Doctorate course in Chemical Sciences

Ph.D Thesis

Lewis Acid catalysis in the Synthesis of Small Molecules: Carbon-Nitrogen bond formation

Cycle XXXII

Scientific-sector CHIM/06

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The mind is like a parachute.

It only works if you open.

(A. Einstein)

The present work was carried out between the laboratories of organic chemistry of Prof. Enrico Marcantoni at the University of Camerino and of Prof. Jérôme Lacour at the University of Geneva.

The first part of this thesis work was carried out between January 2017 and December 2018 in the laboratories of Prof. Marcantoni, under the supervision of Dr. Cristina Cimarelli.

The second part was carried out from January 2019 to Jun 2019 at the University of Geneva in the laboratory of prof. Jérôme Lacour, under the supervision of Dr. Alexandre Homberg.

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First Part:

Lewis Acid catalysis for the Carbon-Nitrogen bond formation in the Synthesis of Small Molecules.

1. Introduction

Nitrogen containing compounds are of great importance due to their interesting and different biological activities. The construction of C-N bond is for this of significant importance because it allows the introduction of the nitrogen atoms in organic molecules. Despite the numerous advancements, the construction of the C-N bond is still a major challenge especially the development of alternative, milder and cheaper methodologies.

The project during my doctorate in the group of prof. Cristina Cimarelli and prof. Enrico Marcantoni has been mainly focused on the application of *Lewis* acid catalysis for the formation of C – N bonds in the synthesis of small molecules, in particular to the formation of secondary propargylamines.

A brief introduction to importance of propargylamines both from biological point of view and as versatile buildings block for the synthesis of nitrogen containing heterocycles will be given. Then the A^3 coupling reaction will be presented, the most common synthetic strategies to afford these class molecules. Finally the key-role of copper acetylides in various reactions and the applications of two different *Lewis* acids, iodine and cerium trichloride hephtahydrate in the formation of the C – N bond.

2. Small Molecules

Small molecules are low molecular weight compounds with a well-defined chemical structures that help regulate biological processes mainly by metabolic degradation.

The first set of medically employed drugs were in fact small molecules obtained mainly from natural products or extracts. Nowadays they are applied for different medical therapeutic uses with great success: from the most dreaded diseases like cancer, epilepsy, obesity to more common diseases as cough, fever, cold, amongst others. Rasagiline, for example, is a powerful sencodary propargylamine used against Parkinson's disease (Figure 1).[1]

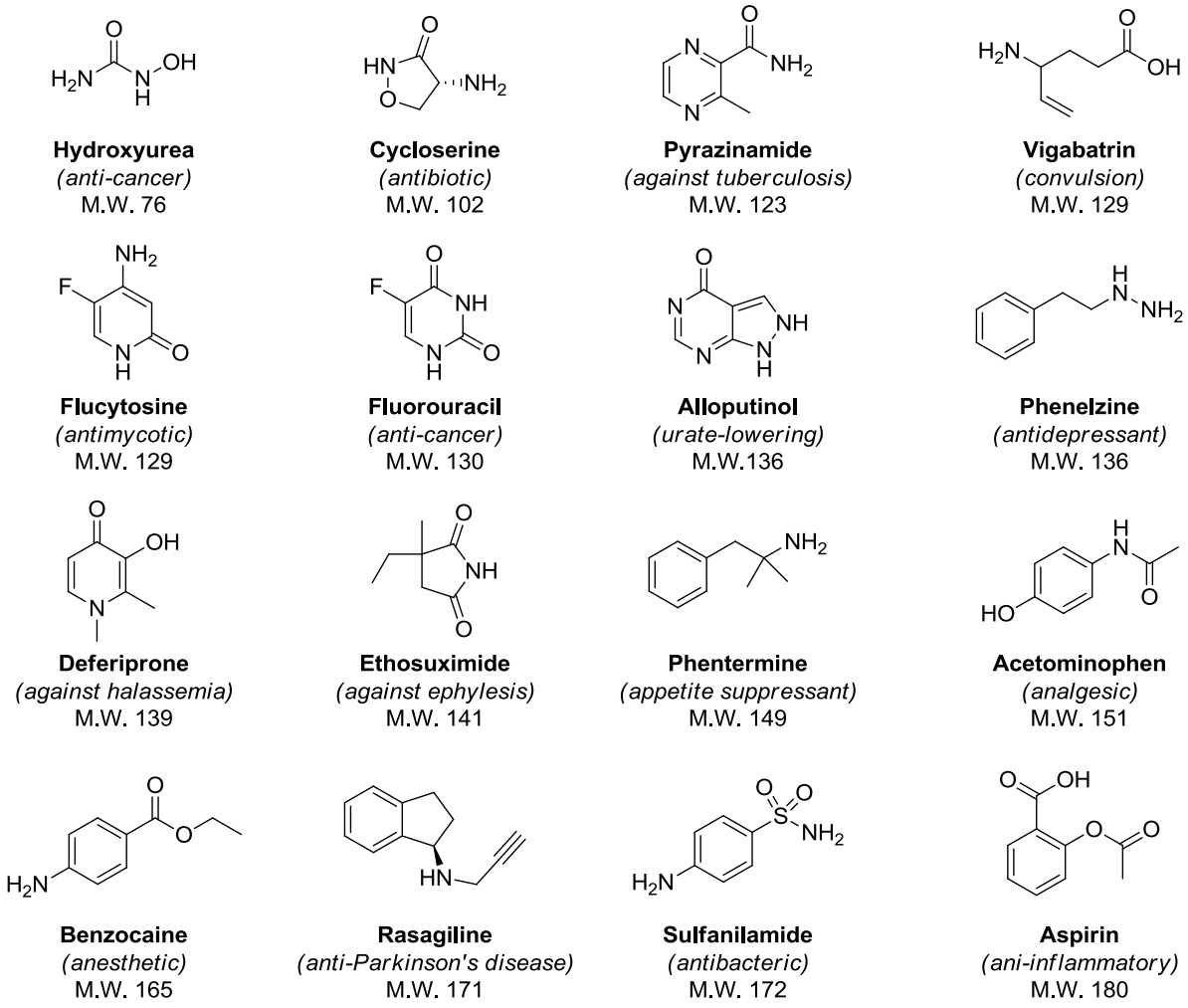


Figure 1. *Most common small molecules.*

3. Propargylamines

3.1. Importance

Propargylamines are a class of small molecules that have seen an increasing interest in research, finding various applications especially in medicine for the treatment of different neurodegenerative disorders (ND) such as Alzheimer's or Parkinson's diseases.

Selegiline and Rasagiline are the most well-known propargylamines that are irreversible selective inhibitors of MAO-B (monoamine-oxidase type B) enzyme, responsible for catalyzing the oxidative degradation of dopamine typical in Parkinson's disease, with the addition of a neuroprotective activity (Figure 2).[2]

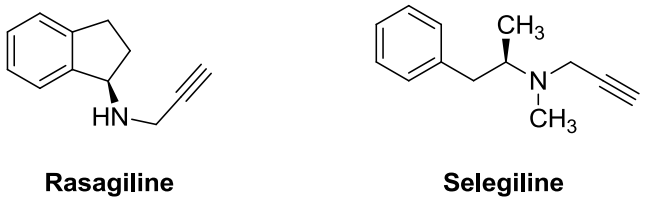
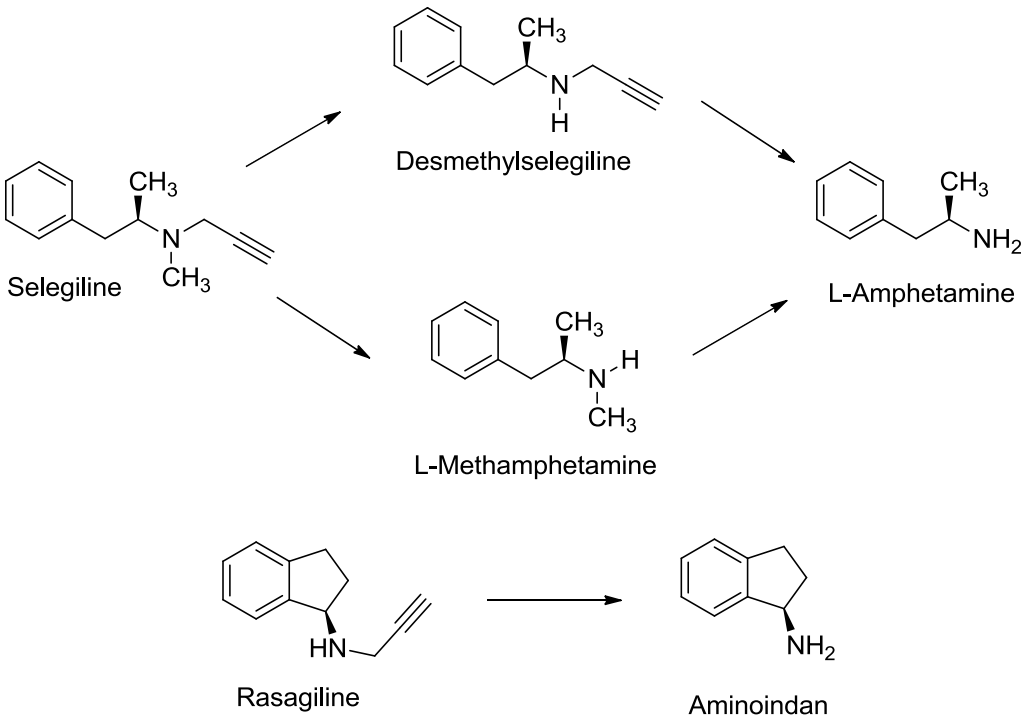


Figure 2. *Structure of well-known propargylamines.*

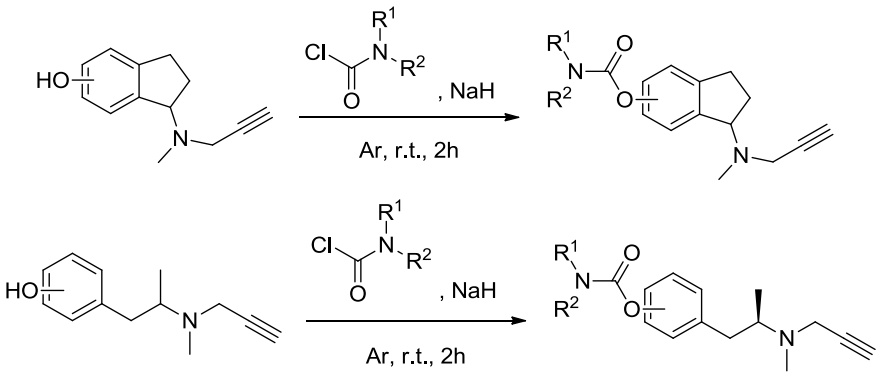
These two drugs give rise to different metabolites with distinct pharmacologic properties.[3] Selegiline, a first-generation MAO-B inibithor, undergoes metabolism in the liver to L-methamphetamine and desmethylselegiline, which are then converted into L-amphetamine. These compounds have no effects on MAO-B: chronic exposure to them induces neuronal toxicity in experimental models and have been associated with cardiac and psychiatric effects in patients with Parkinson disease's (Scheme 1).

Rasagiline, instead, is a second-generation MAO-B inhibitor and is more potent than Selegiline: structure-activity studies demonstrate in fact that maintaining a distance of no more than 2 carbon units between the aromatic ring and the N-propargyl terminal results in a higher specificity for MAO-B. It is metabolized to aminoindan which, on the contrary of Selegeline metabolites, doesn't exhibit the amphetamine-like negative side effects (Scheme 1).



Scheme 1. *Metabolism and by-products of selegiline and rasagiline.*

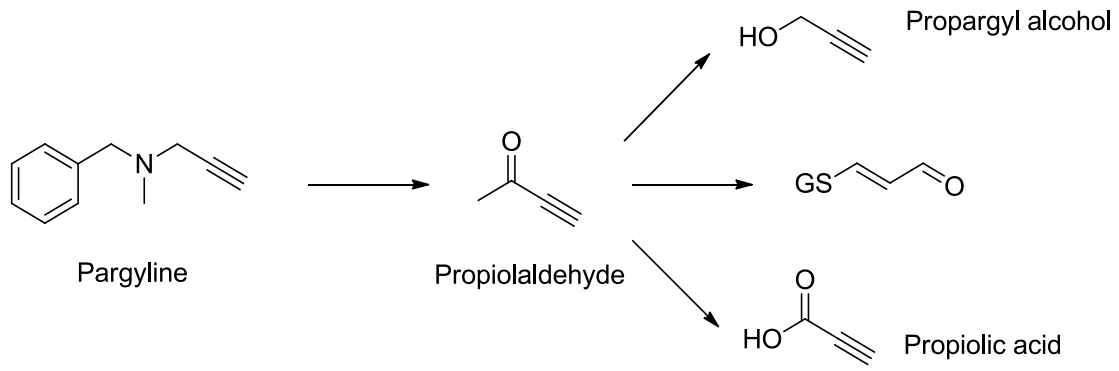
In addition, also the carbamate derivatives of both Rasagiline and Selegiline can be used in the treatment of neurodegenerative diseases: they are synthesized via a multistep procedure from the corresponding hydroxyl precursor and display combined inhibitory activities of both acetylcholine esterase (AChE) and monoamine oxidase (MAO) by virtue of their carbamoyl and propargylamine pharmacophores (Scheme 2). [4]



Scheme 2. *Propargylcarbammates derivatives.*

Pargiline is a monoamine oxidase (MAO) inhibitor that is used clinically in the treatment of hypertension. This drug is methabolized to give propiolaldehyde, a highly reactive

intermediate involved in the decrease of hepatic GSH and covalent binding to proteins (Scheme 3).[5]



Scheme 3. *Metabolism and by-product of pargyline.*

Other examples of propargylamines with biological activity include AMG-3969, a compound that disrupts the glucokinase-glucokinase regulatory protein interaction, important for the treatment of diabetes,[6] or Ladostigil which is a combined MAO-B inhibitor, reversible acetylcholinesterase and butyrylcholinesterase inhibitor used to treat Alzheimer's or Lewy body disease.[7] Dhydroquinazoline DPC 961 is an HIV non-nucleoside reverse transcriptase inhibitor (NNRTI), an analogue of Efavirenz (Figure 3).[8]

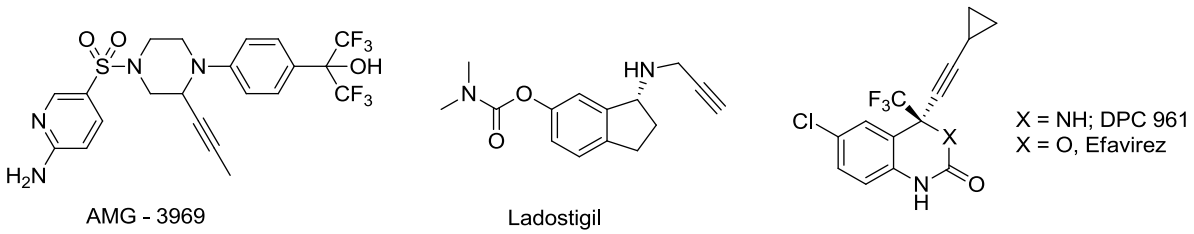


Figure 3. *Examples of therapeutics containing a propargylamine moiety.*

The propargyl moiety is also present in natural products as Dynemicin A, isolated from *Micromonospora Chersina* and *Uncialamycin*, obtained from *Cladonia Uncialis*. These are powerful antibiotics whose biological activity strongly depends on their enediyne structure (Figure 4). [9]

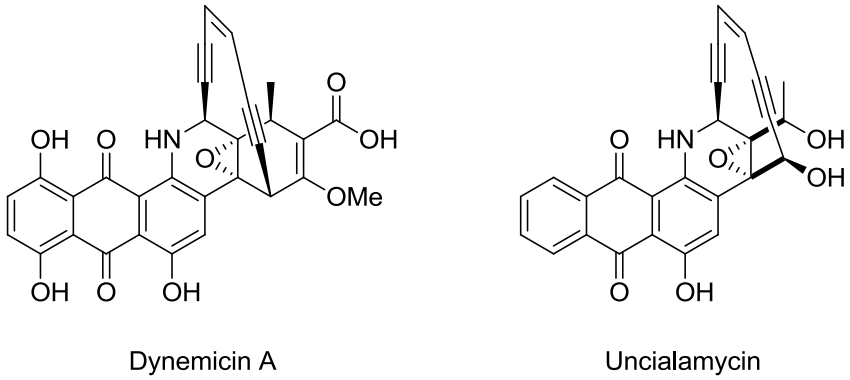


Figure 4. *Natural products with antibiotic activity.*

Propargylamides, that can be obtained directly by propargylamines acylation, represent the core of a range of biologically relevant molecules and are useful substrates in the synthesis of heterocycles as well as biomimetic polymers.

Oxotremorine and its ring-opened analog Oxo-2 for example, are partial muscarinic agonists producing large guanine nucleotide shifts in the heart which suggests a strong M2 agonist-like effects. The corresponding piperidinic analog Oxo-Pip, instead, produced only a weak shift in the concentration response curve with the addition of the stable guanine nucleotide analog. Thus, the change from a pyrrolidine to a piperidine ring is able to change a partial agonist into an antagonist.

Furthermore, the propargylamides moiety is also present in various herbicides and fungicides such as Propyzamide (Figure 5).[10]

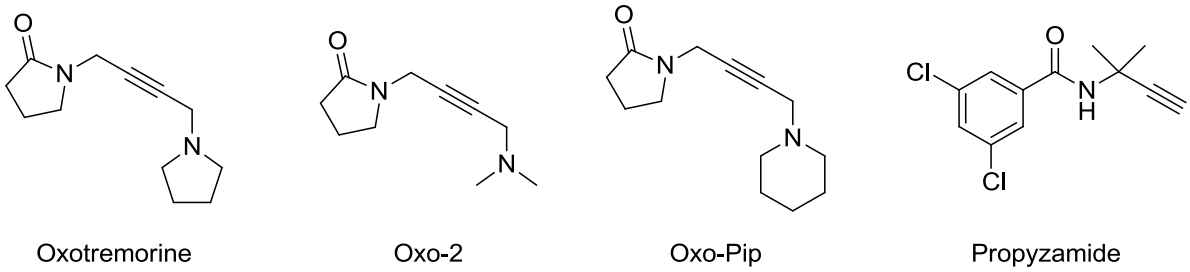


Figure 5. *Propargylamides with biological activity.*

3.2. Synthetic utility: nitrogen-containing heterocycles

Propargylamines can be direct precursors or starting materials for the preparation of key intermediates in the synthesis of various important nitrogen-containing heterocyclic scaffolds such as imidazoles, pyrroles, pyridine, quinolines, oxazoles or thiazoles (Figure 6). They are in fact susceptible to many different chemical transformations because of their structure which contains an amine, suitable for nucleophilic reactions, placed at the β-position to an alkyne moiety that can act both as an electrophile and as a source of electrons in nucleophilic reactions. [11] The synthesis of heterocyclic structure will be described more in detail in the next paragraphs.

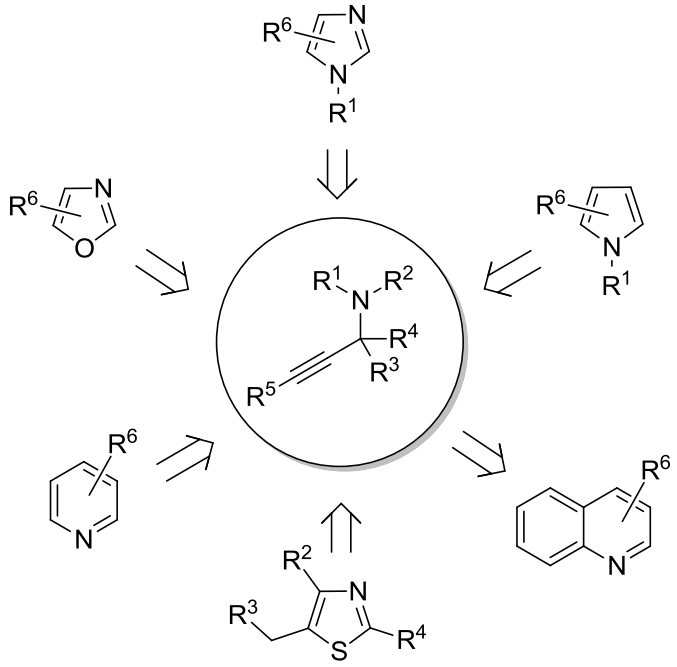


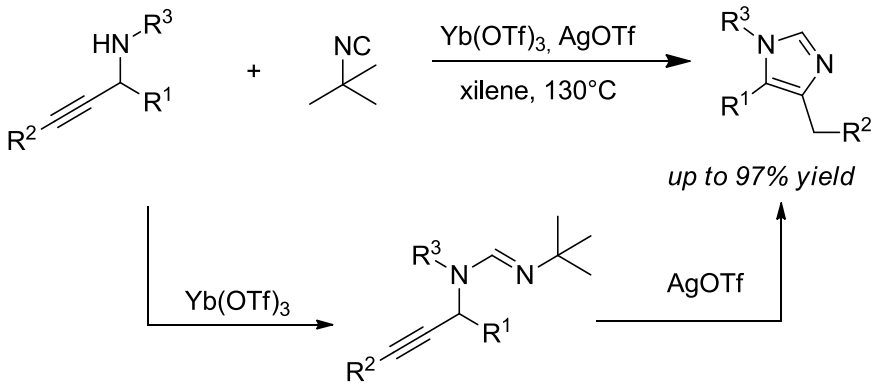
Figure 6. *Versatile intermediate for nitrogen-containing heterocycles.*

3.2.1. Imidazoles

Among all of the nitrogen-containing heterocycles, imidazole is one of the most important motif in organic and medicinal chemistry.

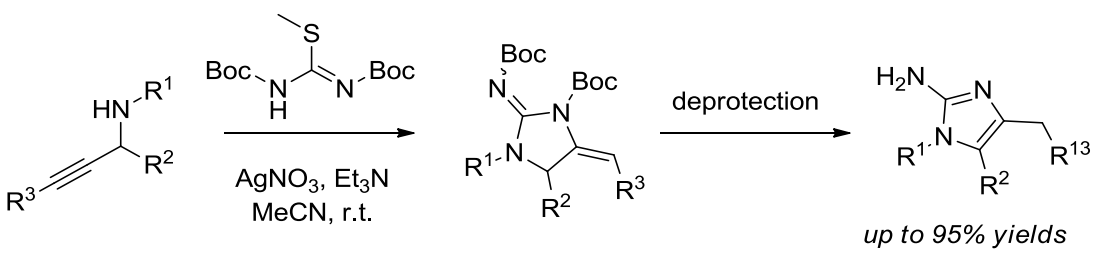
Different synthetic methods have been developed but it is still challenging to achieve a high efficient and regioselectivity synthesis of the imidazole core. In this context, propargylamines represent a valid starting material. [12]

The group of Zhu reported the synthesis of 1,4,5-trisubstituted imidazoles in the presence of a catalytic amount of both $Yb(OTf)_3$ and AgOTf starting from *tert*-butylisonitrile and secondary propargylamines in excellent yields. In these multiple systems, the ytterbium(III) catalyzes the insertion of the isonitrile to the N-H bond of amine, whereas the silver(I) promotes the *5-exo-dig* cyclization (Scheme 4).[13]



Scheme 4. *Synthesis of imidazoles of Zhu.*

Secondary propargylamines are a good option also for the synthesis of diversely substituted 2-aminoimidazoles, alkaloids of the naamine family, which otherwise require long experimental procedures with many protection/deprotection steps and the use of unstable precursors as α-aminoketones, α-bromoaldehydes and organomagnesium or organolithium reagents. In Figure is reported the synthetic protocols developed for these compounds by the group of Van der Eycken (Scheme 5). [14]

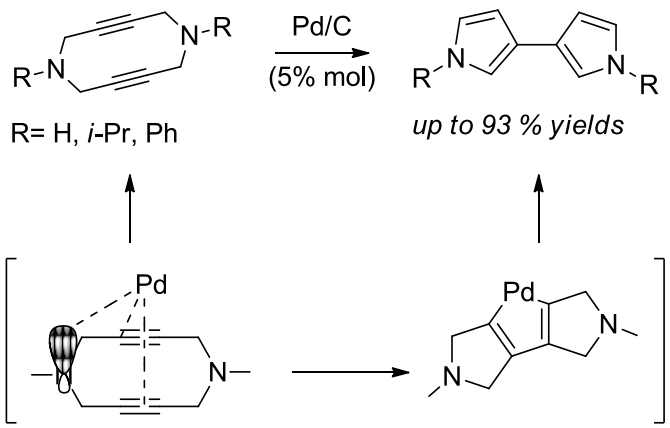


Scheme 5. *Synthesis of 2-aminoimidazoles of Van der Eycken.*

3.2.2. Pyrroles

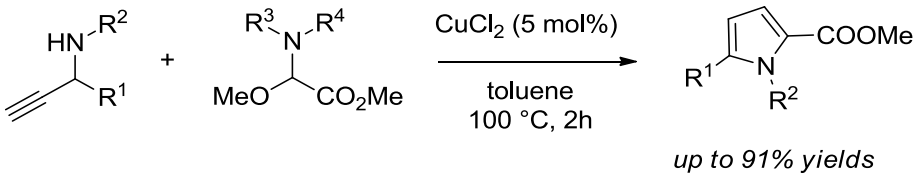
The synthesis of the pyrrolic core from N-propargylamines has undergone explosive growth in recent years with respect to traditional protocols as metal-catalyzed cross-coupling or multicomponent reaction that instead require expensive catalyst or let to the production of harmful waste. The advantages over more conventional methodologies are in fact formation of nontoxic by-products, high atom economy, ease of handling and generation of environmentally friendly processes with high yields. [15]

The most used metal catalyst is palladium since it possesses a great affinity for triple bonds. Gleiter and Ritter described an efficient Pd-catalyzed synthesis of N,N'-dialkyl-3,3'-bispyrroles from cyclic propargylamines in which the substrate was treated with Pd/C. The palladium efficiently coordinates to both triple bond thanks also to the support of nitrogen lone pair which then leads to the final product (Scheme 6). [16]



Scheme 6. *Synthesis of bispyrroles of Gleiter and Ritter.*

In addition to palladium, Sakai and co-workers described the versatile synthesis of 1,2,5-substituted pyrroles from the reaction between secondary-*N*-propargylamines and N,O-acetyls under copper catalysis via *5-endo-dig* cyclization (Scheme 7). [17]

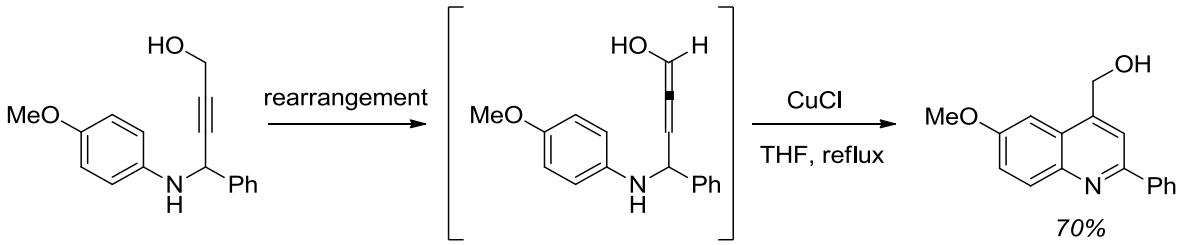


Scheme 7. *Synthesis of pyrroles of Sakai.*

3.2.3. Quinolines

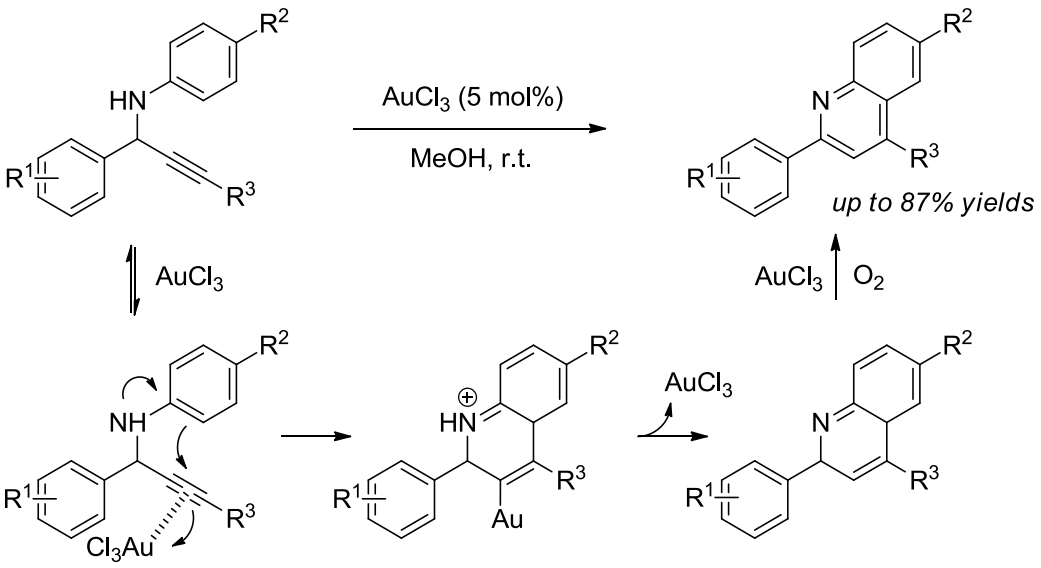
Among bicyclic heterocycles, quinolines are the most prominent since they constitute important classes of natural products, synthetic pharmaceuticals, pesticides and dyes.

Cyclization of propargylamines has emerged over the past years as a powerful and novel strategy in the synthesis of quinolines offering several positive aspects as a shorter synthetic route with high functional group tolerance.[18] The early report appeared in 2002 using the *N*-propargylamine under copper(I) catalysis (Scheme 8). [19]



Scheme 8. *Early synthesis of quinolines.*

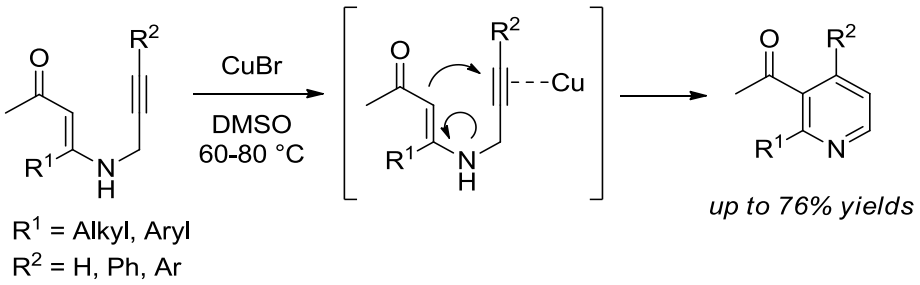
Since then, many strategies have been developed with different metal catalyst: the group of Wang, for example, reported the synthesis of 2,4,6-trisubstituted quinolines via intramolecular cyclization of secondary-*N*-propargylamines using gold(III) salt (Scheme 9). [20]



Scheme 9. *Synthesis of quinolines of Wang.*

3.2.4. Pyridines

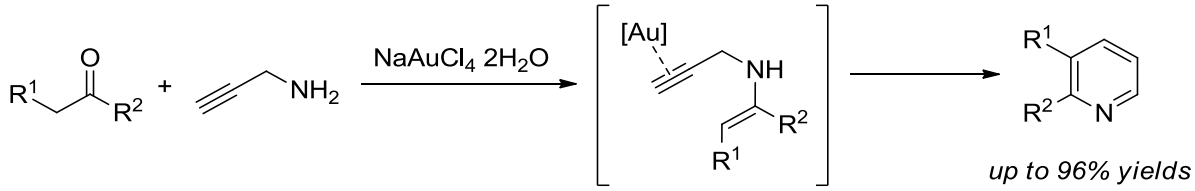
Propargylamines are versatile buildings blocks also for the synthesis of pyridines. An early example was reported by Cacchi and co-workers that obtained 3-pyridinones from N-propargylic-β-enaminones through a copper-catalyzed *6-endo-dig* cyclization (Scheme 10). [21]



Scheme 10. *Synthesis of pyridines of Cacchi.*

Abbiati synthesized pyridines in good yields starting from commercial primary propargylamines with different ketones under gold catalysis. The formation of pyridines was suggested to occur through the sequential amination of carbonyl compounds followed

by a regioselective 6-endo-dig cyclization of the *N*-propargylenamine intermediate and subsequent aromatization (Scheme 11). [22]



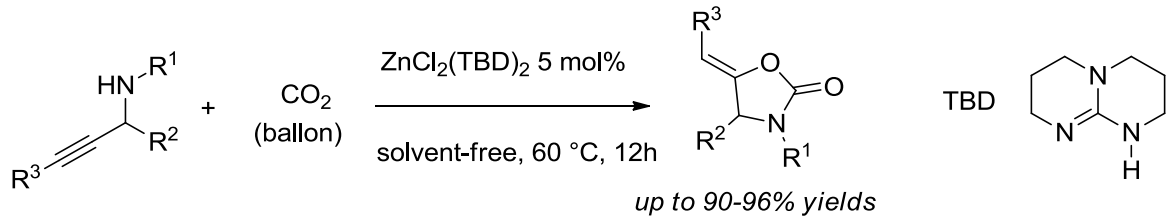
Scheme 11. *Synthesis of pyridine of Abbiati.*

3.2.5. 2-Oxazolidinones

2-Oxazolidinones are an important heterocyclic structure having a significant role as chemical intermediates or chiral auxiliaries in organic synthesis as well as in pharmaceutical chemistry as antibacterial drugs.

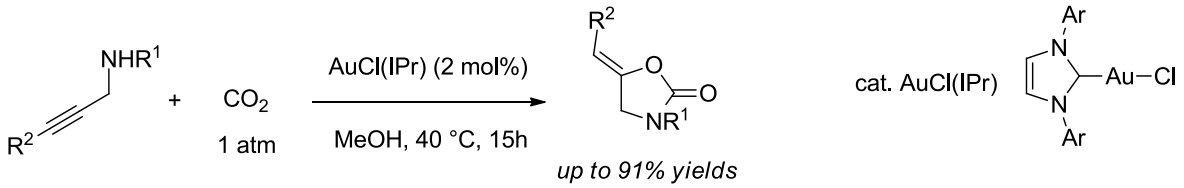
Therefore, many efforts have been made for their synthesis. Recently, the employment of propargylamines in combination with CO_2 represents an important and atom economic reaction to access 2-oxazolidinone through a carboxylative cyclization process. Several catalysts have been applied and studied mainly based on ruthenium, palladium, silver, copper and zinc.

In 2017, L. He and co-workers described the use of $ZnCl_2(TBD)_2$ generated in situ from $ZnCl_2$ with 1,5,7-triazabyciclo[4.4.0]dec-5-ene (TBD) for the synthesis of 2-oxazolidinones from propargylamines and CO_2. Mild reaction conditions, good yields and relatively short reaction times are the main advantages of this solvent-free protocol (Scheme 12). [23]



Scheme 12. *Synthesis of 2-oxazolidinones of He.*

Kayaky and Ikariya demonstrated the applicability of gold catalyst for carboxylative cyclization process. They obtained better yields with propargylamine with aliphatic substituents at the alkyne terminus than aromatic one (Scheme 13).[24]

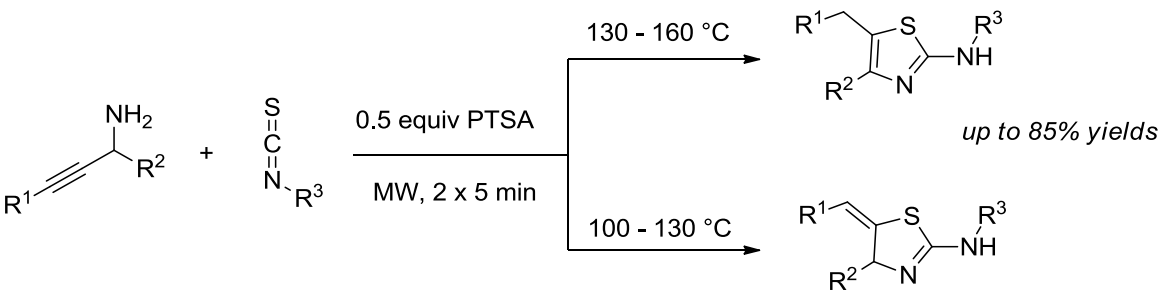


Scheme 13. *Synthesis of 2-oxazolidinones by Hase, Kayaky and Ikariya.*

3.2.6. Thiazoles

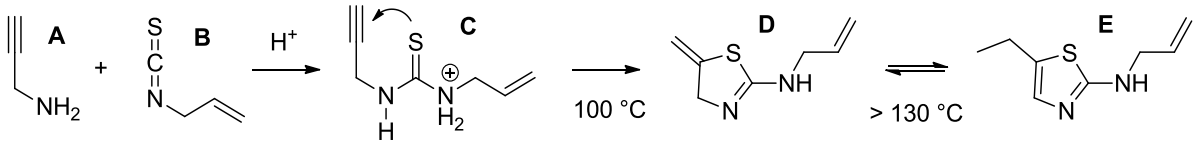
Thiazoles are an important class of azole compounds that have received a considerable attention since they exhibit a wide variety of pharmacological activities.

Many strategies have been developed for the synthesis of thiazoles including the possibility to obtain them by cyclization from *N*-propargylamine. In the early protocol CS_2 was used as a source of sulphur, later substituted by isothiocyanates for safety and healthy reasons. In this context, the group of Castagnolo, for example, reported a simple and versatile microwave-assisted protocol for the synthesis of 2-aminothiazoles from propargylamines and isothiocyanates in the presence of catalytic PTSA at temperatures above 130 °C and in a few minutes. The same reaction carried out at lower temperatures leads to the formation of the tautomeric 2-amino-4-methylenethiazolines (Scheme 14). [25]



Scheme 14. *Synthesis of thiazoles of Castagnolo.*

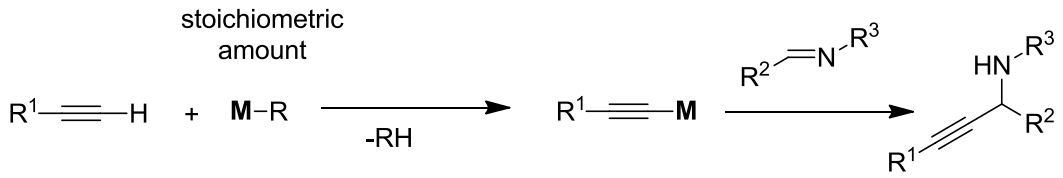
The propargylamine **A** reacts almost instantaneously with the isocyanate **B** leading to the formation of the thiourea intermediate **C**. The intermediate **C**, in acidic medium, undergoes a 5-exo-dig cyclization leading to the formation at 100 °C of a thiazoline **D** that upon heating above 130°C tautomerises to thiazole **E** (Scheme 15).



Scheme 15. *Tautomerism.*

3.3. A^3 coupling: development and prospectives

The classical synthesis of propargylamines is done by the addition of a pre-formed metal acetylide applying a strong base as *n*-BuLi or LDA to an imine (Scheme 16). [26]



Scheme 16. *Stoichiometric addition of metal acetylide.*

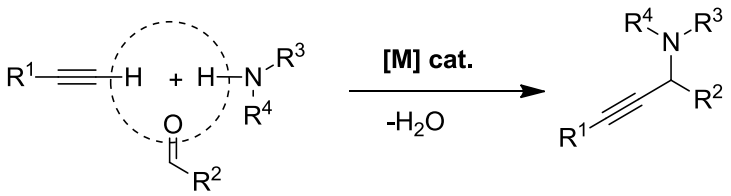
The main limitation of using lithium acetylides lies in the harsh reaction conditions. The reaction need to be carried out at low temperatures and the use of anhydrous solvents and inert atmosphere is essential. Moreover, the difficulties in the preparation or handling and the necessity of stoichiometric amounts of organometallic reagents represent a further drawback. An alternative could be the use of Grignard reagents or aluminium

acetylides. Nevertheless, the use of lithium acetylides sometimes represents a valid method to access specific and particular propargylamines.[27]

A more convenient way to obtain propargylamines is the transition metal-catalyzed addition of a terminal alkyne to an imine or enamine (Scheme 17).[26]

Scheme 17. *Transition metal-catalyzed addition.*

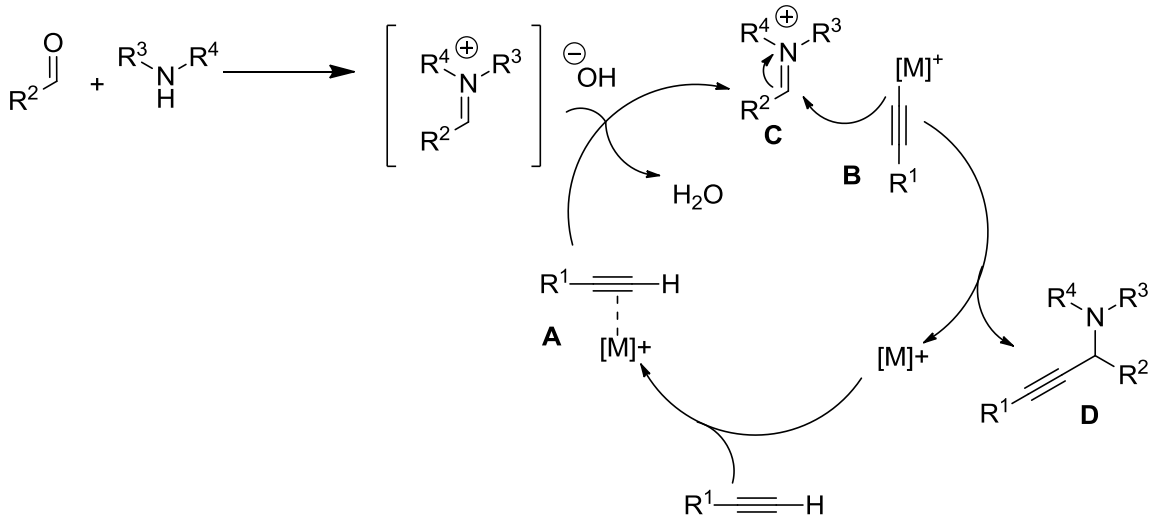
The possibility to form the imine or iminium ion *in situ* in a one-pot reaction by condensation of an aldehyde and an amine led to the discovery of transition-metal catalyzed three-component coupling of an aldehyde, an alkyne and an amine commonly referred to as A^3–coupling with only one equivalent of water as the sole by-product (Scheme 18).[11,26]



Scheme 18. *A^3 coupling reaction.*

The first synthesis of propargylamine through this way was carried out in 1953 by Guermont and only in 2002 Li introduced the term "A^3 coupling".

The proposed mechanism involves C–H activation of the alkyne by the transition metal through the formation of a metal-π-alkyne complex **A**. This renders the C-H bond more acidic so that it can be deprotonated by any weak base present in the reaction medium (starting amine, intermediate imine or final propargylamine). The formed metal acetylide **B** reacts with the imine/iminium ion **C** to form the propargylamine **D** with the concomitant regeneration of the metal catalyst for another reaction cycle (Scheme 19).[11,26]

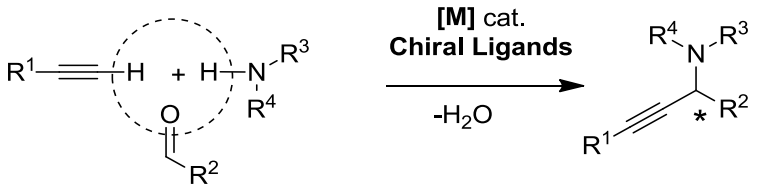


Scheme 19. *A^3 coupling mechanism.*

A great number of transition-metal catalysts were exploited in order to activate the C–H bond of the terminal alkyne in the A^3-coupling process, with copper being one of the most extensively utilised that will be described more in details. Silver and gold salts[28] are extensively studied as well as iron, zinc or nickel.[29]

The possibility to replace aldehydes with ketones gives rise to KA^2 coupling: this reaction is still considered difficult since ketimines are considerated a more challenging substrates for alkynylation than aldimines. [30]

The asymmetric A^3 coupling (AA^3) has emerged as an important class of reactions which allows the enantioselective synthesis of propargylamines by using the addition of a chiral ligands complexed metal catalyst (Scheme 20).[31]



Scheme 20. *Asymetric A^3 coupling reactions.*

The early report appeared in 2002 by Li who used a catalytic amount of copper and Pybox ligand. Since then there has been remarkable progress in the field of asymmetric A^3 coupling in terms of ligand/catalyst design to improve the enantioselectivity and substrate scope.

In term of catalyst, the copper salts are the most used with both primary or secondary amines but in terms of chiral ligands, nitrogen-containing tridentate or bidentate ligands are highly successful with primary amines whereas axially chiral P,N-ligands found a great applications with secondary amines (Figure 7).

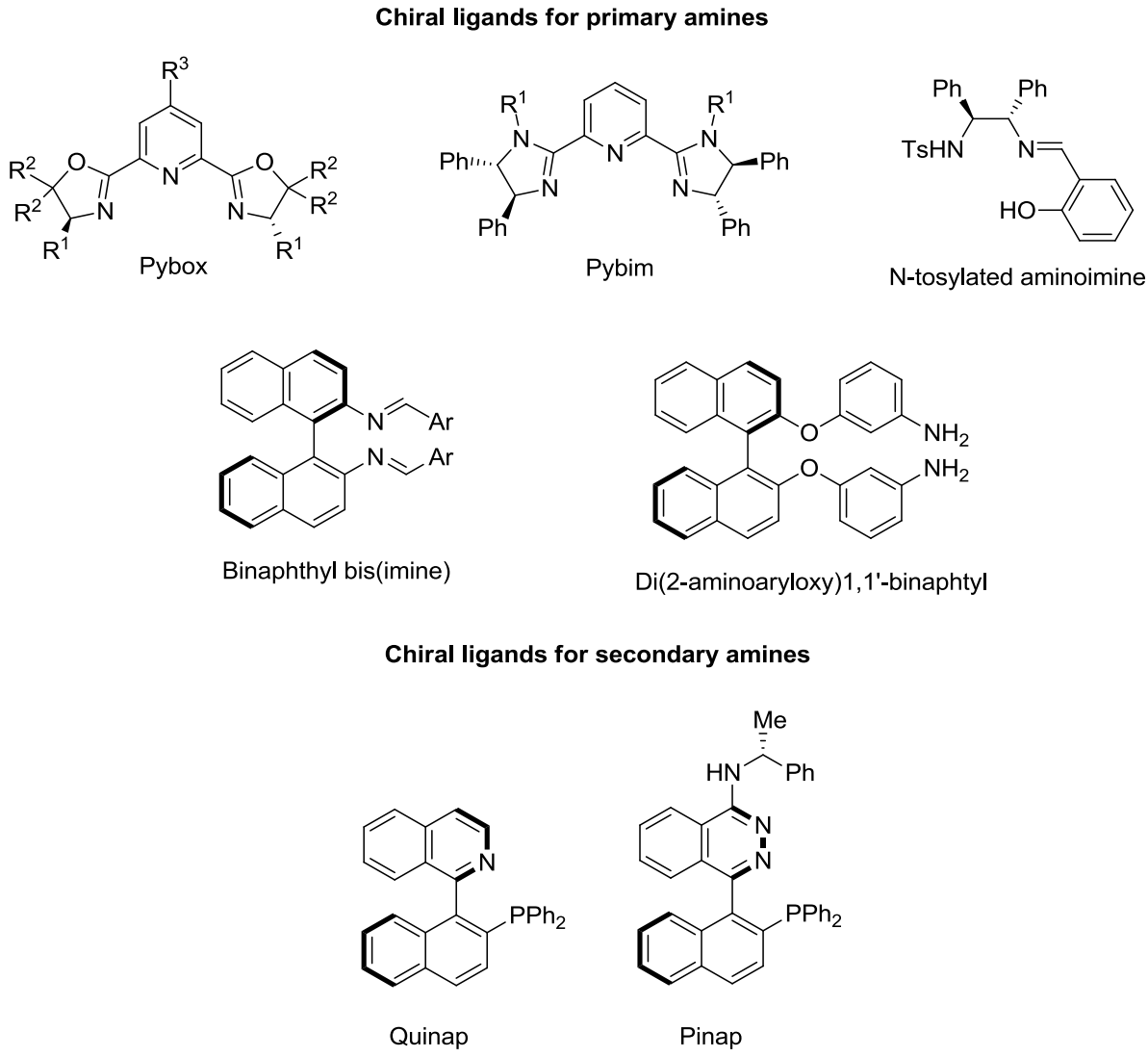


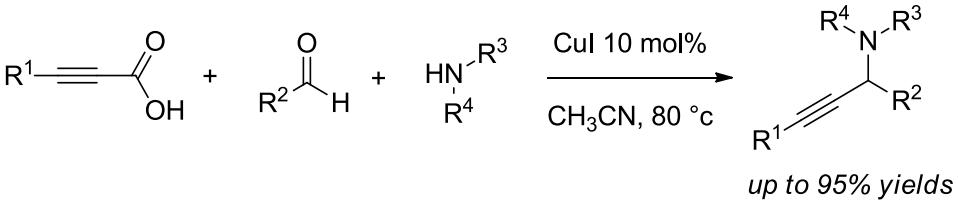
Figure 7. *Chiral ligands for primary and secondary amines in AA^3 coupling reactions.*

Further extensions of the A^3 coupling reaction are the decarboxylative A^3 coupling and the redox A^3 coupling.[32]

In the decarboxylative A³ couplings along the reaction process one molecule of carbon dioxide is lost. The carboxylic acid group can either be a part of the alkyne, the amine or

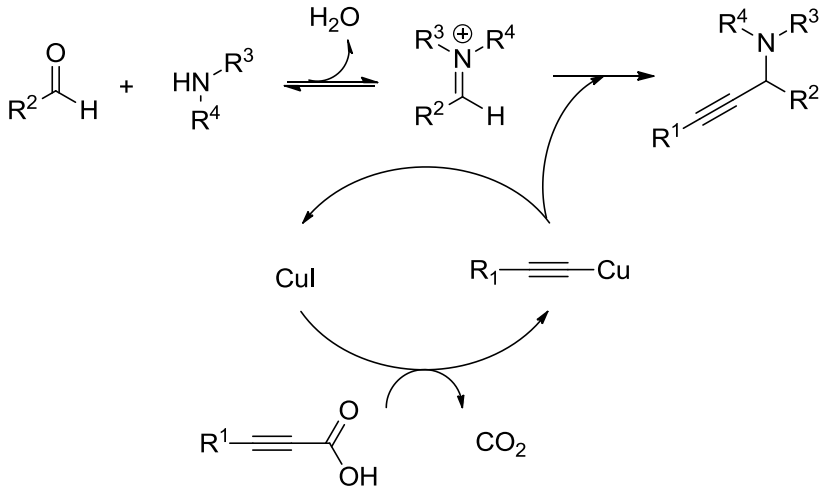
the aldehyde component even if in the majority of these reactions the CO_2H group is bound to the alkyne moiety.

The group of Lee reported the application of aryl alkynyl carboxylic acids under copper catalysis to generate the propargylamines (Scheme 21).[33]



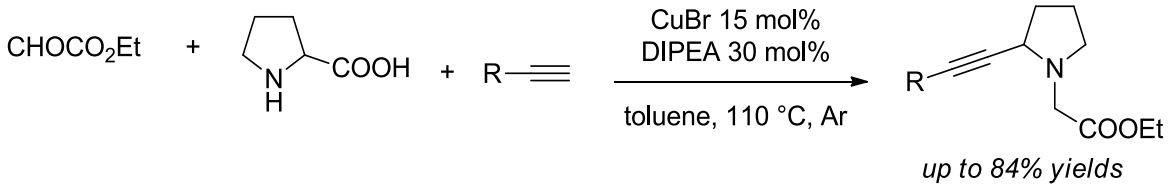
Scheme 21. *Decarboxylative A³ coupling reactions of Lee.*

As reported in Scheme 22, CuI reacts with propiolic acids and causes decarboxylation, forming copper acetylide which then undergoes normal A³ coupling.



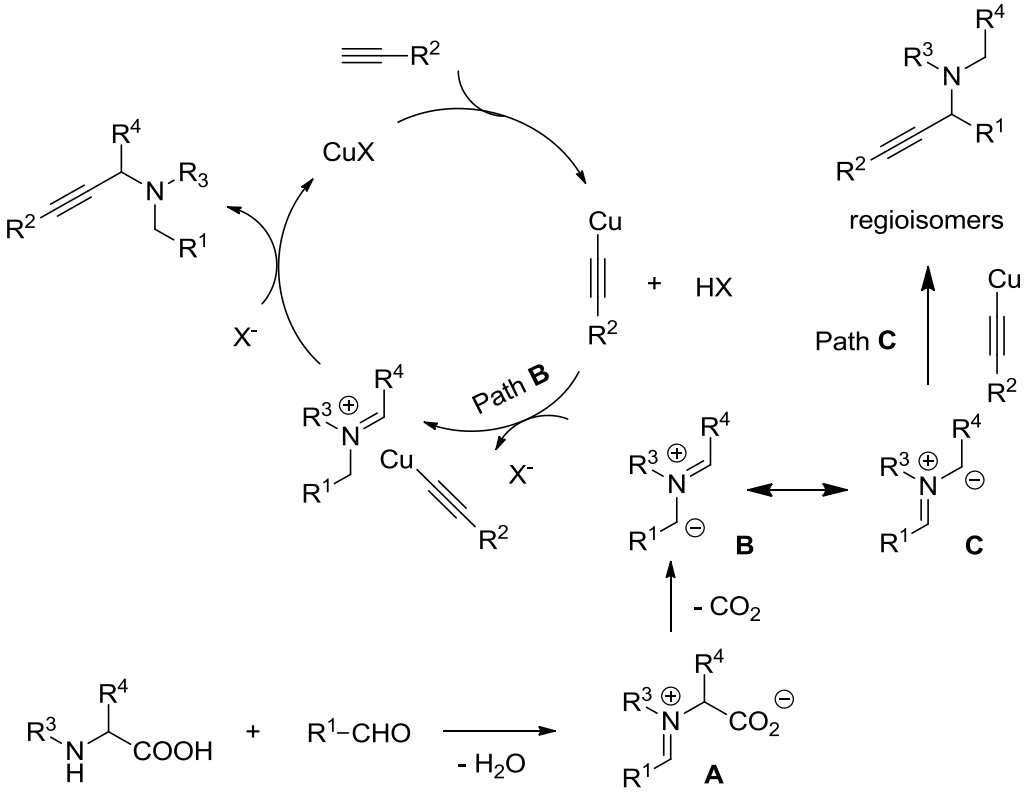
Scheme 22. *Mechanism for decarboxylative A³ coupling reactions with alkynyl carboxylic acids.*

The group of Li successfully applied the decarboxylative A^3 coupling also to α-amino acids affording the synthesis of different kind of propargylamines due the presence of an equilibrium of the imine intermediate (Scheme 23).[34]



Scheme 23. *Decarboxylative A³ coupling reactions of Li.*

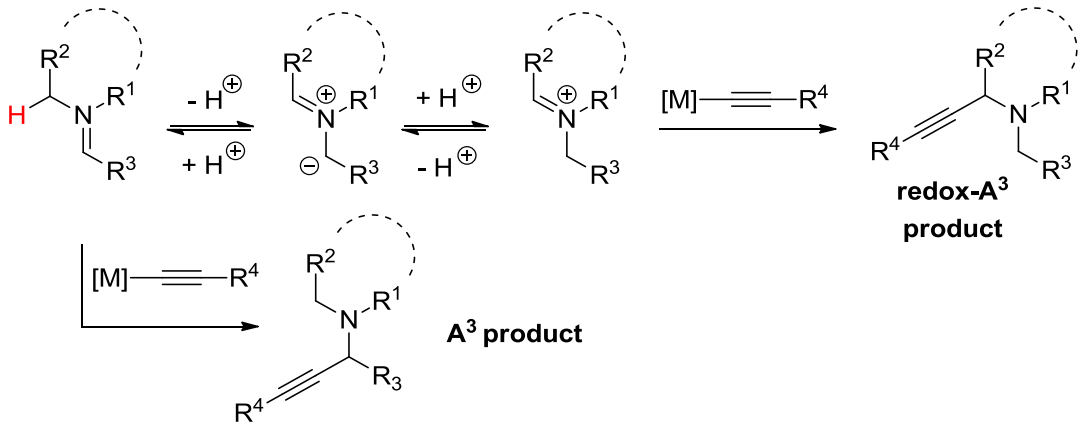
The mechanism is reported in Scheme 24. The first step, also in this case, is the formation of an iminium-type intermediate **A**, which then undergoes decarboxylation to form intermediate **B** and its mesomeric form **C**. Then, reaction of **B** (*path B*) or **C** (*path C*) with copper acetylide affords the final propargylamine. The regioselectivity depends on the relative stability of the two resonance structure and favours *path B* with respect to *path C*.



Scheme 24. *Mechanism for decarboxylative A³ coupling reactions with α-amino acids.*

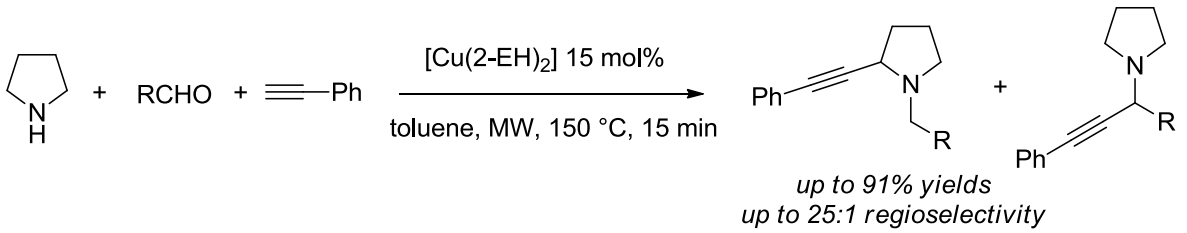
In the redox-A³ coupling an isomerization of the *in situ* formed iminium occurs, leading to α-alkynylation of the imine. This isomerisation, which is likely to go via azomethine ylide intermediates, only occurs when a more stable iminium species can be formed.

The realization of a three-component redox-A^3 reaction requires for the iminium isomerization pathway to effectively compete with the direct addition of metal acetylide. This could be achieved with aldehydes more sterically hindered that complicate direct alkynylation of iminium or with electron-withdrawing substituents that stabilize azomethine ylide or alternatively, using an unsaturated amine that will be conjugated with the newly formed iminium bond (Scheme 25).



Scheme 25. *Mechanism for redox-A^3 coupling reaction.*

The early example of redox-A^3 coupling reaction was reported by Seidel who used pyrrolidine and phenylacetylene with different aldehydes (Scheme 26) finding a good selectivity between the two propargylamines.[35]



Scheme 26. *Redox-A^3 coupling reaction of Seidal.*

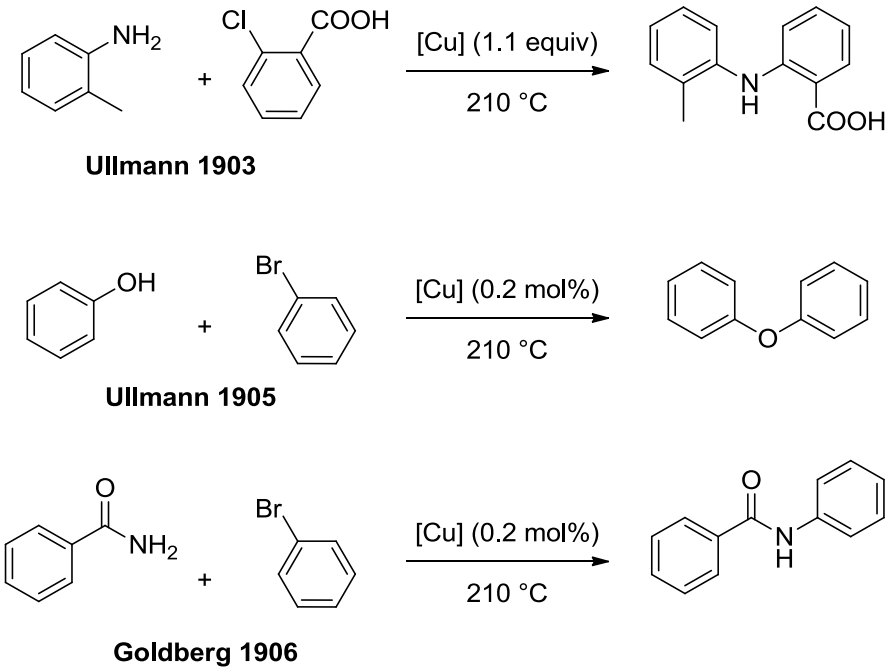
The A^3 coupling reactions and their variations are an area of research which continues to expand in different way especially on the development of cost effective and eco-friendly protocols with the design of new catalysts.

4. Copper

4.1. Relevance in catalysis

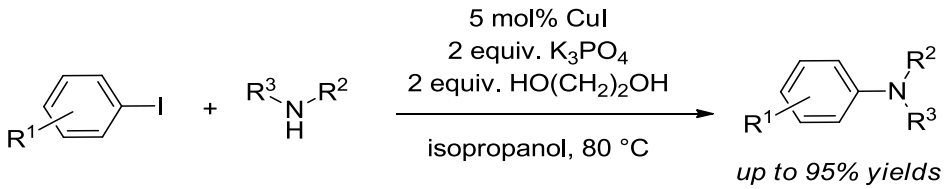
Copper is an inexpensive, earth-abundant, non-toxic metal that is found to have extensive applications in catalysis thanks to the different easily accessible oxidation states 0, +I, +II and +III. It can act through one-electron or two-electron processes and as a result, both radical pathways and powerful two-electron bond-forming pathways via organometallic intermediates can occur. In addition, the different oxidation states of copper associate well with a large number of different functional groups via *Lewis* acid interactions or π-coordination.[36]

The foundations of modern copper-mediated chemistry lie in the pioneering and remarkable work of Fritz Ullmann and Irma Goldberg for the synthesis of biaryl linkages. Since then, the copper-catalysed reactions have seen an increasing development (Scheme 27). [37]



Scheme 27. *Pioneerig work of Ullmann and Goldberg.*

Recently, the group of Buchwald reported the copper(I)-catalyzed amination of aryl iodides with ethylene glycol as ligand which allows the formation of C-N bond in good yields with a variety of functionalized aryl iodides as well as several amines. The advantage of this procedure is the fact that it is relatively insensitive to moisture and can be performed under an air atmosphere with comparable yields (Scheme 28).[38]



Scheme 28. *Copper-catalyzed amidation of Buchwald.*

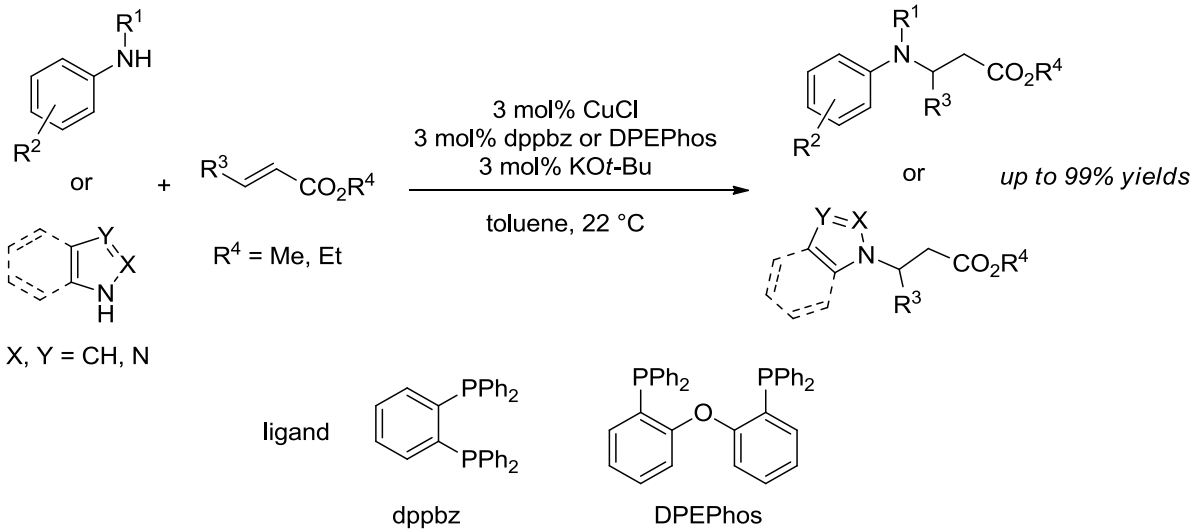
Copper salts are extensively used as *Lewis* acid catalyst: they have found a broad range of application in the field of organic chemistry due to their ability to promote many organic transformations such as additions, cycloaddition, condensation, oxidations and rearrangements as well as stereoselective transformation. The main reason for the continued attraction for copper salts are: (i) ready availability and/or accessibility, (ii) two oxidation states (the most used are +I and +II), (iii) moderate *Lewis* acidity.

In the next paragraph it will be shown the versatility of copper (in +I and +II oxidation state) in the formation of C – N bonds in view of the final aim of the project.

The aza-Michael reaction is one of the simplest and most effective strategies to get β-amino carbonyls from the direct addition of (hetero)aryl amines to α,β-unsaturated olefins. The most common methods are unfortunately limited to aliphatic amines. A variety of *Lewis* acid metal catalysts, including early- and late-transition metals as well as lanthanides, have been considered to overcome these limitations.

The group of Lee proposed a highly efficient and mild Cu(I)-catalyzed conjugate addition reaction of various weak nucleophilic aromatic amines and aza-heterocycles to α,β-unsaturated olefins. The transformation is promoted by a Cu complex generated in situ from a mixture of inexpensive CuCl, a readily available phosphines, and *t-Bu*OK at room temperature.[39]

A wide range of (hetero)aryl amine substrates including aniline, indole, carbazole, pyrroles, imidazole, pyrazol and triazole derivatives are converted to the desired β-amino carbonyl compounds with excellent yields (Scheme 29).

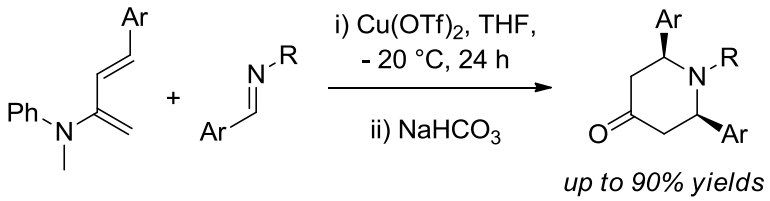


Scheme 29. *Copper(I)- catalyzed conjugate addition of Lee.*

Copper catalysis overcomes the most common drawbacks of metal-catalyzed aza-Michael addition such as application of expensive precious metals, use of air- and moisture sensitive metal catalyst.

Another kind of reaction in which copper has found application is the *aza*-Diels-Alder reaction which allows the formation of a new C – N bond with the nitrogen atom present in the diene or dienophile. This reaction has been much less explored and exploited in organic synthesis nevertheless, it remains the most efficient methods for the synthesis of six membered nitrogen-containing heterocycles.

The group of Cabal developed a stereoselective synthesis of *meso*-2,6-disubstituted-4-piperidones via imino-Diels–Alder reaction of 2-amino-1,3-butadienes with imines in the presence of catalytic amount of $Cu(OTf)_2$ as *Lewis* acid catalyst (Scheme 30).[40]

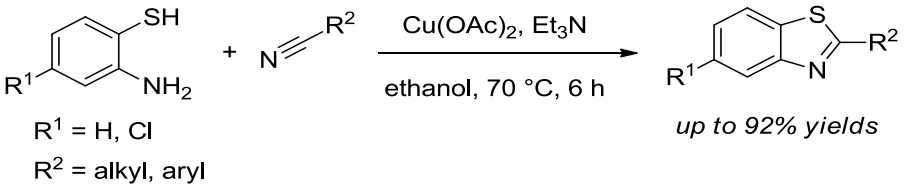


Scheme 30. *Copper(II)-catalyzed aza-Diels-Alder of Cabal.*

The high diastereoselectivity observed in the reaction is in agreement with an *endo* approach of the phenyl ring of the imine on a formal [4+2] cycloaddition.

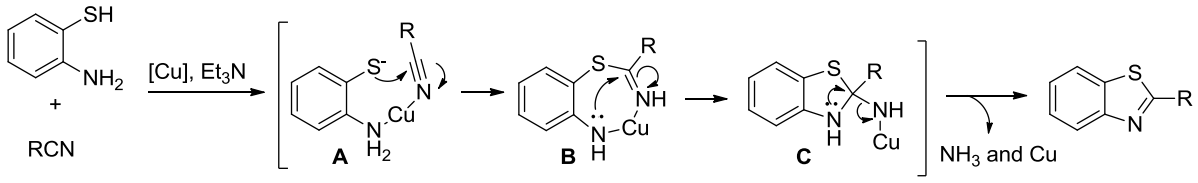
Copper is a versatile *Lewis* acid catalyst in several condensation reactions from various starting materials which allow the formation of different molecular structures.

Jiang and his collaborators reported an efficient and convenient copper(II) catalyzed condensation of 2-aminobenzenethiols with nitriles for the synthesis of 2-substituted benzothiazoles. This strategy allows the formation of the product in high yields and it is applicable to a wide range of nitriles. Moreover, it doesn't involve harsh reaction conditions or low functional group tolerance of the most common synthetic approach for these class of molecules (Scheme 31).[41]



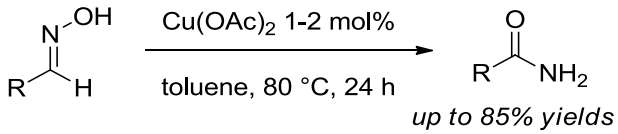
Scheme 31. *Copper(II)-catalyzed condensation reaction of Jiang.*

Copper first promotes the nucleophilic attack of 2-aminobenzenethiol to the nitrile, probably through the coordination with intermediate **A**, to provide sulfilimine **B**. Then, a copper-induced intramolecular nucleophilic addition of sulfilimine with amine affords intermediate **C**, which releases copper and NH_3 to furnish benzothiazoles (Scheme 32).



Scheme 32. *Mechanism for the synthesis of benzothiazoles in the Cu(II) catalyzed reaction.*

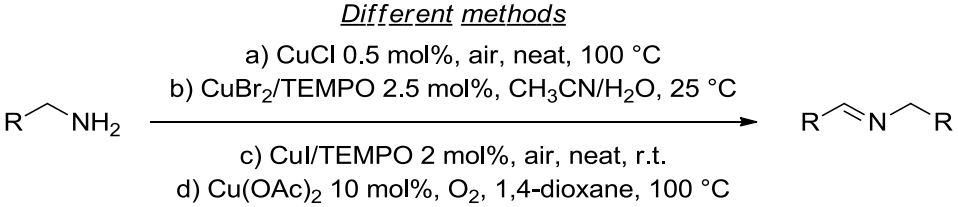
The group of Williams found that a simple copper salt $Cu(OAc)_2$ allows the Beckmann rearrangement of oximes into primary amides. Due to the importance of this reaction, several precious metals have been taken into account such as Rh, Ir, Ru, Pd and Ag/Au. Moreover, the conventional approach for the synthesis of amides requires the use of a stoichiometric amount of catalyst to activate carboxylic acids. The approach of Williams instead, is atom-efficient, uses relatively mild reaction condition and catalyst loading. It can be performed with either conventional or microwave heating (Scheme 33).[42]



Scheme 33. *Copper(II)-catalyzed Beckmann rearrangement.*

The copper-catalyzed oxidation of organic compounds has made considerable progress in combination with molecular oxygen, aqueous hydrogen peroxide, *tert*-butyl hydroperoxide and peroxyesters as terminal oxidants.

In this context, the oxidation of primary amines provides a convenient synthetic route to get imines (Scheme 34). [43]



Scheme 34. *Copper(I) catalyzed oxidative coupling of primary amines.*

4.2. Applications of copper acetylides

Copper(I) salts act as coordinating π-*Lewis* acids to unsaturated carbon–carbon bonds especially with alkynes. The resultant Cu–alkyne complex **A** significantly enhances the acidity of the terminal proton, allowing the deprotonation using a relatively mild base and also under aqueous conditions. The product is commonly represented as a Cu-acetylide **B** even if dinuclear copper–alkyne adducts **C** and **D** are also possible (Figure 8).

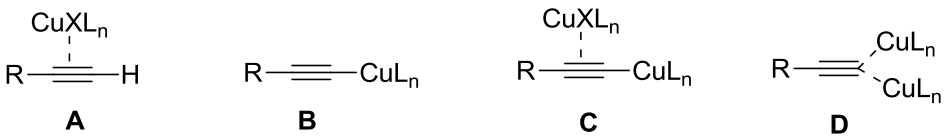


Figure 8. *Possible forms of copper acetylide.*

Gaining a detailed mechanistic understanding of such processes is, however, hampered by several facts: low reduction potential of Cu(I), facile disproportionation of copper species in solution, poor back bonding of copper to ligands and hence ligand dissociation and finally propensity to form aggregates both in organic and in aqueous media. Tremendous efforts have been done to understand the mechanism and to develop new reaction.

Copper(I) acetylides play a central role in various catalytic transformation which involve alkynes such as in Glaser-Hay coupling, Sonogashira cross-coupling, CuAAC reactions and in the A^3 coupling reactions. [44]

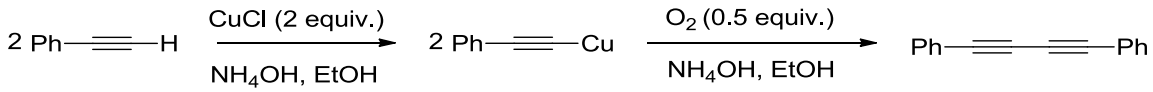
In the next paragraph a detailed description of each reaction will be given with a particular attention on the possible way of coordination between copper and alkyne.

4.2.1. Oxidative Coupling Reactions: Glaser and Hay reactions

The chemistry of copper catalysis increases exponentially in combination with molecular oxygen. It is an highly atom-economical, environmentally benign and abundant oxidant, which makes it ideal in many ways. Moreover, it can act as either a sink for electrons

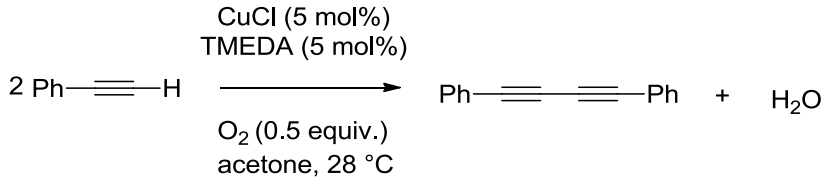
(oxidase activity) or a source of oxygen atoms that are incorporated into the product (oxygenase activity) or both.

The oxidation of copper(I) phenylacetylide into diphenyldiacetylene in air was discovered by Glaser in the XIXth century (Scheme 35). This transformation has become a standard procedure for the homocoupling of terminal alkynes. [45]



Scheme 35. *Original Glaser oxidative coupling.*

The Hay coupling represents an implementation of Glaser coupling reaction since the presence of TMEDA as bidentate ligand increases the solubility of the copper species, allowing for substoichiometic metal loadings, and so milder reaction conditions and in general an improvement in the overall outcome of the reaction (Scheme 36). [46]

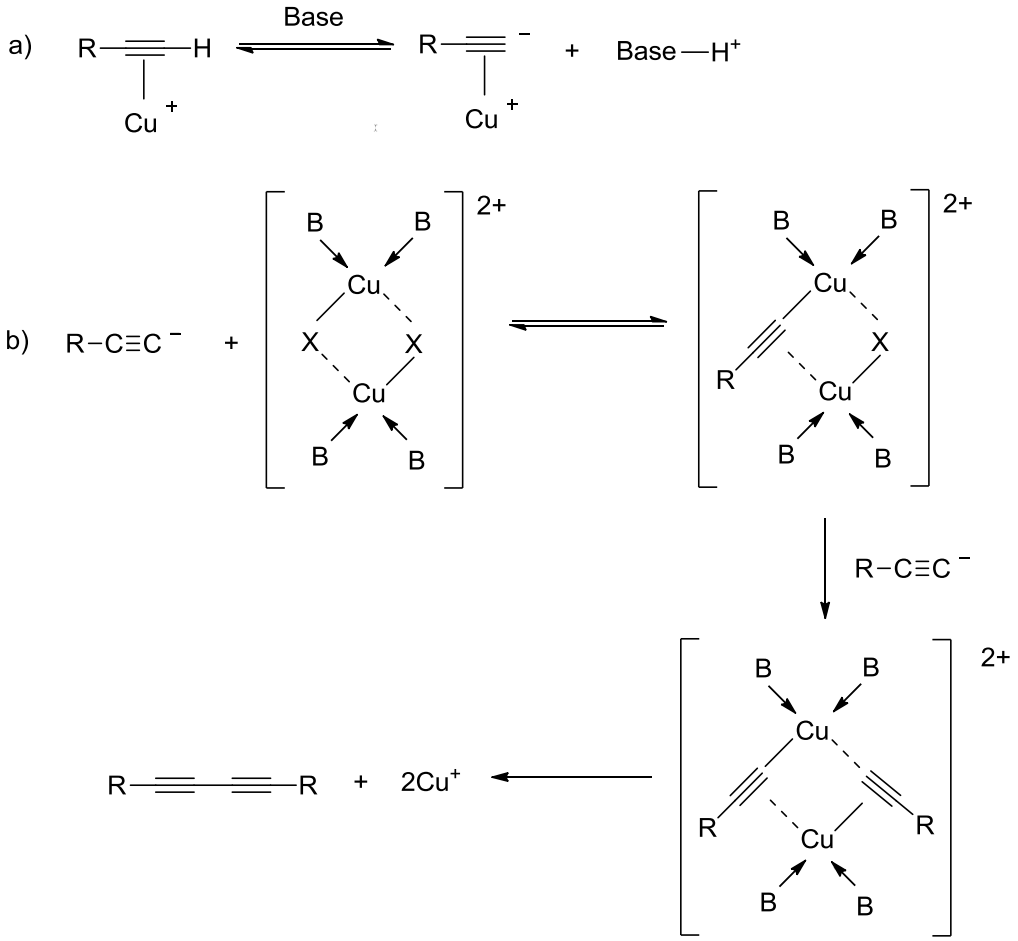


Scheme 36. *Original Hay oxidative coupling.*

Although the copper-mediated homocoupling of alkynes is the oldest of the many coupling reactions and proceeds through a very simple procedure, there is no mechanistic investigation that clearly demonstrates the mechanism of the process. Early proposal were based on the involvement of free radicals that were gradually abandoned. The most widely accepted mechanism was developed by Bohlmann and his collaborators (Scheme 37). [47]

Based on their scheme, the reaction starts with the π-coordination of the triple bond to a copper(ı) species that facilitates the activation of the terminal C–H bond by an external base (*path a*).

They also proposed that the 1,3-diyne is formed by reductive elimination from a dinuclear copper(II) acetylide species (*path b*).



Scheme 37. *Mechanistic investigation of Glaser coupling.*

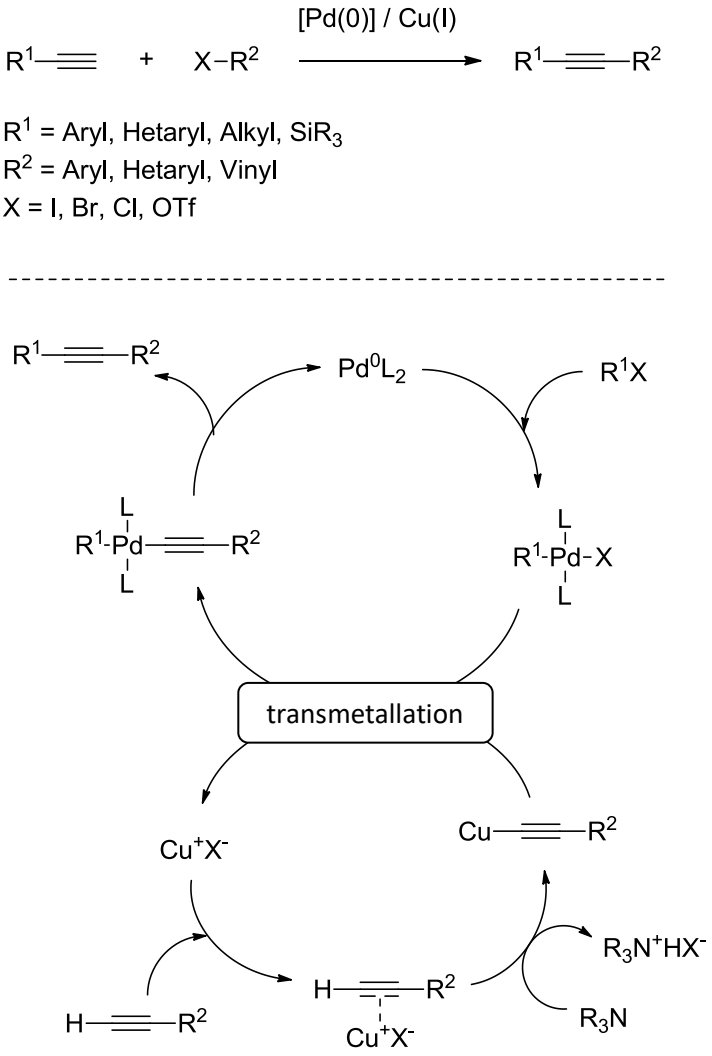
4.2.2. Cross-coupling: the Sonogashira reaction

The Sonogashira reaction is a well-kwon palladium/copper catalysed cross-coupling between aryl or vinyl halides (or triflate) and terminal acetylenes. This represents one of the most important and widely used sp^2–sp carbon–carbon bond formation reactions in organic synthesis.

The presence of copper as co-catalyst is fundamental for the formation of copper-acetylide that would then transmetallate the alkynyl moiety onto palladium(II) center.

However, the addition of copper, although beneficial in terms of increasing the reactivity of the system, added some drawbacks.

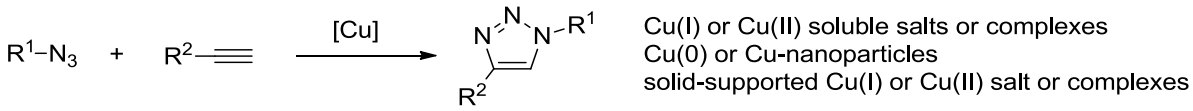
The reaction must be carried out under inert atmosphere in order to block the homocoupling of the alkyne, i.e. Glaser coupling (Scheme 38). [48]



Scheme 38. *Sonogashira cross-coupling reaction and mechanism.*

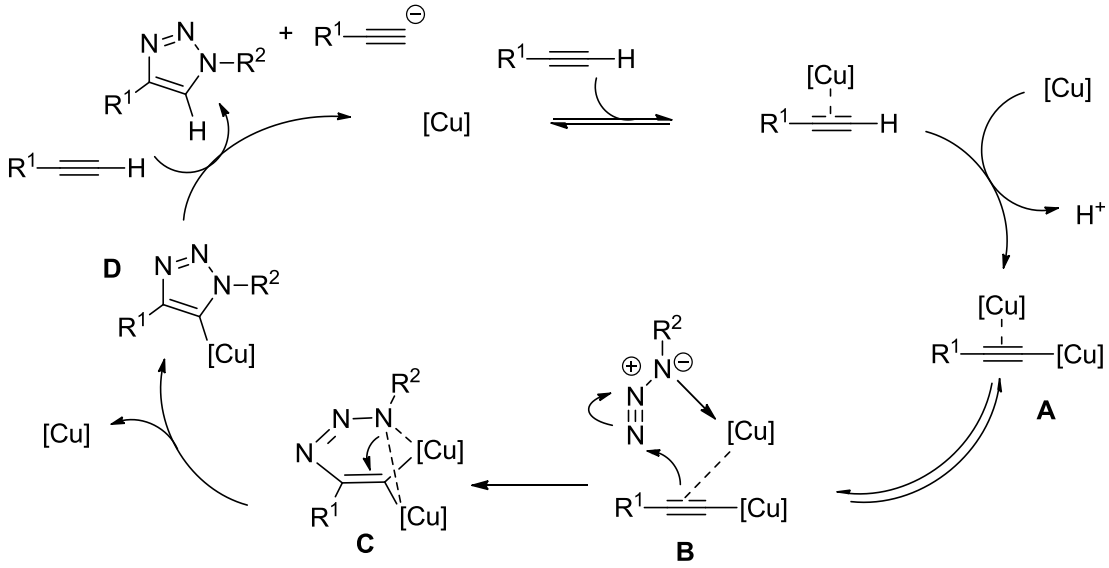
4.2.3. Cycloadditions: CuAAC reaction

Copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) represents an excellent way to form 1,2,3-triazoles that allows the use of any kind of copper since the catalytically active Cu(I) specie is formed in the reaction medium (Scheme 39).



Scheme 39. *Copper catalysed Azide-Alkyne Cycloaddition (CuAAC).*

Mechanistic studies of CuAAC were initially focused on a concerted mechanism later changed in a stepwise catalytic cycle. Nowadays the most accredited mechanism for this reaction is binuclear. The Scheme 40 reflects the up-to date understanding of CuAAC reaction in which a σ-bound Cu(I)-acetylide bearing a π complexed copper atom **A** reacts with an organoazide forming a bridging dicopper acetylide intermediate **B**. Metallacycle formation occurs **C**, followed by reductive ring contraction to afford the copper(I) triazolide **D**, which deprotonates an alkyne leading to the product and completing the catalytic cycle. [49]



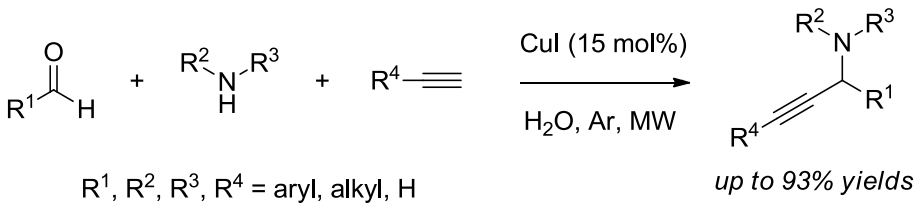
Scheme 40. *Mechanism of CuAAC reactions.*

4.3. Versatility in the A^3 reactions for secondary amines

The catalytic activation of the C-H bond of terminal alkynes in the A^3 coupling reaction has been primarily achieved with complexes or salts of the late transition metals (e.g. Ir,[50] Zn,[51] Fe,[52] Co,[53] Ni,[54] Ag,[55] Au,[56] Ru[57] and also In[58]) but by far the most studied metal is copper, due to its high affinity towards π-bonds of the alkyne and nitrogen atom. Both Cu(I) or Cu(II) salts as well as copper in heterogeneous version (solid-supported or nanoparticles) have been studied and applied mainly with secondary amines or anilines leading to the formation of the corresponding tertiary propargylamines and N-aryl-propargylamines.[10,25,56] Only few approaches have been developed for primary amines with copper or in general with other metals.[59]

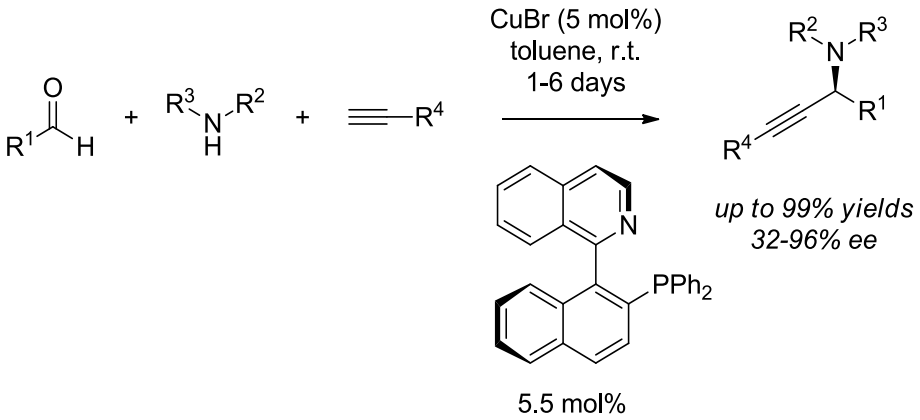
Secondary amines are relatively more reactive in the A^3 coupling reaction, since they generate an iminium ions which is much more electrophilic than the (neutral) imine obtained from primary amines towards nucleophilic attack by copper acetylides and for this reason are more applied.

Copper(I)-catalyzed reactions are the most widespread. The group of Tu, for example, investigated the possibility to combine the use of copper(I) iodide with the advantages of microwave irradiation for the synthesis of both tertiary propargylamines and N-aryl-propargylamines obtaining high yields in few minutes without any co-catalyst. This method has proved to be applicable to a wide range of substrates: both aromatic and aliphatic aldehydes and alkynes as well as secondary amines, anilines and tert-butyl amines (Scheme 41).[60]



Scheme 41. Cu(I) catalyzed s*ynthesis of propargylamines of Tu.*

Knochel applied copper(I) bromide with (2-phosphino-1-naphthyl) isoquinoline (Quinap) ligand for the synthesis of optically active tertiary propargylamines finding that aliphatic aldehydes result in better enantioselectivities (82-96% ee) than aromatic aldehydes (32-87% ee). High yields with a good enantioselectivity are also obtained with the use of both dibenzyl and diallylamines. The alkyne can bear either an aryl or an alkyl substituent (Scheme 42).[61]

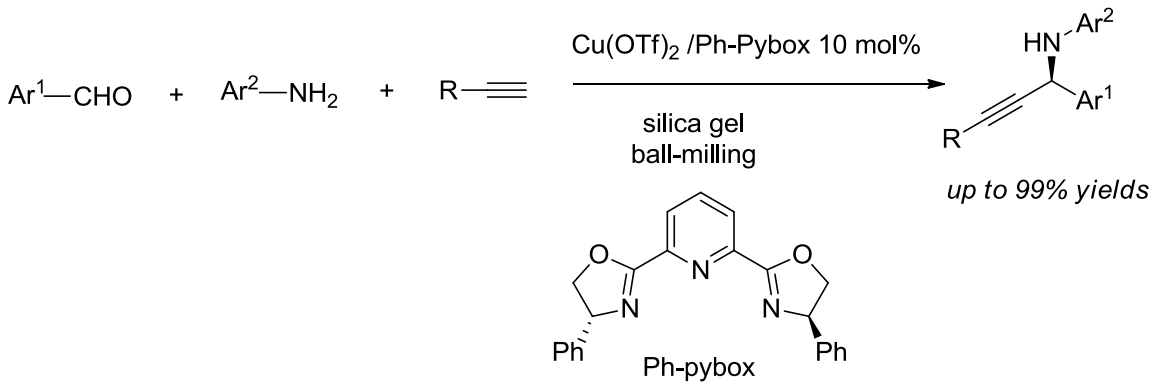


Scheme 42. *Cu(I)-catalyzed enantioselectie synthesis of propargylamines ofKnochel.*

The possibility to use Cu(II) salts have been explored to access the synthesis of propargylamine derivatives due to their higher stability to air oxidation and lower cost with respect to Cu(I) salts.

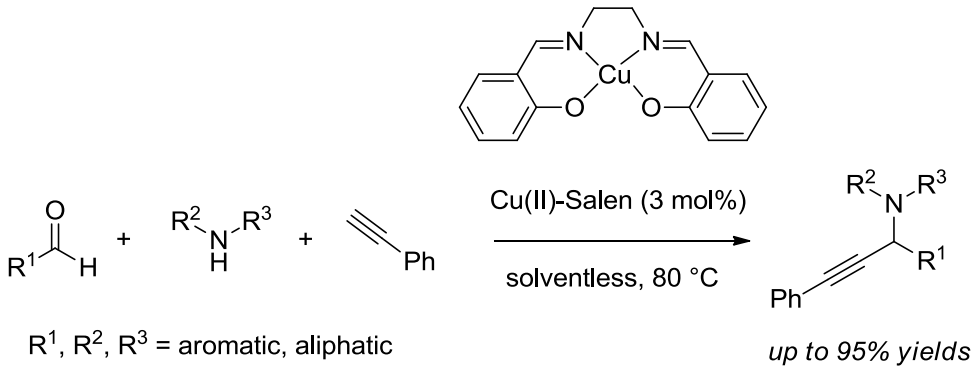
The group of Su developed an asymmetric Cu(II)-catalyzed reaction for the enantioselective synthesis of *N*-aryl-propargylamines using $Cu(OTf)_2$ and Ph-Pybox under solvent- free conditions by using ball-milling within just 60 minutes.

They assume that Cu(II) is a source of Cu(I) obtainble using stainless-steel jars and balls or thanks the same alkyne (Scheme 43).[62]



Scheme 43. *Cu(II)-catalyzed enatioselective synthesis of propargylamine of Su.*

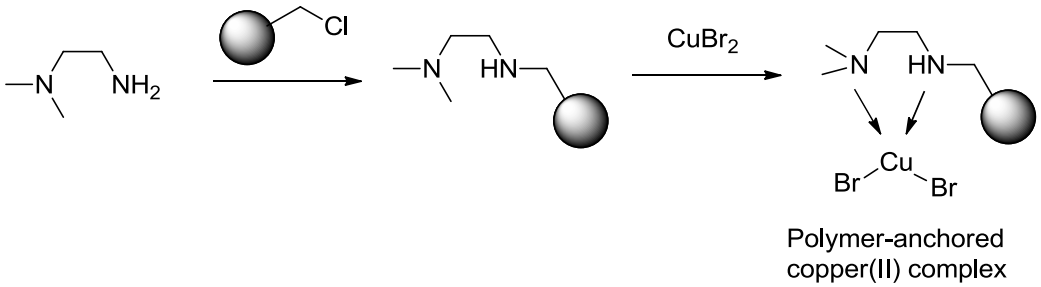
Tajbaksh and his collaborators described a Cu(II) Salen complex under solvent-free conditions for the A^3 coupling reaction for tertiary propargylamines. They proposed a possible mechanism in which the Cu(II)-(Salen) complex activates the C-H bond of phenylacetylene to generate the copper(I) acetylide. This method provides a wide range of substrate applicability because both electron-donating or electron-withdrawing substituents are well tolerate, as well as cyclic or acyclic amines. The lower cost and the higher catalytic activity are other advantages (Scheme 44).[63]



Scheme 44. *Cu(II)-catalyzed synthesis of propargylamines of Tajbaksh.*

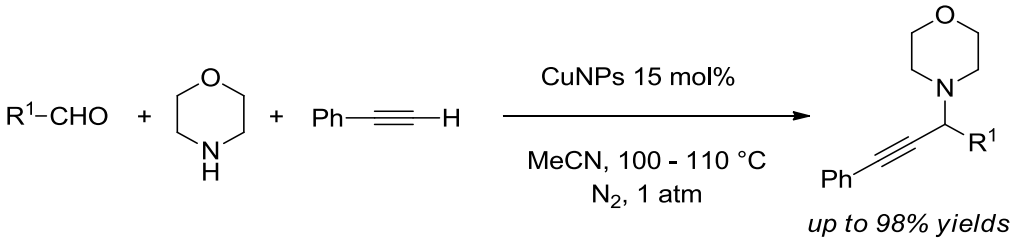
Solid-supported copper catalyst or copper nanoparticles have been widely used in the propargylamine synthesis via A^3 coupling reaction, due to the main important advantages deriving from heterogeneous catalysis such as easy separation, possibility to recycle and reuse several time the catalyst, waste minimization and low reaction time.

Sreedhar developed a silica-gel anchored CuCl catalyst that was recovered almost quantitatively by simple filtration, whereas Fodor applied 4 Å molecular sieve-supported Cu(II) catalyst obtained by simply mixing the $CuCl_2 \cdot 2H_2O$ with the molecular sieves under solvent-free conditions with high yields. More recently, Mandapati synthesized and used the polymer-anchored Cu(II) complex for the A^3 coupling reactions (Scheme 45). All these solid supported copper catalyst are mainly addressed to the formation of tertiary propargylamines.[64]



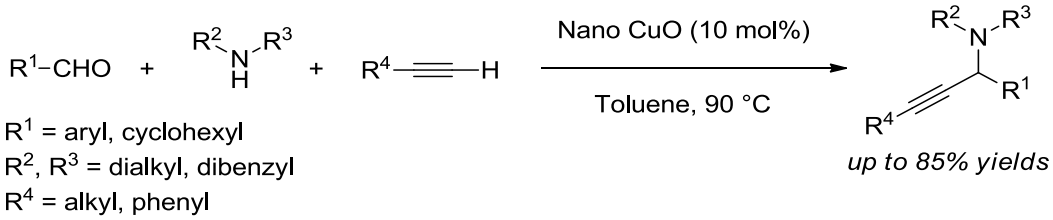
Scheme 45. *Formation of polymer-anchored copper(II) complex.*

Kidway reported the first example of application of copper nanoparticle to the synthesis of propargylamines from morpholines (Scheme 46).[65]



Scheme 46. *Copper nanoparticle in the synthesis of propargylamines.*

The group of Kantam described the advantages of nano crystalline $Cu^{II}O$ that can be recovered in quick time and recycled for several times with a minimal reduction in activity. Also in this case tertiary propargylamines are obtained (Scheme 47).[66]



Scheme 47. *Nano crystalline CuO in the synthesis of propargylamines.*

5. Cerium

5.1. Cerium and its salts

Lanthanides, considered for a long time the forgotten elements of the periodic table, thanks also to the work of Kagan and Luche, in the last three decades, they have known an increasing growth in the search for affordable and environmentally benign synthetic methodologies. Despite it is generally referred to them as “rare earths”, they are relatively common in the earth crust. [67]

Cerium, for example, is one the most abundant lanthanides, even more of the commonly used metals as cobalt, zinc or tin. Cerium shows mainly +4 and +3 oxidation state. Cerium(IV) compounds, especially cerium ammonium nitrate (CAN) have been extensively used as convenient and effective one-electron oxidants for a variety of chemical transformations. [68] However, the most stable oxidation state of cerium is +3 and cerium(III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$) is the most common source of Ce^{+3}, a powerful *Lewis* acid catalyst in both carbon-carbon and carbon-heteroatom bond forming reactions.

According to the HSAB terminology of Pearson, Ce^{3+} is an “hard cation” and, as a consequence, it exhibits a strong affinity towards oxygen or nitrogen donor ligands, described as “hard bases”. However, given that the *Lewis* acidity depends on the charge density (Z/r) and thus on the ionic radius, the salts and the complexes of the large Ce^{3+} ion are considered as a mild *Lewis* acid promoter. [69]

The main advantages that led to an increasing use of $CeCl_3 \cdot 7H_2O$ are the low cost and scarce toxicity which is comparable to the one of sodium chloride: that are important feature in the perspective of reducing the impact of chemical processes both from economy and safety points of view (Table 1). [70]

Compound	LD_{50} (mg/kg)[a]
NaCl	3000
$FeCl_3$	450
$CoCl_2$	80
$NiCl_2$	681
$CuCl_2$	584
$CeCl_3$	**2800**

[a]Lethal dose in rats. Data from safety data sheets.

Table 1. *Toxicity of $CeCl_3$ compared with other commonly used chloride salts.*

Furthermore, unlike many other *Lewis* acids, it's easy manipulated and water tolerant, but despite this, the hydrated $CeCl_3$ is sometimes only modestly active (Figure 9).

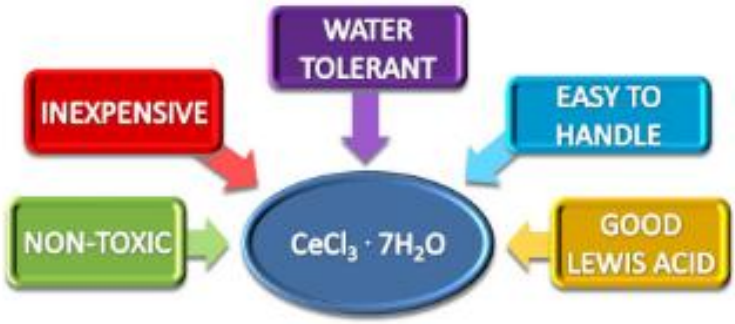


Figure 9. *Main advantages in using $CeCl_3 \cdot 7H_2O$.*

The discovery that presence of iodide anions can dramatically increase the *Lewis* acid activity of cerium trichloride heptahydrate led to an increase in the applications. In the last years the research group of Marcantoni is focusing on $CeCl_3 \cdot 7H_2O/M_xI_y$ system as *Lewis* acid promoter system for many chemical transformations involving carbon-carbon or carbon-heteroatom bond.[71]

5.2. Organocerium compounds

The nucleophilic addition of an organometallic reagent, such as organomagnesium (Grignard reagents, RMgX) or organolithium compounds, to an electrophilic carbon represents one of the most important strategies to obtain new C –C bonds.

The usefulness of RMgX and RLi is universally recognised and for this they find a broad applicability. In spite of their broad utility, they cause serious drawbacks: in the reaction with carbonyl compounds, for example, side reactions such as enolization, self-condensation and reduction can compete with or even prevail over on the expected addition process.

Lanthanide(III) salts, when used as additives in combination with organolithium or Grignard reagents, represent a good alternative allowing the straightforward formation of carbon-carbon bonds.[69]

Firstly employed by Inamoto,[72] organocerium derivatives are used to be added to electrophilic compounds, which have acidic hydrogens or a high reduction potential.[70] They must be freshly prepared by reaction of Grignard or organolithium reagents with anhydrous $CeCl_3$ (equation 1) and display interesting properties such as high nucleophilicity and low basicity.

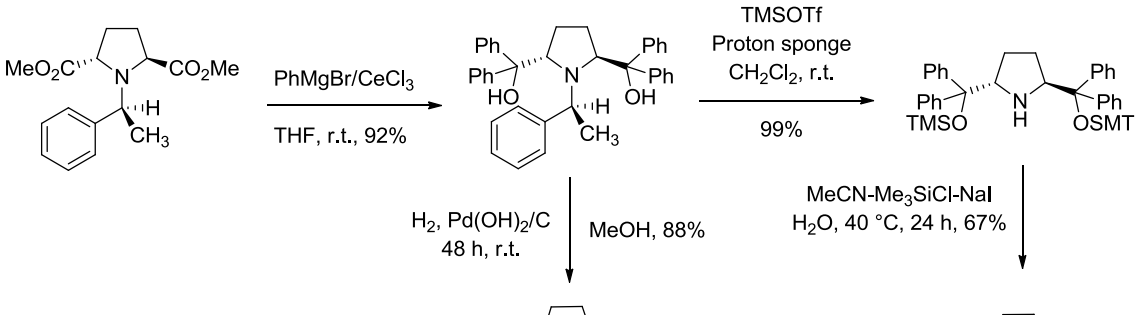
$$\mathrm{RLi} + \mathrm{CeCl_3} \rightarrow \mathrm{RCeCl_2} + \mathrm{LiCl}$$

$$\mathrm{RMgX} + \mathrm{CeCl_3} \rightarrow \mathrm{RMgX \cdot CeCl_3}$$

Equation 1. *Formation of organocerium derivatives.*

The organocerium addition to a carbonyl group has found a broad application in carbon-oxygen bond forming reactions, owing to the much more smooth reaction conditions wih respect to those of the parent organolithium or organomagnesium reagents. In fact various carbonyl compounds are converted in high yields to alcohols even in the presence of substrates susceptible to enolization, metal-halogen exchange reduction and pinacol coupling reaction.[73,74]

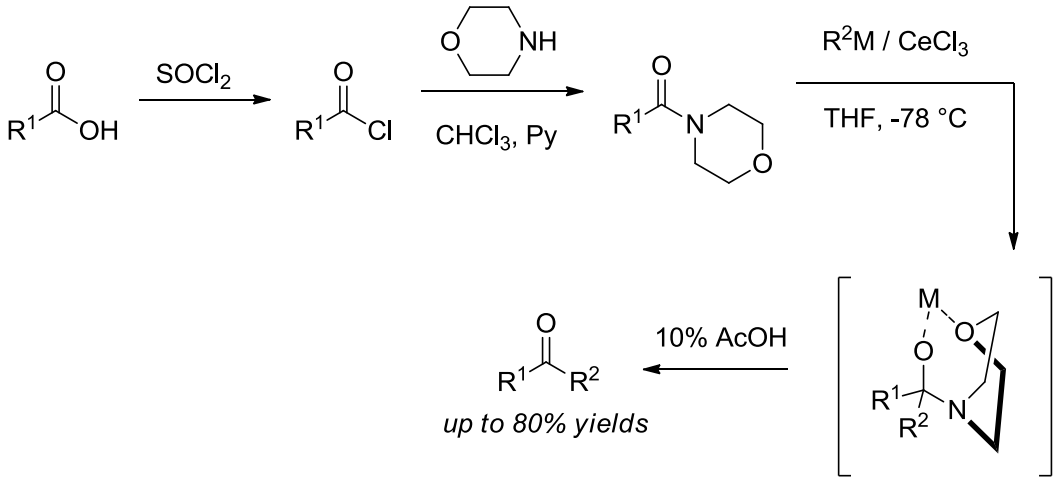
The superiority of organocerium in this kind of reaction can be seen in the synthesis of *trans*-(2S,5S)-(1,1-diphenylmethyl)pyrrolidine. When the starting pyrrolidine reacts with $PhMgBr/CeCl_3$, the resulting alcohol is obtained in high yield (92%) whereas if the Grignard reagent is used alone, the complete degradation of the starting ester is observed (Scheme 48).[75]



Scheme 48. *Application of organocerium in the synthesis of pyrrolidines.*

The addition of organocerium to carboxylic acids or to their derivatives must be performed at low temperature (-78 °C). Acyl chlorides, anhydrides or ester, afford the formation of the corresponding ketones in good yields without overalkylation of the obtained products to tertiary alcohols.

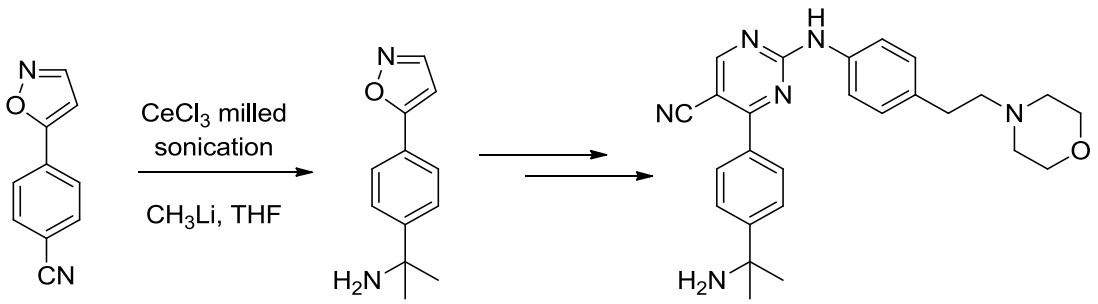
An example is reported in Scheme 49. The enhancement of reactivity in this case is due to the $R^2M/CeCl_3$ complex that acts as a *Lewis* acid, coordinating to the morpholine oxygen atom, decreasing the basicity of the morpholine nitrogen and thereby increasing the electrophilicity of the amide carbonyl group. Even in the presence of an excess of $R^2M/CeCl_3$ complex no tertiary alcohol has been detected.[69,76]



Scheme 49. *Applications of organocerium in the synthesis of ketones.*

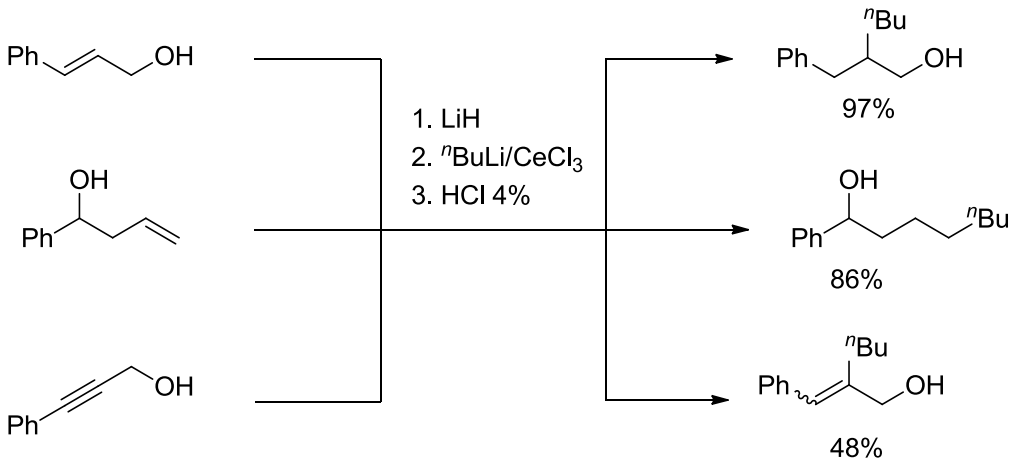
Organocerium compounds play an interesting role even in the formation of carbon-nitrogen bonds. They represent a good alternative in the double addition to nitriles and/or tertiary carbinolamines.

An example is the synthesis of VEGF-R2 kinase inhibitor that has a significant oral activity against tumor growth in murine models. This procedure is easily reproducible and scaled by calculating the optimal and necessary $CeCl_3$ quantity to be milled (Scheme 50).[77]



Scheme 50. *Applications of organocerium in the C-N bond formation.*

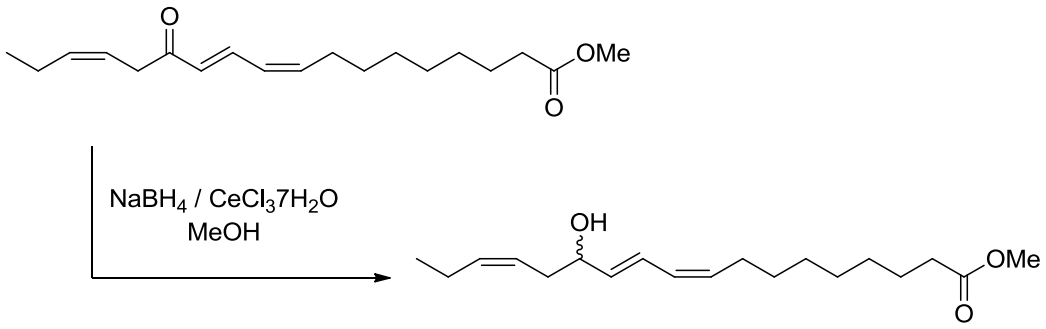
Several methods have been studied in order to overcome the inertness of C=C bonds towards nucleophilic attack due to the harsh reaction conditions that they usually need. In this context, it has been reported an efficient cross-coupling between various $RLi/CeCl_3$ complexes and a range of allyl, homoallyl, and propargyl alcohols. The procedure is efficient and the products are obtained without chromatographic purification in a very good yield (Scheme 51).[78]



Scheme 51. *Application of organoceriums towards C=C and C≡C bonds.*

5.3. $CeCl_3$ mediated reductions

Luche was the first one who demonstrated the utility of cerium in combination with $NaBH_4$ in the reduction of carbonyl groups (Scheme 52). [79]



Scheme 52. *Luche reduction of carbonyls.*

The mechanism accounting for the regio- and diastereoselectivity of the reaction has been proposed on the basis of the Pearson's hard-soft principle. $CeCl_3 \cdot 7H_2O$ is crucial in the conversion of $NaBH_4$ to $[BH_{4-n}(OMe)_n]^-$ species. The carbonyl group is activated by hydrogen bonding, and this carbonyl, being harder than the non-activated one, is attacked

by the hard borohydride to give the corresponding alcohol. This strategy maintains the stereochemistry of the starting material unaltered (Figure 10).[80]

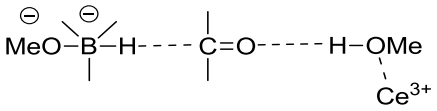
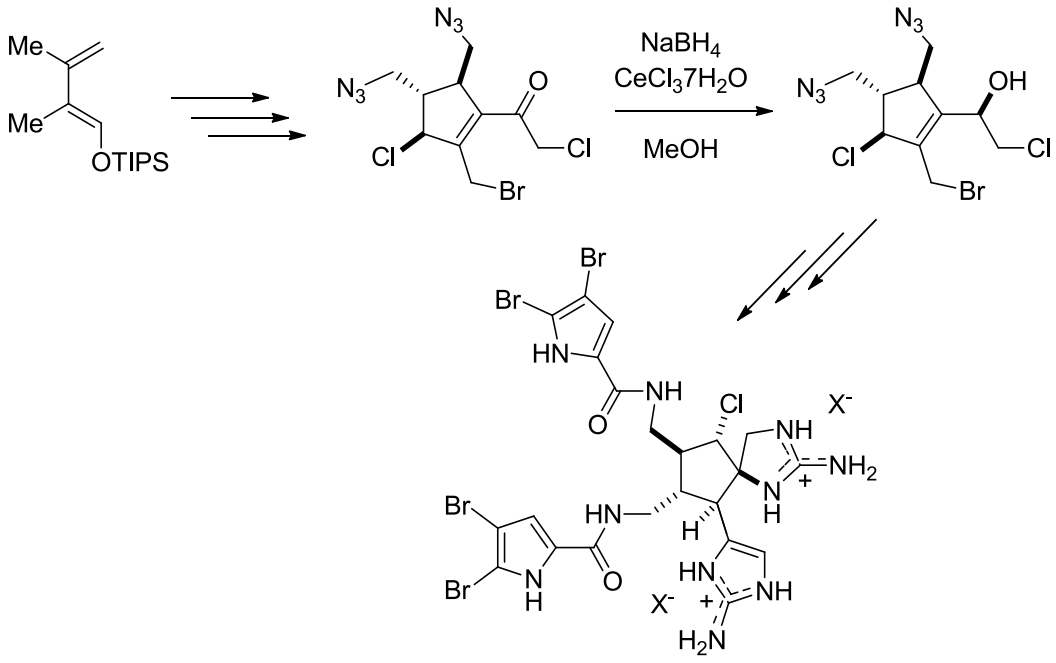


Figure 10. *Key-intermediate.*

The Luche reduction methodology ($CeCl_3$ and metal hydride) is a valid alternative to classical reductions and it has been used for the synthesis of complex biologically active molecules.

An important example is opened by Baran's research group that studied the synthesis of 1,9-deoxypreaxinellamine, a marine-derived natural product, in which Cerium(III) chloride allows the successful reduction of the carbonyl group because of the high covalent character of cerium-oxygen bond that makes the reduction irreversible and kinetically favoured (Scheme 53).[81]



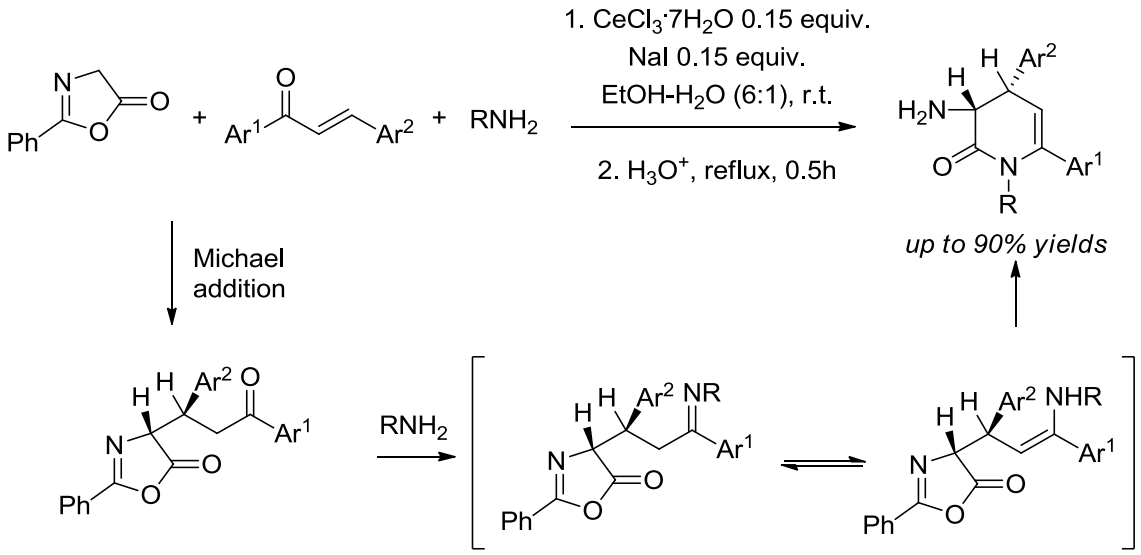
Scheme 53. *Application of $CeCl_3 \cdot 7H_2O$ in the synthesis of 1,9-deoxypreaxinellamine by Baran.*

5.4. Cerium trichloride-metal iodide system: formation of carbon-nitrogen bond

The importance of $CeCl_3$ as *Lewis* acid increased after the discovering of the effect of metal iodides on the activation of the catalyst. The presence of a small amount of iodide anion is sufficient to have shorter reaction times, less by-product formation and improved yields. The most valuable hypothesis about the mechanism of activation is that the iodide ion can break the weakly active chlorine-bridged oligomeric structure of $CeCl_3$, leading to a more active monomeric arrangement, but this assumption has yet to find strong experimental evidences. It was possible to exclude through XPS analysis (X-ray Photoelectron Spectroscopy) an increase of activity due to trans-halogenation process since an halogen exchange doesn't occur on the Ce(III) core. [67,69]

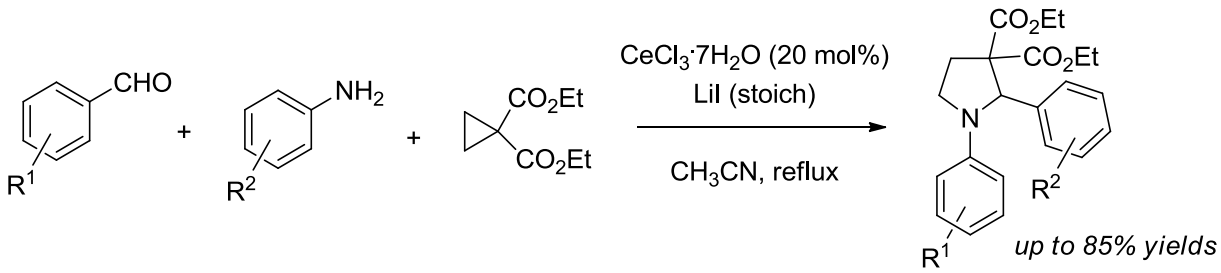
The first applications of the multicomponent promoting system based on Ce(III) salts and inorganic iodides were simple transformations such as deprotections, [82] reductions, [83] oxidations [84] or condensations. [85] Nowadays the $CeCl_3 \cdot 7H_2O/M^+I^-$ provides a straightforward approach for the formation of carbon-nitrogen bond which has found a wide application in the synthesis of polysubstituted nitrogen-containing heterocycles.

Yadav, for example, developed the multicomponent stereoselective synthesis of 3-amino-2-(*1H*)-pyridinones starting from 2-phenyl-1,3-oxazolon-5-one, chalcones and primary amines, using $CeCl_3 \cdot 7H_2O$/NaI system. This transformation shows an excellent anti diastereoselectivity probably due to the large size of complex generated by $CeCl_3 \cdot 7H_2O$ in combination with sodium iodide and its participation in the first Michael addition step (Scheme 54).[86]



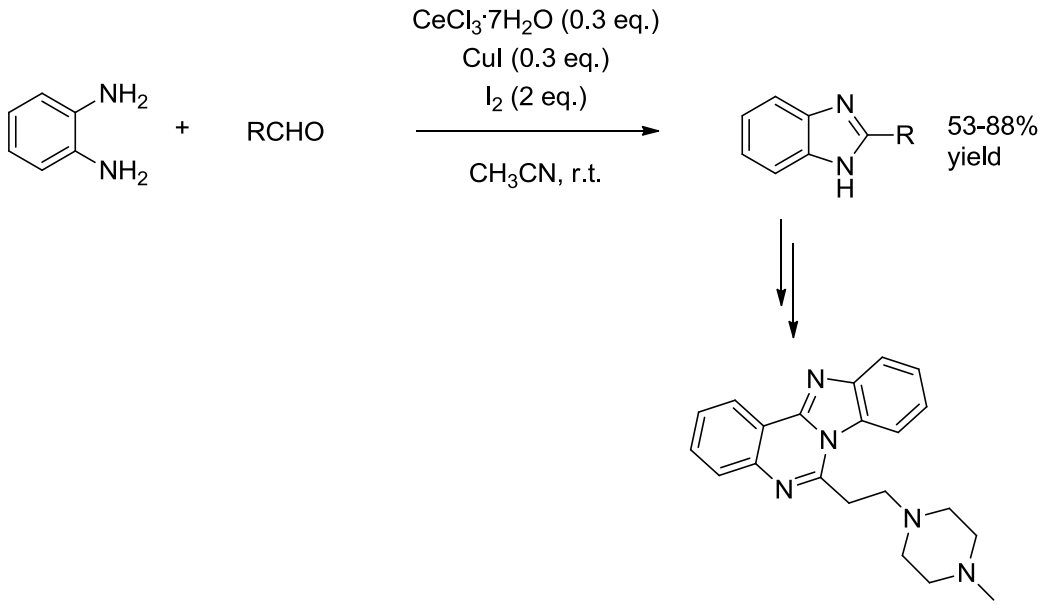
Scheme 54. *Synthesis of 3-amino-2(1H)-pyridinones of Yadav.*

The same research group reported the use of $CeCl_3 \cdot 7H_2O$ also in combination with LiI used in stoichiometric amounts for the synthesis of pyrrolidines via the cycloaddition of in situ prepared imines with cyclopropane-1,1-dicarboxylate (Scheme 55). [87]



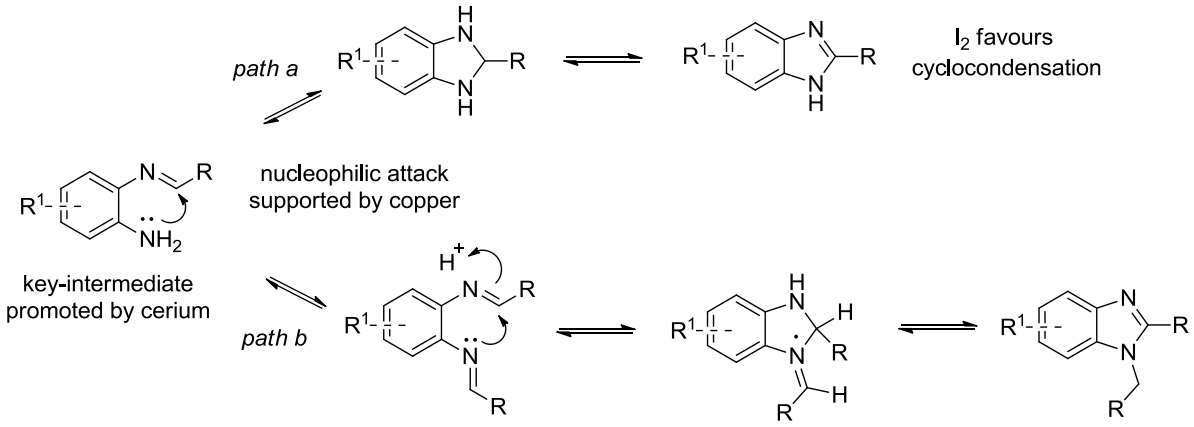
Scheme 55. *Synthesis of pyrrolidines of Yadav.*

Marcantoni's research group developed the synthesis 2-substituted benzimidazoles in high yields and short reactions time applying $CeCl_3 \cdot 7H_2O$ with CuI and I_2 starting from 1,2-phenylenediamine and aldehydes obtaining high yields and short reactions time. [88] This same methodology was successfully applied for the formation of benzimidazo[1,2-c]quinazolines, a new class of antiviral and antitumor compounds (Scheme 56).



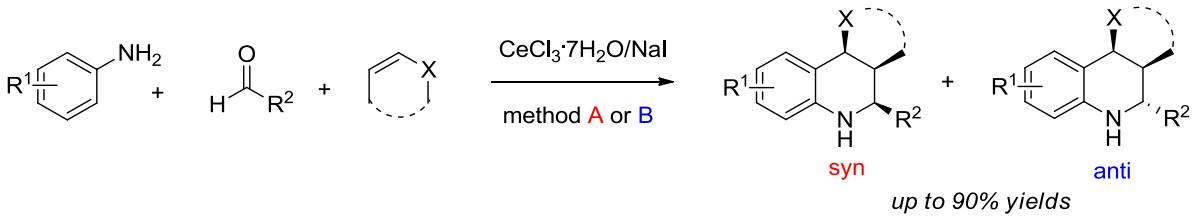
Scheme 56. *Synthesis of benzoimidazoles through $CeCl_3 \cdot 7H_2O$/NaI system.*

In the synthesis, the presence of iodine is fundamental because it plays also the role of oxidant. In the hypothesized mechanism, the formation of the key intermediate, an imine, is promoted by cerium, copper facilitates intramolecular nucleophilic attack and iodine favours the formation of cyclocondensation product through *path a* rather than a successive condensation with a second molecule of aldehyde molecule path *b* (Scheme 57).



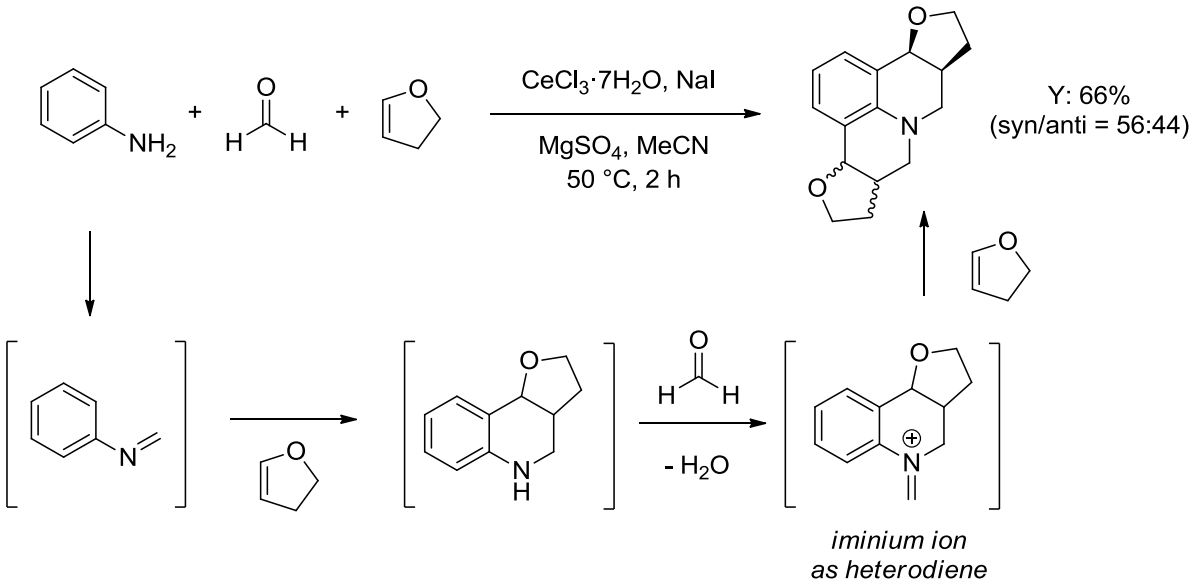
Scheme 57. *Mechanism of $CeCl_3 \cdot 7H_2O$/NaI/I_2 in the synthesis of 2-benzoimidazoles.*

Finally, $CeCl_3 \cdot 7H_2O$ with NaI was applied for the one-pot stereocontrolled synthesis of tetrahydroquinolines through Povarov reaction. [88] It allows to obtain either the *syn*- or the *anti*-isomer with a good selectivity by performing the reaction respectively in solventless conditions and - 10 °C (method A) or with solvent and at 50 °C (method B) (Scheme 58).[89]



Scheme 58. *Stereoselective synthesis of tetrahydroquinolines.*

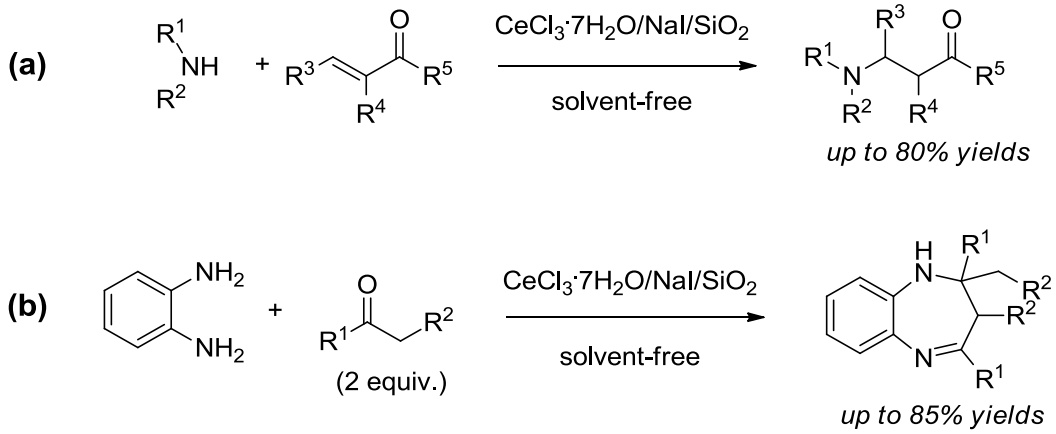
The same reaction conditions can be applied for the formation of the julolidine, which has proved to have important biological activity through two successive Povarov reactions (Scheme 59).



Scheme 59. *Synthesis of julolidine through $CeCl_3 \cdot 7H_2O$/NaI catalytic system.*

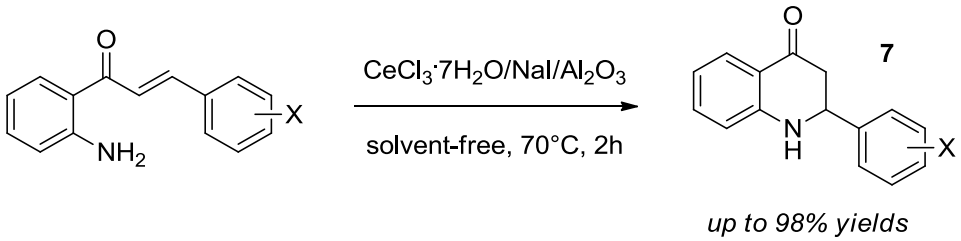
An implementation of this catalyst was made by supporting it on SiO_2 or Al_2O_3, enhancing the activity of the catalyst itself and avoiding the need for the final extraction step in the synthesis, making the whole process more environment friendly.

After the early works of Marcantoni, who employed the $CeCl_3 \cdot 7H_2O/NaI$ on silica gel surface in solventless conditions for the conjugate additions on α,β-enones (Scheme 60a),[90] Sabitha et al. applied the same catalyst for the synthesis of 1,5-benzodiazepines starting from *o*-phenylenediamines and ketones. [91] The catalyst has proved to be effective even when used multiple times, with only a slight decrease of isolated yield (Scheme 60b).



Scheme 60. *Supported $CeCl_3 \cdot 7H_2O/NaI$ on SiO_2 in the synthesis of C-N bond*.

The $CeCl_3 \cdot 7H_2O/NaI$ supported on alumina were used by Ahmed and van Lier for the cyclization of 2-aminochalcones to 2,3-dihydroquinolin-4(1H)-ones in short reaction times and excellent yields (Scheme 61). [92]



Scheme 61. *Supported $CeCl_3 \cdot 7H_2O/NaI$ on Al_2O_3 in the synthesis of C-N bond*.

6. Iodine

6.1. General considerations

Iodine (I_2) is one of the heaviest non-radioactive elements in the Periodic Table classified as a non-metal. It is the largest, the least electronegative, and the most polarizable of the halogens and these properties make it highly reactive and prone to radical reaction. Iodine is known to form both organic and inorganic compounds in various oxidation states ranging from –I to +VII, that have structural feature and reactivity pattern similar to the derivates of heavy transition metals. As a consequence of its high electronegativity, it forms mainly iodides (I^-) with most elements, in which iodine possesses the formal oxidation state -I.[93]

The I_2 molecule is well known to form charge-transfer compounds with a large number of compounds (for example aromatic molecules) in which acts as *Lewis* acid. With strong nucleophilic donors, such as organic amines, iodine tends to split heterolytically to form I^- ions.

Molecular iodine has gained a considerable importance as *Lewis* acid since it catalyzes various organic reaction with high efficiency and selectivity, combined with short reaction times and operational simplicity. In addition, it offers various advantages over the vast majority of other *Lewis* acids, especially the metallic catalysts. It is not only non-toxic, but also water tolerant, relatively cheap and environmentally friendly. It is able to perform its catalytic activity both in dilute solutions and under highly concentrated media, as well as in reactions carried out under solvent-free conditions.[94]

Recently, another interesting achievement comes from the catalytic activity of iodine in numerous oxidative transformations leading to the formation of new C-O, C-N and C-C bonds in organic compounds, which has solved the problem of residual metal in transition-metal catalysis.[95]

6.2. Powerful *Lewis* acid in imines activation

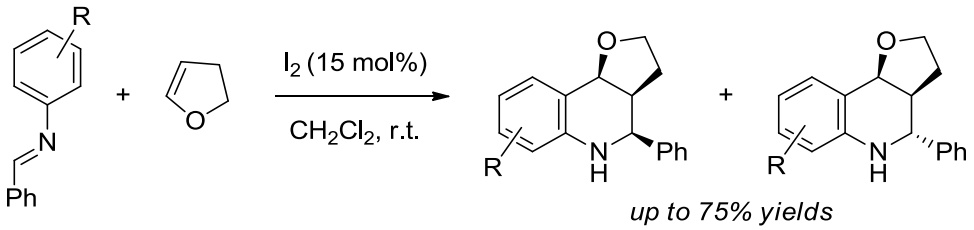
Imines are useful intermediates for carbon-carbon or carbon-heteroatom bond forming reactions such as imino Diels–Alder reactions and nucleophilic addition.

The imino-Diels-Alder reaction is an highly efficient strategy for the synthesis of various nitrogen-containing heterocycles such as tetrahydroquinolines or quinolines. This reaction has been widely studied, especially in a one-pot method, in order to find an efficient catalyst.

Several *Lewis* acids have been considered in order to activate imines. Unfortunately, in most cases, they have to be used in stoichiometric amounts since even the corresponding amino products may act as a *Lewis* base, resulting in the deactivation of *Lewis* acid. Therefore, typical *Lewis* acids such as $TiCl_4$ or $BF_3{\cdot}OEt_2$ are required in excess to complete the process. Rare-earth metal triflates can be used in catalytic amounts to activate imines, owing to their stability toward most popular functional groups including imines and amines but in some cases, their acidity is too strong and the high cost prohibited their use as a versatile reagents. Furthermore, it must also be considered that most imines are hygroscopic, unstable at high temperature, and difficult to purify by distillation or column chromatography.

In recent years, iodine has emerged as a very effective *Lewis* acid catalyst also because it is relatively inexpensive compared to other *Lewis* acid including rare-earth metal triflate and it is more tolerant in comparison to typical *Lewis* acids/bases. It can also be easily adapted to commercial applications since its handling does not require special precautions and it is readily reduced to relatively nontoxic iodide during work-up procedures. [96]

The group of Yan reported the use of molecular iodine in the activation of N-arylimines towards Diels-Alder reaction to provide tetrahydroquinolines in good yields. Mild reaction conditions and facile experimental procedure render this new method very attractive (Scheme 62).[97]



Scheme 62. I_2 catalyzed synthesis of tetrahydroquinolines of Yan.

The same authors explored the catalytic mechanism of iodine through IR and ^{1}H-NMR analysis and proposed two different way of coordination: imine could coordinate with iodine with lone pair electrons of nitrogen or π electrons of C═N double bond (Figure 11).

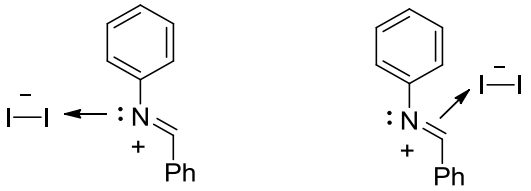
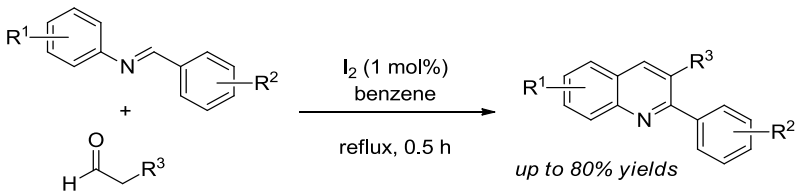


Figure 11. *Two possible iodine-imine coordination ways.*

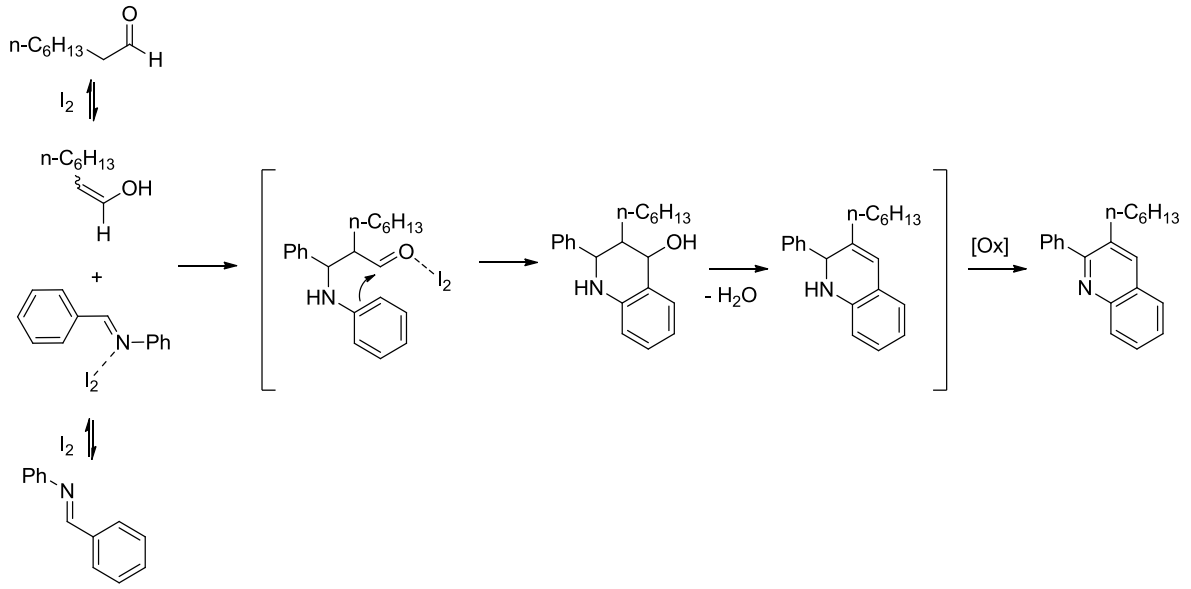
Later, Rai and co-workers demonstrated the application of iodine even with aliphatic N-arylaldimines but using a larger amount of catalyst (30% mol).[98]

Wang exploited the *Lewis* acidity of iodine in the synthesis of 2-arylquinolines from imines and enolizable aldehydes (Scheme 63).[99]



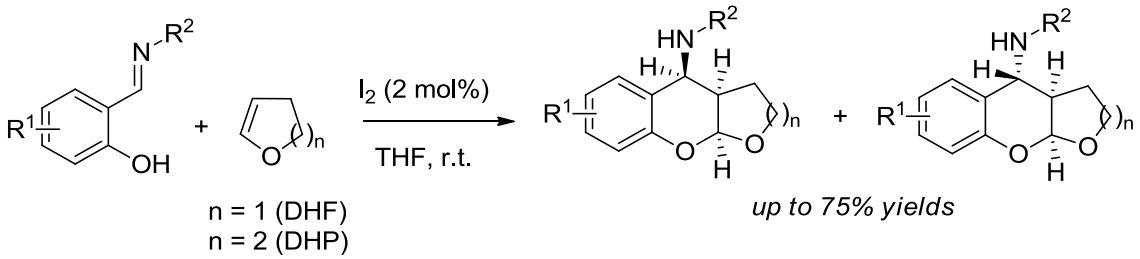
Scheme 63. I_2 catalyzed s*ynthesis of 2-arylquinolines of Wang.*

According to literature, they proposed that octanal, in presence of iodine, is in equilibrium with the enol form that reacts with the iodine-activated imine to form the intermediate that upon intramolecular Friedel-Crafts cyclization, followed by dehydration and oxidation gives the final product (Scheme 64).



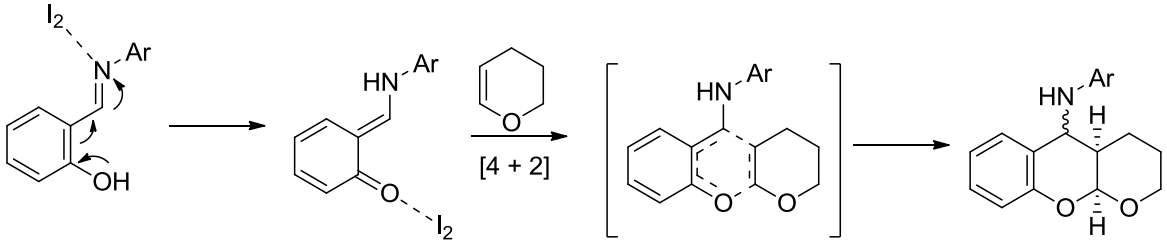
Scheme 64. *Mechanism of 2-arylquinolines' synthesis.*

Wang and Li developed the diastereoselective synthesis of *cis*-fused pyranobenzopyrans and furanobenzopyrans via iodine-catalyzed reaction of *o*-hydroxybenzaldimines with 3,4-dihydro-2H-pyran (DHP) or 2,3-dihydrofuran(DHF) (Scheme 65).[100]



Scheme 65. I_2 catalyzed s*ynthesis of pyranobenzopyrans and furanobenzopyrans of Wang and Li.*

Iodine acts as a mild *Lewis* acid and promotes the transformation of the *o*-hydroxybenzaldimine to oxadiene, which is followed by a [4+2] cycloaddition to give pyranobenzopyrans or furanobenzopyrans (Scheme 66).

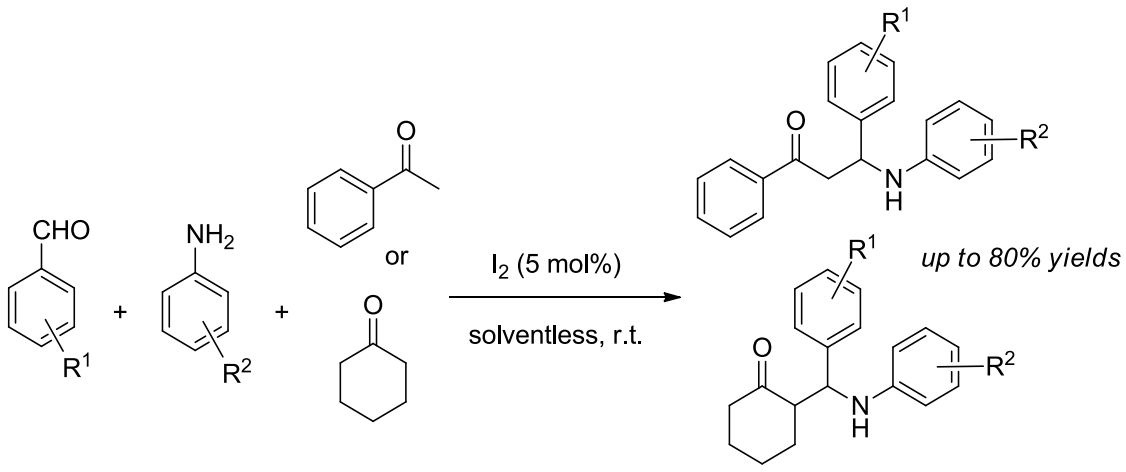


Scheme 66. *Mechanism.*

Iodine has proved to be a good *Lewis* acid also in the three component Mannich reaction that represents one of the most important carbon–carbon bond forming reactions in organic synthesis and one of the most fundamental and convenient methods for preparation of β-amino carbonyl compounds, which are essential synthetic intermediates for many pharmaceuticals and natural products.

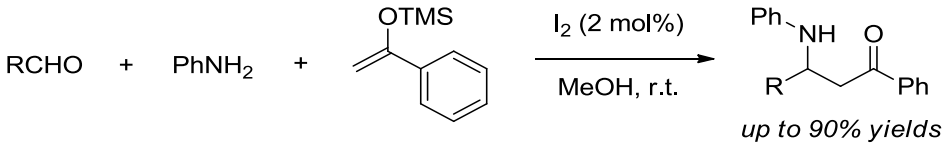
Most of commonly used methods suffer from some serious drawbacks such as long reaction time, harsh reaction condition, difficulty in product separation, expensive reagents or catalysts, the use of large amount of catalysts, pollution of water or use of toxic organic solvents.

Gang and his collaborators successfully reported the application of a small amount of molecular iodine at room temperature under solvent-free condition to afford the β-amino carbonyl compounds from ketones, aromatic aldehydes and aromatic amines with moderate to excellent yields (Scheme 67).[101]



Scheme 67. *I_2 catalyzed synthesis of β-amino carbonyl compounds of Gand.*

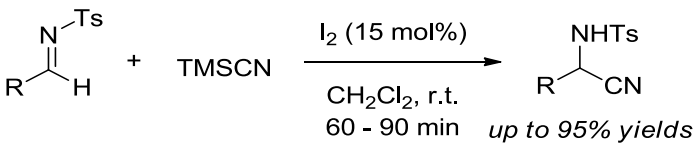
The same reaction was performed starting from silyl enol ether and also in this case Iodine catalysis was exploited. The group of Janda reported that it is sufficient just a little amount of I_2 (2 mol%) to have the desired product. They also proved that there is no deactivation or inhibition of iodine which is of interest considering that the reactants and/or amine product might act as a *Lewis* base (Scheme 68).[102]



Scheme 68. *I_2 catalyzed Mannich reaction with silyl enol ether.*

In Strecker reaction the nucleophile is a cyanide ion, that offers one of the most direct feasible methods for the synthesis of α-aminonitriles. The experimental procedure of this reaction is tedious: several modified methods have been subsequently introduced using various cyanide reagents and various *Lewis* acids, *N*-heterocyclic carbenes and metal complexes.

In 2009, the group of Das reported the efficient application of catalytic amount of iodine in the synthesis of the protected α-aminonitrile from *N*-tosylaldimines with trimethylsilyl cyanide at room temperature in high yields (Scheme 69).[103]



Scheme 69. *Application of I_2 in Strecker reaction.*

6.3. Oxidative coupling reactions

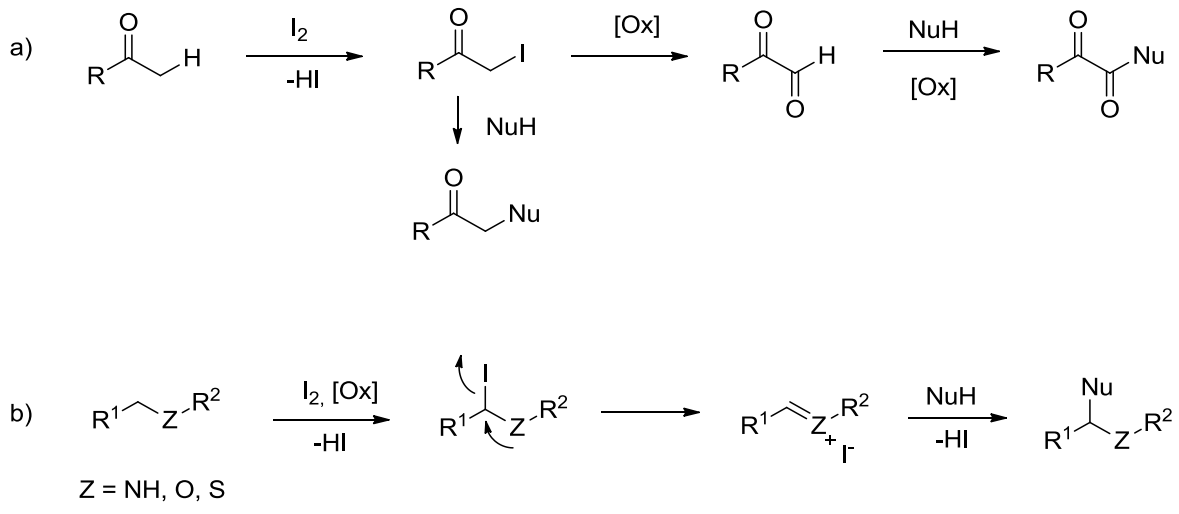
Iodine-catalyzed oxidative coupling reactions (or cross-dehydrogenative coupling) have undergone rapid advances also because they have solved the problem of residual metal in transition-metal catalyzed reactions which had greatly restricted their application in pharmaceutical synthesis. Moreover, iodine catalysis possesses evident advantages over transition-metal catalysis such as greater atom economy; greener, milder reaction conditions and broader substrate compatibility.

Various bond-formation methods utilizing iodide-catalyzed oxidative coupling reactions have been revealed in the past ten years. However, the understanding of the exact role of iodine catalysts in those types of transformations is still rather limited.[104]

Based on different roles of iodine, they can be divide in three classes (1) α-carbon activation, (2) radical initiator and (3) heteroatom activation that will be analyzed more in details.[105]

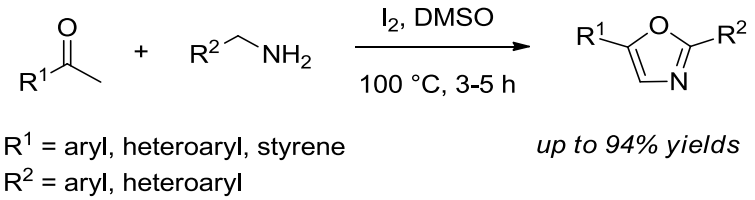
6.3.1. α-Carbon activation

Iodine can play a fundamental role in the α-carbon activation (bond adjacent to C=O, heteroatom, or aryl) to form a C-I bond as key intermediate (Scheme 70)



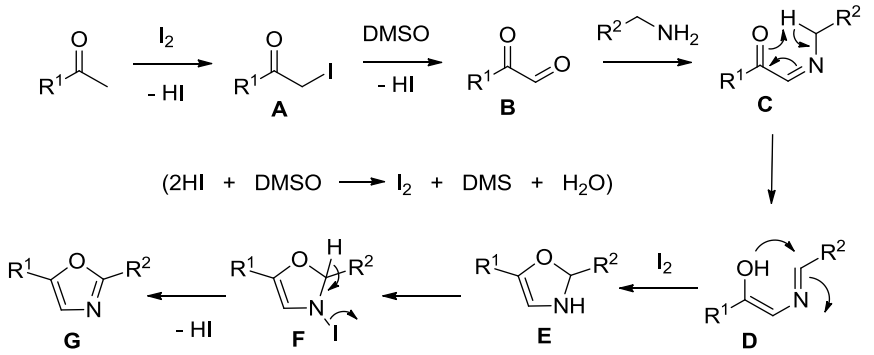
Scheme 70. *General strategies for α-carbon activation by I_2.*

An example of this method is reported by the group of She and Wu who proposed the synthesis of 2,5-disubstituted oxazoles from easy and available methyl aryl ketones and benzylamines by C(sp^3) functionalization. The reactions shows a wide applicability: both electron-rich and electron-deficient substituents as well as heteroaryl ketones give the desired product in good to excellent yields. Moreover various substituted benzylamines and heteroaryl methylene amines can be used (Scheme 71).[106]



Scheme 71. *I_2 catalyzed synthesis of 2,5-oxazoles.*

Initially, the ketone reacts with I_2 to form a iodo intermediate **A** which undergoes a Komblum oxidation in the presence of DMSO to give glyoxal **B**. Condensation with (het)arylamine give **C** followed by enolization of resultant keto–imine species **C** produces intermediate **D** that by intramolecular cyclization produces **E**, and. Subsequent oxidation affords oxazole **G** via **F**. DMSO oxidizes in situ generated HI to give I_2 for the next catalytic cycle (Scheme 72).



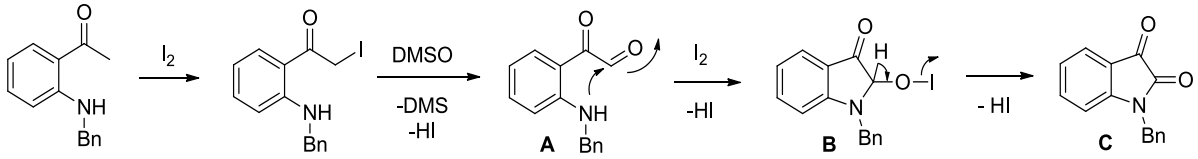
Scheme 72. *Mechanism.*

A similar procedure was exploited by the group of Sakar and Rajeshkumar. They synthesized isatins through C(sp^3)–H oxidation and intramolecular C–N bond formation from 2-aminoacetophenones with excellent yields. The reaction can be performed with

different substituents on the phenyl ring and amine nitrogen atom. In addition it is also suitable for gram scale synthesis and retained its high yields (Scheme 73).[107]

Scheme 73. *I_2 catalyzed synthesis of isatins.*

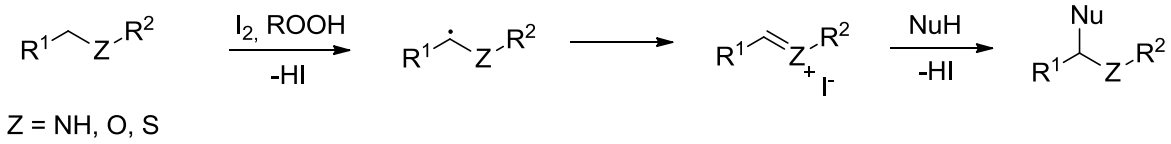
A possible reaction mechanism is presented in Scheme 74. The α-iodination of methyl ketone is followed by Kornblum oxidation **A** and subsequent annulation that provides intermediate **B**, which eliminates HI to form isatin **C**. The catalytic cycle is then closed by oxidation of HI to I_2 by DMSO as depicted in Scheme 72.



Scheme 74. *Mechanism.*

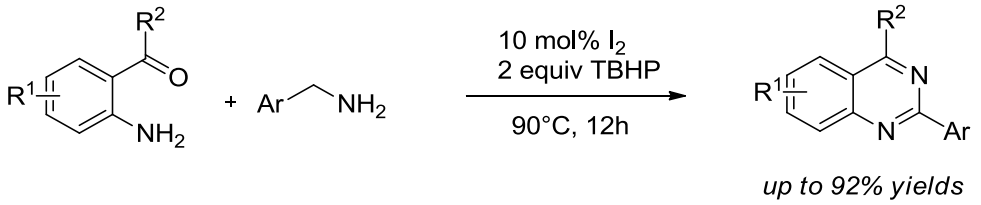
6.3.2. Radical initiator

Iodine can also act as radical initiator (Scheme 75).



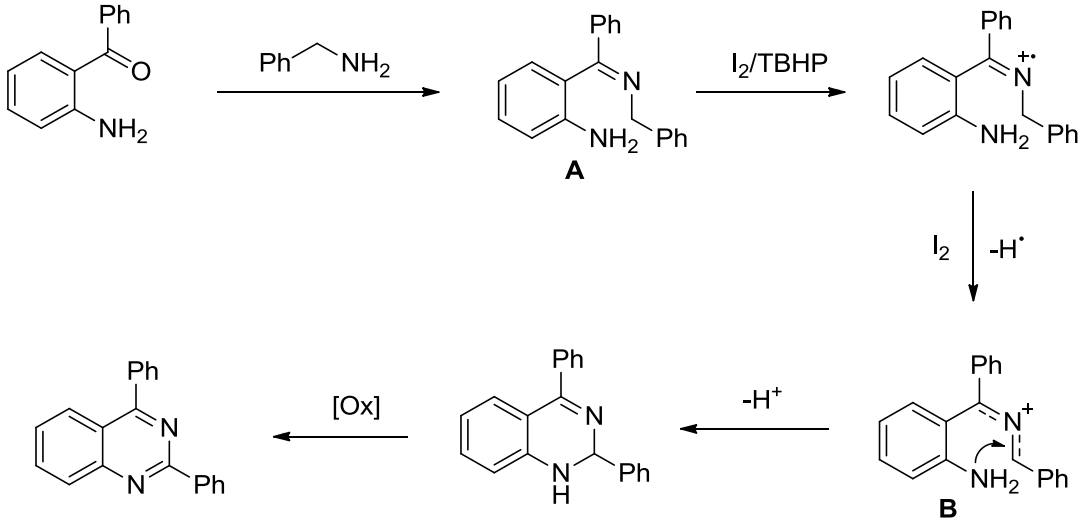
Scheme 75. *General strategies for radical initiation by I_2*

Wang and co-workers reported a simple synthesis of 2-phenylquinazolines by employing the system I_2 and TBHP. Various 2-phenylquinazolines were prepared in good yields by condensation of easily available 2-aminobenzophenones and benzylamine through tandem reaction following Csp^3–H functionalization (Scheme 76).[108]



Scheme 76. *I_2 catalyzed synthesis of 2-phenylquinazolines.*

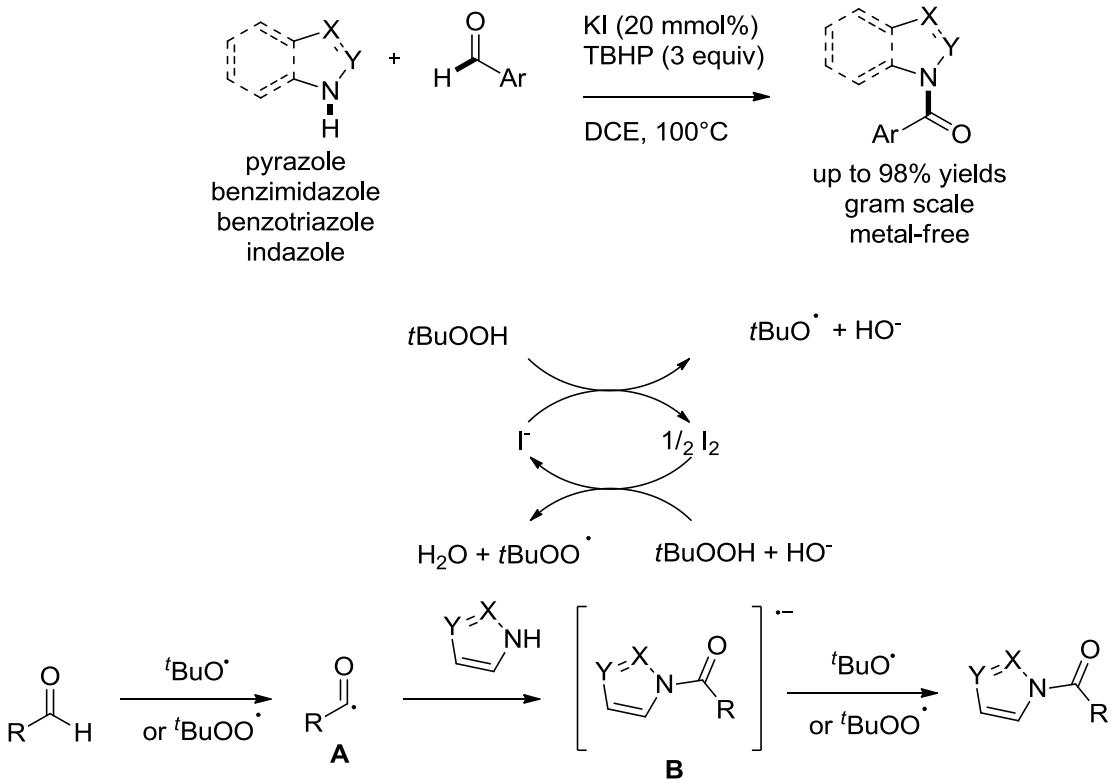
A tentative mechanism showed that an imine intermediate **A** was generated by condensation of ketone and amine, and subsequently oxidized by molecular iodine to form a nitrogen-centered cation intermediate **B** through a two-step single-electron transfer process. Final intramolecular cyclization and further oxidation afforded the desired product (Scheme 77).



Scheme 77. *Mechanism.*

Subsequently, Li and co-workers developed a KI-catalyzed *N*-acylation of azoles using aldehydes as the acyl sources and nitrogen heterocycles. With KI as the catalyst and TBHP as the oxidant, a series of N-acylated azoles, such as pyrazoles, benzimidazoles, benzotriazoles, and indazoles, could be obtained in good to excellent yields and interestingly, such transformation could be efficiently scaled up.

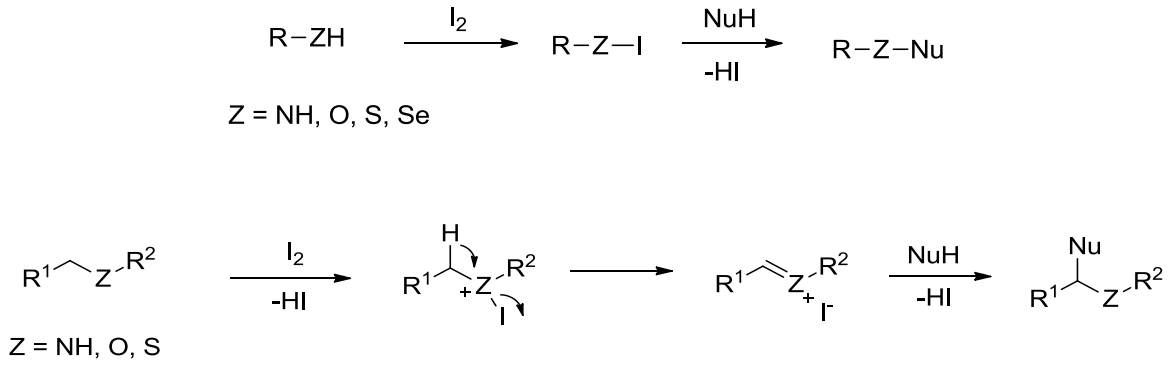
Mechanistic research revealed that KI served as a radical initiator to decompose TBHP into tBuO·, and radical coupling between an acyl radical and an azole radical afforded the desired product (Scheme 78).[109]



Scheme 78. *KI-catalyzed N-acylation of azoles and possible mechanism*

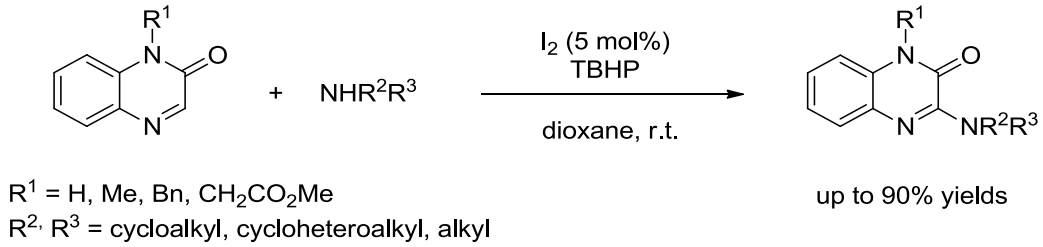
6.3.3. Heteroatom activation

Finally iodine can be determinant in the heteroatom activation to form a Het-I containing key intermediate (Scheme 79).



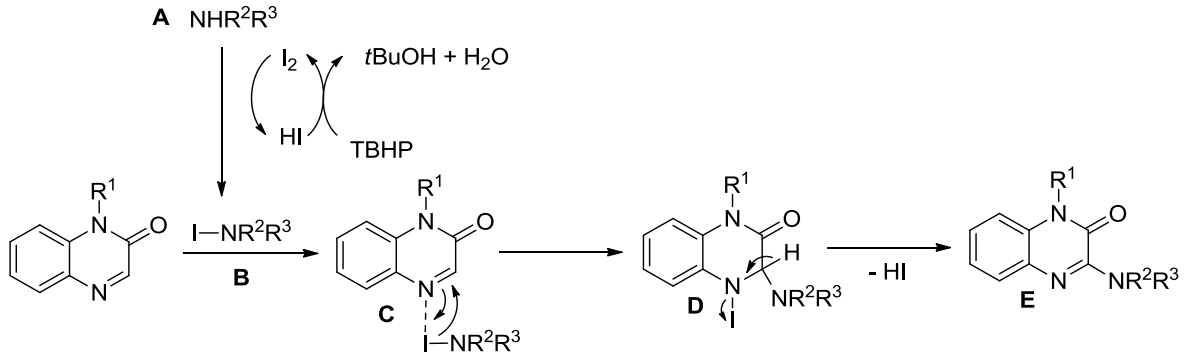
Scheme 79. *General strategies for heteroatom activation by I_2.*

Gupta reported an example for the coupling of amines (N–H) with quinoxalinones through C(sp^2)–H activation by using catalytic iodine and TBHP as the terminal oxidant under ambient conditions to form 3-aminoquinones in moderate to high yields.[110] Quinoxalinones bearing electron-donating and electron-withdrawing groups on the aryl ring react smoothly with secondary amines to give the products in good to excellent yields. In general, electron-rich and halide-substituted quinoxalinones give better results than the electron-poor one. The versatility of this reaction has been examined with primary amines, and the corresponding products are formed in moderate to good yields (Scheme 80)



Scheme 80. *I_2 catalyzed synthesis of 3-aminoquinoxalinones.*

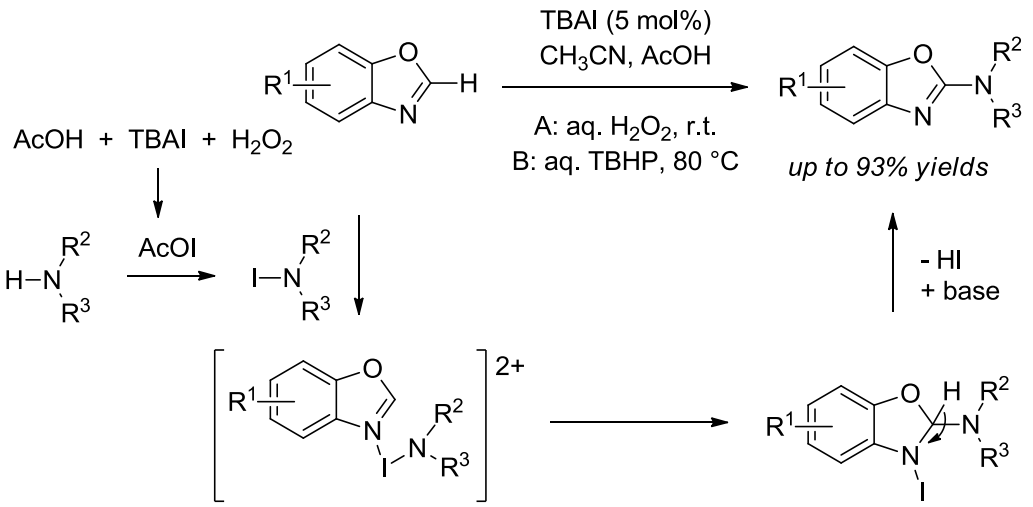
Iodine reacts with amine **A** to generate *N*-iodo amine species **B**, which coordinates with the N4 atom of starting quinoxalinone **C**; this results in polarization of the C3=N4 bond of **C**. Nucleophilic attack of the amine at C3 produces the *N*-iodo intermediate **D**, which eliminates HI to provide product **F** (Scheme 81).



Scheme 81. *Synthesis of quinoxalinones*

Nachtsheim and co-workers communicated a novel iodine-catalyzed oxidative C-H amination of benzoxazoles using TBAI as catalyst and H_2O_2 and TBHP as oxidants. Various substituted 2-aminobenzoxazoles could be produced in good yields.[111]

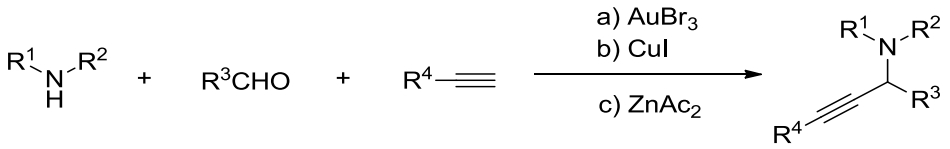
Mechanistic analysis revealed that TBAI could react with H_2O_2 in the presence of AcOH to generate AcOI, which further reacted with an amine to produce the iodinated amine. Subsequent N-I bond insertion into the C=N bond of benzoxazole generated another N-I-bonded intermediate. Final elimination of HI in the presence of base delivered the desired product. Some years later, in 2012, the same group expanded this oxidative C-N bond-formation protocol to the use of simple aliphatic amines, even ammonia (Scheme 82).



Scheme 82. I_2 catalyzed synthesis of 2-aminobenzoxazoles and mechanism.

7. Project

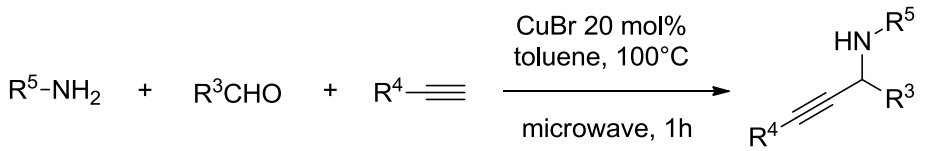
Despite huge advancements in the synthesis of propargylamines, mainly anilines and secondary amines in combination with different metal catalyst have been studied which led to the formation of corresponding N-arylpropargylamines or tertiary propargylamines (Scheme 83).



Scheme 83. *Applications of secondary amines.*

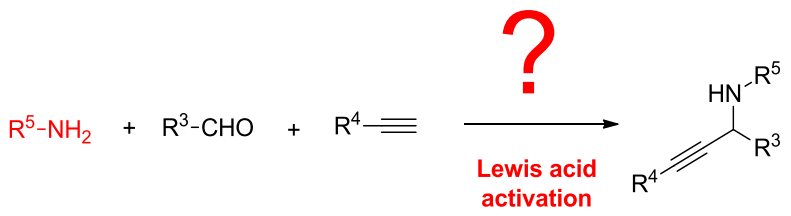
Primary amines are instead considered to be difficult substrates in the synthesis of secondary propargylamines and their application is scarcely reported in the literature because secondary amines give rises to an iminium ions that is by-definition more reactive than the imine.

This represents a limit due to the importance of this class of propargylamine in the context of small molecules (see Rasagiline that is a secondary propargylamine). The most straightforward method to afford these compounds nowadays is through CuBr catalysis (Scheme 84).[59]



Scheme 84. *Applications of primary amines.*

Our goal was the development of a green and simple *Lewis* acid catalyzed or promoted methodology for the activation of primary amines for the synthesis of the secondary propargylamines (*Chapter 8.1*, Scheme 85).



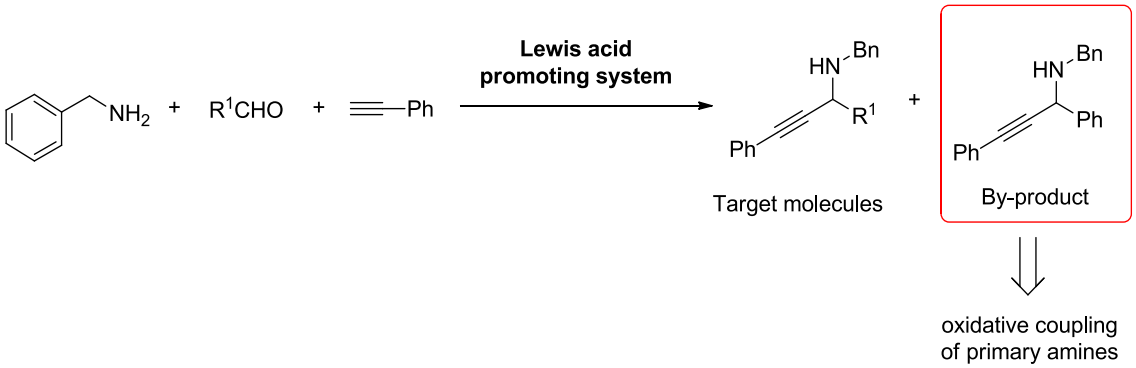
Scheme 85. *Lewis acid activation of primary amines.*

Two different *Lewis* acid have been taken in consideration: iodine and cerium trichloride heptahydrate.

Iodine possesses a strong C–C multiple bond coordination ability and may be both a σ- and a π-electrophilic *Lewis* acid. Furthermore, it has been used as a mild *Lewis* acid to activate imines in the synthesis of quinolines via a three-component reaction of amines, aldehydes and alkynes (*Chapter 6*)

Cerium trichloride heptahydrate, is a powerful *Lewis* acid characterized by high efficiency, low toxicity and cost and for the ease of application also under non-anhydrous conditions. Furthermore, when used with different inorganic iodide, its catalytic activity increases and has been successfully applied in the formation of C-N bond in several nitrogen containing heterocycles (*Chapter 5*).

Furthermore, the presence of an unexpected propargylamine when aldehydes different than benzaldehydes are used with one of the two *Lewis* acid promoting systems developed, led us to the possibility to explore a new way to obtain imine through oxidative coupling of primary amines which avoid the use of easily oxidable and reactive aldehydes (*Chapter 8.2*, Scheme 86).



Scheme 86. *From by product to new strategies.*

A study to obtain secondary propargylamines in an diastereoselective way was tried due to the different selectivity observed using chiral starting material with the two *Lewis* acid promoting system developed (*Chapter 8.3*, Figure 12).

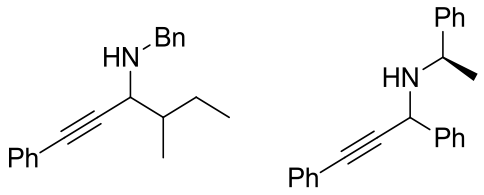


Figure 12. *Different selectivity with chiral starting material.*

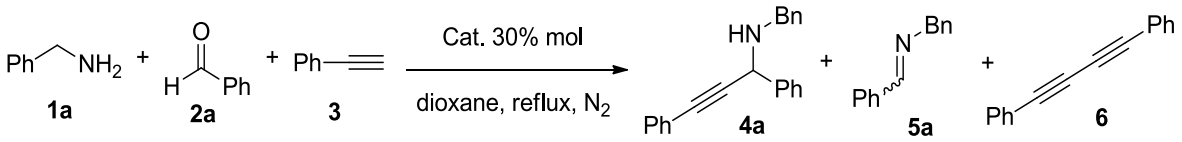
8. Results and discussion

8.1. Activation of primary amines by *Lewis* acid for the synthesis of secondary propargylamines

8.1.1. Catalyst screening

As discussed in Chapter 4.3, several *Lewis* acid have been considered and copper(I) or copper(II) are the most useful and frequently applied metal in the synthesis of propargylamines. In general, the coordination of *Lewis* acids with the final propargylamine is stronger than with the intermediate imine and the presence of a second *Lewis* acid may offset this unfavourable factor. For this the potentiality of iodine and cerium trichloride heptahydrate have been explored.

In order to find the best conditions for the synthesis of secondary propargylamines, a preliminary screening of the pilot reaction among benzylamine **1**, benzaldehyde **2** and phenylacetylene **3** in dioxane at reflux and under nitrogen atmosphere was carried out, as depicted in Scheme 87. The results obtained are reported in Table 2.



Scheme 87. *Pilot reaction for Lewis acid screening.*

It is clear that the CuI/I_2 promoting system is active in the reaction and that its action results from the synergy of both copper(I) and iodine, as shown by the very poor results obtained when the two components are used independently (entries 1-3).

On the other hand also $CeCl_3 \cdot 7H_2O$, alone or in combination with other *Lewis* acids, showed to be a good promoter for the synthesis of imine, as just known in literature, but in

solution it did not afford the product, except with CuI, with comparable result to CuI/I_2 (entries 5-10). Copper(I) gave a much better performance than copper(II) (entries 1,11).

Entry	Catalyst	4a (Y%)	5a (Y%)	6 (Y%)
1[a]	CuI/I_2	27	29	4
2	CuI	2	92	<1
3[b]	I_2	-	70	-
4	NaI	-	94	-
5	$CeCl_3 \cdot 7H_2O/NaI$	-	>99	-
6	$CeCl_3 \cdot 7H_2O/CuI$	28	20	
7	$CeCl_3 \cdot 7H_2O$	-	43	-
8	dry $CeCl_3$	-	30	-
9[c]	$CeCl_3 \cdot 7H_2O/NaI/I_2$	-	25	-
10	$CeCl_3 \cdot 7H_2O/CuI/I_2$	-	41	10
11	$CuSO_4/I_2$	<2	22	6

All the reaction were performed mixing 1 mmol of **1a**, 1 mmol of **2a** and 1 mmol of **3** together with 0.30 mmol of catalyst under nitrogen atmosphere in refluxing dioxane and allowed to stand until a constant composition of the mixture was reached. Chromatographic yields.
[a] 4% of diiodostyrene is formed
[b] 23% of diiodostyrene is formed
[c] 44% of diiodostyrene is formed

Table 2. *Catalyst screening for the synthesis of secondary propargylamines.*

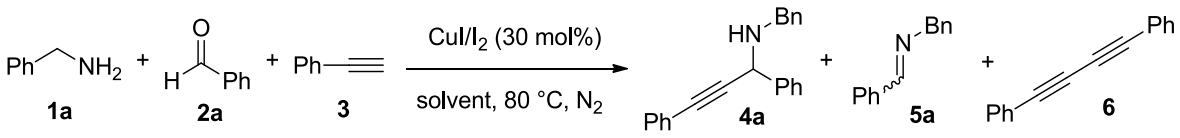
Several attempts have been made in order to generate iodine directly *in situ* especially in copper-catalyzed reactions which avoid the direct manipulation I_2 and results to be more active. CuI/I_2 system can be obtained by direct reaction of copper(II) perchlorate[112] or sulphate[113] with NaI. For this reason, also the potentiality of the CuI/I_2 formed directly *in situ* by using a $CuSO_4$/NaI couple will be studied.

Starting from the preliminary results also the $CeCl_3 \cdot 7H_2O$/CuI system will be evaluated with the scope to develop two different copper(I)-based *Lewis* acid promoting system to activate primary amine for the synthesis of secondary propargylamines.

8.1.2. CuI/I_2 from $CuSO_4$/NaI

CuI/I_2 was considered first. The solvent effect on the outcome of the Cu/I_2 of the pilot reaction at 80 °C was evaluated and the results are reported in Table 3.

Propargylamine **4a** is obtained in higher yields than in dioxane (entry 1) when water or water/ethanol mixture were used but together with consistent amount of product **6** coming from the parallel dimerization of phenylacetylene (entries 7, 10). A similar result was also reached in acetonitrile (entry 1), whereas, in pure alcohols and ethylacetate only the imine was formed (entries 2-6).



Entry	Solvent	4a (Y%)	5a (Y%)	6 (Y%)
1	CH_3CN	29	45	13
2	AcOEt	-	49	-
3	Pr^iOH	1	53	-
4	dry EtOH	-	81	-
5	MeOH	-	90	10
6	EtOH	-	80	8
7	H_2O	33	6	40
8	EtOH/H_2O[a]	43	30	26
9	EtOH/H_2O[b]	11	62	25
10	EtOH/H_2O[c]	-	77	22

All the reaction were performed mixing 1 mmol of **1a**, 1 mmol of **2a** and 1 mmol of **3** together with 0.30 mmol of the catalyst (1:1 mixture) under nitrogen atmosphere until a constant composition of the mixture was reached. GC-MS yields.
[a] EtOH : H_2O = 25 : 70 vol/vol
[b] EtOH : H_2O = 50 : 50 vol/vol
[c] EtOH : H_2O = 75 : 25 vol/vol

Table 3. *Solvent screening.*

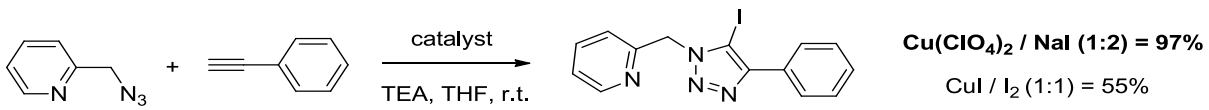
Later, the possibility to carry out the reaction in solventless conditions was taken into account together with the influence of temperature on the formation of the final product. From the results reported in Table 4, the absence of solvent determined an increasing of the yields without any significant difference between 80 °C or 100 °C (entries 2,3) even if the amount of the unreacted imine was still considerable. At room temperature the propargylamine was not formed (entry 1).

Entry	T (°C)	4a (Y%)	5a (Y%)	6 (Y%)
1	r.t.	-	87	-
2	80	40	50	1
3	100	39	56	1

All the reaction were performed mixing 1 mmol of **1a**, 1 mmol of **2a** and 1 mmol of **3** together with 0.30 mmol of the catalyst (1:1 mixture) in solventless conditions under nitrogen atmosphere until a constant composition of the mixture was reached. GC-MS yields.

Table 4. *Temperature screening in solventless conditions.*

The CuI/I_2 system results more reactive when it is generated *in situ* than when it is obtained by direct mixing of CuI and I_2 in the same ratio, as reported by the group of Zhu in the synthesis of 5-iodotriazoles who applied $Cu(ClO_4)_2$/NaI (Scheme 88). [112]



Scheme 88. *Synthesis of Zhu for 5-iodotriazoles.*

The $CuSO_4$/NaI couple revealed to be a good way to generate the actual promoting system CuI/I_2 *in situ* by direct mixing, through a quick, quantitative and spontaneous reaction. The lower cost, the major commercial availability and the ease of use of $CuSO_4$ and NaI make them an interesting alternative (Equation 2).

$$2\ CuSO_4 + 4\ NaI \rightarrow 2\ CuI + I_2 + 2\ Na_2SO_4$$

Equation 2. *Formation of CuI/I_2 in situ from $CusO_4$/NaI.*

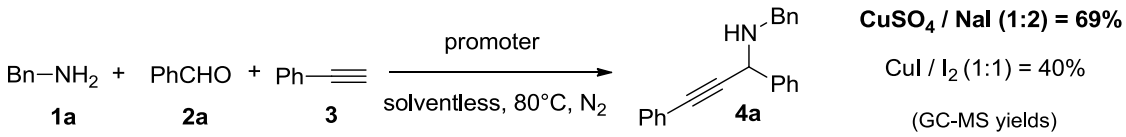
As depicted in Equations 2, the reactions of Cu^{2+} and I_2/I^- may produce also different ions, depending on their relative amounts that could be involved or interfere in the formation of the propargylamine.

$$CuI + I^- \rightarrow [CuI_2]^-$$
$$I_2 + I^- \rightarrow [I_3]^-$$

Equation 3. *Different ions produced.*

The pilot reaction was then performed under conditions that allow the formation of $[I_3]^-$ only or of $[CuI_2]^-$ and CuI/I_2. The results clearly indicate that $[I_3]^-$ acts only as an iodinating agent of phenylacetylene due to the only formation of diiodostyrene without any trace of the desired product (entry 6). The addition of an equimolecular amount of NaI to CuI improved the yield of propargylamine more than the same amount of iodine (Table 5, entry 1 vs Table 4, entry 2).

The $CuSO_4$/NaI system works as a good precursor of the CuI/I_2 promoter (entries 3-5). The best result was obtained under solventless conditions at 80 °C using a mixture of dry $CuSO_4$ and NaI with a 1:2 ratio to prepare the CuI/I_2 system *in situ* (Scheme 89). This result is in accordance with the stoichiometry of Equation 2.



Scheme 89. *$CuSO_4$/NaI precursor of CuI/I_2.*

An increase in the $CuSO_4$/NaI ratio to 1:3 did not improve the yield (entry 8) whereas a lack afforded a lower yield (entry 6). In addition, the use of dry $CuSO_4$ is indispensable as demonstrated, by the poor yield obtained when the $CuSO_4 \cdot 5H_2O$ was used as such (entry 2).

Entry	Promoter (mol%)	NaI (mol%)	4a (%)	5a(%)	6(%)
1	CuI 30	30	60	33	0
2	$CuSO_4 \cdot 5H_2O$ 30	30	10	78	11
3	$CuSO_4$ 30	30	39	42	15
4	**$CuSO_4$ 30**	**60**	**69**	15	4
5	$CuSO_4$ 30	90	55	29	4
6[a]	I_2 30	30	-	73	-

Reaction conditions: **1a** (1 mmol), **2a** (1 mmol) and **3** (1 mmol) were mixed together with the promoter and variable amount of NaI, at 80 °C under N_2 atmosphere, until a constant composition of the mixture was reached. GC-MS yields.

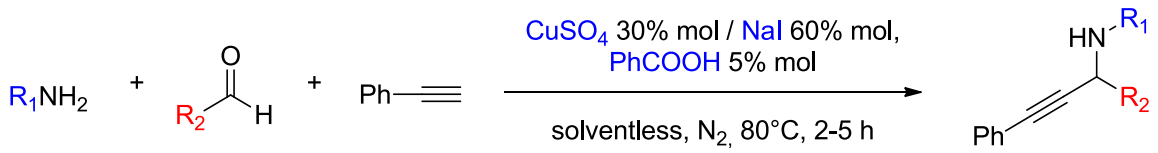
[a] 18% diiodostyrene was formed.

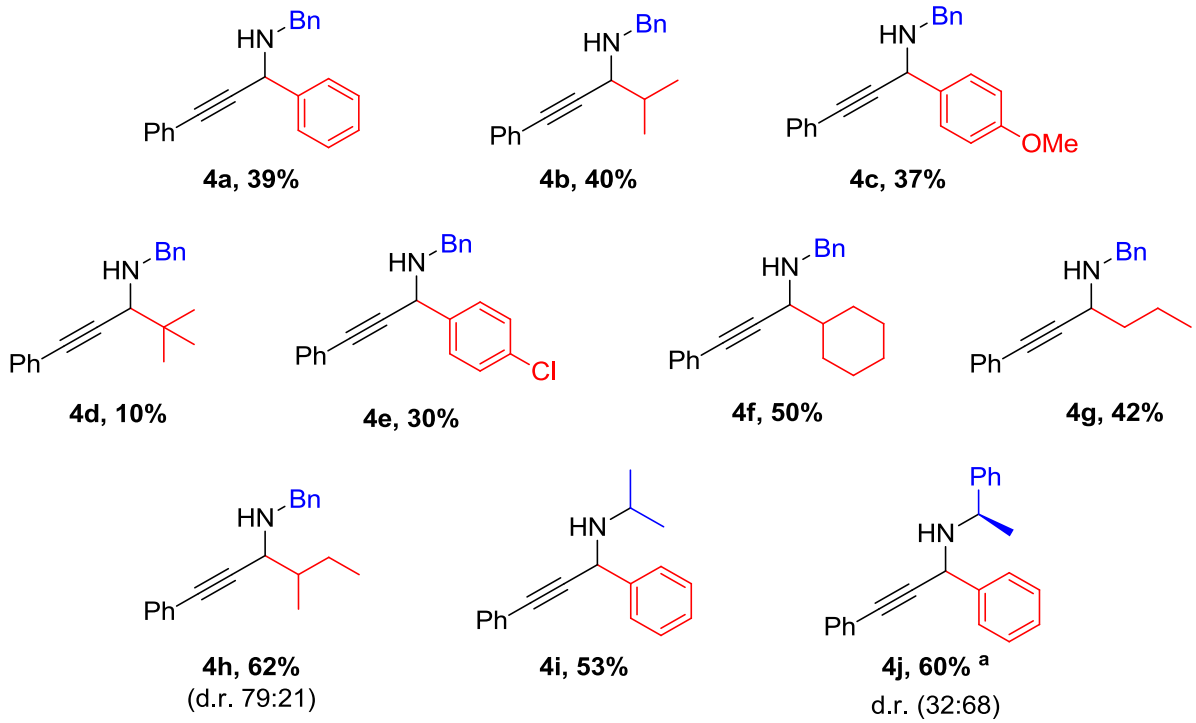
Table 5. *$CuSO_4$/NaI precursor of CuI/I_2.*

In almost all the reactions variable amount of 1,4-diphenylbuta-1,3-diyne ranging from 4% to 15% was found formed from phenylacetylene through Glaser coupling. This side reaction substracts reagent towards an undesired product, decreasing the final yield of the propargylamine, and can be suppressed by the addition of a small percentage of benzoic acid.[114]

With the best conditions now found, the versatility of the system was explored performing the reaction starting from various amines and aldehydes.

Aldehydes and phenylacetylene were mixed in the reaction vessel under inert atmosphere, then NaI and dry $CuSO_4$ were added. As the two salts get mixed, a deep brown color develops, indicating that the reaction in Equation 1 has gone to completion, then amines were added. The mixture was stirred at 80 °C until a constant composition was reached (2–5 h). The final propargylamines were obtained in yields from acceptable to good, with slightly better results starting from aliphatic aldehydes (Table 6).





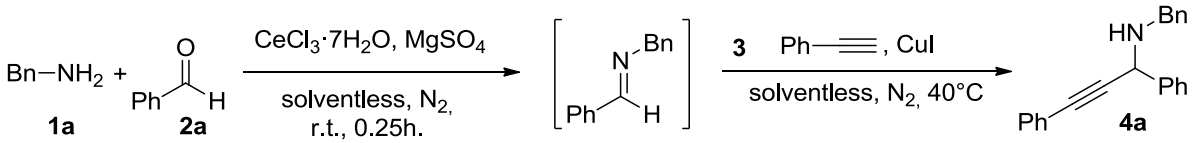
[a] $CuSO_4$ (15 mol%) / NaI (30 mol%)

Table 6. *$CuSO_4$/NaI- promoting system substrate scope.*

8.1.3. $CeCl_3 \cdot 7H_2O$/CuI

Then, the application of $CeCl_3 \cdot 7H_2O$ instead of iodine was examined in order to obtain better yields and a more general scope of the reaction, with the added value which would be given by a safer procedure.

The conditions for the pilot reaction with $CeCl_3 \cdot 7H_2O$/CuI (Scheme 90) were optimized with respect to temperature and amount of promoting system as illustrated in Table 7.



Scheme 90. *Pilot reaction for the optimization of $CeCl_3 \cdot 7H_2O$/CuI.*

Entry[a]	**Promoter**[b]	**Conditions**		
	$CeCl_3 \cdot 7H_2O$/CuI (1:1)	25 °C[c]	**40 °C**[d]	80 °C[e]
			Yield of 4a	
1	10 mol%	70	80	49
2	**30 mol%**	87	**85**	70
3	60 mol%	60	78	65
4	100 mol%	55	60	62

[a] Reaction conditions: benzylamine (**1a**, 1 mmol) and benzaldehyde (**2a**, 1mmol) were stirred in the presence of $CeCl_3 \cdot 7H_2O$ and $MgSO_4$ and then, after formation of the imine, phenylacetylene (**3**, 1.6 mmol) and CuI were added. The reactions were stopped when a constant composition of the mixture was reached. Isolated yields.
[b] mol% of each *Lewis* acid.
[c] Constant composition reached in 24 h.
[d] Constant composition reached in 15 h.
[e] Constant composition reached in 5 h.

Table 7. *Optimization of the catalyst amount and temperature in the $CeCl_3 \cdot 7H_2O$/CuI promoting system.*

The reaction had good performance already at room temperature, comparable with the results obtained at 40°C that were reached in shorter reaction times. At 80°C better results were not obtained. So the best results was found at 40°C, in 15 hours, with not more than 30 mol% of promoting system.

With 30 mol% of catalyst the difference between the percentage of conversion to GC-MS and the isolated chromatographic yields was smaller, independently of the temperature. While, using a lower or higher quantity there was a discrepancy because of degradation of the product or reagents (Figure 13).

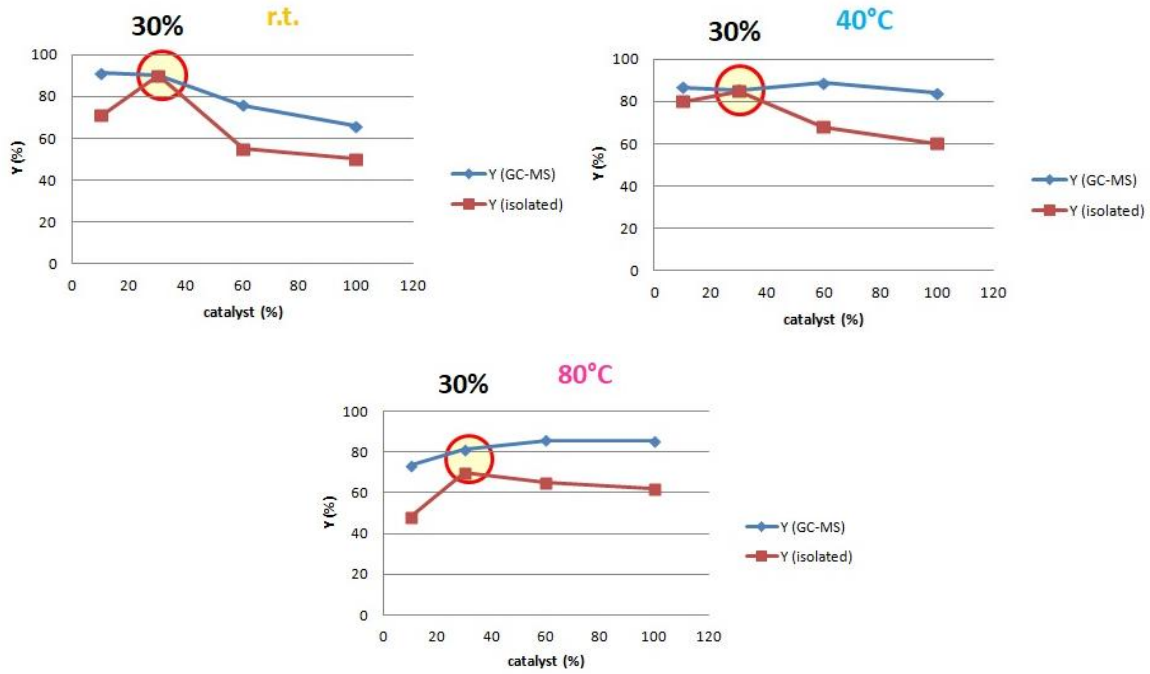
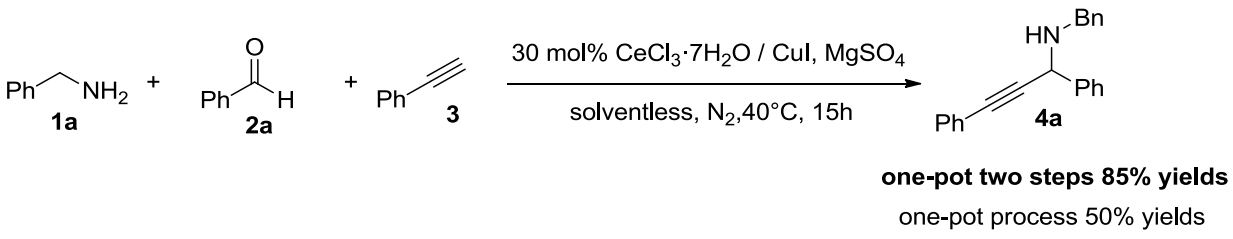


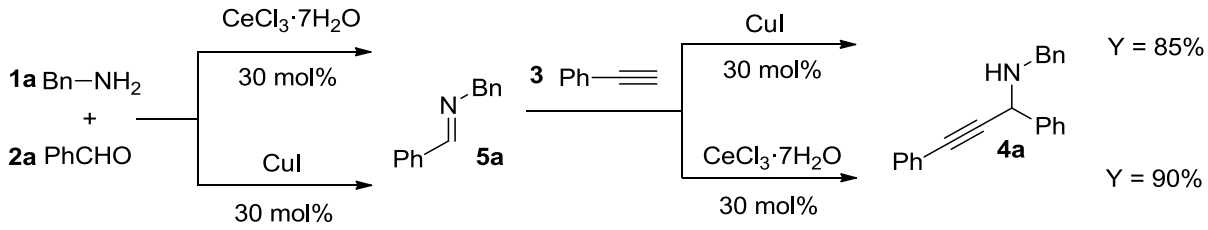
Figure 13. *Comparison*.

The pre-formation of the imine is in fact fundamental to have high yields. When the reaction was performed by mixing all together the reagents and the catalyst in a one-pot process, the propargylamines was afforded in 50% yield. However when the process was splitted in two stages, with first the formation of the imine and then the stepwise addition of the alkyne, the propargylamine was formed in 85% yield (Scheme 91).



Scheme 91. *Importance of pre-formation of the imine.*

Further, the order of addition of the two *Lewis* acids in the synthesis of propargylamine was also investigated (Scheme 92).

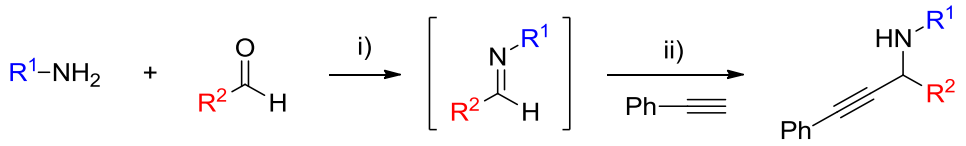


Scheme 92. *Influence of Lewis Acids.*

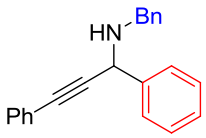
The results were very similar one another either when the order of addition of the two acids was changed: 90% yield of **4a** starting from CuI and 85% starting from $CeCl_3 \cdot 7H_2O$ after 24 hours in both cases. Despite this, the reaction mixtures obtained using CuI first and then $CeCl_3 \cdot 7H_2O$ resulted in more viscous mixtures and were therefore difficult to work up, so the procedure that uses $CeCl_3 \cdot 7H_2O$ in the first step and CuI in the subsequent step was chosen.

The generality the system was then evaluated performing the reaction starting from several *para*-substituted aromatic aldehydes, then aliphatic aldehydes and also with different primary amines.

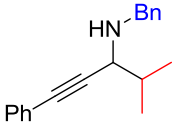
Amines and aldehydes were mixed in the presence of $CeCl_3 \cdot 7H_2O$ and $MgSO_4$ at room temperature under inert atmosphere, and the formation of the corresponding imines, monitored by GC or NMR spectroscopy in some cases, took place generally in 85–90% yield after 15 minutes. Then, phenylacetylene and CuI were added, and the reaction mixture was warmed and left at 40 °C until a constant composition was reached (12–15 h), then worked up. The final propargylamines were isolated in good yields. In case of solid imines (*a*) the reaction was performed with 2 mL of CH_3CN (Table 8).



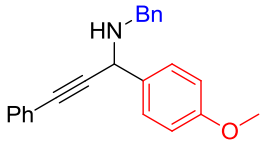
Reaction conditions: i) $MgSO_4$, **$CeCl_3 \cdot 7H_2O$** 30% mol, solventless, N_2, r.t., 0.25 h.
ii) **CuI** 30% mol, solventless, N_2, 40°C, 15 h



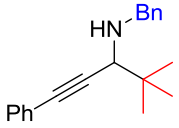
4a, 85%



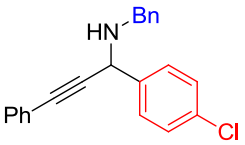
4b, 76%



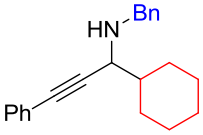
4c, 50%



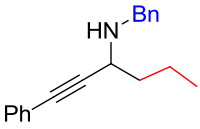
4d, 50%



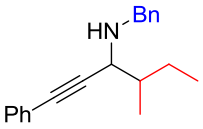
4e, 67%[a]



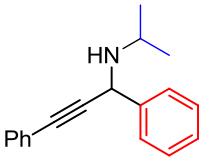
4f, 75%



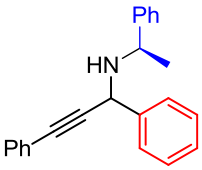
4g, 52%



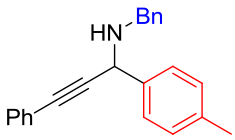
4h, 95%
d.r. 32:68



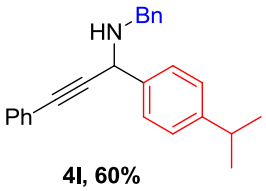
4i, 72%



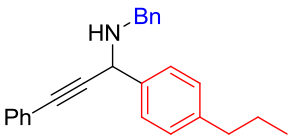
4j, 64%
d.r. 28:72



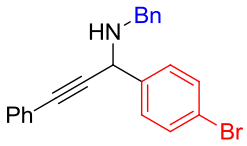
4k, 57%



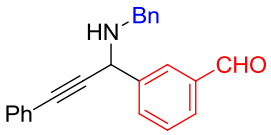
4l, 60%



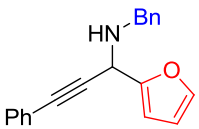
4m, 78%



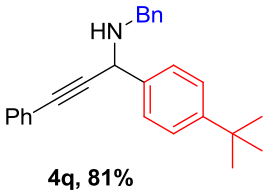
4n, 55%[a]



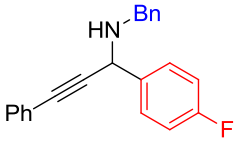
4o, 70%



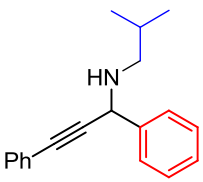
4p, 45%



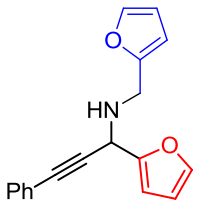
4q, 81%



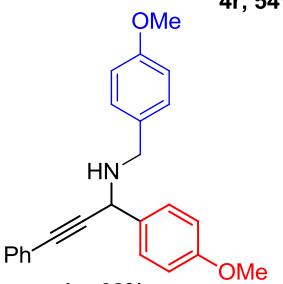
4r, 54%



4s, 71%



4t, 47%



4u, 62%

Table 8. *$CeCl_3 \cdot 7H_2O$/CuI promoting system substrate scope.*

There is not a particular difference of yields between aromatic aldehydes bearing electron donating and/or electron withdrawing groups in para positions. Different heteroaromatic aldehydes have been tested but only the 2-furan-carboxaldehyde reacts, as reported in Table 8.

Aliphatic aldehydes display also good yields with the particular case of (±)2-methyl-butanal for which a quantitative yield is reached with a moderate stereoselectivity. Interestingly, for this substrate, the diastereomeric ratio of product coming from the $CeCl_3 \cdot 7H_2O$/CuI promoting system is reversed with respect to the same reaction promoted by $CuSO_4$/NaI. This together with the analysis of by-products coming from different side reaction could suggest two distinct possible mechanism.

Different primary amines and also chiral one have been considered in combination with various aldehydes obtaining good yields.

8.1.4. Comparison of two systems

Generally, the $CuSO_4$/NaI-promoted reactions are faster (2-5 hours) and better yields are obtained with aliphatic aldehydes than with aromatic aldehydes, although the yields are lower than the ones obtained using $CeCl_3 \cdot 7H_2O$ promoting system.

The $CeCl_3 \cdot 7H_2O$ promoting system shows a wider applicability and results in good yields with both with aliphatic and aromatic aldehydes as well as with different amines even in longer reaction times (Table 9).

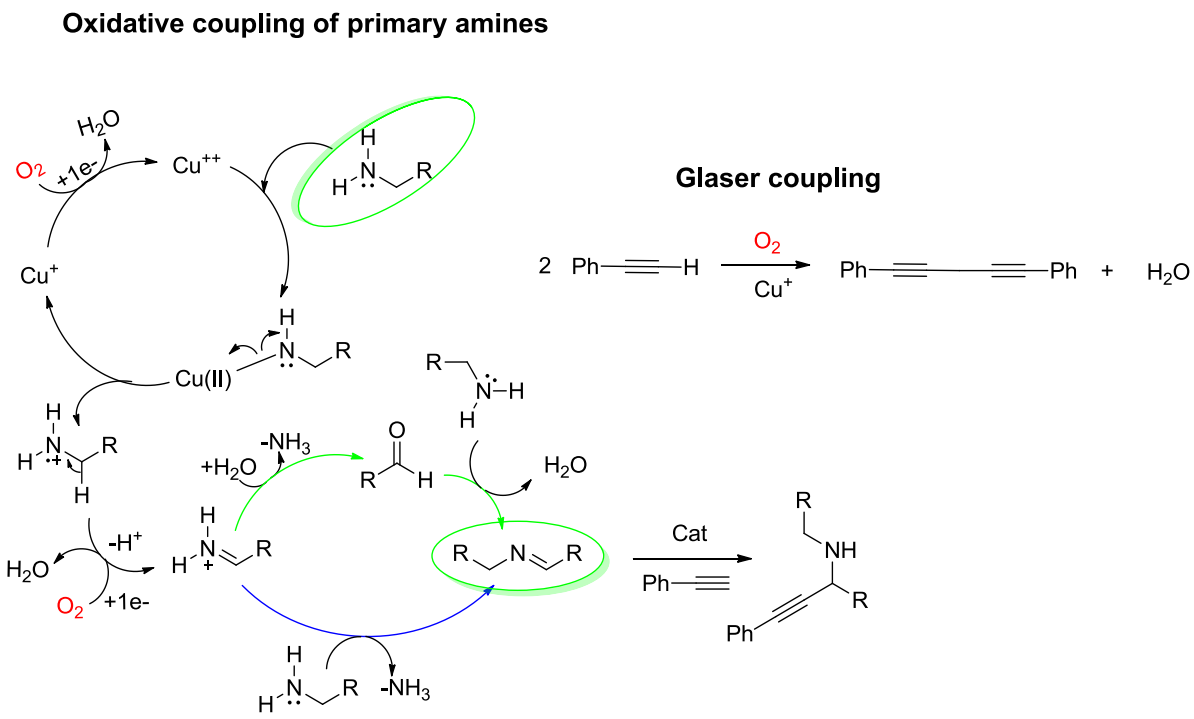
Parameter	$CuSO_4$/NaI	$CeCl_3 \cdot 7H_2O$/CuI
Yield	Up to 62%	Up to 95%
Versatility	Narrower	Wider
Time	Fast (2-8 h)	Slow (15 h)
Cost	Simple, accessible and easy handled inorganic salts	

Table 9. *Comparison of two system.*

8.1.5. Two different mechanism

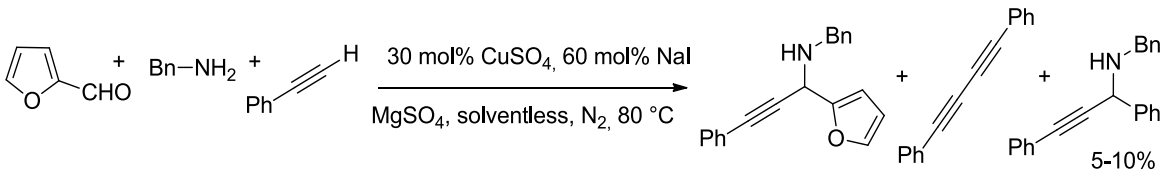
On the basis of some observations which are the diverse diastereoselectivity for the propargylamines obtained from chiral starting materials and the by-products detected in the $CuSO_4$/NaI catalyzed reaction it was hypothesized that the $CuSO_4$/NaI and $CeCl_3 \cdot 7H_2O$ promoted reactions proceed according to two different mechanisms.

The reaction promoted by $CuSO_4$/NaI clearly takes place under oxidative coupling conditions, as demonstrated by the dimerization of phenylacetylene and by the presence of small percentages of derivatives obtained by oxidative coupling of the starting amine. (Scheme 93)



Scheme 93. *Side-reactions in $CuSO_4$/NaI system.*

In Figure 14 is depicted the chromatogram of the reaction of furfuraldehyde (Scheme 94). It is clearly visible the peak of a second propargylamine that corresponds to the product of the reaction of benzaldehydes.



Scheme 94. *$CuSO_4$/NaI promoting reaction with furfuraldehyde.*

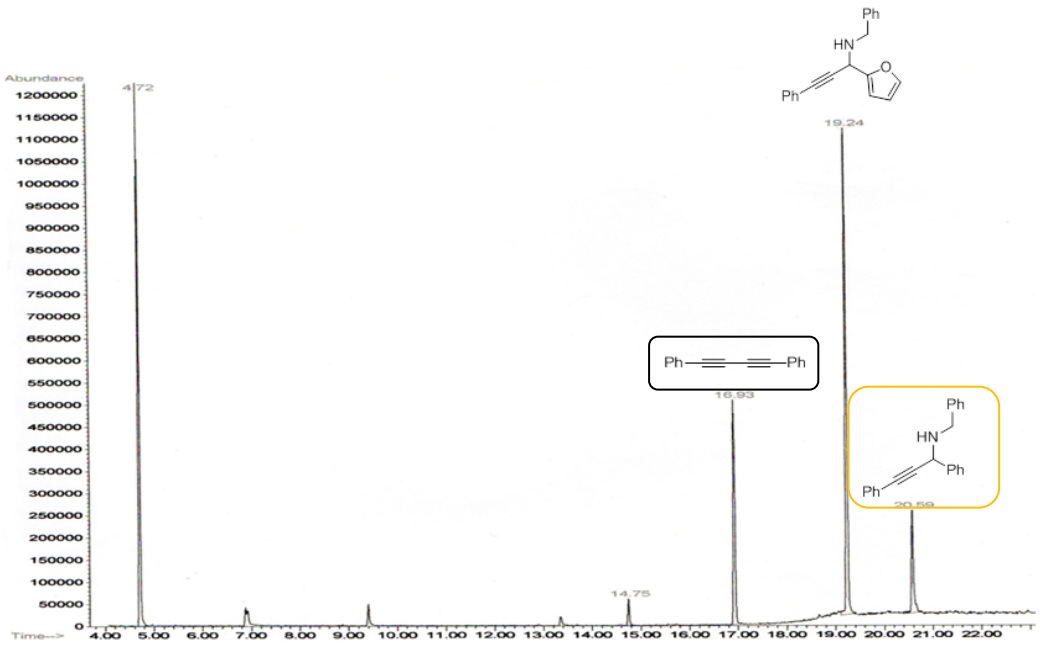
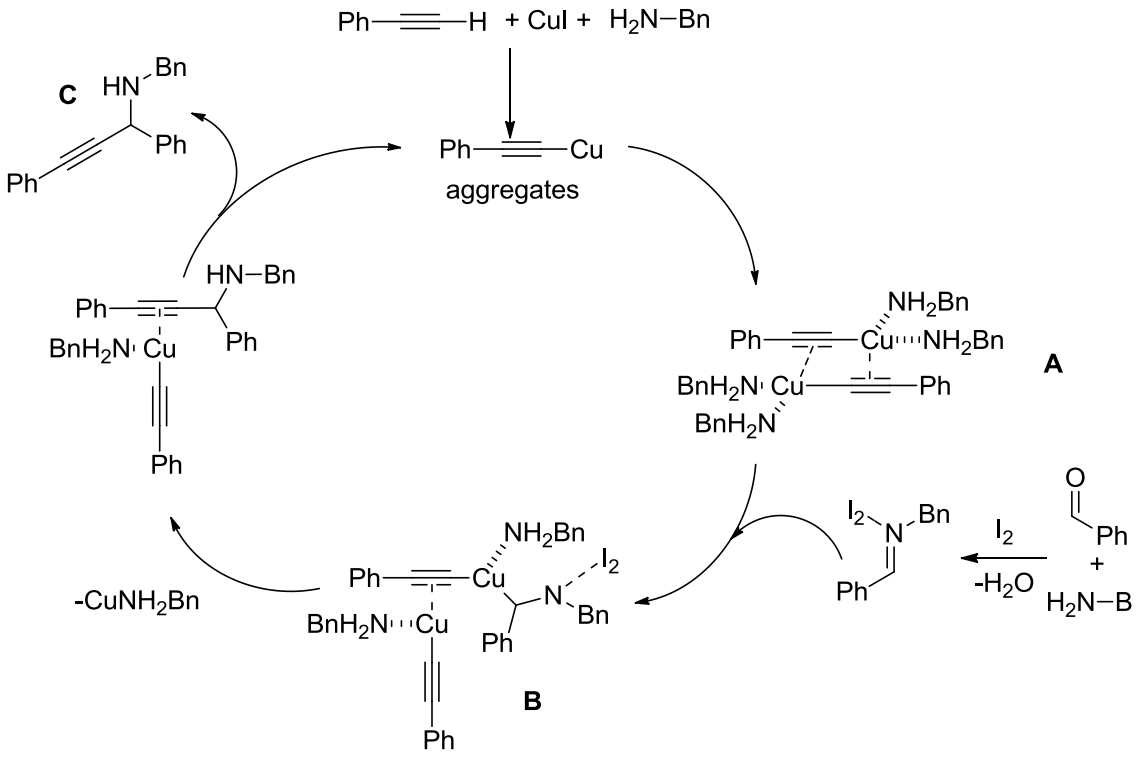


Figure 14. *Chromatogram of the presence of by-products.*

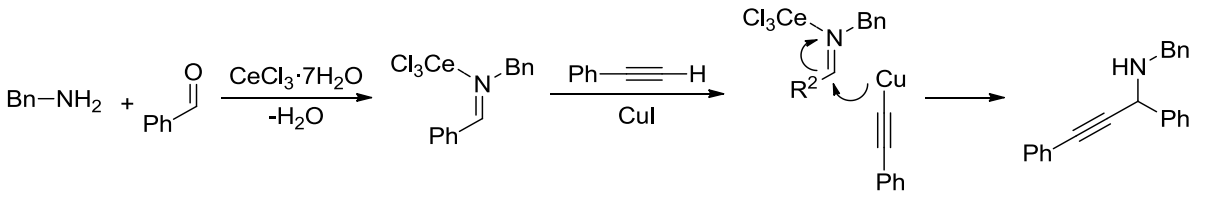
The highlighted product indicates the presence in the reaction mixture of N-benzylidene-1-phenylmethanamine produced by oxidative coupling of benzylamine, probably due to little percentages of oxygen in the N_2 atmosphere of the reaction vessel, according to the mechanism depicted in Scheme 93.

Based on experimental observation and on literature, a hypothesis of mechanism for the $CuSO_4$/NaI promoting system is shown in Scheme 95. The copper acetylide forms a binuclear complex **A** that reacts with the imine generated in situ from aldehydes and amines, activated by coordination with the iodine, to form the key-intermediate **B**. From this the final propargylamine **C** is formed after the release of the two copper ligands.



Scheme 95. *Proposed mechanism for $CuSO_4$/NaI promoting system.*

The by-products found in the $CuSO_4$/NaI promoted reaction are completely absent in the reactions promoted using $CeCl_3 \cdot 7H_2O$/CuI, which instead gives better results upon pre-forming the imine, as just seen previously. In these reactions it possible to assume that the cerium activates the imine towards nucleophilic attack by the copper acetylide (Scheme 96).

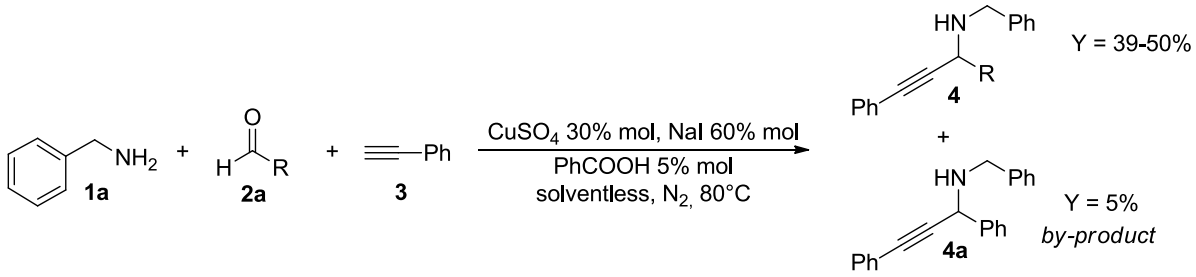


Scheme 96. *Proposed mechanism for $CeCl_3 \cdot 7H_2O$/CuI promoting system.*

8.2. From by-products to new strategies

8.2.1. Oxidative coupling of primary amines

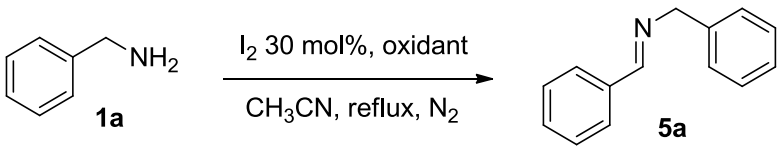
The parasite reaction that led to the formation of variable amount of propargylamine **4a** obtained by oxidative coupling of the starting amine, when aldehydes other than benzaldehydes were used in the $CuSO_4$/NaI catalyzed reactions (precursor of CuI/I_2) was then taken into account (Scheme 97).



Scheme 97. *Parasite reaction in $CuSO_4$/NaI promoting system.*

In order to have a major comprehension of this reaction and to explore if it could become part of a wider synthetic methodology, the possibility to obtain imines by oxidative coupling of primary amines was studied.

Imines are a important class of compounds due to their versatile applications as synthetic intermediates. Among the existing methods for imine synthesis, the oxidative self-coupling of amines to imines has attracted more attention, because of the clear advantage to avoid the use of reactive and easily oxidable aldehydes. In literature Cu^I catalyzed oxidative coupling of primary amine is widely explored[36] whereas iodine has never been applied in such reaction. Iodine, however, must be paired with a terminal oxidant to obtain imines from primary amines (Scheme 98).



Scheme 98. *Pilot reaction for oxidative-coupling reaction.*

A screening to find the best oxidants was performed with the same amount of iodine generated in the $CuSO_4$/NaI promoting system (that is 30 mol%) of the pilot reaction using benzylamine in CH_3CN as solvent at refluxing conditions. The results obtained are collected in Table 10.

Entry	Oxidant	mmol/mol 1	5a (Y%) [a]	1a (Y%) [a]
1	MCPBA	1.5	40	60
2	H_2O_2	1.5	19	81
3	Oxone	1.5	56	44
4	Luperox	1.5	24	76
5	TBHP	1.5	86	14
6	TBHP	2	93	7

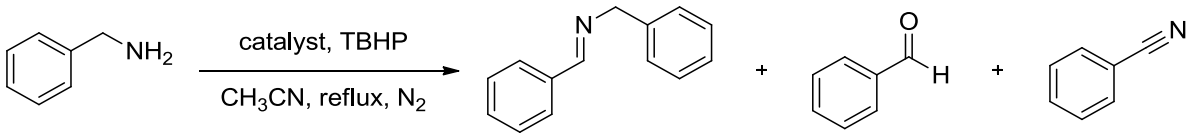
All the reaction were performed mixing 2 mmol of **1a** in CH_3CN with I_2 under N_2 atmosphere adding the oxidant diluited in CH_3CN dropwise until a constant composition of the mixture was reached.
[a]Gas-chromatographic yield

Table 10. *Screening of the oxidants.*

Hydrogen peroxyde and Luperox gave the lower yields, 19% and 24% (entry 2, 4) of the desired imine, even after several hours of reaction. Imine formation using I_2/MCPBA did not give satisfying results as well obtaining a yield of 40% (entry 1). Test with Oxone as oxidant (entry 3) provided the imine product in 56% yield, which is still not acceptable. Finally, TBHP showed the best performance amongst the oxidants tested and with an increase from 1.5 to 2 equivalents afforded an excellent yield (entry 5,6).

A second screening was done to determine the better amount of iodine (Table 11). Despite the good results obtained with 30% of I_2, the possibility to obtain good results by lowering the catalyst loading was checked to develop a methodology more friendly for the environment.

The major by-products of the reactions are the aldehyde deriving from hydrolysis of the imine and the nitrile deriving from the double oxidation of the amine as known in literature.



1a **5a** **2a** **7a**

Entry	Catalyst (% mol)	Oxidant (equiv.)	Time (min)	5a[a]	1a[a]	2a[a]	7a[a]
1	I_2 (0)	TBHP (2)	60	59	34	0	2
2	**I_2 (1)**	**TBHP (2)**	**60**	**98**	0	0	0
3	I_2 (5)	TBHP (2)	60	77	0	9	7
4	I_2 (10)	TBHP (2)	60	78	0	4	9
5	NaI (2)	TBHP (2)	15	81	8	0	1
6	I_2 (1)	without	60	1	95	0	0
7	I_2 (1)	TBHP (3)	45	92	2	2	1
8	I_2 (1)	TBHP (4)	60	34	0	44	2

All the reaction were performed mixing 2 mmol of **1a** in CH_3CN with the catalyst under N_2 atmosphere adding the TBHP diluited in CH_3CN dropwise until a constant composition of the mixture was reached.
[a] Gaschromatographic yields.

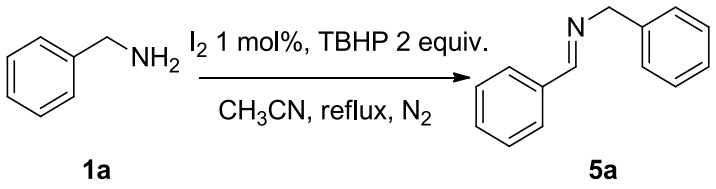
Table 11. Screening of the iodine catalyst.

Lowering the loading of the catalyst to 10 mol% (entry 4) produced a result quite promising (78% GC conversion) with no residual amine detected. This result encouraged to perform other tests with even lower amount of I_2. Moving to 5 mol% (entry 3) did not provide any substantial change in the outcome of the reaction, while 1 mol% of iodine (entry 2) afforded an excellent GC conversion of 98%. A reaction was performed using NaI as catalyst (entry 5). In those conditions the imine is formed in very short time (about 15 minutes) in slightly lower yield (81%) and with little percentage of benzaldehyde and benzonitrile. After this time the conversion of the imine to the known by-product started. Blank tests were also carried out without iodine (entry 1) or without oxidant (entry 6): in the first case only 59% of desired imine is detected in the reaction mixture, while in the second case the reaction didn't not work at all. A further test was also carried increasing the amount of TBHP (entry 7, 8): a slight decrease in the yield is detected when 3

equivalents of TBHP were used, while increasing to 4 equivalents the formation of benzaldehydes prevailed over the desired imine (44% vs 34%).

Hence, the best conversion of the amine to the corresponding imine by oxidative coupling is obtained with 1 mol% of iodine with 2 equivalent of TBHP (entry 2).

Once discovered the best reaction conditions, the pilot reaction was monitored over the time to have a better understanding about the mechanism. Samples from the reaction mixture taken every 10 minutes were analyzed, after workup, by gas chromatography (Figure 15).



1a **5a**

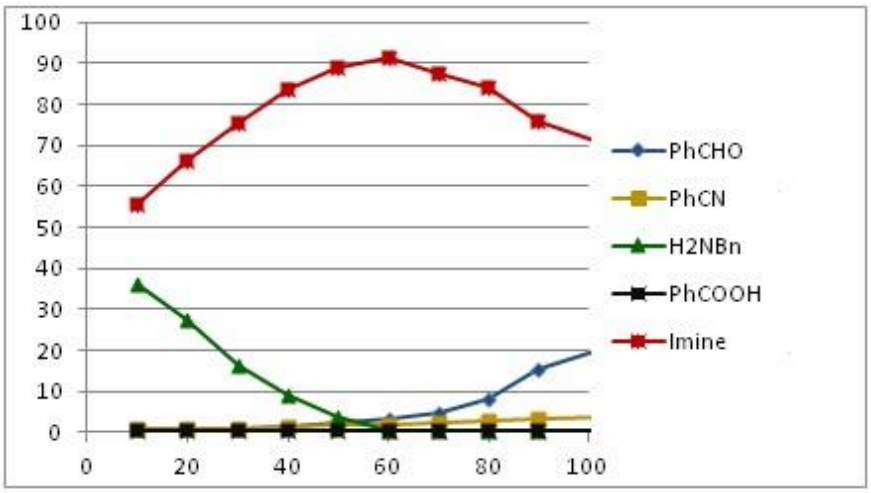
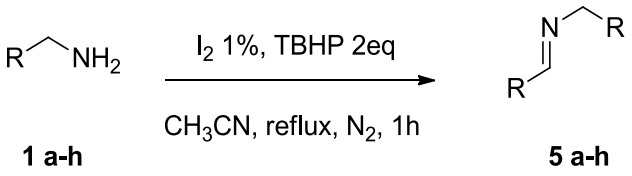


Figure 15. *Monitoring of imine formation from benzylamine.*

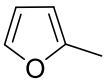
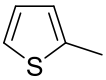
The reaction is quite fast: just after 10 minutes 55% of conversion in imine is observed which reach the maximum in 1 hour. After 60 minutes, a decreasing of the product is observed, due to degradation of the imine, as confirmed by the increasing amount of aldehyde, deriving from the hydrolysis of the imine itself. Detection of a little amount of benzoic acid is due to the subsequent oxidation of the aldehyde, while benzonitrile comes from the oxidation of the imine.

The scope of the reaction was extended to a series of aliphatic and aromatic amines. Different para-substituted benzylic primary amines were studied to understand if the presence of a substituent could influence the reaction outcome.

Heteroaromatic primary amines such as furfurylamine and 2-picolylamine were then tested, and behave as the benzylic amines. The overall results are reported in Table 12.



1 a-h **5 a-h**

Entry	1	R	5 (Y%)[a]	5 (Y %)[b]
1	**1a**	Ph	98	87
2	**1b**	*p*-Cl-Ph	93	85
3	**1c**	*p*-F-Ph	96	77
4	**1d**	*p*-OMe-Ph	91	91
5	**1e**		85	76
6	**1f**		83	73
7	**1g**	CH_2Ph	32[c]	-
8	**1h**	*n*-C_3H_7	61[c]	-

[a] Gascromatographic yields
[b] Isolated yields
[c] Data obtained by GC-MS of the crude

Table 12. *Applications of I_2/TBHP.*

The reaction works quite well with benzylamine and *p*-substituted aromatic amines. The pilot reaction (entry 1) reports the formation of the imine in a 98% GC conversion and 87% yield. *p*-Chloro, fluoro and methoxy benzylamines (entries 2,3 and 4, respectively) give GC conversions higher than 90% in every case, and yields ranging from 77 to 91%.

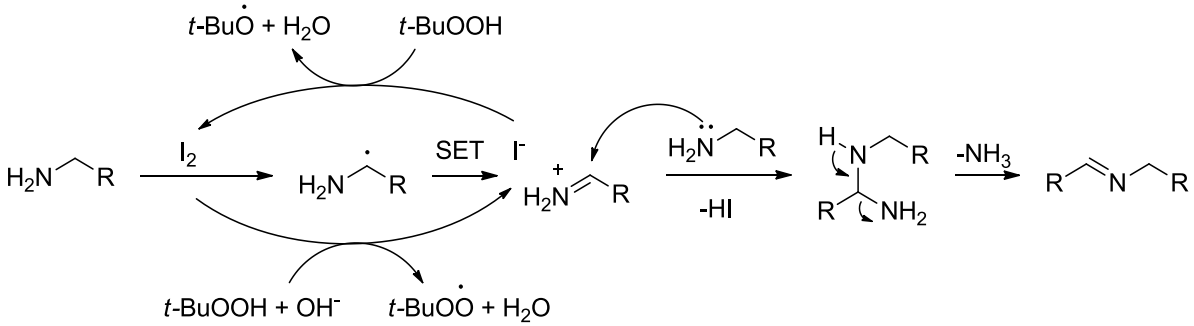
Moving to heteroaromatic amines results are still encouraging with GC conversions higher than 80% in the case of furfurylamine (entry 5) and 2-thiophenemethylamine (entry 6) with an isolated yield of 76% for the first one and 83% for the second one.

The pure imine are obtained without any chromatographic separation that could lead to the degradation of the product, but through a simple exctraction with 5% of $Na_2S_2O_3$.

Non-benzylic amines, however, do not provide high conversion to the desired product. In fact, phenethylamine give only 32% of conversion (entry 7), while *n*-butylamine provide 61% gas chromatographic conversion (entry 8). Probably, oxidative coupling of aliphatic amines is disadvantaged because the resulting imine is not stabilized by conjugation of the azomethinic bond with phenyl ring. Furthermore, the reaction with *n*- butylamine was performed at room temperature because of the low boiling point (78°C) of the starting material.

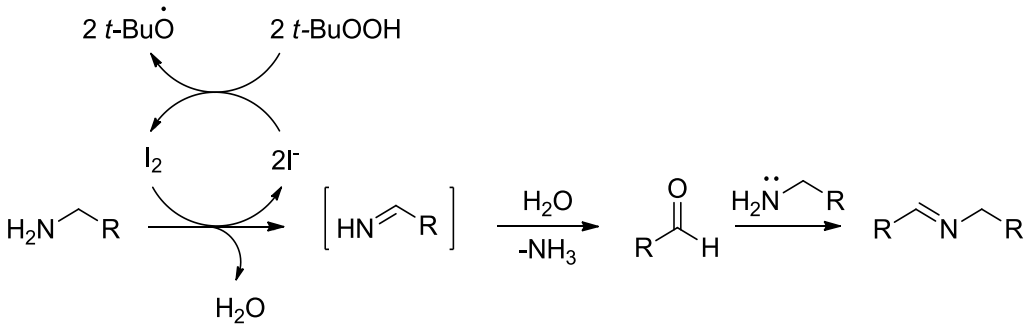
According to literature and mainly on the role of iodine, two hypothesis of mechanism for the oxidative coupling of primary amine to give imines can be done.

In the first hypothesis iodine reacts with tert-buthylhydroperoxide forming an hydroperoxyl radical that reacts with the starting amine and forms a radical on the carbon atom in α position to the substituted phenyl ring (or to the eterocyclic ring). Then a Single Electron Transfer process affords to the electrophilic iminium cation that undergoes to nucleophilc attack by a second amine molecule. Elimination of ammonia affords to the final imine (Scheme 99)



Scheme 99. *First hypothesis mechanism.*

In the second hypothesis, direct oxidation of the starting amine by iodine affords to an iminic intermediate, that eliminates ammonia affording to the aldehyde. Subsequent condensation with a second molecule of amine affords to the final imine (Scheme 100).



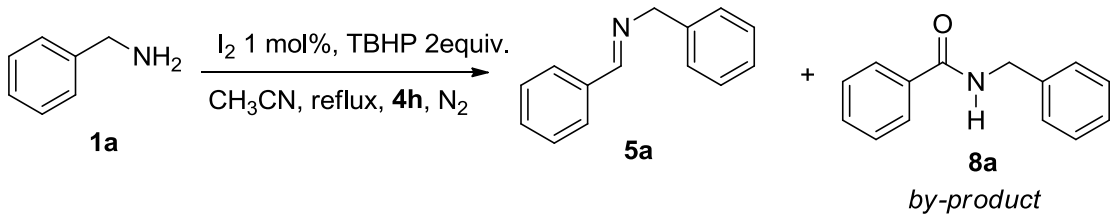
Scheme 100. *Second hypothesis mechanism.*

Further studies are ongoing to ascertain the nature of the mechanisms. At the moment neither an in situ iodination based oxidative coupling pathway may be excluded.

8.2.2. Possible application of imines

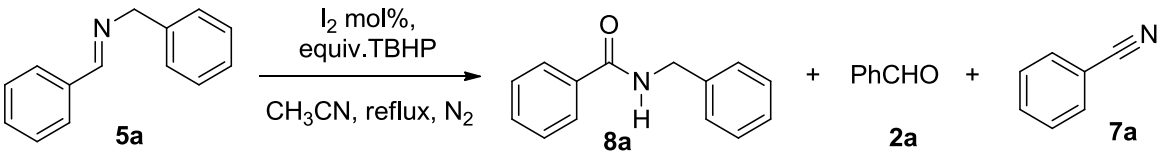
The possibility to extend the use of the I_2/TBHP oxidant system to the further oxidation of imines to amides was explored.

The starting point arises from the kinetic study of the pilot reaction in the synthesis of imine. In fact if the reaction is left to react for more than 4 hours a 35% of *N*-benzylamide is found as a by-product (Scheme 101).



Scheme 101. *Possible amide formation.*

With this aim, imines were prepared following the previously reported procedure and used as crude for the following transformation. Then, the screening of the reaction conditions has been performed, with respect to catalyst, oxidant and solvent.



Entry	I_2 (mol %)	TBHP (equiv.)	Time[a] (h)	8a%[b]	5a%[b]	2a%[b]	7a%[b]
1	1	1	1.5	3	77	5	2
2	1	2	3	29	20	28	7
3	1	3	3	38	7	35	11
4	1	4	5	38	0	25	9
6[c]	**1**	**3**	**5.5**	**46**	8	20	3
7	5	1	3	12	49	21	7
8	5	2	3	30	11	36	12

All the reaction were performed with 1 mmol of **5a** in CH_3CN with the catalyst under N_2 atmosphere adding the TBHP diluited in CH_3CN dropwise until a constant composition of the mixture was reached.
[a] The reported times indicated that beyond that time the concentration of by-products increases at the expense of the maximum concentration of amide obtained
[b] The reported N-benzylbenzamide concentration is the maximum obtained by monitoring the reaction over time. Beyond each reaction time reported, the concentration of by-products increases at the expense of that of the amide. GC-MS yields.
[c] Reaction performed in toluene as solvent

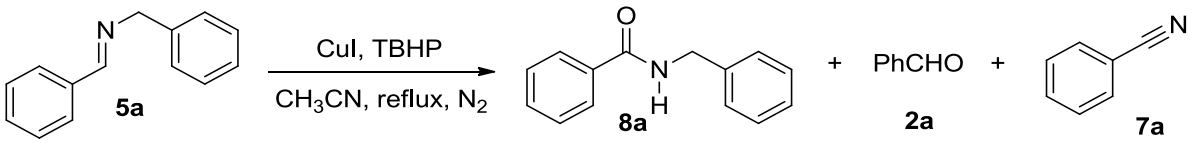
Table 13. *I_2/TBHP for the synthesis of amides.*

Initially, the amount of iodine was fixed at 1 mol% while the amount of TBHP was changed from 1 to 4 equivalent: a 38% of amide was obtained (entry 3, 4) using independently 3 or 4 equivalent TBHP with an increasing in the reaction time. However, in both cases there is the completely consumption of the starting imines but with the formation of large quantities of by-products, mainly benzaldehyde.

On the other hand, increasing the amount of iodine to 5 mol% (entry 7,8), afforded similar results after 3 hours of reaction. There is not in fact a big difference between 1 or 2 equivalent of TBHP. In both cases there is still a substantial amount of the starting imine (49% entry 7, 11% entry 8) and more benzaldehyde than the desired *N*-benzylbenzamide (21% entry 7, 36% entry 8).

The reaction was explored at higher temperature, in toluene, using 1 mol% and 3 equivalents of TBHP which led to a 45% of amide. This is the best result obtained so far, but with the disadvantage of a longer reaction time and a low yield yet.

According to literature, many oxidative coupling of aldehydes or alcohols and amines are catalyzed by copper salts.[36] So copper iodide was taken in consideration which gather the advantages of both metal catalyzed reactions and the effect iodide with the scope to obtain higher conversion (Table 14).



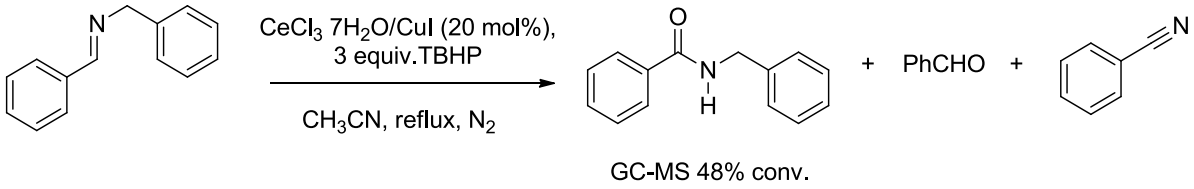
Entry	CuI (mol%)	TBHP (equiv.)	Time (h)[a]	8a%[b]	5a%[b]	2a%[b]	7a%[b]
1	1	2	24	7	49	3	0
2	5	2	24	35	3	12	30
3	10	2	24	35	37	11	15
4	20	2	2	17	36	20	25
5	10	3	24	52	37	2	2.6
6	40	3	2	43	0	32	18
7	**20**	**3**	**2**	**47**	0	29	16
8	10	4	2	38	0	24	18
9	20	4	2	37	0	17	29

All the reaction were performed with 1 mmol of **5a** in CH_3CN with the CuI under N_2 atmosphere adding the TBHP diluited in CH_3CN dropwise until a constant composition of the mixture was reached.
[a] The reported times indicated that beyond that time the concentration of by-products increases at the expense of the maximum concentration of amide obtained
[b] The reported N-benzylbenzamide concentration is the maximum obtained by monitoring the reaction over time. Beyond each reaction time reported, the concentration of by-products increases at the expense of that of the amide. GC-MS yields.

Table 14. *CuI/TBHP for the synthesis of amides.*

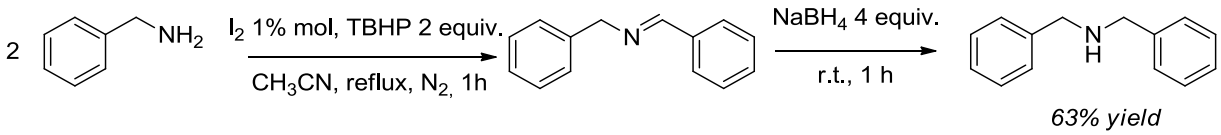
The pilot reaction was performed with variable amount of copper iodide from 1 to 40 mol% maintaining fixed the TBHP at 2 equivalents (entry 1-4). Only a 35% of amide was obtained after 24 hours with the use independently of 5 or 10 mol% of CuI (entries 2,3). The amount of TBHP was increased (entries 5-9) and with 3 equivalents of TBHP and 20 mol% of CuI the imine was completely converted into amide in just 2 hours but with the corresponding formation of non negligible by-products (entry 7).
Unfortunately, from the experiments carried out until now the concentration of *N*-benzylbenzamide did not exceed 50% of GC-conversion.

It was also tried $CeCl_3 \cdot 7H_2O$ in combination with CuI with the aim to increase the reactivity of the imine but also in this case the conversion in amide was not higher than 48% (Scheme 102).



Scheme 102. *$CeCl_3 \cdot 7H_2O$/CuI for the synthesis of amides.*

Parallel studies are underway to develop a synthetic methodology to obtain secondary amines from primary ones, by reduction of the imines formed in the first step by oxidative coupling. To date only one test has been performed employing $NaBH_4$ obtaining the desired dibenzylamine in a promising 63% yield (Scheme 103).

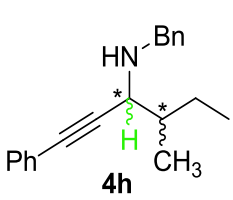


Scheme 103. *Reduction to secondary amines.*

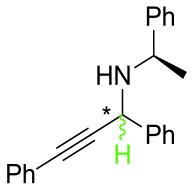
8.3. Diastereoselective synthesis of chiral propargylamines

Asymmetric synthesis of propargylamines has seen a growing interest and can be realized in an entioselective or diastereoselective way. The first has been widely studied with the development and corresponding application of several chiral ligands in combination with various metal catalyst. The second, instead, has been accomplished mainly with secondary amines and in particular with derivatives of *L*-proline containing different nitrogen or oxygen atoms or with sulfinylimines and phosphonylimines.[116]

The different stereoselectivity observed using the $CeCl_3 \cdot 7H_2O$/CuI or $CuSO_4$/NaI system in the reactions performed starting from (±)2-methylbutanal or (R)-(+)phenylethylamine was taken in consideration with the aim to develop a diastereoselective synthesis of secondary propargylamine in which the chiral information comes from the substrate, amines or aldehydes (Figure 16).



4h



4j

Promoter	**Y**	**d.r.** (A:B)	**Y**	**d.r.** (A:B)
$CuSO_4$/NaI	62%	(79:21)	59%	(32:68)
$CeCl_3 \cdot 7H_2O$/CuI	95%	(32:68)	64%	(28:72)

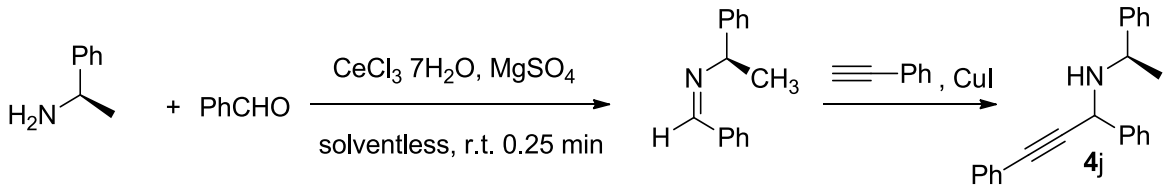
Figure 16. *Different selectivity.*

As almost all the chiral propargylamines obtained are unknown in literature and their absolute configuration is not assigned yet, the diastereomeric ratio (d.r.) will be written according to the position of the signal in the ^{1}H-NMR spectrum of the proton bonded to the stereogenic center formed in the reaction highlighted in green.

This signal in fact appear always more deshielded in one diastereomer than in the other; so the diastereomer that shows the more deshielded signal is named ***A*** and the one that shows the less deshielded signal is named ***B*** and this label is used along the chapter.

The pilot reactions were performed starting in turn from (R)-(+)-phenylethylamine and (±)-2-methylbutanal with both promoting systems in different reaction conditions.

The $CeCl_3 \cdot 7H_2O$/CuI was considered first, performing the reaction reported in Scheme 104 starting from (R)-(+)-phenylethylamine, benzaldehyde and phenylacetylene at 80 °C with different amount of catalyst and gave the results reported in Table 15.



Scheme 104. *$CeCl_3 \cdot 7H_2O$/CuI with (R)-(+)-phenylethylamine.*

The yields are increased going from 3 mol% to 15 mol% of $CeCl_3 \cdot 7H_2O$/CuI, maintaining in each case the same stereoselectivity. The product is obtained in less time and in higher yield using 15 mol% at 80 °C (entry 3). Higher temperature or amount of catalyst did not change the d.r. (entry 4).

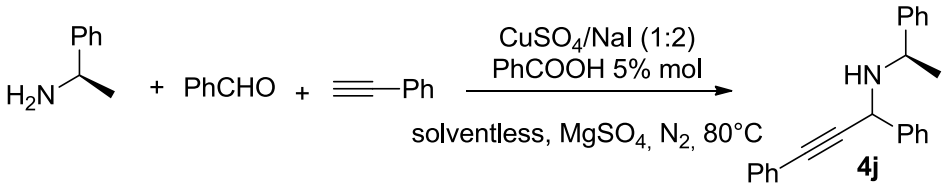
Entry	$CeCl_3 \cdot 7H_2O$ /CuI (1:1) mol%	t (h)	T (°C)	4j (%)[a]	d.r. (A:B)
1	3	22	80	49	28:72
2	10	3	80	63	29:71
3	15	6	80	84	31:69
4	30	15	40	64	28:72

All the reaction were performed mixing (R)-(+)-phenylethylamine (1 mmol) and benzaldehyde in the presence of $CeCl_3 \cdot 7H_2O$ and $MgSO_4$ and then, after formation of the imine, phenylacetylene (1.6 mmol) and CuI were added. The reactions were stopped when a constant composition of the mixture was reached.

[a] Chromatographic yields

Table 15. *Results obtained with (R)-(+)-phenylethylamine and $CeCl_3 \cdot 7H_2O$/CuI.*

Then, for the same pilot reaction (Scheme 105), the $CuSO_4$/NaI system was explored and, also in this case, different amounts of the promoter are considered always maintaining the ratio 1:2.



Scheme 105. *$CuSO_4$/NaI with (R)-(+)-phenylethylamine.*

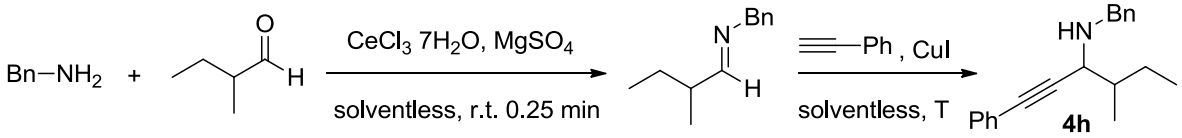
Only when a 15 mol% of $CuSO_4$ and 30 mol% of NaI are used the propargylamine is formed with a good stereoselectivity, that is the same to the one observed in the case of $CeCl_3 \cdot 7H_2O$/CuI. Lower (10:20) or higher (30:60) amounts didn't allow the formation of the target molecule (Table 16).

Entry	$CuSO_4$(mol%)	NaI (mol%)	t (h)	4j (%)[a]	d.r. (A:B)
1	10	20	2	n.r.	-
2	15	30	3	57	65:35
3	30	60	3	n.r.	-

All the reactions were performed mixing (R)-(+)-phenylethylamine (1 mmol), benzaldehyde (1 mmol) and phenylacetylene (3 mmol) in the presence of $CuSO_4$/NaI until a constant composition of the mixture was reached.
[a] Chromatographic yields

Table 16. *Results obtained with (R)-(+)-phenylethylamine and $CuSO_4$/NaI.*

The best reaction conditions found for each promoting system using (R)-(+)-phenylethylamine were then applied to (±)2-methylbutanal. The pilot reaction was first considered for $CeCl_3 \cdot 7H_2O$/CuI system (Scheme 106).



Scheme 106. *$CeCl_3 \cdot 7H_2O$/CuI with (±)2-methylbutanal.*

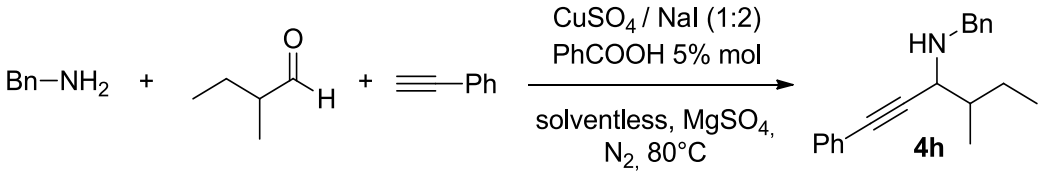
From the result reported in Table 17, a change in the d.r. is observed which strongly depends on the amount used of $CeCl_3 \cdot 7H_2O$/CuI (entry 1, 2) and also on the temperature for which an inversion occurs (entry 2,3) (Table 17).

Entry	$CeCl_3 \cdot 7H_2O$/CuI (1:1) mol%	T (°C)	t(h)	4h (%)[a]	d.r. (A:B)
1	10	80	18	86	43:27
2	15	80	24	67	77:23
3	30	40	15	95	32:68

All the reaction were performed mixing (±)-2-methylbutanal (1 mmol) and benzylamine in the presence of $CeCl_3 \cdot 7H_2O$ and $MgSO_4$ and then, after formation of the imine, phenylacetylene (1.6 mmol) and CuI were added. The reactions were stopped when a constant composition of the mixture was reached.
[a] Chromatographic yields

Table 17. Results obtained *with (±)2-methylbutanal and $CeCl_3 \cdot 7H_2O$/CuI.*

Then the $CuSO_4$/NaI promoting system was evaluated with the chiral aldehyde obtaining that also in this case the d.r. is influenced by the reaction conditions (Table 18).



Entry	$CuSO_4$ (mol%)	NaI (mol%)	t (h)	4h (%)[a]	d.r. (A:B)
1	15	30	3	57	46:54
2	30	60	2	62	79:21

All the reactions were performed mixing benzylamine (1 mmol), (±)-2-methylbutanal (1 mmol) and phenylacetylene (3 mmol) in the presence of $CuSO_4$/NaI until a constant composition of the mixture was reached.
[a] Chromatographic yields

Table 18. Results obtained *with (±)2-methylbutanal and $CuSO_4$/NaI.*

From the preliminary data obtained until now the stereoselectivity of **4j** doesn't change using $CeCl_3 \cdot 7H_2O$/CuI or $CuSO_4$/NaI whereas in the case of **4h** it is strongly affected by the reaction conditions.

8.3.1. Assignement of absolute configuration of product 4j

On propargylamine **4j**, a theoretical study was carried out to assign the absolute configuration that is still unknow. The calculations were carried out in collaboration with prof. Corrado Bacchiocchi of University of Camerino and Dr. Manuel Petroselli, post-doc at the University of Shanghai.

The approach followed consists in the theoretical calculation of the structure of the most stable conformer of each diastereomer and of the corresponding simulated ^{1}H-NMR spectrum which will be then compared with the real recorded spectrum.

The first aspect that need to be clarified is if the two diastereomers have actually just one conformer in solution or not. The calculations gave an affirmative answer for both epimers, with a percentage of the majority conformer of 99.5% for RR and 97% for RS.

The Figure 17 shows the lowest energy conformer of the RS diastereomer on the left and the RR one on the right, with the same orientation of the atoms 10,21,17.

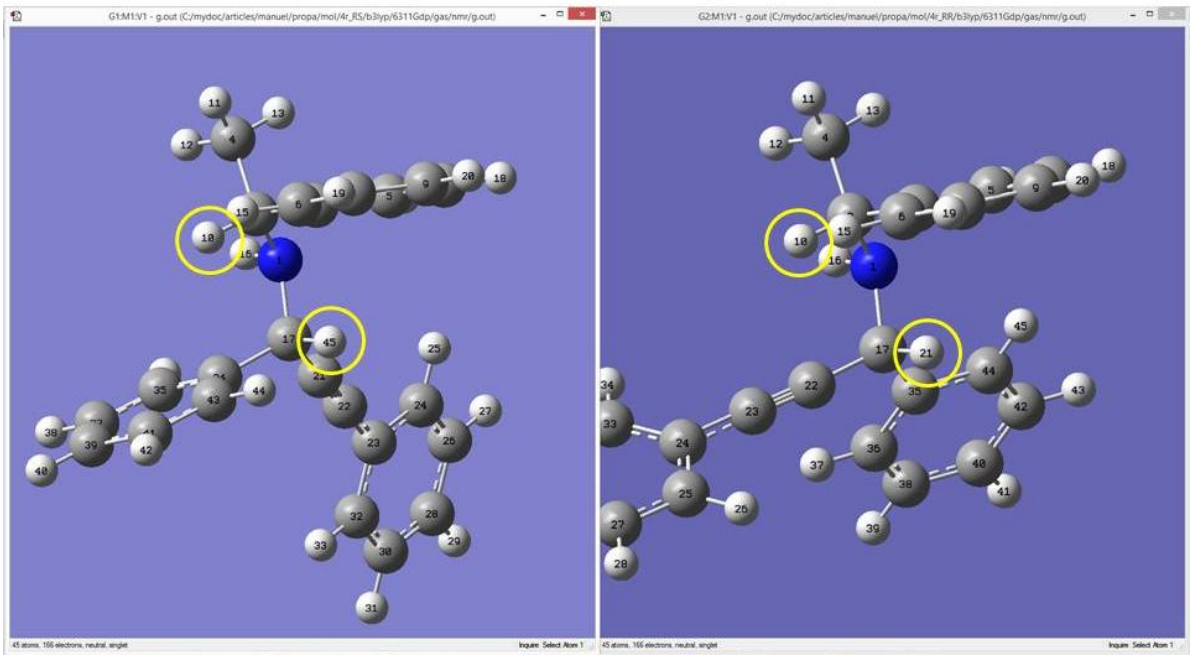


Figure 17. *RS diastereomer (on the left) and the RR one (on the right).*

The proton marked with the number 10, highlighted by the yellow circle, is located on the stereocenter of the starting chiral amine. In the most stable conformer of the RS diastereomer the proton 10 is shielded by the phenyl group bonded to the second stereocenter, the one formed in the reaction, while in the RR diastereomer this doesn't happen. This difference in the effects incurred of the protons of the two diastereomers is well described by the comparison between the ^{1}H-NMR spectra from diastereomer A and B that show a difference in the chemical shift of proton 10 of almost 1 ppm (Figure 18).

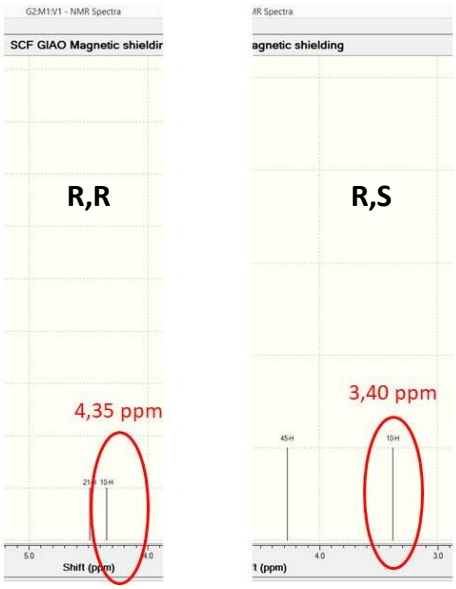


Figure 18. *Difference in chemical shifts for H10.*

Proton 21 and proton 45 are located on the stereocenter created after the reaction. Both protons are shielded by effect of the phenyl ring of the chiral center of the original amine and the triple bond contribute similarly to both stereoisomers.

In the lower energy conformer of diastereomer RS proton 45 results coplanar with respect to the phenyl ring of the original benzaldehydes while the corresponding proton 21 in diastereomer RR is located far from the same phenyl ring.

This situation produces a slight deshielding of proton 45 with respect to proton 21, that results in a difference of only 0.20 ppm of the corresponding signal in the calculated ^{1}H-NMR spectrum (Figure 19).

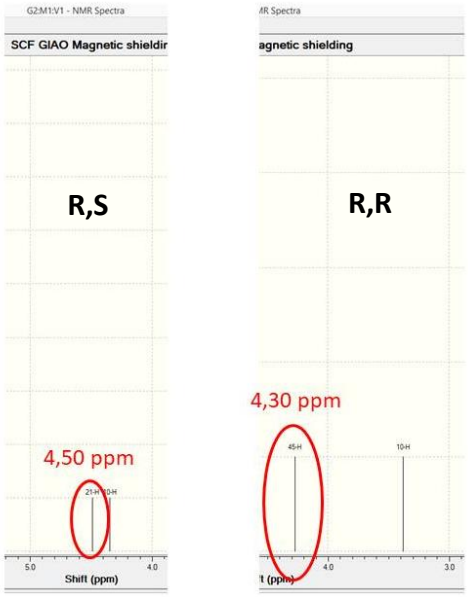


Figure 19. *Difference in chemical shifts for H21 and H45.*

The diastereomers of product **4j** were isolated as a mixture and analyzed in mixture. The d.r. was calculated from the ratio of the integral of the peaks of the two pairs of protons H45-H21 and H-10. These signals can be easily attributed because H10 gives a quartet in each isomer and H45 and H21 are two singlets. The signals belonging to the same molecule are easily identified as in the sample analyzed the two diastereomers are in the ratio 28:72 and so the difference in size between the peaks is evident.

The sequence of signals in the real spectrum is:

4.71 ppm, singlet

4.50 ppm, singlet

4.41 ppm, quartet

3.96 ppm, quartet

The integrals of the peaks indicate that the singlet at 4.71 ppm belongs to the same molecule as the quartet at 3.96 ppm, while the singlet at 4.50 ppm matches with the quartet at 4.41 ppm (Figure 20).

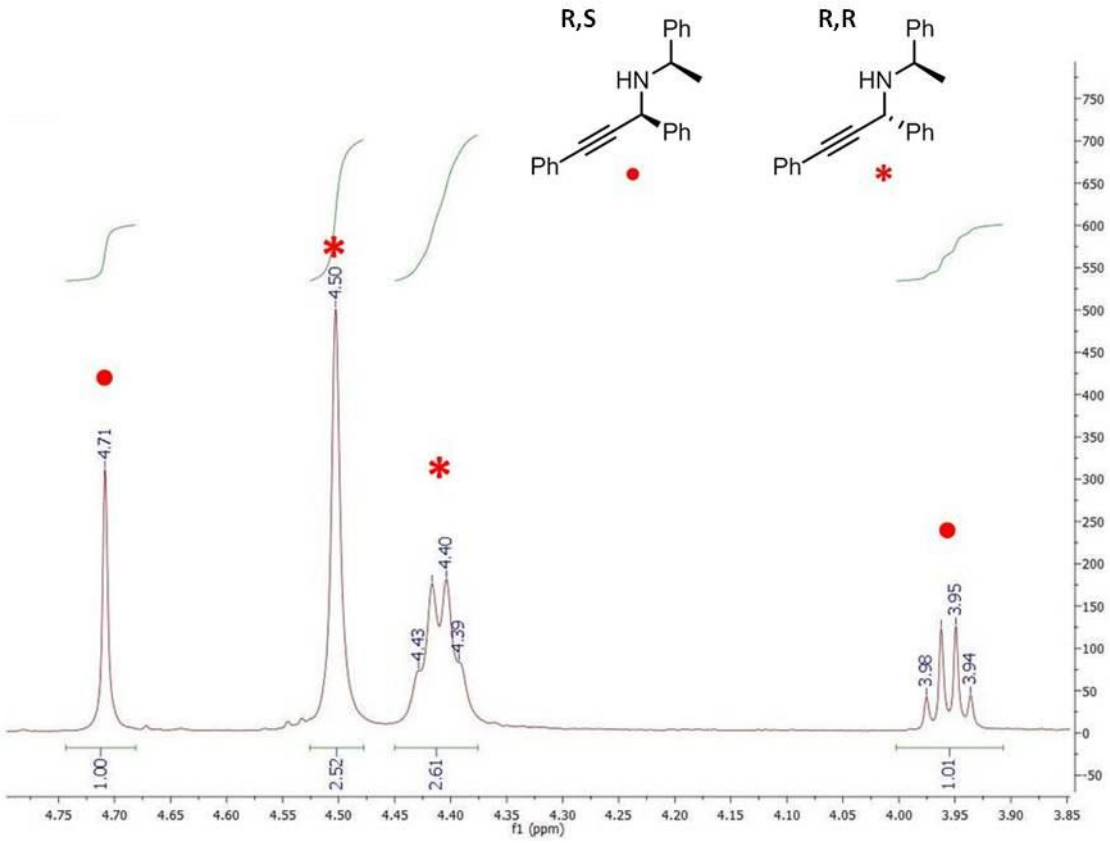


Figure 20. *^{1}H-NMR.*

These data are in line with the conclusions based on theoretical calculations, according to which the quartet of a diastereomer must be more shielded than the other, because of the effect of the phenyl coming from the aldehyhde while the singlet of the same diastereomer undergoes an opposite and minor effect that is it is more deshielded because it is almost coplanar with the same phenyl ring.

The overall result of these shielding and deshielding effects is that the signals of one diastereomer are found externally to those of the other, and it is precisely what is observed in the real spectrum.

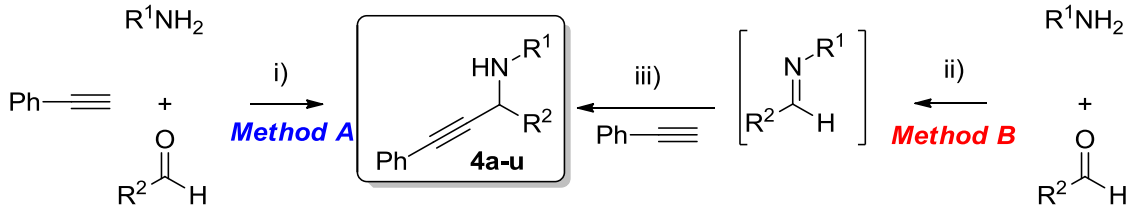
9. Conclusions and future perspective

Two different *Lewis* acid based promoting systems, CuI/I_2 and $CeCl_3 \cdot 7H_2O/CuI$, were developed and successfully applied in the synthesis of secondary propargylamines with the less studied primary amines.

The CuI/I_2 can be generated *in situ* by the $CuSO_4$/NaI couple which has revealed a good and practical precursor for the real catalytic system more active than mixing the two reagents separately.

The $CeCl_3 \cdot 7H_2O/CuI$ promoter represents an improvement with respect to $CuSO_4$/NaI in terms of yields, although with longer reaction times, and with the added value of a lower toxicity because avoids the use of molecular iodine.

The desired propargylamines were obtained in yields ranging from moderate to good and in several cases unprecedented products were synthesized (Scheme 107).[115]



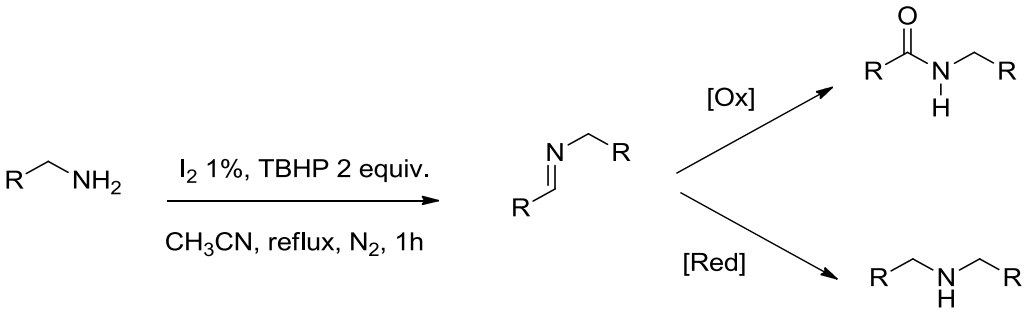
Method A*: *10 examples up to 62% yield
i) $CuSO_4$ 30% mol/NaI 60% mol,
PhCOOH 5% mol, solventless, N_2, 80°C

Method B*: *20 examples up to 95% yield
ii) $MgSO_4$, $CeCl_3 \cdot 7H_2O$ 30% mol, solventless, N_2, r.t., 0.25h.
iii) CuI 30% mol, solventless, N_2, 40°C

Scheme 107. *Two copper(I)-based Lewis acid promoting system.*

Furthermore, from the analysis of by-product which led to the hypothesis of two different mechanism, a new strategy for the synthesis of imines from primary benzylic amines was developed which requires only 1 mol% of iodine and TBHP with the added value of a simple extraction to get the pure product without the need the of further purification.

Future perspective deals with the possibility to find a better catalyst to perform the oxidation into amides and exploit the opportunity to obtain secondary amines by a subsequent reduction step. Both reactions allow the preparation of the corresponding products without using easily oxidable and reactive aldehydes (Scheme 108).



Scheme 108. *Future perspective.*

The $CuSO_4$/NaI and $CeCl_3 \cdot 7H_2O$/CuI promoting system allow the diastereoselective synthesis of secondary propargylamine that have been applied for now just to two different chiral starting (**4h** and **4j**). They will be extended in the future to other substrate with a better understanding of the influence of reaction conditions in the stereoselectivity of the final product especially with chiral aldehydes.

10. Experimental section

All reagents and solvents were purchased from commercial suppliers and used without further purification, unless mentioned otherwise.

Dry $CuSO_4$ was freshly prepared by heating $CuSO_4 \cdot 5H_2O$ in an oven at 200 °C for 3 h, until the blue powder became white. Chiral 2-butanal was used as racemates. All reactions were monitored by TLC using EMD/Merck silica gel 60 pre-coated plates (0.25 mm), and the compounds were visualized by using UV light (254 nm) or iodine vapors as developing agent. Purification of the reaction products was carried out by column flash chromatography using silica gel (0.25 mm). IR specra were recorded on a Perkin Elmer UATR two instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz and 100 MHz, respectively). Chemical shifts are given in ppm with reference to residual H in deuterated solvents as the internal standard. Coupling constants *J* are reported in Hz. Diastereomeric ratios were determined by integration of the respective 1H NMR signals of the diastereomers isolated as a mixture by column chromatography. Mass spectra were obtained using an Agilent 6850 gas chromatograph equipped with a HP5MS column (0.25 mm diameter) and an Agilent 5973N mass selective detector. Microanalyses were performed with an EA1108 CHNS D Fisons instrument.

General Procedure for the $CuSO_4$/NaI-Promoting system

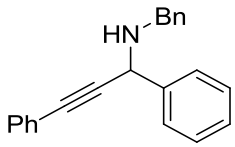
Aldehyde (1 mmol), phenylacetylene (0.306 g, 3 mmol), NaI (0.090 g, 0.6 mmol), dry $CuSO_4$ (0.048 g, 0.3 mmol), $MgSO_4$ (0.050 g), benzoic acid (0.006 g, 0.05 mmol) and amine (1 mmol) were put in this order, under an inert atmosphere, in a three-necked flask equipped with magnetic stirring. The mixture was heated at 80 °C and the reaction monitored by TLC and GC-MS until a constant composition was reached (2–5 h). The mixture was then diluted with CH_2Cl_2 and washed with 0.5 M ammonia/ammonium chloride buffer. The organic phase was separated and dried over Na_2SO_4, then filtered and

the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (hexane/EtOAc, 9:1) to afford the desired propargylamine.

General Procedure for the $CeCl_3 \cdot 7H_2O$/CuI Promoting system

Aldehyde (1 mmol) and amine (1 mmol) were put in a three-necked flask equipped with magnetic stirring and under N_2 atmosphere. $MgSO_4$ (0.050 g) and $CeCl_3 \cdot 7H_2O$ (0.112 g, 0.3 mmol) were added and the mixture was stirred at r.t. for 15 min, checking for the complete formation of the corresponding imine by TLC and GC-MS. Phenylacetylene (0.163 g, 1.6 mmol) and CuI (0.057 g, 0.3 mmol) were added and the mixture was heated at 40 °C under N_2 atmosphere for 15 h. Then, the mixture was diluted with CH_2Cl_2 and washed with 0.5 M ammonia/ammonium chloride buffer solution. The organic layer was separated and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure. The crude was purified by flash chromatography (hexane/EtOAc, 9:1) to afford the desired propargylamine.

_N_-Benzyl-1,3-diphenylprop-2-yn-1-amine (4a)



Method A: yield: 0.116 g (39%); *Method B*: yield: 0.253 g (85%); oil.

IR: 3065, 3024, 1595, 1492, 1448, 1065, 1028, 755, 689 cm^{-1}.

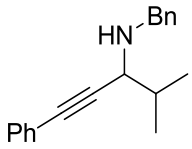
^{1}H-NMR (500 MHz, C*D*Cl_3): δ = 7.65 (d, *J* = 7.5 Hz, 2 H), 7.55–7.50 (m, 2H), 7.47–7.29 (m, 11 H), 4.84 (s, 1 H), 4.03 (s, 2 H), 1.71 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.2, 139.6, 132.0, 129.09, 128.8, 128.7, 128.5, 128.4, 128.1, 128.0, 127.4, 123.3, 89.1, 86.0, 53.8, 51.2.

GC-MS (EI, 70 eV): *m/z* (%) = 297 (M^+, 19), 296 (39), 220 (52), 191 (100), 91 (66).

Anal. Calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 89.15; H, 6.24; N, 5.01.

_N_-Benzyl-4-methyl-1-phenylpent-1-yn-3-amine (4b)



Method A: yield: 0.105 g (40%); *Method B*: yield: 0.200 g (76%); oil.

IR: 2926, 2852, 1487, 1443, 1068, 1027, 755, 683 cm^{-1}.

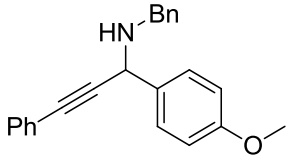
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.58–7.26 (m, 10 H), 4.17 (d, *J* = 13.0 Hz, 1 H), 3.95 (d, *J* = 13.0 Hz, 1 H), 3.46 (d, *J* = 5.4 Hz, 1 H), 2.01 (d hept, *J* = 6.5, 6.5 Hz, 1 H), 1.59 (br s, 1 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.12 (d, *J* = 6.8 Hz, 3 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.3, 131.8, 128.5, 128.4, 128.3, 127.9, 127.0, 123.6, 89.9, 84.8, 56.3, 51.9, 33.0, 19.9, 18.2.

GC-MS (EI, 70 eV): *m/z* (%) = 263 (M^+, 69), 262 (23), 248 (15), 220 (91), 162 (16), 91 (100).

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.57; H, 8.29; N, 5.47.

_N_-Benzyl-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine (4c)



Method A: yield: 0.121 g (37%); *Method B*: yield: 0.164 g (50%); oil.

IR: 2895, 2832, 1610, 1506, 1241, 1171, 1035, 821, 759, 693 cm^{-1}.

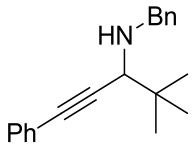
^{1}H-NMR (500 MHz, C*D*Cl_3): δ = 7.57 (d, *J* = 8.6 Hz, 2 H), 7.54–7.52 (m, 2H), 7.47 (d, *J* = 7.4 Hz, 2 H), 7.38–7.28 (m, 6 H), 6.93 (d, *J* = 8.7 Hz, 2 H), 4.80 (s, 1 H), 4.01 (s, 2 H), 3.82 (s, 3 H), 2.08 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 159.4, 131.8, 129.4, 129.1, 128.8, 128.5, 128.3, 127.4, 126.6, 122.9, 114.15, 113.9, 88.4, 86.3, 55.3, 52.8, 50.6.

GC-MS (EI, 70 eV): *m/z* (%) = 327 (M^+, 17), 326 (25), 236 (41), 221 (100), 178 (21), 91 (44).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.78; H, 6.74; N, 4.12.

_N_-Benzyl-4,4-dimethyl-1-phenylpent-1-yn-3-amine (4d)



Method A: yield: 0.030 g (11%); *Method B*: yield: 0.138 g (50%); oil.

IR: 2955, 2863, 1480, 1439, 1097, 1031, 755, 692 cm^{-1}.

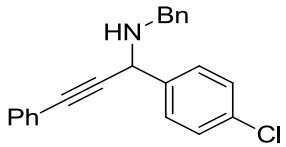
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.50–7.44 (m, 4 H), 7.37–7.26 (m, 6 H), 4.19 (d, *J* = 13.3 Hz, 1 H), 3.92 (d, *J* = 13.3 Hz, 1 H), 3.19 (s, 1 H), 1.45 (br s, 1 H), 1.10 (s, 9 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 134.6, 131.9, 128.6, 128.5, 128.4, 128.0, 127.2, 127.1, 90.5, 84.8, 60.3, 52.5, 35.4, 26.9.

GC-MS (EI, 70 eV): *m/z* (%) = 277 (M^+, 66), 276 (17), 262 (19), 220 (100), 173 (16), 144 (42), 117 (87), 91 (86).

Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.47; H, 8.21; N, 5.23.

_N_-Benzyl-1-(4-chlorophenyl)-3-phenylprop-2-yn-1-amine (4e)



Method A: yield: 0.100 g (30%); *Method B*: yield: 0.222 g (67%); oil.

IR: 3027, 2843, 1488, 1444, 1090, 1013, 829, 752, 693 cm^{-1}.

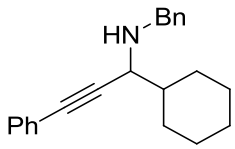
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.68–7.26 (m, 14 H), 4.82 (s, 1 H), 4.02 (s, 2 H), 1.94 (br s, 1H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 139.8, 139.1, 132.0, 129.4, 128.9, 128.8, 128.7, 128.6, 128.5, 128.0, 127.5, 123.1, 88.8, 86.4, 53.2, 51.3.

GC-MS (EI, 70 eV): *m/z* (%) = 331 (M^+, 25), 330 (45), 254 (25), 225 (100), 189 (41), 128 (11), 91 (70).

Anal. Calcd for $C_{22}H_{18}ClN$: C, 79.63; H, 5.47; Cl, 10.68; N, 4.22. Found: C, 79.57; H, 5.39; Cl, 10.91; N, 4.36.

_N_-Benzyl-1-cyclohexyl-3-phenylprop-2-yn-1-amine (4f)



Method A: yield: 0.152 g (50%); *Method B*: yield: 0.227 g (75%); oil.

IR: 2924, 2845, 1492, 1451, 1070, 752, 690 cm^{-1}.

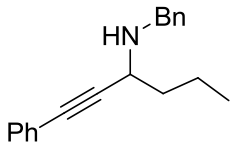
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.50–7.26 (m, 10 H), 4.14 (d, *J* = 13.4 Hz, 1 H), 3.93 (d, *J* = 13.4 Hz, 1 H), 3.43 (d, *J* = 5.8 Hz, 1 H), 2.00–1.60 (m, 7 H), 1.35–1.19 (m, 5 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.4, 132.0, 128.7, 128.6, 128.5, 128.1, 127.2, 123.8, 90.4, 85.0, 55.7, 52.0, 42.9, 30.5, 29.1, 26.8, 26.5, 26.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 303 (M^+, 1), 302 (1), 220 (100), 91 (35).

Anal. Calcd for $C_{22}H_{25}N$: C, 87.08; H, 8.30; N, 4.62. Found: C, 87.23; H, 8.22; N, 4.46.

_N_-Benzyl-1-phenylhex-1-yn-3-amine (4g)



Method A: yield: 0.110 g (42%); *Method B*: yield: 0.137 g (52%); oil.

IR: 2059, 1597, 1491, 1458, 1325, 1031, 755, 736, 589 cm^{-1}.

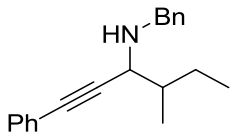
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.49–7.23 (m, 10 H), 4.11 (d, *J* = 13.0 Hz, 1 H), 3.92 (d, *J* = 13.0 Hz, 1 H), 3.62 (dd, *J* = 6.3, 7.4 Hz, 1 H), 1.90 (br s, 1 H), 1.80–1.65 (m, 2 H), 1.64–1.50 (m, 2 H), 0.97 (t, *J* = 7.3 Hz, 3H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.1, 131.9, 128.7, 128.6, 128.5, 128.2, 127.3, 123.6, 91.1, 84.3, 51.7, 50.0, 38.4, 19.7, 14.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 263 (M^+, 1), 262 (2), 220 (100), 115 (10), 91 (44).

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.48; H, 7.88; N, 5.44.

_N_-Benzyl-4-methyl-1-phenylhex-1-yn-3-amine (4h)



Method A: yield: 0.173 g (62%); d.r. 21:79; *Method B*: yield: 0.264 g (95%); d.r. 68:32; oil.

IR: 3027, 2961, 1735, 1584, 1488, 1451, 1381, 1028, 748, 685, 527 cm^{-1}.

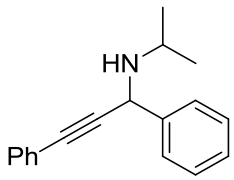
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.52–7.23 (m, 20 H), 4.14 (d, *J* = 13.0 Hz, 2 H), 3.92 (d, *J* = 13.0 Hz, 2 H), 3.56 (d, *J* = 5.0 Hz, 1 H), 3.49 (d, *J* = 5.0 Hz, 1 H), 1.81–1.59 (m, 6 H), 1.43–1.29 (m, 2 H), 1.08 (d, *J* = 6.6 Hz, 6 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 0.94 (t, *J* = 7.2 Hz, 3 H). Diastereomers isolated as a mixture; the d.r. was determined by comparing the relative areas of the proton signals at δ 3.56 and 3.49.

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.1, 131.9, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.3, 123.7, 89.6, 85.1, 55.1, 54.9, 53.9, 52.0, 51.4, 39.9, 39.7, 29.9, 27.1, 25.5, 16.1, 15.1, 11.9.

GC-MS (EI, 70 eV): *m*/*z* (%) = 277 (M^+, 71), 262 (22), 249 (60), 220 (65), 200 (25), 186 (29), 144 (38), 117 (47), 91 (100).

Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.84; H, 8.23; N, 4.77.

_N_-Isopropyl-1,3-diphenylprop-2-yn-1-amine (4i)



Method A: yield: 0.132 g (53%); *Method B*: yield: 0.180 g (72%); oil.

IR: 2959, 1594, 1491, 1167, 753, 692 cm^{-1}.

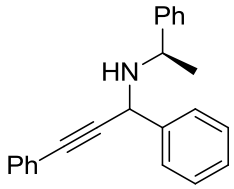
^{1}H-NMR (400 MHz, C*D*Cl3): δ = 7.64–7.32 (m, 10 H), 4.88 (s, 1 H), 3.28 (hept, *J* = 6.2 Hz, 1 H), 1.60 (br s, 1 H), 1.19 (d, *J* = 6.2 Hz, 6 H).

^{13}C-NMR (100 MHz, C*D*Cl3): δ = 141.2, 132.0, 128.9, 128.7, 128.4,128.0, 127.8, 123.5, 89.9, 85.4, 52.5, 46.6, 23.9, 22.4.

GC-MS (EI, 70 eV): *m*/*z* (%) = 249 (M^+, 7), 248 (9), 234 (16), 206 (11), 191 (100), 172 (13), 130 (9), 128 (9), 77 (10).

Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.91; H, 7.47; N, 5.68.

1,3-Diphenyl-*N*-(1-phenylethyl)prop-2-yn-1-amine (4j)



Method B: yield: 0.200 g (64%); d.r. 72:28; oil.

IR: 3054, 3028, 2970, 2863, 2250, 1491, 1443, 1104, 1031, 751, 696 cm^{-1}.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.65–7.25 (m, 30 H), 4.72 (s, 1 H), 4.51(s, 1 H), 4.42 (q, *J* = 6.5 Hz, 1 H), 3.96 (q, *J* = 6.5 Hz, 1 H), 1.75 (br s, 2 H), 1.46 (d, *J* = 6.5 Hz, 3 H), 1.43 (d, *J* = 6.5 Hz, 3 H).

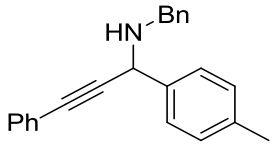
Diastereomers isolated as a mixture; the d.r. was determined by comparing the relative areas of the proton signals at δ 4.72 and 4.51. Data in agreement with literature.47

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 144.9, 141.0, 132.0, 128.9, 128.7, 128.5, 128.4, 128.0, 127.8, 127.5, 127.2, 123.5, 56.4, 55.5, 52.4, 25.3, 23.8.

GC-MS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 8), 310 (7), 296 (32), 234 (12), 206 (24), 191 (100), 105 (13), 77 (6).

Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.54; H, 6.97; N, 4.31.

***N*-Benzyl-3-phenyl-1-(*p*-tolyl)prop-2-yn-1-amine (4k)**



Method B: yield: 0.177 g (57%); oil. Spectroscopic data in agreement with literature.45

IR: 3024, 2921, 1488, 1444, 1025, 814, 755, 685 cm^{-1}.

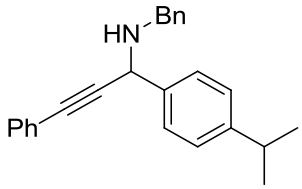
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.55–7.21 (m, 14 H), 4.82 (s, 1 H), 4.03 (s, 2 H), 2.39 (s, 4 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 137.6, 131.8, 129.2, 128.6, 128.5, 128.3, 128.2, 127.7, 127.6, 127.2, 123.2, 89.0, 85.8, 53.3, 51.0, 21.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 311 (M^+, 30), 310 (49), 220 (62), 205 (100), 91 (52).

Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.97; H, 6.98; N, 4.33.

_N_-Benzyl-1-(4-isopropylphenyl)-3-phenylprop-2-yn-1-amine (4l)



Method B: yield: 0.203 g (60%); oil.

IR: 2960, 1697, 1489, 1215, 830, 754, 693 cm^{-1}.

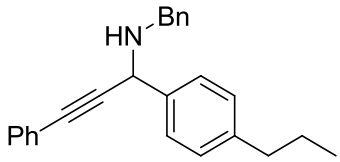
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.60–7.25 (m, 14 H), 4.83 (s, 1 H), 4.08 (d, *J* = 13.1 Hz, 1 H), 4.03 (d, *J* = 13.1 Hz, 1 H), 2.96 (sept, *J* = 6.9 Hz, 1H), 1.94 (br s, 1 H), 1.30 (d, *J* = 6.9 Hz, 6 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 148.7, 140.0, 137.9, 132.0, 128.8, 128.7, 128.6, 128.4, 127.9, 127.4, 126.9, 123.5, 89.7, 85.8, 53.6, 51.4, 34.1, 24.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 339 (M^+, 38), 338 (52), 296 (48), 250 (40), 233 (100), 218 (48), 91 (95).

Anal. Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.33; H, 7.49; N, 4.02.

_N_-Benzyl-3-phenyl-1-(4-propylphenyl)prop-2-yn-1-amine (4m)



Method B: yield: 0.265 g (78%); oil.

IR: 2961, 2924, 2862, 1488, 1448, 1090, 755, 685 cm^{-1}.

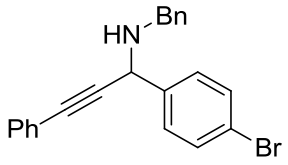
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.65 (d, *J* = 7.5 Hz, 2 H), 7.57–7.25 (m, 10 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 4.82 (s, 1 H), 4.07 (d, *J* = 12.0 Hz, 1 H), 4.03 (d, *J* = 12.0 Hz, 1 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 2.03 (br s, 1 H), 1.68 (sext, *J* = 7.5 Hz, 2 H), 0.99 (t, *J* = 7.3 Hz, 3 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 142.6, 140.0, 137.8, 132.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.8, 127.4, 123.5, 89.7, 85.9, 53.6, 51.4, 38.0, 24.9, 14.2.

GC-MS (EI, 70 eV): *m*/*z* (%) = 339 (M^+, 48), 338 (64), 296 (39), 262 (25), 248 (49), 233 (100), 204 (58), 91 (63).

Anal. Calcd for $C_{25}H_{25}N$: C, 88.45; H, 7.42; N, 4.13. Found: C, 88.39; H, 7.47; N, 4.06.

_N_-Benzyl-1-(4-bromophenyl)-3-phenylprop-2-yn-1-amine (4n)



Method B: yield: 0.206 g (55%); oil.

IR: 3061, 3028, 2843, 1484, 1455, 1072, 1009, 821, 755, 693 cm^{-1}.

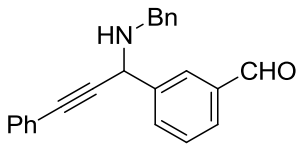
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.54–7.48 (m, 6 H), 7.43–7.26 (m, 8 H), 4.78 (s, 1 H), 3.99 (s, 2 H), 2.11 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 139.5, 139.4, 132.0, 131.8, 129.7, 128.8, 128.7, 128.6, 128.5, 127.5, 123.0, 122.0, 88.6, 86.4, 53.2, 51.2.

GC-MS (EI, 70 eV): *m/z* (%) = 376 ([M + 1]$^+$, 31), 374 (M+, 30), 286 (33), 284 (34), 271 (75), 269 (74), 220 (32), 189 (78), 91 (100).

Anal. Calcd for $C_{22}H_{18}BrN$: C, 70.22; H, 4.82; Br, 21.23; N, 3.72. Found: C, 70.11; H, 4.93; Br, 21.31; N, 3.56.

3-[1-(Benzylamino)-3-phenylprop-2-yn-1-yl]benzaldehyde (4o)



Method B: yield: 0.228 g (70%); oil.

IR: 3024, 2836, 2729, 1694, 1595, 1488, 1440, 1138, 755, 693 cm^{-1}.

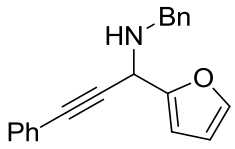
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 10.06 (s, 1 H), 8.17 (s, 1 H), 7.95 (d, *J* = 7.6 Hz, 1 H), 7.85 (d, *J* = 6.6 Hz, 1 H), 7.57–7.10 (m, 11 H), 4.90 (s, 1 H), 4.03 (s, 2 H), 2.15 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 192.5, 141.6, 139.5, 136.9, 134.2, 132.3, 132.1, 129.5, 129.4, 129.3, 128.8, 128.7, 128.6, 127.6, 123.0, 88.3, 86.8, 53.4, 51.4.

GC-MS (EI, 70 eV): *m/z* (%) = 325 (M$^+$, 44), 324 (55), 298 (15), 248 (43), 234 (51), 219 (100), 218 (74), 189 (43), 91 (69).

Anal. Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.76; H, 5.94; N, 4.22.

_N_-Benzyl-1-(furan-2-yl)-3-phenylprop-2-yn-1-amine (4p)



Method B: yield: 0.130 g (45%); oil. Spectroscopic data in agreement with literature.46

IR: 3061, 3026, 2843, 1489, 1144, 1073, 1007, 754, 728, 693 cm^{-1}.

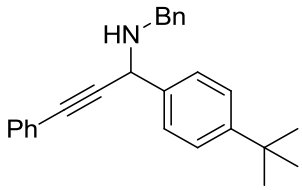
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.52–7.25 (m, 11 H), 6.48–6.44 (m, 1H), 6.38–6.35 (m, 1 H), 4.93 (s, 1 H), 4.02 (d, *J* = 13.0 Hz, 1 H), 3.98 (d,*J* = 13.0 Hz, 1 H), 2.61 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 152.6, 142.8, 139.2, 132.1, 128.8, 128.7, 128.6, 128.5, 127.5, 122.9, 110.5, 108.0, 86.5, 85.2, 50.8, 47.9.

GC-MS (EI, 70 eV): *m/z* (%) = 287 (M^+, 12), 286 (20), 258 (11), 196 (49), 181 (100), 152 (50), 91 (42).

Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.72; H, 5.83; N, 4.63.

_N_-Benzyl-1-(4-*tert*-butylphenyl)-3-phenylprop-2-yn-1-amine (4q)



Method B: yield: 0.286 g (81%); oil.

IR: 3028, 2958, 2869, 1492, 1455, 1274, 1109, 829, 752, 689 cm^{-1}.

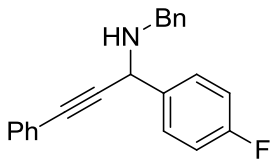
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.62 (d, *J* = 8 Hz, 2 H), 7.58–7.56 (m, 2 H), 7.48 (t, *J* = 8 Hz, 4 H), 7.43–7.37 (m, 5 H), 7.33 (d, *J* = 7.4 Hz, 1 H), 4.86 (s, 1 H), 4.11 (d, *J* = 13.0 Hz, 1 H), 4.07 (d, *J* = 13.0 Hz, 1 H), 2.05 (br s, 1 H), 1.40 (s, 9 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 151.0, 140.1, 137.6, 132.1, 128.8, 128.7, 128.6, 128.4, 127.6, 127.4, 125.8, 123.5, 89.7, 85.9, 53.6, 51.5, 34.8, 31.7.

GC-MS (EI, 70 eV): *m/z* (%) = 353 (M^+, 63), 352 (76), 296 (78), 247(100), 217 (62), 91 (78).

Anal. Calcd for $C_{26}H_{27}N$: C, 88.34; H, 7.70; N, 3.96. Found: C, 88.17; H, 7.57; N, 4.32.

_N_-Benzyl-1-(4-fluorophenyl)-3-phenylprop-2-yn-1-amine (4r)



Method B: yield: 0.170 g (54%); oil.

IR: 3027, 2847, 1602, 1506, 1219, 1153, 832, 759, 689 cm^{-1}.

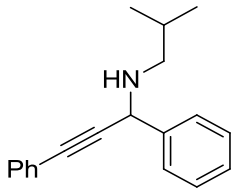
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.64–7.60 (m, 2 H), 7.53–7.51 (m, 2 H), 7.48–7.26 (m, 8 H), 7.11–7.05 (m, 2 H), 4.81 (s, 1 H), 4.01 (s, 2 H), 1.97 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 162.6 (d, 1*J*C–F = 248.6 Hz), 139.8, 136.2, 132.0, 129.6 (d, 3*J*C–F = 8.2 Hz), 128.7 (d, 4*J*C–F = 2.2 Hz), 128.6, 128.5, 128.0, 127.4, 123.2, 115.5 (d, 2*J*C–F = 22.4 Hz), 89.0, 86.3, 53.1, 51.3.

GC-MS (EI, 70 eV): *m*/*z* (%) = 315 (M^+, 20), 314 (34), 238 (21), 224 (54), 209 (100), 91 (40).

Anal. Calcd for $C_{22}H_{18}FN$: C, 83.78; H, 5.75; F, 6.02; N, 4.44. Found: C, 84.11; H, 6.03; F, 5.87; N, 4.77.

_N_-(2-Methylpropyl)-1,3-diphenylprop-2-yn-1-amine (4s)



Method B: yield: 0.187 g (71%); oil.

IR: 2961, 1492, 1448, 1098, 755, 685 cm^{-1}.

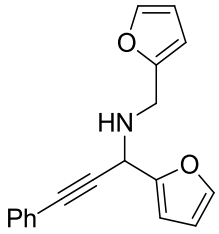
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.64 (d, *J* = 7.6 Hz, 2 H), 7.51–7.25 (m, 8H), 4.84 (s, 1 H), 2.65 (dd, *J* = 11.4, 7.0 Hz, 1 H), 2.58 (dd, *J* = 11.4, 6.5Hz, 1 H), 2.02 (br s, 1 H), 1.83 (hept, *J* = 6.5 Hz, 1 H), 0.98 (dd, *J* = 3.5,6.6 Hz, 6 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 140.1, 131.7, 128.5, 128.3, 128.1, 127.8, 127.7, 123.2, 89.2, 85.5, 55.1, 54.7, 28.3, 20.9, 20.7.

GC-MS (EI, 70 eV): *m*/*z* (%) = 263 (M^+, 4), 262 (3), 220 (24), 191 (100), 165 (7).

Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.43; H, 7.85; N, 5.39.

_N_-(4-Methoxybenzyl)-1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-amine (4t)



Method B: yield: 0.221 g (62%); oil.

IR: 2833, 1608, 1505, 1244, 1027, 828, 751, 692 cm^{-1}.

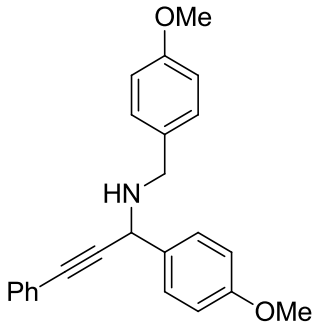
^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.55–7.53 (m, 4 H), 7.36–7.33 (m, 5 H), 6.93–6.89 (m, 4 H), 4.76 (s, 1 H), 3.94 (s, 2 H), 3.82 (s, 3 H), 3.81 (s, 3H), 2.14 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 159.4, 159.0, 132.6, 132.0, 130.0, 129.1, 128.5, 128.4, 123.4, 114.3, 114.1, 114.0, 89.6, 85.9, 55.6, 55.5, 53.1, 50.6.

GC-MS (EI, 70 eV): *m*/*z* (%) = 357 (M^+, 22), 356 (19), 280 (22), 250 (17), 236 (34), 221 (100), 178 (20), 121 (55).

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.51; H, 6.67; N, 3.78.

1-(Furan-2-yl)-_N_-(furan-2-ylmethyl)-3-phenylprop-2-yn-1-amine (4u)



Method B: yield: 0.130 g (47%); oil.

IR: 3014, 1664, 1597, 1487, 1439, 1222, 1009, 747, 692 cm^{-1}.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ = 7.50–7.26 (m, 7 H), 6.49–6.47 (m, 1 H),6.37–6.28 (m, 3 H), 4.97 (s, 1 H), 4.03 (d, *J* = 14.2 Hz, 1 H), 4.00 (d, 14.2 Hz, 1 H), 2.70 (br s, 1 H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ = 152.6, 152.0, 142.9, 142.4, 132.1, 128.7, 128.5, 122.8, 110.6, 110.5, 108.3, 108.1, 85.9, 85.4, 47.7, 43.3.

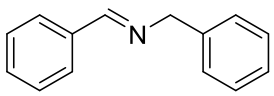
GC-MS (EI, 70 eV): *m*/*z* (%) = 277 (M^+, 6), 276 (21), 260 (11), 248 (26), 200 (32), 181 (100), 152 (51), 109 (63), 81 (34).

Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.21; H, 5.37; N, 5.31.

General Procedure for the oxidative coupling

Primary amines (2 mmol) and I_2 (1 mol%) were dissolved in 1.5 mL of CH_3CN in a three neck bottom flask under an inert atmosphere. After the completely dissolution of I_2, the TBHP (4 mmol) diluted with 1.5mL of CH_3CN was slowly added to the reaction mixture dropwise (one drop every 8 sec. ca.). The mixture was heated at 95 °C and the reaction monitored via GC-MS for the formation of the imine. The CH_3CN was then evaporated, the crude diluted with CH_2Cl_2 and washed with $Na_2S_2O_3$ at 5%. The organic phase was separated and dried over Na_2SO_4 then filtered and the solvent was evaporated under reduced pressure to recover the desired imine.

N-benzylidene-1-phenylmethanamine 5a



General method: 0.524g (yield 87%, GC-conversion 98%); oil.

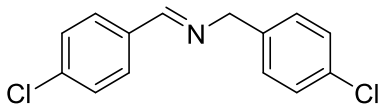
^{1}H-NMR (400 MHz, C*D*Cl_3): δ 8.40 (s, 1H), 7.80-7.68 (m, 2H), 7.43-7.26 (m, 8H), 4.83 (s, 2H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ 162.3, 131.0, 128.8, 128.7, 128.5, 128.2, 127.2, 65.3.

GC-MS (EI, 70 eV): *m/z* (%) 195 (29), 194 (30), 165 (5), 117 (15), 92 (33), 91 (100), 65 (18), 51 (5).

Anal. Calcd. for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17%. Found C, 86.25; H, 6.65; N, 7.05%.

N-(4-chlorobenzylidene)-4-chlorobenzylamine 5b



General method: 0.240g (yield 85%, 93% GC-conversion); crystals

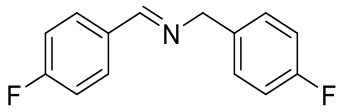
^{1}H-NMR (400 MHz, C*D*Cl_3): δ 8.83 (s, 1H), 7.71 (d, J = 8.36 Hz, 2H), 7.38 (d, J =8.36 Hz, 2H), 7.33-7.25 (m, 4H), 4.76 (s, 2H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ 161.1, 137.8, 137.1, 134.7, 133.0, 129.7, 129.5, 129.2, 128.9, 64.4.

GC-MS (EI, 70 eV): m/z (%) 265 (13), 264 (12), 263 (20), 262 (15), 151 (9), 128 (4), 127 (33), 126 (13), 125 (100), 99 (4), 91 (4), 90 (5), 89 (20), 75 (4), 63 (5).

Anal. Calcd. for $C_{14}H_{11}Cl_2N$: C, 63.66; H, 4.20; Cl, 26.84; N, 5.30%. Found: C, 63.58; H, 4.10; Cl, 26.73; N, 5.23%.

N-(4-fluorobenzylidene)-4-fluorobenzylamine 5c



General method: 0.185g (yield 77%, GC-conversion 96%); crystals.

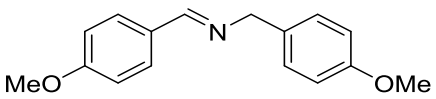
^{1}H-NMR (400 MHz, C*D*Cl_3): δ 8.33 (s, 1H), 7.79-7.75 (m, 2H), 7.31-7.28 (m, 2H), 7.11-7.01 (m, 4H), 4.75 (s, 2H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ 165.9, 163.4, 160.8, 135.3, 132.6, 130.5, 130.4, 129.8, 116.1, 115.8, 115.6, 115.4, 64.3.

GC-MS (EI, 70 eV): m/z (%) 232 (4), 231 (25), 230 (12), 136 (2), 135 (8), 134 (2), 122 (2), 110 (14), 109 (100), 108 (7), 107 (8), 83 (11), 56 (3).

Anal. Calcd. for $C_{14}H_{11}F_2N$: C, 72.72; H, 4.79; F, 16.43; N, 6.06%. Found: C, 72.62; H, 4.83; F, 16.35; N, 6.10%.

N-(4-methoxybenzylidene)-4-methoxybenzylamine 5d



General method: 0.257g (yield 91%, GC-conversion 91%); oil

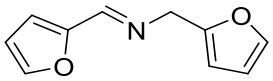
^{1}H-NMR (400 MHz, C*D*Cl_3): δ 8.30 (s, 1H), 7.72 (d, J = 8.76 Hz, 2H), 7.25 (d, J = 8.60 Hz, 2H), 6.93-6.88 (m, 4H), 4.73 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H).

^{13}C-NMR (100 MHz, C*D*Cl_3): δ 161.9, 161.2, 158.9, 131.9, 130.1, 129.4, 114.2, 114.1, 64.6, 55.6, 55.5.

GC-MS (EI, 70 eV): m/z (%) 256 (3), 255 (17), 254 (2), 147 (5), 132 (2), 122 (10), 121 (100), 120 (2), 91 (6), 89 (2), 78 (4), 77 (7), 65 (2), 51 (2).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.23; H, 6.75; N, 5.40%.

N-furfurylidenefurfurylamine 5e



General method: 0.142g (yield 76%, GC-conversion 85%); oil

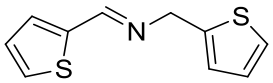
^{1}H-NMR ($CDCl_3$): δ 8.1 (s, 1H), 7.48 (s, 1H), 7.35 (s, 1H), 6.75 (d, J = 3.32 Hz , 1H), 6.45-6.44 (m, 1H), 6.32-6.24 (m, 2H), 4.72 (s, 2H).

^{13}C-NMR ($CDCl_3$): δ 152.0, 151.5, 145.2, 142.5, 114.8, 111.9, 110.6, 108.2, 57.0.

GC-MS (EI,70 eV): m/z (%): 175 ($[M]^+$, 25), 147 (7), 94 (2), 81 (100), 53 (20), 39 (7).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00%. Found: C, 68.48; H, 5.20; N, 8.05%.

N-(2-tiophenemethylidene)-2tiophenemethylamine 5f



General method: 0.181g (yield 73%, GC-conversion 83%); oil.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ 8.45 (s, 1H), 7.44 (d, J = 0.7 Hz, 1H), 7.36 (d, J = 2.9 Hz, 1H), 7.26 (dd, J = 4.9, 1.3 Hz, 1H), 7.09(dd, J = 12.5, 6.3 Hz, 1H), 7.00 (m, 2H), 4.98 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 155.4, 142.0, 141.5, 130.9, 129.3, 127.4, 126.8, 125.3, 124.8, 58.5.

GC-MS (EI, 70 eV): *m/z* (%) = 207 ($[M]^+$, 25), 174 (10), 110 (5), 97 (100), 63 (22), 46 (8).

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.93; H, 4.38; N, 6.76%. Found: C, 57.85; H, 4.42; N, 6.80%.

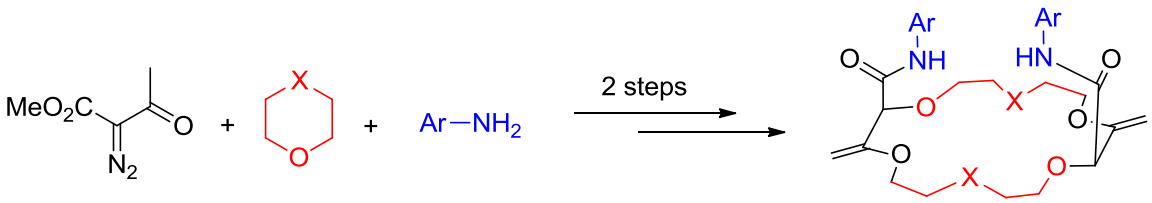
Second part:

Synthesis, resolution and properties of chiral luminescent Terbium(III) polyether macrocycle conjugates

11. Introduction

Since their first synthesis by Charles J. Pedersen in the 1960's, crown ether or cyclic polyethers have received a particular attention.[117] The unique structure of the crown ethers has attracted the attention of many scientists both in organic synthesis and in drug delivery process with also the formulation of nano-drugs.[118]

Recently, the group of Prof. Jérôme Lacour reported the straightforwards synthesis of chiral crown ethers (cyclic polyethers) obtained from simple cyclic ether building blocks (5,6,7-membered rings), α-diazo- β-ketoesters and aromatic amines (Scheme 109).[119] This particular family of molecule were applied in field as various as asymmetric catalysts, ion and salt receptors, (chiro)optical switches and pH-indipendent nanosensors.[120]



Scheme 109. *Two-steps synthesis of chiral crown ethers.*

The project during my internship in the group was to study through various spectroscopic techniques the possibility to use the chiral macrocycles as chiral ligand for metal ions and in particular lanthanides. The interaction between terbium(III) salt and various macrocycles (ligand) bearing different aromatic moieties (antenna) was studied. Depending on the nature of the cyclic ring and the antenna, the affinity of terbium for the ligand could be measured by absorbance, fluorescence, circular dichroism (ECD) and circularly polarized luminescence (CPL). A brief introduction on the importance and general synthesis of macrocycles and later on crown ethers with their applications will be presented first. Then the macrocyclization strategies from diazo precursor, a versatile building blocks for various reaction. A particular focus on the synthetic approach developed by the group of prof. Jérôme Lacour in Geneva for the chiral crown ether synthesis will be given. Finally the formation of the complex with lanthanide and the CPL will be described.

12. Macrocycles

12.1. Importance

Macrocyclic structures (molecule containing a cyclic framework of at least twelve atoms) are a common feature in nature: more than 20% of known products possess a cyclic structure. Although the size of natural macrocycles can have more than 50+ atoms in the largest ring, a recent analysis of natural products suggested that 14-, 16-, and 18-membered frameworks are the most common.[121]

Naturally occurring macrocycles often display remarkable biological activities and many of them (or their derivatives) are used as drugs.[122] Therefore the study and the analysis of chemical diversity of these compounds may provide inspiration for innovative drug. Natural occurring macrocycles possess in fact a complex structure (variety in ring size or the chemical constitution) which is strictly connected/related to the their remarkably high activities.[123] It is postulated that there is an equilibrium or a compromise between the conformational preorganization and the flexibility to achieve the optimal binding towards their final biological target.

The variety in structure and biological activity of naturally occurring macrocycles can be understood by comparing the compounds in Figure 21.

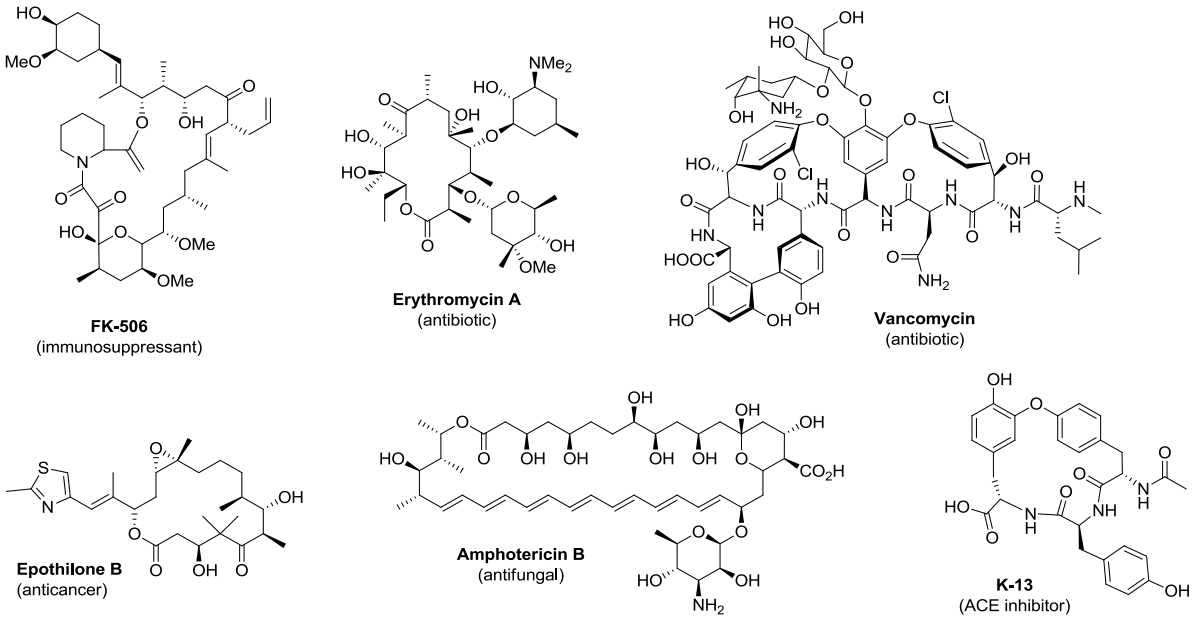


Figure 21. *Some naturally occurring macrocycles displaying a variety of medicinally important biological activities*

Macrocycles however, in addition to interesting biological and medicinal properties, are used in chemical analysis for the sensing and quantification of various analytes.[124] For this ability to selectively sequester cations or anions they have been incorporated to different techniques such as solvent extraction, liquid membranes, capillary electrophoresis and chromatography. Finally, some applications in nanotechnologies are possible as nanosized reactors (cages), switches or shuttles.[125]

Of particular interest, crown ethers are a family of macrocycles with supramolecular abilities that will be presented in the next section.

12.2. Macrocyclization strategies

The construction of macrocycles (cyclization step) is generally considered as a crucial and challenging theme for organic chemists. For this over the last several decades, numerous efforts have been undertaken toward the efficient preparation of macrocyclic structures and fortunately great progresses have been made to advance in the field of total synthesis.[126]

Macrocyclic compounds can be obtained using a large variety of chemical reactions for the key ring-closing step. The choice depends on the specific functionalities in the target molecules or with features that can favour the efficiency of the cyclization. A good example is the preparation of the antitumor macrolide Rhizoxin D for which different macrocyclization approaches were considered finding in the Horner−Emmons olefination the best way (Figure 22).[127]

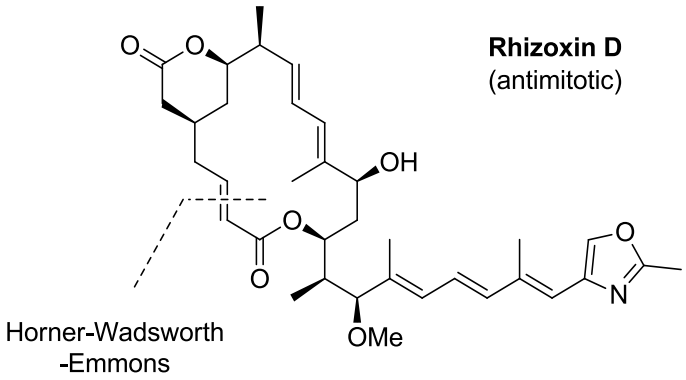


Figure 22. *Rhizoxin D.*

Fitzgerald and co-workers described two different synthetic ways for the final step of cyclization to obtain 12-membered macrolactams which are an intramolecular S_NAr reaction or a macrolactamization with different yields (Figure 23).[128]

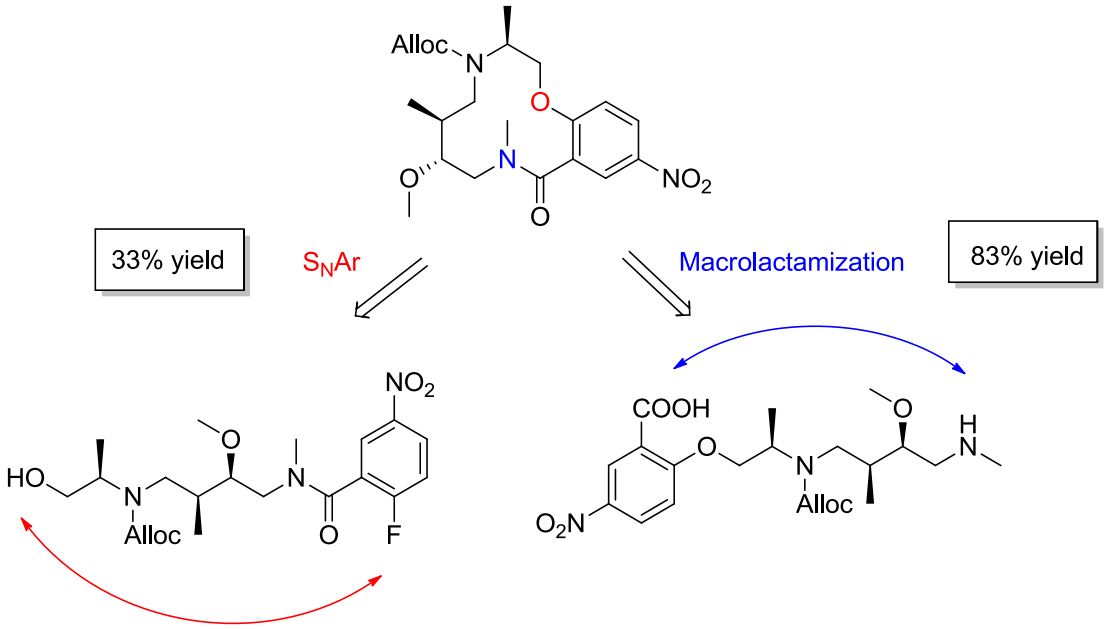


Figure 23. *12-membered macrolactams.*

Lactonization and lactamization reactions are some of the more common processes found in macrocyclization due to the occurrence of lactone and lactam groups in many macrocyclic structures, either natural or synthetic (Figure 24).[129]

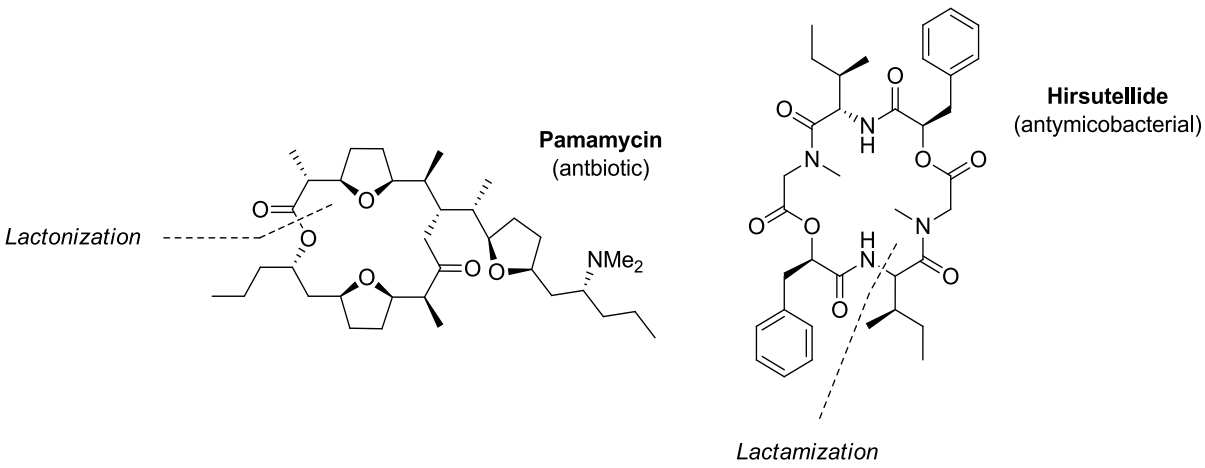


Figure 24. *Pamamycin and Hirsutellide.*

Many other reactions have been reported for macrocyclizations such as nucleophilic substitution reactions, including aromatic substitution, which constitute one of the simplest conceptual approaches for cyclization. These reactions are crucial for the

formation of polyoxa, polythia, or polyaza macrocycles (crown ethers, thiacrown, and azacrown derivatives) (Figure 25).[130]

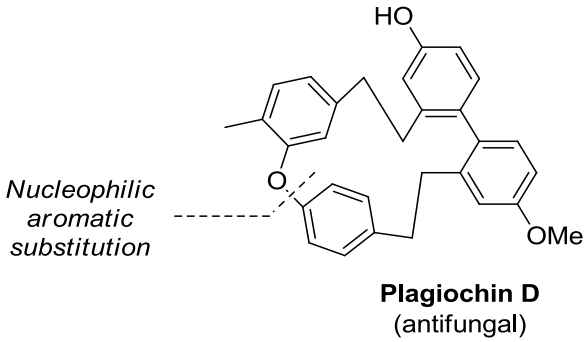


Figure 25. *Plagiochin D.*

Another way for macrocyclization involves C–C bond forming reactions with the use of transition-metal catalysis: the ring closing metathesis (RCM) and related processes are among the most usual and suitable one. RCM reactions have been applied to the preparation of a variety of cyclic natural products and are usually carried out under diluted conditions to avoid the competence of intermolecular processes (Figure 26).[131]

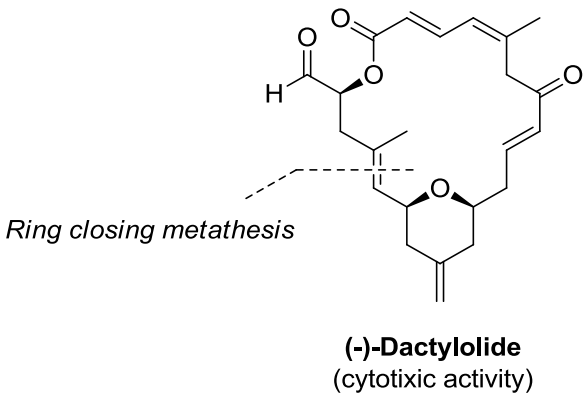


Figure 26. *(-)-Dactylolide.*

Diels–Alder reaction is well-known in the formation of small-to-medium size cycles: the synthesis of the natural product Abyssomicin C is an example of its application (Figure 27).[132]

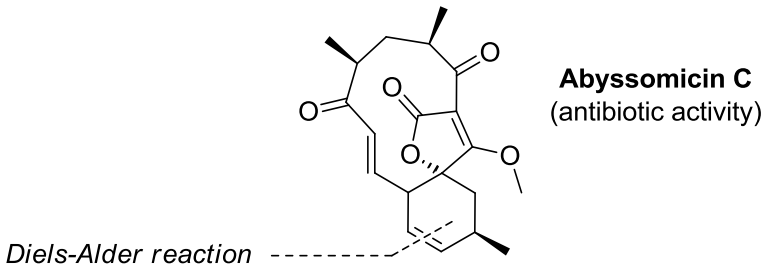


Figure 27. *Abyssomicin C.*

Copper catalyzed azide-alkyne cycloaddition (CuAAC) and click chemistry are a valuable additional tool to obtain macrocyclic structures from oligomeric or polymeric open-chain precursors (Figure 28).[133]

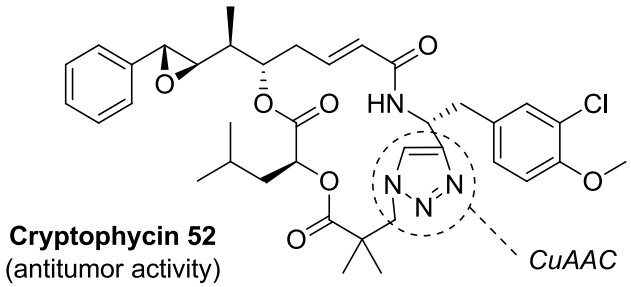


Figure 28. *Cryptophycin 52.*

Although the head-to-tail cyclization of the corresponding open-chain precursor is a very common approach, nowadays multiple multicomponent processes are more applied since they allow to obtain macrocyclic structures of different complexities from simple buildings blocks in a single step, without performing the linear precursor prior to cyclize.[134]

13. Crown ether

13.1. General aspect

Polyether macrocycles (or crown ethers) have always received a particular attention from the synthetic point of view and from the binding properties. They are defined as a cyclic compound composed of repetitive ether units in which oxygen atoms can also be (partially) replaced by other heteroatoms such as nitrogen (aza crown ether) or sulfur atoms (thia crown ethers). The term "crown" refers to the resemblance between the structure of a crown ether bound to a cation and a crown sitting on a head. Various ring sizes (typically 9- to 32-membered ring) can be found with different substitutions or functionalizations (Figure 29).[125, 135]

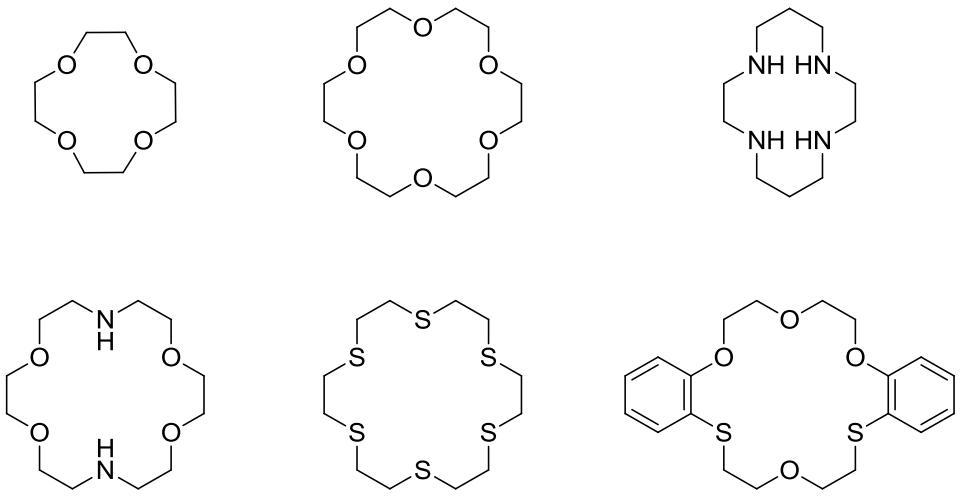


Figure 29. *Structures of various crown ether.*

13.2. Synthesis

The first efficient synthesis of crown ethers dates back to 1967 by Charles Pedersen. He was trying to prepare a complexing agent for divalent cations with the aim to link two catechol molecules through their hydroxyl groups that could wrap up the metal ion.
The result of the synthesis was not what Pedersen expected: he separated a by-product strongly complexed to potassium cations. He later discovered that the compound was dibenzo-18-crown-6, a new class of complexing agents that were capable of binding alkali metal cations (Figure 30).[117]

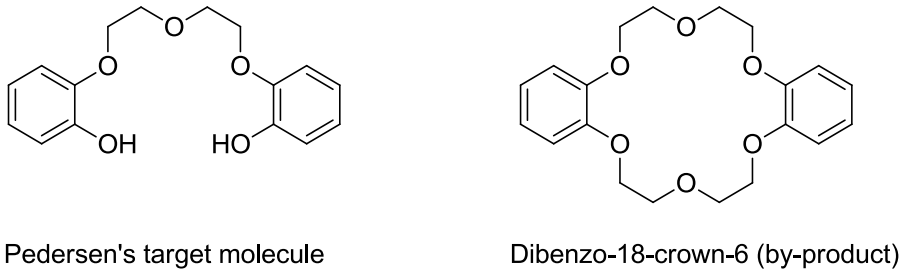
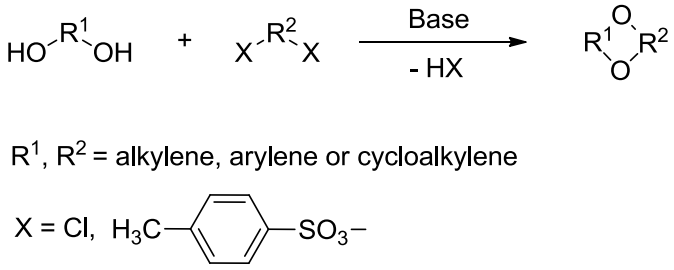


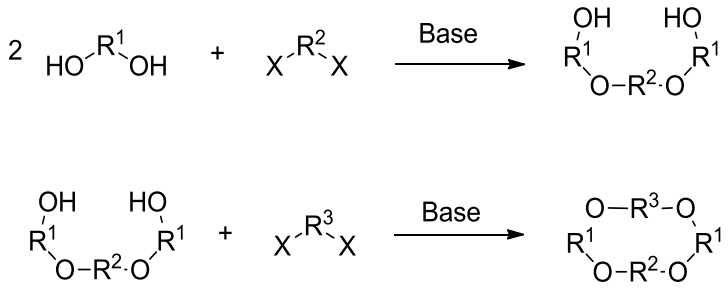
Figure 30. *Pedersen's molecules.*

Most of the synthetic approaches applied nowadays for the production of crown ethers are analogous to the Williamson ether synthesis.[136] The ether ring is formed by reaction of diols that act as nucleophiles with bifunctional components that possess (terminal) leaving groups such as chlorides or tosylates (Scheme 110).



Scheme 110. *Analogous ether synthesis.*

The reaction is usually performed in the presence of a base as an alkali metal hydroxide or carbonate, cesium fluoride, potassium tert-butoxide or sodium hydride. The most common solvents used are *n*-butanol, *tert*-butanol, tetrahydrofuran (THF), and, less frequently, dimethylformamide (DMF) or dimethyl sulfoxide (DMSO). Cyclization can take place in a single step or in sequence (Scheme 111).



Scheme 111. *Cyclization in one or two steps.*

When cations of compatible size with the crown ether are added, a template effect is observed which translate selectivity plus an enhancement in yield and reaction rate. In addition, the concentration of the reactive species have a great influence on the yield of the macrocycles and high dilutions are often required for an efficient synthesis.[137]

A good alternative to traditional methods is the synthesis of macrocyclic compounds under phase transfer catalysis (PTC) conditions in which the substrate is contained in the organic phase at relatively high concentration whereas the base in the polar phase. The reaction occurs at the interface and in this way the reactive species can be maintained at low concentration.[138]

13.3. Applications

Crown ethers have found applications in many areas based on their ability to selectively recognize cations of different ionic radii via ether oxygen atoms. They exhibit strong affinity especially for alkali and alkaline earth metal as reported in Figure 30 in which are

reported some binding constant between mono or divalent ions and dicyclohexyl-18-crown-6 in water (Figure 31).[139]

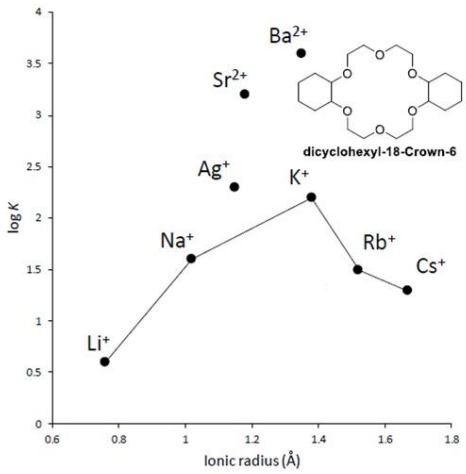


Figure 31. Binding constant as a function of ionic radii for dicyclohexyl-18-crown-6 in water.

The "host-guest" chemistry of crown ethers (wherein the crown plays the "host" and the "guest" is the incoming species) can have a fundamental role in the movement of essential elements in the body and can also play the part of very complicated biological reactions, such as enzyme functions, which can be applied to develop new pharmaceuticals.[140]

In analytical chemistry, the property of crown ether to be selective cation binder is exploited in separation and transport processes for the recovery or the removal of cations, from very dilute solutions and in the design of ion-selective electrodes. Furthermore, they have also been used as stationary phase in chromatographic techniques.

The group of Hyun reported the preparation of a novel crown ether-based chiral stationary phase (CSP) starting from diphenyl substituted *cyclo*-BINOL and showed its application to the resolution of α-amino acid enantiomers (Figure 32).[141]

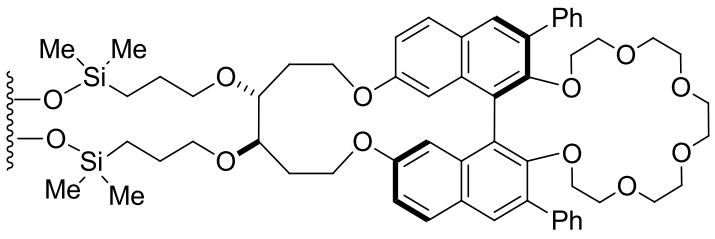
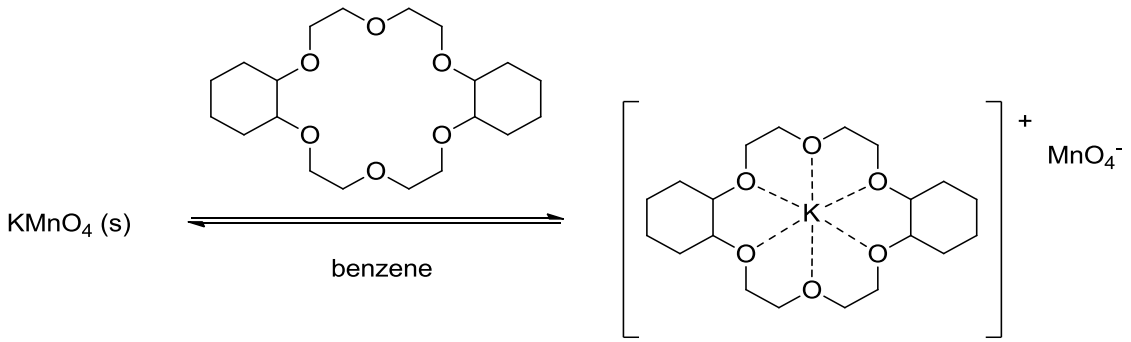


Figure 32. *Crown ether-based chiral stationary phase.*

Crown ethers also helps dissolve salts such as potassium salts in organic media by changing the cation/anion interaction (i.e., by shielding the cation and activating the anion) and for this they have been used in many syntheses as catalysts in phase-transfer catalysis (PTC) or enzyme mimics. The first example of such transfer properties was reported by Sam and Simmons in 1972 when they mixed $KMnO_4$ with dicyclohexyl-18-crown-6 in benzene. The normally insoluble salt became soluble in the presence of crown ether as observed by the coloration of the solution (Scheme 112).[142]



Scheme 112. *Transfer properties.*

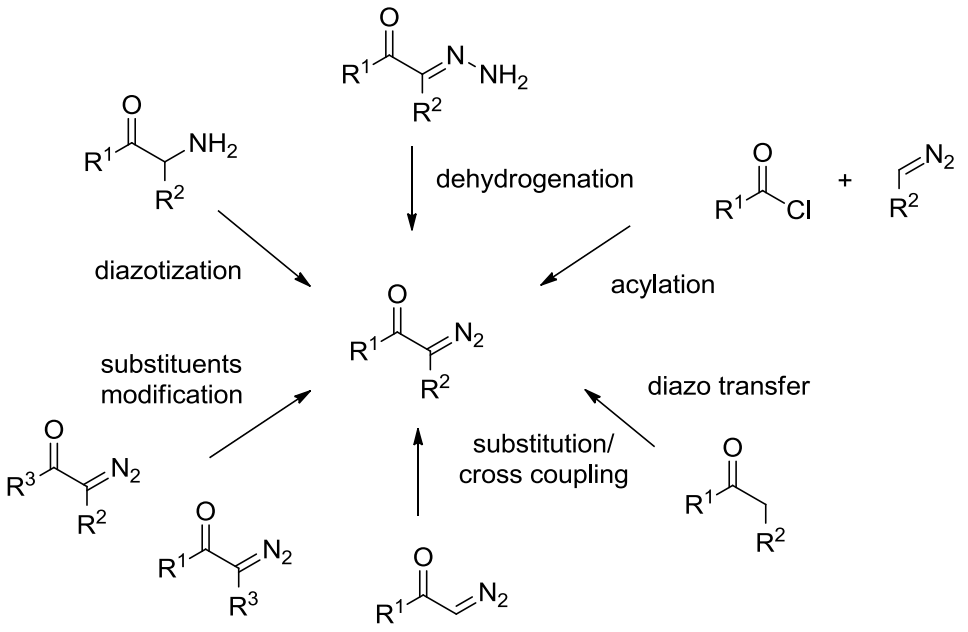
14. Macrocyclization from diazo precursors

14.1. Diazo compounds

The diazo compounds are versatile intermediates that have fascinated organic chemist since Theodor Curtius synthesized ethyl diazoacetate (EDA) for the first time in 1883. Even today, after more than a century of research, they still play a fundamental role especially for the generation of metal carbene. The advantages of using this type of reagent are the smooth reaction conditions required and the N_2 gas as only by-product generated during the reaction. However, these compounds can be hazardous to manipulate due to the possible sudden N_2 extrusion, leading to explosion.

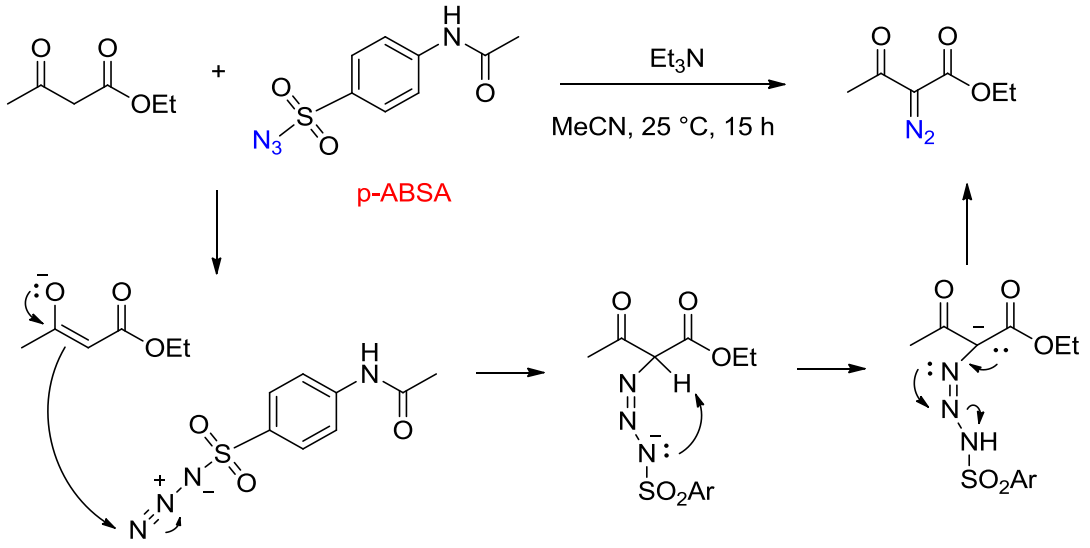
14.1.1. Synthesis

Several reviews have been published based on the development of the synthesis of diazo carbonyl compounds which can be accomplished by several methods as reported in Scheme 2. The classical routes include: *(1)* amine diazotization, *(2)* modification of oximes, hydrazones, and tosylhydrazones, *(3)* acylation of diazoalkanes, and *(4)* diazo transfer to an acid derivative or a ketone. To this list we can also add other approaches as *(5)* substitution or cross-coupling at the diazo carbon and *(6)* substituent modification at either side of the diazocarbonyl group (Scheme 113).[143]



Scheme 113. *Strategies for the synthesis of diazo-α-carbonyl.*

However the most practical is a N_2 transfer reaction from an organic azide reagent to a carbonyl neighbor group[144] as reported more in detailed in the Scheme 114.



Scheme 114. *N_2 transfer reaction for the synthesis of carbonyl diazo compounds.*

Diazo reagents possess a mesomeric form which show a formal negative charge on the carbon adjacent to the N_2 moiety and, hence, a *Lewis* basicity and nucleophilicity.

The possibility to delocalize the negative charge can stabilize these moieties leading to relatively stable compounds (Figure 32).

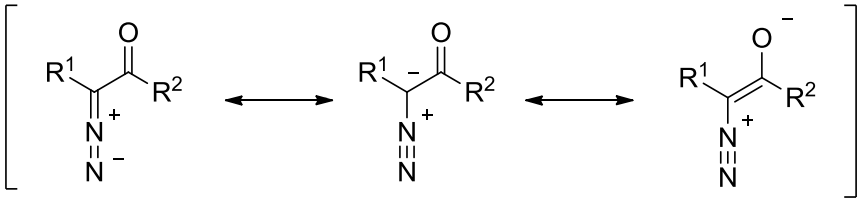


Figure 32. *Mesomeric forms of a carbonyl diazo moiety.*

The diazo reagents stabilized by carbonyl groups are the most used in catalysis and can be classified into three main classes: (i) acceptor-acceptor, (ii) acceptor, and (iii) donor-acceptor diazo derivatives. Due to charge delocalization, acceptor-acceptor diazo derivatives are the less reactive with respect to the donor-acceptor that are instead the most reactive showing enormous differences in decomposition kinetics (Figure 34).[145]

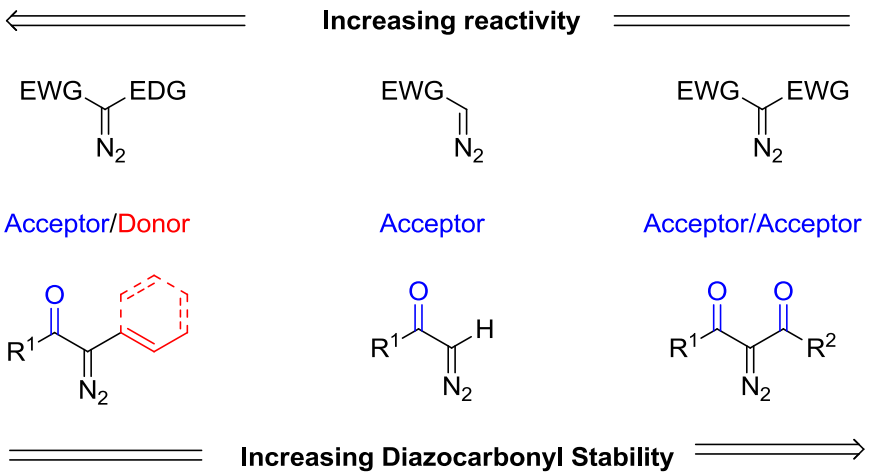
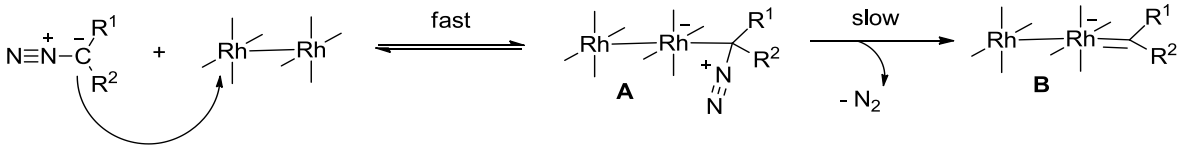


Figure 34. *Classification, reactivity and stability of diazo reagents.*

14.1.2. Decomposition

The *Lewis* basic diazo reagent reacts with *Lewis* acidic dirhodium complexes to generate the metal carbene. In this process, several steps have to be taken into account. In 1952, Yates proposed a mechanism for the diazo decomposition catalyzed by Cu catalyst.[146] For Rh(II)-catalyzed reaction, the most likely model involves the initial complexation of the negatively polarized carbon of the diazo compound to the apical site of the Rh(II) catalyst

which is coordinatively unsaturated (Scheme 115). Subsequent irreversible extrusion of N_2 from the diazonium ion adduct **A** generates the Rh(II) carbene intermediate **B**. In this model, the first step is a fast equilibrium whereas the second step is slow and rate limiting, as suggested by a previous study. [147]



Scheme 115. *Dirhodium metal carbene formation.*

The first step of this process can be alternatively considered as a *Lewis* acid/*Lewis* base interaction with an electron donation from the filled orbital of the diazo reagent to the vacant orbital of the dirhodium complex. The second step involves π-backdonation from the *d*-electrons of rhodium into the σ* orbital of the C –N bond which leads to irreversible extrusion of N_2 (Figure 35).

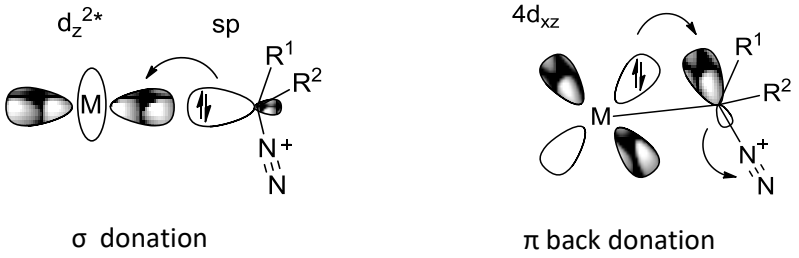


Figure 35. *Lewis acid/Lewis base interaction.*

Once the metal carbene is formed, the R^1 and R^2 groups play a crucial role in directing the reactivity of the intermediate as shown in Figure 36. The acceptor groups, in fact, destabilized the electrophilic carbon and hence acceptor-acceptor metal carbene are more reactive than acceptor and donor-acceptor

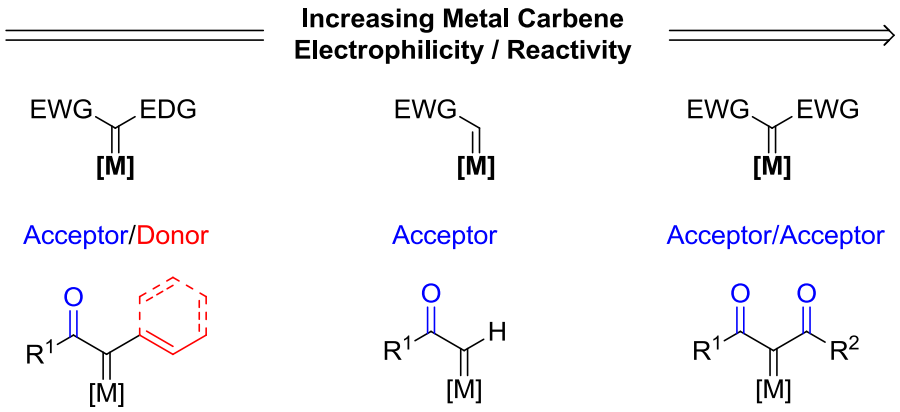
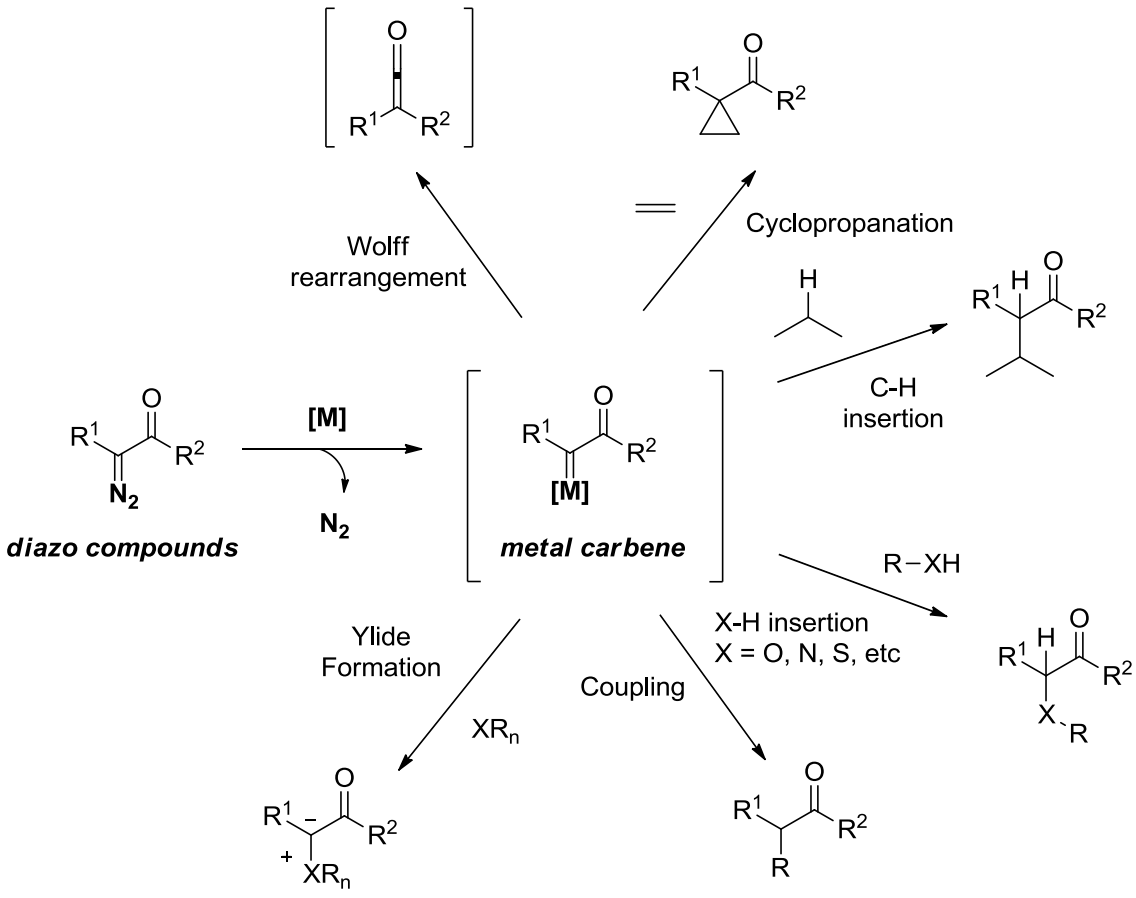


Figure 36. *Metal carbene reactivity.*

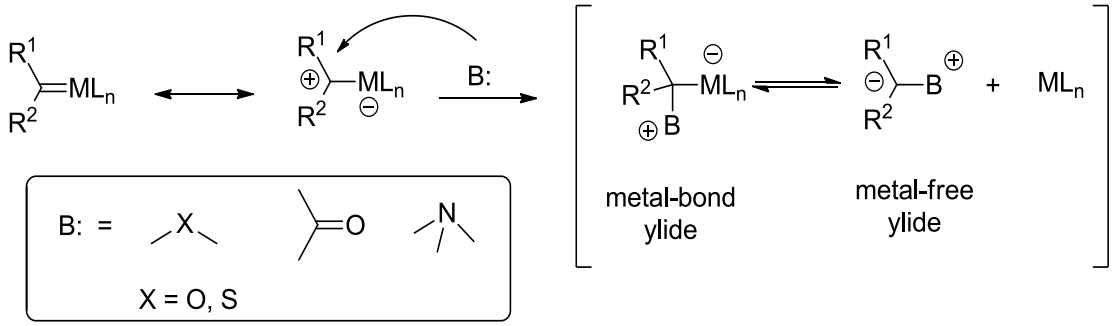
14.1.3. Reactivity

Electrophilic metal carbenes generated from diazo decompositions are too reactive to be isolated, but they can undergo various transformation as reported in Scheme 116.[143,148]



Scheme 116. *Possible transformations of metal carbene.*

The metal carbene derived from diazocarbonyl compounds are highly electrophilic and one of their characteristic reactions is the ylide formation as reported in the Scheme 116. They readily form adduct upon addition of a *Lewis* base (B:), the most common one include ethers, sulphides, amines and carbonyl compounds. The adduct generated can either dissociate to form a "metal-free ylide" or react as a metal-bond ylide complex (Scheme 117).[149]



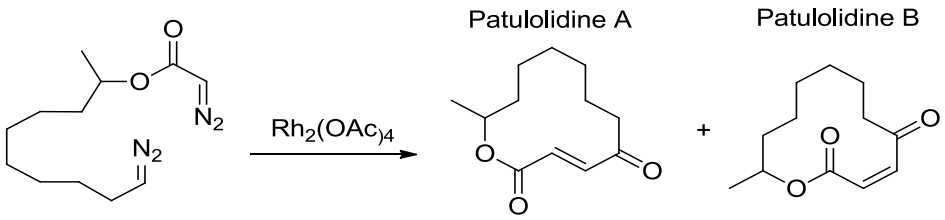
Scheme 117. *Metal-bond and metal free ylide.*

These ylides are usually highly reactive species and readily undergo further reactions, both inter- and intramolecularly, to give more stable products. The most common reactions include [2,3]-sigmatropic rearrangement of allyl-substituted intermediates, [1,2]-insertion or Stevens rearrangement (typical of oxonium, sulfur, and nitrogen ylides), and dipolar cycloaddition (typical of carbonyl ylides).[150] An interesting application of ylides and mainly oxonium ylides generated from diazo compounds is the synthesis of a particular class of polyether macrocycles reported by the group of Prof. Lacour that will be explained more in detail.

14.2. Macrocycles synthesis

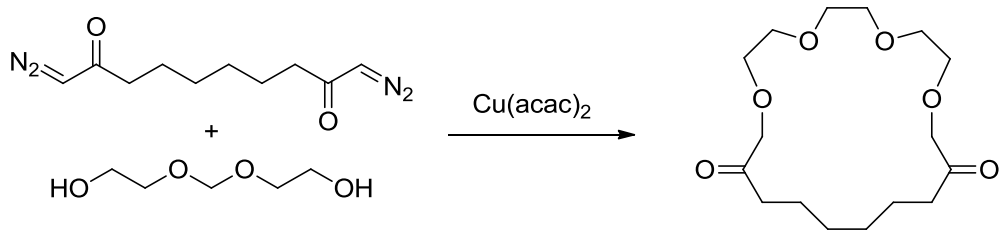
The formation of electrophilic metal carbene from diazo compounds can undergo various transformations as dimerizations, insertions, cyclopropanation and ylide formation can be applied to the macrocyclization strategies.

For istance, Doyle proposed the synthesis of Patulolides A and B by intramolecular cross-coupling of *bis*-diazo acetates through formal dimerization of carbenes under dirhodium catalyst (Scheme 118).[151]



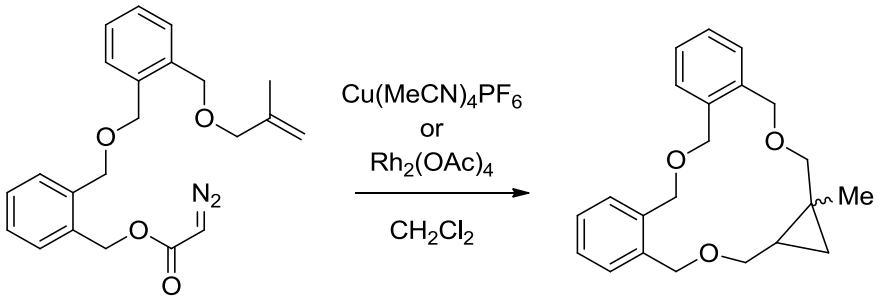
Scheme 118. *Synthesis of Patulolides A and B (Cross-coupling).*

McKervey also synthetized polyether macrocycles of different sizes applying an OH insertion for the key ring closure step from *bis*-diazo-ketones and symmetrical polyethylene glycols using $Cu(acac)_2$ (Scheme 119).[152]



Scheme 119. *McKervey synthesis of polyether macrocycles (OH-insertion).*

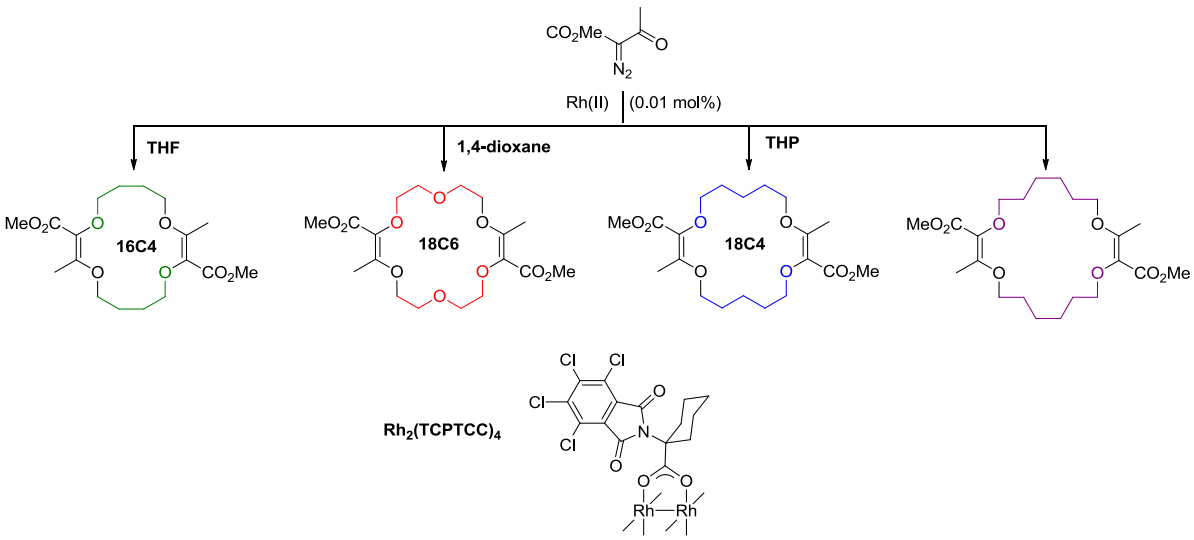
Metal carbenes formed under dirhodium catalysis are known to undergo cyclopropanation reactions in the presence of double bonds (or cyclopropenation with alkyne). Doyle took advantage of this reactivity to form macrocyclic lactones by intramolecular reaction of α- diazoesters linked to remote alkenes under Rh(II) catalysis (Scheme 120). [153]



Scheme 120. *Doyle synthesis of macrocycles (cyclopropanation).*

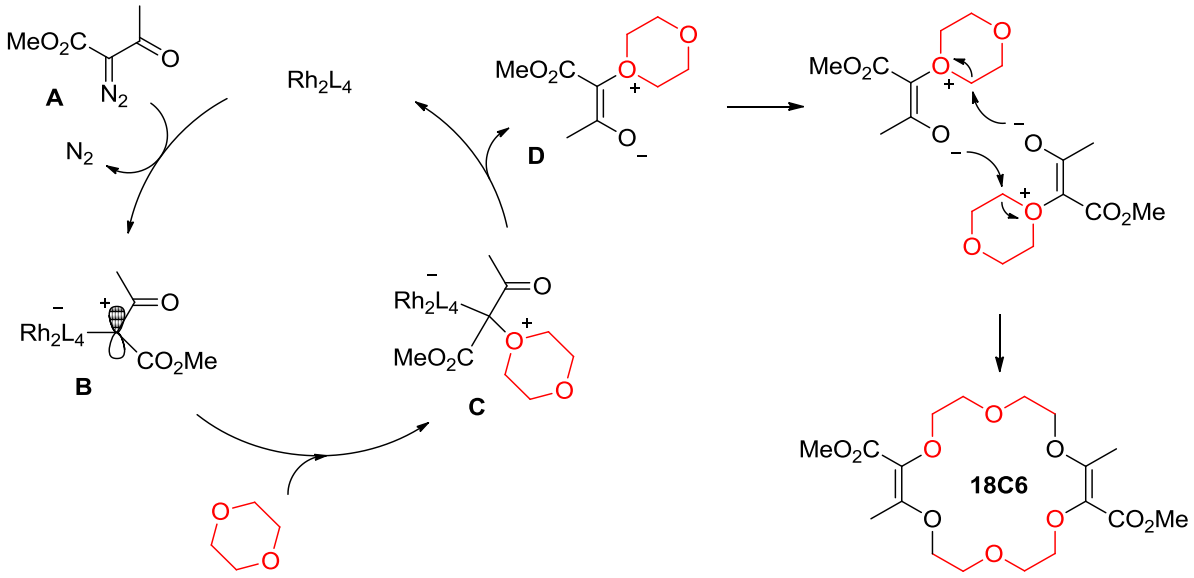
In this framework it is particularly interesting the reactivity of diazo compounds under rhodium catalysis developed by Lacour and his collaborators to afford the synthesis of original macrocycles from simple cyclic ethers and oxetanes through the generation of oxonium ylides.

The group reported the one-pot rhodium(II)-catalyzed synthesis of 16- to 20-membered polyether macrocycles by [3+X+3+X] (X = 5 to 7) condensations of different α-diazo-β-ketoesters with, THF (tetrahydrofuran), 1,4-dioxane THP (tetrahydropyran), or oxepane with moderate to good yields (Scheme 121). The most important advantages of this methodologies are the possibility to make it on-gram scales and the easy purification just a simple exctraction.[154]



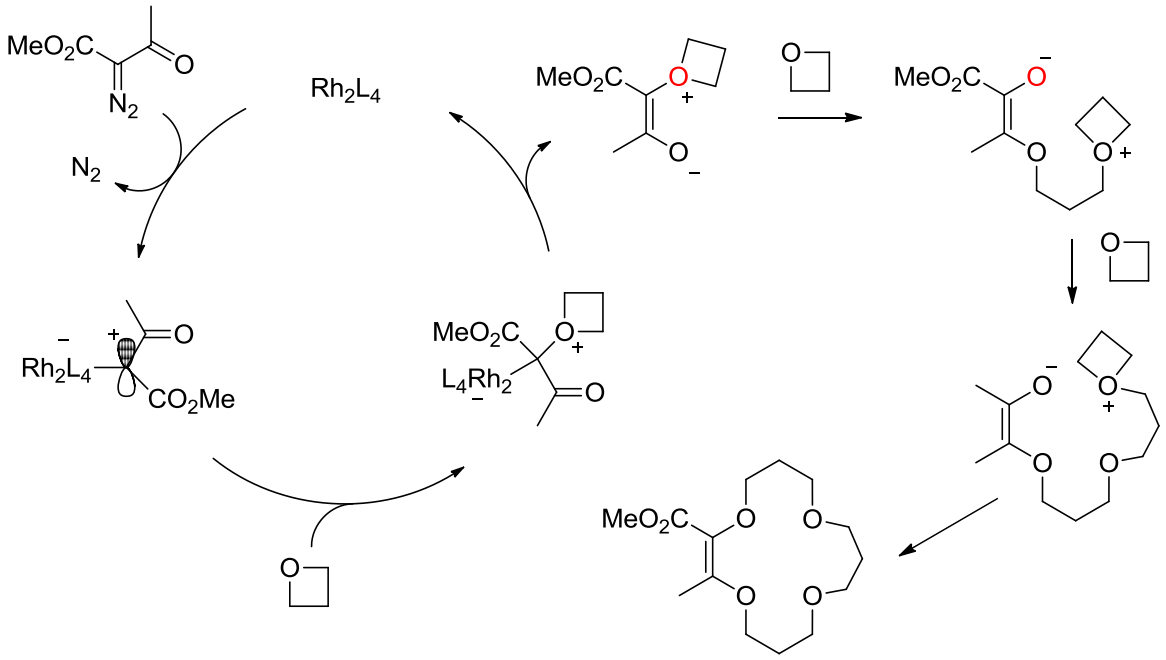
Scheme 121. *Rh(II) catalyzed [3+6+3+6] condensation of α-diazo-β-ketoesters and 1,4-dioxane.*

The mechanism for this reaction is reported in Scheme 122 for 1,4-dioxane. The diazo compound **A** is decomposed by the dirhodium catalyst to form an electrophilic metal carbene **B**. Then a cyclic ether (here 1,4-dioxane) acts as a *Lewis* base and generates the metal bound oxonium ylide **C**. After release of the catalyst and formation of the metal free oxonium ylide **D**, this specie dimerizes to form the **18C6** macrocycle.



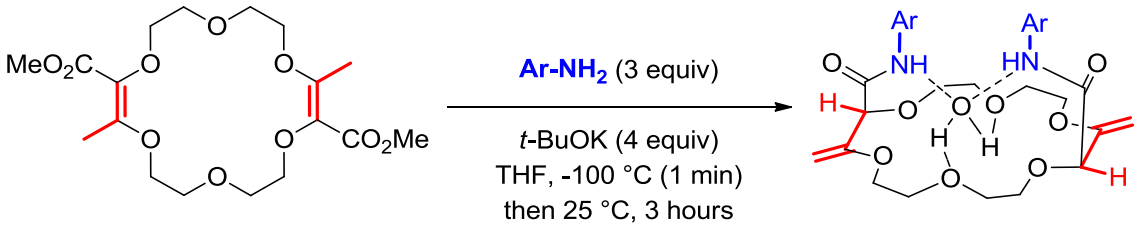
Scheme 122. *Mechanism for 1,4-dioxane for 18C6.*

When oxetanes are used instead 1,4-dioxane, 15-membered ring macrocycles are afforded.[155] In this case, the reaction followed a different mechanism which leads to [3+4+4+4] condensation product (Scheme 123). After decomposition of the diazo reagent and formation of ylide, there is not the dimerization of the oxonium ylide but two successive additions of two additional oxetanes which act as nucleophile to afford the final product ring closure.



Scheme 123. *Mechanism for oxetanes.*

A transposition protocol was developed by the research group of prof. Lacour and **18C6** or similar macrocycles can be transformed in one pot into chiral polyether macrocycles in the presence of an excess of aromatic amines in strongly basic conditions (Scheme 124).[156]



Scheme 124. *Amidation/transposition protocols.*

In this process two transformations occur (i) an amidation of the ester functions and (ii) the transposition of the olefins from an endocyclic to exocyclic position. The reaction is highly diastereoselective as only the chiral (racemic) diastereoisomer is generally formed; the achiral (*meso*) diastereoisomer being not observed.

The product formed assumes a limited number of conformation with the carbonyl groups facing outwards orthogonally oriented to the plane of the polyether ring, due to minimization of the allylic strain formed by the olefins and the C-H group of the stereogenic centers. As a consequence, the two aromatic moieties lie at immediate spatial proximity in front of each other (Figure 37).

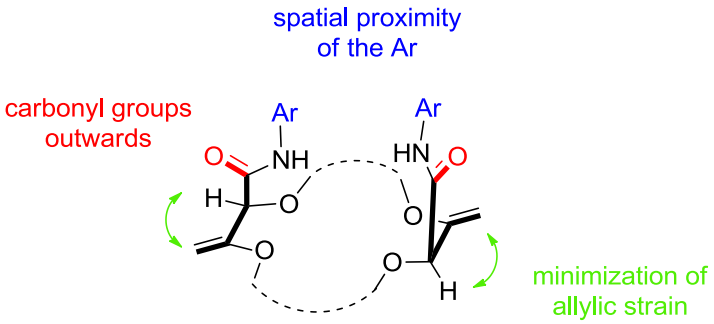


Figure 37. *Particular structure.*

A water molecule can also be complexed inside the crown ether linked by hydrogen bonding with the N-H amide and the oxygen atoms of the ring in a limited number of case. Moderate yields are obtained using various electron-rich or electron poor anilines and aromatic amines of 2-naphtalene and pyrene or pyridines. However, this transformation is only limited to aromatic amines and anilines. The use of aliphatic amines in the one-pot process led to extensive decomposition of the substrate and a complete lack of isolable products.

15. Lanthanide

15.1. Luminescence property

The research on metal macrocyclic complexes has had a significant impact on different fields since their earliest application to our days in which the transition metals are replaced with lanthanides or actinides. Their use introduced a significant contribution due to their unique physicochemical properties arising from their inherent electronic structure, promoting many of actual technological applications like optics, optoelectronics (LED and OLED), magnetism (single molecule magnets), magnetic resonance imaging, luminescent probes, biomarkers ...

One important aspect of the lanthanide ions are their particular spectroscopic properties with sharp and characteristic emisions band due to fact that 4f orbitals are shielded by the 5s and 5p orbitals and do not suffer from external influences. Trivalent cations in particular display poor absorption and emission effectiveness that correspond to the low extinction coefficients of the Laporte forbidden f-f electronic transitions (parity rule), making the direct excitation of the metals inefficient. The use of strongly absorbing antenna (chromophores) is a strategy to stimulate luminescence of lanthanide elements conferring strongly emissive and long-lived excited states (antenna effect).

The general architecture of emissive lanthanide complexes consists of the metal center surrounded by a chelate or an antenna. The antenna harvests energy through high molar absorption to the singlet excited state. After undergoing intersystem crossing to the triplet state usually also favoured by the heavy atom effect of the lanthanide, the antenna transfers energy to the excited ^5D_J state of the lanthanide. The radiative transition of electrons from the excited ^5D_J state to the ^7F_J states (now favoured by the Laporte rules) results in bright luminescent emission from the lanthanide ion (Figure 38).

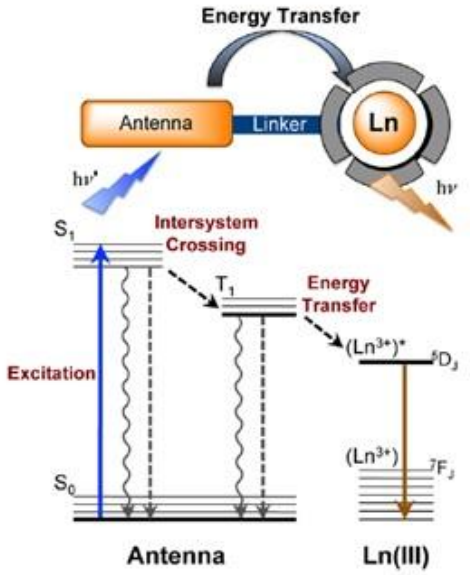


Figure 38. *Property of lanthanide.*

In Figure 39 are represented the luminescent 4f−4f transitions of europium and terbium complexes and the commonly observed emission wavelengths for each one: red for Eu^{3+} and green for Tb^{3+} respectively. They have received considerable attention due to several factors which are mainly the higher emission intensities and the longer luminescent lifetimes (millisecond instead of nanosecond or microsecond) than other metals.

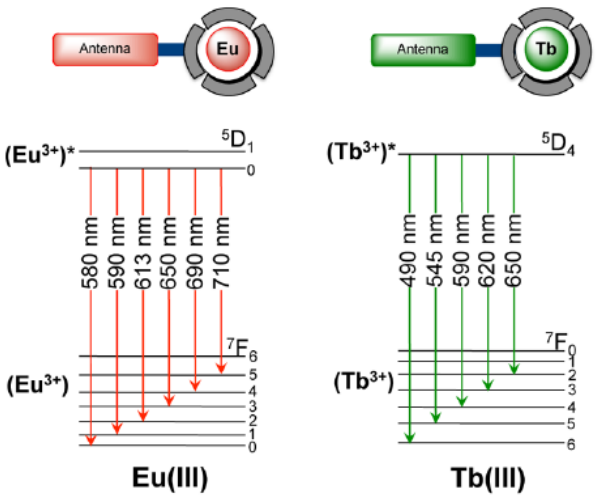


Figure 39. *Eu(III) and Tb(III) transitions.*

Two general strategies can be employed in the design of an effective antenna to have luminescence: the pendant antenna, derived from existing organic chromophores that are attached to the Ln(III) ions through linker, or the chelating antenna, which absorbs incident light and also coordinate the metal (Figure 40).[157]

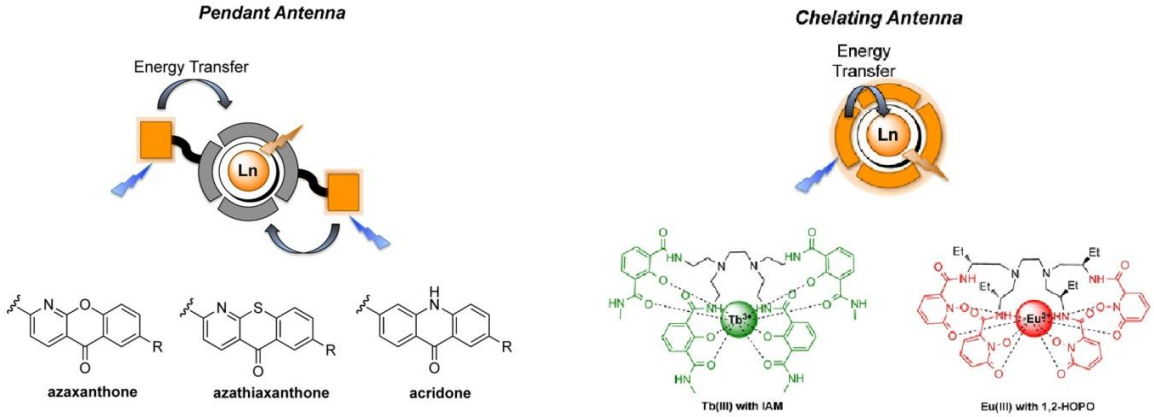


Figure 40. *Two different type of antenna.*

Macrocyclic compounds especially polyamines such as 1,4,8,11-tetraazacyclotetradecane (cyclam), 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,7-triazacyclononane (tacn) are widely employed as useful frameworks to construct functional chelating ligands in coordination chemistry. The group of Nakai and Ogo showed the high luminescent of a Tb(III) complex of a tris-aryloxide functionalised 1,4,7-triazacyclononane ligand (Figure 41).[158]

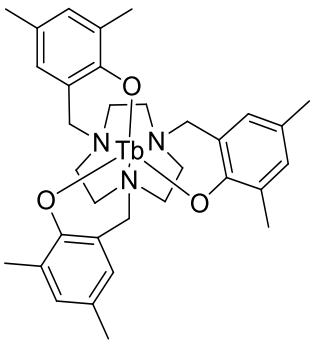


Figure 41. *Nakai and Ogo Tb(III) luminescent macrocycle.*

The group of Galup and Picard designed a 15-membered macrocyclic ligand with the aim of sensitizing the visible luminescence of the Tb^{3+} ion in water. This octadentate ligand is based on a intracyclic N,C-pyrazolylpyridine chromophore and a diethylenetriamine-triacetic acid core. It react with equimolar amount of $TbCl_3$ salt to yield the complex (Figure 42).[159]

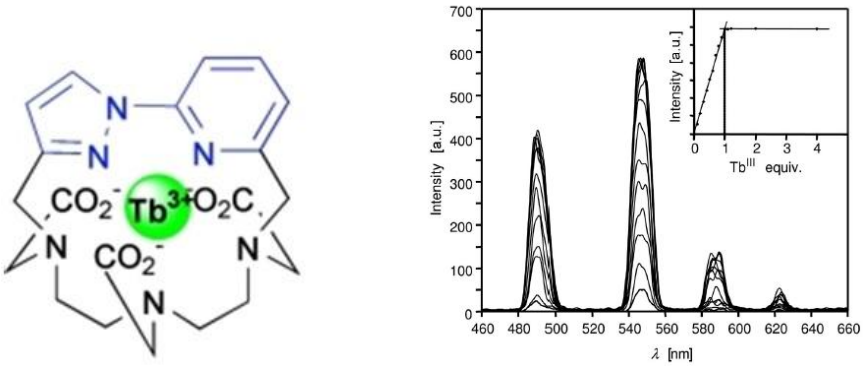


Figure 42. *Galup and Picard Tb(III) luminescent macrocycle.*

15.2. Circularly polarized luminescence

Circularly polarized luminescence (CPL) has emerged as another important parameter in the design of luminescent lanthanides. It provides the differential emission intensity of right and left circularly polarized light, giving information about the excited state properties of the chiral molecular systems. The CPL signatures can be used as a powerful tool to obtain stereochemical, conformational and three-dimensional structural information of molecules. In recent years, there has been a growing interest toward the development of chiral and enantiopure lanthanide complexes with the appropriate organic chromophore that can produce a well-defined and intense CPL signals.[160]

A wealth of europium complexes exhibiting CPL has been reported until now, in line with this metal's exceptional suitability for observing CPL. Though the electronic nature of the $^5D_4 \rightarrow {}^7F_5$ transition of terbium is less favorable for the observation through of CPL, the generally high luminescence of this lanthanoid is beneficial for the detection of CPL and many examples have been reported.[161]

The group of Piccinelli reported the synthesis of two different water-soluble Eu(III) and Tb(III) complexes with a detailed optical and chiroptical characterization which reveals a strong CPL activity. A value of g_{lum} around 0.1 for the Tb-based complex has been found which is one of the highest values measured up to now for chiral Tb complexes (Figure 43).[162]

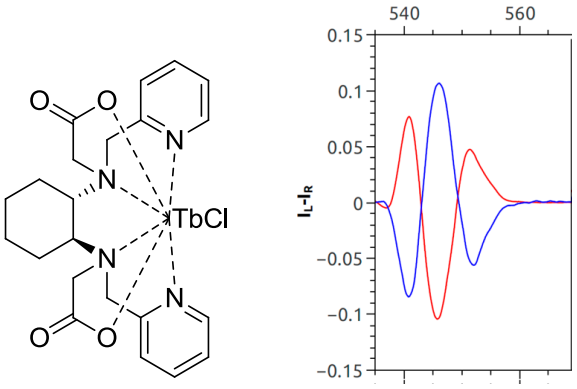


Figure 43. *CPL of a water-soluble Tb(III) complex.*

Terbium complexes exhibit in general lower g_{lum} value with respect to europium complexes: the group of Piscitelli, for example, has successfully reached the value of 0.82 for a diketonate complex with Eu(III) ions (Figure 44).[163]

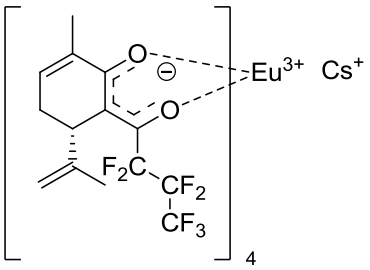


Figure 44. *Diketonate complex with Eu(III).*

16. Project

The group of prof. Jérôme Lacour in the last few years reported various applications for chiral polyether macrocycles of type reported in Figure 45. The proximity of the two aromatic units offer elegant excimer fluorescent properties that can be modulated by addition of metal. This type of compounds finds applications for example as probes or heteroditopic receptors for salts.

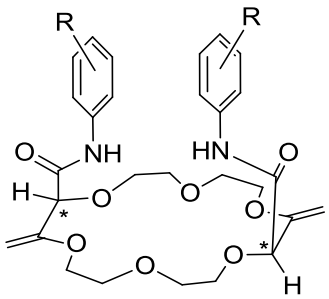


Figure 45. *Lacour's macrocycle.*

In 2018 they published the synthesis and resolution of a series of chiral fluorescent macrocycles together with their strong excimer fluorescence (EF), with an intense associated circularly polarized luminescence (CPL) and also good electronic circular dichroism (ECD) properties (Figure 46).[164]

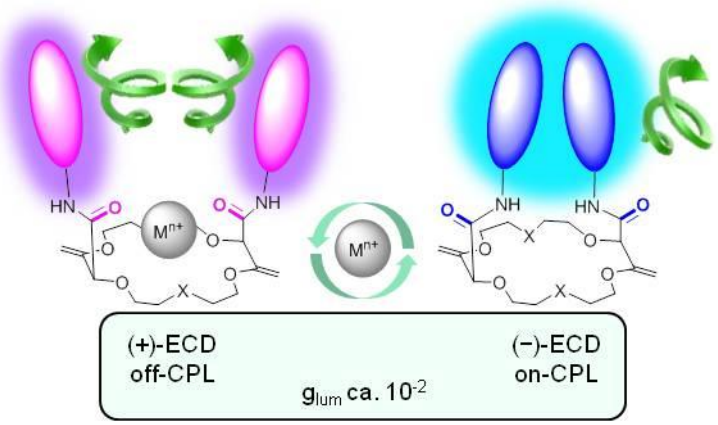
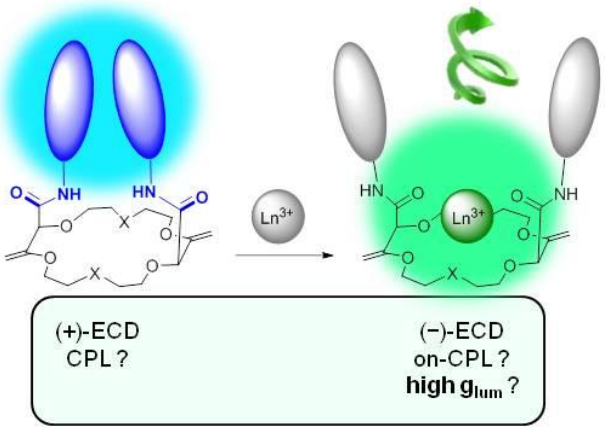


Figure 46. *Ecximer associated CPL.*

The EF, ECD and CPL signals are strongly affected by the presence of metals ions as sodium or barium since their coordination induces important change in the conformation. In fact, upon binding with cations, the amide group can turn inwards to favour the cation complexation. As a consequence, the two aromatic units (chromophores) part from each other elongating in this way the distance between them. Hence the excimer fluorescence as well as the CPL signal are totally quenched. At the same time also the ECD signal is inverted upon complexation. Upon decomplexation of the metals ions original signals is recovered. The designed macrocycles display thus a remarkable combination of both +/− ECD and on/off CPL reversible switching over several cycles.

The aim of the project was to extend the application of the chiral macrocycles by using them possibly as chiral ligand for lanthanides. Lanthanides are poor chromophore and fluorophore as such due to the fact that f-f- transitions are Laporte-forbidden, but when associated to a proper ligand, they can emit light efficiently after energy transfer from the ligand. Of importance, if the ligand is chiral, strong CPL could also be measured.[165] We focus particularly our attention on the study of the luminescence of terbium(III) complexed by different macrocycles bearing various (hetero)aromatic units .

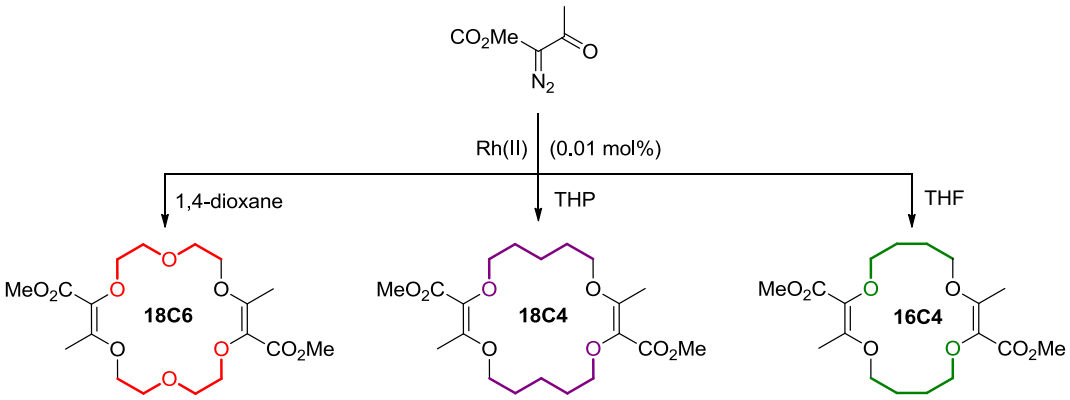


Scheme 125. *Aim of the project.*

17. Results and discussion

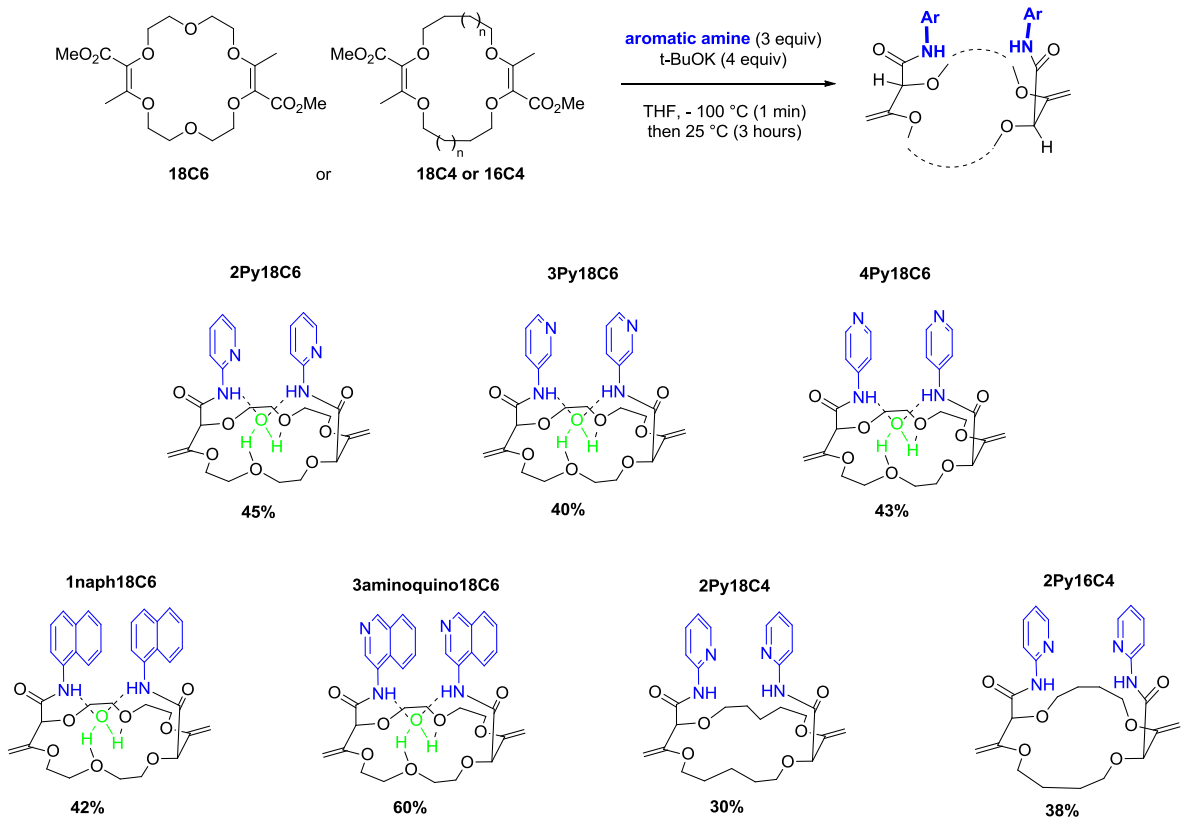
17.1. Synthesis and resolution of macrocyles

The unsaturated macrocycles 18C6, 18C4 and 16C4 were selected as building blocks for the synthesis of the chiral macrocycles. The synthesis of 18C6 was achieved on multigram scale by a Rh(II)-catalyzed (0.01 mol%) decomposition of α-diazo-β-keto ester 1 in presence of 1,4-dioxane (used as solvent). This procedure was applied on gram scale also for the preparation of 18C4 and 16C4 from 1 with THP or THF respectively (Scheme 126).[154]



Scheme 126 . *Synthesis of unsaturated macrocycles 18C6, 18C4 and 16C4.*

Treatment of the three derivatives with an excess of aromatic amines under strongly basic conditions (t-BuOK) afforded in one step, the corresponding functionalized macrocycles in moderate to good yields (17–80%). In all cases, the diastereoselectivity of the reaction was excellent (d.r. > 49 : 1) in favor of the chiral (racemic) diastereomers (Scheme 127).



Scheme 127. *Synthesis of functionalized macrocycles.*

The CSP-HPLC resolution of 2Py18C6 was performed to record later the ECD and CPL spectra. The protocol already developed by the group for similar compound which use CHIRALPAK® IG columnas CSP and a mixture of CH_2Cl_2 and CH_3CN with diethylamine additive (0.1%) as mobile phase was not efficient due to problem of solubility of 2Py18C6 in the solvent mixture.[164] This was overcome through the use of a solvent mixture of CH_2Cl_2 and MeOH (99:1) with 0.1% of diethylamine (Figure 46, on left). Unfortunately only the first peak (or enantiomer) is well resolved with respect to the other. Thanks to the help of Chiraltek, the diethylamine was replaced with diethanolamine and a stock solution of the mobile phase was prepared instead of using the mixer of the HPLC apparatus to prevent an inhomogeneous mix due to the difference of viscosity between the solvents (Figure 47, on right). So using the final conditions CH_2Cl_2-MeOH (99:1, 0.1% diethanolamine), 2Py18c6 was separated efficiently on a semipreparative scale (1st eluted enantiomer ee = 99%, 2nd eluted enantiomer ee = 95%).

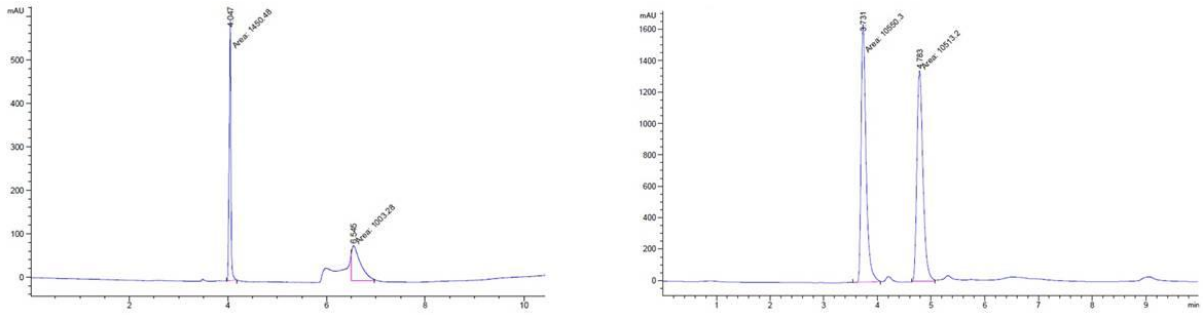
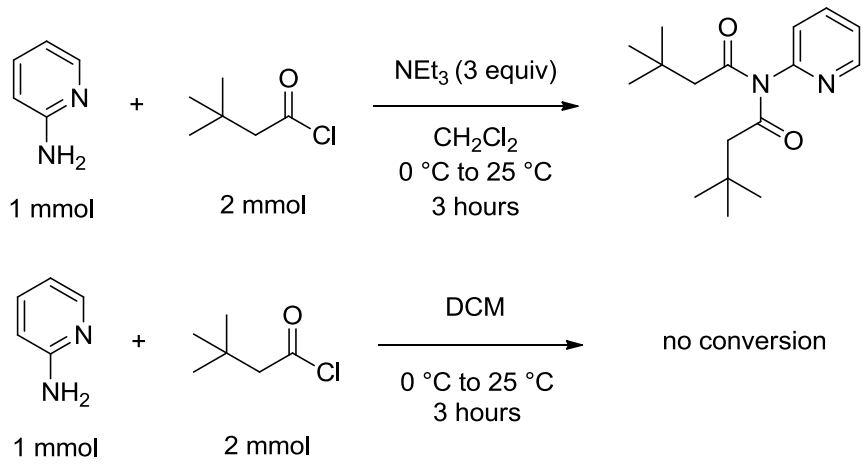


Figure 47. *Resolution of 2Py18C6.*

17.2. Synthesis of Monomer

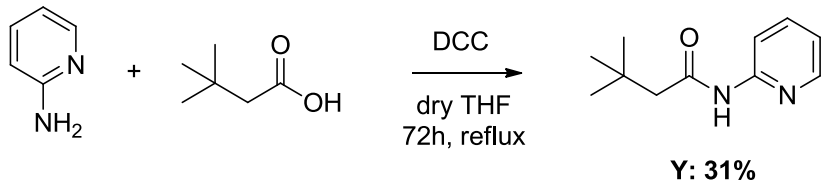
The 2Py-monomer was synthesized with the aim of having a reference molecule to be compared with the optical properties of the corresponding 2Py18C6 macrocycle. Neopentylcarboxamide was selected as monomeric reference for the macrocycles. Several procedures have been tried in order to obtain this compound required for spectroscopic analysis.

In the preliminary attempt, the direct acylation conditions used for other studies were applied using the amine, the acyl chloride and trietylamine obtaining only the product of double addition of the neopentylcarboxyl units. Attempts of the same procedure in absence of external base prevented the reaction to proceed (Scheme 128).



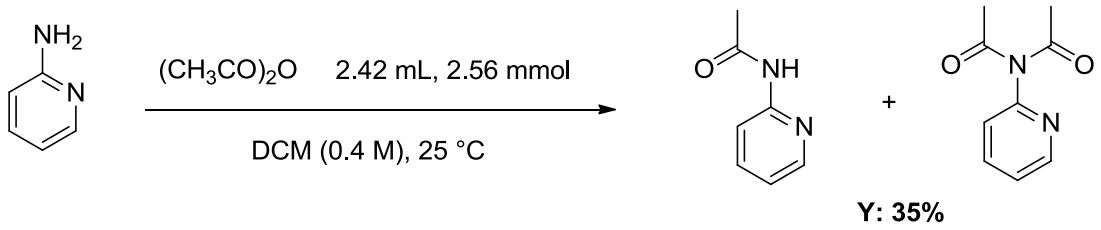
Scheme 128. *Preliminary synthesis of 2Py-monomer.*

Then the amidation of carboxylic acid mediated by DCC (N,N'-dicyclohexylcarbodiimide) was tested. Unforunately, only a very low yield was obtained after 72 hours with sensible amount of DCC by-product contaminating the final product (Scheme 129).



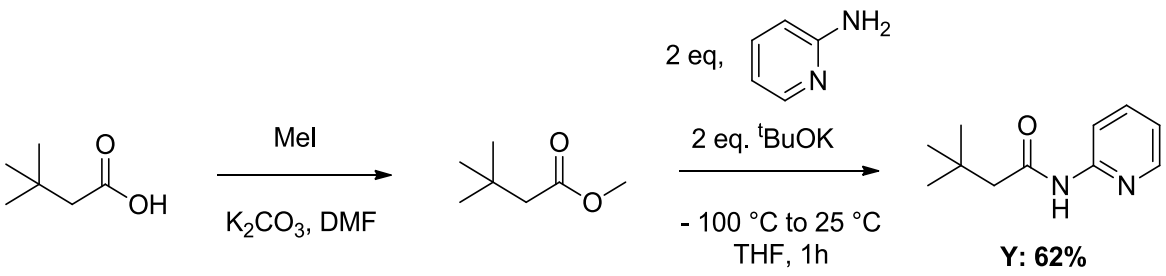
Scheme 129. *Synthesis of 2Py-monomer with DCC.*

The condition developed by Kathiravan and Nicholls for the preparation of acetanilides were examined next starting from acetic anhydride instead of acyl chloride or carboxylic acids as reported in Scheme 130. Sadly in this case the product was contaminated with non-neglibible amount of the product of double addition.[166]



Scheme 130.*Kathiravan and Nicholls conditions.*

The best result for the synthesis of the 2Py-monomer was obtained applying the same reaction used for amidation/transposition of macrocycles from the corresponding methylester (Scheme 131).[156]



Scheme 131. *Application of amidation/transposition condition to 2Py-Monomer.*

17.3. Formation of terbium complex

First, the luminescence of the complex between 2Py18C6 and terbium(III) was tested qualitatively under the UV lamp (254 nm) adding $Tb(OTf)_3$ to a solution of the macrocycle in acetonitrile (Figure 48, on left) and performing preliminary absorption and emission spectra (Figure 48, on right). As expected, neither the terbium or the macrocycle alone exhibit fluorescence in the visible range. Only when both are associated a bright green emission is observed.

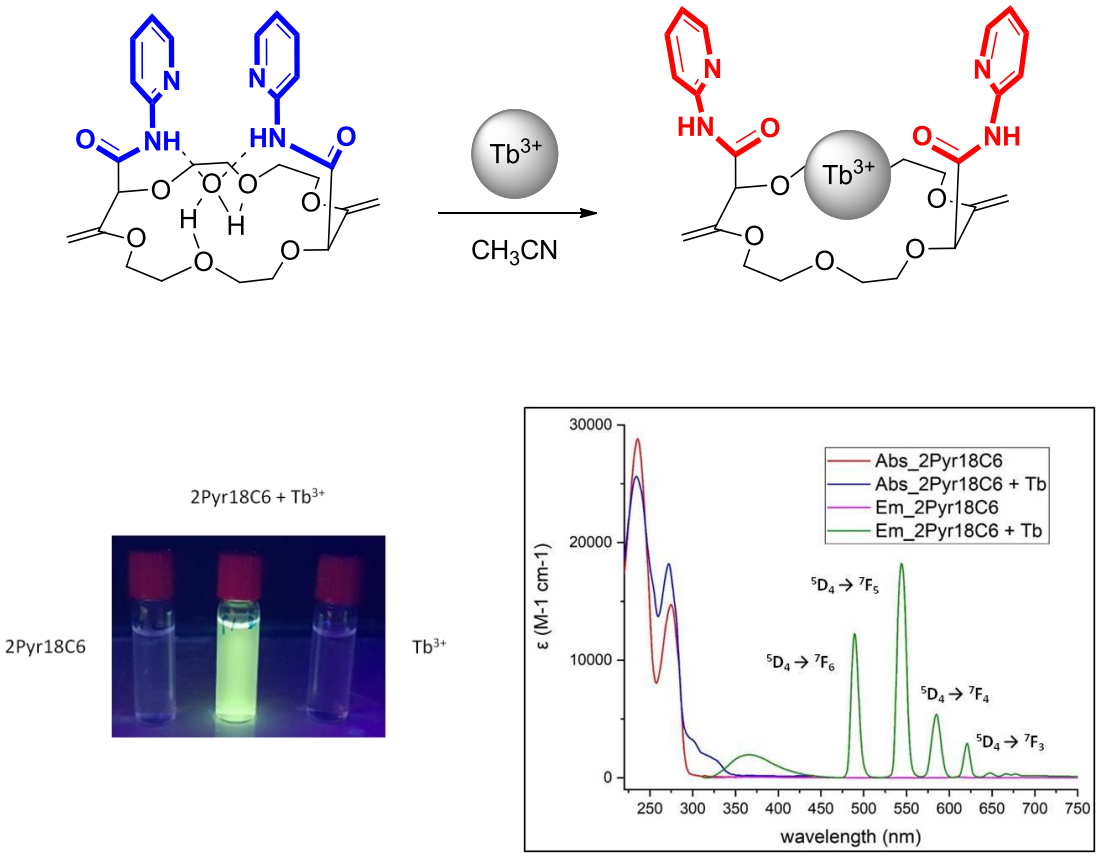


Figure 48. *Luminescent 2Py18C6.*

17.3.1. Absorbance and emission titration studies

The formation of the complex between 2Py18C6 and terbium(III) was therefore monitored through spectrophotometric titration using both UV-Vis absorption and fluorescence spectroscopy. In the titration experiment, $Tb(OTf)_3$ aliquots were added to the macrocycle solution. The evolution in the UV-Vis absorption spectra during the titration is presented in Figure 49 on left. The free ligand spectrum (red line) displays two strong absorption bands with maxima at 238 nm and 270 nm which can be assigned to the n → π* of the carbonyl groups and to the π → π* of pyridine.

Upon $Tb(OTf)_3$ addition up to 1.5 equivalents, the two absorption bands behave differently: the most red shifted one undergoes a small hypochromic effect with respect to the more blue shifted one, which, on the contrary, experiences a small hyperchromic effect**.** Furthermore, as the equivalents of terbium(III) increase, a new weak band around 300 nm appears related to the coordination of the lanthanide with macrocycle.

The spectra do not evolve further after the addition of more than 1.5 equivalents as shown by the plateau (Figure 49, on right).

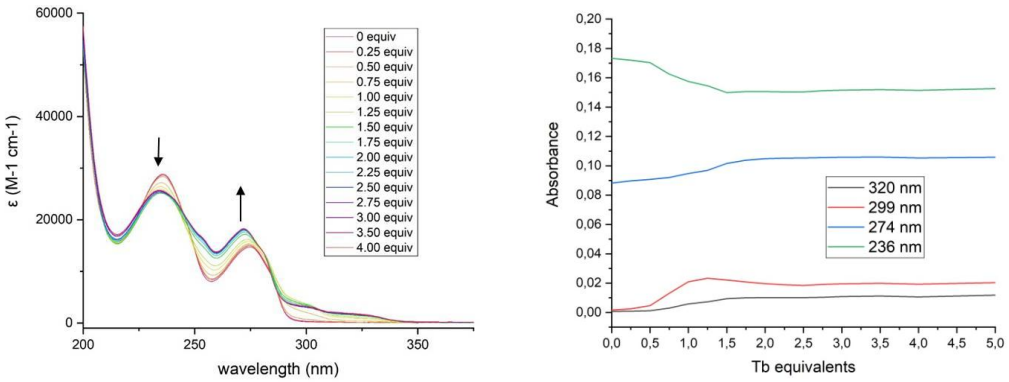


Figure 49. *Absorbance spectrum of 2Py18C6 and Tb.*

To try to understand the coordination behaviour of terbium, the same titration was performed using $Ba(ClO_4)_2$, for which the way of coordination with analogous macrocycles is already known (the ones containing for example pyrene or perylene moiety).[164] The results obtained are reported in Figure 50 in which the same transitions bands evolve with the related increase\decrease similarly to the case of $Tb(OTf)_3$ indicating that probably the binding mode may be the same.

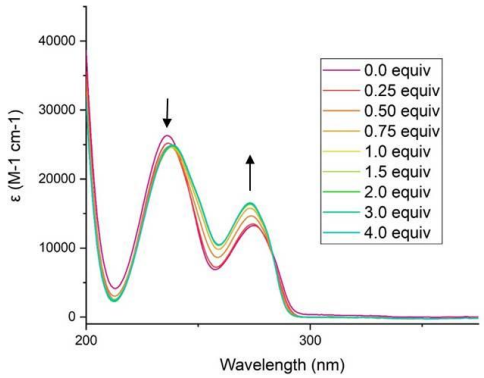


Figure 50. *Absorbance spectrum between 2Py18C6 and Ba.*

At the same time, the change in luminescence emission spectrum was measured. The $Tb(OTf)_3$ titration is presented in Figure 51 on left. The corresponding spectra were recorded from 300 nm to 700 nm upon excitation at 305 nm, i.e. at the new absorption band observed in the UV-Visible spectrum. In the absence of $Tb(OTf)_3$, no emission spectrum can be observed for the 2Py18C6. Upon addition of up to 1.5 equivalents of $Tb(OTf)_3$, sharp emission bands, characteristic for the $^5D_4 \rightarrow {}^7F_j$ (j = 6 - 3) terbium transitions appear at 485 nm, 545 nm, 580 nm and 620 nm, respectively. The maximum emission amplitude has been reached for 1:1.5 ratio between the ligand and cation. No further spectral evolution was observed with additional amounts of $Tb(OTf)_3$ once maximum was reached. This is also visible from the graph of the equivalent vs fluorescence in which, as in the case of the UV-Visible titration, a plateau was reached (Figure 51 on right). Additionally, a quantum yield of 5% was measured using 9,10-diphenylanthracene as the reference.

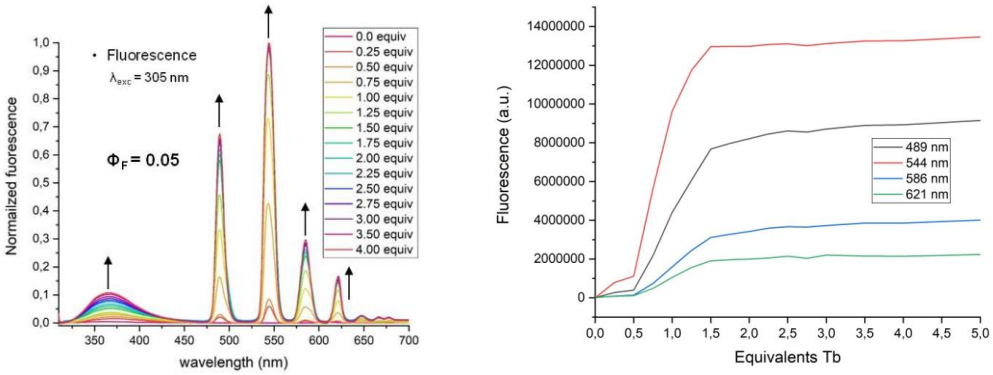


Figure 51. *Fluorescence spectrum of 2Py18C6 and Tb.*

A 1:1 binding mode between the terbium and the macrocycles is hypothesized based on the similarity with the previous studies of the interaction of this macrocycle family and barium cation. More precisely, the coordination of the terbium should occur between the six oxygen atoms of the polyether ring and the two carbonyl groups that rotate inward to reach eightfold coordination pattern. A preliminary calculation of the binding constant (log β) was performed and gave a value of 5.65 which is similar to the one obtained with La^{3+} and 2Py18C6.[167] However, the reliability of the determination is poor as only weak change in the absorbance signals are observed.

Moreover, multiple sub-species could also compete and skew this result. Isolation of the Tb-macrocycle complex were attempted (to confirm the nature of the complex), but they were never successful (Figure 52).

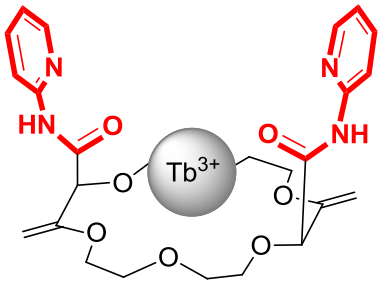


Figure 52. *Proposed 1:1 Binding mode 2Py18C6 and Tb^{3+}*

With further additions after one equivalent of $Tb(OTf)_3$, the broad transition around 325 – 400 nm increases. Once the core of the crown ether is saturated, the terbium acts as a *Lewis* acid and coordinates between the carbonyl group and the nitrogen of the pyridine (6 membered interaction) and hence the new emission band observed (Figure 53).

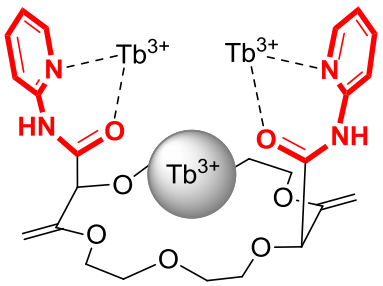


Figure 53. *Lewis acid interaction 2Py18C6 and Tb^{3+}*

To obtain more insight on the last proposition, the titration was performed in emission between 300 nm and 500 nm between 2Pyr-monomer and $Tb(OTf)_3$ salt. The same emission band was observed (Figure 54, on left). Additionally, *Lewis* acid $Zn(OTf)_3$ was used instead of terbium (Figure 54, on right) and the same band appeared even though weaker. The nature of the *Lewis* acid-*Lewis* base interaction was confirmed by this comparison.

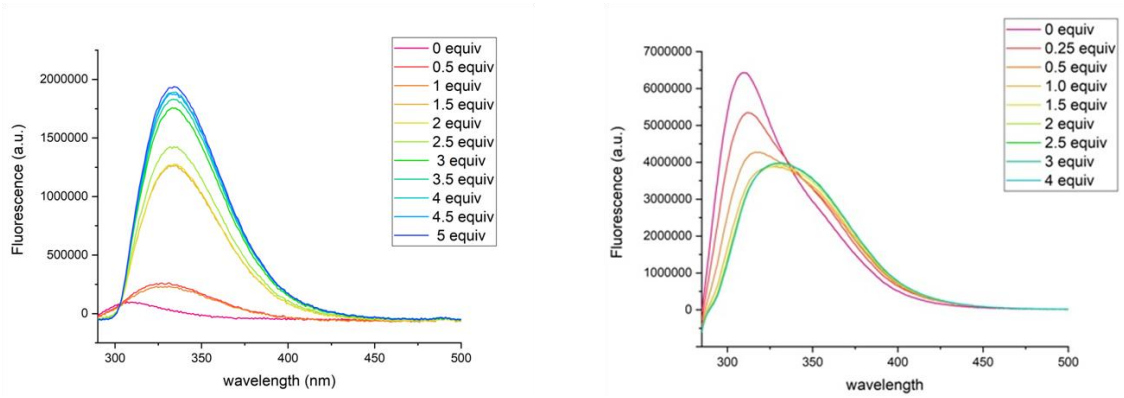


Figure 54. *Lewis acid interaction Tb(III) on left and Zn(III) on right.*

17.3.2. Binding studies

The necessity to show that the coordination occurs inside the macrocycle (and not with the pyridine) and is the key point for the emission of the terbium was deemed important. To do so, the binding studies were also performed with 3Py18C6, 1naph18C6 and 3-amino-quino18C6 which possess different antenna which are respectively 3-pyridine, 1naphtylamine adn 3-aminoquinoline (Figure 55).

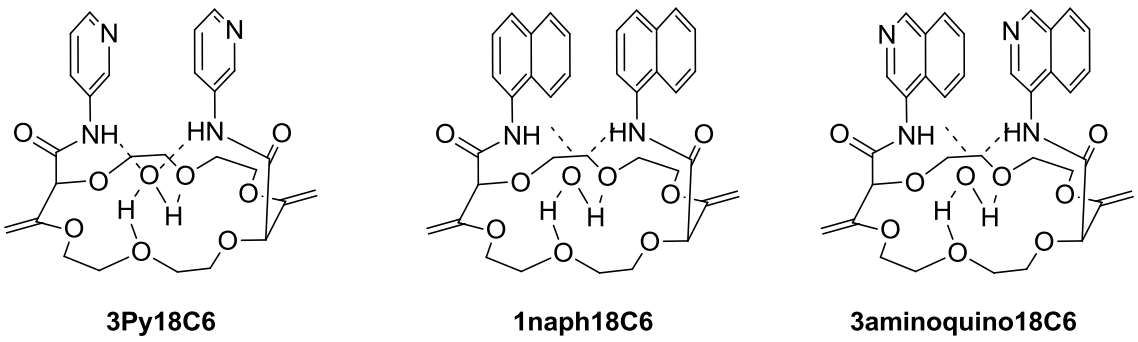


Figure 55. *Macrocycles for the antenna studies.*

The titrations between 3Py18C6 and $Tb(OTf)_3$ was performed first and are reported in Figure 56. The absorbance spectrum exhibits mainly two bands. Similarly to the titration with 2Py18C6, an hypochromic and an hyperchromic shift are observed for the two main transition. Of importance, the appearance of the new transition around 300 nm is also observed. In the emission spectrum for the 3Py18C6 it is possible to recognise the typical pattern of terbium with the 4 sharp transitions. However, the absence of the transition around 300 – 400 nm compared to the 2Py18C6 titration is noticeable. In this case the divalent coordination of the terbium with the nitrogen of the pyridine and the oxygen of the carbonyl is not possible anymore (7 membered instead of 6 membered) and hence the absence of emission.

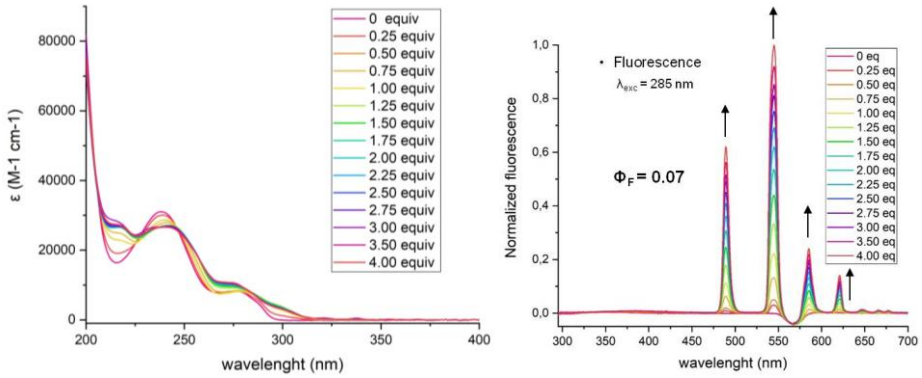


Figure 56. *Absorbance and emission spectra of 3Py18C6 with Tb(III).*

Then the titration between 1napht18C6 and $Tb(OTf)_3$ was performed. This time no basic nitrogen is present on the antenna and the results could be different. In absorbance, the successive addition of terbium did not lead to major change on the spectra. The absence of new transition with 1napht18C6 corroborates the proposition of the *Lewis* acid-*Lewis* base interaction in the previous cases. In fluorescence, the story is different. At first, a broad emission around 400 nm is observed. This transition corresponds to the fluorescence of the naphthyl moieties. Upon incremental addition of terbium, the intensity of this emission decreased while the four band of the terbium appeared showing the energy transfer from the antenna (naphthyl) to the metal (Figure 57).

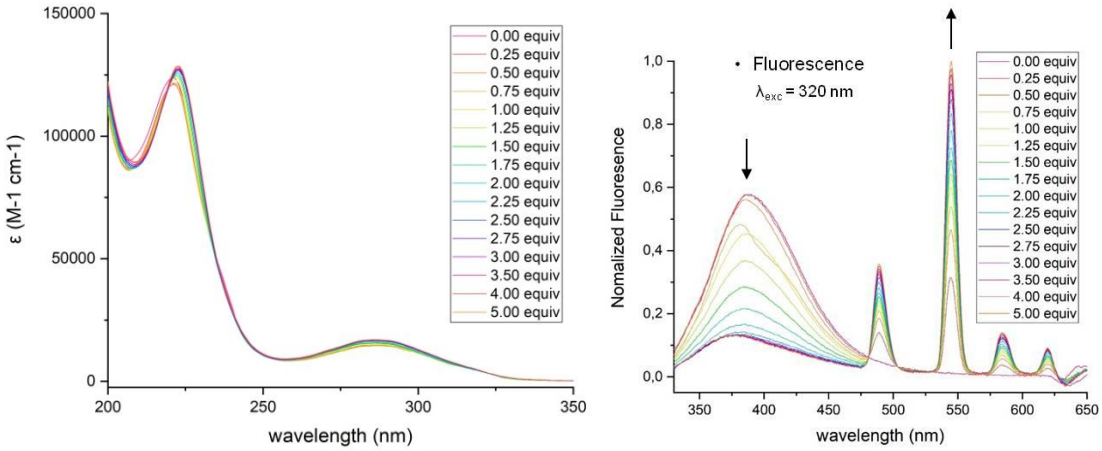


Figure 57. *Absorbance and emission spectra of 1naph18C6.*

Finally the titration between 3-amino-quino18C6 and $Tb(OTf)_3$ was performed. In absorbance, a completely different pattern was observed with respect to the previous macrocycles studied. In fluorescence, it behaves approximately like 1naph18C6. At first, a broad emission around 380 nm is observed due to the fluorescence of the 3-amino-quinoline moieties. Upon incremental addition of terbium, the intensity of this emission decreased while the four band of the terbium started to appear even with a lower intensity with respect to other macrocycles (Figure 58).

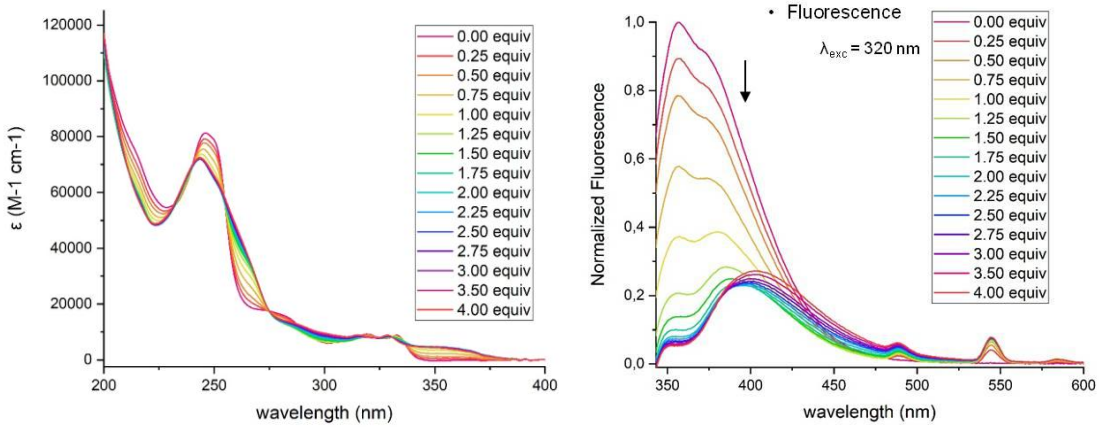


Figure 58. *Absorbance and emission spectra of 3-amino-quino18C6.*

The hypothesis of the type of coordination of terbium ion with the macrocycle previously reported through the six oxygen atoms of the polyether ring and the two carbonyl groups has been postulated through the titration of 2Py18C6 with terbium as well as barium.

The results obtained from the titration of 3Py18C6 and 1naph18C6 also gave additional insights. It was then decided to perform the titration with 2Py18C4. This macrocycle is deficient of two oxygen atoms in the platform in comparison to 2Py18C6. If the coordination goes indeed through this polyether ring, removing two coordination site should disfavour the binding of the terbium as lanthanides have typically from 7 to 9 coordination number (Figure 59).

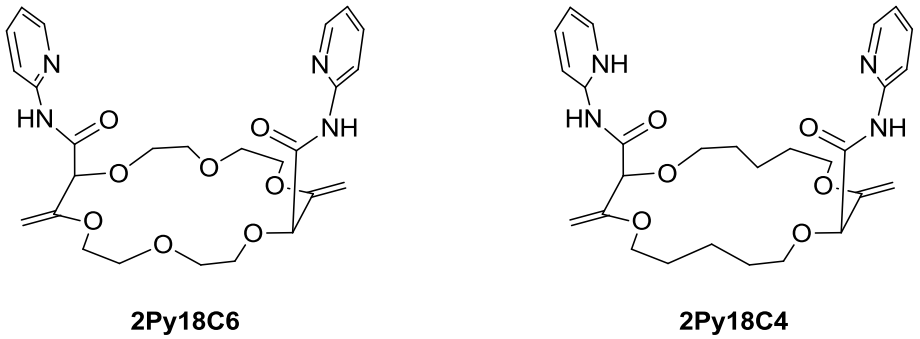


Figure 59. *Macrocycles for the binding studies.*

Fist the titration was performed in absorbance with incremental amount of $Tb(OTf)_3$ to a solution of 2Py18C4. The 2Py18C4 displays a completely different behaviour with respect to 2Py18C6. The two main bands display an hypsochromic effect upon addition of terbium. Then in the emission, it is possible to mainly observe the direct *Lewis* acid interaction between the terbium and the antenna (broad signal between 300-400 nm).

The characteristic emission pattern of Tb^{3+} observed previously in only weakly measured in this case. These two results corroborate the postulation that the terbium ion coordinates to the polyether ring and requires the six ethers and the two carbonyls (Figure 60).

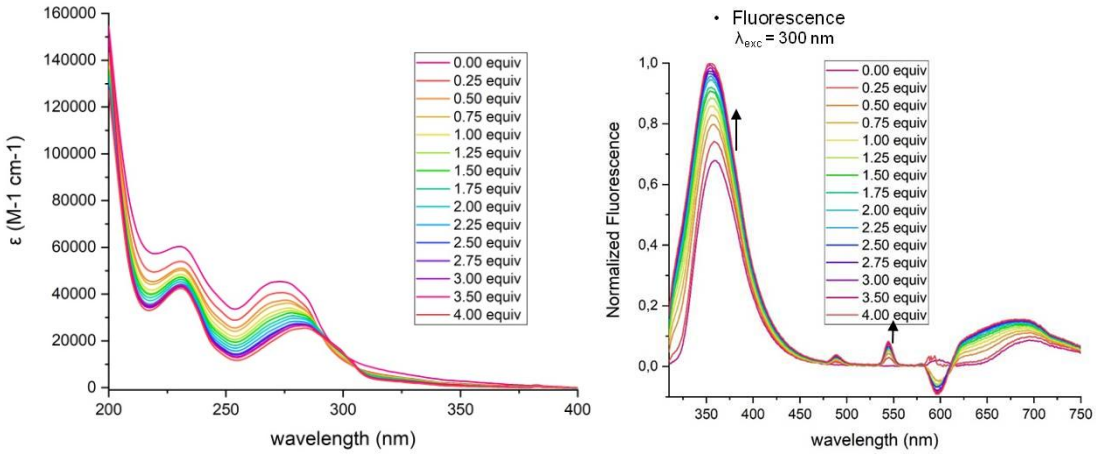


Figure 60. *Absorbance and emission spectra of 2Py18C4.*

17.3.3. Chiroptical studies (ECD and CPL)

After considering the optical properties using racemic material, the chiroptical properties were studied then. First the ECD spectra were considered for each enantiomer of the 2Py18C6 previously separated by CSP-HPLC. Both enantiomers present a perfect mirror image even if the intensity of the signal is relatively weak ($\Delta\varepsilon$ <5). Then addition of terbium and barium salts to the enantiomers were performed separately. From the titration spectra, a plateau is reached at ca. 1.5 equivalents. Thus, addition of 3 equivalents of each metals was selected to be sure to have full formation of the complex in solution. Addition of either the lanthanide or the alkaline earth ions gave very similar results (Figure 61).

An excitonic couplet is observed in both cases. The spectra undergo a remarkable ECD sign reversal for the two main transitions between 200 nm and 300 nm. Furthermore, the ECD spectra display mainly a monosignate signal for the first absorption band around 240 nm for both Tb^{3+} and Ba^{2+} which is typical of carbonyl groups (n → π*).[168]

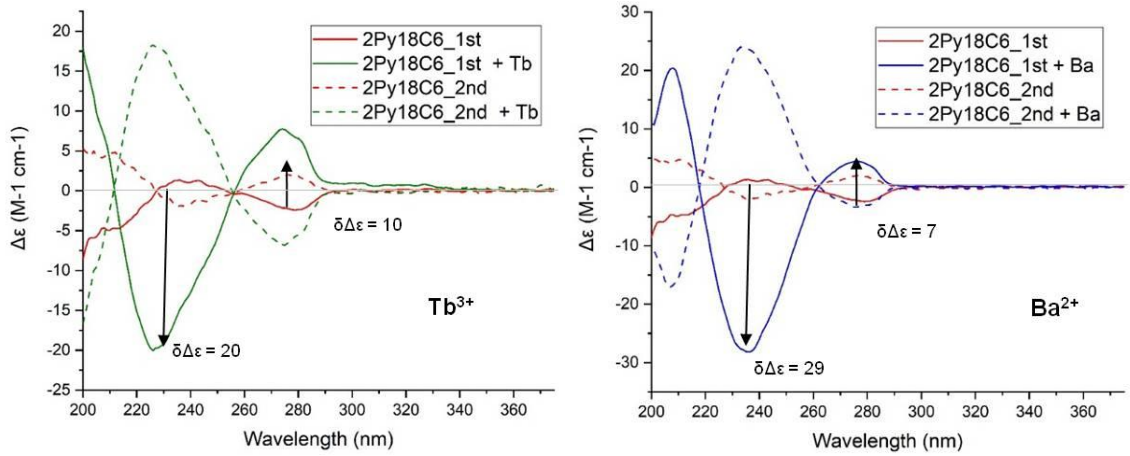


Figure 61. *ECD spectra for Tb^{3+} and Ba^{2+} for 2Py18C6.*

In addition to the sign inversion, the intensity of the ECD signal increases significantly and could originate from the conformational changes induced by the rotation of the carbonyls and the decrease of the number of conformations with possibly opposite CD bands, partly cancelling out the signal. The change in intensity in ECD can be quantified using δΔε, which is the difference in normalized intensity in presence and absence of tested metal ions (Equation 4).

$$\delta\Delta\varepsilon = |\Delta\varepsilon(\text{cation}) - \Delta\varepsilon(\text{without})|$$

Equation 4.

The δΔε values for the 2Py18C6 with terbium and barium are summarized in Table 19 with their corresponding ionic radii. The similarity between both cations in ECD tends to confirm the same binding pattern and supports the previous postulations on the binding mode (Table 19).

Compound	Metal	λ_{abs} (nm)	δΔε (M^{-1} cm^{-1})	Ionic Radius (A)
2Py18C6	Tb^{3+}	225	20	0.92
	Ba^{2+}	235	29	1.35

Table 19. *Calculation of* δΔε

The magnitude of a CD signal can be quantified by the absorption dissymmetry factor (g_{abs}) which is the ratio of molar CD to molar extinction coefficient (Equation 5).

$$g_{abs} = \frac{\Delta\varepsilon}{\varepsilon}$$

Equation 5. *Dissymetry factor.*

The results are reported in Figure 62. The value of g_{abs} of the adduct between the macrocyle and the metal ion are higher for barium than terbium for the first band. Whereas for the second bands the gabs values are quite similar.

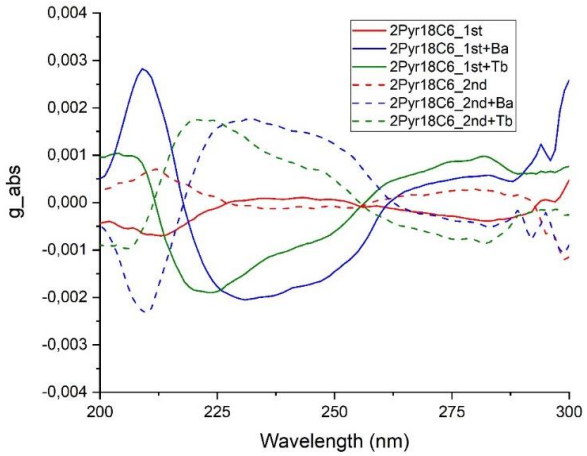


Figure 62. *Absorption dissymetry factor..*

Finally, the CPL signal for 2Py18C6 in presence of 3 equivalents of $Tb(OTf)_3$ in acetonitrile was measured by Dr. Francesco Zinna of the Di Bari group at the University of Pisa. The spectra are reported in Figure 63. A sharp and intense signal of the 545 nm Tb^{3+} transition is observed clearly. The fine structure observed for the $^5D_4 \rightarrow {}^7F^5$ transition originate from the different non-degenerate M_J sublevels of the transition.

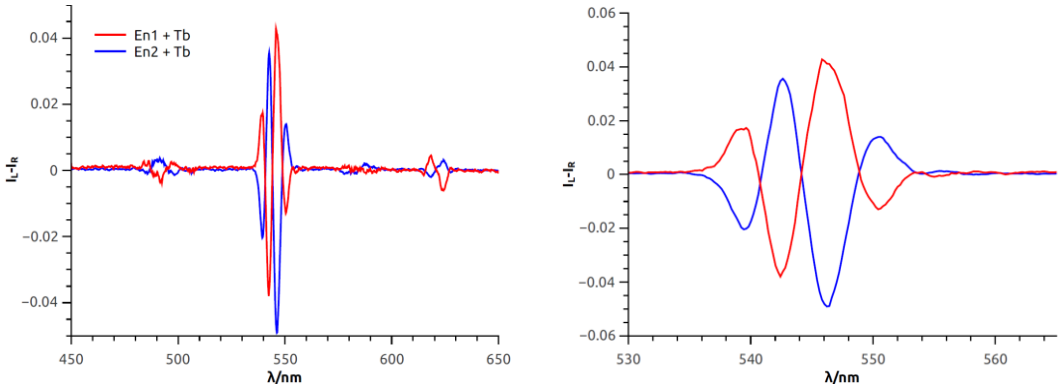


Figure 63. *CPL spectra*

To quantify the circular polarization degree of the emission, the luminescence dissymmetry factor g_{lum} was used as defined by Equation 6 where I_L and I_R correspond to left and right circularly polarized component of the emission respectively.

$$g_{lum} = 2\,\frac{I_L - I_R}{I_L + I_R}$$

Equation 6. *Luminescence dissymetry factor.*

The g_{lum} factors for the $^5D_4 \rightarrow {}^7F_5$ transition is 0.05 (Figure 63) at 546 nm. This value is quite good with respect to other complex with the terbium. Three more terbium transitions ($^5D_4 \rightarrow {}^7F_J$ with J=6,4,3 at 485 nm, 580 nm and 620 nm respectively) are visible but remain weak. The signal being noisy, it is difficult to quantify a g_{lum} value accurately (Figure 64).

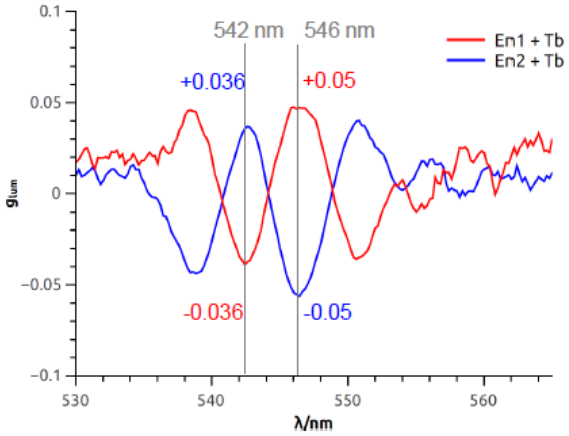
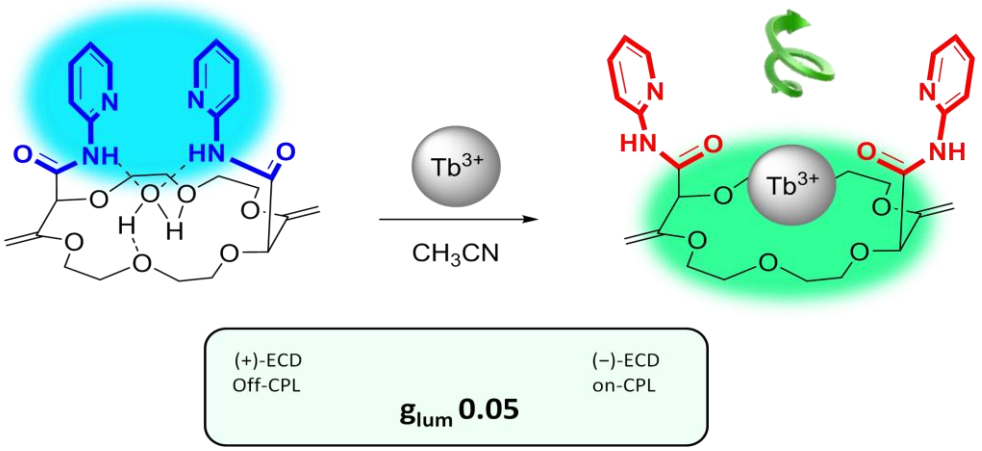


Figure 64. *Luminescence dissymmetry factor.*

18. Conclusions and perspectives

Polyether macrocycles can be applied as chromophore/antenna with lanthanide. Different compounds have been taken into account and characterised both in absorbance and in fluorescence. From these studies a definite number of oxygen atom inside the crown ether is crucial to have coordination and the (hetero)aromatic units present in the macrocycle determine an essential energy transfer in order to have luminescence.

These macrocycles are interesting also regarding the chiroptical properties: they can give rise a reversible switch off/on to the ECD and CPL upon addition of the terbium(III) ion.



Scheme 132. *Conclusion.*

In the future others macrocycles could be evaluated also in combination with various lanthanides as europium. In term of application, they could be used as CP-OLEDs since so far only Eu-based CP-OLEDs, which are red, are described. So, it would be interesting to have green lanthanide-based CP-OLEDs.

19. Experimental Section

General information and Materials

All reagents were purchased from commercial sources and used without further purification. Dioxane, THF and THP were dried by distillation over Na/benzophenone and stored over 4 Å molecular sieves. t-BuOK was sublimed prior to use.

Analytical thin-layer chromatographies (TLC) were performed with Silicagel 60 F_{254} aluminium sheets from Merck. Flash column chromatographies were performed with Silica SiliaFlash P60, 40-63 µm (230-400 mesh) and Aluminium oxide (neutral, Brockmann I, 50-200 µm, 60 Å).

NMR spectra were recorded on Brucker AMX-400 MHz or ARX-500 MHz. ^{1}H-NMR chemical shifts are given in ppm relative to Me_4Si using solvent resonances as internal standards ($CDCl_3$ δ = 7.26 ppm). Data were reported as follows: chemical shift (δ) in ppm, multiplicity (s = singulet, d = doublet, t = triplet, q = quartet, hept = heptuplet and m = multiplet), coupling constant (Hz) and integration. ^{13}C-NMR chemicals shifts are given in ppm relative to Me_4Si with solvent resonances used as internal standards ($CDCl_3$ δ = 77.16 ppm). NMR chemicals shifts are given in ppm.

IR spectra were recorded with a Perkin-Elmer 1650 FT-IR spectrometer using a diamond ATR Golden Gate sampling and are reported in wave numbers (cm^{-1}).

Melting points (m.p.) were measured in open capillary tubes with a Büchi B-550 melting point apparatus and were uncorrected.

Low resolution electrospray mass spectra (LR-ESI-MS) were obtained on an API 150EX (AB/MDS Sciex) spectrometer.

CSP-HPLC analyses were performed on a Agilent 1100 apparatus (binary pump, autosampler, column thermostat and diode array detector).

UV-Visible spectra were measured on a JASCO V-650 spectrophotometer at 20 °C. Fluorescence spectra were recorded on a Horiba FluoroMax 3.

ECD spectra were performed on a JASCO J-815 spectrophotometer at 20 °C. CPL measurements were conducted in collaboration with the group of prof. Lorenzo Di Bari at the University of Pisa.

Synthetic procedure

Synthesis of polyether macrocycle

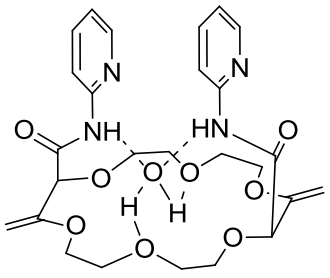
18C6, 18C4 and 16C4 were synthesized according to the reported procedure.[154,169]

Synthesis of polyether macrocycle with aromatic amines

General procedure

In a one neck flask under nitrogen atmosphere, dry tetrahydrofuran was added to 1 equivalent of polyether macrocycle (**18C6, 18C4** or **16C4**) and 3 equivalents of aromatic amine. The mixture was cooled down to -100 °C (EtOH/liquid nitrogen bath). Then 4 equivalents of freshly sublimed *t*-BuOK were added in one portion. After stirring for ca. 2 minutes at -100 °C (EtOH/liquid nitrogen bath), the cooling bath was removed and the reaction was allowed to reach 25 °C on its own and stirred for an additional 3 hours. The conversion was followed by TLC analysis and LR-ESI-MS (soft positive mode, CH_2Cl_2). Upon completion, the reaction was quenched by adding a few drops of methanol and directly purified by column chromatography (SiO_2) without further treatment. A second column chromatography (Al_2O_3, neutral) could be required. Finally, the resulting oil or solid was purified by selective precipitation (dissolution in a minimal amount of CH_2Cl_2 required for solubility, followed by addition of a large excess of pentane) affording the desired chiral polyether macrocycle.[119b]

2Py18C6



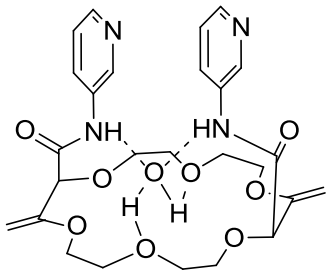
According to general procedure, 303 mg (0.75 mmol) of **18C6**, 211 mg (2.25 mmol) of 2-aminopyridine, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 184 mg (0.34 mmol, 546 g/mol, 45%) of **2Py18C6** as a white solid.

Purification: column (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%, 20%).

Precipitation: CH_2Cl_2 then pentane.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ/ppm = 1.60 (s, 2H, H_2O), 3.60 – 3.90 (m, 16H), 4.20 (d, 2H), 4.30 (d, 2H), 4.48 (s, 2H), 7.01 (m, 2H), 7.68 (m, 2H), 8.23 – 8.28 (m, 4H), 9.22 (s, 2H).

3Py18C6



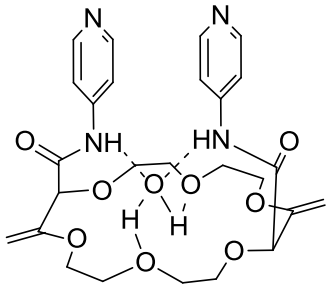
According to general procedure, 303 mg (0.75 mmol) of **18C6**, 211 mg (2.25 mmol) of 3-aminopyridine, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 160 mg (0.29 mmol, 546 g/mol, 40%) of **3Py18C6** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%, 20%); column 2 (Al_2O_3, neutral) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: CH_2Cl_2 then pentane.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ/ppm = 1.80 (s, 2H, H2O), 3.59 – 3.88 (m, 14H), 3.96 – 4.01 (m, 2H), 4.30 (d, J = 2.9 Hz, 2H), 4.35 (s, 2H), 4.43 (d, 2H), 7.10-7.20 (m, 2H), 8.20– 8.30 (m, 4H), 8.75 (s, 2H), 9.52 (s, 2H).

4Py18C6



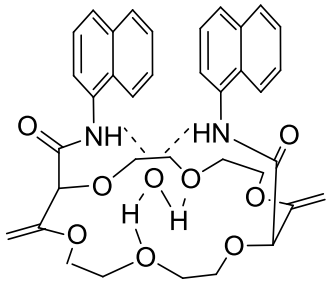
According to general procedure, 303 mg (0.75 mmol) of **18C6**, 211 mg (2.25 mmol) of 4-aminopyridine, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 175 mg (0.32 mmol, 546 g/mol, 43%) of **3Py18C6** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%, 20%); column 2 (SiO_2) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: CH_2Cl_2 then pentane.

^{1}H-NMR (400 MHz, C*D*Cl_3): δ/ppm = 2.25 (s, 2H, H_2O), 3.59 – 3.88 (m, 16H), 4.34 (d, 2H), 4.40 (s, 2H), 4.49 (d, 2H), 7.10-7.20 (m, 2H), 8.20– 8.30 (m, 4H), 8.75 (s, 2H), 9.52 (s, 2H).

1naph18C6



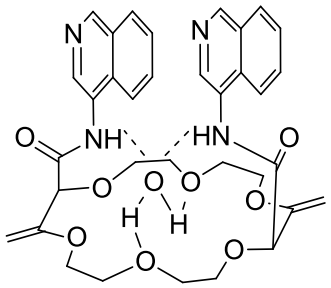
According to general procedure, 303 mg (0.75 mmol) of **18C6**, 321.7 mg (2.25 mmol) of 1-naphtylamine, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 205 mg (0.32 mmol, 640 g/mol, 42%) of **3Py18C6** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%, 20%); column 2 (SiO_2) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: CH_2Cl_2 then pentane.

^{1}H-NMR (500 MHz, C*D*Cl_3): δ/ppm = 1.68 (s, 2H, H_2O), 3.72-4.02 (m, 16H), 4.32 (d, 2H), 4.46 (d, 2H), 4.52 (s, 2H), 7.15 (t, 2H), 7.22 (t, 2H), 7.30 (t, 2H), 7.50 (d, 2H), 7.58 (d, 2H), 7.77 (d, 2H), 7.83 (d, 2H), 9.31 (s, 2H).

3aminoquino18C6



According to general procedure, 303 mg (0.75 mmol) of **18C6**, 321.7 mg (2.25 mmol) of 3-amino-quinoline, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 290 mg (0.45 mmol, 646 g/mol, 60%) of **3aminoquino18C6** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%); column 2 (SiO_2) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: CH_2Cl_2 then pentane.

R_f = 0.6 (SiO_2, CH_2Cl_2/MeOH (10%));

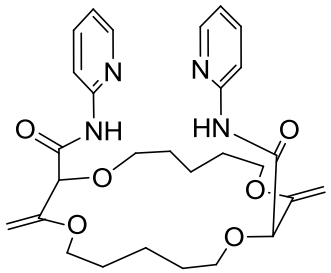
m.p.: 112 °C - 114 °C;

^{1}H-NMR (500 MHz, C*D*Cl_3): δ/ppm = 1.97 (s, 2H, H_2O), 3.56-3.99 (m, 16H), 4.28 (d, 2H), 4.40 (s, 2H), 4.45 (d, 2H), 7.36 (t, 2H), 7.47 (t, 2H), 7.61 (d, 2H), 7.84 (d, 2H), 8.70 (d, 2H), 9.00 (d, 2H), 9.69 (s, 2H).

^{13}C-NMR (126 MHz, C*D*Cl_3): δ/ppm = 67.0, 68.6, 69.0, 70.0, 82.9, 88.6, 123.9, 126.8, 127.7, 128.1, 128.9, 131.5, 144.8, 145.2, 156.5, 168.3.

IR (neat): ṽ/cm-1 3311.4, 2922.4, 2869.5, 1687.5, 1639.1, 1609.0, 1536.8, 1489.4, 1422.8, 1368.4, 1287.2, 1242.9, 1136.1, 1093.5, 992.5, 926.3, 900.0, 824.4, 784.1, 750.6.

2Py18C4



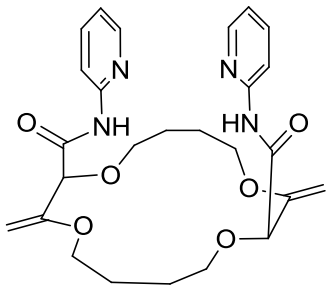
According to general procedure, 303 mg (0.75 mmol) of **18C4**, 211 mg (2.25 mmol) of 2-aminopyridine, 7.5 mL of THF and 336 mg (3.0 mmol) of *t*-BuOK yield 115 mg (0.22 mmol, 524 g/mol, 30%) of **2Py18C4** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%); column 2 (SiO_2) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: CH_2Cl_2 then pentane.

^{1}H-NMR (500 MHz, C*D*Cl_3): δ/ppm = 1.36 – 1.84 (m, 14H), 3.49 – 3.84 (m, 6H), 4.19-4.23 (m, 6H), 6.93 – 6.96 (m, 2H), 7.61 – 7.70 (m, 2H), 8.12 – 8.16 (m, 4H), 9.09 (s, 2H).

2Py16C4



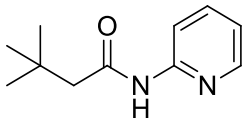
According to general procedure, 60 mg (0.16 mmol) of **16C4**, 45 mg (0.48 mmol) of 2-aminopyridine, 7.5 mL of THF and 72 mg (0.64 mmol) of *t*-BuOK yield 30 mg (0.06 mmol, 496 g/mol, 38%) of **2Py18C4** as a white solid.

Purification: column 1 (SiO_2) EtOAc for the remaining aniline, EtOAc:MeOH (10%), then CH_2Cl_2/MeOH gradient (1%, 3%, 5%, 10%); column 2 (SiO_2) CH_2Cl_2 for the packing of the column, then CH_2Cl_2/MeOH gradient (1%, 3%, 5%).

Precipitation: EtOAc then pentane.

^{1}H-NMR (400 MHz, C*D*Cl$_3$): δ/ppm = 1.51 – 1.63 (m, 4H), 1.82 – 1.92 (m, 4H), 3.42 – 3.57 (m, 6H), 3.75 – 3.76 (m, 2H), 4.20 (s, 2H), 4.25 (s, 2H), 4.28 (s, 2H), 6.98 (t, 2H), 7.63 (t, 2H), 8.18 (d, 2H), 8.26 (d, 2H), 9.0 (s, 2H).

Synthesis of 2Py monomer



In a one neck flask under nitrogen atmosphere, dry tetrahydrofuran was added to 2.30 equivalent of methyl 3,3-dimethylbutanoate (300 mg) and 2 equivalents of 2-aminopyridine (188 mg). The mixture was cooled down to -100 °C (EtOH/liquid nitrogen bath). Then 2 equivalents of freshly sublimed *t*-BuOK (224 mg) were added in one portion. After stirring for 1-2 minutes at -100 °C, the cooling bath was removed and the reaction was allowed to reach 25 °C on its own and stirred for an additional 1 hours. The conversion was followed by TLC analysis and LR-ESI-MS. After evaporating the THF under reduced pressure, H_2O (50 mL) and CH_2Cl_2 (100 mL) were added and the organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the corresponding amides were obtained by isolation by silica gel column chromatography with ethyl acetate and pentane (3:7).

m.p.: 78 °C-79 °C

1H-NMR (500 MHz, C*D*Cl$_3$): δ/ppm = 1.00 (s, 9H), 2.17 (s, 2H), 6.96 (t, 1H), 7.64 (t, 1H), 8.17 (m, 2H), 8.58 (m, 1H).

13C-NMR (126 MHz, C*D*Cl$_3$): δ/ppm = 30.0, 31.3, 51.4, 114.3, 119.6, 138.5, 147.6, 151.9, 170.8.

IR (neat): ṽ/cm-1 3245.3, 3074.9, 2952.9, 2863.2, 1659.0, 1576.7, 1523.8, 1456.4, 1428.5, 1362.1, 1328.2, 1286.1, 1233.8, 1134.4, 1096.3, 1051.9, 974.3, 910.0, 846.3.

HR MS (ESI) $[M+H]^+$ *m/z* calculated for $C_{11}H_{16}N_2O$ 192.2654, observed 192,2678.

Spectroscopic data

UV-Vis absorption and fluorescence spectroscopies

Procedure

In a typical experiment, UV-Vis absorbance and fluorescence spectra of a solution of interest compound (ca 10^{-6} M) in acetonitrile were recorded in a 1 cm cell. For the titration experiments, various equivalents (10^{-3} M stock solutions) of $Tb(OTf)_3$ or $Ba(ClO_4)_2$ were added to the solution of the macrocycle and the UV-Vis absorbance and fluorescence spectra were recorded again.

CSP-HPLC resolution

Procedure

The 2Py18C6 was resolved by chiral stationary phase HPLC using a semi-preparative CHIRALPAK® IG column with a mobile phase previously prepared of CH_2Cl_2:MeOH (99:1) with diethanolamine as additive (0.1%). The first eluted is at 3.95 min, the second eluted is at 5.04 min. It is worth mentioning that it is necessary to remove traces of $Et_2NH{\cdot}HCl$ present in the separated compounds. The residue was thus dissolved in CH_2Cl_2, the organic phase was washed three times with H_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the pure products.

ECD and CPL spectroscopies

Procedure

In a typical experiment, the ECD (or CPL) spectrum of a solution of enantiopure compound (ca. 10^{-5} M) in acetonitrile was recorderd in a 1 cm cell. For the complexation experiments, 3.0 equivalents (10^{-3} M stock solutions) of $Tb(OTf)_3$ or $Ba(ClO_4)_2$ in acetonitrile were added to the solution and the ECD (or CPL) spectrum was recorded again.

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