Synthesis of ruthenium COD 2Cl⁻ complex



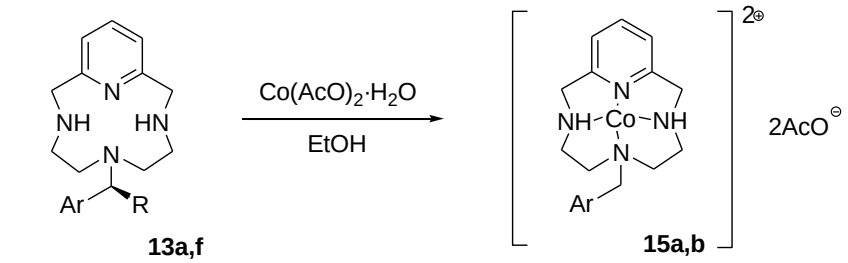
Complex **14b** (20.0 mg 0.035 mmol) was loaded into a sealed NMR tube and dissolved therein with DMSO d_6 (0.8 mL). NMR spectra is recorded. The solution is added to a tube containing $AgBF_4$ (13.0 mg, 0.07 mmol) and kept under nitrogen. After few second of stirring a white precipitated formed, the sample tube was then brought to non-inert atmosphere and the solid removed by centrifugation.

^{1}H-NMR (400 MHz, DMSO, T = 300 K) δ 7.95 (t, *J* = 7.8 Hz, 1H, H_b), 7.57 (d, *J* = 7.8 Hz, 2H, H_a), 7.41 – 7.39 (m, 3H, H_{Ar}), 7.26 – 7.23 (m, 2H, H_{Ar}), 7.13 (s, 2H, NH), 5.29 (dd, *J* = 18.5, 6.5 Hz, 2H, $H_{2,10}$), 4.63 (d, *J* = 18.5 Hz, 2H, $H_{2,10}$), 4.54 (s, 2H, $H_δ$), 4.21 (t, *J* = 13.7 Hz, 2H, $H_{4,8}$), 3.97 (s, 2H, H_{13}), 3.51 (s, 2H, $H_α$), 3.37 (s, 2H, $H_{4,8}$), 2.72 (d, *J* = 13.7 Hz, 2H,$H_{5,7}$), 2.71 – 2,65 (m, 4H,$H_γ$), 2.39 – 2.19 (m, 4H,$H_β$), 2.09 (t, *J* = 13.7 Hz, 2H, $H_{5,7}$).

^{13}C-NMR (300 MHz, DMSO, T = 300 K) δ 160.11 ($C_{1,11}$), 138.82 (CH_a), 133.80 (CH), 130.92 (CH), 128.85 (CH), 120.45 (C_b), 86.67 ($C_α$), 85.16 ($C_δ$), 64.78 (C_2 and C_{10}), 59.08($C_{4,8}$), 52.33 (C_5 and C_7), 51.77 (C_{13}), 29.35 ($C_β$), 28.80 (Cγ).

3.2.16 – Cobalt complexes

Synthesis of cobalt 2AcO⁻ complexes



13a,f **15a,b**

13a - Ar = Ph, R = H
13f - Ar = Naphthyl, R = Me

15a - Ar = Ph, R = H
15b - Ar = Naphthyl, R = Me

A solution of $Co(AcO)_2 \cdot H_2O$ (154.2 mg, 0.62 mmol) in MeOH (2.4 mL) was added dropwise to a solution of **13** (0.62 mmol) in EtOH. The solution was allowd to react at 75°C for 1 hour and 30 minutes. The solvent was evaporated and the crude was washed with CH_2Cl_2 and then purified by precipitation from *n*-Hexane.

Yield a – 45%

b – 40%

Elem. An. **a** – Found: C, 49.61; H, 6.31; N, 10.14 %

a – Calculated: C, 55.81; H, 6.39; N, 11.83 %

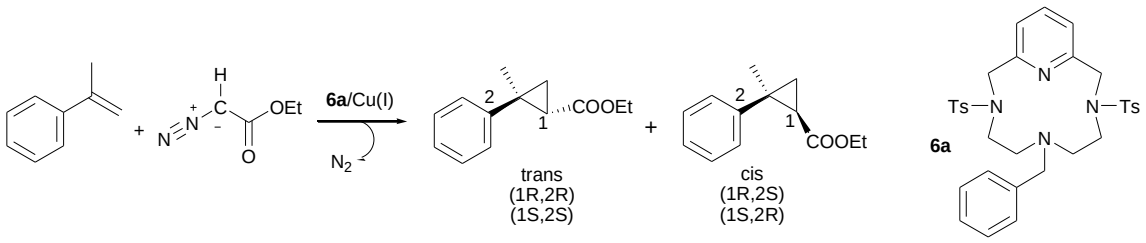
b – Found: C, 55.58; H, 5.95; N, 9.64 %

b – Calculated: C, 60.33; H, 6.38; N, 10.42 %

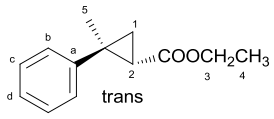
3.3 – Catalysis

3.3.1 - Cyclopropanation reaction

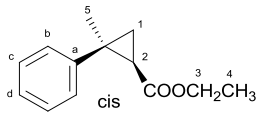
Optimization of the catalyzed cyclopropanation reaction



All the reactions carried out for the optimization were conducted between a-methylstyrene and ethyldiazoacetate (EDA) with ligand **6a.** Reactions were performed with a 1:1 Cu(I)/**6a** ratio, with equimolar amounts of Cu salt (0.030 mmol) and **6a** in the specified solvent. Copper salt, the ligand **6a** (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 **6a** and a-methylstyrene, (Cu/**6a**/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 diastereoisomers 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 diastereoisomeric ratio was determined by GC-MS.



^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 7.33-7.22 (m, 5H, H_{Ar}), 4.22 (q, J = 7.2 Hz, 2H, CH_3), 1.97 (dd, J = 8.3 Hz, J = 2.3 Hz, 1H, H_2), 1.55 (s, 3H, H_5), 1.47-1.44 (m, 2H, H_1), 1.32 (t, J = 7.2 Hz, 3H, H_4).



^{1}H-NMR (400 MHz; $CDCl_3$; T = 300 K) δ 7.33-7.22 (m, 5H, H_{Ar}), 1.92 (m, 1H, H_3), 1.80 (t, J = 4.9 Hz, 1H, H_2), 1.49 (s, 3H, H_5), 1.17 (m, 1H, H_1), 0.96 (t, J = 7.1 Hz, 3H, H_4).

Copper source screening

The screening of the best copper sources and so of the best counterion for the complex, was made using a-methylstyrene (5 mmol) as substrate and employing the following ratio between the reagents: **6a**/EDA/a-methylstyrene = 1/1/33/166. Distilled 1,2 - dichloroethane (5 mL) was used as solvent.

Entry	Copper source	EDA addition time	Temperature	Yield	cis : trans
1	$(CF_3SO_3Cu)_2\ C_6H_6$	One pot	r. t.	31%	42 : 58
2	$(CF_3SO_3Cu)_2\ C_7H_8$	One pot	r. t.	33%	42 : 58
3	CuI	One pot	r. t.	32%	42 : 58
4	$(CF_3SO_3Cu)_2\ C_6H_6$	100 minutes	0 °C	89%	43 : 57
5	$[Cu(CH_3CN)_4]\cdot BF_4$	100 minutes	0 °C	45%	43 : 57
6	$Cu(CF_3SO_3)_2$	100 minutes	0 °C	89%	43 : 57
7	$CuCl_2$	100 minutes	0 °C	10%	44 : 56
8	$Cu(OAc)_2\cdot H_2O$	100 minutes	0 °C	16%	45 : 55
9[a]	$(CF_3SO_3Cu)_2\ C_6H_6$	100 minutes	0 °C	32%	44 : 56
10[b]	$(CF_3SO_3Cu)_2\ C_6H_6$	100 minutes	0 °C	43%	45 : 55

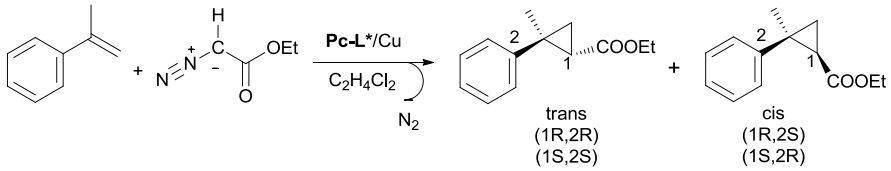
[a] molecular sieves added. [b] double equivalents of ligand used

Solvent screening

The screening of the best solvent, was made using $(CF_3SO_3Cu)_2$ C_6H_6 as copper source, a-methylstyrene (5 mmol) as substrate and employing the following ratio between the reagents: Cu/**6a**/EDA/a-methylstyrene = 1/1/33/166. EDA was added to the solution in 100 minutes at 0 °C.

Entry	Solvent	Yield	*cis : trans*
11	CH_2Cl_2	44%	64 : 36
12	CH_3CN	10%	50 : 50
13	Toluene	50%	77 : 23
14	Chlorobenzene	47%	72 : 28
15	THF	19%	66 : 34
16	Dichloroethane (not distilled)	37%	40 : 60

Asymmetric cyclopropanation of α-methylstyrene



All the reactions carried out for this section were conducted between α-methylstyrene 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 ^{1}H-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).

Ligands screening

The screening of the ligands was made using α-methylstyrene (5 mmol) as substrate and employing the following ratio between the reagents: Cu/**6**/EDA/a-methylstyrene = 1/1/33/166. EDA was added to the solution in 100 minutes. Distilled 1,2 - dichloroethane (5 mL) was used as solvent.

Entry	**Ligand**	**Copper source**	**T**	**Yield**	***cis : trans***	***ee cis (1S, 2R)***	***ee trans (1S, 2S)***
17	6b	$(CF_3SO_3Cu)_2\ C_6H_6$	r. t.	75%	55 : 45	-44%	-35%
18	6b	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	90%	65 : 35	-50%	-38%
19	6c	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	91%	65 : 35	50%	38%
20	6c	$(CF_3SO_3Cu)_2\ C_6H_6$	-20°C	80%	64 : 36	53%	38%
21	6c	$[Cu(CH_3CN)_4]\cdot BF_4$	0°C	78%	57 : 43	33%	36%
22	6f	$[Cu(CH_3CN)_4]\cdot BF_4$	0°C	70%	55 : 45	45%	44%
23	6f	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	99%	60 : 40	53%	65%
24	6e	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	99%	60 : 40	-53%	-65%
25	6g	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	99%	33 : 67	30%	60%
26	6h	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	98%	50 : 50	88%	99%
27	6h	$Cu(CF_3SO_3)_2$	0°C	96%	52 : 48	70%	77%
28	6i	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	66%	35 : 65	57%	52%
29	6n	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	91%	52 : 48	21%	16%
30	6o	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	95%	42 : 58	23%	59%
31	6m	$(CF_3SO_3Cu)_2\ C_6H_6$	0°C	48%	60 : 40	74%	79%
32		Complex h	0°C	98%	57 : 43	55%	66%

Reaction scope with different substrates

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 addition of 2,4-dinitrotoluene as internal standard and the solution was then evaporated to dryness *in vacuo* and analyzed by quantitative ^{1}H-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 (Daicel Chiralpak) using a solution of *n*-hexane:*i*-PrOH as eluant.

Entry	L	Olefin	Yield	*cis : trans*	Column	Hex:iPrOH	λ	*ee cis (1S, 2R)*	*ee trans (1S, 2S)*
33	6f	Styrene	72%	50 : 50	OJ	98 : 2	230 nm	33%	50%
34	6h	Styrene	97%	38 : 62	OJ	98 : 2	230 nm	99%	87%
35	6f	p-Me Styrene	66%	53 : 47	OJ	99 : 1	220 nm	34%	45%
36	6g	p-Me Styrene	79%	25 : 75	OJ	99 : 1	220 nm	33%	40%
37	6f	p-Cl Styrene	88%	47 : 53	OJ	99 : 1	220 nm	36%	50%
38	6h	p-Cl Styrene	86%	42 : 58	OJ	99 : 1	220 nm	66%	78%
39	6f	diphenyl ethylene	64%	-	AD	99.66 : 0.33	230 nm	50%	
40	6g	diphenyl ethylene	85%	-	AD	99.66 : 0.33	230 nm	62%	
41	6h	diphenyl ethylene	45%	-	AD	99.66 : 0.33	230 nm	88%	
42	6f	2,5 - dimethyl 2,4 - hexadiene	81%	67 : 33	OJ	99.975 : 0.025	230 nm	30%	15%
43	6f	methyl-2-furoate	54%	1 : 99	OJ	9 : 1	254 nm	-	57%
44	6g	methyl-2-furoate	55%	1 : 99	OJ	9 : 1	254 nm	-	28%
45	6h	methyl-2-furoate	74%	1 : 99	OJ	9 : 1	254 nm	-	76%
46	6h	1-octene	73%	38 : 62	OJ	99 : 1	236 nm	75%	55%

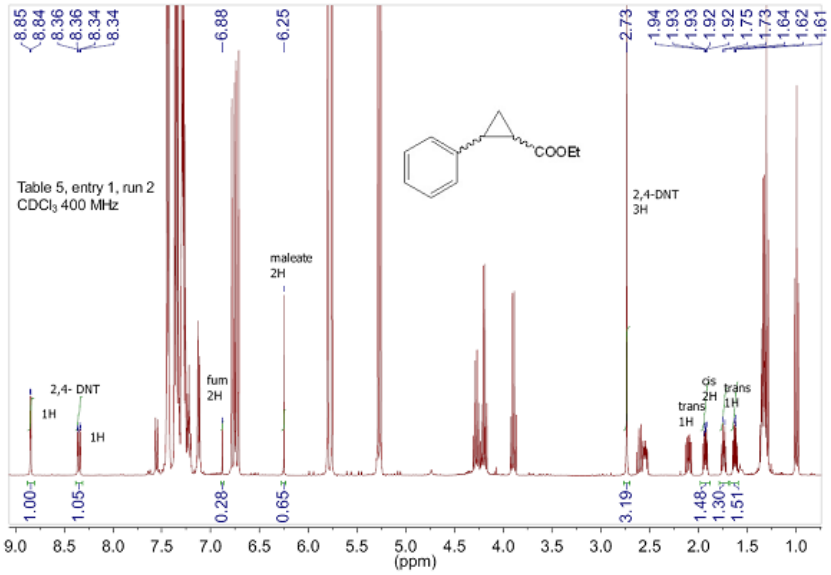


Table 5, entry 1, run 2
CDCl3 400 MHz
COOEt
2,4-DNT
3H
maleate
2H
fum
2H
2,4- DNT
1H
1H
cis
2H
trans
1H
trans
1H
(ppm)

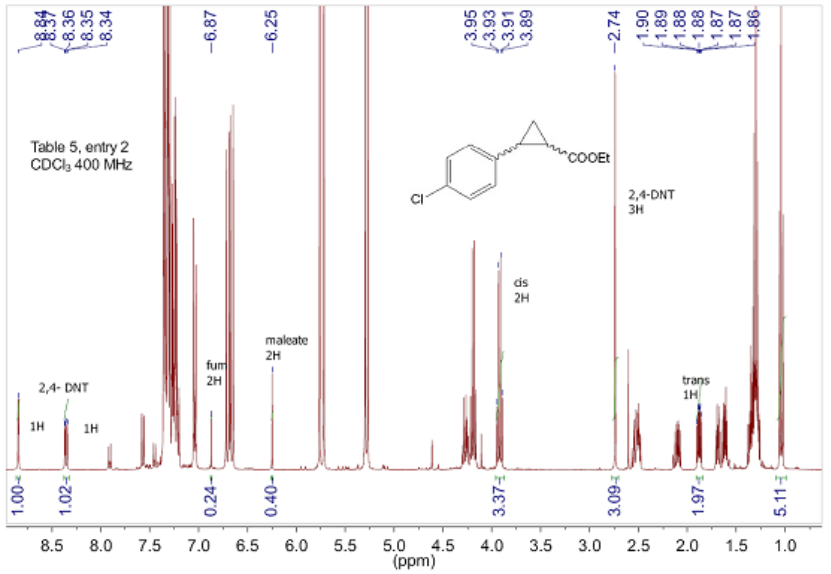


Table 5, entry 2
CDCl3 400 MHz
COOEt
Cl
2,4-DNT
3H
cis
2H
maleate
2H
fum
2H
2,4- DNT
1H
1H
trans
1H
(ppm)

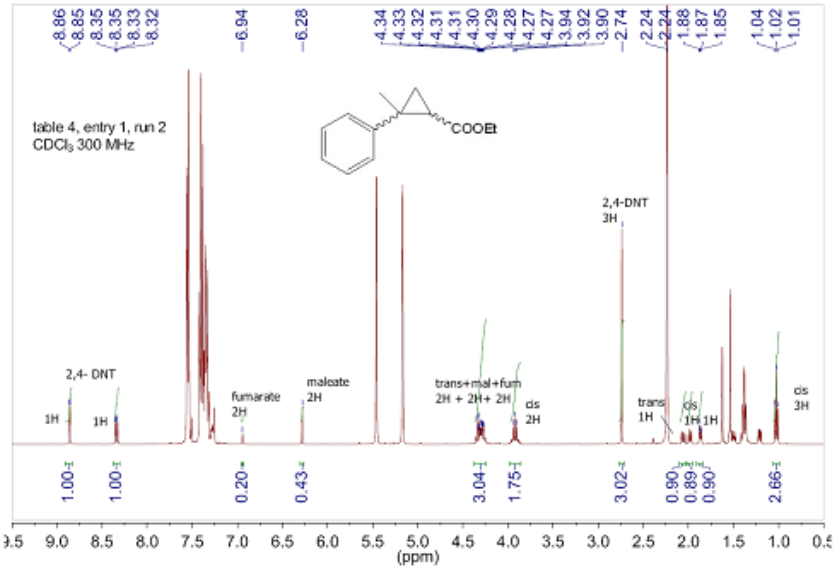


table 4, entry 1, run 2
CDCl3 300 MHz
COOEt
2,4-DNT
3H
2,4- DNT
1H
1H
fumarate
2H
maleate
2H
trans+mal+fum
2H + 2H+ 2H
cis
2H
trans
1H
cis
1H
1H
cis
3H
(ppm)

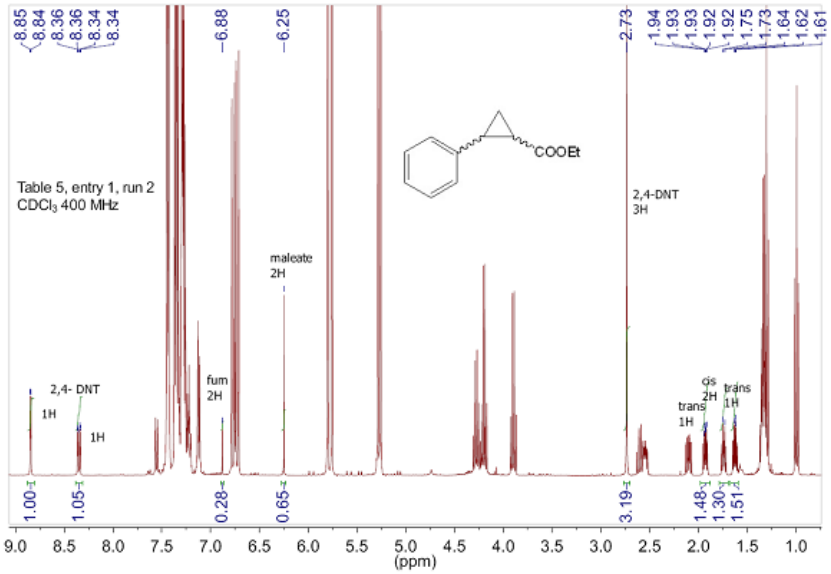


Table 5, entry 1, run 2
CDCl3 400 MHz
COOEt
2,4-DNT
3H
maleate
2H
2,4- DNT
1H
1H
fum
2H
trans
1H
cis
2H
trans
1H
(ppm)

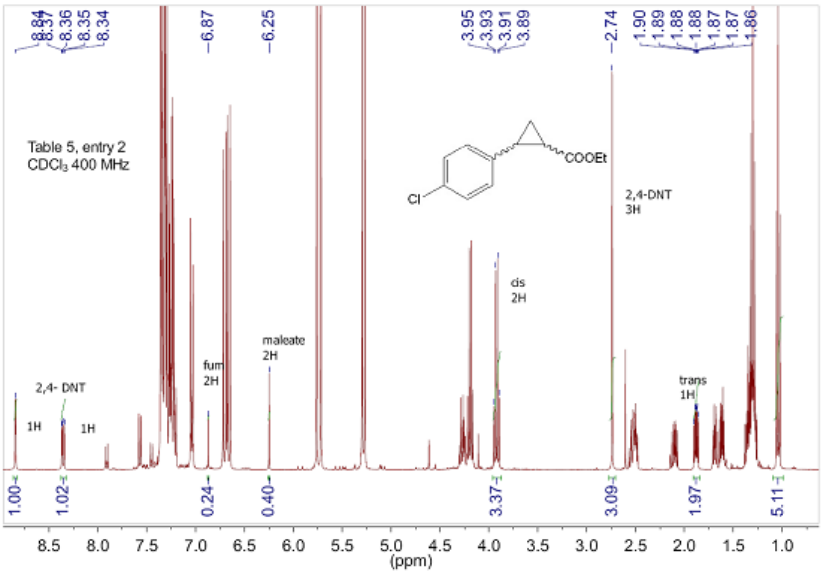


Table 5, entry 2
CDCl3 400 MHz
Cl
COOEt
2,4-DNT
3H
cis
2H
maleate
2H
fum
2H
2,4- DNT
1H
1H
trans
1H
(ppm)

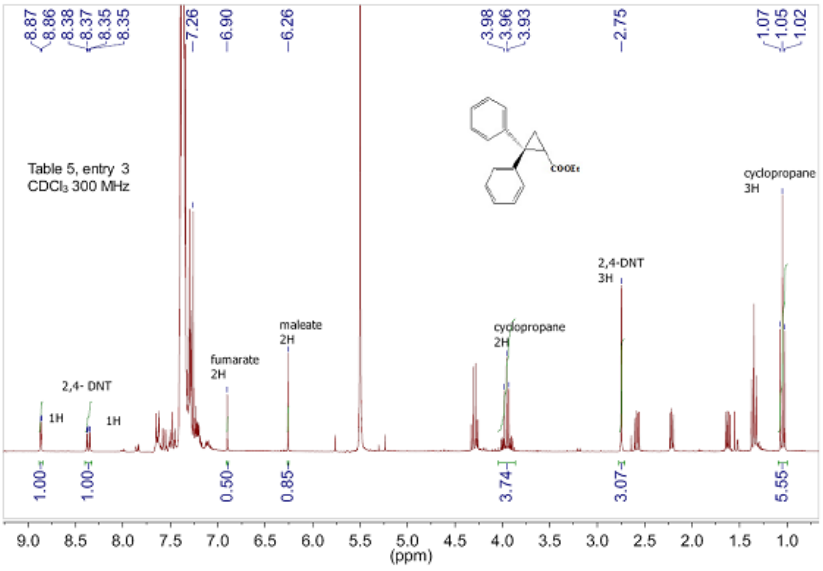
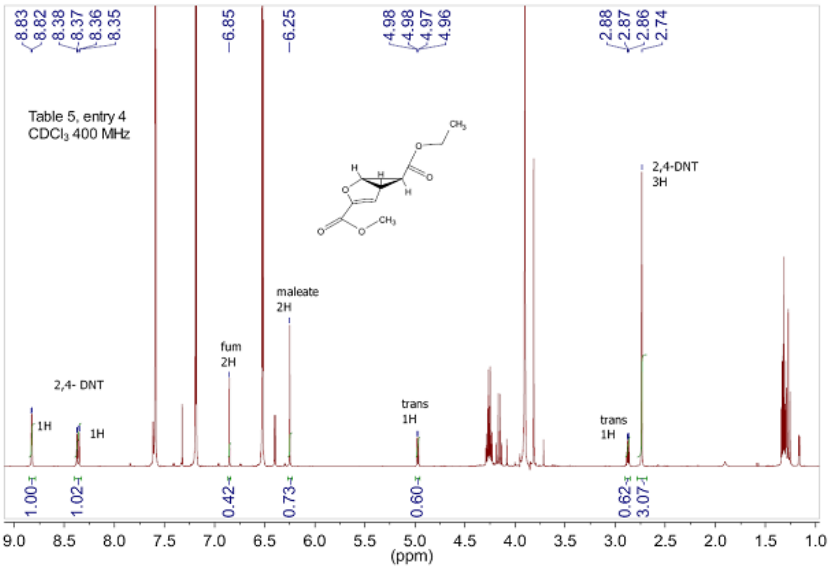
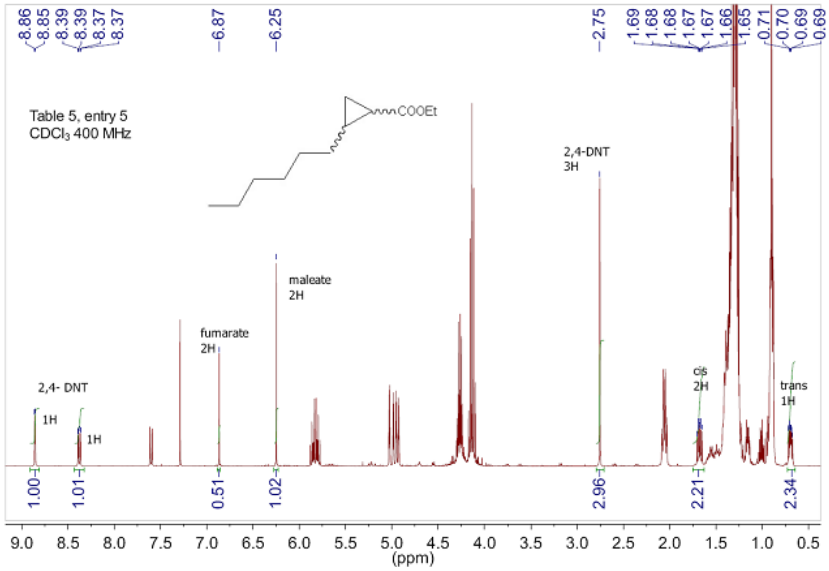


Table 5, entry 3
CDCl3 300 MHz
cyclopropane
3H
2,4-DNT
3H
maleate
2H
cyclopropane
2H
fumarate
2H
2,4- DNT
1H
1H
(ppm)

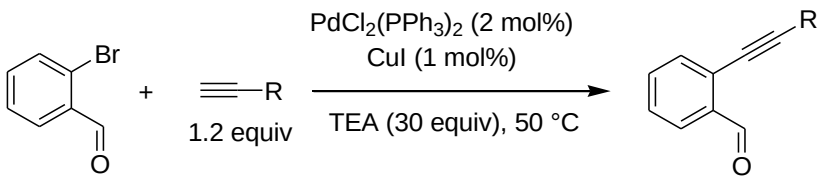

8.83
8.82
8.38
8.37
8.36
8.35
6.85
6.25
4.98
4.98
4.97
4.96
2.88
2.87
2.86
2.74
Table 5, entry 4
CDCl3 400 MHz
2,4-DNT
3H
maleate
2H
fum
2H
2,4- DNT
1H
1H
trans
1H
trans
1H
1.00
1.02
0.42
0.73
0.60
0.62
3.07
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)


8.86
8.85
8.39
8.39
8.37
8.37
6.87
6.25
2.75
1.69
1.68
1.68
1.67
1.67
1.66
1.65
0.71
0.70
0.69
0.69
Table 5, entry 5
CDCl3 400 MHz
COOEt
2,4-DNT
3H
maleate
2H
fumarate
2H
2,4- DNT
1H
1H
cis
2H
trans
1H
1.00
1.01
0.51
1.02
2.96
2.21
2.34
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)

3.3.2 – Synthesis of isochromenes

General Procedure for the synthesis of 2-alkynylbenzaldehydes 11a-e

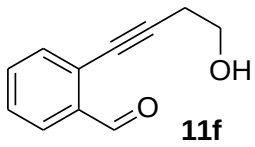
To a solution of *o*-bromobenzaldehyde (600 mg, 3.24 mmol) in dry TEA (30 equiv), the appropriate alkyne (3.89 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium(II) (2 mol%) were added, under a nitrogen atmosphere. The reaction was stirred at rt for 10 min, and then CuI (1 mol%) was added. The reaction mixture was stirred at 50 °C until no more starting product was detectable by TLC analysis (eluant: hexane/ethyl acetate). The solvent was then evaporated under reduced pressure and the crude material was purified by flash chromatography over a silica gel column.



11a-e

11	R	t (h)	Yield (%)
a	*p*-MeO-Ph-	3	96
b	*p*-Me-Ph-	2	77
c	*m*-F-Ph-	6	85
d	*n*-Pr-	5	79
e	TMS-	2	60

Alkynylbenzaldehydes **11a**,[222] **11b** and **11c,**[223] **11d**[224] and **11e**[223] are known compounds. They were characterized by ^{1}H-NMR and spectral data are in good agreement with literature values.



11f

Synthesis of 2-(4-hydroxybut-1-ynyl)benzaldehyde 11f:[225] To a solution of *o*-bromobenzaldehyde (1.20 g, 6.48 mmol), and TEA (1.18 g, 1.62 mL, 11.67 mmol) in dry DMF (10 mL), but-3-yn-1-ol (0.5 g, 0.539 mL, 7.13 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium(II) (90.9 mg, 0.13 mmol) were added under a nitrogen atmosphere. The reaction was stirred at rt for 10 min, and then CuI (24.7 mg, 0.13 mmol) was added. The reaction mixture was stirred at rt overnight, until no more starting product was detectable by TLC analysis (eluant: hexane/ethyl acetate = 6 : 4). The reaction mixture was poured in water (200 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure. The crude was purified by flash column chromatography on silica gel (Eluant: hexane/ethyl acetate = 8 : 2) to give corresponding 2-(4-hydroxybut-1-ynyl)benzaldehyde (1.12 g, 99 %) as viscous yellow oil.

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[222] (a) S. Zhu, Z. Zhang, X. Huang, H. Jiang, Z. Guo, *Chem. Eur. J.* **2013**, *19*, 4695-4700. (b) Q. Huang, J. A. Hunter, R. C. Larock, *J. Org. Chem.* **2002**, *67*, 3437–3444

[223] M. Dell'Acqua, D. Facoetti, G. Abbiati, E. Rossi, M. Alfonsi, A. Arcadi, *Eur. J. .Org. Chem.* **2009**, 2852-2862.

[224] L. Castedo, E. Guitian, D. Pena, D. Perez, *Eur. J. Org. Chem.* **2003**, 1238-1243

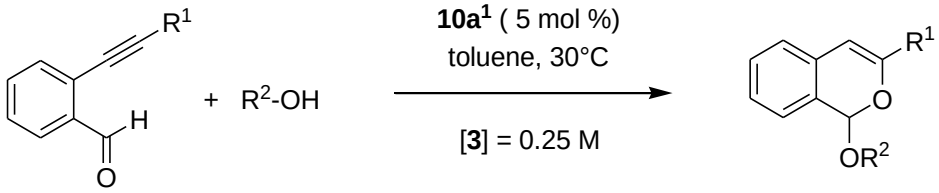
[225] B. V. S. Reddy, S. Jalal, P. Borkar, J. S. Yadav, P. G. Reddy, A. V. S. Sarma, *Tetrahedron Lett.* **2013**, *54*, 1519-1523

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 10.44 (s, 1H, CHO), 7.86 (d, *J* = 7.7 Hz, 1H, H_{ar}), 7.54-7.39 (m, 3H, H_{ar}), 3.87 (t, *J* = 6.2 Hz, 2H, CH_2-O), 2.76 (t, *J* = 6.2 Hz, 2H, C_{sp}-CH_2) ppm.

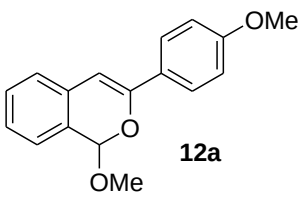
Spectral data are in good agreement with literature values.

General Procedure for the synthesis of 1-alkoxyisochromenes 12 a-l

To a stirred solution of the appropriate *o*-alkynylbenzaldehyde **11a-e** (60 mg) in dry toluene ([3] = 0.25 M), the catalyst **10a**[1] (5 mol%) and the alcohol (1.05 equiv) were added. The reaction mixture was stirred at 30 °C until no more starting product was detectable by TLC analysis (eluant: toluene/ ethyl acetate = 100:1). The reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 ml) and extracted with ethyl acetate (3 × 10 ml). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure. Unless otherwise stated, after this work-up the products **12** were sufficiently pure and did not need further purification.



11 a-e **12 a-l**



12a

1-Methoxy-3-(4-methoxyphenyl)-1*H*-isochromene 12a: Reaction time: 2 h. White solid. Yield: 99 % (67 mg). Mp 124-126 °C.

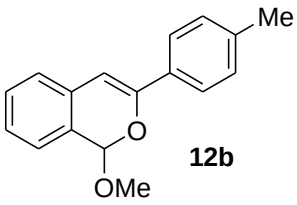
^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.76 (d, *J* = 8.8 Hz, 2H, H_{ar}), 7.40 – 7.16 (m, 4H, H_{ar}), 6.94 (d, *J* = 8.8 Hz, 2H, H_{ar}), 6.49 (s, 1H, C_{sp2}-H), 6.13 (s, 1H, C_{sp3}-H), 3.85 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 160.43 (C_q), 149.69 (C_q), 130.77 (C_q), 129.64 (CH_{ar}), 127.38 (C_q), 126.98 (C_q), 126.55 (CH_{ar}), 126.48 (CH_{ar}), 125.99 (CH_{ar}),

124.46 (CH_{ar}), 114.12 (CH_{ar}), 100.04 (C-H), 99.00 (C-H), 55.55 (CH_3), 55.31 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 291.0 (45) $[M + Na]^+$, 269.3 (4) $[M + H]^+$, 237.2 (100) $[M – OCH_3)]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{17}H_{17}O_3$ 269.1172, found 269.1170.



12b

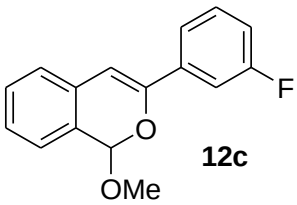
1-Methoxy-3-(p-tolyl)-1*H*-isochromene 12b:[150] Reaction time: 24 h. White solid. Yield: 97 % (67 mg). Mp 100-102 °C.

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.74 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.29 – 7.22 (m, 6H, H_{ar}), 6.59 (s, 1H, C_{sp2}-H), 6.16 (s, 1H, C_{sp3}-H), 3.62 (s, 3H, OCH_3), 2.41 (s, 1H, CH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 149.89 (C_q), 139.03 (C_q), 131.96 (C_q), 130.67 (C_q), 129.65 (CH_{ar}), 129.42 (CH_{ar}), 127.20 (C_q), 126.70 (CH_{ar}), 126.03 (CH_{ar}), 125.05 (CH_{ar}), 124.63 (CH_{ar}), 100.01 (C-H), 99.86 (C-H), 55.33 (CH_3), 21.54 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 253.1 (20) $[M + H]^+$, 221.2 (100) $[M^+ – OCH_3)]^+$.

Spectral data are in good agreement with literature values.



12c

3-(3-Fluorophenyl)-1-methoxy-1*H*-isochromene 12c: Reaction time: 24 h. White solid. Yield: 98% (68 mg). Mp 93–95 °C.

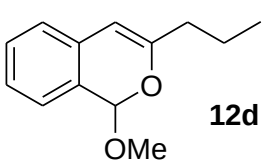
^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.59 (m, 1H, H_{ar}), 7.51 (m, 1H, H_{ar}), 7.42-7.15 (m, 5H, H_{ar}), 7.04 (ddt, *J* = 8.3, 2.6, 0.9 Hz, 1H, H_{ar}), 6.62 (s, 1H, C_{sp2}-H), 6.15 (s, 1H, C_{sp3}-H), 3.61 (s, 3H, OCH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 163.32 (d, $^1J_{C\text{-}F}$ = 245 Hz, C_q-F), 148.44 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, C_q), 137.07 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, C_q), 130.17 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH_{ar}), 130.05

(C_q), 129.78 (CH_{ar}), 127.39 (C_q), 127.33 (CH_{ar}), 126.09 (CH_{ar}), 124.97 (CH_{ar}), 120.63 (d, $^4J_{C\text{-}F}$ = 2.7 Hz, CH_{ar}), 115.72 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 111.97 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 101.59 (CH), 100.08 (CH), 55.53 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 225.3 (30) $[M^+ - OCH_3]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{16}H_{14}FO_2$ 257.0972, found 257.0967



12d

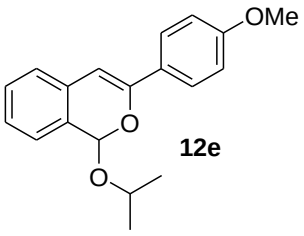
1-Methoxy-3-propyl-1*H*-isochromene 12d:[146, 150] Reaction time: 2 h. Yellow oil. Yield (simple work-up): 98% (69 mg). Flash column chromatography: celite plug/neutral alumina 50%/silica 50%. Eluant: hexane/CH_2Cl_2 = 8:2 + 5% TEA. Yield (after column): 76% (53 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.32 – 7.18 (m, 4H, H_{ar}), 7.05 (d, *J* = 7.4 Hz, 2H, H_{ar}), 5.95 (s, 1H, C-H), 5.79 (s, 1H, C-H), 3.53 (s, 3H, OCH_3), 2.29 (dt, *J* = 7.2, 4.4 Hz, 2H, CH_2), 1.67 (hex, *J* = 7.3 Hz, 2H, CH_2), 0.98 (t, *J* = 7.3 Hz, 3H, CH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 154.26 (C_q), 130.59 (C_q), 129.47 (CH_{ar}), 126.46 (C_q), 126.07 (CH_{ar}), 126.04 (CH_{ar}), 123.63 (CH_{ar}), 100.49 (C-H), 99.85 (C-H), 55.18 (CH_3), 36.15 (CH_2), 20.55 (CH_2), 13.79 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 205.1 (32) $[M + H]^+$, 173.2 (78) $[M^+ - OCH_3]^+$.

Spectral data are in good agreement with literature values.



12e

1-Isopropoxy-3-(4-methoxyphenyl)-1*H*-isochromene 12e: Reaction time: 6 h. Yellow solid. Yield (simple work-up): 99% (74 mg). Mp 120–122 °C.

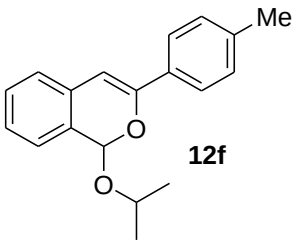
^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.75 (d, *J* = 9.0 Hz, 2H, H_{ar}), 7.38-7.17 (m, 4H, H_{ar}), 6.94 (d, *J* = 9.0 Hz, 2H, H_{ar}), 6.50 (s, 1H, C_{sp2}-H), 6.30 (s, 1H, C_{sp3}-H), 4.38 (hept, *J* = 6.2 Hz, 1H, CH *i*-Pr), 3.85 (s, 3H, OCH_3), 1.32 (d, *J* = 6.2 Hz, 3H, CH_3 *i*-Pr), 1.19 (d, *J* = 6.2 Hz, 3H, CH_3 *i*-Pr) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 160.31 (C_q), 149.72 (C_q), 130.91 (C_q), 129.33 (CH_{ar}), 127.71 (C_q), 127.59 (C_q), 126.54 (CH_{ar}), 126.42 (CH_{ar}), 125.71 (CH_{ar}),

124.51 (CH_{ar}), 114.06 (CH_{ar}), 99.01 (C_{sp2}-H), 97.24 (C_{sp3}-H), 70.00 (CH *i*-Pr), 55.54 (CH_3), 23.83 (CH_3), 22.22 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 319.1 (10) $[M + Na]^+$, 297.2 (5) $[M + H]^+$, 237.3 (100) $[M - OCH(CH_3)_2]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{19}H_{21}O_3$ 297.1485, found 297.1479.



12f

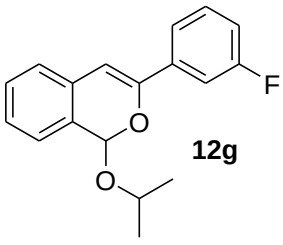
1-Isopropoxy-3-(*p*-tolyl)-1*H*-isochromene 12f: Reaction time: 24 h. Yellow solid. Yield: 97% (77mg). Mp 76– 78 °C.

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.69 (d, *J* = 8.3 Hz, 2H, H_{ar}), 7.42 – 7.14 (m, 6H, H_{ar}), 6.55 (s, 1H, C_{sp2}-H), 6.29 (s, 1H, C_{sp3}-H), 4.37 (hept, *J* = 6.1 Hz, 1H, CH *i*-Pr), 2.38 (s, 3H, CH_3), 1.31 (d, *J* = 6.1, 3H, CH_3 *i*-Pr), 1.17 (d, *J* = 6.1 Hz, 3H, CH_3 *i*-Pr) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 149.88 (C_q), 138.83 (C_q), 132.26 (C_q), 130.79 (C_q), 129.34 (CH_{ar}), 127.76 (C_q), 126.61 (CH_{ar}), 125.72 (CH_{ar}), 125.02 (CH_{ar}), 124.63 (CH_{ar}), 99.83 (C_{sp2}-H), 97.18 (C_{sp3}-H), 69.98 (CH *i*-Pr), 23.80 (CH_3), 22.19 (CH_3), 21.52 (CH_3) ppm (one CH_{ar} signal is obscured).

MS ESI(+) *m/z* (%) = 303.1 (100) $[M + Na]^+$, 221.2 (10) $[M - OCH(CH_3)_2]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{19}H_{21}O_2$ 281.1536, found 281.1531.



12g

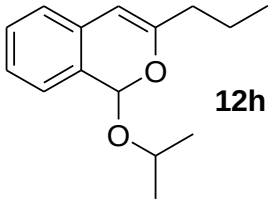
3-(3-Fluorophenyl)-1-isopropoxy-1*H*-isochromene 12g: Reaction time: 24 h. Yellow solid. Yield: 97% (77mg). Mp 73 –75 °C.

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.69–7.20 (m, 7H, H_{ar}), 7.03 (td, *J* = 8.3, 2.3 Hz, 1H, H_{ar}), 6.61 (s, 1H, C_{sp2}-H), 6.30 (s, 1H, C_{sp3}-H), 4.35 (hept, *J* = 6.1 Hz, 1H, CH *i*-Pr), 1.31 (d, *J* = 6.1 Hz, 3H, CH_3 *i*-Pr), 1.17 (d, *J* = 6.1 Hz, CH_3 *i*-Pr) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 163.27 (d, $^1J_{C\text{-}F}$ = 245 Hz, C_q), 148.48 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C_q), 137.41 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, C_q), 130.21 (C_q), 130.06 (d, $^3J_{C\text{-}F}$ = 8.4 Hz, CH_{ar}), 129.42 (CH_{ar}), 127.99 (C_q), 127.22 (CH_{ar}), 125.76 (CH_{ar}), 124.95 (CH_{ar}), 120.61 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, CH_{ar}), 115.55 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, CH_{ar}), 111.94 (d, $^2J_{C\text{-}F}$ = 23.4 Hz, CH_{ar}), 101.57 (C_{sp2}-H), 97.28 (C_{sp3}-H), 70.27 (CH_3), 23.75 (CH_3 *i*-Pr), 22.18 (CH_3 *i*-Pr) ppm.

MS ESI(+) *m/z* (%) = 307.2 (65) $[M + Na]^+$, 225.4 (42) $[M – OCH(CH_3)_2]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{18}H_{18}FO_2$ 285.1285, found 285.1291.



12h

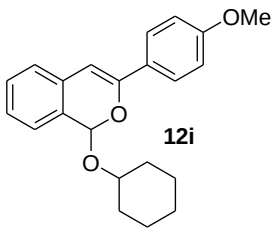
1-Isopropoxy-3-propyl-1*H*-isochromene 12h:[146] Reaction time: 1 h. Yellow oil. Yield (simple work-up): 89% (72 mg). Flash column chromatography: celite plug/neutral alumina 50%/silica 50%. Eluant: hexane/CH_2Cl_2 = 8:2 + 5% TEA. Yield (after column): 62% (50 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.30-7.14 (m, 3H, H_{ar}), 7.03 (m, 1H, H_{ar}), 6.11 (s, 1H, C-H), 5.77 (s, 1H, C-H), 4.24 (hept, *J* = 6.2 Hz, 1H, CH *i*-Pr), 2.25 (dt, *J* = 7.0, 3.0 Hz, 2H, CH_2), 1.64 (hex, *J* = 7.4 Hz, 2H, CH_2), 1.27 (d, *J* = 6.1 Hz, 3H, CH_3 *i*-Pr), 1.21 (d, *J* = 6.1 Hz, CH_3 *i*-Pr), 0.98 (t, *J* = 7.3 Hz, 3H, CH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 154.23 (C_q), 130.82 (C_q), 129.13 (CH_{ar}), 126.80 (C_q), 125.97 (CH_{ar}), 125.79 (CH_{ar}), 123.65 (CH_{ar}), 100.34 (C_{sp2}-H), 96.90 (C_{sp3}-H), 69.69 (CH *i*-Pr), 36.32 (CH_2), 23.75 (CH_3), 22.07 (CH_3), 20.37 (CH_2), 13.91 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 255 (70) $[M + Na]^+$, 173.3 (50) $[M – OCH(CH_3)_2]^+$.

Spectral data are in good agreement with literature values.



12i

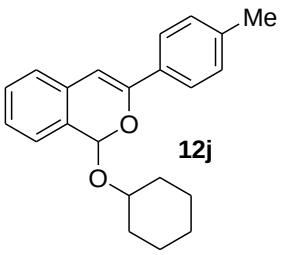
1-(Cyclohexyloxy)-3-(4-methoxyphenyl)-1*H*-isochromene 12i: Reaction time: 24 h. White solid. Mp 57–59 °C. Yield (simple work-up): 92% (79 mg). Flash column chromatography: celite plug/neutral alumina 50%/silica 50%. Eluant: hexane/CH_2Cl_2 = 7:3 + 5% TEA. Yield (after column): 67% (57 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.73 (d, *J* = 9.0 Hz, 1H, H_{ar}), 7.37 – 7.16 (m, 4H, H_{ar}), 6.94 (d, *J* = 9.0 Hz, 1H, H_{ar}), 6.48 (s, 1H, C_{sp2}-H), 6.33 (s, 1H, C_{sp3}-H), 4.02 (m, 1H, H Cy), 3.85 (s, 3H, CH_3), 2.10 (m, 1H, CH_2 Cy), 1.82-1.13 (m, 9H, CH_2) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 160.29 (C_q), 149.81 (C_q), 130.97 (C_q), 129.24 (CH_{ar}), 127.78 (C_q), 127.71 (C_q), 126.54 (CH_{ar}), 126.36 (CH_{ar}), 125.74 (CH_{ar}), 124.44 (CH_{ar}), 114.05 (CH_{ar}), 98.96 (C_{sp2}-H), 97.11 (C_{sp3}-H), 76.03 (CH Cy), 55.54 (CH_3), 33.92 (CH_2), 32.30 (CH_2), 25.82 (CH_2), 24.60 (CH_2), 24.49 (CH_2) ppm.

MS ESI(+) *m/z* (%) = 359.2 (70) $[M + Na]^+$, 336.2 (15) $[M + H]^+$, 237.2 (100) $[M – OC_6H_{11}]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{22}H_{25}O_3$ 337.1798, found 337.1795.



12j

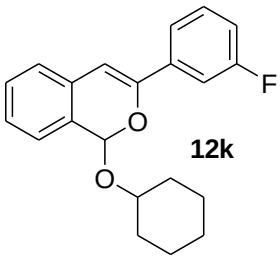
1-(Cyclohexyloxy)-3-(*p*-tolyl)-1*H*-isochromene 12j:[150] Reaction time: 24 h. Yellow solid. Mp 68-70 °C. Yield: 94 % (83 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.68 (d, *J* = 8.2 Hz, 2H, H_{ar}), 7.32 – 7.17 (m, 6H, H_{ar}), 6.55 (s, 1H, C_{sp2}-H), 6.34 (s, 1H, C_{sp3}-H), 4.02 (m, 1H, H Cy), 2.39 (m, 3H, CH_3), 2.08 (m, 1H, CH_2 Cy), 1.81-1.13 (m, 9H, CH_2) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 150.02 (C_q), 138.78 (C_q), 132.35 (C_q), 130.89 (C_q), 129.33 (CH_{ar}), 129.24 (CH_{ar}), 127.94 (C_q), 126.55 (CH_{ar}), 125.76 (CH_{ar}), 125.05 (CH_{ar}), 124.58 (CH_{ar}), 99.79 (C_{sp2}-H), 97.10 (C_{sp3}-H), 76.00 (CH Cy), 33.91 (CH_2), 32.30 (CH_2), 25.85 (CH_2), 24.56 (CH_2), 24.47 (CH_2), 21.50 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 343.5 (15) $[M + Na]^+$, 221.4 (10) $[M – OC_6H_{11}]^+$.

Spectral data are in good agreement with literature values.



12k

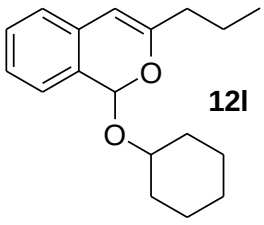
1-(Cyclohexyloxy)-3-(3-fluorophenyl)-1*H*-isochromene 12k: Reaction time: 48 h. Yellow oil. Yield: 96% (84 mg).

^{1}H NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.65 – 7.20 (m, 7H, H_{ar}), 7.05 (tdd, *J* = 8.3, 2.5, 0.9 Hz, 1H, H_{ar}), 6.62 (s, 1H, C_{sp2}-H), 6.36 (s, 1H, C_{sp3}-H), 4.03 (m, 1H, H Cy), 2.11 (m, 1H, CH_2 Cy), 1.82 – 1.15 (m, 9H, CH_2 Cy) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 163.31 (d, $^{1}J_{C\text{-}F}$ = 245 Hz, C_q), 148.61 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, C_q), 137.51 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz, C_q), 130.31 (C_q), 130.07 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, CH_{ar}), 129.36 (CH_{ar}), 128.16 (C_q), 127.19 (CH_{ar}), 125.83 (CH_{ar}), 124.92 (CH_{ar}), 120.64 (d,$^{4}J_{C\text{-}F}$ = 2.4 Hz, CH_{ar}), 115.53 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz, CH_{ar}), 111.97 (d, $^{2}J_{C\text{-}F}$ = 23.4 Hz, CH_{ar}), 101.55 (C_{sp2}-H), 97.18 (C_{sp3}-H), 76.25 (CH Cy), 33.89 (CH_2), 32.29 CH_2), 25.81 (CH_2), 24.49 (CH_2), 24.41 (CH_2) ppm.

MS ESI(+) *m/z* (%) = 347.3 (15) $[M + Na]^+$, 363.3 (25) $[M + K]^+$, 225.3 (85) $[M – OC_6H_{11}]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{21}H_{22}FO_2$ 325.1598, found 325.1602.



12l

1-(Cyclohexyloxy)-3-propyl-1*H*-isochromene 12l: Reaction time: 2 h. Yellow oil. Yield: 94% (89 mg).

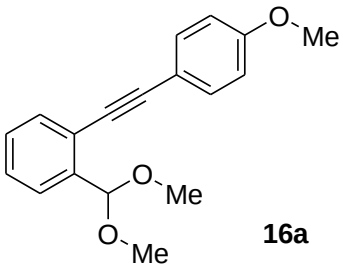
^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.30-7.13 (m, 3H, H_{ar}), 7.02 (m, 1H, H_{ar}), 6.16 (s, 1H, C-H), 5.76 (s, 1H, C-H), 3.89 (m, 1H, H Cy), 2.25 (dt, *J* = 7.0, 3.1 Hz, 2H), 2.07 (m, 1H, CH_2), 1.95 – 1.48 (m, 6H, CH_2), 1.40-1.15 (m, 5H, CH_2), 0.98 (t, *J* = 7.3 Hz, 3H, CH_3) ppm.

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ = 154.32 (C_q), 130.83 (C_q), 129.06 (CH_{ar}), 127.23 (C_q), 125.92 (CH_{ar}), 125.85 (CH_{ar}), 123.60 (CH_{ar}), 100.28 (C_{sp2}-H), 96.81 (C_{sp3}-H), 75.79 (CH Cy), 36.36 (CH_2), 33.96 (CH_2), 32.22 (CH_2), 25.90 (CH_2), 24.64 (CH_2), 24.45 (CH_2), 20.38 (CH_2), 13.91 (CH_3) ppm.

MS ESI(+) *m/z* (%) = 295.2 (100) $[M + Na]^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{18}H_{25}O_2$ 273.1849, found 273.1854.

Mechanistic studies

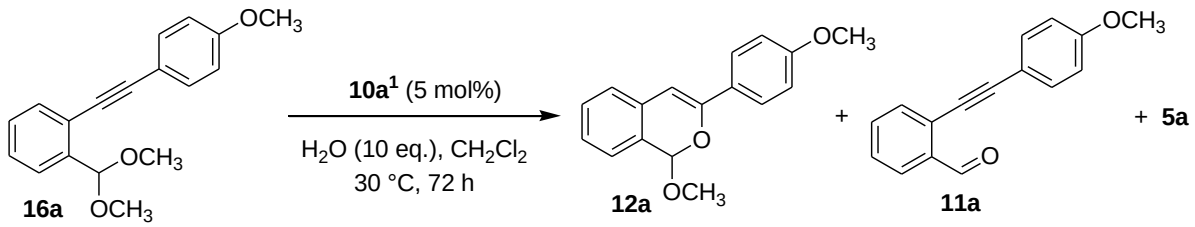


16a

Synthesis of 1-(dimethoxymethyl)-2-((4-methoxyphenyl)ethynyl)-benzene 18a: To a solution of **10a**[1] (30 mg, 0.127 mmol) in dry MeOH (1.5 mL) *p*-toluenesulfonic acid (2.2 mg, 0.013 mmol) acid and 30 mg of molecular sieve (3 Å) were added. The mixture was stirred at 30 °C and the progress of the reaction was followed by TLC (Eluant: toluene/ethyl acetate = 99:1). After 20 h, the yellow solution was poured into a saturated solution of $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure to give **16a** as yellow oil (36 mg, quantitative). The crude was sufficiently pure and was used without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.63-7.58 (m, 1H, H_{ar}), 7.55-7.46 (m, 3H, H_{ar}), 7.38-7.29 (m, 2H, H_{ar}), 6.89 (d, *J* = 8.9 Hz, 1H, H_{ar}), 5.75 (s, 1H, C-H), 3.83 (s, 3H, CH_3), 3.44 (s, 6H, CH_3) ppm.

Reaction of acetal 5a with the catalyst 2a:



ratio **12a**/**11a**/**16a** = 20 : 20 : 60

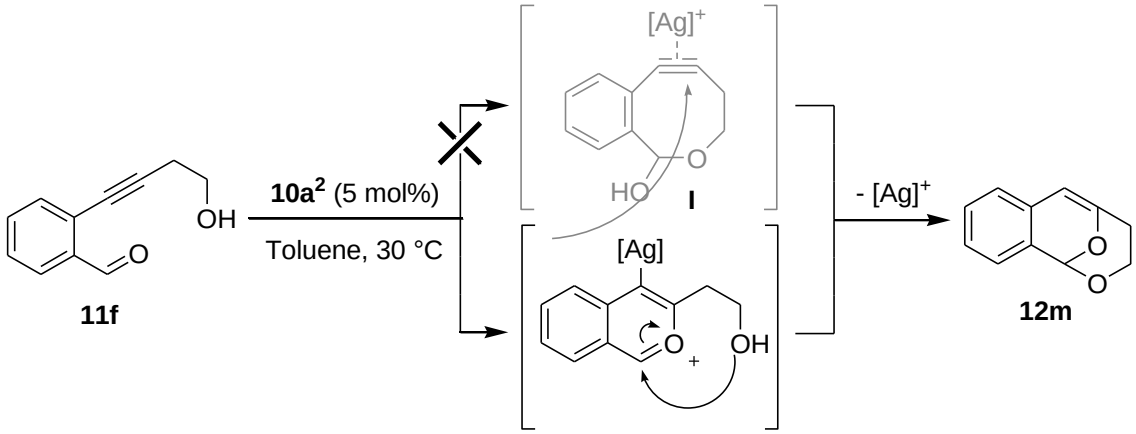
To a solution of dimethyl-acetal **16a** (27 mg, 0.095 mmol) in CH_2Cl_2 (2 mL), **10a**[1] (4 mg, 0.0048 mmol) and distilled water (17 mg, 17 μL, 0.95 mmol) were added. The pale yellow mixture was vigorously stirred at 30 °C for 72 h. The organic phase was separated by the water drop, dried with Na_2SO_4 and then evaporated to dryness under reduced pressure. The ^{1}H-NMRanalysis of the reaction crude displayed the presence of a mixture of isochromene **12a**, aldehyde **11a** and unreacted starting material **16a** in 20:20:60 ratio.

Stability experiments of isochromene 12a

Under acidic conditions: 12a (80 mg, 0.298 mmol) was dissolved in ethyl acetate (1.20 mL) and *p*-toluenesulfonic acid (11.3 mg, 0.06 mmol) was added. The yellow solution was stirred at rt and the progress of the reaction was followed by TLC (Eluant: toluene/ethyl acetate = 99:1). After 2 h the starting material was almost completely disappeared on TLC (one main new spot with lower rf became visible) and the solution was turned to orange. After 24 h, the mixture was poured in water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure to give an orange oil. The crude was roughly purified by filtration on a silica gel-plug (Eluant: hexane/ethyl acetate = 1:1) to give a yellow oil (60 mg) analyzed by ^{1}H-NMRspectroscopy.

Under alkaline conditions: 12a (80 mg, 0.298 mmol) was dissolved in ethyl acetate (1.20 mL) and triethylamine (6.03 mg, 8.3 μL, 0.06 mmol) was added. The pale yellow cloudy solution was stirred at rt and the progress of the reaction was followed by TLC (Eluant: toluene/ethyl acetate = 99:1). After 84 h, the TLC analysis showed the starting material practically unmodified. The mixture was poured in water (30 mL) and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure to give white solid (77 mg). The ^{1}H-NMRanalysis confirmed that the product was **12a** unmodified.

Trapping experiment



Synthesis of isochromene 12m:[146, 163] To a stirred solution of 2-(4-hydroxybut-1-ynyl)benzaldehyde **11f** (60 mg, 0.344 mmol) in dry toluene (1.4 mL), the catalyst **10a²** (16.6 mg, 0.172 mmol) was added. The reaction mixture was stirred at 30 °C for 4.5 h, until no more starting product was detectable by TLC analysis (Eluant: hexane/ethyl acetate = 7:3). The reaction mixture was diluted with sat. aq. $NaHCO_3$ (20 ml) and extracted with ethyl acetate (3 × 10 ml). The organic layer was dried with Na_2SO_4 and then evaporated to dryness under reduced pressure. The crude was purified by flash column chromatography on a short silica gel column (Eluant: hexane/ethyl acetate = 100 : 1, + 3% triethylamine) to give corresponding isochromene **12m** (30 mg, 50 %) as a white solid.

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ = 7.31-7.17 (m, 3H, H_{ar}), 6.97 (d, *J* = 7.2 Hz, 1H, H_{ar}), 6.00 (s, 1H, C-H), 5.77 (s, 1H, C-H), 4.62 (ddd, *J* = 10.4, 8.7, 4.3 Hz, 1H, CH_2), 3.75 (dt, *J* = 8.7, 3.3 Hz, 1H, CH_2), 2.53 (m, 2H, CH_2) ppm.

Spectral data are in good agreement with literature values.

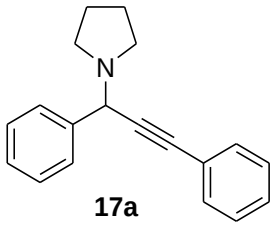
3.3.3 – A^3 coupling

General procedure for the A^3-coupling under conventional heating

The reactions were performed in a 0.5 mmol scale in open air. The catalyst (**10d**[1] or **10d**[2], 0.03 mmol) was dissolved in dry solvent (1 mL) in a screw-cap test tube equipped with a stirring bar. Benzaldehyde (0.5 mmol), pyrrolidine (0.75 mmol) and phenylacetylene (0.75 mmol) were added to the stirred solution, according to this order. The mixture was stirred and heated with an oil-bath at 100 °C. The reaction mixture was diluted with ethyl acetate (20 mL) and the organic layer was washed with water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash column chromatography over a silica gel column with gradients of *n*-hexane/ethyl acetate as eluant.

Entry	cat. (mol%)	solvent	Mol. sieves 3 Å	T (°C)	t (h)	Yield (%)[a]
1	(3)	MeOH	yes	100	4	60
2	(3)	Ph-Me	yes	100	3	57
3	(3)	Ph-Me	yes	rt	90	31
4	(6)	Ph-Me	no	100	5	87
5[b]	(6)	Ph-Me	no	100	5	96

[a] Yields of pure isolated product. [b] **10d**[2] was used as catalyst

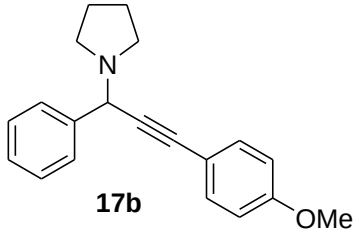


17a

Pale yellow oil. Yield: 96% (125 mg).[170d]

^{1}H NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.61 (dd, *J* = 7.8, 1.7 Hz, 2H, H_{Ar}), 7.53–7.44 (m, 2H, H_{Ar}), 7.42–7.27 (m, 6H, H_{Ar}), 4.89 (s, 1H, CH), 2.69 (pt, *J* = 6.7 Hz, 4H, N–CH_2), 1.98–1.61 (m, 4H, CH_2). Spectral data are in good agreement with literature values.

General procedure for the A^3-coupling under dielectric heating. The reactions were performed in a 0.5 mmol scale in open air. The catalyst (**10d^1** or **10d^2**, 0.015 mmol) was dissolved in dry toluene (1 mL) in a sealed microwave vial equipped with a stirring bar. The suitable aldehyde (0.5 mmol), amine (0.515 mmol) and alkyne (0.515 mmol) were added to the stirred solution, according to this order. The mixture was heated in a single-mode microwave oven at 150 °C for 15 min. The reaction mixture was diluted with ethyl acetate (20 mL) and the organic layer was washed with water (20 mL) and brine (20 mL). The organic layer was dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The reaction crude was purified by flash column chromatography over a silica gel column with gradients of *n*-hexane/ethyl acetate as eluant. (When the reaction yields were calculated by ^{1}H-NMRwith the internal standard, a precise amount of DMT (around 45 mg) was added to the reaction crude before the work-up, and the ^{1}H-NMRwas recorded with a prolonged delay time (d1 = 10)).



17b

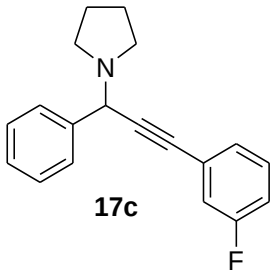
Pale yellow oil. Yield: 75% (109 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.60 (dd, *J* = 7.8, 1.2 Hz, 2H, H_{ar}), 7.42 (d, *J* = 8.9 Hz, 2H, H_{ar}), 7.37–7.27 (m, 3H, H_{ar}), 6.84 (d, *J* = 8.9 Hz, 2H, H_{ar}), 4.86 (s, 1H, CH), 3.81 (s, 3H, O–CH_3), 2.68 (pt, *J* = 6.6 Hz, 4H, N–CH_2), 1.83–1.75 (m, 4H, CH_2).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 159.7 (C_q), 139.9 (C_q), 133.4 (CH_{ar}), 128.54 (CH_{ar}), 128.46 (CH_{ar}), 127.8 (CH_{ar}), 115.6 (C_q), 114.2 (CH_{ar}), 87.0 (C_{sp}), 85.3 (C_{sp}), 59.4 (CH), 55.5 (O–CH_3), 50.5 (N–CH_2), 23.8 (CH_2).

MS ESI(+) m/z (%) = 292.1 (4) $[M + H]^+$, 221.2 (100) $[M – pyrrolidine]^+$

HRMS ESI $(M + H)^+$ calculated for $C_{20}H_{22}NO^+$, 292.1696; found, 292.1701.



17c

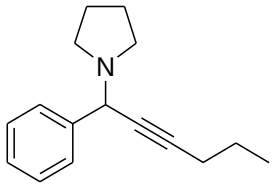
Pale yellow oil. Yield: 83% (116 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.67–7.53 (m, 2H, H_{ar}), 7.44–7.23 (m, 6H), 7.23–7.13 (m, 1H), 7.11–6.90 (m, 1H), 4.91 (s, 1H, CH), 2.71 (pt, *J* = 6.6 Hz, 4H, N–CH_2), 1.88–1.76 (m, 4H, CH_2).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 162.6 (d, $^{1}J_{C–F}$ = 246.4 Hz, C_q), 139.3 (C_q), 130.0 (d, $^{3}J_{C–F}$ = 8.7 Hz, CH_{ar}), 128.54 (CH_{ar}), 128.47 (CH_{ar}), 127.92 (CH_{ar}), 127.89 (d, $^{4}J_{C–F}$ = 3.2 Hz, CH_{ar}), 125.3 (d, $^{3}J_{C–F}$ = 9.5 Hz, C_q), 118.8 (d, $^{2}J_{C–F}$ = 22.7 Hz, CH_{ar}), 115.7 (d, $^{2}J_{C–F}$ = 21.2 Hz, CH_{ar}), 88.5 (C_{sp}), 86.0 (d, $^{4}J_{C–F}$ = 3.3 Hz, C_{sp}), 59.3 (CH), 50.5 (N–CH_2), 23.7 (CH_2).

MS ESI(+) m/z (%) = 280.2 (100) $[M + H]^+$, 209.4 (48) [M – pyrrolidine]$^+$

HRMS ESI $(M + H)^+$ calculated for $C_{19}H_{19}FN^+$, 280.1496; found, 280.1493.



17d

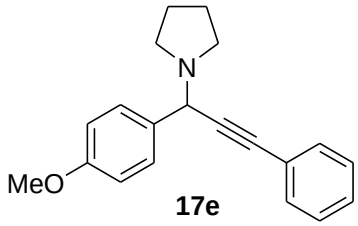
Pale yellow oil. Yield: 53% (60 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.53 (dd, *J* = 7.5, 1.5 Hz, 2H, H_{ar}), 7.44–7.19 (m, 3H, H_{ar}), 4.60 (t, *J* = 2.0, 1H, CH), 2.59 (pt, *J* = 6.2 Hz, 4H, N–CH_2), 2.26 (dt, *J* = 7.1, 2.0 Hz, 2H, CH_2), 1.79–1.73 (m, 4H, CH_2), 1.58 (ses, *J* = 7.1 Hz, 2H, CH_2), 1.02 (t, *J* = 7.2 Hz, 3H, CH_3).

^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 140.3 (C_q), 128.5 (CH_{ar}), 127.6 (CH_{ar}), 87.2 (C_{sp}), 77.3 (C_{sp}), 59.0 (CH), 50.4 (N–CH_2), 23.7 (CH_2), 22.7 (CH_2), 21.0 (CH_2), 13.8 (CH_3).

MS ESI(+) m/z (%) = 228.1 (100) $[M + H]^+$.

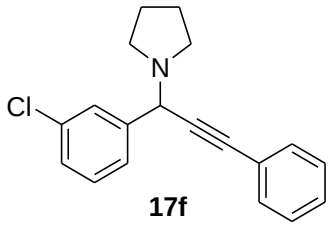
HRMS ESI $(M + H)^+$ calculated for $C_{16}H_{22}N^+$, 228.1747; found, 228.1750.



17e

Pale yellow oil. Yield: 78% (114 mg).[226]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.46–7.54 (m, 4H, H_{ar}), 7.29–7.32 (m, 3H, H_{ar}), 6.89 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 1H, H_{ar}), 4.82 (s, 1H, CH), 3.81 (s, 3H, CH_3), 2.71–2.64 (m, 4H, N–CH_2), 1.82–1.76 (m, 4H, CH_2). Spectral data are in good agreement with literature values.



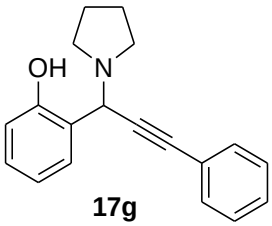
17f

Pale yellow oil. Yield: 79% (117 mg).[227]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.63 (s, 1H, H_{ar}), 7.58–7.41 (m, 3H), 7.40–7.20 (m, 5H), 4.91 (s, 1H, CH), 2.84–2.60 (m, 4H, N–CH_2), 1.96–1.67 (m, 4H, CH_2).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 141.9 (C_q), 134.4 (C_q), 132.0 (CH_{ar}), 129.7 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 128.5 (CH_{ar}), 128.0 (CH_{ar}), 126.6 (CH_{ar}), 123.2 (C_q), 87.7 (C_{sp}), 85.9 (C_{sp}), 58.7 (CH), 50.3 (N–CH_2), 23.79 (CH_2).

MS ESI(+) m/z (%) = 298.1/296.1 (30/100) $[M + H]^+$. Spectral data are in good agreement with literature values.

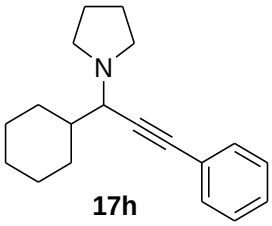


17g

[226] Zhua, W.; Qiana, W.; Zhang, Y. *J. Chem. Res.* **2005**, 410–412
[227] Lo, V. K.-Y.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem. Commun.* **2010**, *46*, 213–215

Pale yellow oil. Yield: 83% (115 mg).[228]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.57–7.50 (m, 3H, H_{ar}), 7.41–7.32 (m, 3H, H_{ar}), 7.29–7.17 (m, 1H, H_{ar}), 6.95–6.79 (m, 2H, H_{ar}), 5.29 (s, 1H, CH), 2.96–2.75 (m, 4H, N–CH_2), 1.96–1.82 (m, 4H, CH_2). Spectral data are in good agreement with literature values.



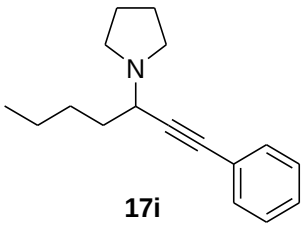
17h

Colorless oil. Yield: 98% (131 mg).[169]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.48–7.38 (m, 2H, H_{ar}), 7.35–7.22 (m, 3H, H_{ar}), 3.36 (d, *J* = 8.4 Hz, 1H, CH), 2.80–2.60 (m, 4H, N–CH_2), 2.12–1.92 (m, 2H, $C_{sp3}H$), 1.85–1.52 (m, 8H, $C_{sp3}H$), 1.30–1.05 (m, 5H, CH_2).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 131.9 (CH_{ar}), 128.4 (CH_{ar}), 127.9 (CH_{ar}), 123.9 (C_q), 88.1 (C_{sp}), 86.0 (C_{sp}), 61.5 (CH), 50.3 (N–CH_2), 41.6 (CH), 30.9 (CH_2), 30.5 (CH_2), 26.9 (CH_2), 26.5 (CH_2), 23.8 (CH_2).

MS ESI(+) m/z (%) = 268.2 (100) $[M + H]^+$. Spectral data are in good agreement with literature values.



17i

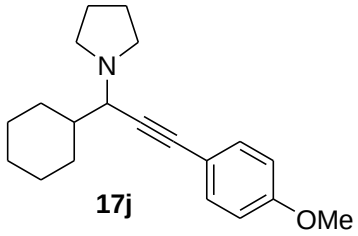
Colorless oil. Yield: 61% (74 mg).[169]

[228] Dilman, A. D.; Arkhipov, D. E.; Belyakov, P. A.; Struchkova, M. I.; Tartakovsky V. A. *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 517–522

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.45–7.40 (m, 2H), 7.31–7.26 (m, 3H, H_{ar}), 3.67 (dd, *J* = 7.9, 6.7 Hz, 1H, CH, H_{ar}), 2.78–2.67 (m, 4H, N–CH_2), 1.84–1.26 (m, 10H, CH_2), 0.93 (t, *J* = 7.0 Hz, 3H, CH_3).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 131.9 (CH_{ar}), 128.4 (CH_{ar}), 127.9 (CH_{ar}), 123.8 (C_q), 88.7 (C_{sp}), 85.4 (C_{sp}), 55.4 (CH), 49.9 (N–CH_2), 35.1 (CH_2), 30.9 (CH_2), 29.1 (CH_2), 23.7 (CH_2), 22.7 (CH_2), 14.2 (CH_3).

MS ESI(+) m/z (%) = 242.1 (100) $[M + H]^+$, 171.2 (12) $[M – pyrrolidine]^+$. Spectral data are in good agreement with literature values.



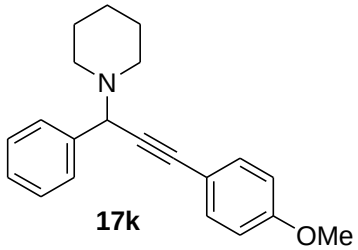
17j

Colorless oil. Yield: 89% (132 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.36 (d, *J* = 8.9 Hz, 2H, H_{ar}), 6.82 (d, *J* = 8.9 Hz, 2H, H_{ar}), 3.80 (s, 1H, O–CH_3), 3.32 (d, *J* = 8.3 Hz, 1H, CH), 2.77–2.57 (m, 4H, N–CH_2), 2.10–1.90 (m, 2H, $C_{sp3}H$), 1.83–1.49 (m, 8H, $C_{sp3}H$), 1.28–1.04 (m, 5H, CH_2).

^{13}C-NMR (75.5 MHz, $CDCl_3$, T = 300 K): δ 159.6 (C_q), 133.4 (CH_{ar}), 116.3 (C_q), 114.2 (CH_{ar}), 86.7 (C_{sp}), 85.9 (C_{sp}), 61.7 (O–CH_3), 55.7 (CH), 50.4 (N–CH_2), 41.8 (CH), 31.1 (CH_2), 30.7 (CH_2), 27.1 (CH_2), 26.6 (CH_2), 23.9 (CH_2).

HRMS ESI $(M + H)^+$ calculated for $C_{20}H_{28}NO^+$, 298.2165; found, 298.2162.

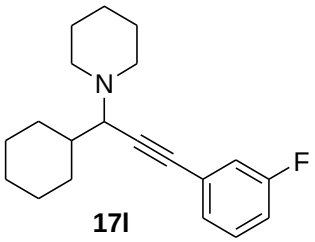


17k

Pale yellow oil. Yield: 91% (139 mg).[229]

[229] Sreedhar, B.; Surendra Reddy, P.; Vamsi Krishna, C. S.; Vijaya Babu, P. *Tetrahedron Lett.* **2007**, 48, 7882–7886

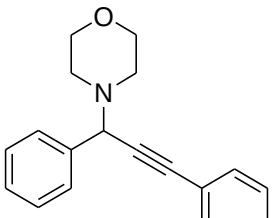
^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.66–7.60 (m, 2H, H_{ar}), 7.45 (d, *J* = 8.9 Hz, 2H, H_{ar}), 7.40–7.28 (m, 3H, H_{ar}), 6.86 (d, *J* = 8.9 Hz, 2H, H_{ar}), 4.77(s, 1H, CH), 3.82 (s, 3H, CH_3), 2.55 (pt, *J* = 5.2 Hz, 4H, N–CH_2), 1.66–1.53 (m, 4H, CH_2), 1.50–1.40 (m, 2H, CH_2). Spectral data are in good agreement with literature values.



17l

Pale yellow oil. Yield: 96% (144 mg).[230]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.32–7.18 (m, 2H, H_{ar}), 7.17–7.09 (m, 1H), 7.04–6.92 (m, 1H), 3.10 (d, *J* = 9.9 Hz, 1H, CH), 2.68–2.55 (m, 2H, N–CH_2), 2.44–2.32 (m, 2H, N–CH_2), 2.11–1.99 (m, 2H, CH_2), 1.80–1.38 (m, 10H, CH_2), 1.33–0.88 (m, 5H, CH_2). Spectral data are in good agreement with literature values.



17m

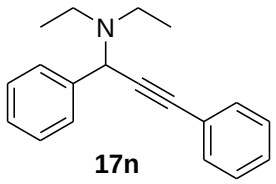
Colorless oil. Yield: 59% (82 mg).[231]

^{1}H-NMR (200 MHz, $CDCl_3$, T = 300 K): δ 7.68–7.63 (m, 2H, H_{ar}), 7.57–7.50 (m, 2H), 7.44–7.31 (m, 6H), 4.81 (s, 1H, CH), 3.80–3.71 (m, 4H, O–CH_2), 2.74–2.59 (m, 2H, N–CH_2).

^{13}C-NMR (50.3 MHz, $CDCl_3$, T = 300 K): δ 138.1 (C_q), 132.0 (CH_{ar}), 128.8 (CH_{ar}), 128.53 (CH_{ar}), 128.45 (CH_{ar}), 128.0 (CH_{ar}), 123.3 (C_q), 88.7 (C_{sp}), 85.3 (C_{sp}), 67.4 (O–CH_2), 62.3 (CH), 50.2 (N–CH_2) (one signal obscured).

MS ESI(-) m/z (%) = 276.5 (100) $[M - H]^-$, 191.4 (75) $[M – morpholine]^-$. Spectral data are in good agreement with literature values.

[230] B. Sreedhar, A. Suresh Kumar, P. Surendra Reddy, *Tetrahedron Lett.* **2010**, 51, 1891–1895
[231] B. Karimi, M. Gholinejad, M. Khorasani, *Chem. Commun.* **2012** , 48, 8961–8963



17n

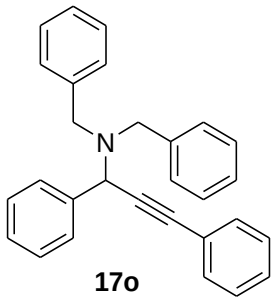
Colorless oil. Yield: 57% (75 mg).

^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.73 (dd, *J* = 7.4, 0.8 Hz, 2H, H_{ar}), 7.57–7.52 (m, 2H, H_{ar}), 7.43–7.30 (m, 6H, H_{ar}), 5.09 (s, 1H, CH), 2.71–2.53 (m, 4H, N–CH_2), 1.11 (t, *J* = 7.1 Hz, 6H, CH_3).

^{13}C-NMR (75.5 MHz, $CDCl_3$, δ): 140.2 (C_q), 132.0 (CH_{ar}), 128.6 (CH_{ar}), 128.5 (CH_{ar}), 128.3 (CH_{ar}), 127.5 (CH_{ar}), 126.7 (C_q), 87.7 (C_{sp}), 86.4 (C_{sp}), 57.3 (CH), 44.8 (N–CH_2), 13.9 (CH_3) (one signal obscured).

MS ESI(+) m/z (%) = 264.0 (100) $[M + H]^+$, 191.4 (20) [M – diethylamine]$^+$.

HRMS ESI $(M + H)^+$ calculated for $C_{19}H_{22}N^+$, 264.1747; found, 264.1744.



17o

Colorless oil. Yield: 61% (118 mg).[170a]

^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.77 (d, *J* = 7.5 Hz, 2H, H_{ar}), 7.67 (dd, *J* = 6.0, 2.6 Hz, 2H, H_{ar}), 7.52–7.20 (m, 16H, H_{ar}), 4.98 (s, 1H, CH), 3.84 (d, *J* = 13.5 Hz, 2H, N–CH_2), 3.58 (d, *J* = 13.5 Hz, 2H, N–CH_2). Spectral data are in good agreement with literature values.