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PHD THESIS "EN COTUTELLE"

DEVELOPMENT OF CYCLOISOMERIZATION REACTIONS FOR THE SYNTHESIS OF NITROGEN OR OXYGEN CONTAINING HETEROCYCLES

(CHIM/06)

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A chi ama Dio tutto é possibile.

San Francesco di Paola

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Chapter 1

Heterocyclic chemistry

1.1: Heterocyclic compounds.

Heterocyclic compounds are an important class of organic chemical compounds characterized by the presence at least of one element other than carbon in their ring molecules.[1] The presence of the heteroatom gives to the heterocyclic compounds special physical and chemical properties that are often quite distinct from those of their all-carbon-ring analogs. The most common heterocycles are those having five- or six- membered rings and containing heteroatoms of nitrogen (N), oxygen (O), or sulfur (S). The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophene.

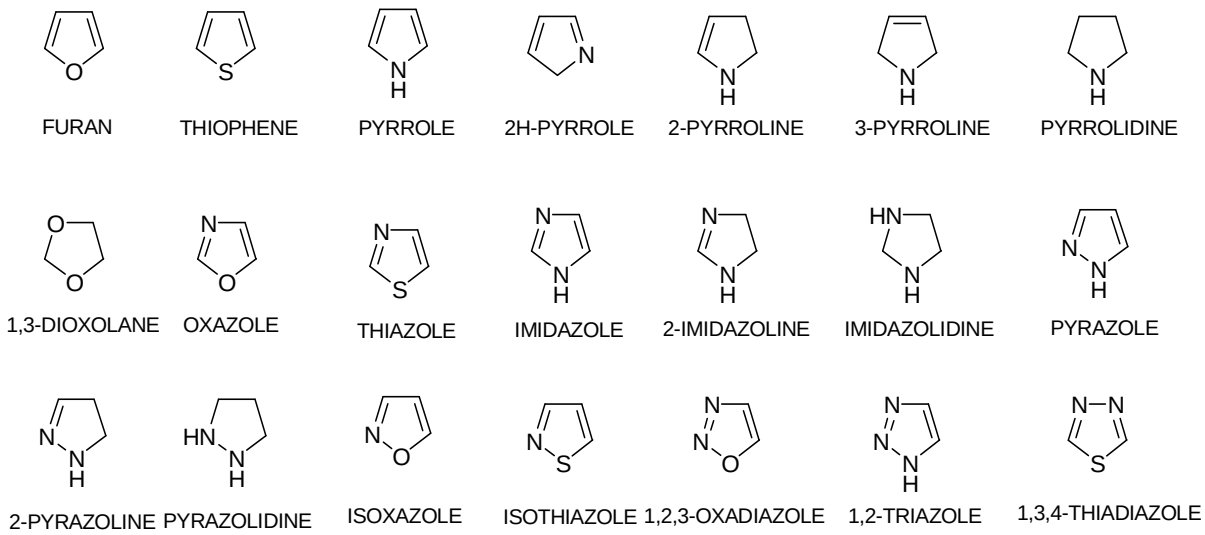


Figure 1.1: Five - membered rings.

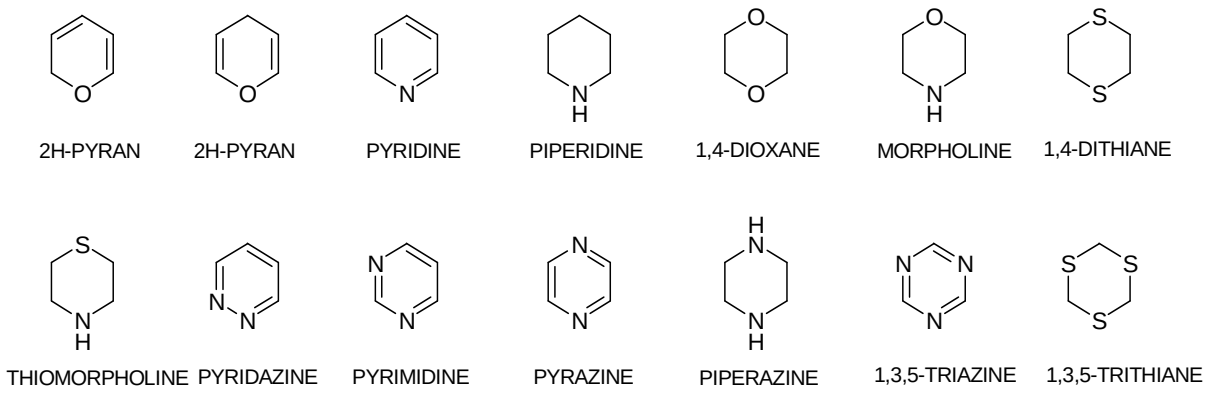


Figure 1.2: Six - membered rings.

Starting from the simple systems with one heteroatom is possible to obtain the benzo-analogues.

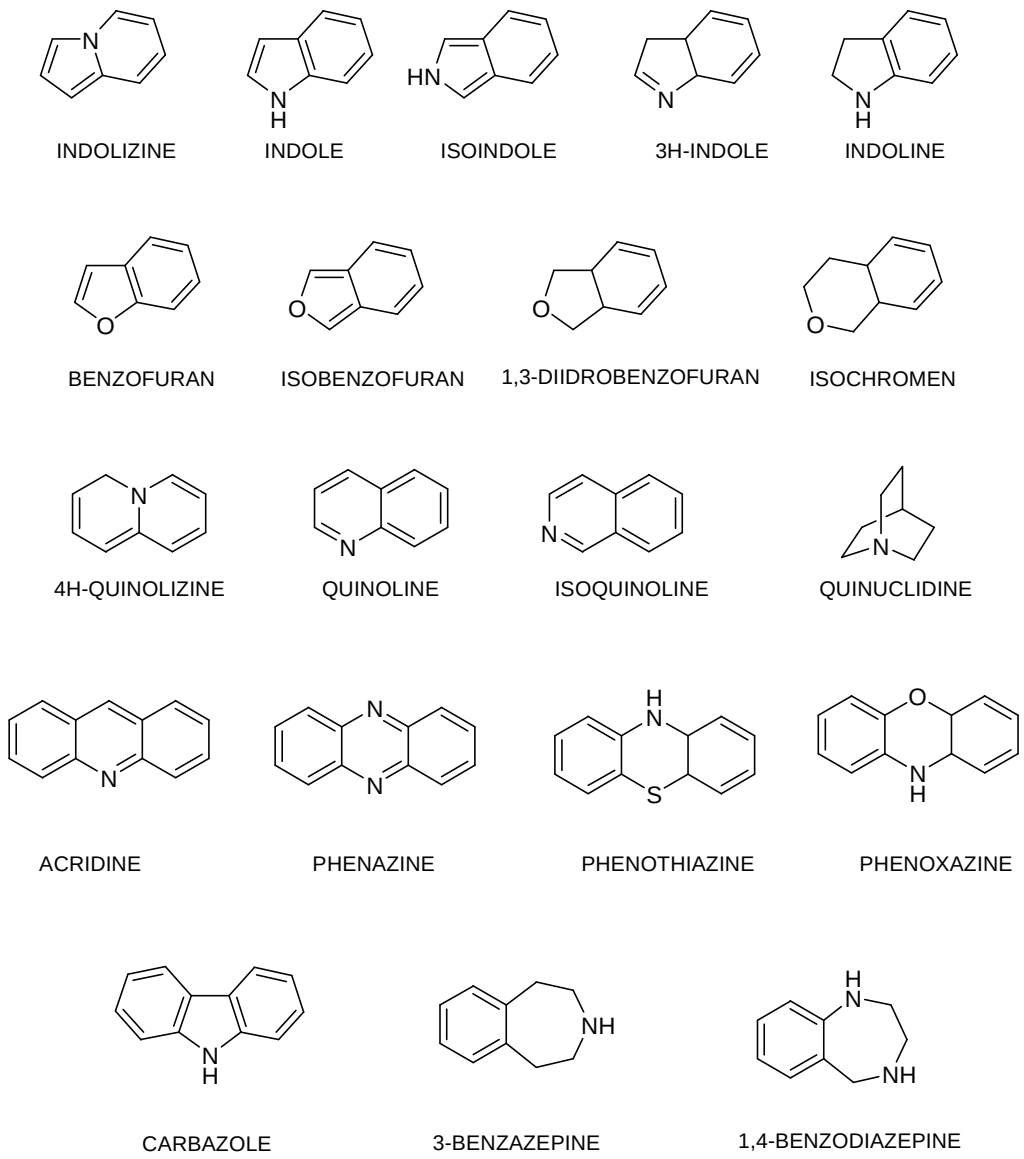


Figure 1.3: Fused-heterocycles

Heterocycles are ubiquitous structural features of naturally occurring and/or biologically active chemical compounds. Many pharmaceutical products are mimics of natural products with biological activity, which include often heterocycles.[2]

Heterocyclic chemistry is an inexhaustible resource of novel compounds. Almost unlimited combinations of carbon, hydrogen, and heteroatoms can be designed, making available

compounds with the most diverse physical, chemical, and biological properties. Heterocycles provide the main source of new aromatic compounds.[3]

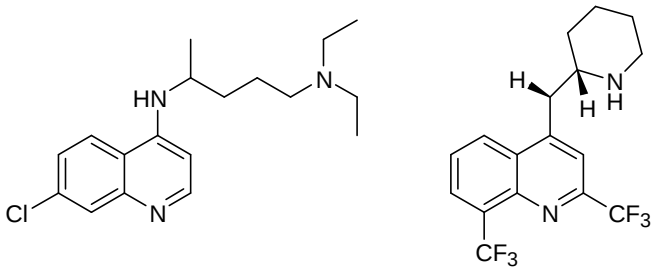
In this work we have synthesized a large number of heterocyclic systems such as quinolines, furans, pyrroles, isocromenes, di-hydrobenzofurans, pyrrolinones, isoquinolines. Most of then present a large number of biological and pharmaceutical properties.

An exhaustive description of all the heterocycles and their biological properties is out of our scope. We present here a selection of heterocyclic structures.

1.2: Quinoline systems.

Compounds containing quinoline motif are most widely used as antimalarials, antibacterials, antifungals and anticancer agents.[4, 5] Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents. They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes. Furthermore, these compounds find applications in chemistry of transition metal catalyst for uniform polymerization and luminescence chemistry. Quinoline derivatives also act as antifoaming agent in refineries. Owing to such significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry.

Quinoline-containing antimalarial drugs, such as chloroquine, quinine and mefloquine, are mainstays of chemotherapy against malaria (Figure 1.4). The molecular basis of the action of these drugs is not completely understood, but they are thought to interfere with hemoglobin digestion in the blood stages of the malaria parasites life cycle. The parasite degrades hemoglobin, in an acidic food vacuole, producing free heme and reactive oxygen species as toxic by-products.[6]



A **B**

Figure 1.4: Antimalarial quinolines, chloroquine (A) and mefloquine (B).

2-Substituted quinoline alkaloids (Figure 1.5) are used to treat cutaneous leishmaniasis. The activities of 2-substituted quinoline alkaloids against other strains causing cutaneous leishmaniasis or visceral leishmaniasis was demonstrated with oral treatments of mice susceptible to Leishmania spp.[7, 8]

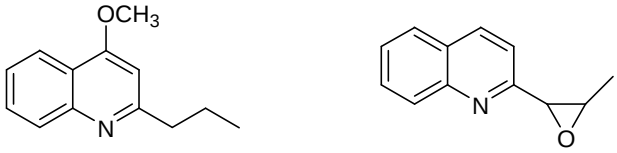


Figure 1.5: Chimanines.

Tacrine and Physostigmine represent "reversible" anticholinesterase agents employed clinically, both containg in a heterocyclic system and Tacrina a quinoline ring (Figure 1.6).

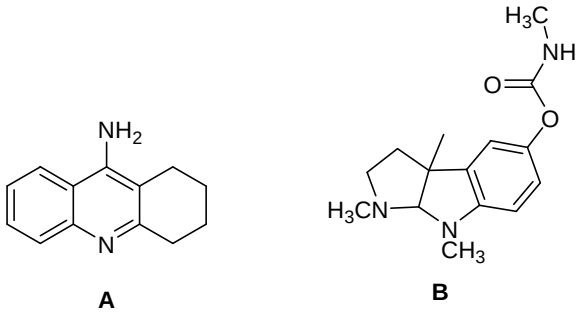


Figure 1.6: Tacrine (A) and Physostigmine (B).

Dibucaine is a local anesthetics (Figure 1.7), and they present in the structure a hydrophobic (aromatic) moiety, a linker region and a substituted amine (hydrophilic region).[9]

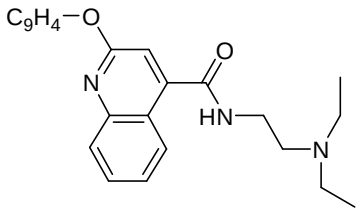
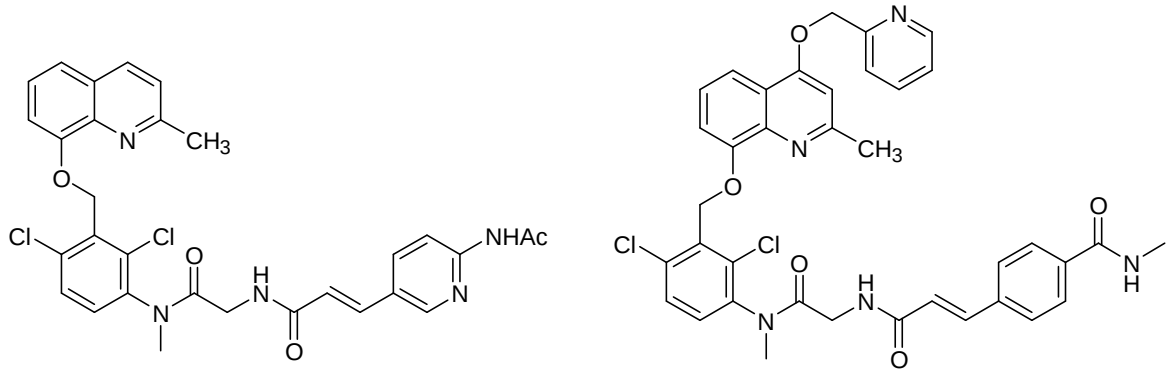


Figure 1.7: Dibucaine.

FR 173657 (Figure 1.8, A), the first effective nonpeptide kinin β_2 receptor antagonist, has been tested in four preparations from different species (human, pig, rabbit, and guinea pig). The new compound shows high apparent affinity for the four β_2 receptors, with pA2 values ranging from 8.2 to 9.4. FR 173657 is a selective β_2 receptor antagonist that does not interact with human, pig, or rabbit B1 receptors.[10]

FR190997, a novel bradykinin B2 agonist, expresses longer action than bradykinin in paw edema formation and hypotensive response (Figure 1.8, B).[11]



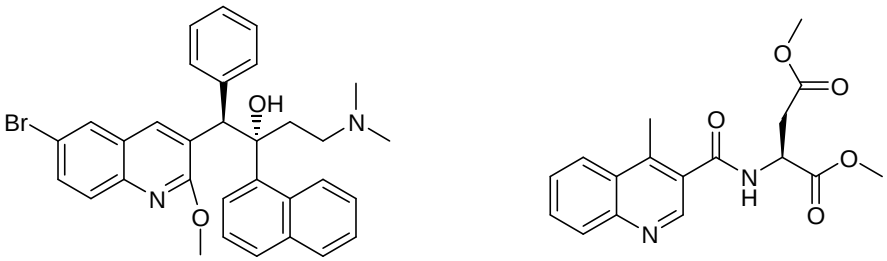
A: FR173657 **B**: FR190997

Figure 1.8: FR173657 antagonist B2 (A), FR190997 agonist B2 (B).

TMC-207 is a diarylquinone discovered by Andries et al in 2005 (Figure 1.9, A). TMC-207 acts by targeting subunit c of the ATP synthase of *M.tuberculosis*, leading to inhibition of the proton pump activity of the ATP synthase. Thus, the compound targets bacillary energy metabolism.

HIV/AIDS remains a formidable disease with millions of individuals inflicted worldwide. Although treatment regimens have improved considerably, drug resistance brought on by viral mutation continues to erode their effectiveness. Intense research efforts are currently underway in search of new and improved therapies. [12]

Novel quinoline derivatives present HIV-1 Tat–TAR interaction inhibitors. CS3 revealed mild inhibitory activity and antiviral potency (Figure 1.9, B).[12]



A: TMC20 **B**: CS3

Figure 1.9: Structures of TMC20 (A) and CS3(B).

Over the last two decades, poly(quinoline)s (Figure 1.10) have become the subject of intense research as electroluminescent materials, for example organic light-emitting diodes (OLEDs), thanks to their superior physical properties such as high electron mobility, photoluminescent efficiency, and stability.[13]

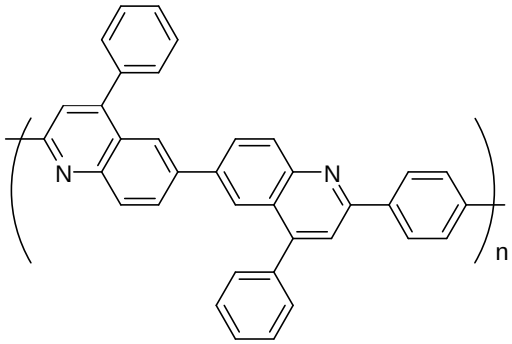


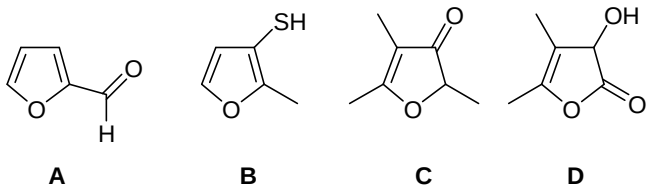
Figure 1.10: Poly(quinoline) monomer.

1.3 Furan systems.

Furans represent an important class of heterocyclic compounds as they are prevalent in many biologically active natural products, as well as numerous pharmacologically interesting compounds.[14]

The aromatic furan ring is found in a wide range of aroma chemicals, especially those produced by the Maillard reaction. They include both low odour materials such as furfural (A) and high impact materials such as 2-methylfuran-3-thiol (B).[15] Among the most important are the hydroxyfuranones especially 4-hydroxy-2,5-dimethyl-furan-3(2*H*)-one (C),

which is a material of unusual reactivity (Figure 1.11). This compound is the major contributor to the flavor of coffee, wine and a variety of fruits such as strawberry.

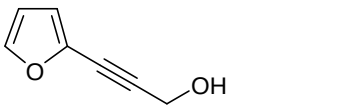


A **B** **C** **D**

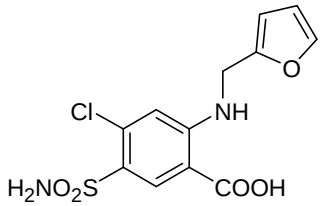
Figure 1.11: Aromatic furan rings.

The anti-inflammatory effect against carrageenin induced paw edema of acetylenic furans (Figure 1.12, A) was higher than the classical anti-inflammatory containing acetylsalicylic acid (ASA).[9] Carrageenin-induced inflammation is mediated by a variety of agents, including vasoactive amines, bradykinin and arachidonic acid metabolites.

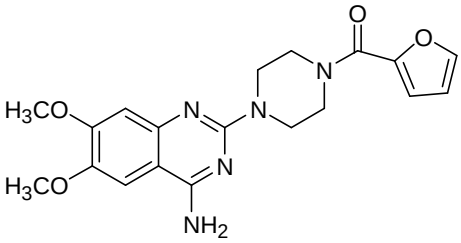
Figure 1.12: Furan systems.



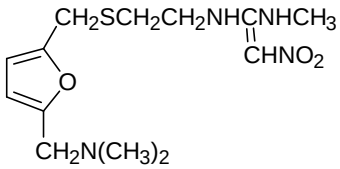
A: Acetylenic furans.



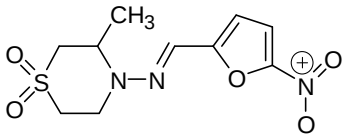
B: Furosemide



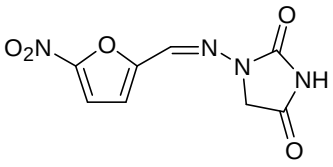
C: Prazosin



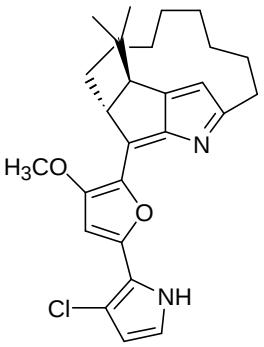
D: Ranitidine.



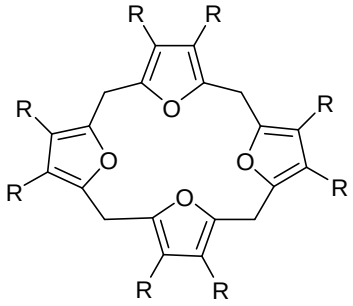
E: Nifurtimox.



F: Nitrofurantoin.



G: Roseophilin.



E: Calixfurans.

Furosemide are one of drugs in diuretic inhibit activity of the Na^{+}-K^{+}-$2Cl^{-}$ symporter in the thick ascending limb of the loop of Hence; this structure present furan moiety (Figure 1.12, B).[9]

Prazosin is the prototypical α_1-selective antagonist. Interestingly, the drug also is a relatively potent inhibitor of cyclic nucleotide phosphodiesterases, and it originally was synthesized for this purpose. It is in the family of piperazinyl quinazolines (Figure 1.12, C).

Ranitidine is a histamine H_2-receptor antagonist that inhibits stomach acid production (Figure 1.12, D). The H_2 receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H_2 receptors on the basolateral membrane of parietal cells.[9]

A variety of nitrofurans (Figure 1.12, E) and nitroimidazole analogs are effective in experimental infections with American trypanosomiasis caused by *T.cruzi*. Of these, nifurtimox and benzimidazole are currently used clinically to treat the disease.

Nitrofurantoin is a synthetic nitrofuran that is used for the prevention and treatment of infections of the urinary tract (Figure 1.12, F).[9]

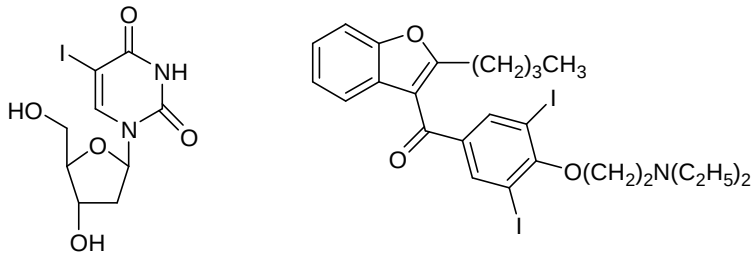
Roseophilin is a unique and extraordinary structure isolated from Streptomyces griseoviridis which displays significant antitumour activity (Figure 1.12, G).[16]

Calixpyrroles have attracted a lot of attention because of their applications in designing receptors and molecular devices and for their oxidation to porphyrins. In addition to the potential capability of calixfurans as receptor molecules (Figure 1.12, H), the furan rings in their framework have high chemical lability, which enables them to be used as a building block in organic synthesis.[17]

1.4 Iodo-compounds.

Idoxuridine (5-iodo-2'-deoxyuridine, Figure 1.13, A) is an iodinated thymidine analog that inhibit the *in vitro* replication of various DNA viruses, including herperviruses and poxviruses.[9]

Amiodarone exerts a multiplicity of pharmacological effects (Figure 1.13, B), none of which is clearly linked to its arrhythmia-suppressing properties. It is a structural analog of thyroid hormone,[9] it is anti-arrhythmic drug, highly lipophilic, it is concentrated in many tissues and it is eliminated extremely slowly.



A **B**

Figure 1.13: Idoxuridine (A) and Amiodarone (B)

1.5 Pyrrole systems.

Pyrrole (1*H*-pyrrole, azole) is a five-member heterocyclic compound and it is a biochemically important material which is found in heme, chlorophylle and many alkaloid structures.

It is also used in electric/electronic applications because of the high electroconductivity of its polymer (polypyrrole).

Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics.

Phthalocyanine is an intensely blue-green coloured macrocyclic compound that is widely used in dyeing (Figure 1.14). Phthalocyanines form coordination complexes with most elements of the periodic table. These complexes are also intensely colored and also are used as dyes or pigments. The porphyrin ring is present not only in the various heme enzyme and

heme proteins but also in the chlorophylls of green plant cell. Porphyrins are derivatives of the parent tetrapyrrole compound porphyn. Protoporphyrin contains four methyl groups, two vinyl groups, and two propionic acid groups. Since protoporphyrins contain three different kinds of substituent groups, they may exist in fifteen isomeric forms depending on the sequence of substitution in the eight available side chain positions. Among these, many possible forms, protoporphyrin IX (Figure 1.14, B), is the most abundant. It is found in hemoglobin, myoglobin, and most of the cytochromes. Protoporphyrin forms quadridentate chelate complexes with metal ions such as iron, magnesium, zinc, nickel, cobalt, and copper.[18]

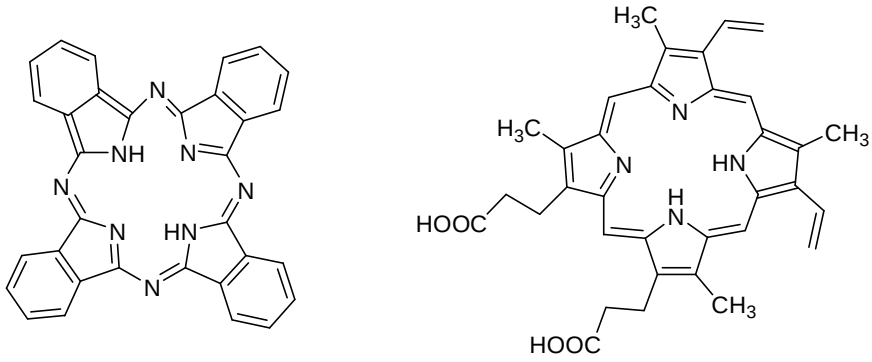


Figure 1.14: Phthalocyanine (A) and Photoporphyrin (B).

The lamellarins and related pyrrole-derived alkaloids (lukianols, polycitrins, polycitones, storniamides, didemnimides, ningalins, and purpurone, Figure 1.15) have shown a diverse range of bioactivities such as cytotoxicity and antitumor activity, reversal of multidrug resistance (MDR), HIV-1 integrase inhibition, antibiotic activity, human aldose reductase (h-ALR2) inhibition, cell division inhibition, immunomodulation, antioxidant activity.[19, 20]

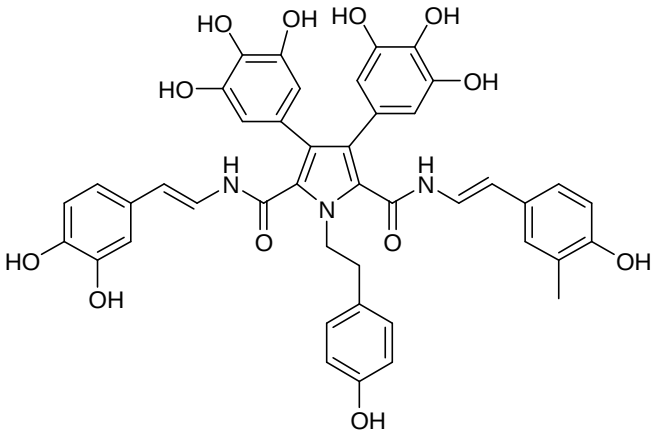
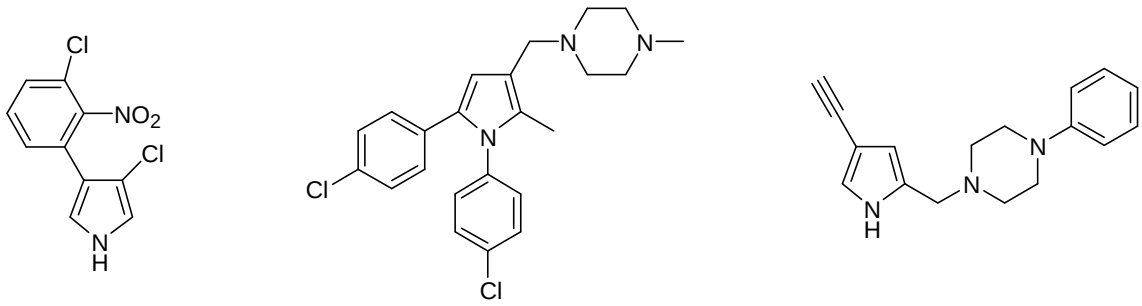


Figure 1.15: Lamellarins derivatives.

Many pyrroles were synthesized by us as pyrrolnitrin analogues (Figure 1.16, A). These compounds, showing both antibacterial and antifungal activities, have been tested against wild-type MTB and drug-resistant clinical isolates, as well as toward M. avium and other atypical mycobacteria. It was discovered that 1,5-(4-chlorophenyl)-2-methyl-3-(4-methylpiperazin-1-yl)methyl-1*H*-pyrrole (BM212, Figure 1.16, B) is a compound in a new class of antimycobacterial pyrrole derivatives with potent in vitro activity against mycobacteria and with low cytotoxicity.[21, 22]



A **B** **C**

Figure 1.16: Pyrrolnitrin (A), BM212 (B) and FAUC 356 (C).

Receptor binding studies and the measurement of dopamine D4 ligand efficacy indicated analogous binding modes for the general compound families of type A and B. The most interesting activity profile was discovered for the ethynylpyrrole FAUC 356 (Figure 1.16, C) exerting selective D4 recognition and substantial ligand efficacy (66 %), which might be of interest for the treatment of attention deficit hyperactivity disorders (ADHD).[23]

Recently, 2,3,5-triaryl-1*H*-pyrrole and 2,4,5-triaryl-1*H*-imidazole derivatives (Figure 1.17) have been reported to possess significant hepatic glucose lowering properties by acting as inhibitors of glucagon receptor. Among them, the compounds A and B were found highly potent and selective glucagon receptor antagonists in various cell based assays. Though 2,3,5-triaryl-1*H*-pyrrole has been explored for their antihyperglycemic activity, but little efforts have been made to exploit the therapeutic potential of 3,4,5-triaryl-1*H*-pyrroles as antihyperglycemic agents.[24]

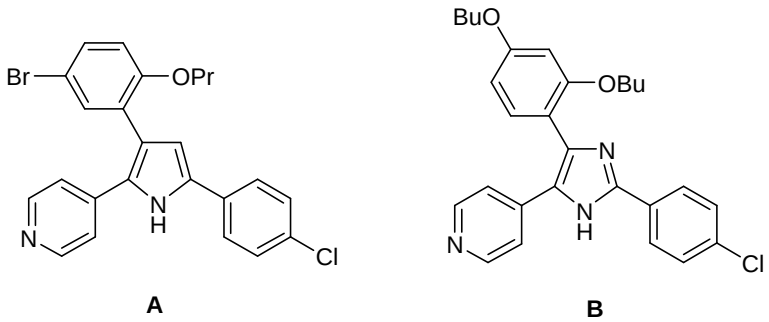


Figure 1.17: 2,3,5-Triaryl-1H-pyrrole (A) and 2,4,5-triaryl-1H-imidazole derivatives (B).

The combination of the 2-phenylpyrrole side chain with the tertiary amine containing moiety of fluanisone resulted in compound showed in Figure 1.18, A, which scored a high oral activity in apomorphine-induced climbing behavior and conditioned avoidance responding (CAR) tests, and exhibited selectivity towards dopamine D2 receptors over α^1-adrenoceptors, making it the prototype of a new class of sodium-independent dopamine antagonists having a low propensity to induce acute extrapyramidal side effects.[25]

VPA-985 (lixivaptan) is a selective Vasopressin (V2R) receptor antagonist (Figure 1.18, B).[9]

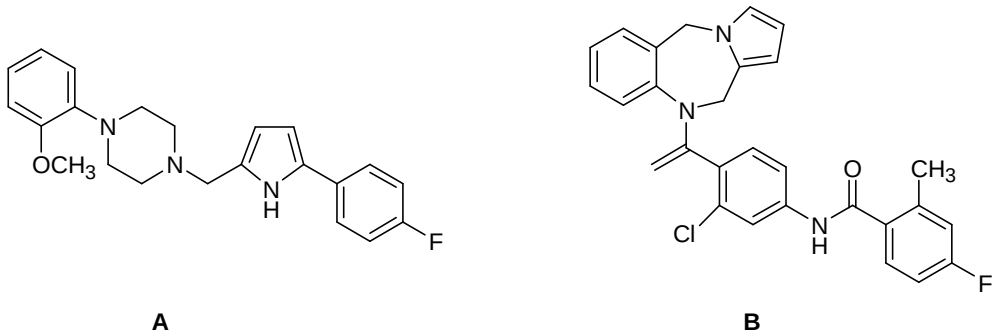


Figure 1.18: 2-Phenylpyrrole derivatives (A) and VPA-985 (lixivaptan B).

Insecticides are agents of chemical or biological origin that control insects. Control may result from killing the insect or otherwise preventing it from engaging in behaviors deemed destructive. Insecticides may be natural or manmade and are applied to target pests in a myriad of formulations and delivery systems.

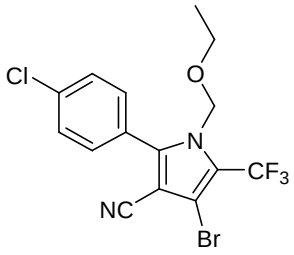
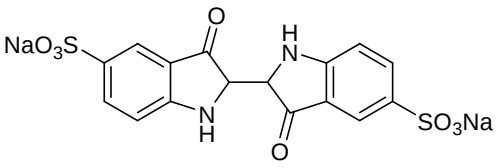


Figure 1.19: Insecticide compoud: Chlorfenapyr.

Chlorfenapyr (Alert®, Pirate®) is the first and only member of pyrrole chemical group, as both a contact and stomach insecticide-miticide (Figure 1.19). Chlorfenapyr is an "uncoupler" or inhibitor of oxidative phosphorylation, preventing the formation of the crucial energy molecule adenosine triphosphate (ATP).[26]

1.6. Pyrrolin-4-one systems.

Food dyes, natural or synthetic, are used as coloring agents in processed foods. This class of compounds is also constituted by an heterocyclic system containing pyrazole and pyrrolinone derivatives (Figure 1.20). Because food dyes are classed as food additives, they are manufactured to a higher standard than some industrial dyes.



FD&C Blue 2

Figure 1.20: Food dye.

Tetrapyrrolinone somatostatin (SRIF) mimetics (Figure 1.21), based on a heterochiral (d,l-mixed) pyrrolinone scaffold, were designed, synthesized, and evaluated for biological activity. Binding affinities at two somatostatin receptor subtypes (hsst) 4 and 5 reveal micromolar activity, demonstrating that the *d,l*-mixed pyrrolinone scaffold can be employed to generate functional mimetics of peptide β-turns.[27]

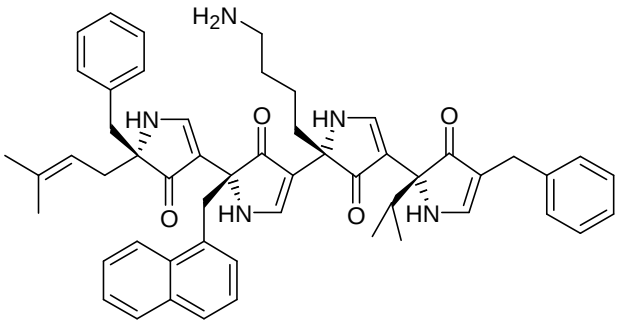


Figure 1.21: Tetrapyrrolinone somatostatin mimetics.

Mimetics based on pyrrolinones have shown potential in the development of enzyme inhibitors of proteolytic enzymes, including HIV-1 protease (Figure 1.21), renin, and matrix metalloproteases, ligand for the class II major histocompatability complex (MHC) protein HLA-DR1 and as a generic technology for the construction of mimetics of many peptide systems.[27]

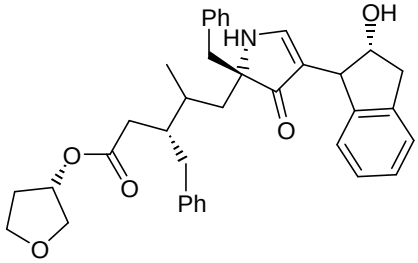


Figure 1.22: HIV-1 protease inhibitor

In the pyrrolinone system, the amide backbone is “rearranged” to replace the central amide group with a 5-membered pyrrolinone ring system (Figure 1.22). This transformation preserves the positioning of the side chain groups from the peptide while preventing the enzymatic degradation that would destroy normal peptides before they could reach their target receptors.

1.7: Isoquinoline systems.

Papaverine and some of its derivatives are known to exhibit interesting biological activities, such as muscle relaxation, hepatoxicity, and antimalarial activity, the modification of papaverine has been attractive in organic synthesis (Figure 1.23, A).

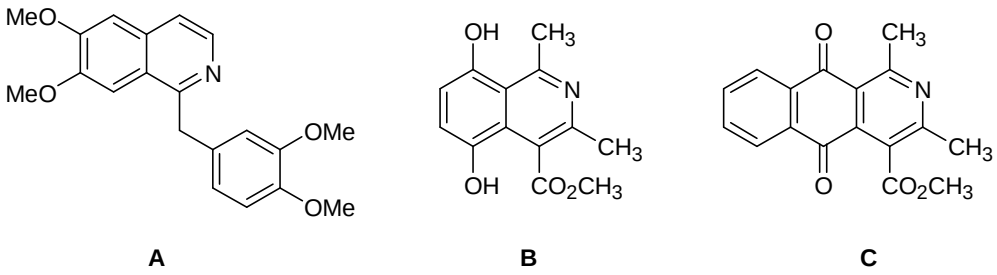


Figure 1.23: Papaverine (A) and isoquinolines 3-carboxyl esters (B-C).

Cytotoxic activity of isoquinolines 3-carboxyl esters (Figure 1.23, B-C) displayed significant *in vitro* activity on normal human MRC-5 lung fibroblasts and human AGS gastric adenocarcinoma cell lines, HL-60 leukemia cells, SKMES-1 squamous lung cancer cells, and J82 bladder carcinoma cells.[28]

1.8: Isochromene systems.

Substituted furano-, benzofurano-, pyrano-, and indolocoumarins and their isostructural analogs are present in plant, microorganism, and animal sources and manifest a wide range of pharmacological activities, including antitumoral, antibacterial, and antiviral (anti-HIV-1) properties (Figure 1.24). Acetylcholinesterase inhibitory activities potentially interesting for the treatment of neurodegenerative diseases such as Alzheimer's disease have been also reported.[29]

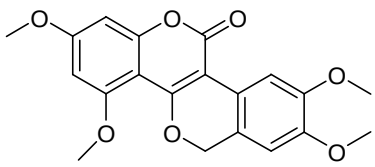


Figure 1.24: 6H,11H-[2]Benzopyrano-[4,3-c][1]benzopyran-11-ones

1.9: Conclusion.

This initial chapter has reported some examples of heterocyclic systems commonly used in life such as drugs.

Chapter 2

Cyclization reactions in Green context.

2.1: Introduction.

The sustainable chemistry consists in the development of alternatives methods of chemical processes. Catalysis, alternative solvents and atom economy are key areas for the development of versatile strategies in organic synthesis.

2.2: The platinum group metal catalysts.

The platinum group metal catalysts that included the precious metals Gold, Iridium, Osmium, Palladium, Platinum, Rhodium, Ruthenium and Silver and all transition metals are widely used in chemical processes for reactions ranging from homogeneous and heterogeneous catalysis, gas phases oxidation through selective for power generation. Although platinum group metals are more expensive in initial cost than base metal catalysts, they often prove to be more reactive and selective and require less severe reaction conditions. In addition, the spent catalyst can be recovered and the precious metal reprocessed into fresh catalyst.
The key properties for a good catalyst are:

- ✓ High activity: for fast reaction rate and a short reaction time to maximize production throughput.
- ✓ High selectivity: to maximize the yield; eliminate by-products and reduced purification costs.
- ✓ High recycle capability: to rapidly separate the catalyst and the final product, ensuring maximum production rates.

Homogeneous catalyst is an area of increasing importance within the chemical industry. Recent advances in process technologies, particularly in regard to product purification, catalyst separation and recycling, are changing economics in favour of homogeneous versus heterogeneous catalysis routes for many chemicals.

2.2.1: Homogeneous catalysis.

Homogeneous catalysis provides an excellent choice where highly specific reactions are desired.

By definition, a catalytic reaction in which the reactants and the catalyst are present together in a single phase is homogeneous catalysis. Homogeneous catalysis commonly refers to catalytic reactions where all components are in the liquid phase.

A homogeneous-catalyzed reaction contains the catalyst in the same phase as at least of the reactants. Almost invariably the catalyst is dissolved in a liquid phase. For the platinum group metal catalyzed reactions the advantages of a homogeneous system over a heterogonous one are:

- ✓ Better utilization of metal – all of the catalytic metal is equally available to the reactants
- ✓ Exploitation of different metal oxidation states and ligands
- ✓ Kinetic rather than mass transfer control of reaction rates
- ✓ Easy exotherm removal – no localized overheating

2.2.2: Heterogeneous catalysis.

The major factors effecting the properties of a heterogeneous catalyst are the selection of the most appropriate support material and the location of the metal on and/or within the pore structure of the support.

2.3: Separation of catalyst from reaction mixture.

A key consideration for homogeneous catalyst users is product/catalyst separation with subsequent product work up and catalysts recycling.

All common separation techniques have been employed in full-scale commercial operation as well as on the laboratory scale. These include:

- ✓ Distillation, usually under reduce pressure;

- ✓ Liquid-liquid solvent extraction, particularly in application where the spent catalyst is rendered soluble in water;
- ✓ Crystallization of the product by addition of a precipitating solvent such as diethyl ether or a hydrocarbon such as hexane;
- ✓ Flash chromatography on neutral alumina or silica gel, using various solvents, including acetone, hexane, ethyl acetate and mixtures of these. The spent catalyst is retained on the column while the desired product passes through
- ✓ Adsorption followed by filtration using ion exchange polymers to selectively remove the spent catalyst;
- ✓ Selectively precipitating the catalyst and removing it from the reaction medium by filtration. The desired product is then further purified by vacuum distillation or recrystallization.

To be reused, a catalyst has to be rendered soluble again, so further processing is essential. Such systems can be quite complex, but the chemical transformations that are made possible with homogeneous catalyst may justify this extra processing.
In some cases, the platinum group metal homogeneous catalyst is so active that there is no economic need to recover the metal values.

2.4: Platinum and Gold catalysts.

Complexes and salts derived from late transition metals Pt and Au (gold (III) and cationic gold (I)) have shown an exceptional ability to promote a variety of organic transformations of unsaturated precursors. These processes result from the peculiar Lewis acid properties of these metals: the alkynophilic character of these soft metals and the π-acid activation of unsaturated groups promotes the intra- or intermolecular attack of a nucleophile.
The pioneering efforts in this area in the early 1990s utilized simple metal salts, such as halides ($PtCl_2$ and $AuCl_3$) due to their apparent insensitivity under aqueous conditions and ability to successfully promote a diversity of synthetic transformations, but a decade later, Au(I) cationic species have proven to be superb catalysts for both carbon-carbon and carbon-heteroatom bond formations. Because the activation process invokes electrophilicity

enhancement, a move toward cationic metal templates, which may be stabilized by a suitable spectator ligand, results in increased activity.

These catalysts allow us to overcome additional problems associated with other metal complexes that also promote the same transformations, such as Hg salts, since they are considered essentially nontoxic. Furthermore, they combine high affinity to the π system with the advantages of a kinetically labile carbon-metal bond that can be readily cleaved under the reaction conditions, thus ensuring efficient turnover.

These reactions provide an atom-economical entry into functionalized cyclic and acyclic scaffolds useful for the synthesis of natural and non-natural products under mild conditions with excellent chemoselectivity and high synthetic efficiency. Consequently, during the last years an explosive increase of interest in Au and Pt catalysis has taken place, thus becoming an extremely dynamic and innovative field of catalysis research.

Examples of the myriad of reaction types involving transition metal catalyzes[30, 31] that comprise this class of chemical transformations are presented in this chapter.

2.5: Synthetically approach for the preparation of heterocyclic rings.

Chemical methods that enable the concise, selective and efficient de novo synthesis of nitrogen or oxygen heterocycles empower the scientific community to gain access to known biologically active small molecules as well as provide an opportunity to create as yet unknown compounds with potential biological activity, which may be discovered through medicinal chemistry studies.

The important methods for synthesizing heterocyclic compounds can be classified under five headings. Three are ways of forming new heterocyclic rings from precursors containing either no rings (acyclic precursors) or one fewer ring than the desired product; one is a way of obtaining a heterocyclic ring from another heterocyclic ring or from a carbocyclic ring; and one involves the modification of substituents on an existing heterocyclic ring.

In the formation of rings from acyclic precursors, the key step is frequently the formation of a carbon-heteroatom linkage (C−Z, in which Z represents an atom of nitrogen, oxygen, sulfur, or a more unusual element). The actual ring closure, or cyclization, however, may involve the formation of a carbon-carbon bond. In any case, ring formation reactions are divided into

three general categories according to whether the cyclization reaction occurs primarily as a result of nucleophilic or electrophilic attack or by way of a cyclic transition state.
Different synthesis can be applied:
1) Nucleophilic ring closure.
2) Electrophilic ring closure.
3) Ring closure by way of cyclic transition states.
4) Conversion of one heterocyclic ring into another.
5) Modification of an existing ring.

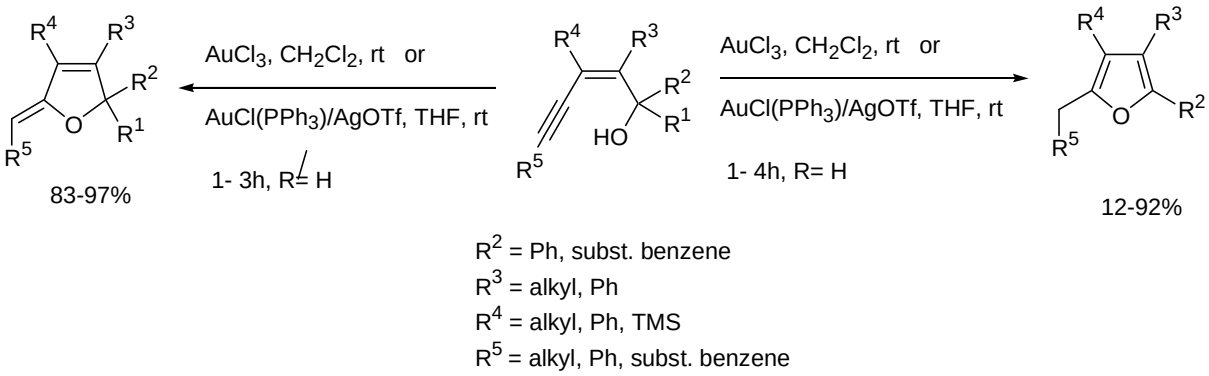
2.6: Synthesis of aromatic heterocycles from acyclic substrates by metal-catalyzed cycloisomerization reactions.

Cycloisomerization reaction is a series of transformations that occur with complete atom economy minimize utilization of raw material and produce no waste and thus represent an upper limit of synthetic efficiency. Transition metal-catalyzed cycloisomerizations represent a major class of atom economical reactions.
Every year is possible to observed several significant advances in the field of heterocyclic chemistry, with particular highlights including several new approaches to nitrogen, oxygen compounds and their derivatives. Several papers and reviews have described these transformations using gold,[32-35] platinum or palladium[36] as catalysts.

Au(I) and Au(III) complexes have increasingly been used as catalysts in a variety of organic transformations, and the majority of such transformations draw on the propensity of gold ions to activate alkynes toward nucleophilic addition.
A large number of reviews described the potentiality of gold[37] in C–C bond formations[38, 39] using also homogeneous catalysis by gold[40] and cycloaddition.[41]

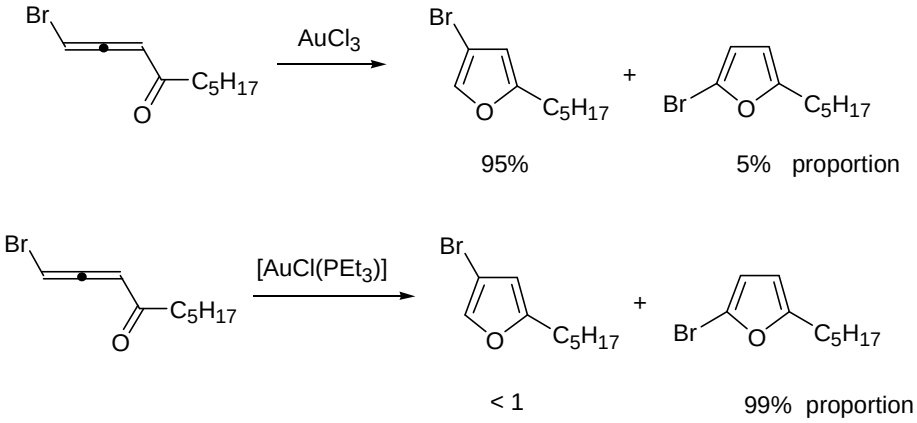
Hashmi and co-workers have reported that aromatic heterocycles can be obtained from secondary enyne alcohols by an intramolecular hydroalkoxylation followed by a double bond isomerization (Scheme 2.1).[42, 43] The initial hydroalkoxylation product is believed to be the exocyclic olefin, as indicated by the isolation of such a compound in the reaction of the

corresponding tertiary enyne alcohols. In the latter case, the double bond geometry indicates that the 5-*exo*-trig cyclization is an anti-oxyauration step.



Scheme 2.1: Intramolecular hydroalkoxylation of secondary enyne alcohols.

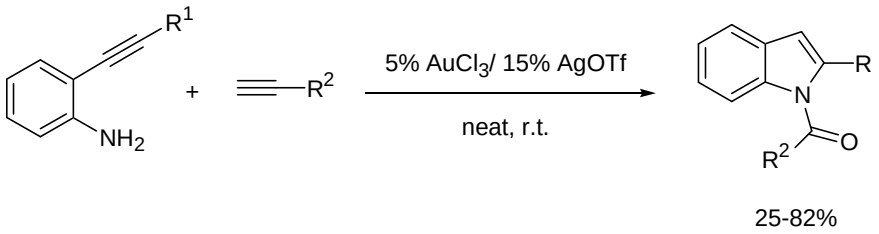
The oxidation state of gold influences the catalytic properties. This can be explain from a synthesis of halofurans by the cyclization of bromoallenylketones (Schemes 2.2) However, in processes where such a discrepancy in reactivity is not apparent, some ambiguity can remain as to the actual nature of the active specie.[44, 45]



Scheme 2.2: Cyclization of bromoallenylketones.

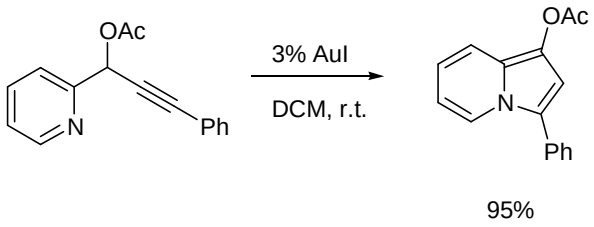
Ortho-alkynylanilines are known to be suitable substrates for gold-catalyzed indole syntheses. However, Li et al. showed that, in the presence of a terminal alkyne, the intermolecular hydroamination occurs first. The resulting Schiff bases can then cyclize onto the pendant alkyne. Indole does not undergo hydroamination with terminal alkyne in a

control experiment. $AuCl_3$ efficiently catalyzes this reaction with neat substrate, although addition of AgOTf gives higher yields under milder conditions (Scheme 2.3).[32]



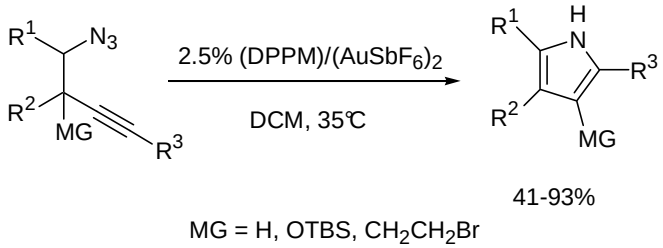
Scheme 2.3: Gold-catalyzed indole syntheses.

Pyridines serve as nucleophiles for intramolecular additions. Gevorgyan's laboratory screened a plethora of metals, and most, including gold (I) and gold (III), are competent catalysts for this reaction.[46] The mechanism involves a cascade reaction via isomerization to a gold-vinylidene, followed by a hydride shift (Scheme 2.4).



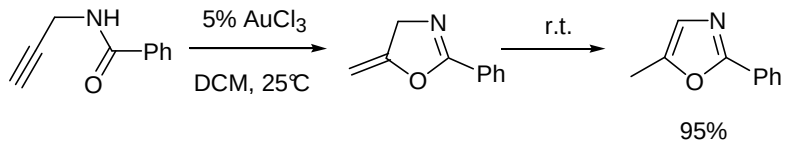
Scheme 2.4: Intramolecular additions of nitrogen by gold (I).

Toste et al. exploited that a variation of Schmidt reaction can carried out using gold(I) where a nucleophile with a latent leaving group attached can add intramolecularly to an unactivated alkyne.[47, 48] At this point, rather than proto-deauration, gold backbonds electron density to the substrate, expelling N_2. The most effective combination for the synthesis of pyrroles was the dinuclear bisphosphine $(dppm)Au_2Cl_2$ activated by $AgSbF_6$ (Scheme 2.5).



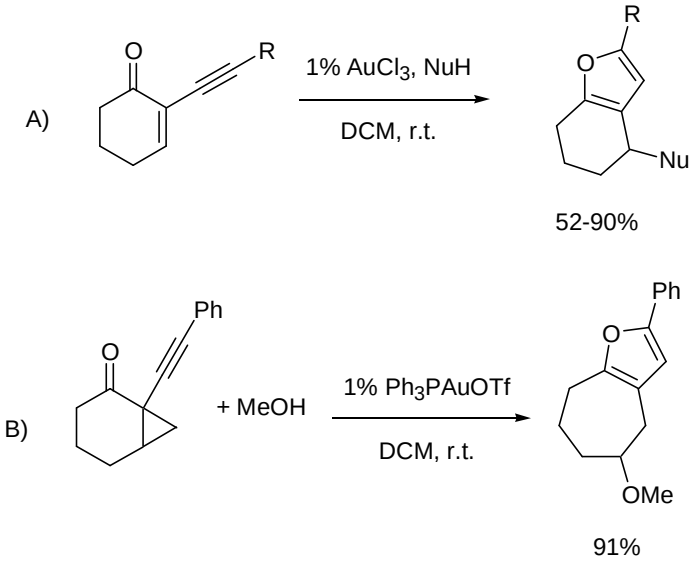
Scheme 2.5: Synthesis of pyrroles by dinuclear bisphosphine $(dppm)(AuSbF_6)_2$ as catalyst.

Hashmi et al. published work on the formation of oxazoles *via N*-propargylcarboxamide cyclization.[49] He was able to trap the methylene dihydrooxazole intermediate at lower temperatures. Isolated yields from room temperature examples were typically excellent (>95%) (Scheme 2.6).



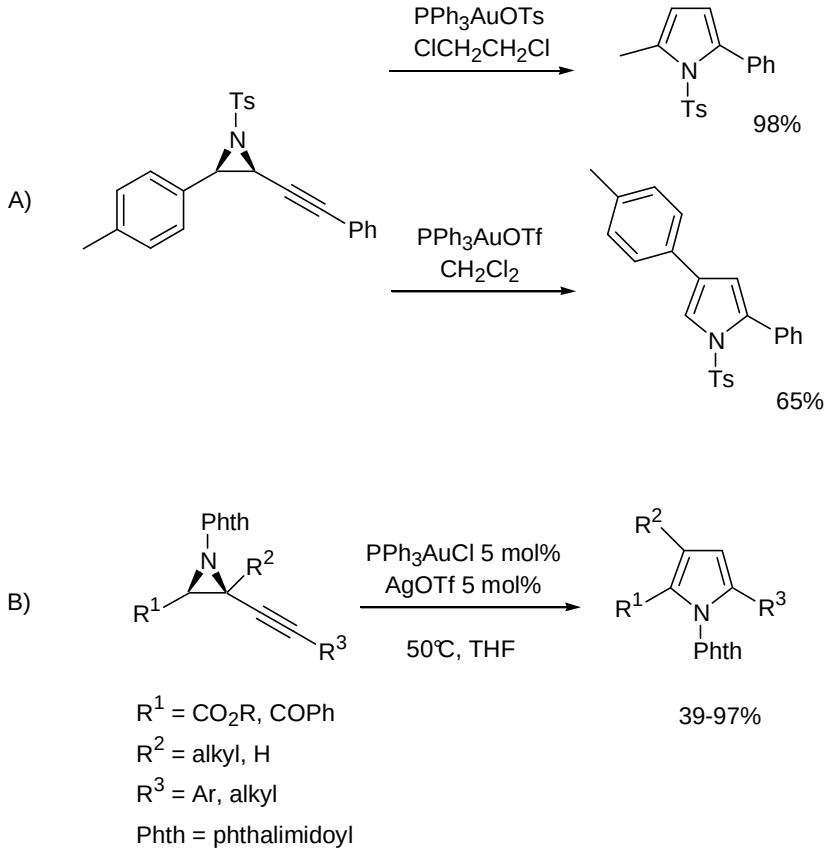
Scheme 2.6: Formation of oxazoles via N-propargylcarboxamide cyclization.

Larock and co-workers have used conjugated alkynyl enones as substrates that undergo tandem intramolecular carbonyl addition/intermolecular nucleophilic attack to generate highly substituted furans (Scheme 2.7, A).[50] Notably, a variety of different nucleophiles add successfully, including alcohols, -diketones, indoles, and even arenes. Schmalz et al. later showed that substituting the olefin with cyclopropane leads to ring-expansion products (Scheme 2.7, B).[51] Yields are quite good with a range of alcohols and some heterocycles acting as nucleophiles.



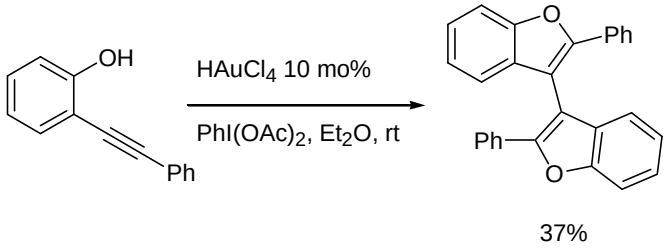
Scheme 2.7: Synthesis of furans by intramolecular carbonyl addition/intermolecular nucleophilic attack.

Gold-catalyzed cycloisomerization reaction of alkynyl aziridines can give 2,5-disubstituted pyrroles in high yields.[52] Davies and Martin have reported that, in some cases, aryl-substituted *N*-tosyl alkynyl aziridines underwent a gold-catalyzed ring expansion to afford 2,5-substituted or 2,4-substituted pyrrole products (Scheme 2.8, A).[53] Interestingly, the reaction pathway was determined by the counter ion of the gold catalyst. The formation of 2,5-substituted pyrroles proceeds with PPh_3AuOTs as the catalyst whilst a novel reaction pathway is accessed on changing the catalyst system to PPh_3AuOTf and leads to 2,4-substituted pyrroles. Recently, the same authors reported an efficient and synthesis of 2,5-substituted pyrroles by gold catalyzed ring expansion of alkynyl aziridines (Scheme 2.8, B).[54]



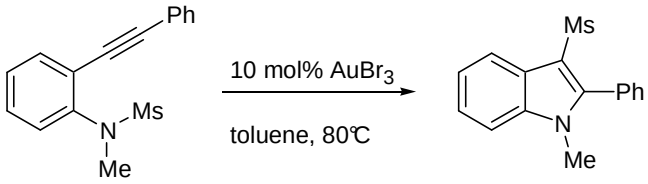
Scheme 2.8: Gold-catalyzed cycloisomerization reaction of alkynyl aziridines.

Wegner and co-workers[55] have reported a heterogeneous gold-catalyzed system for the domino cyclization oxidative coupling of 2-alkynyl phenols for the formation of 3,3'-bisbenzofurans (Scheme 2.9). This method provides access to this novel structural theme in two steps starting from commercially available chemicals.



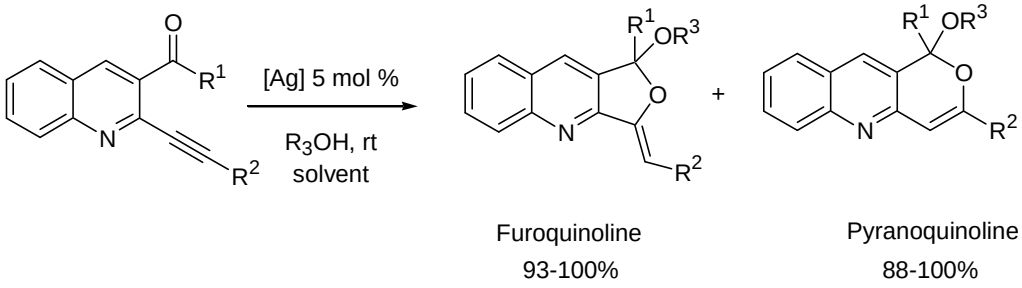
Scheme 2.9: Domino cyclization oxidative coupling by gold-catalyzed system.

Gold-catalyzed reactions of ortho-alkynyl-*N*-sulfonylanilines produced the corresponding 3-sulfonylindoles in good to high yields (Scheme 2.10). Nakamura and co-workers synthesized 3-mesyl-1-methyl-2-propylindole, 3-mesyl-1-methyl- 2-phenylindole, and 3-mesyl-1-methylindole from *N*-mesyl-*N*-methyl-2-(1-pentynyl)aniline, *N*-mesyl-*N*-methyl-2-(phenylethynyl)aniline, and 2-ethynyl-*N*-mesyl-*N*-ethylaniline in moderate to high yield with $AuBr_3$ as the catalyst.[56]



Scheme 2.10: Gold-catalyzed reactions of ortho-alkynyl-N-sulfonylanilines.

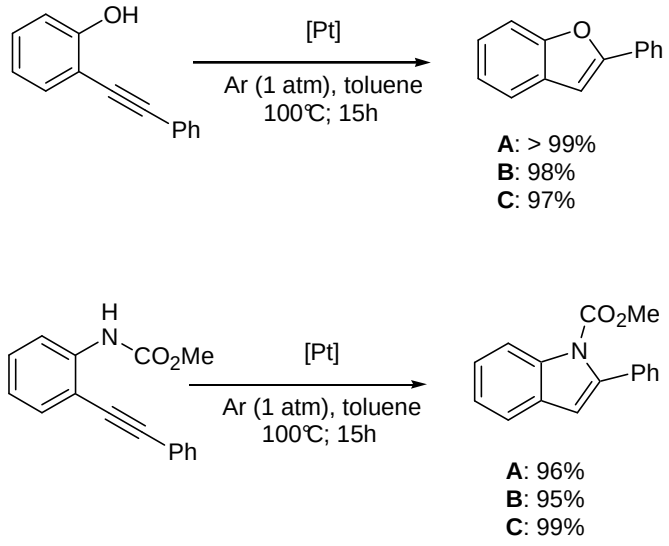
Belmont and co-workers have reported a tandem process of acetalization-cycloisomerization reactions of 1-alkynyl-2-carbonylquinolines.[57] The reactions were carried out using Au(I) or Ag(I)[58] as catalysts to obtain furoquinoline and pyranoquinoline derivatives (Scheme 2.11).



Scheme 2.11: Synthesis of furoquinolines and pyranoquinolines.

Toste and co-workers have reported the application of heterogeneous catalysts to known homogeneous catalytic reactions through the design and synthesis of electrophilic platinum nanoparticles.[59] Cyclization reactions were carried out using either PVP- or dendrimer-encapsulated nanoparticules results in good to excellent yields of nitrogen- and oxygen-containing heterocycles through π-bond activation by electrophilic Pt (Scheme 2.12).

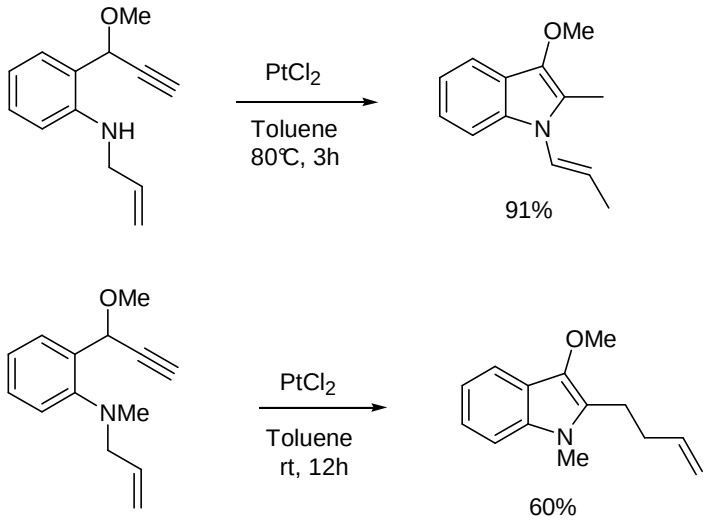
These nanoparticles are selectively oxidized by the hypervalent iodine species $PhICl_2$. Furthermore, a size and capping agent study revealed that Pt PAMAM dendrimer capped nanoparticles demonstrate superior activity and recyclability compared with larger, polymer-capped analogues.



A: 2.9 nm Pt/PVP/SBA-15 (2.5 mol%), $PhICl_2$ (7.5 mol%)
B: Pt_{40}/G4OH/SBA-15 (4 mol%), $PhICl_2$ (12 mol%) 98%
C: $PtCl_2$ (5 mol%) (2 h)

Scheme 2.12: Cyclization reactions using Pt nanoparticles.

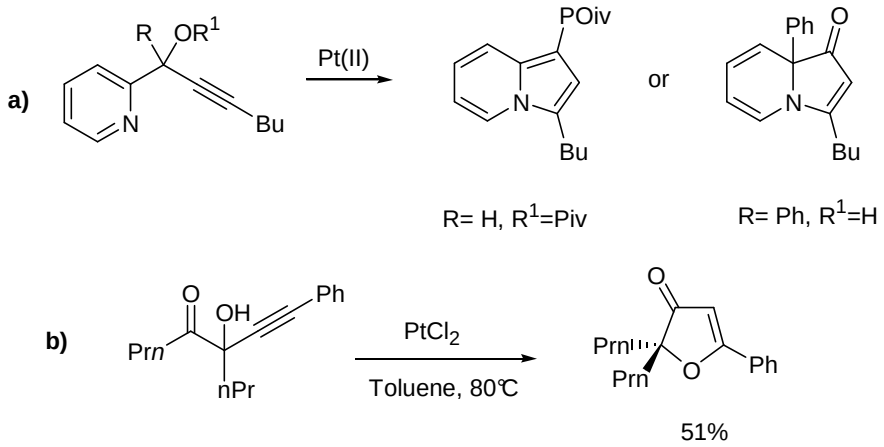
The use of propargylic precursors with oxyge or nitrogen heteroatom, and alkyne substituents can give to 2,3-functionalized indoles and notably 3-alkoxyindoles (Scheme 2.13), which relies on the use of $PtCl_2$ or proton catalysis. The most intriguing aspect of this process is that the tuning of substituents on the nitrogen atom, as well as reaction conditions, notably temperature, allows an easy and versatile access to a myriad of indole substrates.[60]



Scheme 2.13: Synthesis of 2,3-functionalized indoles.

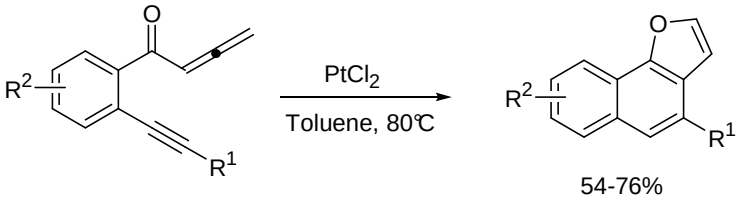
Sarpong and co-workers have reported the synthesis of indolizine, pyrrolone, and indolizinone heterocycles by Pt (II)-catalyzed cycloisomerization (Scheme 2.14, a). The access of these systems can by involve by direct cyclization or tandem cyclization/1,2-migration of pyridine propargylic alcohols and derivatives.[61]

Key step of synthesis of 3(2*H*)-furanone is also heterocyclization followed by 1,2-migration (Scheme 2.14, b). It is hypothesized that coordination of the alkyne moiety of propargylic alcohol to a suitable transition-metal catalyst induces the intramolecular attack of the carbonyl group. The intermediate oxonium ion then triggers a 1,2-alkyl migration analogous to a formal a ketol rearrangement, and subsequent protonation affords 3(2*H*)-furanone and regenerates the catalyst.[62]



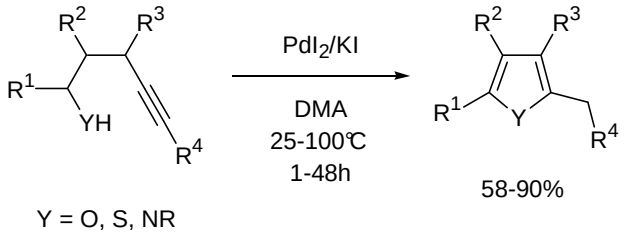
Scheme 2.14: Heterocycles synthesis by Pt (II)-catalyzed cycloisomerization.

Xu and co-workers have reported the synthesis of naphtho[1,2-b]furan (Scheme 2.15) by tandem catalysis induces a cycloisomerization of allenyl ketone, followed by a 6π-electrocyclization-type reaction of carbene intermediate. The metal carbene proved to be an effective intermediate in the 6π-electrocyclization-type reaction. Reactions were carried out with allenyl ketone with 10 mol % of $PtCl_2$ in toluene at 80 °C.[63]



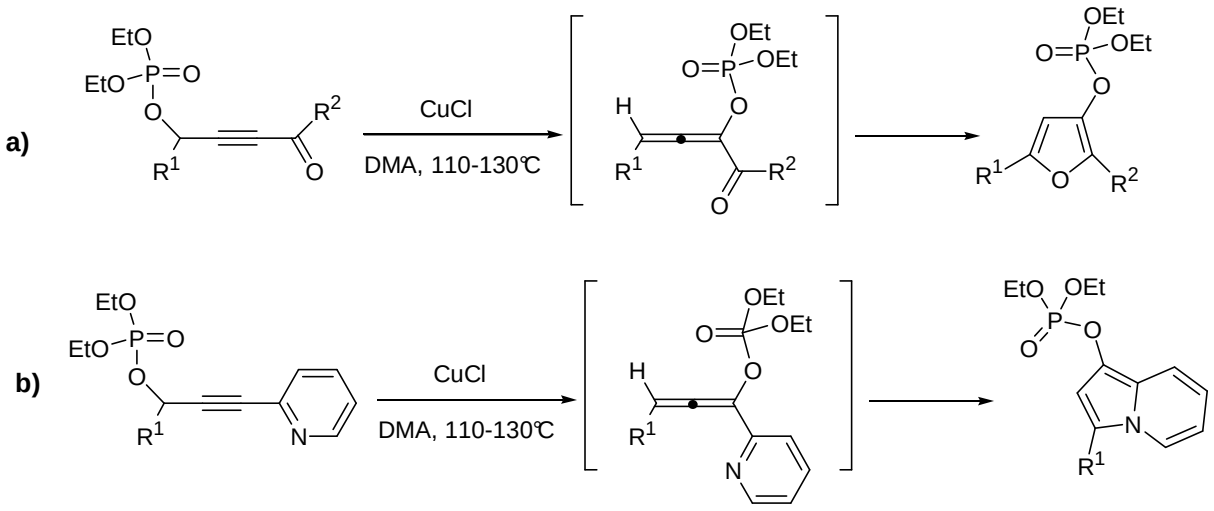
Scheme 2.15: Cycloisomerization of allenyl ketone.

Gabriele and co-workers have described the cycloisomerization of (*Z*)-2-en-4-yn-1-ols, (*Z*)-2 en-4-yne-1-thiols, (*Z*)-(2-en-4-ynyl)amines, 2-alkynylbenzyl alcohols to give substituted furans, thiophenes and pyrroles,[36] by PdI_2/KI-catalyzed reactions (Scheme 2.16).



Scheme 2.16: PdI_2/KI-catalyzed reactions.

Gevorgyan and co-workers have developed different modes of cascade cycloisomerizations of alkynyl ketones and imines proceeding via various types of migration of acyloxy, phosphatyloxy, and tosyloxy groups to give multisubstituted furans and indolizines in good to high yields (Scheme 2.17). This set of methodologies allows for the efficient synthesis of tri- and tetrasubstituted furans and *N*-fused heterocycles.[64] Cycloisomerization reaction takes place using silver, copper and gold as catalyst.



Scheme 2.17: Cycloisomerizations of alkynyl ketones and imines.

The transition metal-catalyzed enyne cycloisomerization is among the most important strategies for the synthesis of functionalized cyclic structures. The significance of this process stems from the rapid increase in structural complexity starting with relatively simple acyclic subunits containing ene and yne fragments (Scheme 2.18).[65] Among a range of transition metal complexes capable of catalyzing enyne cycloisomerizations, gold and platinum complexes are particularly powerful as they are capable of delivering a diverse array of cyclic products that are produced under mild conditions, with excellent chemoselectivity and high synthetic efficiency.[66-72]

Activation of alkynes was obtained by Pt transition metal species toward nucleophilic attack[73]

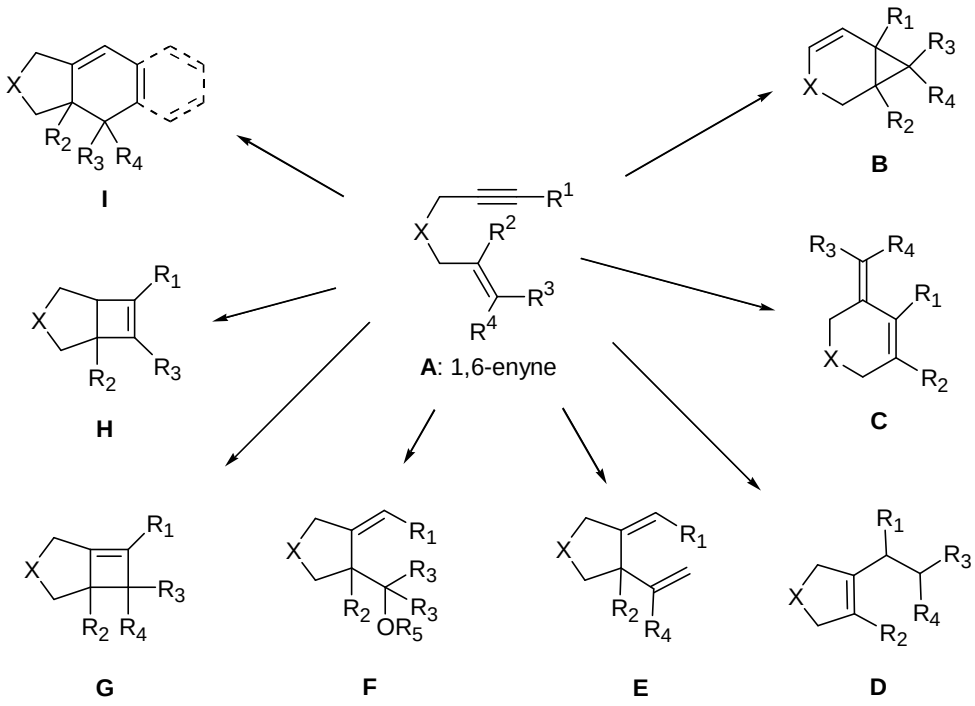


Figure 2.18: Cycloisomerization of 1,6-enynes.

With gold and platinum catalysts, cycloisomerization of 1,6-enynes often leads to skeletal rearrangement. Migration of a 1,2- and 1,3-alkylidene fragment is very interesting in mechanistic and synthetic aspects. In such processes, the olefin double bond of the enyne substrate is cleaved and migrated to the alkyne carbon.[74-76]

The cycloisomerizations of 1,5-enynes can be played by gold- and platinum-catalysis. This catalytic process displays a wide alkyne scope and furnishes a range of highly functionalized 1,4- and 1,3-cyclohexadienes.[77, 78]

2.7: Carbonylation reaction.

An oxidative carbonylation is a process in which carbon monoxide is inserted into an organic substrate under the action of a metal undergoing a reduction of its oxidation state, the reduction Pd(II) → Pd(0) is the most common case.[79] In order to achieve a catalytic reaction, some way must be provided to reconvert the metal in its original oxidation state. In other words, an external oxidant is needed to allow a stoichiometric process to become a catalytic one.

Figure 2.1 represent a typical device, autoclave, for carried out the carbonylation reaction under high pressure of mixture of carbon monoxide and air.

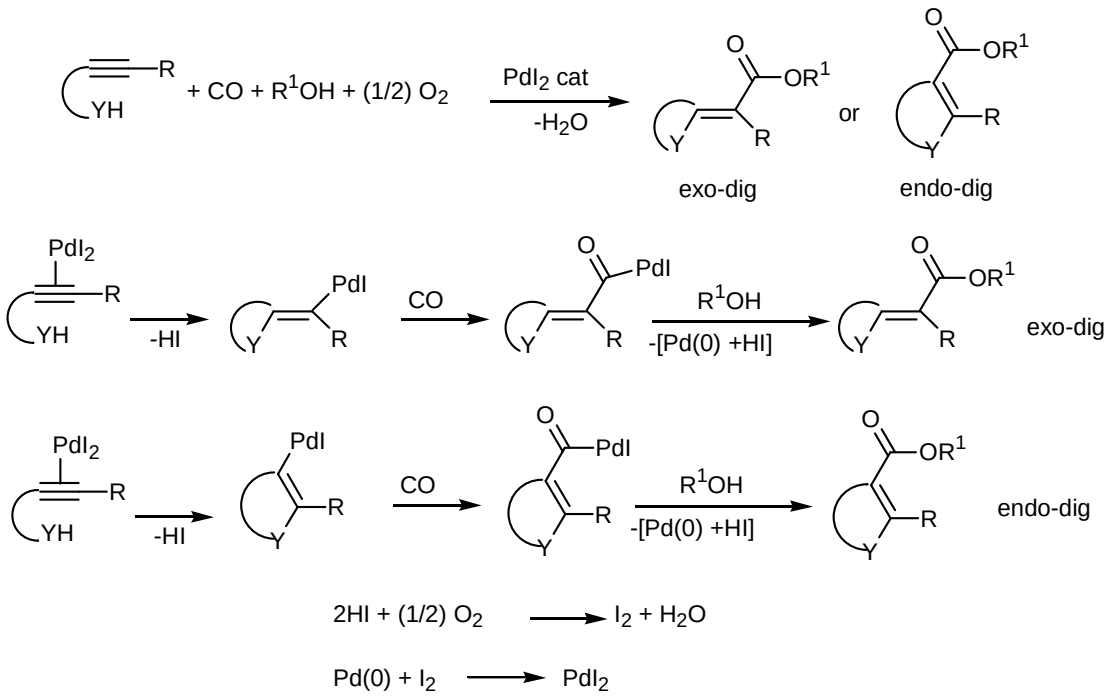
Figure 2.1: Autoclave.

The metal reoxidation process has always been a major problem in oxidative carbonylation, in relation to which a large number of patents have been issued. Either organic or inorganic oxidants, such as benzoquinone (BQ) or copper chloride, have been used as reoxidizing agents. Direct reoxidation with O_2 is also possible, and has proven particularly effective in the case of $Pd(0) \rightarrow PdI_4^{2-}$ reconversion.

Different substrates (alkenes, dienes, allenes, alkynes, ketones, ketenes, aromatic hydrocarbons, aliphatic hydrocarbons, alcohols, phenols, amines) leading to a variety of carbonyl compounds are interested by oxidative carbonylation.

In particular PdI_2-based systems had shown the ability to promote different kind of oxidative carbonylations under mild conditions to afford important carbonyl derivatives with high selectivity and efficiency.[80]

Alkynes bearing a nucleophilic group in suitable position for cyclization are excellent substrates for different kinds of oxidative carbonylation reactions leading to functionalized heterocyclic derivatives. Both oxidative cyclocarbonylation (with incorporation of CO into the cycle) and oxidative cyclization–carbonylation (without incorporation of CO ino the cycle) are possible (Scheme 2.19). All these reactions are catalyzed by Pd(II) species.



Scheme 2.19: Cyclization–alkoxycarbonylation reaction.

In Scheme 2.19 are presented the general mechanism of cyclization–alkoxycarbonylation involving by exo or endo intramolecular nuclophilic attack by YH to the triple bond coordinated to Pd(II) followed by CO insertion and nucleophilic displacement by NuH.
Very efficient mechanism of reoxidation of Pd(0), which involves oxidation of HI by O_2 to I_2, followed by oxidative addition of the latter to Pd(0).

2.8: Iodocyclization.

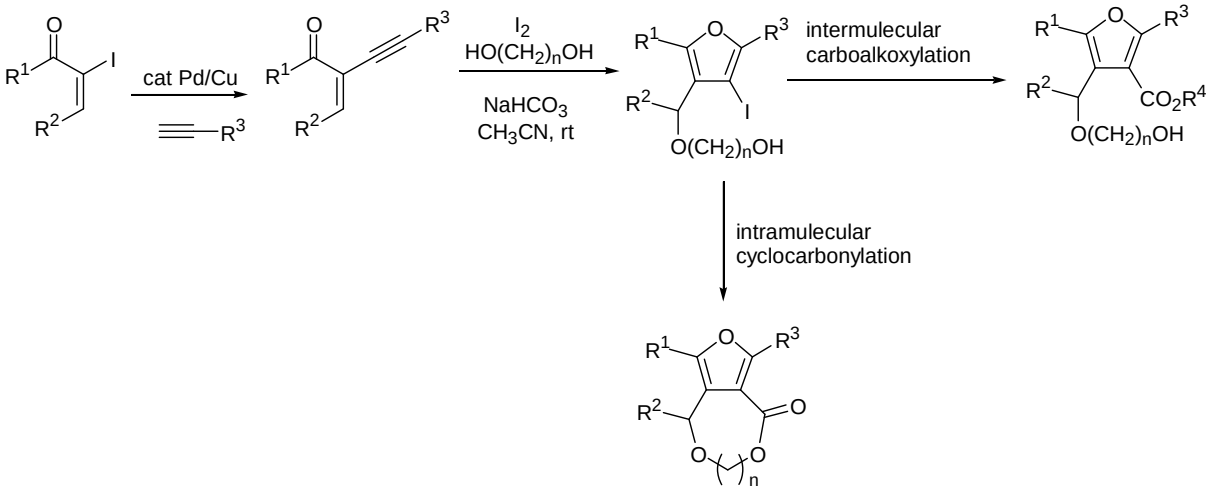
Halocyclization is a reaction whereby the intramolecular nucleophilic group attacks the carbon-carbon double or triple bond activated by electrophilic halogenating reagent to give cyclic compounds. Iodine is a highly polarizable molecule that behaves as electrophilic iodine (I^+) in the presence of a suitable Lewis basa; such as an alkene or an alkyne.[81]
The outcome of this cyclization strategy which has been exploited in recent years for the synthesis of furans, pyrroles and quinolinones and their analogues is rationalized in terms of the rules previously developed by Baldwin for predicting the relative ease of organic ring-forming reactions

We herein focus attention on iodine–mediated cyclization reactions involving O- or N-containing group as an intramolecular nucleophile.

A mild, metal-free, environmently benign and atom economic protocol for the straightforward annulation of five- and six-membered heterocyclic rings or they benzoderivatives is still of high demand. The electrophilic cyclization of heteroatomic nucleophiles, such as oxygen, nitrogen, and sulfur, with alkynes has proven to be an effective method for the synthesis of heterocyclic compounds.

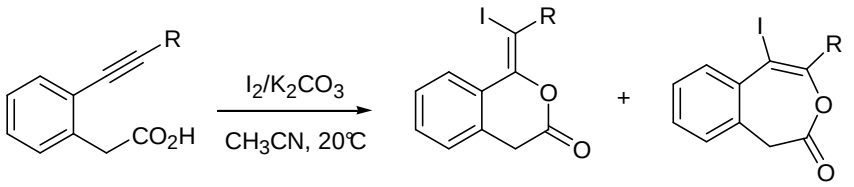
Several reviews and paper have described the use of iodine in organic chemistry[82] and herein we report some examples.

Larock and coworkers have reported the synthesis of various hydroxyl-containing 3-iodofurans readily prepared by a two-step approach involving the Sonogashira coupling of 2-iodo-2-alken-1-ones with terminal alkynes followed by electrophilic cyclization by I_2 in the presence of diols. These hydroxyl-containing 3-iodofurans, in ethylene glycol, by palladium-catalyzed protocol can give for intermolecular carboalkoxylation or intramolecular cyclocarbonylation the corresponding ester-containing furans or the corresponding lactone-containing furans (Scheme 2.20).[83]



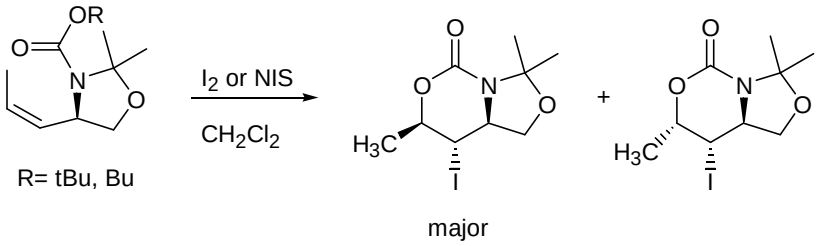
Scheme 2.20: Synthesis of furan esters and lactones by iodocyclization and palladium-catalyzed carboalkoxylation or cyclocarbonylation.

Knight and co-workers have reported iodolactonizations of 2-(alkynyl)phenylacetic acids (Scheme 2.21). Exposure of 2-alkynylphenylacetic acids to excess iodine in acetonitrile containing anhydrous potassium carbonate delivers good yields, either of the corresponding isochroman-3-ones or benzo[d]oxepin-2(1*H*)-ones, depending upon the alkyne substituent: when this is alkyl, the former 6-*exo* products dominate, otherwise the 7-*endo* products are formed largely or, more often, exclusively.[84]



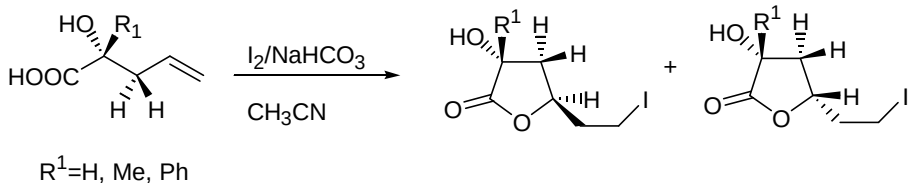
Scheme 2.21: Iodolactonizations of 2-(alkynyl)phenylacetic acids.

Orena and co-workers have reported that 3-alkoxycarbonyl-4-propenyl-2,2-dimethyl-1,3-oxazolidines underwent highly regio- and stereoselective iodocyclization on treatment with iodine or *N*-iodosuccinimide (NIS) in dichloromethane or chloroform, to give, in moderate to low yield, the bicyclic compounds (Scheme 2.22), which were isolated by column chromatography.[85]



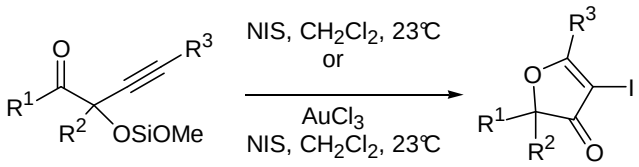
Scheme 2.22: Stereoselective iodocyclization of bycyclic compounds.

Kaur and co-workers have reported the iodine mediated intramolecular cyclizations of 2-allyl derivatives of glycolic, mandelic and lactic acids provide furan-2(5*H*)-one derivatives with OH and CH_2I moieties placed syn to each other as the major or the only product (Scheme 2.23).[86]



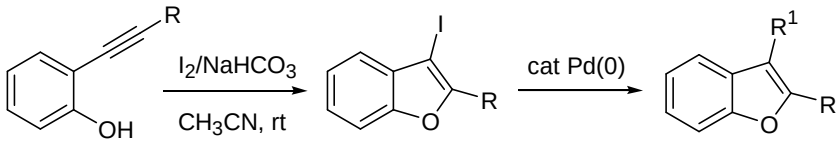
Scheme 2.23: Synthesis of furan-2(5H)-one derivatives.

Kirsch and co-workers have presentes the synthesis of 4-iodo-3-furanones starting from 2-alkynyl-2-silyloxy carbonyl compounds combining a heterocyclization with a 1,2-alkyl shift by electrophilic cyclization directly induced by *N*-iodosuccinimide or $AuCl_3$ catalyzed tandem reaction in the presence of NIS (Scheme 2.24).[87]



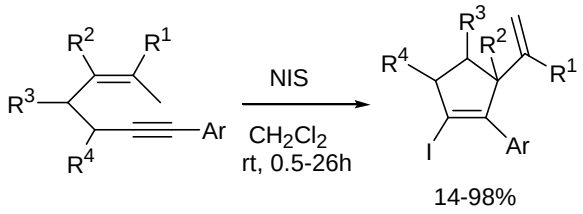
Scheme 2.24: Electrophilic cyclization induced by N-iodosuccinimide or gold.

Arcadi and co-workers have proposed the 5-*endo*-dig-iodocyclization of *o*-alkynylphenols with iodine in the presence of $NaHCO_3$ at room temperature for produce functionalised 2-substituted-3-iodobenzo[*b*]furans (Scheme 2.25). These synthetic intermediates were used for the preparation of 2,3-disubstituted benzo[*b*]furans via palladium-catalysed reactions.[88]



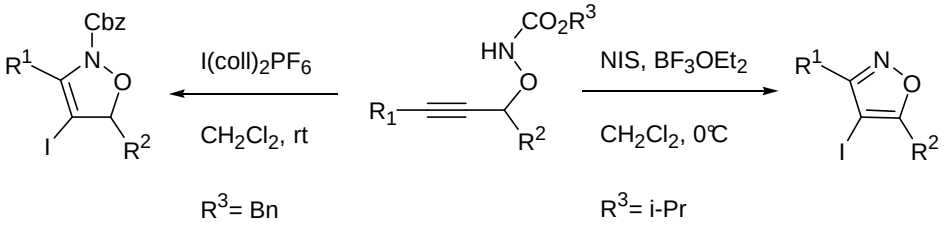
Scheme 2.25: 5-Endo-dig-iodocyclization of o-alkynylphenols.

Michelet and co-workers have reported 5-*endo* diastereoselective process by NIS-promoted iodocarbocyclization reaction of various functionalized 1,5-enynes (Scheme 2.26) The cyclizations are conducted in the presence of 1.2 equiv of N-iodosuccinimide in dichloromethane at room temperature. The reaction conditions are compatible with several functional groups and lead to iodo-functionalized carbocycles.[89]



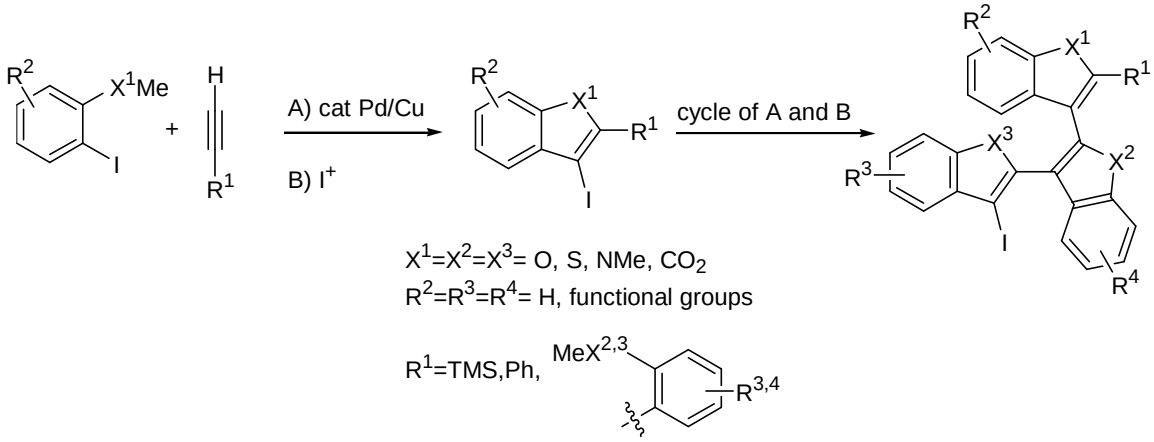
Scheme 2.26: Iodocarbocyclization reaction of 1,5-enynes.

Wada and co-workers have reported the synthesis of 2,5-dihydroisoxazoles and isoxazoles using iodocyclization of N-alkoxycarbonyl O-propargylic hydroxylamines using respectively bis(2,4,6- collidine)iodonium(I) hexafluorophosphate [$I(coll)_2PF_6$] and combination of NIS/ BF_3OEt_2 (Scheme 2.27).[90]



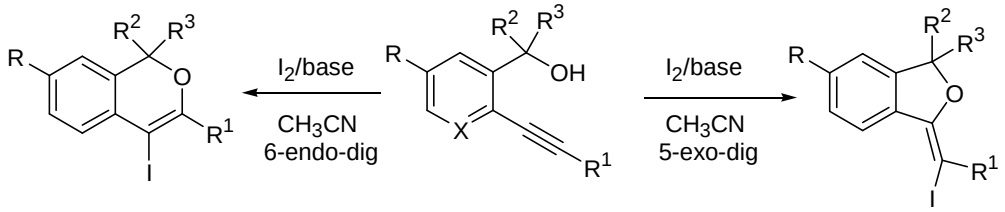
Scheme 2.27: Synthesis of isoxazoles derivatives by iodocyclization.

Larock and co-workers have presented the synthesis of polyheterocyclic compounds obtained by sequential palladium-catalyzed Sonogashira coupling, followed by iodocyclization using I_2 or ICl (Scheme 2.28).[91]



Scheme 2.28: Synthesis of polyheterocyclic compounds.

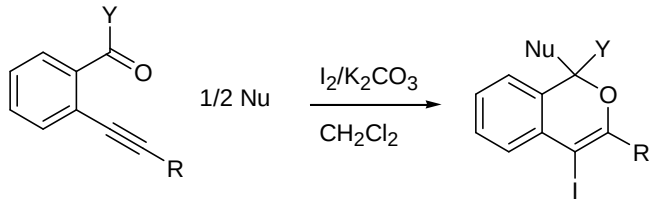
The iodocyclization of 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines could be afford to dihydroisobenzofurans, isochromene or pyranopyridines.[92] The regiochemical outcome of the reaction strongly depends on the substitution pattern of the starting material. In particular, the 5-*exo*-dig cyclization mode, leading to dihydroisobenzofurans, is observed in the case of substrates bearing a tertiary alcoholic group, owing to the gem-dialkyl effect, while the 6-*endo*-dig cyclization mode, leading to isochromene or pyranopyridines, is the usually preferred pathway in the case of substrates bearing a primary or secondary alcoholic group (Scheme 2.29).



X=CH, N R=H, OMe, NO_2 R^1= alkyl, aryl, thienyl R^2=R^3=H, alkyl

Scheme 2.29: Iodocyclization of 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines.

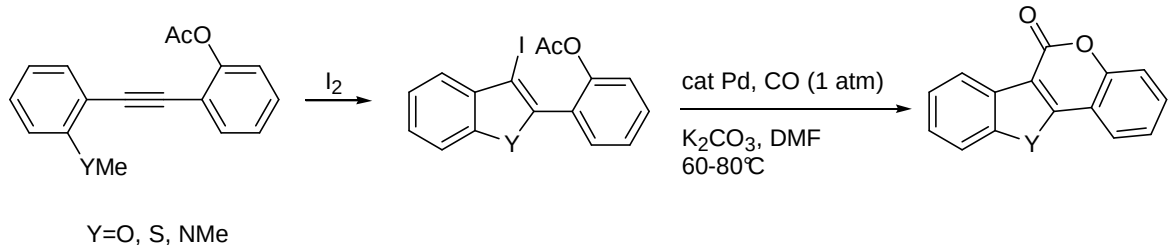
Substituted 1*H*-isochromenes, isobenzofurans, and pyranopyridines can be prepared by allowing *o*-(1-alkynyl)arenecarboxaldehydes and ketones to react with I_2, ICl, NIS, Br_2, NBS, *p*-$O_2NC_6H_4SCl$, or PhSeBr and various alcohols or carbon-based nucleophiles at room temperature.[93]



Y=H, Me
R= alkyl, aryl
Nu= MeOH, EtOH, $PhNH_2$, PhOH, etc.

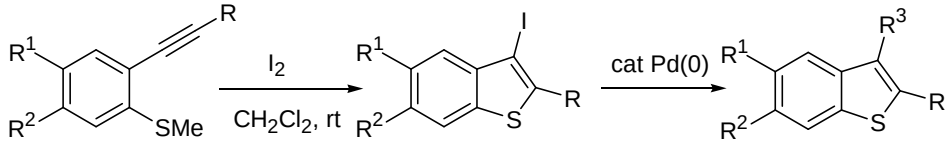
Scheme 2.30: Syntheses of isochromenes by iodocyclization.

The synthesis of coumestan, coumestrol, plicadin, other coumestan analogues was prepared by Sonogashira cross-coupling, iodocyclization, and Pd-catalyzed lactonization using an acetoxy group as the nucleophile (Scheme 2.31).[94]



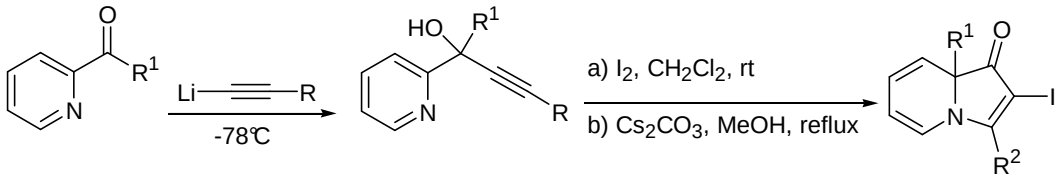
Scheme 2.31: Synthesis of coumestan analogues.

Methyl sulfone-containing 3-iodobenzo[*b*]thiophenes, are readily prepared by iodocyclization and oxidation methodologies from readily available alkynes (Scheme 2.32). From these intermediates by palladium-catalyzed Suzuki-Miyaura, Sonogashira, Heck, carboalkoxylation, and aminocarbonylation reactions were prepared a library of various methyl sulfone-substituted benzo[*b*]thiophenes.[95]



Scheme 2.32: Synthesis of methyl sulfone-substituted benzo[b]thiophenes.

Kim and Kim have proposed that tertiary propargylic alcohol was converted to the corresponding 2-iodoindolizinone via a sequential iodocyclization/1,2-shift (scheme 2.33).[96]



Scheme 2.33: Synthesis of 2-iodoindolizinones.

2.9: Green chemistry.

The Green chemistry or sustainable chemistry consists in the development of alternatives methods of chemical processes designed to reduce or eliminate negative environmental impacts. The use of these chemicals and the relative production may involve reduced waste products, non-toxic components, and improved efficiency and selectivity. Green chemistry is a new point of view, an effective approach to pollution prevention because it applies innovative scientific solutions to real-world environmental situations.

The principle of Green chemistry can be applied in several domains such as organic and inorganic chemistry, analytical and physical chemistry and also biochemistry.

Paul Anastas and John C. Warner developed 12 principles of Green chemistry, which help to explain what the definition means in practice.[97] The principles are present below:

1) **Prevention**
   It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom Economy**
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. **Less Hazardous Chemical Syntheses**
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. **Designing Safer Chemicals**
   Chemical products should be designed to effect their desired function while minimizing their toxicity.

5. **Safer Solvents and Auxiliaries**
   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. **Design for Energy Efficiency**
   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. **Use of Renewable Feedstocks**
   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. **Reduce Derivatives**
   Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. **Catalysis**
   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. **Design for Degradation**
    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. **Real-time analysis for Pollution Prevention**
    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. **Inherently Safer Chemistry for Accident Prevention**
    Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents.

Most of the common organic solvents which have been used for organic synthesis include benzene, chloroform, toluene, carbon tetrachloride etc. Most of these are volatile (VOC) and have undesirable properties like toxicity or being harmful to the environment or may be obtained from non renewable petroleum sources. We consider alternative solvents for organic reaction water,[98] supercritical carbon dioxide,[99] glycerol,[100] ionic liquids[101], polyethylene glycol and its solutions.[102, 103]

2.10: Ionic Liquids.

Ionic Liquids (ILs) are considered as alternatives to volatile organic solvents (VOCs). A lot of paper and reviews are published in the last year that evidence the use of ILs as solvent for organic reactions[101, 104-112].

The ILs could be accelerate some catalytic reaction, increase selectivity, to be effective to stabilize the catalytic species and to be also as catalyst, able to recycle the system catalyst/solvent.

Normally IL consist of nitrogen-containing organic cations and inorganic anions. Common organic cations such as *N*-alkylpyridinium and 1-alkyl-methylimidazolium,[113-116] tetraalkylammonium, tetraalkylphosphonium, *N*-alkylpyridinium, 1,3-dialkylimidazolium and trialkylsulfonium cations are combined with inorganic anions such as Cl^-, NO_3^-, PF_6^-, BF_4^-, bis(trifluoromethanesulfonyl)imide $(CF_3SO_2)_2N^-$ and trifluoromethanesulfonate ($CF_3SO_3^-$) (Figure 2.2).

The choice of cations and anions can lead to a large number of ionic liquids that provide considerable flexibility in the selection of the most suitable pair for a specific chemical application.

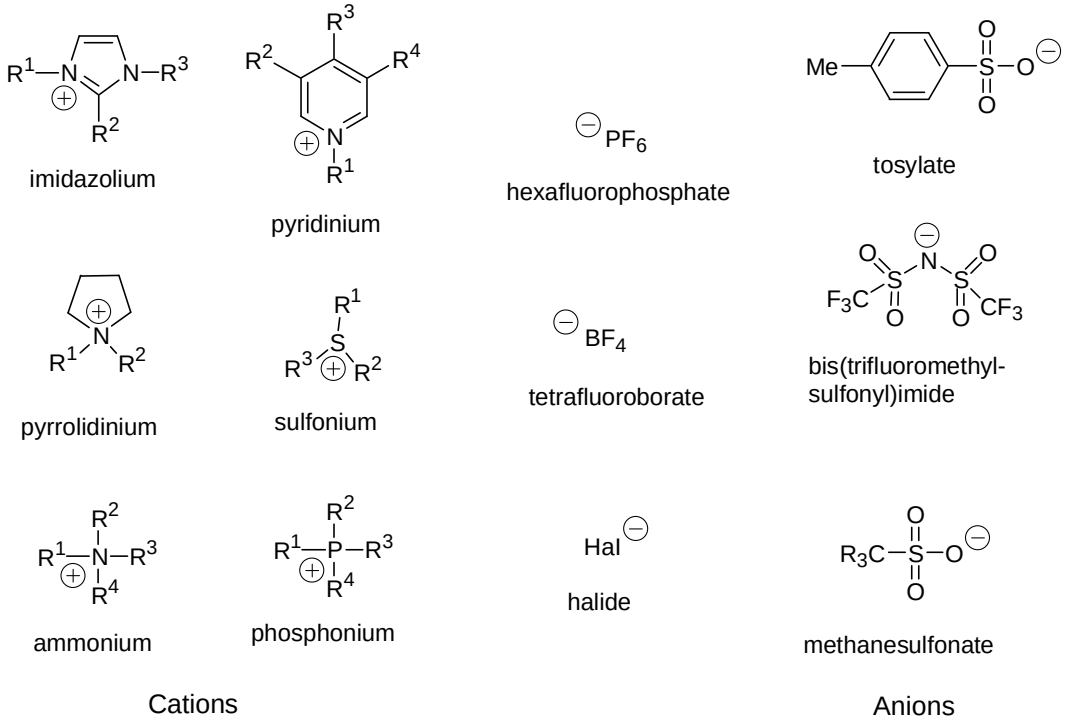


Figure 2.2: Structures of Ionic liquids.

In the past several years, there has been growing interest in ionic liquids for their potential in different chemical processes[117] for example synthetic reactions, separations and extractions,[118] and electrochemical, nanotechnological, biotechnological, and engineering processes.[119]

Ionic liquids (ILs) are ionic compounds that possess a melting temperature below 100°C. Their physical and chemical properties are attractive for various applications. Several organic materials that are now classified as ionic liquids were described as far back as the mid-19th century. The search for new and different ILs has led to the progressive development and application of three generations of ILs: 1) The focus of the first generation was mainly on their unique intrinsic physical and chemical properties, such as density, viscosity, conductivity, solubility, and high thermal and chemical stability. 2) The second generation of ILs offered the potential to tune some of these physical and chemical properties, allowing the formation of "task-specific ionic liquids" which can have application as lubricants, energetic materials (in the case of selective separation and extraction processes), and as more environmentally friendly reaction solvents, among others. 3) The third and most recent

generation of ILs involve active pharmaceutical ingredients, which are being used to produce ILs with biological activity.[120]

The most important physical property of ionic liquids is that their vapour pressure is negligibly small at room temperature. As a result, ionic liquids are odorless. They do not evaporate, even when exposed to vacuum, and most of them do not combust, even when exposed to an open flame. The fact that ionic liquids are non-volatile and non-flammable makes them safer and more environmentally benign solvents than the traditional volatile organic solvents.[109] Other properties of ionic liquids are inherent to salts in the liquid state and include wide liquid temperature range allowing excellent kinetic control in reactions, good thermal stability, high ionic conductivity and wide electrochemical window resulting in high electrochemical stability of ionic liquids against oxidation or reduction reactions.[121]

Furthermore, ionic liquids are good solvents for both organic and inorganic materials,

polar and non-polar, which makes them suitable for catalysis. It is possible to tune the physical and chemical properties of ionic liquids by varying the nature of the anions and cations. Some physico-chemical properties of ionic liquids have beneficial impacts on catalysis, for examples: very low vapour pressure, non-flammable, low melting point, reasonable thermal stability, large working liquid range of temperature, good ionic conductivity. ILs can be combined with electrochemical processes and microwave irradiation.[122]

Ionic liquids have the potential to be polar yet weakly coordinating toward transition metal complexes; they may enhance reaction rates involving cationic electrophilic intermediates.

One of most important characteristic of Il are the recyclability that is one of the reasons why ionic liquids (ILs) are attracting the attention of a growing number of scientists and engineers.[123]

During the last decade, ionic liquids were also found to be suitable solvents for chemical reactions, because they combine excellent thermal and chemical stabilities with good and tunable solubilities and catalytic. Earlier, ionic liquids were developed by electrochemists for use as low temperature water-free electrolytes. Ionic liquids are also good media for bio-catalyzed reactions.[124]

Especially the use of ionic liquids as solvents for transition metal catalysis is at the centre of interest. Transition metal catalysts dissolve well in the ionic liquid, while many organic

reactants and products have a very low solubility in ionic liquids. Examples of transition metal catalyzed reactions in ionic liquids are hydrogenations, hydroformylations,[125] oxidations,[121] cross-coupling reactions,[126] polymerization reactions,[127] Diels-alder reactions,[128, 129] asymmetric synthesis, [130-133] heterocyclic chemistry,[134, 135]

2.11: Poly(ethylene glycol)s.

Poly(ethylene glycol) (PEG), otherwise known as poly(oxyethylene) or poly(ethylene oxide) (PEO), is a synthetic polyether that is readily available in a range of molecular weights. Materials with M_w <100,000 are usually called PEGs, while higher molecular weight polymers are classified as PEOs. These polymers are amphiphilic and soluble in water as well as in many organic solvents (e.g., methylene chloride, ethanol, toluene, acetone, and chloroform). Low molecular weight (M_w <1,000) PEGs are viscous and colorless liquids, while higher molecular weight PEGs are waxy, white solids with melting points proportional to their molecular weights to an upper limit of about 45-50 °C.[136]

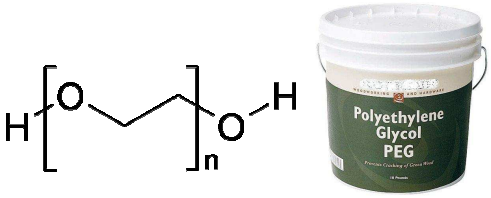


Figure 2.3: Poly(ethylene) glycols.

PEG has been found to be nontoxic and is approved by the FDA for use as excipients or as a carrier in different pharmaceutical formulations, foods, and cosmetics.[137] Polyethylene glycols (PEGs) are neutral, water soluble polymers possessing an impressive array of biomedical and biotechnical applications.[138] Most PEGs with M_w >1,000 are rapidly removed from the body unaltered with clearance rates inversely proportional to polymer molecular weight.[139] This property, combined with the availability of PEGs with a wide range of end-functions, contributes to the wide use of PEGs in biomedical research: drug delivery, tissue engineering scaffolds, surface fucntionalization, and many other applications.

This section lists PEG and PEO polymers classified by end-group functions. The methyl-terminated PEGs are classified as Homobifunctional PEGs.

The abbreviation (PEG) is termed in combination with a numeric suffix which indicates the average molecular weights. One common feature of PEG appears to be the water-soluble. It is soluble also in many organic solvents including aromatic hydrocarbons (not aliphatics).

PEGs are used to make emulsifying agents and detergents, and as plasticizers, humectants, and water-soluble textile lubricants, antidusting agent in agricultural formulations, cleaners, detergents and soaps, mold release agent and lubricant in fabricating elastomers, plasticizer to increase lubricity and to impart a humectant property in ceramic mass, adhesives and binders. softener and antistatic agent for textiles.

Poly(ethylene glycol) is used in a variety of pharmaceuticals and in medications as a solvent, dispensing agent, ointment and suppository bases, vehicle, and tablet excipient and biodegradable hydrogels[140] and consequently in drug delivery.[141, 142]

PEGs form complexes with metal cations. This properties is demonstrate by application of PEGs as “phase transfert agents”. In this application the polymer transfer a salt from solid phase or aqueous phase to organic phase by complexing or coordinating with the metal cation and assisting its partition into the organic phase. The corresponding anion maintains the neutral charge and the anion becames much more reactive because it is poorly solvated or “naked”.

Poly(ethylene)glycols are well known to have similar structures to crown ethers in which oxygens lie at the point of the crown. PEGs show selectivity in metal binding, apparently because the PEGs adopt helical conformation with cavities of preferred sized.[103]

PEG and its aqueous solution are considered as alternative solvent system.[102]

Different transformation are carried out using Peg as the solvent such as the synthesis of α-diazo-β-hydroxy esters,[143] synthesis of β-amino carbonyl compounds via Mannich reaction,[144] polyoxometalate catalyzed aerobic oxidation,[145] Pd/C-catalyzed cyanation of aryl halides, [146] synthesis of quinoxalines,[147] chemoselective deprotection of 1,1-diacetates,[148] Suzuki cross-coupling reaction,[149-151] synthesis of aryl thiocyanates,[152] synthesis of *N*-(quinoline-3-ylmethylene)benzohydrazide derivatives,[153] access to benzo[4,5]imidazo[1,2-*a*]pyrimidines,[154] microwave-mediated transformations of 2-butene-

1,4-diones and 2-butyne-1,4-diones to furan derivatives,[155] copper-catalyzed C–S coupling of thiols with aryl iodides,[156] microwave-assisted Friedländer synthesis of polysubstituted quinolines,[157] microwave-assisted extraction of flavone and coumarin compounds from medicinal plants, [158] Sonogashira-type couplings,[159] hydrogenation of various functional groups[160] and benzene,[161] cycloadditions,[162, 163] $Pd(OAc)_2$/DABCO-catalyzed cross-coupling,[164] Michael additions, [165] Baylis–Hillman reaction, [166] synthesis of dibenz[*b*,*f*]-1,4-oxazepine.[167]

One of important property of PEG is the recyclability of the catalytic system. Different work reported this special use of this cheap solvent for example a recyclable catalyst constituted by PEG-embedded KBr_3 for multicomponent coupling reaction.[168] Lamaty and co-workers have widely demonstrated this characteristic of this special polymer. [169-173]

2.12: Microwave-assisted chemistry.

A significant number of publications on microwave-assisted[174, 175] organic transformations during the past 25 years describe this non-classical heating technology as being “green”, assuming that microwave dielectric heating is more energy efficient than classical conductive heat transfer methods. Conventional methods of organic synthesis are orders of magnitude too slow to satisfy the demand for generation of such compounds.

Microwaves are a portion of the electromagnetic spectrum with frequencies in the range of 300 MHz to 300 GHz. The corresponding wavelengths of these frequencies are 1 m to 1 mm. The most commonly used frequency is 2.45 GHz. The degree of interaction of microwaves with a dielectric medium is related to the material’s dielectric constant and dielectric loss. It was found that microwave irradiation plays a critical role in the formation of the products, temperature also found to be important in the reaction.

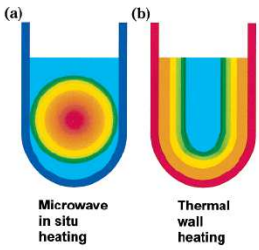


Figure 2.4: Microwave heating.

Figure 2.4 show that the heat is transferred directly into the reaction using mixture microwave in-situ heating. With classic heating, the heat energy must be transferred via the vessel wall.

Microwave chemistry is based on two main principles, the dipolar mechanism and the electrical conductor mechanism. The dipolar mechanism occurs when, under a very high frequency electric field, a polar molecule attempts to follow the field in the same alignment. When this happens, the molecules release enough heat to drive the reaction forward. In the second mechanism, the irradiated sample is an electrical conductor and the charge carriers, ions and electrons, move through the material under the influence of the electric field and lead to polarization within the sample. These induced currents and any electrical resistance will heat the sample.[176]

The main advantages of microwave-assisted reactions over conventional methods in synthesis are: (a) the kinetics of the reaction are increased by one to two orders of magnitude, (b) novel phases are formed, (c) the initial heating is rapid, which can lead to energy savings, (d) selective formation of one phase over another often occurs, e) the successful combination of metal catalysis under air and with water as solvent, f) the use of milder and less toxic reagents at high temperature, g) the possibilities to integrate efficient synthesis with nonchromatographic purifications. One possible hypothesis for these microwave-induced effects is the generation of localized high temperatures at the reaction sites to enhance reaction rates in an analogous manner to that of ultrasonic waves, where both high temperatures and pressures have been reported during reactions.

Microwave (MW)-assisted chemistry techniques is dramatically reducing chemical waste and reaction times in several organic syntheses and chemical transformations.

Some reviews[177-181] have reported the use of microwave heating in organic reactions. Some paper have described the formation of heterocycles by microwave-assisted synthesis[182] and carbonyl chemistry.[183]

Chapter 3

Copper-catalyzed heterocyclization of 1-(2-aminoaryl)-3-yn-1-ols in ionic liquids: a recyclable catalytic system for the synthesis of substituted quinolines.

3.1: Introduction.

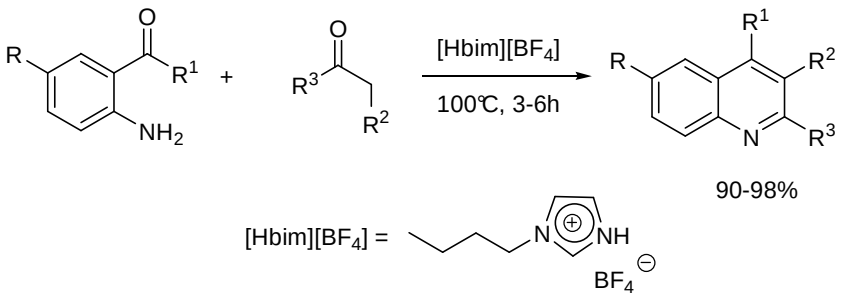
In the contest of the synthesis of heterocyclic compounds we turned our attention to quinoline structures. The pharmaceutical interest for these derivatives requires the development of new sustainable synthetic strategies. For this reason, we are testing the possibility to synthesize substituted quinolines by copper-catalyzed cycloisomerization in alternative solvent using ionic liquids.

Ionic liquids (ILs) are now a well-established class of non-conventional reaction media,[101, 105, 110] which present several useful characteristics: they are stable, non-flammable, non-volatile, recyclable, and in several cases may even promote organic reactions. Another attractive fact of these solvents is related to the possibility to easily separate the products from the reaction mixture (by simple extraction procedures) and, in catalytic reactions, to recycle the solvent - catalytic system several times.[184]

3.2: Bibliographic section.

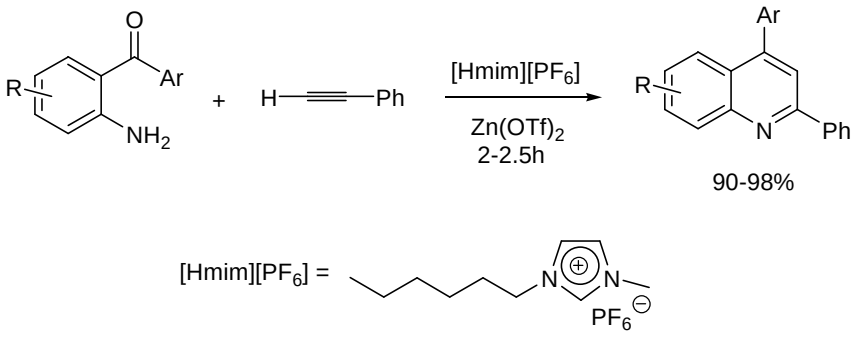
Recently the synthesis of quinolines was widely described in different reviews. [185, 186] Several papers report the synthesis of quinolines in IL and we are presenting some examples.

Palimkar et al. have synthesized biologically active quinolines and fused polycyclic quinolines using [Hbim][BF_4] ionic liquid as the reaction medium (Scheme 3.1). This reaction does not require any additional acid or base catalyst, since the ionic liquid itself acts as a promoter for this reaction.[187]



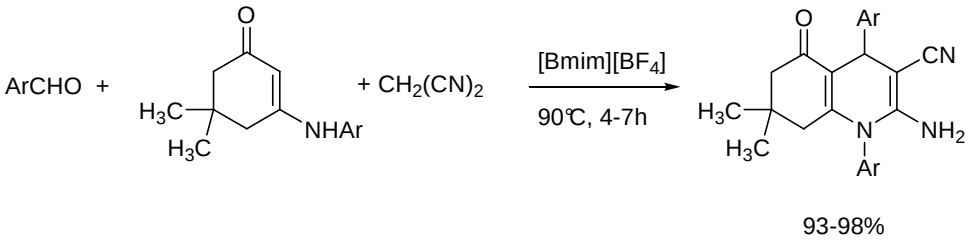
Scheme 3.1: Synthesis of quinolines using using [Hbim][BF_4] as solvent and catalyst.

Sarma and Prajapati have developed an improved method for the synthesis of 2,4-disubstituted quinolines via Meyer–Schuster rearrangement of 2-aminoaryl ketones and phenylacetylenes in the presence of zinc trifluoromethanesulfonate in 1-hexyl-3-methylimidazoliun hexafluorophosphate [Hmim][PF_6] (Scheme 3.2).[188]



Scheme 3.2: Synthesis of 2,4-disubstituted quinolines via Meyer–Schuster rearrangement in IL.

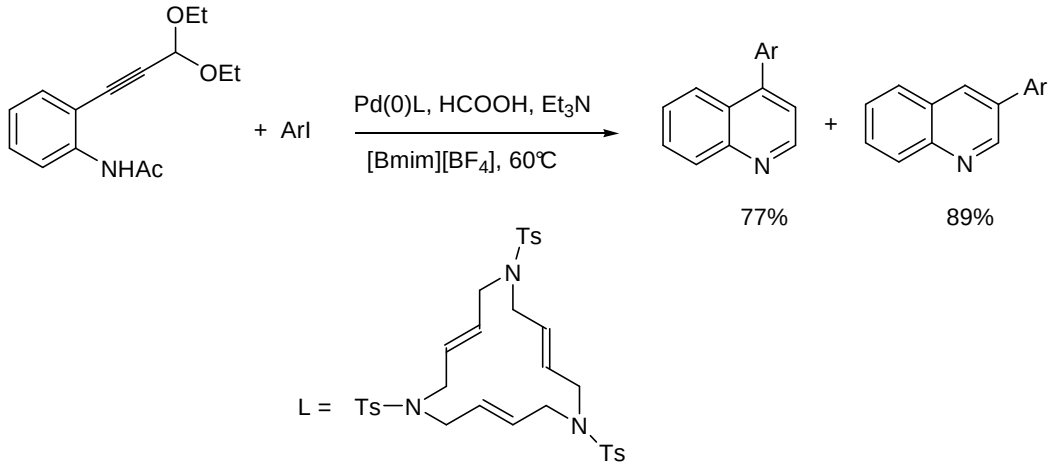
Wang and co-workers have found a method for the syntheses of *N*-arylquinoline-3-carbonitrile derivatives, *N*-arylindeno [1,2-*b*]quinolin-9,11(6*H*,10*H*)-dione derivatives, and *N*-tolylquinoline-2,5(1*H*,6*H*)-dione derivatives by the three component reactions of arylaldehyde, 3-arylamino-5,5-dimethylcyclohex-2-enone, and active methylene compounds (Scheme 3.3). Meanwhile, [Bmim][BF_4] could be reused for several rounds without significant loss of activity.[189]



Scheme 3.3: Synthesis of N-arylquinoline-3-carbonitrile derivatives in IL.

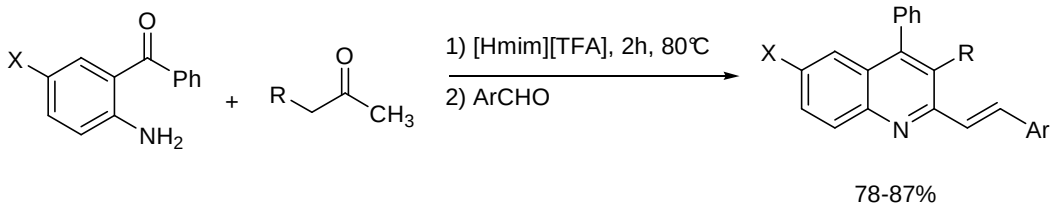
Cacchi and co-workers have present the hydroarylation of alkynes can be successfully conducted in 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim][BF_4]) in the presence of the [(*E*,*E*,*E*)-1,6,11-tris(*p*-toluenesulfonyl)-1,6,11-triazacyclopentadeca-3,8,13-

triene]Pd(0) complex (Scheme 3.4). The catalytic ionic solution can be recycled for reuse in subsequent reaction runs. The procedure has been applied to the preparation of 3-arylquinolines through a domino hydroarylation/cyclization process.[190]



Scheme 3.4: Synthesis of quinolines by hydroarylation of alkynes in ionic liquids.

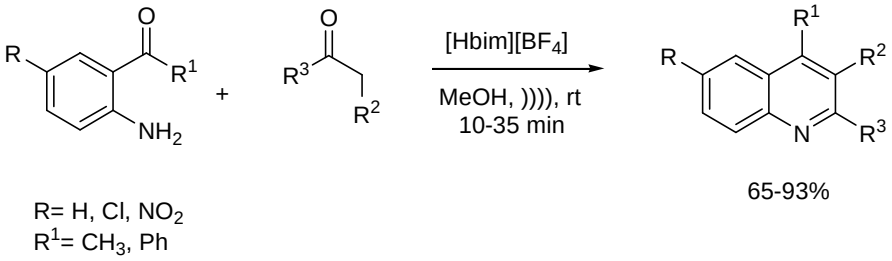
Dabiri and co-workers have presented a one-pot procedure for the synthesis of 2-styrylquinolines that utilize a Friedländer reaction promoted by 1-methyl imidazolium trifluoroacetate [Hmim][TFA], followed by a clean and rapid [Hmim][TFA]-mediated Knoevenagel condensation to afford the corresponding styrylquinoline (Scheme 3.5).[191]



Scheme 3.5: Synthesis of styrylquinolines in IL.

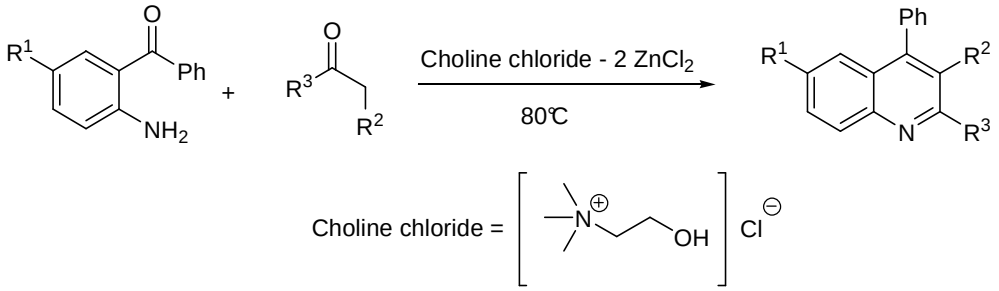
Resa and co-workers have reported the synthesis of quinolines derivatives by a condensation reaction involving an *o*-aminoaryl ketones with α-methylene ketones via the tandem addition/annulation reaction. The strategy used the ionic liquid of 1-butylimidazolium tetrafluoroborate [Hbim][BF_4] as a solvent with methanol as co-solvent at room temperature

under ultrasound irradiation (Scheme 3.6).[192] The use of ionic liquid and ultrasound was effective at room temperature, without the requirement of any added catalyst.



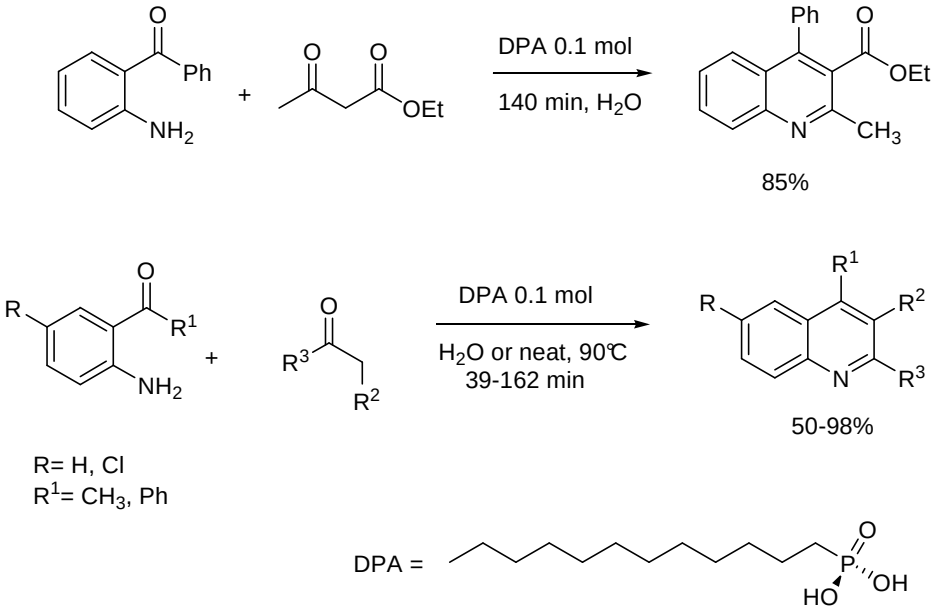
Scheme 3.6: Reaction o-aminoaryl ketones with a-methylene ketones in [Hbim][BF_4].

Wang and co-workers have reported that Lewis acidic ionic liquid choline chloride 2 $ZnCl_2$ was an excellent solvent and efficient catalyst for the synthesis of quinolines via Friedländer annulation under mild conditions (Scheme 3.7).[193]



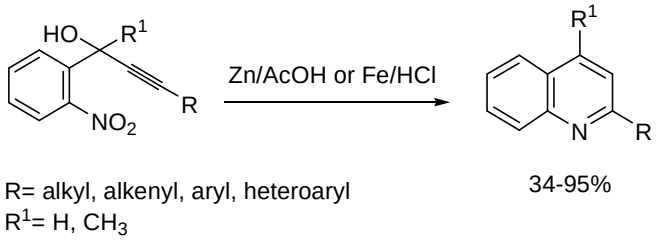
Scheme 3.7: Friedländer synthesis of quinolines using the Lewis acidic IL.

Sardarian and Ghassamipour have reported the synthesis of quinolines and polycyclic quinolines via Friedländer condensation of 2-aminoarylketones with α-methylene ketones using dodecylphosphonic acid (DPA) as a recyclable catalyst in pure water and in solvent-free procedures (Scheme 3.8). The easy preparation of DPA (which is also commercially available), along with the simple experimental procedure, and the ease of recovery and reuse of this novel catalyst, makes these methods simple and convenient for the synthesis of quinolines and their derivatives.[194]



Scheme 3.8: Synthesis of poly-substituted quinolines by DPA catalysis.

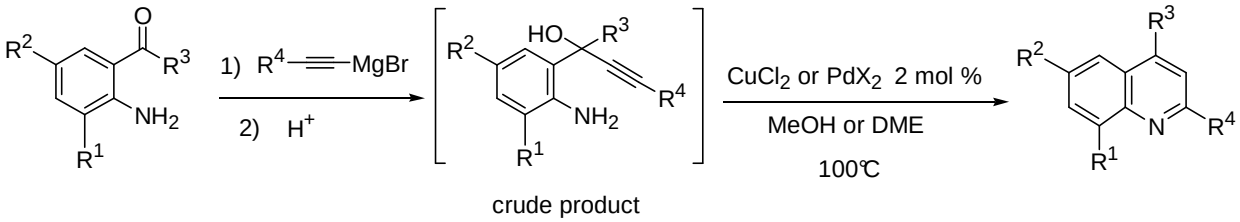
DeShong and co-workers have presented the reduction of secondary and tertiary *o*-nitrophenyl propargyl alcohols followed by acid-catalyzed Meyer-Schuster rearrangement to give 2-substituted and 2,4-disubstituted quinolines respectively (Scheme 3.9). Tertiary propargyl alcohols gave excellent yields of the quinoline derivatives, but they were slightly reduced when secondary propargyl alcohol derivatives were utilized.[195]



Scheme 3.9: Synthesis of 2-alkyl and 2-aryl quinolines by reductive cyclization.

Recently, Gabriele et co-workers have reported that 1-(2-aminoaryl)-2-yn-1-ols, easily obtained by the Grignard reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones, can undergo to a selective Cu- or Pd-catalyzed 6-endo-dig dehydrative heterocyclization to give substituted quinolines in good yields.[196] The cyclizations were

carried out in MeOH or 1,2-dimethoxyethane (DME) as the reaction solvent at 100°C in the presence of $CuCl_2$ (2 mol %) or PdX_2 (2 mol %) together with an excess of KX (X= Cl, I) as the catalyst (Scheme 3.10).

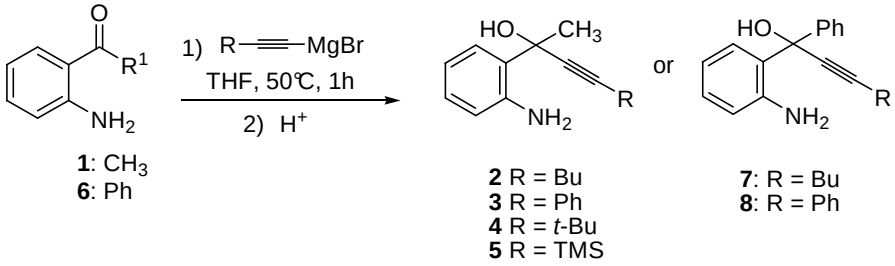


Scheme 3.10: Synthesis of substituted quinolines by copper or palladium-catalyzed cycloisomerization.

3.3: Results and discussion.

However, the reactivity of the system using ionic liquids, as alternative solvents, was also tested in the cycloisomerization reaction of 1-(2-aminoaryl)-2-yn-1-ols catalyzed by copper. Copper is an especially attractive transition metal to use in reaction processes due to its low cost and relatively low toxicity.

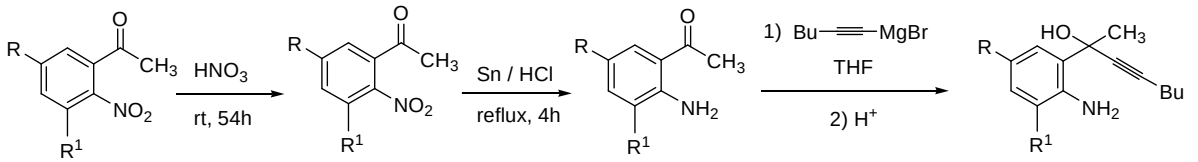
The substrates **2-5** were obtained by reaction of commercially available 2'-aminoacetophenone and alkynylmagnesium bromide in dry THF at 50° for 1h under N_2 (Scheme 3.11).



*Scheme 3.11: Addition of alkynylmagnesium bromide to 2'-aminoacetophenone **1** or 2'-aminobenzophenone **6**.*

Similar substrates, such as **7** and **8** were synthesized in the same fashion using the commercially available 2'-aminobenzophenone and alkynylmagnesium bromide (Scheme 3.11).

The commercially available compounds **9** and **10** were nitrated using HNO_3, reduced to give the corresponding keto-amino compounds **13** and **14** followed by addition of alkynylmagnesium bromide (Scheme 3.12).



9 R = H, $R^1 = OCH_3$
10 R = Cl, R^1 = H

11 R = H, $R^1 = OCH_3$
12 R = Cl, R^1 = H

13 R = H, $R^1 = OCH_3$
14 R = Cl, R^1 = H

15 R = H, $R^1 = OCH_3$
16 R = Cl, R^1 = H

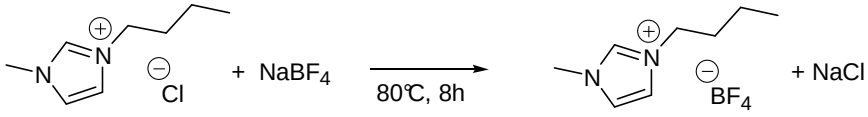
Scheme 3.12: Reduction followed by addition of alkynylmagnesium bromide to substituted 2'-nitroacetophenone.

All the products were unstable and they were used without purification in the following step of cycloisomerization.

3.4: Cyclohydratation reaction of 2-(2-aminophenyl) oct-3-yn-2-ol 2 in ILs.

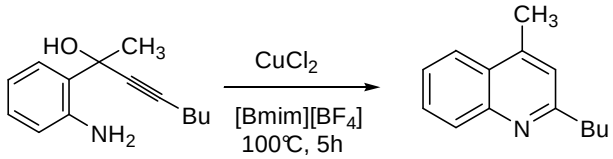
The first part of this work focuses on the possibility to perform the cycloisomerization reaction of 2-(2-aminophenyl) oct-3-yn-2-ol **2**, optimizing the reaction conditions, choosing the appropriate IL and verifying the possibility to recycle the catalytic system.

The first experiment was carried out using 2-(2-aminophenyl) oct-3-yn-2-ol **2** as the substrate and [Bmim][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate) as the solvent. [Bmim][BF_4] was synthesized by anion exchange starting from [Bmim][Cl] (Scheme 3.13), the solvent presents special properties for organic reactions and the literature describes interesting reactions carried out in it.[113]



Scheme 3.13: Synthesis of [Bmim][BF_4].

The cycloisomerization reaction of **2** was carried out in the presence of 2 mol % of $CuCl_2$[197] at 100°C for 15h. At the end of reaction it was possible to identify the formation of expected product 2-butyl-4-methylquinoline **17** but the conversion of substrate **2** was not complete (Scheme 3.14). The result of this preliminary reaction suggests the possibility to obtain the corresponding product using IL as solvent and a copper salt as a catalyst.



2 **17**

*Scheme 3.14: Copper-catalyzed cycloisomerization of 2-(2-aminophenyl) oct-3-yn-2-ol **2** in [Bmim][BF_4].*

To increase the conversion of starting materials we extended the reaction time: after 15h substrate **2** was completely converted in quinoline **17**, which was easily recovered by a simple extraction using diethyl ether. The solvent for the extraction was chosen in order to completely dissolve the reaction product, but unable to mix with the IL. Then, after the extraction, the IL contains the catalyst and it could be also recycled. However the extraction was a little bit cumbersome, and only after 4 times washing, the compound **17** was completely extracted from the IL phase, as demonstrated by GC analysis.

However, even if the solubility of IL in Et_2O is very low, traces of IL were contaminating the crude product **17** that was recovered in a satisfying yield (71%) after a chromatographic purification.

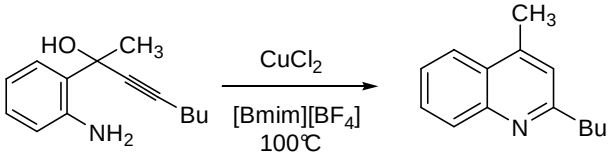
3.5: Recycle of [Bmim][BF_4]/catalyst.

We could also demonstrate that the IL/catalyst mixture recovered from this first run could be further used.

All residual traces of diethyl ether were removed under vacuum, the [Bmim][BF_4] was charged with new substrate and the reaction mixture was heated up in the same conditions as before. After 15h, the expected quinoline **17** is the only product present in the reaction mixture. Extraction and purification afforded compound **17** in a comparable yield as the first run (74%). The active catalytic species is still present in the IL phase and the cycloisomerization reaction can be performed for several further runs.

The reactivity of this system, [Bmim][BF_4]/$CuCl_2$, was tested in 6 runs, and in all cases only the expected product **17** was formed in good yield (69 % - 74 %) (Table 1, entry 1).

*Table 3.1: Synthesis of 2-butyl, 4-methyl quinoline **17** using [Bmim][BF_4]/$CuCl_2$ system.*



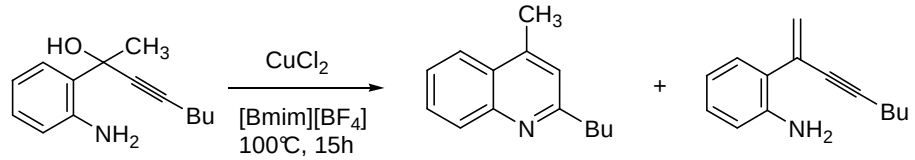
2 **17**

Entry	Time (h)	°C	Mol (%) $CuCl_2$	Yield (%)[a]						
				Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7
1	15	100	2	71	74	70	69	70	71	70
2	24	100	1	76	70	71	69	68	72	68

a) isolated yields.

In order to optimize the experiment the quantity of catalyst was reduced from 2 mol % to 1 mol %. The reaction mixture, composed by [Bmim][BF_4]/$CuCl_2$ and the substrate was heated up for 15h at 100°C. In this case too, it was possible to observe the quantitative conversion of the substrate **2** and the formation of expected product **17** in 66% of yield and a by-product **18** in 7% yield (Table 3.2). ^{1}H NMR and GC-MS allowed to identify the by-product as the enynic derivative **18** obtained after dehydration of the alcoholic function of the substrate. This trend was also verified in the following four recycling experiments (Table 3.2, run 2-5).

*Table 3.2: Synthesis of 2-butyl, 4-methyl quinoline **17** using [Bmim][BF_4]/$CuCl_2$ system.*



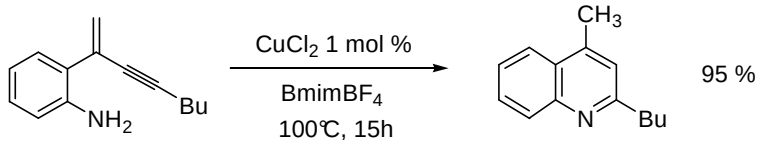
2 **17** **18**

Time (h)	°C	Mol (%) $CuCl_2$	Product	Yield (%)[a]				
				Run 1	Run 2	Run 3	Run 4	Run 5
15	100	1	**17**	66	65	63	64	66
15	100	1	**18**	7	5	5	5	4

a) isolated yields.

We decided to keep low the catalytic loading extending the reaction time to 24 h. In the first experiment it was observed the formation of quinoline **17** as the only product with an increased yield (76 %) with respect to the same reaction using 2 mol % of $CuCl_2$ (Table 3.1, entry 1-2). Recycling was also possible in this case for six runs and the yields were constant (68 – 72 %, Table 3.1, entry 2). In conclusion it possible to affirm that expected product was formed in good yields, no loss of activity was observed for the catalytic system constituted by [Bmim][BF_4]/$CuCl_2$ combination. The best conditions for the reaction were 24 h at 100°C with 1 mol% of catalyst.

However, the formation of compound **18** is not so unpleasant, if we consider it in the role of a possible intermediate during the formation of quinoline **17**. To test our hypothesis, the pure intermediate **18**, isolated by column chromatography, reacted in the optimized cycloisomerization conditions affording the target compound **17** in high isolated yield (95 %) as it was confirmed by NMR and GC analysis (Scheme 3.15).



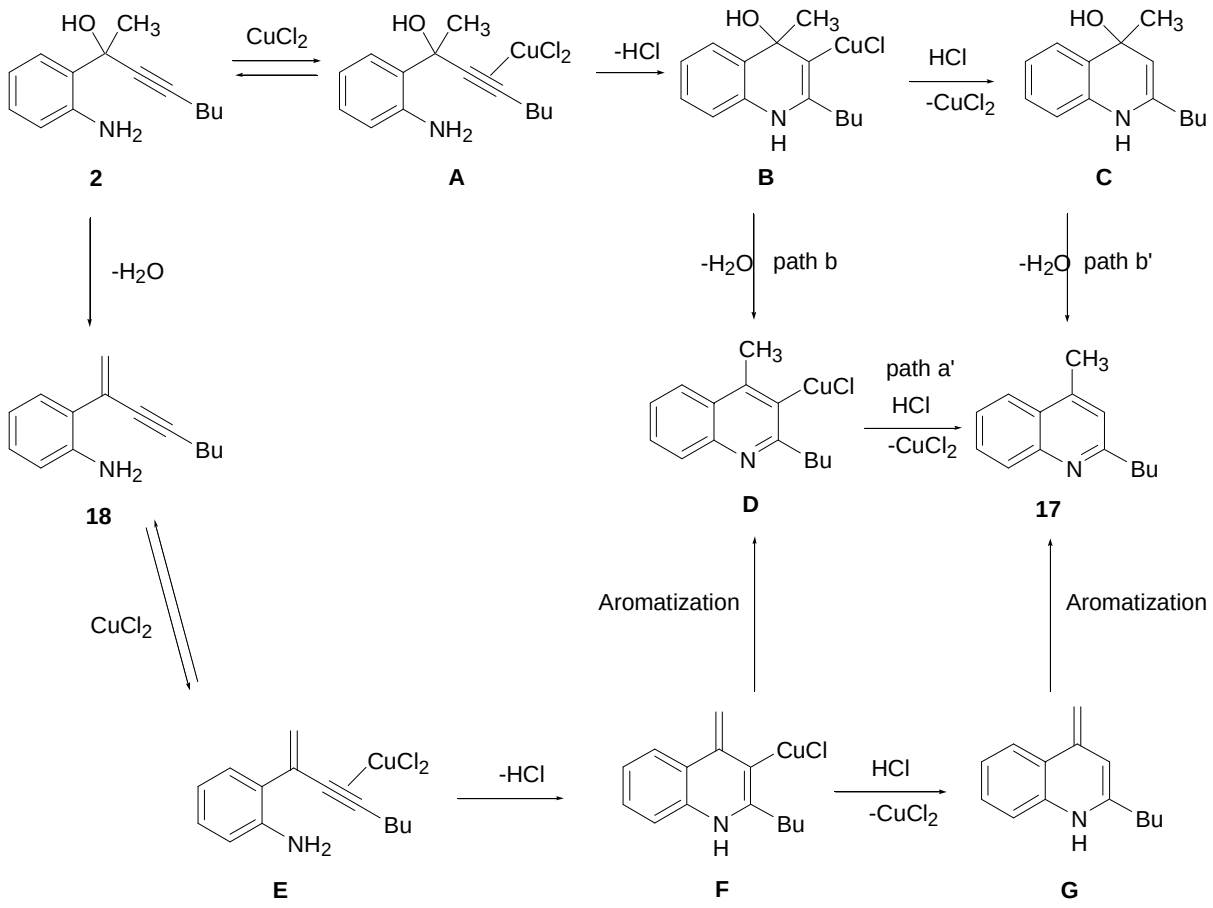
18 **17**

*Scheme 3.15: Copper-catalyzed cycloisomerization of enynic derivative **18** in [Bmim][BF_4].*

3.6: Hypothetical mechanism of copper-catalyzed cycloisomerization reaction.

The plausible reaction mechanism for the formation of quinolines derivatives starting from acyclic susbtrates can involve the coordination of copper (II) species on the triple bond (A), followed by a *6-endo-dig* nucleophilic attack of the amino group on the activated triple bond (Scheme 3.16). The intermediate B can undergo two different pathways: protonolysis, (path a), or to loose one water molecule (path b) leading to C and D respectively. The final compound **17** is then obtained through pathway a' or b'.

However, if the substrate looses water before the copper coordination step on the triple bond occurs, product **18** is formed.



*Scheme 3.16: Plausible reaction mechanism for the conversion of 2-(2-aminophenyl)oct-3-yn-2-ol **2** and 2-(1-methylenehept-2-ynyl)aniline **18** into 2-butyl-4-methylquinoline **17**.*

3.7: Cycloisomerization reaction of substrate 2 in different ILs.

In order to explore the reactivity of the catalytic system as a function of the solvent, we run the reactions in different ILs, studying the influence of different anions in imidazolium solvents (Figure 3.1).

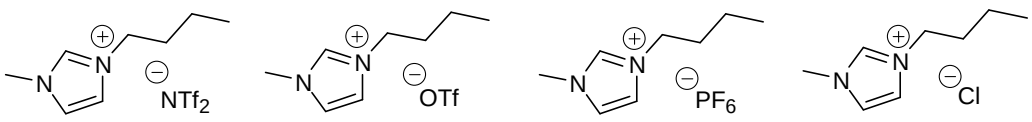
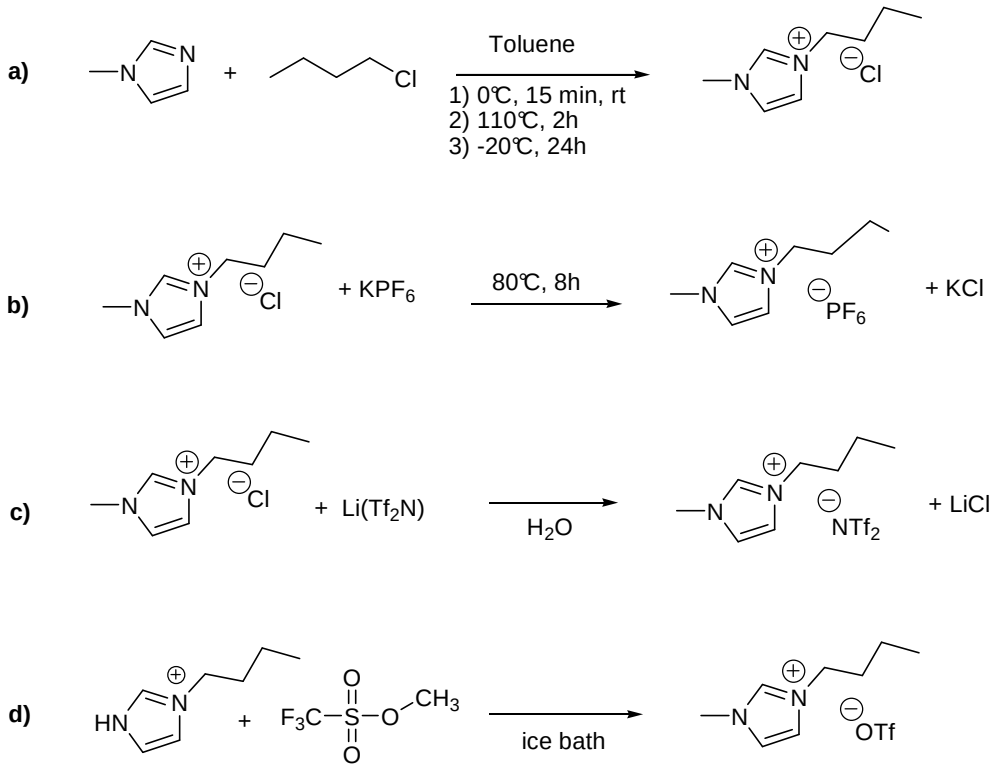


Figure 3.1: Some ILs.

1-Chlorobutane was added to a mixture of 1-methylimidazole in toluene to afford the corresponding [Bmim][Cl] (Scheme 3.17, a).

[Bmim][PF_6] was synthesized by anion exchange starting from [Bmim][Cl] (Scheme 3.17, b).

[Bmim][NTf_2] was prepared starting from [Bmim][Cl] followed by addition of 1.1 molar ratio of Li(Tf_2N) (Scheme 3.17, c).[113]



Scheme 3.17: Synthesis of ILs.

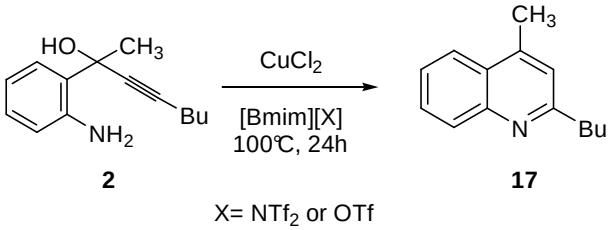
1-Butylimidazole was reacted directly with methyl trifluoromethanesulfonate in an ice bath, forming [Bmim][OTf] (Scheme 3.17, d).[116]

The next IL used was 1-butyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl) imide or [Bmim][NTf_2]. The mixture of substrate **2**, IL and catalyst was heated at 100°C. After 24h of reaction the product **17** was recovered in 65% of yield. The results obtained with [Bmim][BF_4] are better in comparison with the results obtained using [Bmin][NTf_2] (Table 3.3 entry 1). The product was obtained with a yield ranging from 49% to 65%. This suggests that the nature of anions is important for the progress of the reaction, maybe for the interaction with metal.

With methanesulfonate [OTf] as anion, the catalytic system was inferior reactive and the quinoline **17** was obtained in moderate yields (40-58%) (Table 3.3, entry 2).

In any case, with [Bmim][NTf_2] and [Bmim][OTf] as solvent it was possible to recycle the catalytic system several times obtaining the formation of expected product **17**.

Table 3.3: Copper-catalyzed cycloisomerization reaction in [Bmim][NTf_2] and [Bmim][OTf].



2 **17**

X= NTf_2 or OTf

Entry	IL	Yield **17** (%)[a]						
		Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7
1	[Bmim][NTf_2]	65	62	61	61	55	50	49
2	[Bmim][OTf]	51	48	54	53	58	56	55

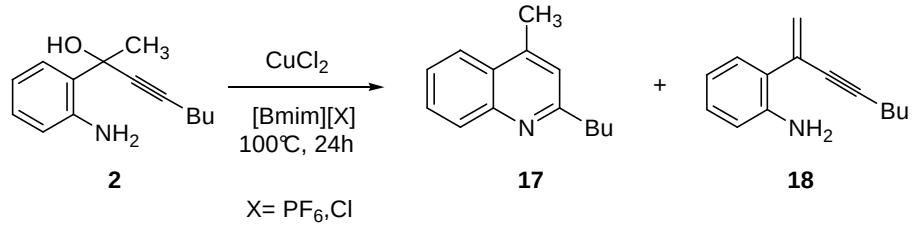
a) isolated yields. All reactions were carried out at 100°C, for 24h, using 1 mol % of $CuCl_2$

Then, we explored the effect of the ionic liquids having chlorine or hexafluorophosphate as counter-ions. However, with organic counter-ions, the cycloisomerization reaction was less efficient after the second run.

In [Bmim][PF_6] quinoline **17** was obtained in good yield in the first two runs (respectively 82% and 76%), while starting from the third run, the formation of enynic derivative **18** was observed (Table 3.4, entry 1, run 3).

With [Bmim][Cl] quinoline **17** was obtained in lower yield since the first run, and in all cases, together with the enynic compound **18**. These results may be explained by high density and viscosity of [Bmim][Cl] (Table 3.4, entry 2).

Table 3.4 Copper-catalyzed cycloisomerization reaction in [Bmim][PF_6] and [Bmim][Cl].



2 **17** **18**

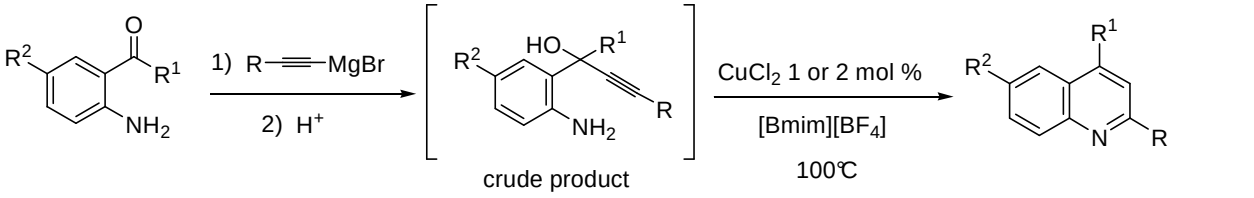
Entry	IL	Product	Yield (%)[a]						
			Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7
1	[Bmim][PF_6]	**17**	82	76	67	59	60	56	48
		18	0	0	6	10	11	11	18
2	[Bmim][Cl]	**17**	48	40	38	42	43		
		18	17	16	15	18	20		

a) isolated yields. All reactions were carried out at 100°C, for 24h, using 1 mol % of $CuCl_2$

In conclusion after the screening of ILs used we can affirm that the best results (yields, selectivity and recycling) were obtained using [Bmim][BF_4].

3.8: Heterocyclization of different 1-(2-aminoaryl)-3-yn-1-ols in [Bmim][BF_4].

The optimized conditions were extended to various substrates bearing alkyl or phenyl substituents on the triple bond, at the benzylic position and on the phenyl ring (Scheme 3.18).



3 R= t-Bu, R^1=CH_3, R^2=H
7 R= Bu, R^1=Ph, R^2=H
8 R= Ph, R^1=Ph, R^2=H
14 R= Bu, R^1=CH_3, R^2=Cl

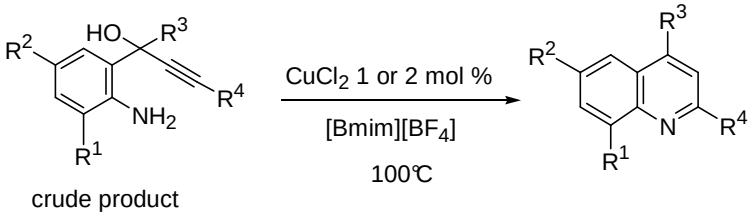
19 R= t-Bu, R^1=CH_3, R^2=H
20 R= Bu, R^1=Ph, R^2=H
21 R= Ph, R^1=Ph, R^2=H
22 R= Bu, R^1=CH_3, R^2=Cl

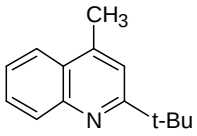
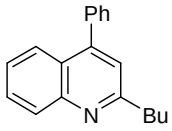
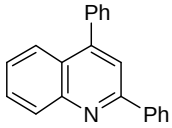
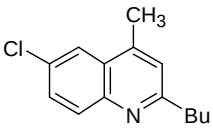
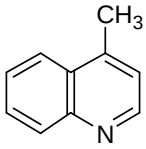
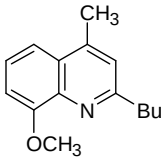
Scheme 3.18: General synthesis of substituted quinolines.

Exclusive formation of quinoline was observed with substrates **3, 7, 8, 16** (Table 3.5).
The products were obtained in good yield, in particular 2-butyl-4-phenyl quinoline **18** (83-75%, Table 3.5, entry 2).
The presence of electron withdrawing group (Cl) in substrate **16** did not influence the reaction (entry 4).

In the case of 2-(2-aminophenyl)-4-trimethylsylanylbut-3-yn-2-ol **5** the TMS group was lost in the course of the process to produce the corresponding mono-substituted quinoline **23** in satisfying yield (58-61%) (entry 5). The presence of an electron donating group (OCH_3) in substrate **15** did not influence the process when it was carried out with 2 mol % of $CuCl_2$ (entry 6).

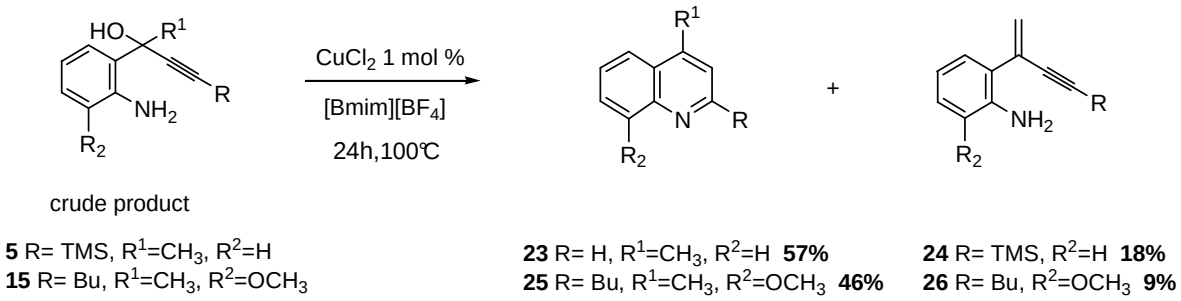
Table 3.5 General copper- catalyzed cycloisomerization reaction.



Entry	Time (h)	Mol % $CuCl_2$	Quinoline	Yield (%)[a]						
				Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7
1	24	1	 **19**	70	68	62	60	63	61	61
2	15	1	 **20**	81	81	75	83	79	76	75
3	24	2	 **21**	60	58	57	55	51	50	52
4	24	1	 **22**	71	69	66	65	66	65	65
5	24	2	 **23**	61	59	60	58	60	61	61
6	24	2	 **25**	73	66	68	66	65	66	66

a) Isolated yields. All reactions were carried out at 100°C in [Bmim][BF_4].

With substrate **5** and **15**, the molar ratio of $CuCl_2$ was important. When 1 mol % of catalyst was used, already in the first run the enynic derivatives **24** or **26** (Scheme 3.19) were formed. The reaction is selective towards the formation of desired products 2 mol % of $CuCl_2$ as catalyst were used in [Bmim][BF_4].



crude product

5 R= TMS, R^1=CH_3, R^2=H
15 R= Bu, R^1=CH_3, R^2=OCH_3

23 R= H, R^1=CH_3, R^2=H **57%**
25 R= Bu, R^1=CH_3, R^2=OCH_3 **46%**

24 R= TMS, R^2=H **18%**
26 R= Bu, R^2=OCH_3 **9%**

*Scheme 3.19: Cycloisomerization reaction of substrates **5** and **15** using 1 mol % of $CuCl_2$.*

3.9: Conclusion.

In conclusion, we have shown that the $CuCl_2$-catalyzed heterocyclodehydration of 1-(2-aminoaryl)-2-yn-1-ols may efficiently take place in [Bmim][BF_4], as the reaction medium. However, the use of the ionic liquid has allowed to recycle the solvent–catalytic system several times, without appreciable loss of activity. This method proved to be very general for the synthesis of a set of quinoline derivatives in a good yield.

The present recyclable catalytic method for synthesis of substituted quinolines thus represents a simple and convenient approach for the production of a very interesting class of heterocyclic compounds.

Experimental section.

3.10: General conditions.

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25°C on a Bruker DPX Avance 300 spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a Jasco FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC–MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analyzed by TLC on silica gel 60 F254 and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh).

3.11: Preparation of ionic liquids.

3.11.1: Preparation of [Bmim][NTf_2] and [Bmim][OTf].

Ionic liquids [Bmim][NTf_2][113] and [Bmim][OTf][116] were prepared according to literature procedures.

3.11.2: Preparation of [Bmim][Cl].

A mixture of 1-methylimidazole (40 mL, 41.2 g, 502 mmol) and toluene (50 mL) maintained at 0°C under nitrogen was stirred for 10 min. 1-Chlorobutane (58 mL, 51.4 g, 555 mmol) was quickly added at 0°C and the resulting mixture was vigorously stirred for 15 min at the same temperature. The solution was allowed to warm up to room temperature and then heated at 110°C for 24 h with stirring. After cooling to room temperature, the mixture was refrigerated (-20°C) and allowed to stand for 24 h. After this time, two phases separated; toluene was

removed by decantation, while the residue was taken up with MeCN. The solvent was removed under vacuum and MeCN (ca. 30 mL) and THF (ca. 30 mL) were added. The resulting mixture was cooled with the aid of an ice-water bath, to give, on standing, [Bmim][Cl] as a whitish solid. The mixture was then cooled at -20°C overnight. After decantation and removal of the solvent, the residue was washed with cold THF and eventually dried in vacuo to give pure [Bmim][Cl] as a whitish solid, which was stored at -20°C under nitrogen.

3.11.3: Preparation of [Bmim][BF_4].

$NaBF_4$ (5.7 g, 51.9 mmol) was added to 9.0 g (51.8 mmol) of [Bmim][Cl] maintained at 80°C under vigorous stirring. The mixture was allowed to stir at 80°C for 8 h and then at room temperature for 15 h. CH_2Cl_2 (ca. 30 mL) was added with stirring, and the solution was cooled to -20°C and allowed to stand at this temperature overnight. The precipitate (NaCl) was removed by filtration, and the solvent was removed under vacuum to give pure [Bmim][BF_4], which was stored under nitrogen at room temperature (9.3 g, 80%).

3.11.4: Preparation of [Bmim][PF_6].

KPF_6 (9.5 g, 51.6 mmol) was added to 9.0 g (51.8 mmol) of [Bmim][Cl] maintained at 80°C under vigorous stirring. The mixture was allowed to stir at 80°C for 8 h and then at room temperature for 15 h. CH_2Cl_2 (ca. 30 mL) was added with stirring, and the solution was cooled to -20°C and allowed to stand at this temperature overnight. The precipitate (KCl) was removed by filtration, and the solvent was removed under vacuum to give pure [Bmim][PF_6], which was stored under nitrogen at room temperature (11.8 g, 81%).

3.12: Preparation of substrates.

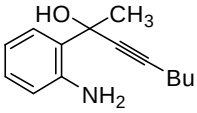
2-Aminoacetophenone **1** and 2-aminobenzophenone **2** were commercially available (Aldrich, Fluka) and were used as received.

To a suspension of Mg turnings (700.0 mg, 28.8 mmol) in anhydrous THF (2.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the

formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.5 mL of EtBr in 15.0 mL of THF; total amount of EtBr added: 2.92 g, 26.8 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of the 1-alkyne (26.8 mmol) in anhydrous THF (7.0 mL) at 0°C with stirring. After additional stirring at 0°C for 15 min, the mixture was allowed to warm up to room temperature, maintained at 50°C for 2 h, and then used as such for the next step. 2-Aminoacetophenone **1** or 2-aminobenzophenone **2** (8.9 mmol) was dissolved under nitrogen in anhydrous THF (7.0 mL) and then added dropwise to the solution of the alkynylmagnesium bromide in THF (prepared as described above) at 50°C under nitrogen. After stirring at 50°C for 1 h (compounds **2**, **15**, **16**) 2 h (compounds **3**, **4**, **5**) or 3 h (compounds **7** and **8**) the mixture was cooled to room temperature.

Saturated NH_4Cl was added with stirring to achieve a weakly acidic pH. After additional stirring at room temperature for 15 min, AcOEt (ca. 20 mL) was added and phases were separated. The aqueous phase was extracted with AcOEt (3x30 mL), and the collected organic layers were washed with brine to neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude products were diluted with Et_2O and transferred into a volumetric flask (50 mL).

2-(2-Aminophenyl)oct-3-yn-2-ol (2)



Yellow oil, 1.16 g, 60% based on **1**.

IR (film): v = 3451 (m), 3365 (s), 2957 (s), 2932 (s), 2871 (m), 2240 (vw), 1614 (s), 1493 (m), 1455 (m), 1368 (w), 1307 (m), 1237 (m), 1159 (w), 1092 (m), 1053 (m), 905 (w), 751 (s) cm^{-1}.

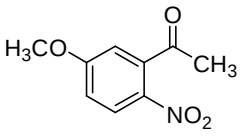
^{1}H NMR (300 MHz): δ (ppm) = 7.48 (dd, *J* = 7.8, 1.5, 1 H), 7.07 (ddd, *J* = 7.8, 7.4, 1.5, 1 H), 6.73 (ddd, *J* = 7.8, 7.4, 1.3, 1 H), 6.63 (dd, *J* = 7.8, 1.3, 1 H), 4.37 (s, br, 2 H), 2.26 (t, *J* = 7.0, 2 H), 1.82 (s, 3 H), 1.58-1.34 (m, 4 H), 0.91 (t, *J* = 7.2, 3 H) (Note: the –OH signal was too broad to be detected).

^{13}C NMR (75 MHz): δ (ppm) = 144.3, 128.7, 126.4, 118.3, 117.8, 85.9, 83.4, 70.3, 30.7, 28.8, 22.0, 18.4, 13.6.

GC-MS: *m/z* = 217 (44) [M+], 202 (15), 199 (18), 184 (19), 171 (12), 170 (53), 158 (20), 157 (97), 156 (66), 155 (22), 154 (21), 144 (25), 143 (13), 130 (38), 129 (28), 128 (30), 120 (100), 118 (10), 117 (11), 115 (12), 92 (23), 77 (12), 65 (19).

Nitration of 3-methoxyacetophenone **9** to give 2-nitro-3-methoxyacetophenone **11**.

To concd. HNO_3 (12 mL) maintained at 0-5°C was quickly added 3-methoxyacetophenone **9** (2.0 g, 13.3 mmol) with stirring. After additional stirring at 0-5 °C for 5 min., the mixture was allowed to warm up to room temperature ant then stirred at room temperature for 54 h. Ice followed by Et_2O (10 mL) was added. Phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The collected organic layers were washed with water and then dried over $MgSO_4$. The solvent was evaporated and the residue was taken up with EtOH. Crystallization at -20°C followed by filtration afforded, after drying, 2-nitro-3 methoxyacetophenone **11** (778.0 mg, 30%).



Colorless solid.

Mp 128-129 °C (lit.[198] 128-129 °C).

IR (KBr): v = 1689 (m), 1580 (w), 1545 (s), 1458 (m), 1379 (m), 1313 (m), 1291 (s), 1048 (m), 977 (m), 864 (m), 789 (m), 614 (w) cm^{-1}.

^{1}H NMR (500 MHz): δ (ppm) = 7.55 (dd, *J* = 8.2, 7.7, 1 H), 7.41 (dd, *J* = 7.7, 1.1, 1 H), 7.29 (dd, *J* = 8.2, 1.1, 1 H), 3.92 (s, 3 H), 2.58 (s, 3 H).

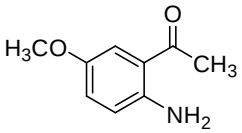
^{13}C NMR (126 MHz): δ (ppm) = 195.7, 151.4, 131.4, 120.9, 117.0, 56.8, 28.0.

GC-MS: *m/z* = 195 (17) [M+], 180 (80), 153 (24), 119 (14), 95 (16), 93 (12), 91 (16), 78 (35), 77 (30), 76 (100), 75 (20), 74 (17), 67 (10), 65 (22).

Reduction of 2-nitro-3-methoxyacetophenone **11** to give 2-amino-3-methoxyacetophenone **13**.

The method of Robbins was employed.[199] A mixture of the 2-nitro-3-methoxyacetophenone **11** (2.22 g, 11.4 mmol), Sn powder (3.81 g, 32.1 mmol), and concd. HCl (8.8 mL) was allowed to reflux for 4 h with stirring. After cooling to 0°C, NaOH (pellets) was added to basic pH. Et_2O (15 mL) was added and phases were separated. The aqueous phase was

extracted with Et_2O (2 × 15 mL) and the collected organic layers were dried over $MgSO_4$. After filtration, the solvent was evaporated to give a brown-yellow solid, which was purified by column chromatography (SiO_2, 7:3 hexane-AcOEt) to give 2-amino-3-methoxyacetophenone **13** (1.41g, 75%).



Pale yellow solid.

Mp: 59-61 °C (lit.[200] 60.5 - 61.5°C).

IR (KBr): v = 3476 (s), 3348 (s), 1636 (s), 1545 (s), 1453 (m), 1440 (w), 1362 (w), 1280 (w), 1243 (m), 1223 (m), 1042 (w), 967 (w), 736 (w) cm^{-1}.

^{1}H NMR (500 MHz): δ (ppm) = 7.31 (dd, *J* = 8.2, 1.1, 1 H), 6.82 (dd, *J* = 7.7, 1.1, 1 H), 6.59 (s, br, 2 H), 6.55 (dd, *J* = 8.2, 7.7, 1 H), 3.84 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (126 MHz): δ (ppm) = 200.7, 147.2, 141.6, 123.3, 117.5, 114.0,112.8, 55.7, 28.1

GC-MS: *m/z* = 165 (88) [M+], 150 (100), 122 (37), 107 (14), 104 (22), 79 (14), 78 (14), 77 (17), 65 (19).

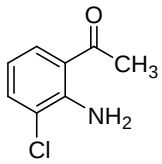
Nitration of 3-chloroacetophenone **10** to give 5-chloro-2-nitroacetophenone **12**.

The method of Robbins was employed.[199] To concd. HNO_3 (8 mL) maintained at 0°C was added in portions with stirring concd. H_2SO_4 (8 × 1.25 mL). After additional stirring at 0°C for 45 min., 3-chloroacetophenone **10** (8.0 g, 52.0 mmol) was added very slowly at 0°C with vigorous stirring. After additional stirring for 2 h at 0 °C, ice was added followed by AcOEt (15 mL). Phases were separated and the aqueous phase was extracted with AcOEt (2 × 15 mL). The collected organic layers were evaporated and Et2O (15 mL) was added to the residue. The orange precipitate was recovered by decantation and then crystallized 2 times from MeOH at ca. -18 °C. The crude 5-chloro-2-nitroacetophenone **12** (3.1 g) thus obtained was then used as such for the next step.

Reduction of 5-chloro-2-nitroacetophenone **12** to give 2-amino-5-chloroacetophenone **14**.

The method of Robbins was employed.[199] A mixture of the 5-chloro-2-nitroacetophenone **12** obtained above, Sn powder (5.36 g, 45.2 mmol), concd. HCl (12.5 mL) was allowed to reflux for 4 h with stirring. After cooling to 0°C, NaOH (pellets) was added to basic pH. Et_2O (20

mL) was added and phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the collected organic layers were dried over $MgSO_4$. After filtration, the solvent was evaporated to give a brown-yellow solid, which was purified by column chromatography (SiO_2, 8:2 hexane-AcOEt) to give 3.97 g, 45% based on 5-chloro-2-nitroacetophenone **12**.



Pale yellow solid.

Mp: 63-64 °C (lit.[201] 65-66 °C).

IR (KBr): v = 3457 (s), 3324 (s), 1654 (s), 1617 (s), 1577 (m), 1544 (m), 1474 (m), 1362 (w), 1231 (m), 1160 (w), 958 (w), 824 (w), 628 (w) cm^{-1}.

^{1}H NMR (500 MHz): δ (ppm) = 7.62 (d, *J* = 2.7, 1 H), 7.16 (dd, *J* = 8.8, 2.7, 1 H), 6.57 (d, *J* = 8.8, 1 H), 6.30 (s, br, 2 H), 2.53 (s, 3 H).

GC-MS: *m/z* = 171 (29) [M^+ + 2], 169 (84) [M+], 156 (33), 154 (100), 128 (11), 126 (38), 99 (20), 90 (18), 65 (13).

3.13: General procedure for the synthesis of quinolines in ionic liquids.

6.2 mL of the solution of 1-(2-aminoaryl)-3-yn-1-ols (formally deriving from 1.10 mmol of **1, 6, 13** and **14**) were transferred under nitrogen to a Schlenk flask containing the ionic liquid (5.0 mL) and $CuCl_2$ (1.5 mg, 1.1 x 10^{-2} mmol, or 3.0 mg, 2.2 x 10-2 mmol). Et_2O was removed under vacuum, and the resulting mixture was heated at 100°C for 15 h or 24 h. After cooling, the product was extracted with Et_2O (6 x 4 mL), and the residue (still containing the catalyst dissolved in the ionic liquid) was used as such for the next recycle. The collected ethereal phases were concentrated and the product purified by column chromatography (SiO_2, hexane/AcOEt from 99:1 to 95:5) to give pure quinolines.

3.14: Recycling procedure.

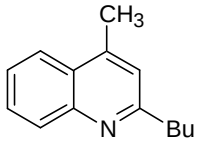
To the residue obtained as described above, still containing the catalyst dissolved in the ionic liquid, were added 6.2 mL of the ethereal solution containing crude. Et_2O was removed under vacuum, and then the same procedure described above was followed.

3.15: Conversion of 2-(1-methylenehept-2-ynyl)aniline 18 into 2-butyl-4-methylquinoline 17.

A solution of pure **18** (297.0 mg, 1.49 mmol) in Et_2O (3.0 mL) was transferred under nitrogen to a Schlenk flask containing [Bmim][BF_4] (6.8 mL) and $CuCl_2$ (2.0 mg, 1.5x10^{-}2 mmol). Et_2O was removed under vacuum, and the resulting mixture was heated at 100°C for 15 h. After cooling, the product was extracted with Et_2O (6x4 mL). The collected ethereal phases were concentrated, and the residue was purified by column chromatography (SiO_2, 95:5 hexane/AcOEt) to give 281.7 mg of quinoline **17** (95%).

3.16: Characterization of quinolines.

2-Butyl-4-methylquinoline (17).



Yellow oil.

IR (film): v = 2955 (m), 2929 (s), 2869 (m), 1604 (s), 1561 (w), 1465 (m), 1379 (w), 1259 (w), 1123 (w), 861 (w), 758 (m) cm^{-1}.

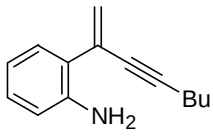
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.05 (ddd, *J* = 8.5, 1.3, 0.7, 1 H), 7.94-7.89 (m, 1 H), 7.65 (ddd, *J* = 8.5, 7.0, 1.5, 1 H), 7.47 (ddd, *J* = 8.3, 7.0, 1.3, 1 H), 7.12 (q, *J* = 1.0, 1 H), 2.96-2.88 (m, 2 H), 2.65 (d, *J* = 1.0, 3 H), 1.84-1.72 (m, 2 H), 1.51-1.37 (m, 2 H), 0.96 (t, *J* = 7.3, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 162.8, 147.7, 144.2, 129.3, 129.0, 126.8, 125.4, 123.6, 122.1, 39.0, 32.2, 22.8, 18.7, 14.0.

GC-MS: *m/z* = 199 (1) [M^{+}], 184 (13), 171 (6), 170 (29), 158 (23), 157 (100), 156 (9), 116 (7), 115 (12).

Anal. calcd for C14H17N (199.29): C, 84.37; H, 8.60; N, 7.03; found C, 84.41; H, 8.59; N, 7.00.

2-(1-Methylenehept-2-ynyl)aniline (18)



Pale yellow oil.

IR (film): 3462 (m, br), 3375 (m, br), 2957 (m), 2931 (m), 2871 (w), 2220 (w), 1618 (s), 1494 (m), 1455 (m), 1308 (m), 904 (m), 748 (s) cm^{-1}.

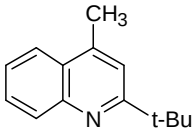
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.17 (dd, J = 7.8, 1.6 Hz, 1H), 7.12–7.05 (m, 1H), 6.72 (td, J = 7.5, 1.2 Hz, 1H), 6.65 (dd, J = 7.7, 1.2 Hz, 1H), 5.67 (d, J = 2.0 Hz, 1H), 5.56 (d, J = 2.0 Hz, 1H), 4.15 (s, br, 1H), 2.34 (t, J = 7.1 Hz, 2H), 1.60–1.34 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 143.7, 129.7, 129.4, 128.9, 125.2, 124.3, 118.3, 116.0, 92.1, 79.9, 30.7, 22.1, 19.1, 13.6.

MS (70 eV, EI): *m/z* (%): 199 (64) [M^+], 184 (9), 170 (35), 157 (100), 156 (85), 155 (27), 154 (40), 144 (16), 130 (38), 129 (43), 128 (44), 127 (20), 115 (20), 89 (13), 77 (28).

Anal. Calcd for C14H17N (199.29): C, 84.37; H, 8.60; N, 7.03. Found: C, 84.45; H, 8.56; N, 7.01.

2-*tert*-Butyl-4-methylquinoline (19)



Yellow oil.

IR (film): v = 2956 (s), 2917 (m), 2863 (m), 1602 (m), 1557 (m), 1506 (m), 1448 (m), 1363 (w), 1153 (m), 1107 (m), 932 (w), 863 (w), 757 (s) cm^{-1}.

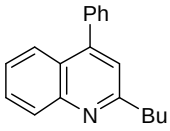
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.06 (ddd, J = 8.4, 1.3, 0.7, 1 H), 7.93-7.86 (m, 1 H), 7.63 (ddd, J = 8.4, 6.9, 1.5, 1 H), 7.46 (ddd, J = 8.2, 6.9, 1.3, 1 H), 7.33 (q, J = 0.8, 1 H), 2.66 (d, J= 0.8, 3 H), 1.45 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.9, 147.3, 143.6, 129.9, 128.7, 126.5, 125.3, 123.3, 118.8, 37.9, 30.1, 18.9.

GC-MS: *m/z* = 199 (36) [M^+], 198 (30), 184 (100), 185 (15), 168 (9), 157 (42), 143 (19), 115 (13).

Anal. calcd for C14H17N (199.29): C, 84.37; H, 8.60; N, 7.03; found C, 84.33; H, 8.62; N, 7.05.

2-Butyl-4-phenylquinoline (20).



Yellow oil.

IR (film): v = 2956 (s), 2929 (m), 2871 (w), 1593 (s), 1557 (m), 1490 (m), 1444 (m), 1408 (m), 1179 (m), 1029 (m), 881 (m), 766 (s), 702 (s) cm^{-1}.

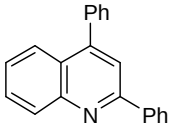
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.12 (ddd, *J* = 8.4, 1.2, 0.6, 1 H), 7.86 (ddd, *J* = 8.4, 1.4, 0.6, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.4, 1 H), 7.51-7.44 (m, 5 H), 7.40 (ddd, *J* = 8.4, 6.9, 1.2, 1 H), 7.23 (s, 1 H), 3.04-2.96 (m, 2 H), 1.89-1.77 (m, 2 H), 1.53-1.39 (m, 2 H), 0.96 (t, *J* = 7.3, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 162.6, 148.5, 148.4, 138.3, 129.5, 129.2, 128.5, 128.3, 125.7, 125.6, 125.3, 121.6, 39.1, 32.2, 22.7, 14.0.

GC-MS: *m/z* = 261 (< 0.5) [M^+], 232 (15), 220 (19), 219 (100), 218 (9), 217 (7).

Anal. calcd for C19H19N (261.36): C, 87.31; H, 7.33; N, 5.36; found C, 87.39; H, 7.31; N, 5.30.

2,4-Diphenylquinoline (21).



Yellow solid.

Mp 107-108 °C, lit.[202] 105-106 °C.

IR (KBr): v = 3054 (m), 1590 (s), 1546 (m), 1489 (m), 1445 (m), 1407 (m), 1358 (m), 1231 (m), 1074 (m), 1031 (m), 890 (m), 770 (s), 702 (s) cm^{-1}.

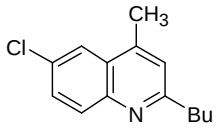
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.24 (ddd, *J* = 8.5, 1.1, 0.6, 1 H), 8.20-8.14 (m, 2H), 7.89-7.84 (m, 1 H), 7.78 (s, 1 H), 7.68 (ddd, *J* = 8.5, 6.9, 1.5, 1 H), 7.54-7.38 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 156.8, 149.2, 148.8, 139.6, 138.4, 130.1, 129.54, 129.49, 129.3, 128.8, 128.6, 128.4, 127.6, 126.3, 125.8, 125.6, 119.3.

GC-MS: *m/z* = 281 (76) [M^+], 280 (100), 278 (7), 202 (16), 176 (6), 139 (10).

Anal. calcd for C21H15N (281.35): C, 89.65; H, 5.37; N, 4.98; found C, 89.71; H, 5.35; N, 4.94.

2-Butyl-6-chloro-4-methylquinoline (22)



Yellow oil.

IR (film): v = 2960 (m), 2928 (w), 2535 (w), 1604 (m), 1437 (w), 1384 (s), 1262 (m), 1088 (s), 1024 (s), 877 (w), 802 (s) (m) cm^{-1}.

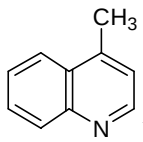
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.13 (d, *J* = 9.0, 1 H), 7.95 (d, *J* = 2.2, 1 H), 7.67 (dd, *J* = 9.0, 2.2, 1 H), 7.28 (q, *J* = 0.9, 1 H), 3.06-2.98 (m, 2 H), 2.70 (d, *J* = 0.9, 3 H), 1.87-1.73 (m, 2 H), 1.44 (sextuplet, *J* = 7.4, 2 H), 0.96 (t, *J* = 7.4, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 162.6, 146.5, 143.7, 132.5, 131.1, 129.2, 127.7, 123.0, 122.9, 37.6, 31.8, 22.6, 18.8, 13.8.

GC-MS: *m/z* = 235 (<0.5) [M^+ + 2], 233 (2) [M^+], 232 (3), 218 (15), 206 (11), 204 (32), 193 (59), 192 (26), 191 (100), 156 (9), 155 (9), 154 (14), 141 (12), 140 (14), 128 (8), 127 (8), 115 (8), 75 (5).

Anal. calcd for C14H16ClN (233.74): C, 71.94; H, 6.90; Cl, 15.17; N, 5.99; found C, 71.85; H, 6.92; Cl, 15.18; N, 6.05.

4-Methylquinoline (23).



Yellow oil.

IR (film): v = 1596 (m), 1580 (m), 1524 (s), 1452 (s), 1310 (m), 1251 (m), 841 (m), 757 (s) cm^{-1}.

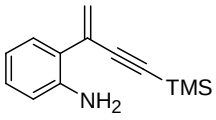
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.74 (d, *J* = 4.3, 1 H), 8.14-8.06 (m, 1 H), 7.92 (dd, *J* = 8.3, 1.4, 1 H), 7.66 (ddd, *J* = 8.4, 6.9, 1.4, 1 H), 7.50 (ddd, *J* = 8.3, 6.9, 1.0, 1 H), 7.14 (d, *J* = 4.3, 1 H), 2.62 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 150.0, 147.8, 144.3, 129.9, 129.1, 128.2, 126.2, 123.8, 121.8, 18.6.

GC-MS: *m/z* = 143 (100) [M^+], 142 (33), 117 (9), 116 (15), 115 (39), 89 (10).

Anal. calcd. for C10H9N (143.19): C, 83.88; H, 6.34; N, 9.78; found C, 83.75; H, 6.36; N, 9.89.

2-(1-Methylene-3-trimethylsilanylprop-2-ynyl)aniline (24)



Pale yellow oil.

IR (film): v = 3466 (m, br), 3378 (m, br), 2960 (m), 2144 (m), 1620 (s), 1495 (m), 1455 (m), 1250 (s), 957 (m), 842 (vs), 759 (m) cm^{-1}.

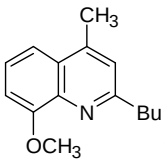
^{1}H NMR (300MHz, $CDCl_3$): δ (ppm) 7.16 (distorted ddd, *J* = 7.5, 1.6, 0.3 Hz, 1H), 7.09 (distorted ddd, *J* = 8.0, 7.5, 1.6 Hz, 1H), 6.72 (td, *J* = 7.5, 1.1 Hz, 1H), 6.64 (distorted ddd, *J* = 8.0, 1.1, 0.3 Hz, 1H), 5.79 (d, *J* = 1.8 Hz, 1H), 5.67 (d, *J* = 1.8 Hz, 1H), 4.17 (s, br, 2H), 0.20 (s, 9H).

^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 144.2, 129.8, 129.7, 129.5, 126.8, 124.4, 118.7, 116.4, 104.3, 96.3, 0.2.

MS (70 eV, EI): m/z (%): 215 (100) [M^+], 200 (97), 198 (33), 184 (44), 174 (16), 170 (15), 160 (56), 100 (14).

Anal. Calcd. for C13H17NSi (215.37): C, 72.50; H, 7.96; N, 6.50. Found: C, 72.64; H, 7.99; N, 4.47.

2-Butyl-8-methoxy-4-methylquinoline (25)



Yellow oil.

IR (film): 2954 (s), 2927 (s), 2858 (m), 1606 (m), 1562 (m), 1508 (m), 1465 (s), 1442 (w), 1407 (w), 1260 (s), 1150 (m), 1046 (m), 747 (m) cm^{-1}.

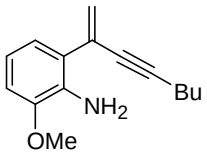
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.48 (dd, *J* = 8.4, 1.1, 1 H), 7.37 (dd, *J* = 8.4, 7.7, 1 H), 7.16 (s, 1 H), 7.00 (dd, *J* = 7.7, 1.1, 1 H), 4.04 (s, 3 H), 3.01-2.97 (m, 2 H), 2.61 (s, 3H), 1.83-1.75 (m, 2 H), 1.45 (sextuplet, *J* = 7.5, 2 H), 0.96 (t, *J* = 7.5, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ (ppm) 161.7, 155.4, 144.0, 139.6, 127.9, 125.3, 122.5, 115.5, 107.4, 56.0, 39.2, 32.3, 22.9, 19.2, 14.0.

GC-MS: *m/z* = 229 (12) [M^+], 228 (29), 200 (29), 188 (18), 187 (100), 185 (13), 172 (39), 170 (24), 169 (23), 157 (11), 115 (11).

Anal. calcd for C15H19NO (229.32): C, 78.56; H, 8.35; N, 6.11; found C, 78.66; H, 8.33; N, 6.09.

2-Methoxy-6-(1-methylenehept-2-ynyl)aniline (26)



Pale yellow oil

IR (film): 3471 (m, br), 3378 (m, br), 2957 (s), 2932 (s), 2864 (w), 2231 (w), 1614 (m), 1562 (m), 1475 (s), 1287 (m), 1211 (m), 1048 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.84 (distorted dd, J = 7.3, 1.6 Hz, 1H), 6.78–6.65 (m, 1H), 5.68 (distorted d, J = 2.0 Hz, 1H), 5.59 (distorted d, J = 2.0 Hz, 1H), 4.36 (s, br, 2H), 3.85 (s, 3H), 2.35 (t, J = 7.1 Hz, 3H), 1.60–1.35 (m, 4H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (75MHz, $CDCl_3$): δ (ppm) 147.1, 133.9, 129.5, 124.9, 124.2, 121.4, 117.2, 109.6, 92.0, 79.9, 55.7, 30.7, 22.1, 19.1, 13.6.

MS (70 eV, EI): *m/z* (%): 229 (100) [M^+], 214 (14), 200 (19), 187 (51), 186 (40), 172 (54), 171 (27), 170 (27), 154 (25), 144 (17), 127 (15), 115 (22).

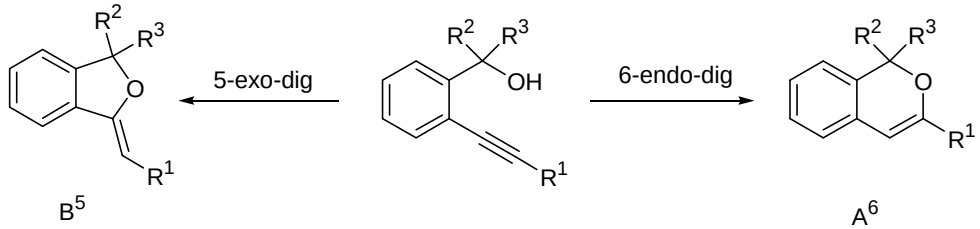
Anal. Calcd for C15H19NO (229.32): C, 78.56; H, 8.35; N, 6.11. Found: C, 78.65; H, 8.33; N, 6.10.

Chapter 4

Synthesis of 1,3-dihydroisobenzofurans and 1H-isochromenes by metal-catalyzed or base-mediated cycloisomerization of 2-alkynylbenzyl alcohols

4.1: Introduction.

We have been interested in the synthesis of isochromene and 1,3-dihydroisobenzofurans starting from 2-alkynylbenzyl alcohols. The intramolecular nucleophilic attack of the –OH group to the triple bond can give 5-*exo*-dig and 6-*endo*-dig cyclization route. The preference towards the 5-*exo*-dig cyclization mode (leading to 1,3-dihydroisobenzofurans) or the 6-*endo*-dig cyclization mode (leading to isochromenes) turned out to be dependent on the substitution pattern of the substrate as well as reaction conditions.



In the search for efficient methods for the selective preparation of five- or six-membered ring we have tested a metal-catalyzed or base mediate cycloisomerization reaction under microwave irradiation in alternatives solvents.

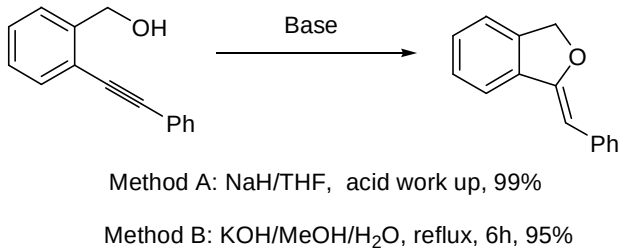
4.2: Bibliographic section.

Various methods are known for the preparation of isochromenes and 1,3-dihydroisobenzofurans in basic conditions or in presence of different metal, such as Au, Ir, Pd, and Ln using 2-alkynylbenzyl alcohols as a substrates.

Weingarten and Padwa in 1995 reported the apparent 6-endo-dig cyclization revealing an unusual acid-catalyzed rearrangement of the initially formed 1,3-dihydroisobenzofurans derivative. Under basic conditions, the hydroxyl functionality of 2-alkynylbenzyl alcohol underwent smooth cyclization with the unactivated acetylenic group. The mode of cyclization seemed to be greatly influenced by the nature of the substituent in the ortho-position of the aromatic ring. It appeared that the 6-endo cyclization of these benzylic alcohols was dependent on the presence of an electron-withdrawing group in the ortho-position.[203] Treatment of 2-(phenylethynylphenyl)methanol with NaH in THF followed by an aqueous

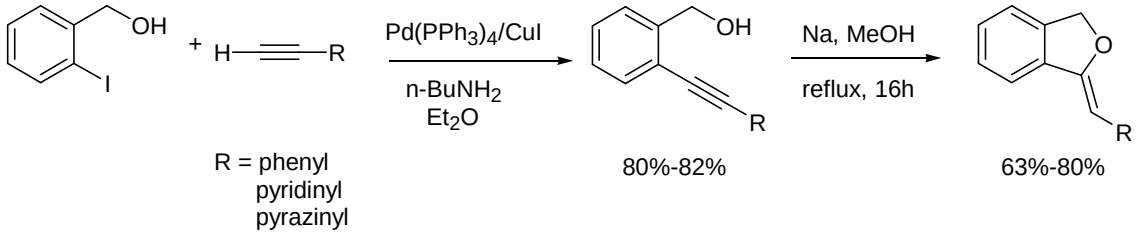
acid workup produced only the 5-*exo*-dig product in quantitative yield (Method A, Scheme 4.1).

The same group reported that alkynyl-substituted alcohols with NaH-THF (aprotic) instead of KOH-MeOH (protic) did not change the product distribution (Method B, Scheme 4.1).[3]



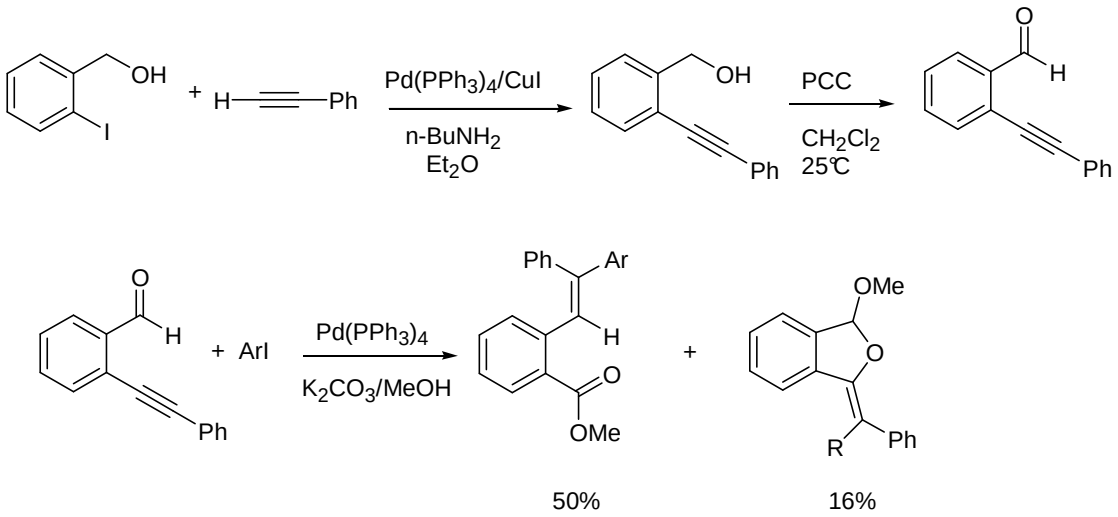
Scheme 4.1: Intramolecular addition of 2-alkynylbenzyl alcohol under basic conditions.

Wu and co-workers have reported the cyclization of 2-(substituted ethynyl)benzyl alcohols.[204] These compounds were prepared by Sonogashira palladium catalyzed coupling reaction of 2-iodobenzyl alcohol with alkynes. Treated with sodium methoxide in refluxing methanol gave the 5-exo products in all cases (Scheme 4.2).



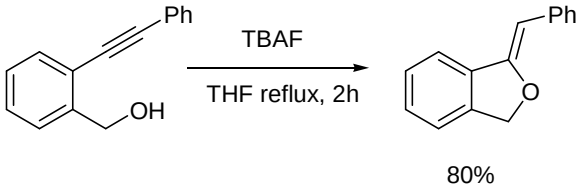
Scheme 4.2: Methanolysis of 2-(substituted ethynyl)benzyl alcohols

Wu and co-workers have also reported the palladium (0)-catalyzed cascade addition/oxidation reaction of 2-alkynylbenzaldehydes with aryl iodides in MeOH, affording in a one-step synthesis of stereoisomerical methyl 2-(2,2-disubstituted-vinyl)benzoates together with the monosubstituted methylene-3-methoxy-3-hydroisobenzofuran (Scheme 4.3). The 2-alkynylbenzaldehyde was obtained by oxidation of 2-(substituted ethynyl)benzyl alcohols with pyridinium chlorochromate (PCC).[205]



Scheme 4.3: Reactions of 2-alkynylbenzaldehydes with aryl iodides in methanol.

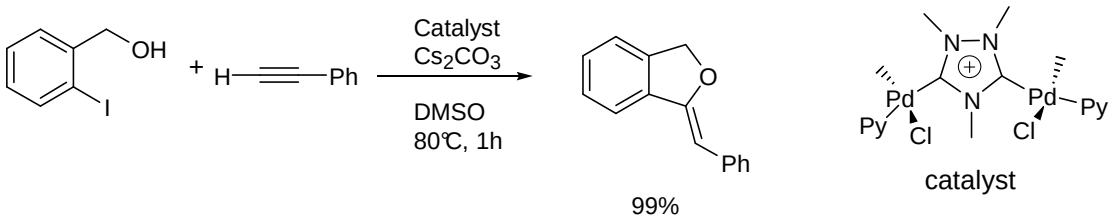
Sakamoto and co-workers have reported the cyclization reactions promoted by tetra-*n*-butylammonium fluoride (TBAF).[206] The tetrabutylammonium cation and fluoride anion are essential for the efficient cyclization reaction. When the benzyl alcohol which have either a hydrogen or aromatic ring on the triple bond were treated with TBAF, the products always aimed a five-membered ring (5-*exo*-dig cyclization, Scheme 4.4). For a smaller alkyl group a mixture of six-membered ring (6-*endo*-dig) and five-membered rings (5-*exo*-dig) was produced. The compound having bulky alkyl group only gave six-membered ring (6-*endo*-dig).



Scheme 4.4: Cyclization reactions of 2-alkynylbenzyl alcohols promoted by TBAF.

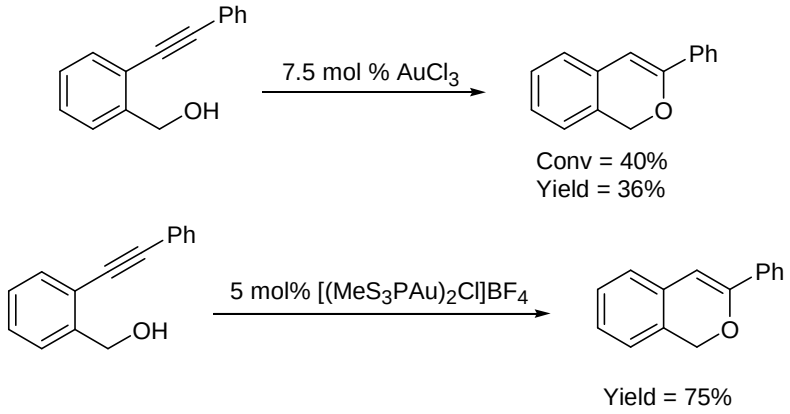
Mata and co-workers[207] have tested the consecutive Sonogashira/cyclic hydroalkoxylation reactions between *o*-hydroxyaryl halides and phenylacetylene to directly afford 1,3-dihydroisobenzofurans by a set of three different NHC-Pd-pyridine complexes where NHC

was 1,2,4-trimethyltriazolyldiylidene, 1,3-dimethylimidazolylidene and 1,4-dimethyltriazolylidene (Scheme 4.5).



Scheme 4.5: Synthesis of 1,3-dihydroisobenzofurans by NHC-Pd-pyridine complexes.

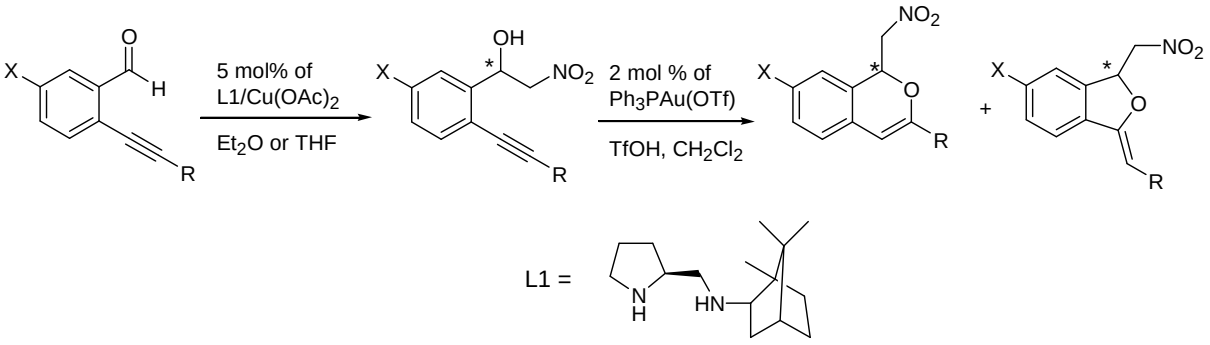
Hashmi and co-workers have reported the 6-*endo*-dig cyclization to give isochromene derivatives starting from 2-alkynylbenzyl alcohols using gold-catalyzed ring closure.[208] In this work when $AuCl_3$ was used as catalyst, significant decomposition of the substrate was observed together with its low conversion. In contrast, the Au (I) catalyst led to good conversion and good yields when the substituent on the triple bond was sterically shielding (Scheme 4.6). Also an unprecedented dimerization of 2-alkynylbenzyl alcohols was obtained with both the gold (I) and the gold (III) catalyst.



Scheme 4.6: Gold-catalyzed conversion of 2-alkynylbenzyl alcohol to 1H-isochromenes.

In 2011 Gong and co-workers have reported the asymmetric Henry reaction followed by gold-catalyzed cycloisomerization sequences (Scheme 4.7).[209] They have presented the copper (II)-catalyzed asymmetric Henry reaction of o-alkynylbenzaldehydes with subsequent gold (I)-catalyzed cycloisomerization to synthesize optically active 1*H*-isochromenes and 1,3-

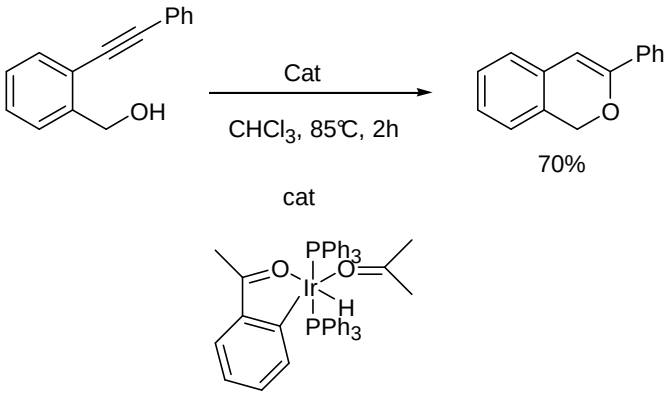
dihydroisobenzofurans in good overall yields with good to excellent enantioselectivities (up to 98%). A correlation between the regioselectivity and electronic nature of the substrates was studied and they suppose, in accord to the literature that the substrates with electrodonating groups at the alkynyl moiety preferred a 6-*endo*-dig cyclization to generate 1*H*-isochromenes as main products (up to >30:1) while the ones with electron-withdrawing groups were inclined to undergo 5-*exo*-dig cyclization to form 1,3-dihydroisobenzofurans (up to 1:5).



Scheme 4.7: Asymmetric Henry reaction/gold-catalyzed cycloisomerization sequences.

Crabtree and co-worker have reported a novel class of hydrido iridium-(III) catalysts for the intramolecular hydroalkoxylation and hydroamination of ortho-substituted aryl alkynes, using a variety of tethered nucleophiles.[210] When regioselectivity is an issue, highly selective 6-*endo*-dig cyclization is observed (Scheme 4.8).

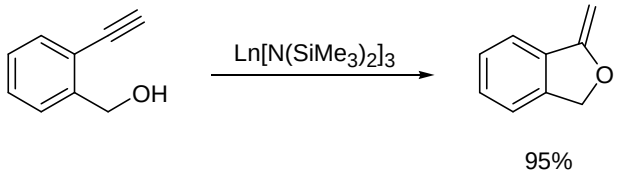
Mechanistic experiments indicate that the reaction likely proceeds via electrophilic activation of the alkyne toward nucleophilic attack, followed by direct protonolysis of the resulting Ir-C bond.



Scheme 4.8: Intramolecular alkyne hydroalkoxylation catalyzed by iridium hydrides.

Marks and co-workers have reported that lanthanide-organic complexes of the general type $Ln[N(SiMe_3)_2]_3$ (Ln) La, Sm, Y, Lu) serve as effective precatalysts for the rapid, exoselective, and highly regioselective intramolecular hydroalkoxylation/cyclization of primary and secondary alkynyl alcohols to yield the corresponding exocyclic enol ethers.[211]

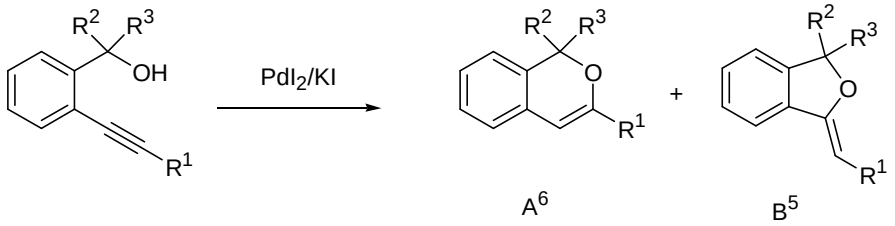
Conversions are highly selective with products distinctly different from those generally produced by conventional transition metal catalysts (Scheme 4.9).



Scheme 4.9: Intramolecular cyclization of alkynyl alcohols using lanthanide catalysts.

Gabriele and co-workers have reported the synthesis of (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and 1*H*-isochromenes by palladium-catalyzed cycloisomerization of readily available 2-alkynylbenzyl alcohols under neutral conditions (Scheme 4.10). Reactions were carried out at 80–100°C in the presence of catalytic amounts (1–2%) of PdI_2 in conjunction with 2 equiv. of KI for 1.5–24 h.

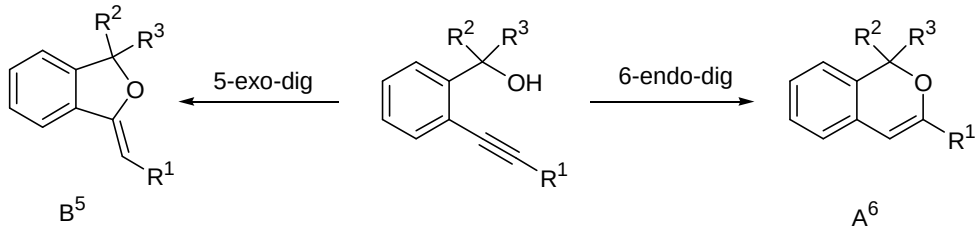
Table 4.1: Synthesis of (Z)-1-alkylidene-1,3-dihydroisobenzofurans and 1H-isochromenes by palladium-catalyzed cycloisomerization.



A[6] B[5]

Entry	R^1	R^2	R^3	Cat.	Solv	°C	Time (h)	A^6 (%)[a]	B^5 (%)[a]
1	Bu	H	H	PdI_2/KI	Dioxane	80	3	63	0
2	Bu	Et	Et	PdI_2/KI	Dioxane	80	8	73	15
3	Bu	Et	Et	PdI_2/KI	MeOH	80	2	77	0
4	Bu	H	Bu	PdI_2/KI	Dioxane	80	2	74	0
5	Ph	H	H	PdI_2/KI	Dioxane	90	2	40	15
6	Ph	H	H	PdI_2/KI	DMA	80	10	9	49
7	Ph	H	Bu	PdI_2/KI	Dioxane	100	15	40	27
8	Ph	H	Bu	PdI_2/KI	DMA	80	6	4	70
9	Ph	Et	Et	PdI_2/KI	MeOH	80	2	0	89
10	H	H	H	PdI_2/KI	CH_3CN	80	2	0	0

a) isolated yield.



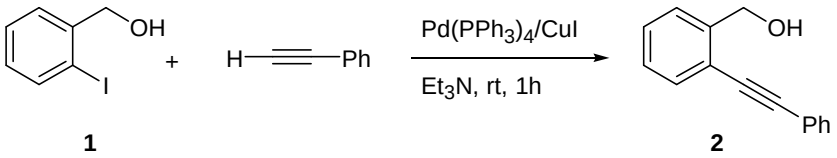
Scheme 4.10: Palladium-catalyzed cycloisomerization of 2-alkynylbenzyl alcohols.

The preference towards the 5-*exo*-dig cyclization mode (leading to 1,3-dihydroisobenzofurans) or the 6-*endo*-dig cyclization mode (leading to isochromenes) turned out to be dependent on the substitution pattern of the substrate as well as reaction conditions. In several cases, by properly adjusting the reaction conditions, the same substrate could be selectively converted into either the dihydroisobenzofuran or the 1*H*-isochromene derivative.[212] The results of this study were reported in Table 4.1. The Pd-catalyzed methodology reported can be successfully applied to substrates bearing in the triple bond alkyl or aryl group.

4.3: Results and discussion.

In order to increase yields and selectivity we turn our interest to the synthesis of 1,3-dihydroisobenzofurans and isochromenes under microwave irradiation using 2-alkynylbenzyl alcohols as substrates.

The first 2-alkynylbenzyl alcohol tested was 2-(phenylethynylphenyl)methanol **2** obtained by Sonogashira coupling between 2-iodobenzyl alcohol **1** and phenylacetylene (Scheme 4.11).



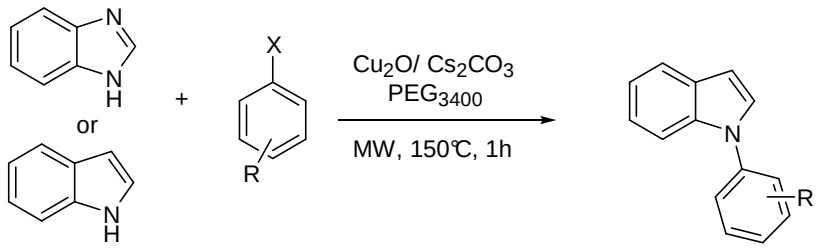
*Scheme 4.11: Synthesis of 2-(phenylethynylphenyl)methanol **2**.*

Recently, liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties. PEGs have thermal stability, are non-volatile, and completly non-halogenated, commercially available, easily degradable and with low toxicity. Poly (ethylene glycol)s are amphipathic polymers miscible in common organic solvents and in water, immiscible with a number of organic solvents such as di-ethyl ether and cyclohexane and able to dissolve common organic solids and metals.

PEGs with low molecular weight (less than 800 Dalton) are liquid at room temperature and PEGs with high molecular weight (more than 800 Dalton) are solids, which melt at moderate temperature and can be used as solvent. Under microwave irradiation PEG is rapidly heated to high temperature, enhancing molecular interaction.

Several works developed in our laboratory have shown the use of PEGs as solvent in particular in cross-coupling reactions.

Lamaty and co-workers have reported a mild, simple and efficient microwave-enhanced copper-catalyzed protocol for N-arylation using poly(ethylene glycol) (PEG_{3400}) as a solvent.[213] Indole and benzimidazole have been N-arylated in the presence of cuprous oxide, cesium carbonate, and PEG_{3400}, under microwave activation, without the addition of supplementary ligands (Scheme 4.12). Simple treatment by precipitation in Et_2O and filtration provided the expected product after evaporation and recovery of the catalytic system as a precipitate. The recovery and one successful re-use of the catalytic system is also described.

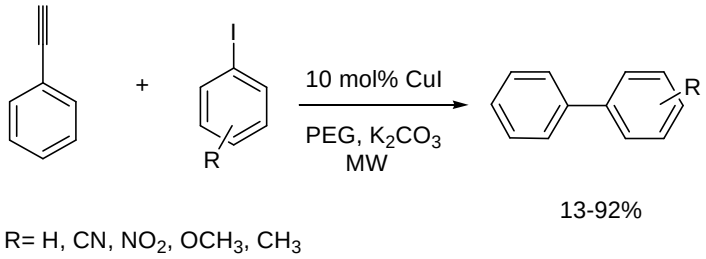


R= H, CN, NO_2, OCH_3, CH_3

Scheme 4.12: N-arylation of indole and benzimidazole in PEG under MW irradiation.

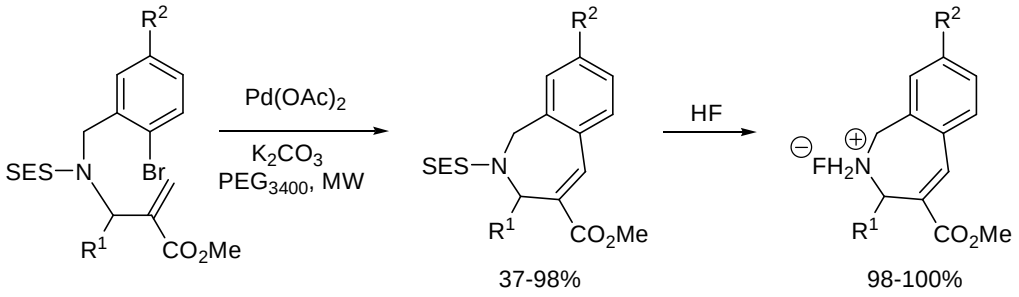
A catalytic system composed of copper salt, potassium carbonate, and appropriate poly(ethylene glycol) (PEG) liquid or solid with molecular weight around 300-3400, was

developed to perform a Sonogashira arylation under microwave activation.[214] In the presence of copper (I) iodide, various substituted diphenylacetylenes could be synthesized (Scheme 4.13).



Scheme 4.13: Synthesis of diphenylacetylenes in PEG under MW activation.

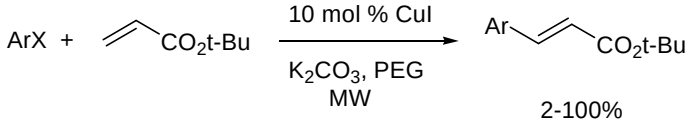
The Heck reaction of alkylated 2-(trimethylsilyl)ethanesulfonyl (SES)-protected β-aminoesters provides benzazepines in good yields (Scheme 4.14). Good selectivity towards cyclization was obtained when the reaction was performed in PEG_{3400} as the solvent under microwave activation. Cleavage of the SES group with HF provides the corresponding free benzazepine.[170]



Scheme 4.14: Synthesis of benzazepines in PEG under MW irradiation.

Heck arylation under microwave activation was developed using a catalytic system constituted by copper salt, potassium carbonate and PEG_{3400}.[172] Copper iodide gave the best results in a short reaction time only 30 min and various substituted *tert*-butyl cinnamates

could be synthesized (Scheme 4.15). Better results were usually obtained after recycling the catalyst/solvent system.



Scheme 4.15: Heck reaction in PEG under MW irradiation.

4.4: Pd-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol 2 in PEGs.

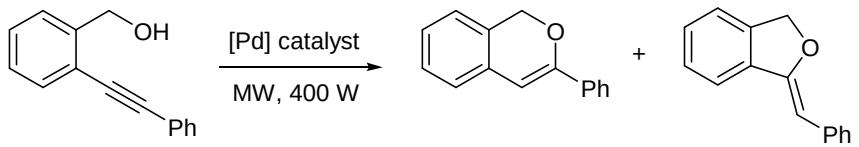
To study the reactivity of palladium as catalyst the reaction was investigated using both classical solvent or non conventional media: ionic liquids, liquid and solid poly(ethylene glycol) PEGs.

The exploratory tests were carried out using dioxane and [Bmim][BF_4] as solvent, under microwave irradiation. In each case the cyclization did not take place at all.

Initial experiments were carried out using PdI_2 in conjunction with KI as catalyst under microwave irradiation.

When liquid PEG in particular PEG_{300} was tested, after 3 h of reaction it was possible to detect the formation of two isomers **3** and **4**. The product was recovered after extraction with diethyl ether. The ratio of the two isomers was depended on the molar ratio of catalyst. In fact with 1 mol % of PdI_2 equimolar quantity of **3** and **4** was observed (Table 4.2, entry 1), with 5 mol % the prevalent formation of **4** was detected (Table 4.2, entry 2).

*Table 4.2: Palladium-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol **2**.*



2 **3** **4**

Entry	Catalyst (eq.)	Additive (eq.)	Solvent	°C	Time (h)	Conv. **2**[a]	Product **3**[a]	Product **4**[a]
1	PdI_2 0.01	KI 0.02	PEG_{300}	150	3	100	12	16
2	PdI_2 0.05	KI 0.1	PEG_{300}	150	3	100	18	40
3	PdI_2 0.01	KI 0.02	PEG_{3400}	150	3	100	0	0
4	PdI_2 0.05	KI 0.1	PEG_{3400}	150	2	100	5	7
5	$Pd(OAc)_2$ 0.05	-	PEG_{3400}	150	2	0	0	0
6	$Pd(OAc)_2$ 0.05	KI 0.1	PEG_{3400}	150	3	80	4	6

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg of $PEG_{3400,}$ 0.25 mL of PEG_{300} microwave-assisted reactions were performer with a Biotage Initiator^{TM} 2.0, microwave vial 0.5-2 mL, initial power 400W.

The demonstrated ability of PEG_{3400} in cross-coupling reaction drove us to use it preferentially in this set of experiments. The reaction mixture composed by substrate, PdI_2/KI and PEG_{3400} was heated up under microwave irradiation. When a temperature above 45°C was reached, PEG melts and becomes the solvent of reaction. The mixture was cooled down, dissolved in a small quantity of dichloromethane and precipitate in diethyl ether. After filtration, two fractions were obtained: the precipitate and the liquor (Figure 4.1). The precipitate constituted by PEG and catalysts and the liquor, the organic phase would contain the expected product.

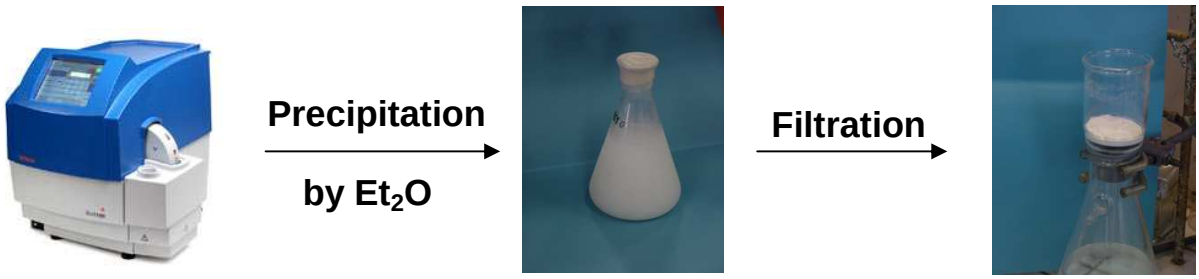


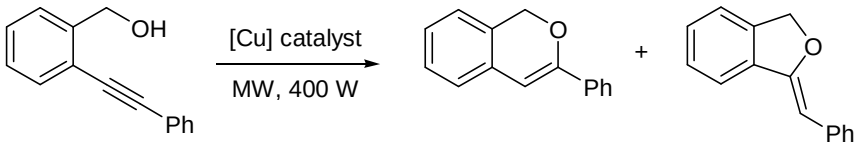
Figure 4.1: Microwave irradiation followed by precipitation-filtration of catalytic system metal-PEG_{3400}.

However, in these conditions, the reaction did not take place at all or only traces of products **3** and **4** were observed (Table 4.2, entries 3-6), suggesting that the catalytic system made of PdI_2/KI/PEG_{3400} is not suitable for this transformation.

4.5: Cu-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol 2 in PEGs.

A second approach explored the copper-catalyzed cycloisomerization of 2-alkynylbenzyl alcohol **2**. Copper is an attractive transition metal to use in reaction process due to its low cost and relatively low toxicity.

*Table 4.3: Copper-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol **2**.*



2 **3** **4**

Entry	Catalyst	Additive	Solvent	°C	Time	Conv. **2**[a]	Product **3**[a]	Product **4**[a]
1	$CuCl_2$ $2H_2O$		PEG_{3400}	150	4h	30	12	2
2	$CuCl_2$ $2H_2O$	1,10-phenantroline	PEG_{3400}	130	4h	0	0	0
3	$CuCl_2$ $2H_2O$	*N*,*N*-dimethyl-ethylendiamine	PEG_{3400}	130	4h	0	0	0
4	CuI		PEG_{3400}	220	30 min	10	0	5
5	CuI	K_2CO_3	PEG_{3400}	220	30 min	100	0	38

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg of PEG_{3400}, microwave-assisted reactions were performer with a Biotage Initiator^{TM} 2.0, microwave vial 0.5-2 mL, initial power 400W.

Very disappointing results were obtained. With $CuCl_2 \cdot 2H_2O$ only traces of products **3** and **4** were detected after 4 h of reaction (Table 4.3 entry 1). When copper ligands such as 1,10-phenantroline or *N*,*N*-dimethyl-ethylendiamine were added, the reaction was not improved (Table 4.3, entries 2-3).

When the reaction was catalyzed by CuI isomer **4** was the major product formed (Table 4.3, entries 4-5) but the results were still poor.

4.6: Au-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol 2 in PEGs.

In an alternative, the gold-catalyzed cycloisomerization was explored. As previously detailed in chapter 2 gold catalysis has emerged in the last decade as catalysts for reactions that proceed through π-activation of carbon–carbon multiple bonds. For this reason we have tested the reaction by using gold (I) and gold (III) catalysis in alternative solvent such as PEG.

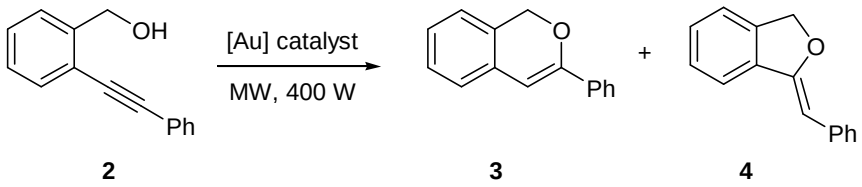
When the reaction was carried out in the presence gold in oxidation state +1 as catalyst the conversion of the substrate **2** was not complete and only traces of product were detected (Table 4.4, entry 1). A complete conversion of substrate **1** was possible if additives such as silver species were used (Table 4.4, entries 2-3). These additives create a cationic species more electrophilic that allowed a more efficient activation of substrate. Two additives were tested: silver hexafluoroantimoniate or silver triflate. Better results in comparison with the other catalytic systems tested were observed. In each case product **3** and **4** were obtained but the regioselectivity between 5-*exo*-dig and 6-*endo*-dig mode was very poor.

The reactions catalyzed by gold in oxidation state +3 gave some interesting information.

When reaction was carried out using $AuCl_3$ as catalyst in CH_3CN, partial conversion of substrate and the formation of 1,3-dihydroisobenzofurans **3** in low yield was detected (Table 4.4 entry 4). The change of solvent, $PEG_{300,}$ induces the formation of mixture of **3** and **4** (Table 4.4, entry 5). In order to optimize the reaction conditions, the additives silver hexafluoroantimoniate and silver triflate was added also when Au (III) was the catalyst. When liquid PEG was used such as $PEG_{550}OMe$, a mixture of **3** and **4** was reported (Table 4.4, entry 8). When solid PEG was used, PEG_{3400} and $PEG_{2000}(OMe)_2$, in every case the 6-*endo*-dig

nucleophilic attack was favoured but the yield of product **3** was poor (Table 4.4, entries 6-7, 9-11).

*Table 4.4: Gold-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol **2**.*



2 **3** **4**

Entry	Catalyst (eq.)	Additive (eq.)	Solvent	Time (h)	Conv **2**[a]	Product **3**[a]	Product **4**[a]
1	$AuCl(PPh_3)$ 0.02		PEG_{3400}	1	20	Trace	Trace
2	$AuCl(PPh_3)$ 0.02	AgOTf 0.02	PEG_{3400}	1	100	37	55
3	$AuCl(PPh_3)$	$AgSbF_6$	PEG_{3400}	1	100	23	26
4[b]	$AuCl_3$ 0.075		CH_3CN	24	60	26	0
5	$AuCl_3$ 0.075		PEG_{300}	2	50	24	19
6	$AuCl_3$ 0.075	AgOTf 0.225	PEG_{3400}	1	100	30	0

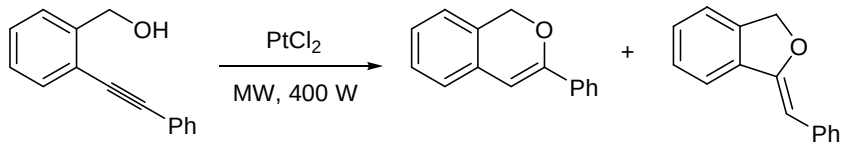
7	$AuCl_3$	$AgSbF_6$	PEG_{3400}	1	100	39	0
	0.075	0.225					
8	$AuCl_3$	$AgSbF_6$	$PEG_{550}OMe$	0.5	100	11	14
	0.075	0.225					
9	$AuCl_3$	$AgSbF_6$	$PEG_{2000}(OMe)_2$	1	100	21	0
	0.075	0.225					
10	$AuCl_3$	$AgSbF_6$	$PEG_{2000}(OMe)_2$	2.45	100	41	0
	0.05	0.15					
11	$AuCl_3$	$AgSbF_6$	$PEG_{2000}(OMe)_2$	4.15	100	46	0
	0.02	0.06					

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. b) Reaction was carried out at room temperature. All the reactions were carried out using 300 mg of PEG_{3400} or $PEG_{2000}(OMe)_2$, 0.25 mL of PEG_{300}, at 50°C under microwave-assisted irradiation performed with a Biotage Initiator™ 2.0, microwave vial 0.5-2 mL, initial power 400W.

4.7: Pt-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol 2 in PEGs.

In order to verify the possibility to shift the selectivity of cycloisomerization process we turned to investigate an other metal transition. The choice of platinum (II) catalyst seemed to us coherent being the platinum salts known for the electrophilic activation of alkenes and alkynes.[66, 215] We performed an evaluation of the activity of platinum di-chloride as catalyst in PEG under microwave activation.

*Table 4.5 Platinum-catalyzed cycloisomerization of 2-(phenylethynylphenyl)methanol **2**.*



2 **3** **4**

Entry	Catalyst (eq.)	Solvent	°C	Time	Conv. **2**[a]	Product **3**[a]	Product **4**[a]
1	$PtCl_2$ 0.05	PEG_{300}	150	30 min	100	38	0
2	$PtCl_2$ 0.05	PEG_{300}	150	1h	100	45	0
3	$PtCl_2$ 0.05	PEG_{300}	100	1h	100	39	37
4	$PtCl_2$ 0.05	PEG_{300}	50	1h	100	42	36
5	$PtCl_2$ 0.05	$PEG_{550}OMe$	150	5min	100	36	19
6	$PtCl_2$ 0.05	PEG_{3400}	150	2h	100	48	0
7	$PtCl_2$ 0.05	PEG_{3400}	150	30 min	100	51	13
8	$PtCl_2$ 0.02	PEG_{3400}	150	30 min	100	68	15
9	$PtCl_2$ 0.02	PEG_{3400}	120	30 min	100	37	15

10	$PtCl_2$ 0.01	PEG_{3400}	150	30 min	100	51	23
11	$PtCl_2$ 0.01	PEG_{3400}	150	15 min	90	40	18
12	$PtCl_2$ 0.02	PEG_{3400}	150	15 min	100	52	22
13	$PtCl_2$ 0.02	$PEG_{2000}(OMe)_2$	150	1h	100	57	0
14	$PtCl_2$ 0.02	$PEG_{2000}(OMe)_2$	80	30 min	100	61	26
15	$PtCl_2$ 0.05	$PEG_{2000}(OMe)_2$	150	10 min	100	71	18

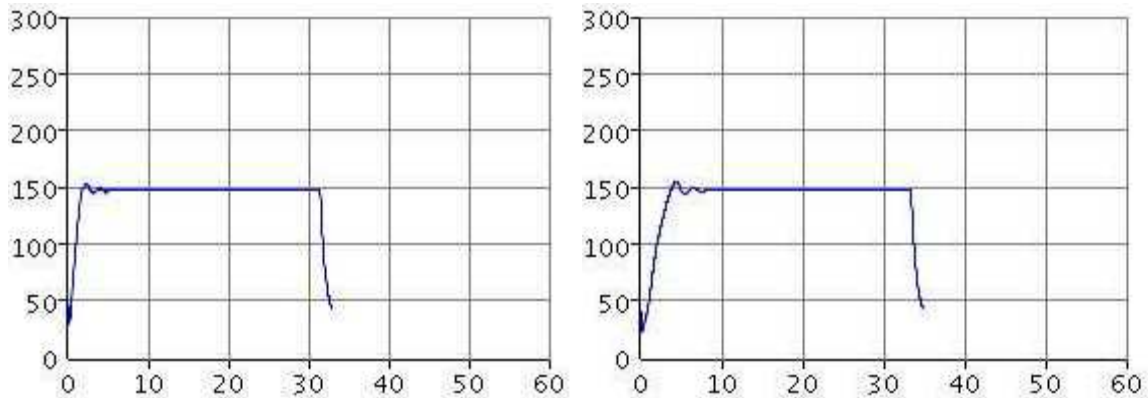
a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg of PEG_{3400} or $PEG_{2000}(OMe)_2$, 0.25 mL of PEG_{300}, microwave-assisted reactions were performer with a Biotage Initiator™ 2.0, microwave vial 0.5-2 mL, initial power 400W.

Since the fist experiment, it was possible to affirm that the cycloisomerization was influenced by the temperature. When the reaction was carried out in PEG_{300} at 150°C only formation of 1,3-dihydroisobenzofurans **3** was observed (Table 4.5, entries 1-2). At 100°C or 50°C the mixture of **3** and **4** was recovered highlighting that the temperature is a fundamental parameter (Table 4.5, entries 3-4) to take into account and a careful control of it, would be the key for achieving complete selectivity.

The catalytic system constituted by $PtCl_2$ and PEG proved to be very reactive towards 2-alkynylbenzyl alcohol **2**. In these cases, the yield of products **3** and **4** was good in comparison with the results obtain using palladium, copper and gold as catalysts.

Interestingly $PEG_{2000}(OMe)_2$ as solvent gives the best results (Table 4.5, entries 14-15). The 1,3-dihydroisobenzofuran **3** was recovered in 71% of NMR yield.

The curves of temperature, under microwave heating shown that, when the temperature of 150°C was reached very fast (less 2.5 min.), the 6-*endo*-dig cyclization is favoured (Figure 4.2, A corresponding reaction Table 4.5, entry 1). When the temperature was reached slowly (more 4 min.) a mixture of the two isomers **3** and **4** was observed (Figure 4.2, B corresponding reaction Table 4.5, entry 8).



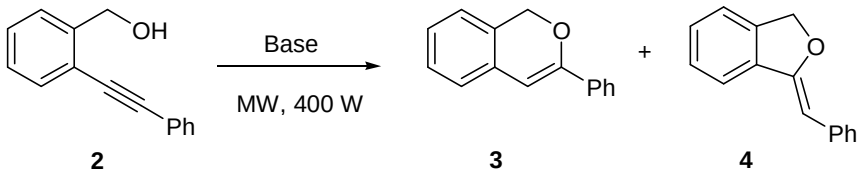
A **B**

Figure 4.2: Profiles of temperature reached by PEG_{300} (A) and PEG_{3400} (B).

4.8: Base-mediated cycloisomerization of 2-(phenylethynylphenyl)methanol 2 in PEGs.

In order to switch the reactivity of the system towards a 5-*exo*-dig nuclephilic attack, we screened different carbonate bases using PEGs (Table 4.6).

*Table 4.6 Base-catalyzed cycloisomerization 2-(phenylethynylphenyl)methanol **2**.*



2 **3** **4**

Entry	Base	Solvent	°C	Time (min)	Conv. **2**[a]	Product **3**[a]	Product **4**[a]
1	K_2CO_3	PEG_{3400}	220	30	100	0	56
2	K_2CO_3	PEG_{3400}	150	30	30	0	19
3	Cs_2CO_3	$PEG_{550}OMe$	180	7	100	0	85
4	Cs_2CO_3	PEG_{3400}	150	10	100	0	90
5	Cs_2CO_3	$PEG_{2000}(OMe)_2$	150	10	100	12	63
6	$NaHCO_3$	$PEG_{550}OMe$	180	7	90	0	0

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg of PEG_{3400} or $PEG_{2000}(OMe)_2$, 0.25 mL of $PEG_{550}(OMe)_2$, 1.5 eq of base, microwave-assisted reactions were performer with a Biotage Initiator™ 2.0, microwave vial 0.5-2 mL, initial power 400W.

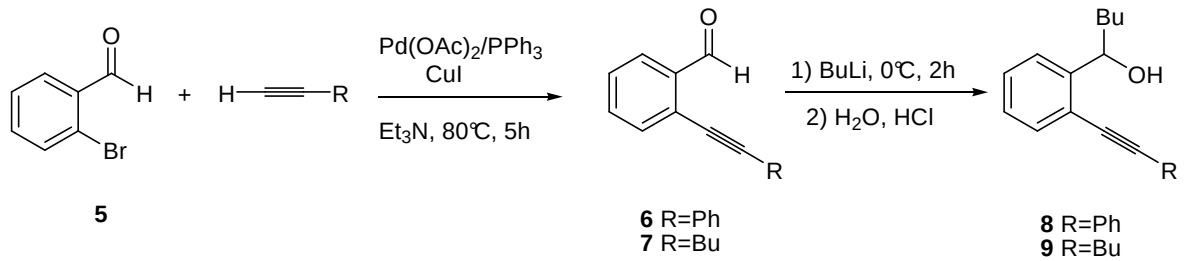
The cycloisomerization reaction carried out at higher temperature (around 180°C-220°C) gives satisfactory results using K_2CO_3 in PEG_{3400} (Table 4.6, entry 1). The best result was

reported using Cs_2CO_3 in $PEG_{550}OMe$ or $PEG_{3400.}$ Isochromene **4** was obtained in 85% or 90% yield in a short time (Table 4.6, entries 3-4). Mixture of **3** and **4** was observed using $PEG_{2000}(OMe)_2$ (Table 4.6, entry 5). With $NaHCO_3$ in $PEG_{550}OMe$ the reaction did not work at all (Table 4.6, entry 6).

4.9: Cycloisomerization reaction of 1-alkynylbenzyl alcohols 8 and 9 bearing a secondary alcoholic group in PEGs.

We have turned our interest to others substrates **8** and **9** that present a butyl group in benzylic position and butyl or phenyl group in the end of the triple bond.

Substrates **8** and **9** were prepared in two steps, Sonogashira coupling reaction followed by addition of a butyl substituent on the aldehyde function (Scheme 4.16).



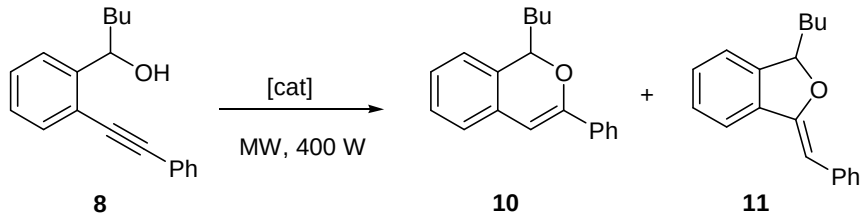
5

6 R=Ph
7 R=Bu

8 R=Ph
9 R=Bu

*Scheme 4.16: Synthesis of 1-(2-phenylethynylphenyl) pentan-3-ol **8** and 3-(2-hex-1-ynylphenyl) pentan-3-ol **9**.*

*Table 4.7: Cycloisomerization reaction of 1-(2-phenylethynylphenyl) pentan-3-ol **8** in PEG under Mw irradiation.*



8 **10** **11**

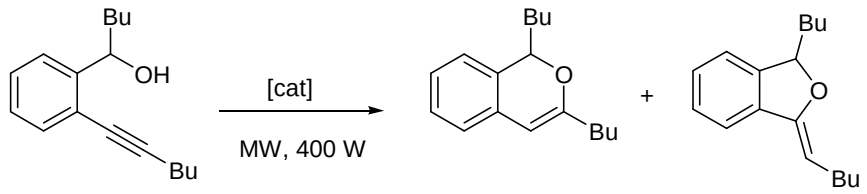
Entry	Catalyst (eq.)	Base (eq.)	Solvent	°C	Time (min)	Conv. **8**[a]	Product **10**[a]	Product **11**[a]
1	$AuCl_3$ 0.05	-	$PEG_{2000}(OMe)_2$	150	10	100	32	63
2	$PtCl_2$ 0.05	-	$PEG_{2000}(OMe)_2$	150	10	100	32	45
3	-	Cs_2CO_3 1.5	$PEG_{550}OMe$	180	7	100	0	71

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg $PEG_{2000}(Ome)_2$, 0.25 mL of $PEG_{550}OMe$, microwave-assisted reactions were performer with a Biotage Initiator™ 2.0, microwave vial 0.5-2 mL, initial power 400W.

A mixture of two isomers **10** and **11** was obtained using gold and platinum as catalysts (Table 4.7, entries 1-2). The selective formation of isochromene **11** was possible when no catalyst was added, but using only a basic medium by Cs_2CO_3 in liquid $PG_{550}OMe$ (Table 4.7, entry 3). These results are in agreement to what previously reported in the literature.[209, 212]

Different catalysts were tested for the cycloisomerization reaction of 3-(2-hex-1-ynylphenyl) pentan-3-ol **9**. PdI_2/KI/PEG_{3400} system proved to be suitable for the obtaintion of product **12** selectively but in a moderate yield.

*Table 4.8: Cycloisomerization reaction of 3-(2-hex-1-ynylphenyl) pentan-3-ol **9** in PEG under Mw irradiation.*



9 **12** **13**

Entry	Catalyst (eq.)	Additive (eq.)	Solvent	°C	Time (h)	Conv. **9**[a]	Product **12**[a]	Product **13**[a]
1	PdI_2 0.02	KI 0.04	PEG_{3400}	130	2	100	40	0
2	$CuCl_2$ 0.05		PEG_{3400}	180	2	80	32	0
3	$AuCl_3$ 0.02		PEG_{300}	50	2	80	14	0
4	$PtCl_2$ 0.02		PEG_{3400}	50	1	100	30	55
5	$PtCl_2$ 0.02		$PEG_{2000}(OMe)_2$	80	0.5	100	64	0

a) Calculated by ^1H NMR using CH_2Br_2 as an internal standard. All the reactions were carried out using 300 mg of PEG_{3400} or $PEG_{2000}(OMe)_2$, 0.25 mL of PEG_{300}, microwave-assisted reactions were performer with a Biotage Initiator™ 2.0, microwave vial 0.5-2 mL, initial power 400W.

Using copper and gold as catalysts, we observed the partial conversion of the substrate **9** but the exclusively formation of corresponding 1*H*-isochromene **12** in poor yields (Table 4.8, entries 2-3).

With $PtCl_2$, product **12** could be obtained selectively with a good yield (Table 4.8, entry 5) when protected PEG was used. It is important to point out the effect of the temperature. At lower reaction temperature was preferred the predominant formation of isomer **13**.

4.10: Conclusion.

In conclusion, we have demonstrate that the cycloisomerization of 2-alkynylbenzyl alcohols **2**, **8** and **9** to (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans (through a 5-*exo*-dig mechanism) and/or 1*H*-isochromenes (through a 6-*endo*-dig mechanism) can be achieved using PEG as solvent. By experimental results we can affirm that the process is depending on substitution on the triple bond, the nature of solvent, the temperature. The 6-*endo*-dig cycloisomerization tends to be favoured when gold (III) or platinum (II) are used as the catalysts. In basic conditions, the 5-*exo*-dig cyclization becomes the favoured process.

The study of reactivity of substituted 2-alkynylbenzyl alcohols is ongoing in our laboratory using Pt or Au catalysis in poly(ethylene glycol) under microwave irradiation.

Experimental section.

4.11: General conditions.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, with Me4Si as internal standard. Chemical shifts and coupling constants (*J*) are given in ppm (δ) and in Hz, respectively. Mass spectra were obtained at 70 eV on a GC–MS apparatus.

4.12: Preparation of substrates.

Coupling between (2-iodophenyl)methanol and phenylacetylene.

To a stirred solution of (2-iodophenyl)methanol (10.0 g, 42.7 mmol) in anhydrous Et_3N (420 mL) were added 3.46 mmol of $Pd(PPh_3)_4$, 6.83 mmol of CuI and 52.0 mmol of phenylacetylene. The mixture was stirred for 1 h at room temperature. Then a saturated solution of NH_4Cl was added followed by CH_2Cl_2. Phases were separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel (7:3 hexane/AcOEt) followed by repeated crystallization from hexane.

Coupling between 2-bromobenzaldehyde **5** and alkynes followed by addition of BuLi.

To a stirred solution of 2-bromobenzaldehyde **5** (10.0 g, 54.0 mmol) in anhydrous Et_3N (164 mL) were added $Pd(OAc)_2$ (108 mg, 0.48 mmol), PPh_3 (218 mg, 0.83 mmol), CuI (16 mg, 0.084 mmol), phenylacetylene or 1-hexyne (80.0 mmol). After being stirred at 80°C for 5 h, the mixture was cooled, filtered and concentrated. Water was added to the residue followed by Et_2O. Phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed several times with H_2O and eventually dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude product was purified by column chromatography on silica gel using as eluent 9:1 hexane/AcOEt (9.4 g of compound **6** (84% of yield); 8.6 g of compound **7** (85% of yield)).

To a stirred solution of the aldehyde **6** or **7**(45 mmol) in anhydrous THF (450 mL) was added dropwise at 0°C 18.0 mL of a 2 M solution of BuLi in pentane (36 mmol). After being stirred at 0°C for 2 h, the mixture was quenched with ice-water and then with a 10% solution of HCl to neutral pH. Phases were separated, and the aqueous layer extracted with Et_2O. The combined organic layers were washed with H_2O and brine, and then dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude product was purified by column

chromatography on silica gel using as eluent 8:2 hexane/AcOEt: **7** was a pale yellow oil (6.6 g, 60% with respect to starting aldehyde) and **6** was a yellow oil (7.1 g, 60% with respect to starting aldehyde).

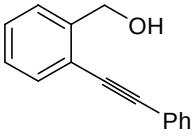
4.13: General procedure for cycloisomerization reaction.

A typical experimental procedure for the heterocyclisation of 2-alkynylbenzyl alcohols is described. To a mixture of metal catalyst (5% or 2%) and solid PEG (300 mg) were added to substrate **2** (0.13 mmol). The resulting mixture was heated by microwave irradiation at 150°C (initial power 400 W) for 30 min.

The reaction mixture was solubilized in CH_2Cl_2 (1.5 or 2.0 mL) and precipitated in Et_2O (200 mL). After 3h at -18°C, filtration of PEG /catalyst and evaporation of ether afforded the products **3** and **4** (measured by ^{1}H NMR using CH_2Br_2 as an internal standard).

4.14: Characterization of substrates and products.

2-(Phenylethynylphenyl)methanol (2)

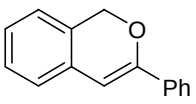


Pale yellow solid, 71%, m.p.: 67-68°C.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.56-7.52 (3H, m), 7.49 (1H, d, J = 7.4 Hz), 7.40-7.34 (4H, m), 7.31 (1H, dd, J = 1.4, 7.7 Hz), 4.93 (2H, s).

MS *m/e* = 208.

3-Phenyl-1*H*-isochromene (3)

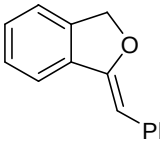


^{1}H NMR ($CDCl_3$): δ (ppm) 5.23 (2 H, s), 6.46 (1 H, s), 7.00-7.75 (9 H, m).

^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 69.0, 101.1, 123.4, 123.7, 125.0, 126.4, 128.0, 128.2, 128.3, 128.8, 132.0, 134.3, 154.1.

MS *m/e*: 208 (M+, 100).

(*Z*)-1-Benzylidene-1,3-dihydroisobenzofuran (4)

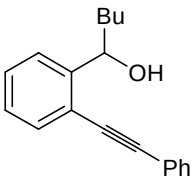


M.p: 51-54°C

^{1}H NMR ($CDCl_3$): δ (ppm) 7.74 (2H, d, J = 7.3 Hz), 7.59 (1H, m), 7.40-7.30 (5H, m), 7.14 (1H, t, J = 7.3 Hz), 5.96 (1H, s), 5.53 (1H, s).

MS *m/e*: 208.

1-(2-Phenylethynylphenyl)pentan-1-ol (8)



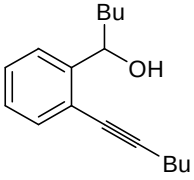
Yellow oil.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.53-7.45 (4H, m), 7.36-7.27 (4H, m), 7.19 (1H, td, J = 7.6, 1.5 Hz), 5.21 (1H, dd, J = 7.8, 5.4 Hz), 1.91-1.68 (2H, m), 1.56-1.24 (4H, m), 0.86 (3H, t, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$): δ (ppm) 147.0, 132.1, 131.4, 128.7, 128.4, 126.9, 125.4, 123.2, 120.5, 94.1, 87.3, 72.2, 38.1, 28.1, 22.6, 14.1.

MS *m/e* 264 (17, M+), 221 (21), 208 (21), 207 (100), 179 (29), 178 (65), 176 (13), 152 (9).

1-(2-Hex-1-ynylphenyl)pentan-1-ol (9)



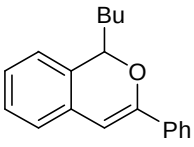
Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.45-7.40 (1H, m), 7.35 (1H, dd, J = 7.3, 1.5 Hz), 7.25 (1H, td, J = 7.3, 1.5 Hz), 7.14 (1H, td, J = 7.3, 1.5 Hz), 5.08 (1H, dd, J = 7.3, 5.4 Hz), 2.43 (2H, t, J = 6.8 Hz), 1.85-1.25 (10H, m), 0.95 (3H, t, J = 7.3 Hz), 0.89 (3H, t, J = 6.8 Hz).

^{13}C NMR ($CDCl_3$): δ (ppm) 146.8, 132.2, 127.9, 126.7, 125.3, 121.4, 95.3, 78.5, 72.4, 37.9, 30.9, 28.2, 22.6, 22.1, 19.2, 14.1, 13.6.

MS *m/e* 244 (5, M^+), 188 (16), 187 (100), 145 (16), 141 (13), 131 (17), 129 (11), 128 (11), 117 (25), 115 (27), 91 (10).

1-Butyl-3-phenyl-1*H*-isochromene (10)



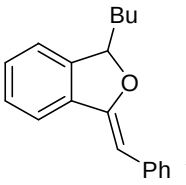
Yellow oil.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.78-7.71 (2H, m), 7.44-7.26 (3H, m), 7.20 (1H, td, *J* = 7.3, 1.5 Hz), 7.14 (1H, td, *J* = 7.3, 1.5 Hz), 7.06 (1H, distorted dd, *J* = 7.3, 1.5 Hz, 1H), 7.03–6.98 (1H, m), 6.39 (1H, s), 5.23 (1H, dd, *J* = 8.8, 4.4 Hz), 2.15-1.99 (1H, m), 1.84-1.70 (1H, m) 1.70-1.27 (4H, m), 0.91 (3H, t, *J* = 7.3 Hz).

^{13}C NMR ($CDCl_3$): δ (ppm) 151.6, 134.7, 131.7, 131.0, 128.6, 128.3, 127.7, 126.3, 125.0, 123.84, 123.78, 100.3, 78.2, 33.5, 27.6, 22.5, 14.1.

MS *m/e* 264 (15, M^+), 208 (16), 207 (100), 178 (22).

(*Z*)-1-Benzylidene-3-butyl-1,3-dihydroisobenzofuran (11)



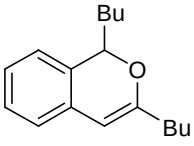
Yellow oil.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.78-7.72 (2H, m), 7.53-7.47 (1H, m), 7.36-7.23 (4H, m),7.22-7.16 (1H, m), 7.16-7.09 (1H, m), 5.88 (1H, s), 5.60 (1H, dd, *J* = 7.8, 3.9 Hz), 2.03-1.89 (1H, m), 1.82-1.67 (1H, m), 1.57-1.29 (4H, m), 0.90 (3H, t, *J* = 7.3 Hz).

^{13}C NMR ($CDCl_3$): δ (ppm) 155.5, 142.7, 136.7, 135.0, 128.6, 128.3, 128.1, 127.7, 125.1, 121.2, 119.9, 95.7, 86.1, 35.7, 27.1, 22.6, 14.0.

MS *m/e*: 264 (100).

1,3-Dibutyl-1*H*-isochromene (12)



Pale yellow oil.

^{1}H NMR ($CDCl_3$): δ (ppm) 7.13 (1H, td, *J* = 7.3, 1.5 Hz), 7.06 (1H, td, *J* = 7.3, 1.5 Hz), 6.92 (1H, dd, *J* = 7.3, 1.5 Hz), 6.88 (1H, dd, *J* = 7.3, 1.5 Hz), 5.55 (1H, s, br), 5.04 (1H, dd, *J* = 8.8, 4.9 Hz), 2.17 (2H, td, *J* = 7.6, 1.0 Hz), 2.05-1.91 (1H, m), 1.73-1.27 (9H, m), 0.92 (3H, t, *J* = 7.3 Hz), 0.91 (3H, t, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$): δ (ppm) 156.4, 131.2, 130.8, 127.6, 125.4, 123.8, 122.6, 99.9, 77.9, 33.8, 33.7, 29.1, 27.5, 22.6, 22.3, 14.0, 13.9.

MS *m/e* 244 (M^+).

Chapter 5

Synthesis of substituted furans and pyrroles by platinum or gold-catalyzed cycloisomerization reaction in PEG under MW irradiation

5.1: Introduction.

The development of routes that allow the facile assembly of substituted furans and pyrroles under mild conditions from simple readily available starting materials remains an important objective. A platinum and gold salts are a highly powerful catalysts for the intramolecular cyclization of 3-alkyne-1,2-diols and the 1-amino-3-alkyn-2-ols in solid PEG under microwave activation. PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations. This new method offers advantages over the known methods for the production of a wider range of substituted furans and pyrroles in excellent yields and the ready availability of the substrates, for the possibility to recover products after the simple precipitation- filtration method. Also the recyclability of catalytic system metal-PEG was tested and very interesting results were obtained. Unprecedented results were reported for platinum catalyzed cycloisomerization in PEG.

In second part we report, for the first time, the iodocyclization reaction of 3-alkyne-1,2-diols and the 1-amino-3-alkyn-2-ols in PEG under microwave irradiation. Iodocycloisomerization reaction offers the possibility to afford the corresponding iodo-derivatives. Also new reactivity was also presented.

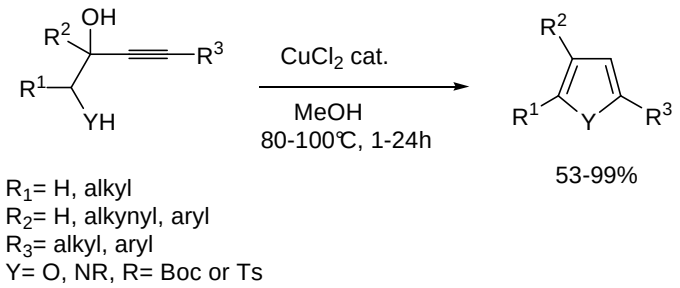
5.2: Bibliographic section.

The cycloisomerization reaction of 3-yne-1,2-diols to give the corresponding furans was previously reported under Cu,[216] Ag,[217-219] Au,[220-222] Ru,[223] Mo,[224, 225] or Pd[226] catalysis. In particular, mild and efficient reaction conditions have been recently developed under Au–Ag co-catalysis.

Also the cycloisomerization reaction of *N*-substituted 1-amino-3-yn-2-ols to give the corresponding pyrroles was previously reported to occur under palladium,[227] gold,[220-222] silver,[228] and copper[216, 229] catalysis.

In the next pages, we are presenting examples of metal-catalyzed cycloisomerization reaction using 3-yne-1,2-diols and 1-amino-3-yn-2-ols as the substrates.

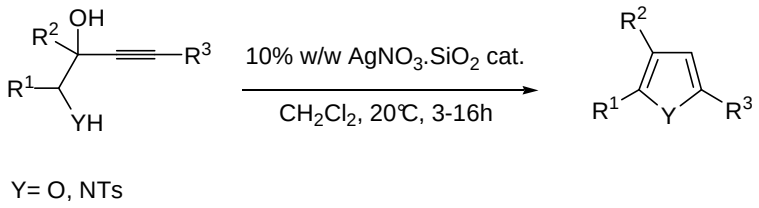
Gabriele and co-workers have described the $CuCl_2$-catalyzed synthesis of substituted furans and pyrroles by 5-*endo*-dig heterocyclodehydration of 3-yne-1,2-diols and *N*-Boc- or *N*-tosyl-1-amino-3-yn-2-ols.[216] Reactions were carried out in MeOH at 80–100°C for 1–24 h affording the corresponding heterocyclic derivatives in 53–99% isolated yields (Scheme 5.1).



Scheme 5.1: Synthesis of furans and pyrroles by copper catalysis.

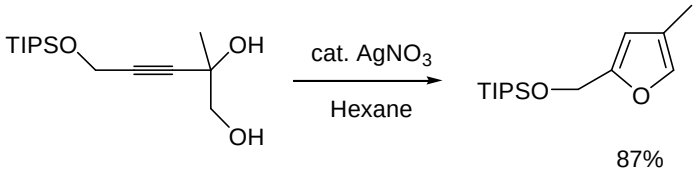
Knight and co-workers[217, 219] have improved an efficient furans and pyrroles synthesis using heterogeneous catalysis. A wide variety of 3-alkyne-1,2-diols have been found to undergo exceptionally clean 5-*endo*-dig cyclisations followed by dehydration at ambient temperature to give the corresponding furans in essentially quantitative yields when exposed to 10% w/w silver(I) nitrate absorbed on silica gel. Also a wide range of 3-alkynyl-hydroxyalkanamine derivatives undergo 5-*endo*-dig cyclisations when exposed to silver nitrate supported on silica gel. Subsequent *in situ* dehydration of the resulting and sometimes isolable hydroxy-dihydropyrroles leads to pyrroles in essentially quantitative yields using this recoverable and reusable heterogeneous catalyst.[228]

The 5-*endo*-dig cyclisations of the anti-γ-ynyl-β-hydroxy-α-amino esters give the hydroxy-dihydropyrroles and subsequently the related pyrroles, followed by elimination. The cycloisomerization can be performed without supported catalyst using copper (I), palladium (II) and mercury (II) salts. The reactions were carried out in 1:1 Et_2O-pyridine in sealed tubes at 90 °C (Scheme 5.2).[229]



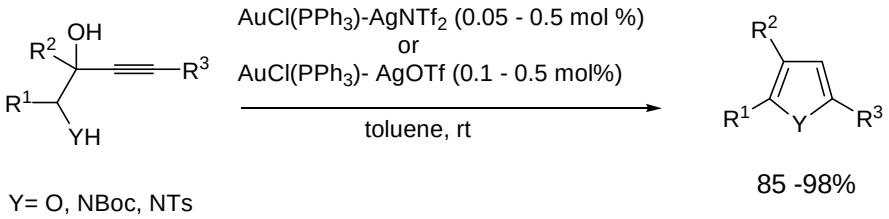
Scheme 5.2: Synthesis of furans and pyrroles by silver heterogeneous catalysis.

Silver catalysis was used for the functionalization of furan[218] under homogenous conditions (Scheme 5.3).



Scheme 5.3: Synthesis of furan by silver catalysis.

Akai and co-workers present the intramolecular cyclizations of the 3-alkyne-1,2-diols and the 1-amino-3-alkyn-2-ols with a low catalyst loading (0.05- 0.5 mol %) of AuCl(PPh_3)-$AgNTf_2$ or AuCl(PPh_3)-AgOTf proceeded at room temperature to provide a variety of substituted furans and pyrroles in excellent yields (85-98% yields). This method is also fully applicable to the conversion of several dozen grams of the substrate using only 0.05 mol % each of the Au and Ag catalysts.[230]

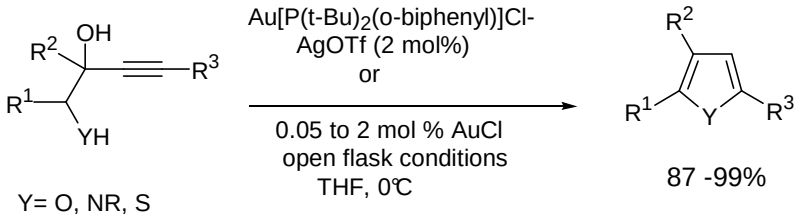


Scheme 5.4: Synthesis of furans and pyrroles by gold-silver catalysis.

The same group in 2011 has reported the reusable and durable immobilized-cationic gold (I) catalysts for environmentally benign bond-forming reactions. Polystyrene-immobilized cationic gold catalysts were synthesized for the first time and found to be highly effective catalysts for the bond-forming reactions via the activation of the C-C triple bonds. The

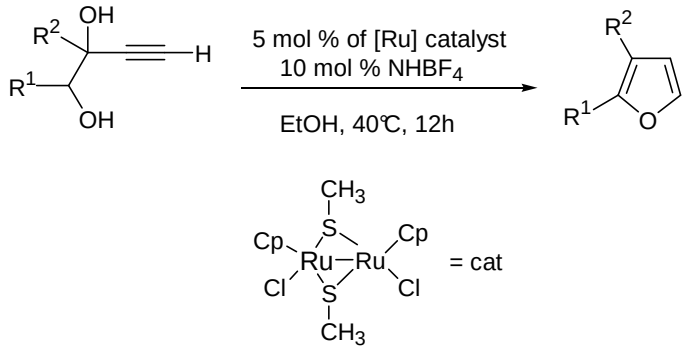
immobilized gold-catalyst was easily and quantitatively recovered from the reaction mixture and reused at least seven times while maintaining the original catalytic activity. Furthermore, a flow reactor containing gold-catalyst was developed for a larger scale continuous production.[221]

Aponick and co-workers have reported the gold-catalyzed dehydrative cyclizations of readily available, heteroatom-substituted propargylic alcohols to obtain furans, pyrroles, and thiophenes. The reactions are rapid, high-yielding, and procedurally simple, giving essentially pure aromatic heterocycles in minutes under open-flask conditions with catalyst loadings as low as 0.05 mol %.[222]



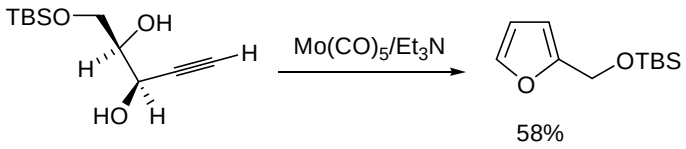
Scheme 5.5: Synthesis of furans and pyrroles by gold-silver catalysis.

Ruthenium-catalyzed intramolecular cyclization of 3-butyne-1,2-diols affords the corresponding substituted furans in good to high yields. This catalytic reaction is proposed to proceed via ruthenium-allenylidene complexes as key intermediates.[223] This method is valid for terminal alkynes to the triple bond in the substrate (Scheme 5.6).



Scheme 5.6: Synthesis of furans by ruthenium catalysis.

McDonald and co-workers have reported that molybdenum pentacarbonyl together with trimethylamine promotes the cyclization of 1-alkyn-4-ols to the isomeric 2,3-dihydrofurans (Scheme 5.7).[224, 225]



Scheme 5.7: Synthesis of furans by molybdenum catalysis.

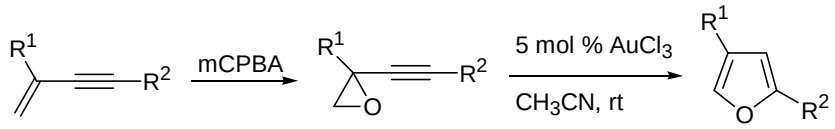
Pyrrole derivatives are prepared in high yields by the catalytic action of a Pd (II) salt on 1-amino-3-alkyn-2-ols which are obtained from conjugate ynones.[227]

A procedure is described for the synthesis of furans from 3-alkyn-1,2-diols or 2-methoxy-3-alkyn-1-ols by palladium catalyzed intramolecular addition of alcoholic moiety to acetylene linkage followed by elimination of water or methanol. The intermediary 3-furylpalladiums can be trapped with allyl halides affording 3-allylfurans in good yields.[226]

Classical approaches to substituted furans involved the cyclocondensation of dicarbonyl compounds or equivalents, or the substitution of an existing furan ring. Alternative route for the synthesis of furan and pyrrole rings used as starting materials alkynyl epoxides,[231, 232] alkynylaziridines,[52, 233] allenes,[42, 234-238] alkynes,[239, 240] sequential reactions,[241] amino acid derivatives,[242] unsaturated acetylenic ketones,[243] (*Z*)-2-En-4-yn-1-ols or (*Z*)-(2-En-4-ynyl)amines,[244-249] alkynyl diols,[250] enyne-1,6-diols,[251] propargylic alcohols,[252] methatesis[253] and different reviews described these transformations.[254-258]

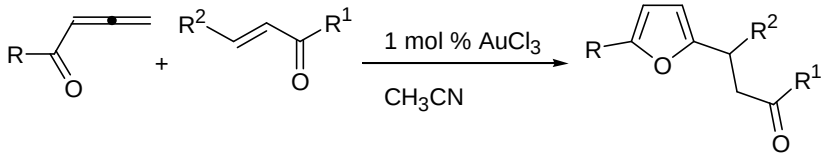
Here we present just some representative examples of these reactions.

Hashmi and co-workers have reported the gold (III) chloride catalyzed isomerization of alkynyl epoxides to furans under mild conditions.[232] The alkynyl epoxides were obtained by Sonogashira coupling to affording the 1,3-enynes followed by epoxidation of the latter with mCPBA leading to the alkynyloxiranes. The last one was added to a catalytic amount of $AuCl_3$ in acetonitrile at room temperature to give the corresponding furans (Scheme 5.8).



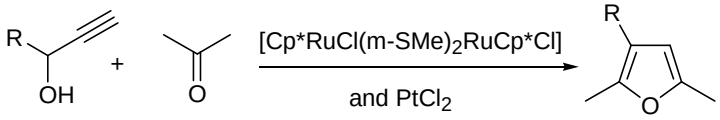
Scheme 5.8: Isomerization of alkynyl epoxides.

The same group also reported the gold-catalyzed reaction that combines both C-O and C-C bond formation and allows the selective cross coupling cycloisomerization/dimerization of terminal allenyl ketones and α,β-unsatured ketones (Scheme 5.9).[42]



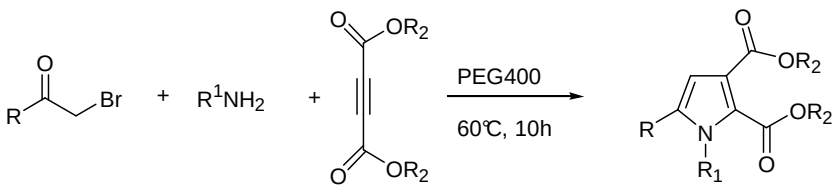
Scheme 5.9: Cross-dimerization with Michael acceptors.

Uemura and co-workers have reported a sequential reaction system by using heterobimetallic catalysts to give the corresponding tri- and tetra-substituted furans and pyrroles in moderate to high yields with complete regioselectivity from the reaction of propargylic alcohols with ketones in the presence of a catalytic amount of both ruthenium catalyst complex and $PtCl_2$.[241]



Scheme 5.10: Synthesis furans and pyrroles from propargylic alcohols and ketones.

One example described the synthesis pyrroles in PEG.[259] Nagarapu and co-workers have reported the synthesis of polysubstituted pyrrole derivatives by treatment of phenacyl bromides, an amine, and dialkyl acetylenedicarboxylate using PEG as a reaction medium (Scheme 5.11).



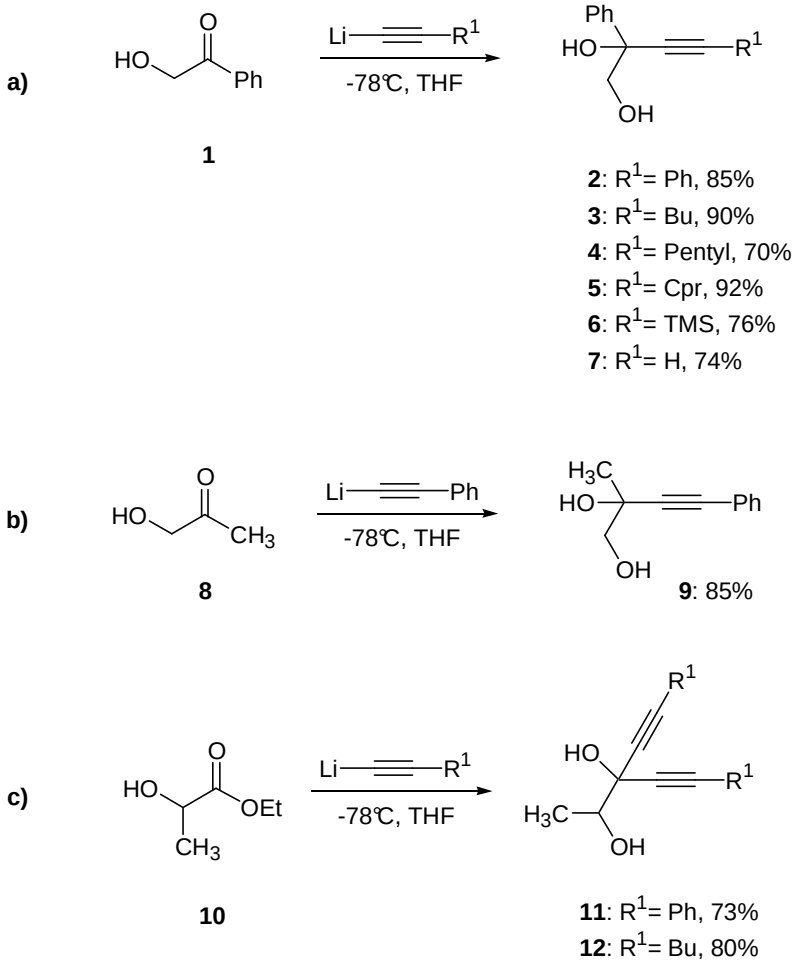
Scheme 5.11: Synthesis of pyrroles in PEG.

5.3: Results and discussions.

5.3.1: Metal catalyzed-cycloisomerization reaction of alkynyldiols.

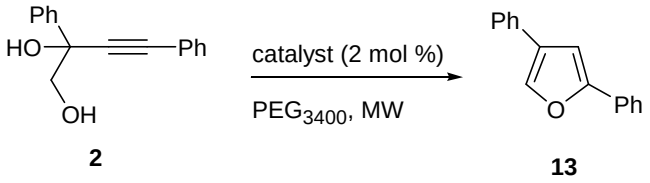
During the course of our studies we turned our interest on platinum and gold catalysis using an alternative solvent such as PEG.

Various alkynyldiols bearing a proton, aromatic and alkyl function at the end of the acetylene functionality, were readily prepared via alkynylation of α-hydroxy carbonyl compound such as α-hydroxyacetone **1**, α-hydroxyacetophenone **2** and (*S*)-α-hydroxypropionic acid ethyl ester **3** (Scheme 5.11, a, b, c).



Scheme 5.12: Synthesis of diol derivatives.

The first experiment was carried out using a mixture of poly(ethylene glycol), PEG_{3400}-OH, gold salts in oxidation state +3 ($AuCl_3$) and the substrate **2** (Scheme 5.13).



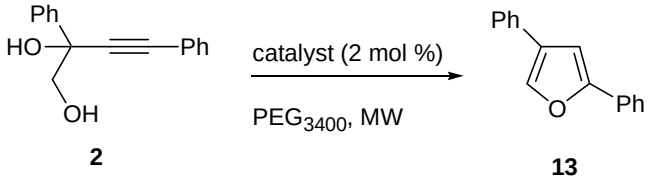
2 **13**

*Scheme 5.13: Cycloisomerization reaction of **2** in PEG.*

The reaction mixture composed by substrate **2**, catalyst and PEG_{3400} was heated up under microwave irradiation. When the temperature above 45°C was reached, PEG melts and becomes the solvent of reaction. The mixture was cooled down, dissolved in a small quantity of dichloromethane and precipitate in diethyl ether. After filtration, two fractions were obtained: the precipitate and the liquor. The precipitate is constituted by PEG and catalyst while the liquor, the organic phase, contains the expected product.
After 60 minutes at 50°C the expected furan **13** is present in the reaction mixture and recovered in 53% of yield (Table 5.1, entry 1). This first experiment has confirmed our initial hypothesis that cycloisomerization reaction can be carried out in solid PEG under microwave activation.

In order to increase the yield a silver species was added: AgOTf and $AgSbF_6$ were tested separately and in the same conditions of the first reaction, but no significant modification in terms of yield was obtained (Table 5.1, entries 2-3). We tried to decrease the reaction time from 60 to 30 minutes. Excellent results were achieved (Table 5.1, entry 4).

Table 5.1: Screening of the conditions for cycloisomerization.



2 **13**

Entry	Catalyst (mol %)	Additive (mol %)	T (°C)	Time (min)	Cooling	Conversion (%)	Yield[a] (%)
1	$AuCl_3$		50	60		100	53
2	$AuCl_3$	AgOTf	50	60		100	52
3	$AuCl_3$	$AgSbF_6$	50	60		100	52
4	$AuCl_3$		50	30		100	85
5	$AuCl_3$		50	30	On	100	79
6	$AuCl_3$		50	15		80	60
7	$AuCl(PPh_3)$		50	60		30	5
8	$AuCl(PPh_3)$	AgOTf	50	60		100	50
9	$AuCl(PPh_3)$	$AgSbF_6$	50	60		100	54
10	$AuCl(PPh_3)$	$AgSbF_6$	50	15		100	81
11	$AuCl(PPh_3)$	$AgSbF_6$	50	15	On	100	98
12 [b]	AgOTf		50	60		50	6
13 [b]	$AgSbF_6$		50	60		46	5
14	$PtCl_2$		50	15	On	0	0
15	$PtCl_2$		50	30	On	15	15
16	$PtCl_2$		80	15		100	70
17	$PtCl_2$		80	30		100	80
18	$PtCl_2$		80	30	On	100	83

a) determined by ^1H NMR using CH_2Br_2 as internal standard.

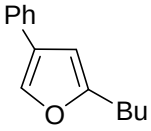
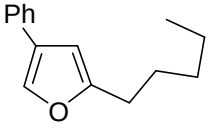
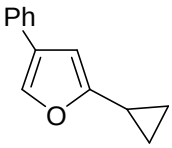
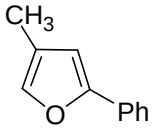
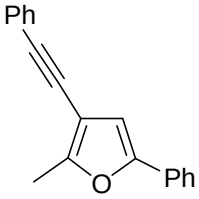
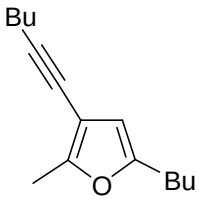
In the case of gold (I) it is necessary to use an additive such as silver species for a complete conversion of substrate. These additives create a cationic species more electrophilic that allowed a more efficient activation of substrate. The best results were obtained using gold (I) and silver hexafluoroantimoniate ($AgSbF_6$). On the contrary when the gold (I) or silver compounds alone were used, only traces of product **13** and different signals of degradation of substrate were observed (Table 5.1, entries 6-8). The combination of $AuCl(PPh_3)$ with $AgSbF_6$ presents a highly powerful catalyst for the intramolecular cyclization (Table 5.1, entry 10). The third catalyst tested was $PtCl_2$. We have tried the reaction at the same temperature used for the gold catalyst but in this case only substrate **2** or low conversion of the diol **2** was observed (Table 5.1, entries 14-15). Full conversion of substrate **2** was reached after 30 minutes at 80°C (Table 5.1, entry 17).

There, each experiment involving $AuCl_3$, $AuCl(PPh_3)/AgSbF_6$ and $PtCl_2$ was repeated heating up the sample with the technique of simultaneous cooling. In principle, it allows higher levels of MW energy to be introduced into a reaction while maintaing the mixture at a particular temperature by passing a stream of compressed air over the reaction vessel. Effectively, better results in comparison with classical microwave heating were obtained using $AuCl(PPh_3)/AgSbF_6$ as catalyst (Table 5.1, entry 11 and 16). This difference could be possibly attributed to the fact that the rate of decomposition of starting material is lower when using simultaneous cooling.

Ideal conditions to carry out the cycloisomerization reaction of substrate 2 were: 80°C for 30 min using 2 mol% of $PtCl_2$. For gold (I) and gold (III), the reaction was carried out at 50°C for 15 or 30 min respectively. All reactions require 300-350 mg of PEG_{3400}, 400W of initial power with technique of simultaneous cooling.

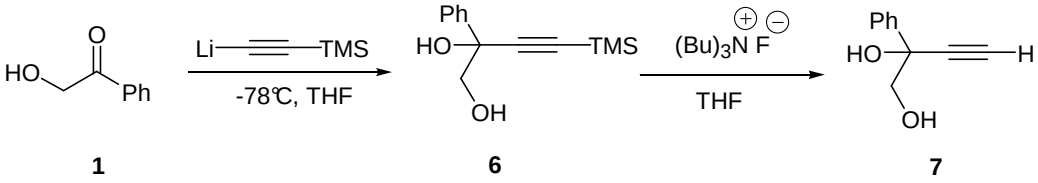
The optimized conditions were applicable to various alkynyl diols bearing aromatic or alkyl substituents at the end of the acetylene functionality. With this method it was possible to obtain di- or tri- substituted furans in good or excellent yields (Table 5.2). It is important to note that in the case of $AuCl_3$ as catalyst, all the reactions were carried out at 50°C for 15 minutes.

Table 5.2: Synthesis of substituted furans by platinum and gold-catalyzed cycloisomerization in PEG_{3400}.

Entry	Furans	$PtCl_2$ Yield (%)[a]	$AuCl_3$ Yield (%)[a]	$AuCl(PPh_3)/AgSbF_6$ Yield (%)[a]
1	 **14**	86	93	89
2	 **15**	75	81	90
3	 **16**	90	100	95
4	 **18**	70	80	94
5	 **19**	95	93	95
6	 **20**	86	93	96

a) determined by ^1H NMR using CH_2Br_2 as internal standard.

We turned our attention on alkynyl diols bearing a proton at the end of the acetylene functionality. The substrate **7** was prepared by addition of corresponding organolithium compound to α-hydroxyacetophenone **2** followed by deprotection of TMS group (Scheme 5.14).



1 **6** **7**

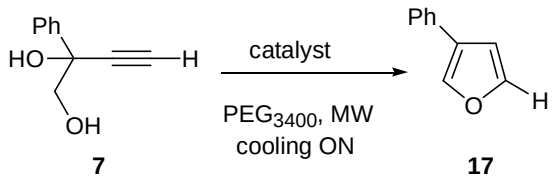
*Scheme 5.14: Synthesis of substrate **7**.*

Having optimized the reaction conditions for the synthesis of furans, we tested the reactivity to substrate **7** in PEG under microwave irradiation. With these conditions we can see the partial conversion of the substrate with the three catalytic systems constituted by platinum and gold (Table 5.3, entries 1, 4 and 7).

We extended the reaction time at 60 minutes at 50°C using gold (I)/silver (I) as catalyst but no complete conversion of diols **7** was reached (Table 5.3, entry 2). With 5 mol % of catalyst only the expected product was recovered (82%, Table 5.3, entry 3).
The ideal molar ratio between catalyst and substrate (5 mol %) was tested also with gold (III) as catalyst. The full conversion was achieved after 30 minutes at 50°C (81%, Table 5.3, entry 6).

Using platinum (II) as catalyst longer reaction times, 60 minutes, were needed and in this case the product was obtained in 60 % yield (Table 5.3, entry 10).

*Table 5.3: Screening of the conditions for cycloisomerization of substrate **7**.*



7 **17**

Entry	Catalyst (mol %)	Time (min)	°C	Conversion[a] (%) of **7**	Yield[a] (%) of **17**
1	$AuCl(PPh_3)/AgSbF_6$ (2)	15	50	40	25
2	$AuCl(PPh_3)/AgSbF_6$ (2)	60	50	60	40
3	$AuCl(PPh_3)/AgSbF_6$ (5)	60	50	100	82
4	$AuCl_3$ (2)	15	50	40	21
5	$AuCl_3$ (5)	60	50	100	65
6	$AuCl_3$ (5)	30	50	100	81
7	$PtCl_2$ (2)	30	80	50	19
8	$PtCl_2$ (2)	30	100	88	33
9	$PtCl_2$ (5)	30	70	100	50
10	$PtCl_2$ (5)	60	70	100	60

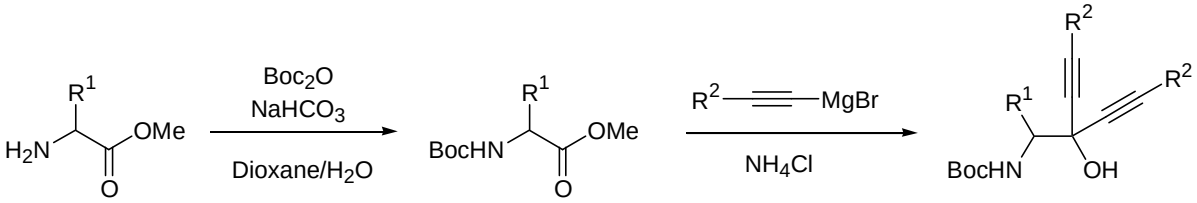
a) determined by ^1H NMR using CH_2Br_2 as internal standard.

Only using ruthenium and gold as catalyst, the intramolecular cyclization of the less reactive terminal alkynes was achieved to give the corresponding furan. This goal was also achieved using our system metal/PEG. In every cases the product was recovered after the simple precipitation-filtration in good yield.

The method described was general for the synthesis of substituted furans.

5.3.2: Metal catalyzed-cycloisomerization reaction of *N*-protected aminoalcools.

The good results obtained for the construction of furans were generalized for the synthesis of nitrogen heterocycles such as pyrroles. The *N*-protected aminoalcool is the substrate for the reaction, and it was prepared from various aminoacids such as alanine, leucine and phenylalanine, having the amine function protected by a Boc group. Then, the methylic ester was reduced in alcohol by reaction of Grignard reagent (Scheme 5.15).



21 R^1= iBu

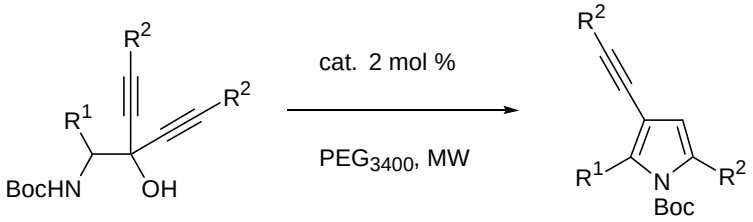
22 R^1=iBu, 95%
23 R^1=CH_3
24 R^1=benzyl

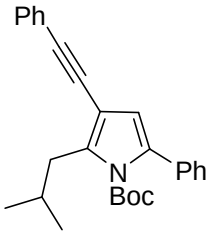
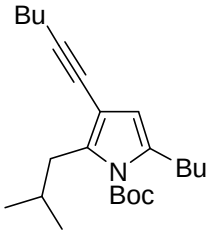
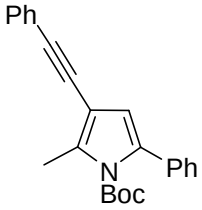
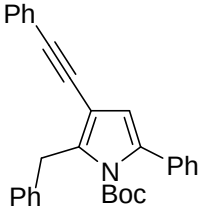
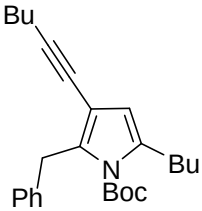
25 R^1= iBu, R^2= Ph, 57%
26 R^1= iBu, R^2= Bu, 53%
27 R^1= CH_3, R^2= Ph, 36%
28 R^1=benzyl, R^2= Ph, 40%
29 R^1= benzyl, R^2= Bu, 35%

Scheme 5.15: Synthesis of alkynyl aminoalcohols.

Using *N*-protected aminoalcools **25-29** as the substrates the cycloisomerization reactions were tested using the PEG_{3400} as solvent under microwave irradiation. The corresponding pyrroles **30-34** were obtained in good to excellent yields after the simple precipitation-filtration step of reaction mixture using platinum or gold as the catalysts (Table 5.4).

Table 5.4: Synthesis of substituted pyrroles by platinum and gold-catalyzed cycloisomerization in PEG_{3400}.



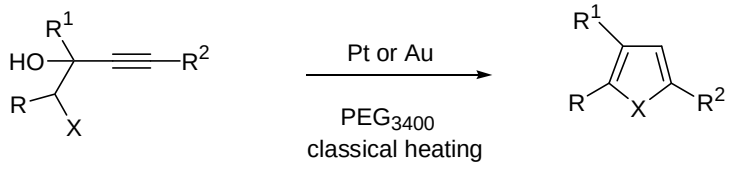
Entry	Pyrroles	$PtCl_2$ Yield (%)	$AuCl_3$ Yield (%)	$AuCl(PPh_3)/AgSbF_6$ Yield (%)
1	 **30**	67	85	76
2	 **31**	74	94	71
3	 **32**	80	85	84
4	 **33**	72	94	85
5	 **34**	78	88	65

a) determined by ^1H NMR using CH_2Br_2 as internal standard.

5.4: Comparison between microwaves and classical heating conditions.

In order to verify the effective efficiency of microwave heating we have tested some reactions using classical heating conditions.

Table 5.5: Reactions with classical heating conditions.



3 X= OH, R= H, R^1=Ph, R^2= Bu
26 X=NHBoc, R= iBu, R^1= CCPh, R^2= Ph

14 X= O, R= H, R^1=Ph, R^2= Bu
30 X=NBoc, R= iBu, R^1= CCPh, R^2= Ph

Entry	Substrate	Catalyst	Time (min)	°C	Conversion[a] (%)	Yield of product[a] (%)
1	**3**	$PtCl_2$	30	80	100	81
2	**3**	Au(I)/Ag(I)	15	50	84	80
3	**3**	$AuCl_3$	15	50	-[b]	-[b]
4	**26**	$PtCl_2$	30	80	17	15
5	**26**	$PtCl_2$	120	80	100	79

a) determined by ^{1}H NMR using CH_2Br_2 as internal standard. b) degradation.

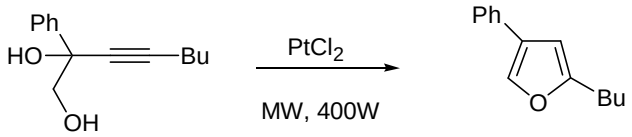
In the first experiment, we have tried the cycloisomerization reaction of substrate **3** at 80°C. After 30 minutes, we have observed the full conversion of the substrate and the formation of expected product **14** in 81% of yield (Table 5.5, entry 1).
When cycloisomerization was carried out at 50°C, the reaction mixture was not homogenous. Using cationic gold (I) the partial conversion of substrate **3** was observed. In the case of gold

(III) as catalyst, ^{1}H NMR analysis showed different signals of degradation (Table 5.5, entry 2-3). For substrate **26**, the full conversion was reached after 2 h at 80°C (Table 5.5, entry 5).
The microwave technique was the method of choice because PEG absorbes of microwaves and ensure rapid melting of the polymer during the reaction.

5.5: Recycling tests.

The previous works developed in the laboratory showed the possibility to recycle the precipitate constituted by PEG and the catalyst.[169, 170, 173] To explore here this possibility, the precipitate was charged with new substrate and heated under MW irradiation.
We have tried the cycloisomerization reaction with different molecular weight and modified PEG.
In Table 5.6 entry 1 it is shown the recycling of catalytic system Pt/PEG_{3400}-OH. The results for the second run are very good and suggest the possibility to further recycle the catalytic system. Indeed it is possible to reuse the catalytic system 3 times without loss of activity.

Table 5.6: Recycling experiments of PEGs- Pt system.



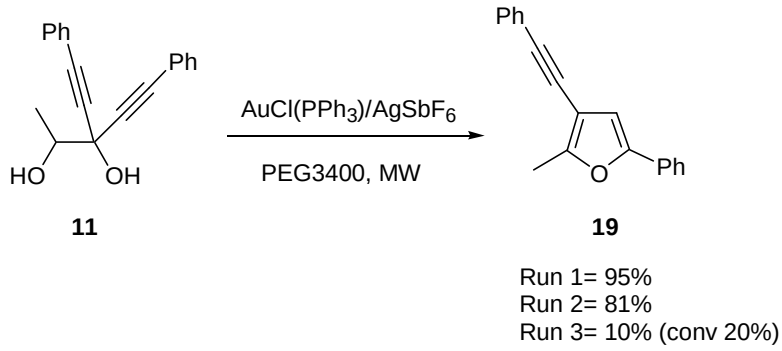
3 **14**

Entry	PEG	Yield of **14** (%)[a]					
		Run 1	Run 2	Run 3	Run 4	Run 5	Run 6
1	PEG_{3400}	86	91	82	92	28	17
2	PEG_{3400} Filtered	99	88	94	59[b]		
3	$PEG_{2000}(OMe)_2$	90	79	77	52[c]		

a) determined by ^{1}H NMR using CH_2Br_2 as internal standard. b) 64% of conversion; c) 54% of conversion.

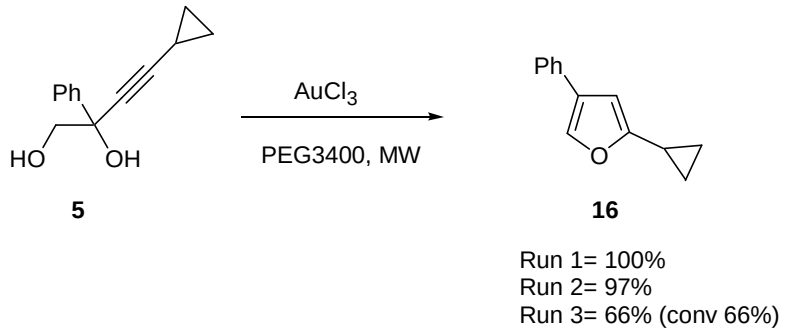
The same substrate **3** was tested using PEG_{3400} filtered before its use to eliminate small sized PEGs. This means that the commercially available PEG_{3400}-OH was dissolved in small amount of CH_2Cl_2 and precipitate in Et_2O. After filtration, the precipitate was used for the first run of cyclisomerization reaction. This operation was carried out in order to remove PEG with low molecular weight that can make some interferences during reaction. In entry 2 it is possible to see that the catalytic system was reused 2 times without loss of activity.
$PEG_{2000}(OMe)_2$ was also tested (Table 5.6, entry 3). The yield of product **14** was lower in comparison with reaction carried out with PEG_{3400} and the catalytic system was reused for 2 times without loss of activity.
The utilization of inexpensive PEGs together with a platinum salt, the efficiency in recycling and higher catalytic efficiency makes this system a more suitable and preferred one over the existing catalytic systems.

We have also studied the possibility to recycle the catalytic system constituted by PEG and gold (I) with the method described before. The substrate was added to the precipitate obtained in the first cycle of reaction and the crude was heated again under microwave irradiation. In this case it was possible to recycle the catalytic system one time without loss of activity (Scheme 5.16).



Scheme 5.16: Recycling experiments of PEG-Gold (I) system.

With the catalytic system constituted by gold (III) it is possible to perform one cycle of reaction (Scheme 5.17).



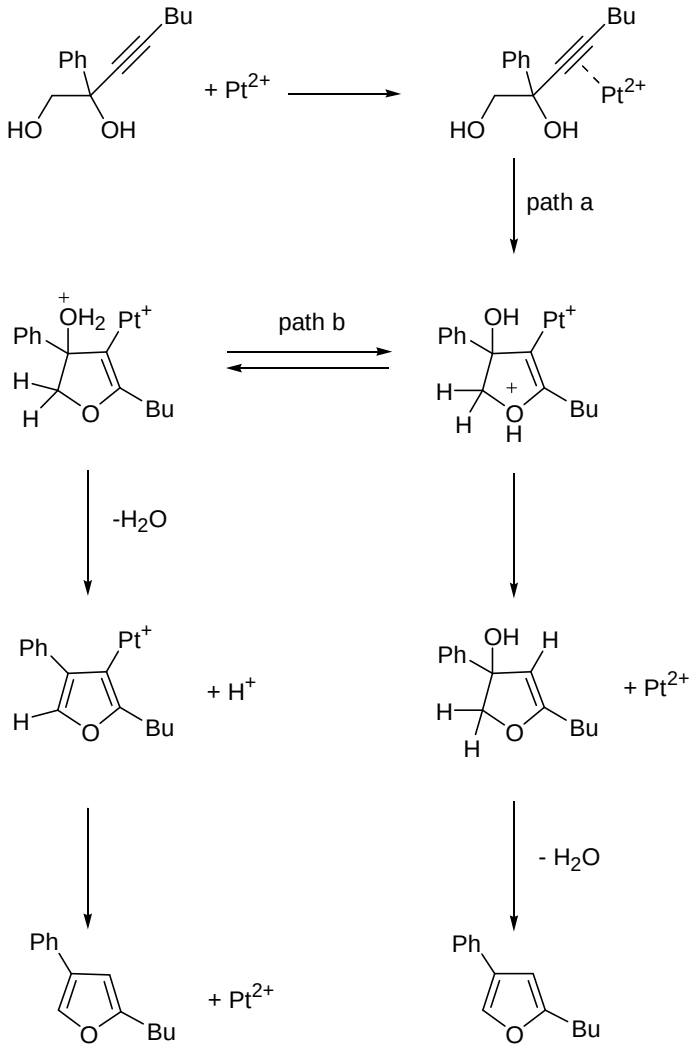
5 **16**

Run 1= 100%
Run 2= 97%
Run 3= 66% (conv 66%)

Scheme 5.17: Recycling experiments of PEG- gold(III) system.

5.6: Hypothetical mechanism of cycloisomerization reaction.

According to the literature[196] we suppose that the triple bond of the substrate coordinates the platinum to help the intermolecular 5-*endo*-dig nucleophilic attack of hydroxyl group on the triple bond. The intermediate I can be involved in two pathways: in the first one (path a) there is a protonolysis of carbon-platinum bond followed by dehydration with formation of the expected product. In the second pathway (path b) the intermediate is involved in the loss of one molecule of water, followed by protonolysis with formation of product and liberation of catalytic species Pt 2+.



Scheme 5.18: The plausible mechanism for the formation of heterocyclic derivatives.

5.7: Analysis section.

To study deeper the catalytic system, in order to understand the mechanism and to find the reason for the loss of activity of the catalytic system constituted by metal and PEG_{3400} we have used different analytical techniques such as TEM, ICP-MS, MALDI and XPS.

5.7.1: TEM analysis.

We have analyzed by transmission electron microscopy (TEM) a mixture of Pt/PEG_{3400}, $Au(I)/PEG_{3400}$ or $Au(III)/PEG_{3400}$ and we have observed the distribution and the size of nanoparticles (NPs) (Figure 5.1). The experimental results showed the formation of nanoparticles of platinum or gold supported and stabilized by PEG_{3400}-OH (Figure 5.1). From TEM images it was possible to determine that the size of platinum nanoparticles was around 5-7 nm.

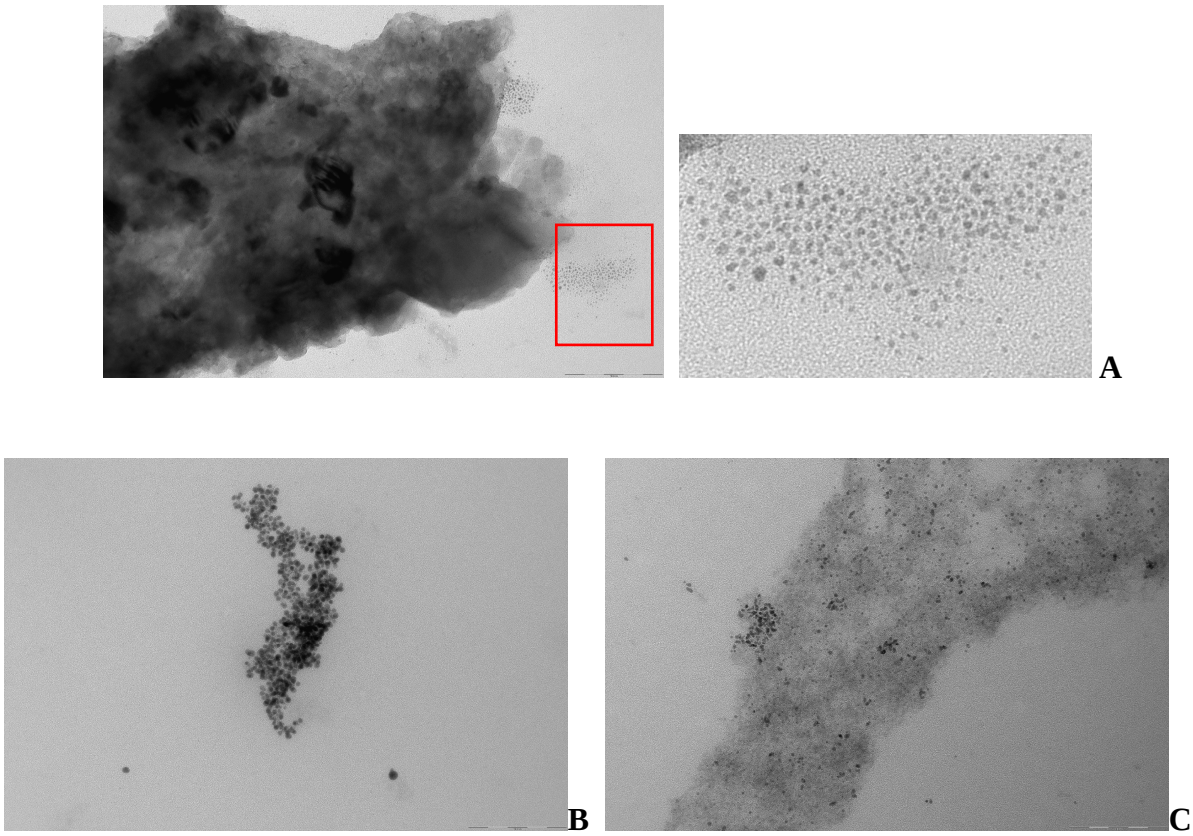


Figure 5.1: TEM imagines: NPs obtained from $PtCl_2$ (A), $AuCl_3$ (B) and $AuCl(PPh_3)/ AgSbF_6$ (C).

PEG chain prevents aggregation of metal nanoparticles wihich are stabilized and suitable for catalysis. However, deactivation of catalyst was still observed in PEG media in the absence of any other ligands probably because of leaching of metal.[260] Problem of leaching[261] is due to the loss of metal from the polymer matrix.

5.7.2: ICP-MS.

In order to determine the quantity of leaching, the product obtained after precipitation-filtration was analyzed by ICP-MS.

Inductively coupled plasma mass spectrometry (ICP-MS) is a type of mass spectrometry that is highly sensitive and capable to determine a range of metals and several non-metals at concentrations below one part per 10^{-12} (part per trillion).

Table 5.7: Results of ICP-MS

Entry	Metal	Run 1	Run 2	Run 3	Run 4
1	Pt (ppm)	4900	2100	-	460
2[a]	Au (ppm)	130	90	-	-
3[b]	Au (ppm)	140	-	-	-
4[b]	Ag (ppm)	80	-	-	-
5[b]	Sb (ppm)	80	-	-	-

a) calculated from $AuCl_3$, b) calculated from $AuCl(PPh_3)$, (-) not performed.

For the $PtCl_2$ as catalyst, leaching of metal occurs as shown by the analysis of furan **14** obtained by Pt-catalyzed cycloisomerization (Table 5.6, entry 1). After the first run, 4900 ppm of Pt were present in the product. In the second run the quantity of platinum was 2100 ppm (0.21%), and in the fourth run 460 ppm. This means that the leaching of metal is important and can reduce the efficacy of catalytic system, explaining why only for 4 runs could be performed.

When gold was the catalyst low degree of leaching was observed. The sample obtained after the first and the second run were presenting a quantity of gold (III) of 130 ppm and 90 ppm respectively (Table 5.7, entry 2). Almost the same quantity of gold was present in the filtrate after the first run, when the reaction was catalyzed by $AuCl(PPh_3)/AgSbF_6$ system. The

sample was also contaminated by 80 ppm of Ag and Sb (Table 5.7, entries 4-5). In this case, this limited loss cannot explain the failure of the recycling process.

5.7.3: XPS analysis.

PEG_{3400} obtained after filtration and precipitation was also analyzed using XPS technique (Figure 5.2).

X-ray photoelectron spectroscopy (XPS) is a quantitative spectroscopic technique that measures the elemental composition, empirical formula, chemical state and electronic state of the elements that exist within a material.

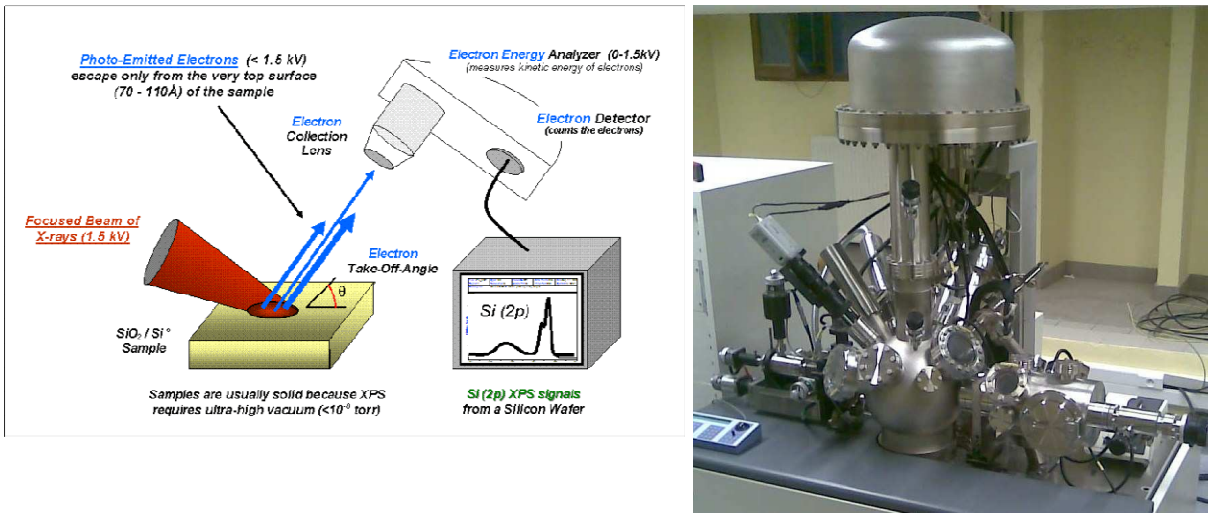


Figure 5.2: Mechanism and picture of XPS instrument.

The sample is irradiated with mono-energetic X-rays causing photoelectrons to be emitted from the sample surface. An electron energy analyzer determines the binding energy of the photoelectrons. From the binding energy and intensity of a photoelectron peak, the elemental identity, chemical state, and quantity of an element are determined. The information that XPS provides about surface layers or thin film structures is of value in many industrial applications including: polymer surface modification, catalysis, corrosion, adhesion, semiconductor and dielectric materials.

We decide to analyse the catalytic system $PtCl_2/PEG_{3400}$ by XPS, in order to detect the nature of the catalytic entity in the sample. We first analyzed a sample of $PtCl_2/PEG_{3400}$ prior to its use in the reaction (Figure 5.4, A). We could confirm, that only Pt (II) was present in the

sample, as demonstrated by the binding energy pic at 73.35 eV (Figure 5.3, A) corresponding to Pt 4f7/2 species, as reported in the literature.[59]

The mixture $PtCl_2/PEG_{3400}$ was then submitted to the first run of the cycloisomerization reaction and the precipitate obtained after work-up was analyzed again.

To our surprise, the binding energy pics associated to Pt (II) were detected together to another platinum species, that could be attributed being platinum at the elementar state Pt (0). More particularly, Pt (II) displays a binding energy at 73.15 eV (curve A), while Pt (0) has a binding energy at 71.76 eV (curve B).

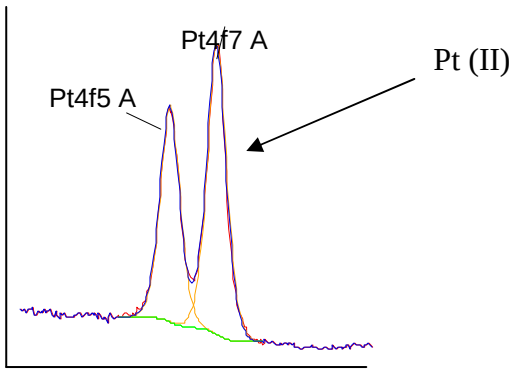


Figure 5.3.A: Platinum (II) before reaction.

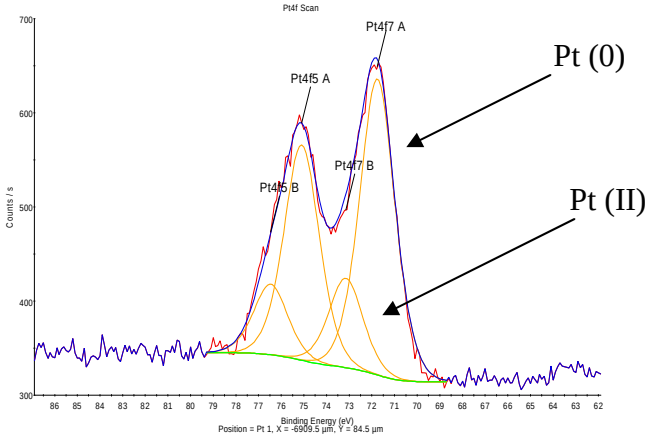
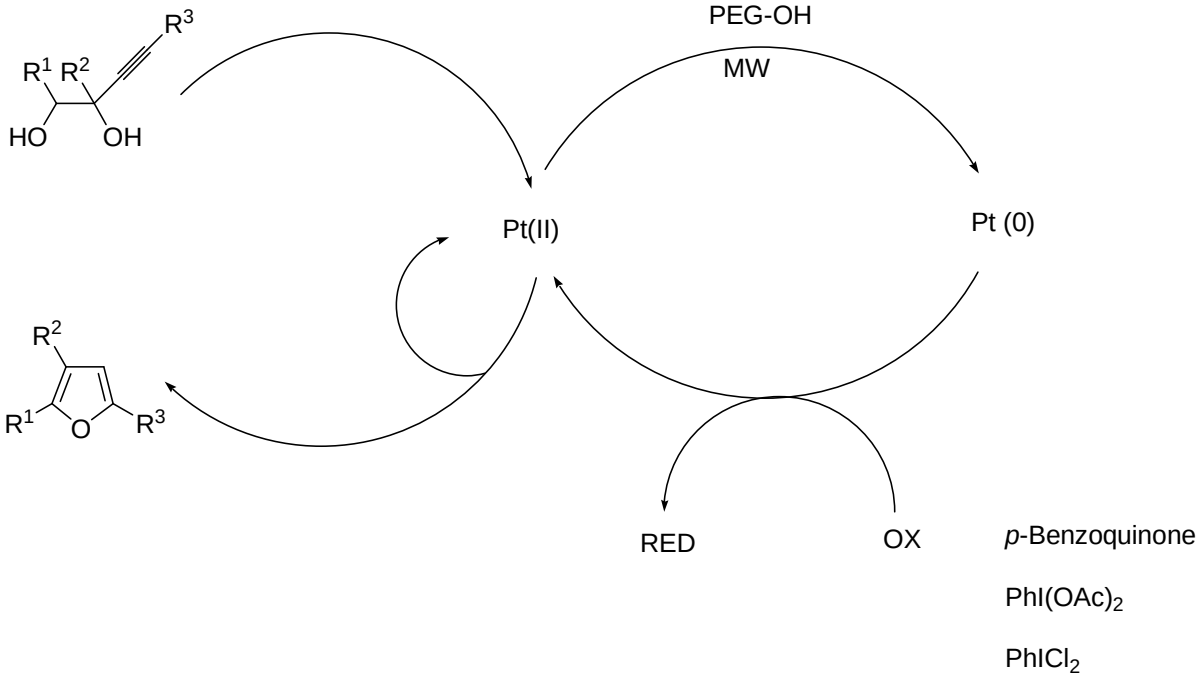


Figure 5.3.B: Platinum after first run of reaction.

If it is true from the mechanism previously described that at the end of the reaction the platinum (II) is regenerated in the end of reaction (Scheme 5.19), the formation of Pt (0) can be possible only if a secondary reaction occurs. It is known in the literature that when a noble

metal is added to ethylene glycol, a poly-ols system, the metal is reduced to its metallic oxidation state.[262-264] We suppose that the formation of Pt (0) is mediated by poly(ethylene) glycol.



Scheme 5.19: Catalytic cycle.

In fact Au, Pt, Pd, Ru and Ir nanoparticles with a narrow size distribution have been synthesized by chemical reduction of their corresponding metal species in ethylene glycol.[265] The electrooxidation of ethylene glycol (EG) gives a large variety of incomplete oxidation products such as glycolaldehyde, glyoxal, glycolic acid, glyoxylic acid and oxalic acid.[266] However, the analysis of PEG recovered after reaction by MALDI analysis should have been shown the presence of oxidation products, but unfortunately they could not be detected!

5.8: Oxidizing agents.

In order to increase the efficiency of the catalytic system, it is of peculiar importance to re-oxidate Pt (0) to Pt (II). The compounds used for oxidation of Pt catalyst inside our system are

organic oxidant such as p-benzoquinone and hypervalent iodine species. The choice is also due to environemental concerns, avoiding the use heavy metal as oxydants.

5.8.1: Hypervalent iodine reagents.

Iodine is large-sized halogen element, easily polarizable and low in electronegativity. It forms hypervalent organoiodanes beyond the octet theory by readily extending its valence.
The representative λ^3-organoiodanes are iodosylbenzene (polymer), (diacetoxyiodo)benzene, (dichloroiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, [hydroxy(tosyloxy)iodo]benzene (Koser reagent), *o*-iodosylbenzoic acid (Figure 5.4). They have been widely used as oxidants for active methylene groups, double and triple bonds, alcoholic and phenolic hydroxyl groups, sulphur and amino compounds.[267]

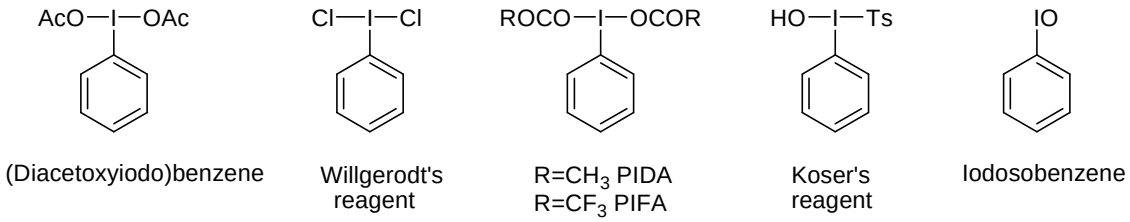


Figure 5.4: Representative hypervalent iodine (III) reagents.

The catalytic utilization of hypervalent iodine reagents, largely in consideration of economical and environmental viewpoints, is a most attractive strategy due to their unique features as extremely useful oxidants, with mild, safe, and environmentally friendly characteristics.[268]
Hypervalent iodine is as very mild oxidants for the conversion of alcohols to carbonyl compounds, which tolerates various functionalities on highly complex molecules. Hypervalent iodine compounds can improve the formation of carbon–carbon bonds in phenol coupling reactions[269] or as precursors in the synthesis of benzyne.
In addition, these reagents can form a range of carbon-heteroatom bonds, inducing rearrangements or fragmentations and consequently can activate carbon-hydrogen bonds. They are also potentially interesting reagents for the development of completely new synthetic transformations,[270, 271] and known to oxidate palladium and platinum species.[272]

5.8.2: Quinone compounds.

Quinone-hydroquinone redox systems have been studied extensively over many decades.[273] Quinones comprise a redox reaction of classical and current importance to organic and biological chemistry, and represent one of the oldest and most basic redox processes.[274] Moreover *p*-benzoquinone was also recognized as an oxidant for the metallic platinum.[275]

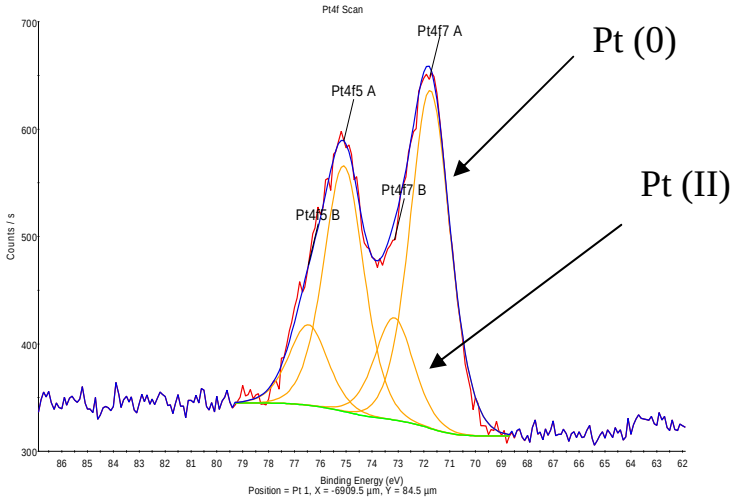


Figure 5.5.A: Before treatment with $PhICl_2$ as oxidant.

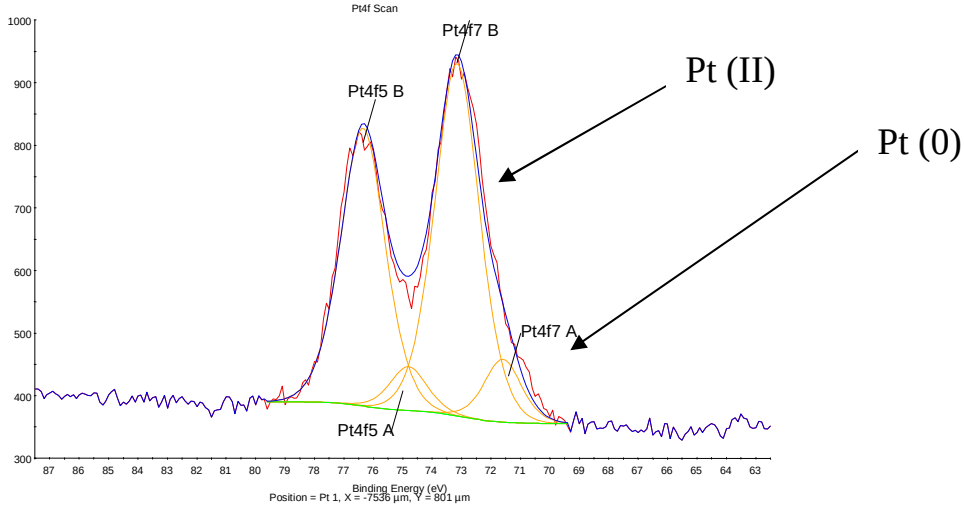


Figure 5.5.B: After treatment with $PhICl_2$ as oxidant.

In order to check if it was possible to re-oxidize Pt (0) to Pt (II) using one of these oxidants, the catalytic system $PtCl_2/PEG_{3400}$ issued after the first run and presenting Pt (0) species was recovered and used in a second run with substrate **3**. This time however the reaction was carried out in the presence of $PhICl_2$ as the oxidant. The precipitate obtained after the second run was analyzed again. As Figure 5.5 B, shown, the oxidation of Pt (0) to Pt (II) took place because the binding energy pic of Pt4f7/2 for Pt (0) [Figure 5.5, A] at 71.60 eV is extremely reduced with respect to curve associate to Pt (II) [Figure 5.5, B] at 73.15 eV.

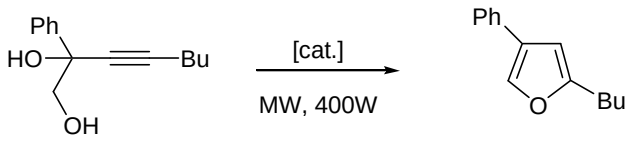
5.9: Recycling with oxidant.

The results obtained using the different types of oxidant are showed in the Table 5.8. In all case 3 mol % of oxidant with respect to the catalyst was used.
In the presence of *p*-benzoquinone as the oxidant the catalytic system could be recycled 4 times without any loss of activities (entry 2), while with $PhI(OAc)_2$ it was possible to perform only two cycles (entry 3).

In the case of gold (I) catalyst (entries 4-5) and in the presence of *p*-benzoquinone or $PhI(OAc)_2$, the product was obtained with good yield only in first reaction and was not possible to recycle the catalytic system. Less encouraging results were obtained with $PhICl_2$ (entry 6) as oxidant. The analysis of liquor showed different signals of degradetion and the yield of product is lower.

The reactions catalyzed by gold (III) were also explored in the presence of the three different oxidants (entries 7-9). *p*-Benzoquinone displayed the best results in terms of both yields and recycling efficiency (4 times).
However, in the case of gold-catalyzed reactions, the failure of recycling can be explained if we consider that its high oxidation potential[276] does not allow its re-oxidation.

Table 5.8: Recycling experiments of PEG_{3400}-metals system with oxidants.



3 **14**

Entry	Cat	Oxidant	Run1	Run2	Run3	Run4	Run5	Run6
1	$PtCl_2$	*p*-benzoquinone	80	90	87	98	89	40 (53)
2	$PtCl_2$	$PhI(OAc)_2$	64	69	75	38 (40)		
3	$PtCl_2$	$PhICl_2$	55	80	63	63	62	40
4	$Au(PPh_3)SbF_6$	*p*-benzoquinone	84	28 (30)	-	-	-	
5	$Au(PPh_3)SbF_6$	$PhI(OAc)_2$	57	27 (40)	-	-	-	
6	$Au(PPh_3)SbF_6$	$PhICl_2$	24	30	-	-	-	
7	$AuCl_3$	*p*-benzoquinone	83	89	89	87	92	18 (22)
8	$AuCl_3$	$PhI(OAc)_2$	65	90	41 (60)			
9	$AuCl_3$	$PhICl_2$	95	64	50	59 (77)		

Yield and conversion determined by ^1H NMR using CH_2Br_2 as internal standard. In parenthesis was reported conversion of substrate. Conditions of reaction: 2 mol % of $PtCl_2$, 6 mol % of oxidant, at 80°C to 30 min; 2 mol % of Au(I)/Ag(I) or Au(III), 6 mol % of oxidant, at 50°C to 15 min. Cooling, 400 W.

5.10: Conclusion.

In summary, we have described a novel catalytic system made of PEG and a transition metal (Pt or Au) for the cycloisomerization of alkynyl diols and amino alcohols. The cyclization is very effective with all substrates and catalysts. The heterocycles thus obtained can be efficiently separated from the reaction mixture by a precipitation/filtration technique and obtained with a high purity without the use of a purification by column chromatography. Furthermore the catalytic system can be used again in further experiments and its activity improved by oxidative modifications conditions using a catalytic amount of an oxidant such as benzoquinone.

Experimental section.

5.11: General remarks.

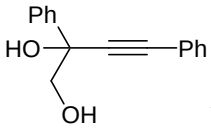
All commercially available compounds (Aldrich, Fluka, Chem) were used as received. The solvent used were purified by distillation over the drying agent. Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for ^{1}H and $CDCl_3$: δ = 77 ppm for ^{13}C. *J*- values are given in Hz. ^{1}H and ^{13}C NMR was registered on Bruker Avance DPX 200 MHz, Bruker AC-300 MHz, Bruker 400 MHz. Microwave-assisted reactions were performer with a Biotage Initiator^{TM} 2.0. Instrument. Temperature was measured with an IR sensor on the surface of the reaction vial. LC-MS: HPLC Waters Alliance 2695 (UV Waters 2489), column Onyx C_{18}, 25mn x 4.6 mn, flow 3 ml/min (H_2O-0.1% HCO_2H (A)/CH_3CN 0.1% HCO_2H (B)) gradient 0 to 100% in 2.5 min. HRMS analysis: Q-Tof (Waters, 2001) with ESI. XPS analysis was performed with a ESCALAB 250 Thermo Electron, monochromatic source Al Ka(1486.6 eV), C1s at 286.4 eV.

$PhICl_2$ was prepared according to the method reported in the literature.[277]

5.12: Preparation of alkynyldiols.

A solution of alkyne (19.23 mmol of 1-hexyne, phenylacetylene, cyclopropylacetylene, ethynyltrimethylsilane) in anhydrous THF (3 mL) was added dropwise under nitrogen to a stirred, cooled (-40°C) mixture of BuLi (12.1 mL of a 1.6 M solution in hexanes, 19.35 mmol) in anhydrous THF (9 mL) and anhydrous hexane (14 mL). To the resulting mixture, maintained at -40°C, was added, with stirring, a solution of LiBr (0.68 g, 7.8 mmol) in THF (3 mL). After 0.5 h, the corresponding hydroxyketone (7.34 mmol of α-hydroxyacetophenone **1** or α-hydroxyacetone **8**), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with Et_2O (x3). The combined organic layers were washed with water and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude that was purified by column chromatography on silica gel.

2,4-Diphenyl-but-3-yne-1,2-diol (2)



Yellow solid, yield 85 %, CAS number: 58294-83-0, m.p.102-104°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.72-7.68 (m, 2H), 7.53-7.50 (m, 2H), 7.44-7.30 (m, 6H), 3.87 (d, 1H, J = 11.2 Hz), 3.75 (d, 1H, J = 11.2 Hz), 3.48 (s, 1H), 2.59 (s, 1H).

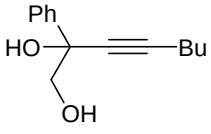
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 140.8, 131.9, 128.8, 128.4, 128.4, 128.3, 125.9, 122.1, 89.3, 86.6, 74.2, 72.

ESIMS *m/z* 221.1 $(M+H-H_2O)^+$, 261.1 $(M+Na)^+$

HMRS (ESI) calcd. for C16H13O $(M^+H-H_2O)^+$: 221.0964, found: 221.0966.

IR v: 3264, 2225, 1486, 1399, 1365, 1247, 1067, 1017 cm^{-1}

2-Phenyl-oct-3-yne-1,2-diol (3)



Yield 90%, yellow oil, CAS number: 63591-04-8.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.68-7.62 (m, 2H), 7.46-7.30 (m, 3H), 3.77 (d, 1H, 11 Hz), 3.68 (d, 1H, *J* = 11 Hz), 2.34 (t, 2H, *J* = 7.0 Hz), 1.59-1.37 (m, 4H), 0.96 (t, 3H, *J* = 7.0 Hz).

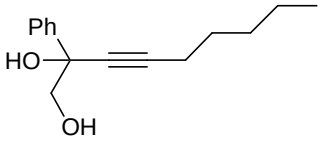
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 141.3, 128.2, 128.0, 125.9, 87.7, 80.5, 73.8, 72.3, 30.7, 22.0, 18.5, 13.6.

ESIMS *m/z* 219.2 $(M+H)^+$, 241.3 $(M+Na)^+$, 201.2 $(M+H-H_2O)^+$

HMRS (ESI) calcd. for C14H17O $(M+H-H_2O)^+$: 201.1274, found: 201.1279**.**

IR v: 3392, 2961, 2931, 2869, 2235, 1448, 1068, 697 cm^{-1}

2-Phenyl-non-3-yne-1,2-diol (4)



Yield: 70%, pale yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 7.58-7.53 (m, 2H), 7.35-7.19 (m, 3H), 3.68-3.50 (m, 2H), 2.96 (s, 1H), 2.23 (t, 2H, *J* = 7.0 Hz), 1.55-1.47 (m, 2H), 1.36-1.19 (m, 4H), 0.84 (t, 3H, *J* = 7.0 Hz).

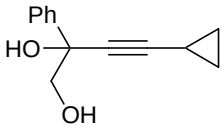
^{13}C NMR ($CDCl_3$, MHz): δ (ppm) 141.2, 128.3, 128.1, 125.9, 87.9, 80.4, 73.9, 72.3, 31.1, 28.3, 22.2, 18.8, 14.0

ESIMS *m/z* 233.3 $(M+H)^+$, 215.3 $(M+H-H_2O)^+$

HMRS (ESI) calcd. for C15H19O $(M+H-H_2O)^+$: 215.1446, found: 215.1436

IR v: 3392, 2957, 2930, 2239, 1746, 1448, 1068, 697 cm^{-1}

4-Cyclopropyl-2-phenyl-but-3-yne-1,2-diol (5)



Yield: 92 %, white solid

M.p. 60-64°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.56-7.49 (m, 2H), 7.33-7.21 (m, 3H), 3.64-3.48 (m, 2H), 3.04 (s, 1H), 2.26 (s, 1H), 1.31-1.21 (m, 1H), 0.80-0.59 (m, 4H).

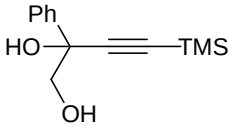
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 141.2, 128.3, 128.0, 125.8, 90.7, 75.6, 73.8, 72.2, 8.5, 8.4, -0.50.

ESIMS *m/z* 225.2 $(M+Na)^+$, 185.2 $(M+H-H_2O)^+$

HMRS (ESI) calcd. for C13H13O $(M+H-H_2O)^+$: 185.0959, found: 185.0966.

IR v: 3373, 2930, 2880, 2232, 1601, 1404, 1351, 1095, 1068, 1034, 929, 889 cm^{-1}

2-Phenyl-4-trimethylsilanyl-but-3-yne-1,2-diol (6)

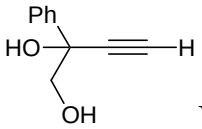


Yield: 76 %, yellow solid

IR v: 3422, 3258, 2955, 2250, 1684, 1600, 1403, 1250, 1017, 836, 694 cm^{-1}

2-Phenyl-but-3-yne-1,2-diol (7)

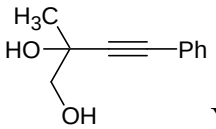
Tetrabutylammonium fluoride (4.3 mL of a 1.0 M solution in THF, 4.3 mmol) was added dropwise to a stirred solution of the foregoing silylated alkyne **6** (4.3 mmol) in THF (20 mL). After 20 min, during which time the colour of the solution change from yellow to brown, the bulk of the THF was evaporated and the residue taken up in ether and water (1:1 20 ml). The resulting layers were separated and the aqueous layer extracted with diethyl ether (3x 20 mL). The combined organic solution were dried, filtered and evaporated to leave a dark oil, which was purified by column chromatography.



Yield: 74 %, white solid.

IR v: 3329, 3272, 2997, 2919, 2116, 1489, 1438, 1242, 1211, 1083, 1071, 1040, 942, 919, 757 cm^{-1}

2-Methyl-4-phenyl-but-3-yne-1,2-diol (9)



Yield 85 %, pale yellow solid, CAS number : 39517-87-8, m.p. 95-98°C;

^{1}H NMR (CDCl3, 300 MHz): δ (ppm) 7.47-7.43 (m, 2H), 7.37-7.28 (m, 3H), 3.80 (d, 1H, J = 11.0 Hz), 3.62 (d, 1H, J = 11.0 Hz), 2.96 (s, 1H), 2.42 (s, 1H), 1.57 (s, 3H).

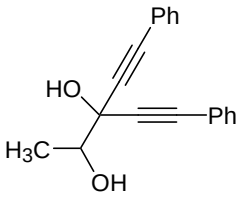
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 131.8, 128.6, 128.3, 122.2, 90.4, 84.5, 70.7, 69.0, 25.4.

ESIMS *m/z* 177.1 $(M+H)^+$

HMRS (ESI) calcd. for C11H11O $(M+H-H_2O)^+$: 159.0823, found: 159.0810.

IR v: 3392, 2977, 2930, 2235, 1598, 1574, 1490, 1280, 1134, 1048, 761 cm^{-1}

5-phenyl-3-phenylethynyl-pent-4-yne-2,3-diol (11)



Yield 73%, yellow solid, m.p. 105-107, CAS number: 309290-18-4

A solution of phenylacetylene or 1-hexyne (51.0 mmol) in anhydrous THF (8 mL) was added dropwise under nitrogen to a stirred, cooled (–78°C) mixture of BuLi (34 mL of a 1.6 M solution in hexanes, 54.4 mmol) in anhydrous THF (22 mL) and anhydrous hexane (34 ml). To the resulting mixture, maintained at – 78°C, was added, with stirring, a solution of LiBr (2.13 g, 24.5 mmol) in THF (7 mL). After 0.5 h, (*S*)-α-hydroxypropionic acid ethyl ester **10**, 2.01 g, 17 mmol), diluted in anhydrous THF (5 mL) was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 2 h, and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with Et_2O (x 3). The combined organic layers were washed with water and then dried oven $MgSO_4$. After filtration and evaporation of the solvent, the crude products **11** and **12** were purified by column chromatography.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.51-7.48 (m, 4H), 7.37-7.31 (m, 6H), 4,12 (q, 1H, J = 6.2 Hz), 3.47 (s, 1H), 2.68 (s, 1H), 1.55 (d, 3H, J = 6.2 Hz) .

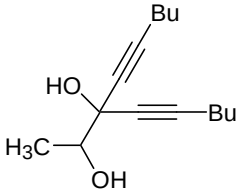
^{13}C NMR ($CDCl_3$, MHz): δ (ppm) 132.0, 131.9, 129.0, 128.9, 128.3, 128.3, 121.8, 121.7, 87.0, 85.9, 85.6, 85.1, 74.5, 68.8, 17.8.

ESIMS *m/z* 277.2 $(M+H)^+$, 299.2 $(M+Na)^+$, 269.2 $(M+H-H_2O)^+$, 575.1 $(2M+Na)^+$

HMRS (ESI) calcd. for C19H15O $(M+H-H_2O)^+$: 259.1128, found: 259.1123.

IR v: 3372, 3202, 2988, 2903, 2225, 1598, 1488, 1130, 1046 cm^{-1}

3-Hex-1-ynyl-non-4-yne-2,3-diol (12)



Yield 80%, pale oil yellow, CAS number: 371158-14-4

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 3.82 (q, 1H, J = 6.2 Hz), 2.92 (s, 1H), 2.35 (d, 1H, J = 5.4 Hz), 2.28-2.21 (m, 4H), 1.57-1.47 (m, 4H), 1.46-1.38 (m, 4H), 1.35 (d, 3H, J = 6.2Hz), 0.91 (t, 3H, J = 7.7 Hz), 0.91(t, 3H, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 86.1, 85.6, 78.9, 77.7, 74.4, 68.0, 30.5, 30.4, 22.0, 21.9, 18.4, 18.4, 17.5, 13.6.

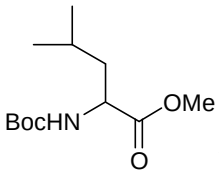
ESIMS *m/z* 237.2 $(M+H)^+$, 219.3 $(M+H-H_2O)^+$

HMRS (ESI) calcd. for C15H23O $(M+H-H_2O)^+$: 219.1746, found: 219.1749.

IR v: 3392, 2961, 2932, 2873, 2239, 1456, 1361, 1112, 1009, 889 cm^{-1}

5.13: Preparation of alkynyl aminoalcohols.

2-tert-Butoxycarbonylamino-4-methyl-pentanoic acid methyl ester (22)



Yield 95 %, colorless oil, CAS number: 69805-63-6

The methyl esther hydrochloride L-Leucine **21** (4.0 g, 22.1 mmol) was added to solution of $NaHCO_3$ (4.43 g, 52.8 mmol) in water (50 mL). Under stirring, was added dropwise to solution of $(Boc)_2O$ (5.23 g, 24 mmol) in dioxane (50 mL). The reaction was carried out at room temperature for 12h. The mixture was evaporated and the water layer was extracted with ether (x3). The combined organic layers were dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain product **22**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.91 (d, 1H, J = 7.8 Hz), 4.31-4.30 (m, 1H), 3.72 (s, 3H), 1.71-1.47 (m, 3H), 1.43 (s, 9H), 0.93 (d, 3H, J = 6.4 Hz), 0.95 (d, 3H, J = 6.4 Hz). 0.94 (d, 3H, J = 6.4 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 174.0, 155.4, 79.8, 52.1, 52.0, 41.8, 26.3, 24.8, 22.8, 21.9.

ESIMS *m/z* 246.3 $(M+H)^+$, 268.2 $(M+H+Na)^+$, 146.1 $(M+H-Boc)^+$, 491.3 $(2M+H)^+$

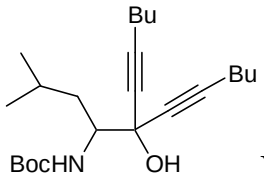
HMRS (ESI) calcd. for C12H24NO4 $(M+H)^+$: 246.1704, found: 246.1705

IR v: 3372, 2957, 2873, 1810, 1749, 1712, 1504, 1366, 1159, 1118, 1047 cm^{-1}

To a suspension of Mg turnings (600 mg, 24.86 mmol) in anhydrous THF (3.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.35 mL of EtBr in 12.0 mL of THF; total amount of EtBr added: 1.85 mL, 24.86 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the

solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of the 1-hexyne (2.9 mL, 24.86 mmol) in anhydrous THF (7.0 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was allowed to warm up to room temperature, maintained at 25 °C for 2 h, and then used as such for the next step. *N*-Boc-Leucine-OMe **22** or *N*-Boc-Phenylalanine-OMe **24** (5.1 mmol) was dissolved under nitrogen in anhydrous THF (7.0 mL) and then added dropwise to the solution of the 1-hexynylmagnesium bromide in THF (prepared as described above) at 25 °C under nitrogen. After stirring at 35 °C over night, the mixture was cooled to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with AcOEt. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude product. After filtration, the solvent was evaporated and the crude products **25** and **29** were purified by column chromatography on silica gel.

(2-Hex-1-ynyl-2-hydroxy-1-isobutyl-oct-3-ynyl)-carbamic acid tert-butyl ester (25)



Yield 57%, 1.1 g, oil pale yellow

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 4.62 (d, 1H, J = 10Hz), 3.9 (t, 1H, J = 10.5 Hz), 3.10 (s, 1H), 2.26-2.18 (m, 4H), 1.74-1.68 (m, 2H), 1.46 (s, 9H), 1.55-1.35 (m, 8H+1H), 0.97-0.89 (m, 12H).

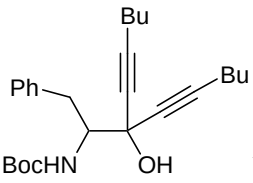
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.6, 79.6, 78.6, 67.7, 58.2, 40.1, 30.5, 30.4, 28.3, 25.0, 23.8, 22.0, 21.5, 18.4, 13.6.

ESIMS *m/z* 378.4 $(M+H)^+$, 360.4 $(M+H-H_2O)^+$, 755.6 $(2M+H)^+$, 777.5 $(2M+Na+H)^+$

HMRS (ESI) calcd. for C23H38NO2 $(M+H-H_2O)^+$: 360.2916, found: 360.2903**.**

IR v: 3440, 2956, 2934, 2869, 2235, 1698, 1502, 1366, 1247, 1162, 1025, 876 cm^{-1}

(1-Benzyl-2-hex-1-ynyl-2-hydroxy-oct-3-ynyl)-carbamic acid tert-butyl ester (29)



Yield 35%, solid white, m.p. 65-66°C

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.36-7.18 (m, 5H), 4.72 (d, 1H, J = 9.9 Hz), 4.17 (q, 1H, J = 7.0 Hz), 3.44 (m, 1H), 2.72 (m, 1H), 2.24-2.33 (m, 4H), 2.08 (s, 1H), 1.44-1.56 (m, 8H), 1.34 (s, 9H), 0.96 (t, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.2, 138.2, 129.2, 128.1, 126.3, 85.6, 79.7, 67.3, 61.0, 37.1, 30.5, 30.4, 28.2, 22.0, 22.0, 18.4, 13.6.

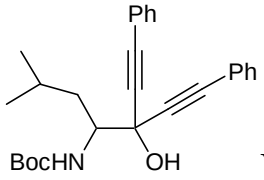
ESIMS *m/z* 412 $(M+H)^+$, 434.4 (M+Na)+, 394.3 $(M+H-H_2O)^+$

HMRS (ESI) calcd. for C26H36NO2 $(M+H-H_2O)^+$: 394.2758, found: 394.2746

IR v: 3382, 3318, 2934, 2869, 2228, 1663, 1601, 1528, 1490, 1355, 1254, 1159, 1063, 1063 cm^{-1}.

A solution of *N*-Boc-Leucine-OMe **22**, *N*-Boc-Phenylalanine-OMe **24** (5.1 mmol) in 7 mL of THF was added dropwise to solution of phenylethynyl magnesium bromide (20 mL, 1.0 M solution in tetrahydrofuran) at 25°C under nitrogen. After stirring at 35 °C over night, the mixture was cooled to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude. After filtration, the solvent was evaporated and the crude products **26** and **28** were purified.

(2-Hydroxy-1-isobutyl-4-phenyl-2-phenylethynyl-but-3-ynyl)-carbamic acid tert-butyl ester (26)



Yield 53%, yellow solid, m.p. 74-76°C

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.52-7.48 (m, 4H), 7.35-7.30 (m, 6H), 4.8 (d, 1H, J = 9.8 Hz), 4.18 (t, 1H, J = 9.9 Hz), 3.63 (s, 1H), 1.88-1.59 (m, 3H), 1.45 (s, 9H), 1.03 (t, 3H, J = 6.3 Hz), 1.01 (t, 3H, J = 6.3 Hz).

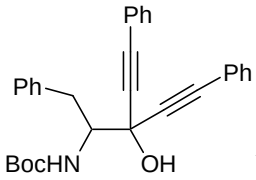
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.8, 132.0, 131.9, 128.8, 128.8, 128.3, 128.2, 122.0, 86.9, 80.0, 68.7, 58.4, 40.1, 28.3, 23.8, 21.6.

ESIMS *m/z* 400.2 $(M+H-H_2O)^+$, 835.5 $(2M+H)^+$, 300.3 $(M-H_2O\text{-Boc})^+$

HMRS (ESI) calcd. for C27H30NO2 $(M+H-H_2O)^+$: 400.2276, found: 400.2277.

IR v: 3383, 2985, 2935, 2230, 1663, 1527, 1489, 1354, 1253, 1156, 752 cm^{-1}

(1-Benzyl-2-hydroxy-4-phenyl-2-phenylethynyl-but-3-ynyl)-carbamic acid tert-butyl ester (28)



Yield 40%, solid white, m.p. 133-135°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.45-7.40 (m, 4H), 7.28-7.13 (m, 11H), 4.79 (d, 1H, *J* = 10.1 Hz), 4.33 (t, 1H, *J* = 9.6 Hz), 3.91 (s, 1H), 3.49 (d, 1H, *J* = 14.4), 2.8 (t, 1H, *J* = 14.0 Hz), 1.24 (s, 9H).

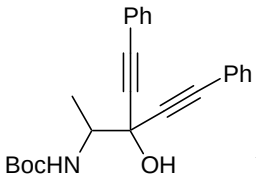
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.4, 137.9, 132.0, 129.2, 129.0, 128.9, 128.4, 128.3, 128.3, 126.4, 121.9, 87.0, 85.1, 80.1, 68.2, 61.1, 37.0, 28.2.

ESIMS *m/z* 451.2 $(M+H)^+$, 434.2 $(M+H-H_2O)^+$, 474.2 $(M+Na)^+$

HMRS (ESI) calcd. for C30H28NO2 $(M+H-H_2O)^+$: 434.2116, found: 434.2120.

IR v:3384, 3028, 2988, 2934, 2225, 1663, 1527, 1489, 1354, 1253, 1157, 1061, 915, 862 cm^{-1}

(2-Hydroxy-1-methyl-4-phenyl-2-phenylethynyl-but-3-ynyl)-carbamic acid tert-butyl ester (27)



Yield 36%, solid pale yellow, m.p. 107-110°C.

To a suspension of Mg turnings (470 mg, 19.6 mmol) in anhydrous THF (3.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.0 mL of EtBr in 12.0 mL of THF; total amount of EtBr added: 1.5 mL, 19.6 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of the phenylacetylene (2.0 g, 19.6 mmol) in anhydrous THF (7.0 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was allowed to warm up to room temperature, maintained at 25 °C for 2 h, and then used as such for the next step. *N*-Boc-alanine-OMe **22** (1.0 g, 4.9 mmol) was dissolved under nitrogen in anhydrous THF (7.0 mL) and then added dropwise to the solution of the phenylethynylmagnesium bromide in THF (prepared as described above) at 25 °C under

nitrogen. After stirring at 35 °C over night, the mixture was cooled to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with AcOEt. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **27**. After filtration, the solvent was evaporated and the crude product **27** was purified by column chromatography on silica gel.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.51-7.48 (m, 4H), 7.34-7.27 (m, 6H), 4.94 (d, 1H, J = 8.8 Hz), 4.27 (m, 1H), 3.97 (s, 1H), 1.48 (d, 3H, J = 6.8 Hz), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 156.4, 132.0, 131.9, 128.8, 128.8, 128.3, 128.2, 122,0, 86.7, 84,8, 84.6, 80.2, 68.6, 55.7, 28.4, 17.1.

ESIMS *m/z* 378.4 $(M+H)^+$, 360.4 $(M+H-H_2O)^+$, 755.6 $(2M+H)^+$, 777.5 $(2M+Na+H)^+$

HMRS (ESI) calcd. for C24H24NO2 $(M+H-H_2O)^+$: 358.1811, found: 358.1807.

IR v: 3384, 2988, 2934, 2228, 1662, 1527, 1489, 1354, 1253, 1157, 1016 cm^{-1}

5.14: Procedure for heterocyclization.

Procedure for the Pt-catalyzed heterocyclisation

A typical experimental procedure for the heterocyclisation of 1,2-diols is described. To a mixture of $PtCl_2$ (0.7 mg, 0.0026 mmol) and PEG_{3400}-OH (300 mg) were added to substrate **3** (28.3 mg, 0.13 mmol). The resulting mixture was heated by microwave irradiation at 80°C (initial power 400W and cooling ON) for 30 min.

The reaction mixture was solubilized in CH_2Cl_2 (1.5 or 2.0mL) and precipitated in Et_2O (150 mL). After 3h at -18°C, filtration of PEG_{3400}-OH/catalyst and evaporation of ether afforded pure 2-Butyl-4-phenyl-furan **(14)** in 86 % of yield (measured by ^{1}H NMR using CH_2Br_2 as an internal standard).

Procedure for the $AuCl_3$-catalyzed heterocyclisation

A typical experimental procedure for the heterocyclisation of 1,2-diols is described. To a mixture of $AuCl_3$ (0.0026 mmol) and PEG_{3400}-OH (300 mg) were added to substrate **3** (28.3 mg, 0.13 mmol). The resulting mixture was heated by microwave irradiation at 50°C (initial power 400W and cooling ON) for 15 min.

The reaction mixture was solubilized in CH_2Cl_2 (1.5 or 2.0 mL) and precipitated in Et_2O (150 mL). After 3h at -18°C, filtration of PEG_{3400}-OH/catalyst and evaporation of ether afforded

pure 2-butyl-4-phenyl-furan **(14)** in 93 % of yield (measured by ^{1}H NMR using CH_2Br_2 as an internal standard).

Procedure for the $AuCl(PPh_3)/AgSbF_6$-catalyzed heterocyclisation

A typical experimental procedure for the heterocyclisation of 1,2-diols is described. To a mixture of $AuCl(PPh_3)$ (1.3 mg, 0.0026 mmol) and $AgSbF_6$ (0.9 mg, 0.0026 mmol) and PEG 3400-OH (300 mg) were added substrate **3** (28.3 mg, 0.13 mmol). The resulting mixture was heated by microwave irradiation at 50°C (initial power 400 W and cooling ON) for 15 min. The reaction mixture was solubilized in CH_2Cl_2 (1.5 or 2.0mL) and precipitated in Et_2O (150mL). After 3h at -18°C, filtration of PEG_{3400}-OH/catalyst and evaporation of ether afforded pure 2-butyl-4-phenyl-furan **14)** in 89 % of yield (measured by ^{1}H NMR using CH_2Br_2 as an internal standard).

5.15: Procedure for to recycle catalytic system.

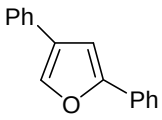
A typical experimental procedure for the recycle to the catalytic system constituted by metal and PEG is described. The substrate **3** (28.3 mg, 0.13 mmol) was added to the precipitate PEG_{3400}/metal obtained after the precipitation-filtration. The mixture was heated under microwave irradiation to give pure product 2-butyl-4-phenyl-furan **(14)** in 91% of yield (measured by ^{1}H NMR using CH_2Br_2 as an internal standard).

Procedure for to recycle catalytic system using an oxidant.

A typical experimental procedure for the recycle to the catalytic system constituted by metal and PEG using as oxidant is described. The substrate **3** (28.3 mg, 0.13 mmol) was added to the precipitate PEG_{3400}/Metal, obtained after the precipitation-filtration, and an oxidant (respectively $PhICl_2$ or $PhI(OAc)_2$ or *p*-Benzoquinone 0.0078 mmol). The mixture was heated under microwave irradiation to give the product 2-butyl-4-phenyl-furan **(14).**

5.16: Characterization of products.

2,4-Diphenyl-furan (13)



Yellow solid, m.p 104-106°C, CAS number: 5369-55-1

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.78-7.72 (m, 3H), 7.43-7.40 (m, 2H), 7.34-7.27 (m, 6H), 6.99 (s, 1H)

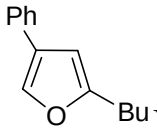
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 154.9, 137.9, 132.4, 130.7, 128.8, 128.7, 128.4, 127.6, 127.1, 125.8, 123.9, 104.0.

ESIMS *m/z* 221.1 $(M+H)^+$

HMRS (ESI) calcd. for C16H13O $(M+H)^+$: 221.0961, found: 221.0966

IR v: 3055, 3035, 1608, 1537, 1486, 1453, 1146, 912, 745 cm^{-1}

2-Butyl-4-phenyl-furan (14)



Yellow oil. CAS number: 63591-11-7.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.51 (s,1H), 7.40-7.37 (m, 2H), 7.27-7.25 (m, 2H), 7.18-7.13 (m, 1H), 6.23 (s, 1H), 2.58 (t, 2H, J = 7.7 Hz), 1.61-1.54 (m, 2H), 1.34-1.27 (m, 2H), 0.87 (t, 3H, J = 7.3 Hz).

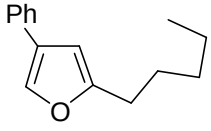
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 157.8, 136.6, 133.0, 128.8, 127.6, 127.0, 126.7, 125.7, 104.0, 30.1, 27.9, 22.3, 13.9.

ESIMS *m/z* 201.1 $(M+H)^+$

HMRS (ESI) calcd. for C14H17O $(M+H)^+$: 201.1253, found: 201.1279

IR v: 2957, 2930, 2863, 1770, 1601, 1551, 1449, 1128, 928, 739 cm^{-1}

2-Pentyl-4-phenyl-furan (15)



Oil yellow, CAS number: 250586-24-4.

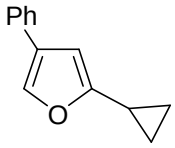
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.51 (s, 1H), 7.37-7-40 (m, 2H), 7.25-7.30 (m, 2H), 7.13-7.18 (m, 1H), 6.23 (s, 1H), 2.56 (t, 2H, J = 7.5 Hz), 1.58-1.63 (m, 2H), 1.27-1.30 (m, 4H), 0.83 (t, 3H, J = 7 MHz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 157.8, 136.5, 132.9, 128.7, 126.1, 126.7, 125.7, 104.0, 31.4, 28.1, 27.6, 22.4, 14.0.

ESIMS *m/z* 215.1 $(M+H)^+$

IR v: 2950, 2927, 2859, 1770, 1601, 1547, 1449, 1368, 1129, 926, 746 cm^{-1}

2-Cyclopropyl-4-phenyl-furan (16)



White solid m.p 64-66°C

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.45-7.12 (m, 5H+1H), 6.19 (s, 1H), 1.88-1.79 (m, 1H), 0.85-0.83 (m, 4H).

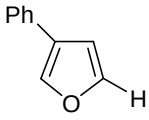
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 158.5, 136.2, 132.8, 128.7, 127.0, 126.7, 125.6, 102.7, 8.8, 6.6.

ESIMS *m/z* 185.3 $(M+H)^+$

HMRS (ESI) calcd. for C13H13O $(M+H)^+$: 185.0970, found: 185.0966**.**

IR v: 3058, 3011, 2920, 1760, 1601, 1550, 1449, 1126, 943, 802 cm^{-1}

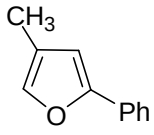
4-phenyl-furan (17)



Yellow oil, CAS number: 13679-41-9

IR v: 2922, 2857, 1753, 1600, 1496, 1448, 1247, 1099, 949, 755, 693 cm^{-1}.

4-Methyl-2-phenyl-furan (18)



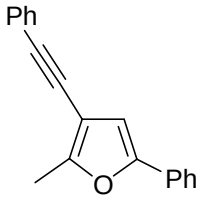
Yellow oil, CAS number: 39517-83-4.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.57-7.54 (m, 2H), 7.29-7.26 (m, 2H), 7.18-7.13 (m, 2H), 6.45 (s, 1H), 1.98 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 153.8, 138.9, 131.1, 128.6, 127.1, 123.6, 122.0, 107.7, 9.9.

IR v: 2930, 2873, 1770, 1598, 1446, 1099, 914 cm^{-1}

2-Methyl-5-phenyl-3-phenylethynyl-furan (19)



Yellow solid, m.p. 65-68°C.

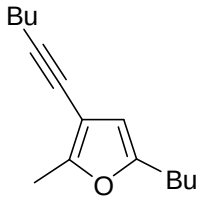
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.57-7.54 (m, 2H), 7.45-7.42 (m, 2H), 7.33-7.25 (m, 5H), 7.20-7.14 (m, 1H), 6.59 (s, 1H), 2.43 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 155.9, 151.9, 131.4, 130.3, 128.7, 128.3, 128.0, 127.4, 123.6, 123.5, 107.6, 105.3, 92.1, 81.6, 13.0.

ESIMS *m/z* 259.2 $(M+H)^+$

IR v: 3059, 2928, 2213, 1598, 1488, 1236, 926, 751 cm^{-1}

5-Butyl-3-hex-1-ynyl-2-methyl-furan (20)



Oil yellow, CAS number: 958230-87-0

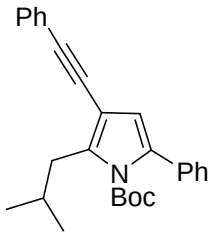
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.88 (s, 1H), 2.49 (t, 2H, J = 6.9 Hz), 2.36 (t, 2H, J = 7.5 Hz), 2.30 (s, 3H), 1.60-1.32 (m, 8H), 0.94 (t, 3H, J = 7.2 Hz), 0.93 (t, 3H, J = 7.3 Hz)

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 154.0, 153.4, 107.6, 103.6, 92.0, 72.8, 31.0, 30.0, 27.5, 22.1, 22.0, 19.2, 13.8, 13.6, 12.5.

ESIMS *m/z* 219.3 $(M+H)^+$, 437.3 $(2M+H)^+$

IR v: 2961, 2930, 2866, 1776, 1581, 1463, 1365, 1122, 950, 798 cm^{-1}

2-Isobutyl-5-phenyl-3-phenylethynyl-pyrrole-1-carboxylic acid tert-butyl ester (30)



Oil yellow

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.40 (m, 2H), 7.27-7.16 (m, 8H), 6.18 (s, 1H), 2.85 (d, 2H, *J* = 7.1 Hz), 2.01-1.88 (m, 1H), 1.13 (s, 9H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 6.6 Hz).

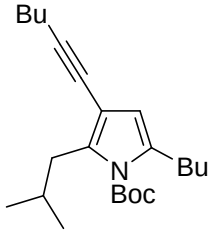
^{13}C NMR ($CDCl_3$, 75 MHz): δ 149.6, 140.7, 134.5, 134.3, 131.2, 128.3, 128.3, 127.9, 127.0, 124.1, 113.7, 106.6, 91.1, 84.5, 84.10, 35.8, 29.7, 27.2, 22.6.

ESIMS *m/z* 400.2 $(M+H)^+$, 300.1 $(M+H\text{-Boc})^+$, 799.4 $(2M+H)^+$

HMRS (ESI) calcd. for C27H30NO2 $(M+H)^+$: 400.2271, found: 400.2277

IR v: 2956, 2930, 2869, 2212, 1741, 1601, 1480, 1319, 1298, 1153, 1133, 846, 753 cm^{-1}

5-Butyl-3-hex-1-ynyl-2-isobutyl-pyrrole-1-carboxylic acid tert-butyl ester (31)



Oil pale yellow

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 5.87 (s, 1H), 2.79 (2H, *J* = 7.2 Hz), 2.72 (t, 2H, *J* = 7.7 Hz), 2.39 (t, 2H, *J* = 6.8 Hz), 1.87-1.82 (m, 1H), 1.60 (s, 9H), 1.60-1.33 (m, 8H), 0.97-0.89 (m, 12H).

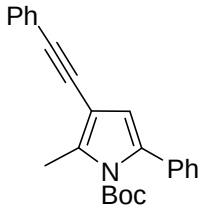
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 150.0, 137.9, 135.3, 111.3, 107.1, 91.3, 83.6, 75.3, 36.3, 31.1, 29.4, 29.0, 27.9, 22.3, 21.9, 19.2, 14.0, 13.6.

ESIMS *m/z* 360.4 $(M+H)^+$, 304.3 $(M+H\text{-}(t\text{-Bu}))^+$, 719.7 $(2M+H)^+$

HMRS (ESI) calcd. for C23H38NO2 $(M+H)^+$: 360.2895, found: 360.2903

IR v = 2956, 2927, 2873, 1738, 1533, 1463, 1318, 1165, 1120, 850 cm^{-1}

2-Methyl-5-phenyl-3-phenylethynyl-pyrrole-1-carboxylic acid tert-butyl ester (32)



Oil pale yellow

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.44-7.41 (m, 2H), 7.25-7.17 (m, 8H), 6.16 (s, 1H), 2.53 (s, 3H), 1.18 (s, 9H).

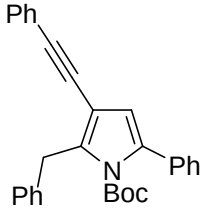
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 149.6, 137.0, 134.6, 134.3, 131.3, 128.5, 128.3, 127.9, 127.7, 127.1, 123.9, 114.1, 106.0, 91.4, 84.1, 83.8, 27.3, 14.1

ESIMS *m/z* 358.2 $(M+H)^+$, 258.2 $(M+H\text{-}Boc)^+$

HMRS (ESI) calcd. for C24H24NO2 $(M+H)^+$: 358.1801, found: 358.1807

IR v: 2981, 2920, 2849, 2212, 1741, 1482, 1369, 1323, 1287, 1153, 1132 cm^{-1}

2-Benzyl-5-phenyl-3-phenylethynyl-pyrrole-1-carboxylic acid tert-butyl ester (33)



Oil yellow

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.41-7.38 (m, 2H), 7.21-7.06 (m, 13H), 6.24 (s, 1H), 4.39 (s, 2H), 0.94 (s, 9H).

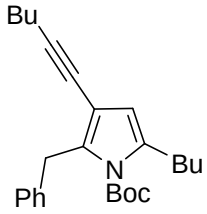
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 149.3, 139.6, 138.7, 134.8, 134.2, 131.4, 128.5, 128.4, 128.3, 127.9, 127.8, 127.2, 126.1, 123.9, 113.6, 107.1, 91.3, 84.2, 83.9, 32.5, 26.9.

ESIMS *m/z* 434.2 $(M+H)^+$, 334.3 $(M+H\text{-}Boc)^+$, 867.4 $(2M+H)^+$

HMRS (ESI) calcd. for C30H28NO2 $(M+H)^+$: 434.2097, found: 434.2120.

IR v = 3031, 2981, 2212, 1742, 1598, 1454, 1480, 1331, 1290, 1152, 1129, 689 cm^{-1}

2-Benzyl-5-butyl-3-hex-1-ynyl-pyrrole-1-carboxylic acid tert-butyl ester (34)



Oil yellow pale.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.18-7.13 (m, 2H), 7.08-6.98 (m, 3H), 5.88 (s, 1H), 4.26 (s, 1H), 2.65 (t, 2H, J = 7.0 Hz), 2.28 (t, 2H, J = 7.0 Hz), 1.54-1.28 (m, 8H), 1.24 (s, 9H), 0.84 (t, 3H, J = 7.3 Hz), 0.81 (t, 3H, J = 7.3 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 149.6, 140.5, 135.9, 135.6, 128.1, 127.9, 125.7, 111.4, 107.8, 91.8, 83.8, 74.7, 33.1, 31.1, 28.8, 27.5, 22.5, 22.0, 19.3, 14.0, 13.6.

ESIMS *m/z* 394.3 $(M+H)^+$, 338.2 $(M+H\text{-}t\text{-}Bu)^+$, 787.5 $(2M+H)^+$

HMRS (ESI) calcd. for C26H36NO2 $(M+H)^+$: 394.2742, found: 394.2746

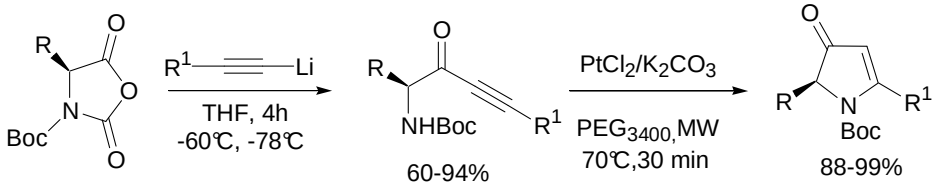
IR v: 2957, 2931, 2866, 2219, 1740, 1537, 1372, 1322, 1127 cm^{-1}

Chapter 6

Versatile UNCAs: synthesis of chiral α-amino-ynone derivatives and their subsequent Pt-catalyzed cycloisomerisation under MW activation in PEG

6.1: Introduction.

In this chapter, we present the original use of urethane *N*-protected carboxyanhydrides of amino acids (UNCAs) as building blocks. In first attempt we tested the addition of organometallics compound to the UNCAs. The ring opening gave in only one step, by controlling temperature and stoichiometry, the product of mono addition: the chiral α-amino-ynone. This versatile route yields to a family of these derivatives with different substituents on the alkyne moiety.



We report also unprecedent results regarding the metal catalyzed cycloisomerization reaction of α-amino-ynones into pyrrolin-4-ones using PEG as solvent under microwave irradiation. These heterocyclic structures may have a pharmacological interest may be inserted as non-peptide peptidomimetic scaffold.

6.2: Bibliographic section.

UNCAs (urethane *N*-protected carboxyanhydrides of amino acids) represent a unique class of stable, isolable and preactivated amino acid derivatives (Figure 6.1).[278]

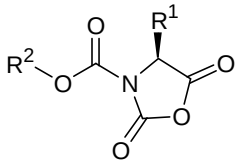


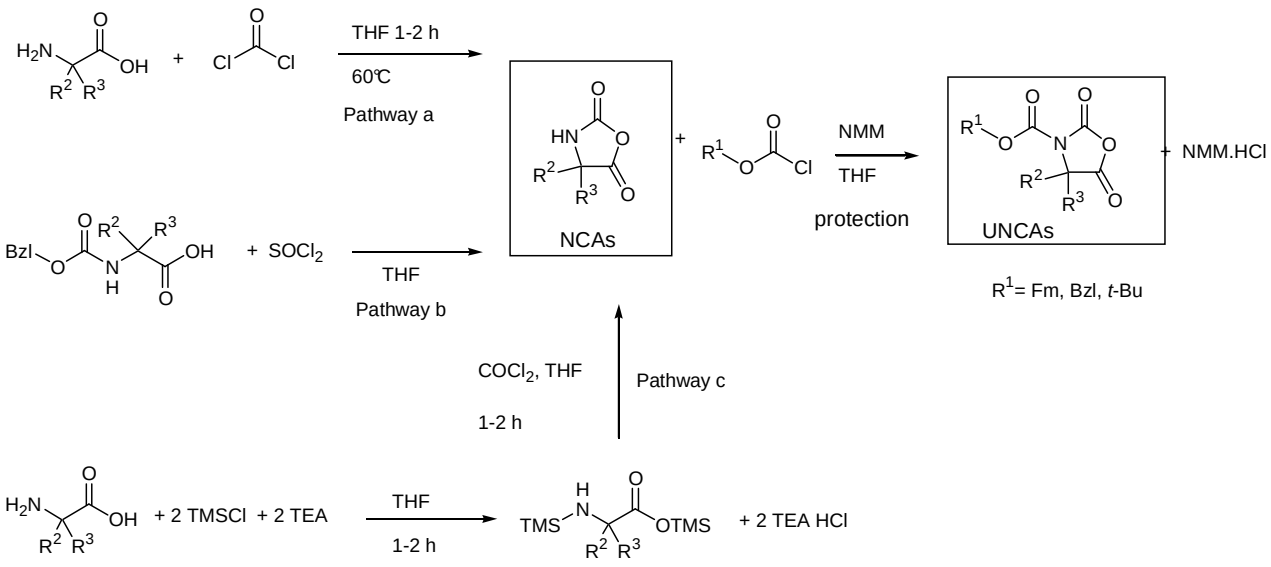
Figure 6.1: Urethane N-protected carboxyanhydrides of amino acids.

The history of these activated acid anhydrides started when Leuchs in 1906 reported the first synthesis of amino acid *N*-carboxyanhydrides (NCAs) followed by polymerization for obtaining poly amino acids.[279]

One of the major problem in the use of NCAs for other proposes was the polymerization. The solution came with the introduction of urethane *N*-protected carboxyanhydrides of amino acids (UNCAs).[280]

The urethane carboxyanhydrides of amino acid (NCAs) are readily prepared by using either direct phosgenation (Scheme 6.1, pathway a), the Leuchs procedure (Scheme 6.1, pathway b), or phosgenation of bis-trimethylsilyl amino acids (Scheme 6.1, pathway c).[281]

The formation of urethane *N*-protected carboxyanhydrides of amino acids (UNCAs) by protection of amino function was achieved by the condensation of acylating reagents (acyl halides, chloroformates, anhydrides, etc.) with NCAs in aprotic solvents such as THF, EtOAc, or CH_2Cl_2 in the presence of N-methylmorpholine (NMM), a base that does not readily promote polymerization or ring-open of the NCAs (Scheme 6.1).[282]



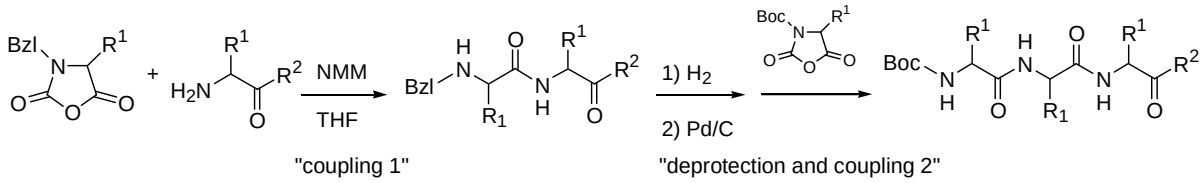
Scheme 6.1: Three methods for the synthesis of α-amino acid N-carboxyanhydrides followed by N-protection for obtaining a urethane protected α-amino acid N-carboxyanhydride.

UNCAs, crystalline solid, are very reactive and can be involved in a wide array of chemical processes such as organic synthesis and peptide chemistry.

In this part we will examine different applications on the use of urethane protected α-amino acid N-carboxyanhydrides.

UNCAs can be used for the synthesis of peptides in solution, on solid support and without use of organic solvents by mechanical activation.[283]

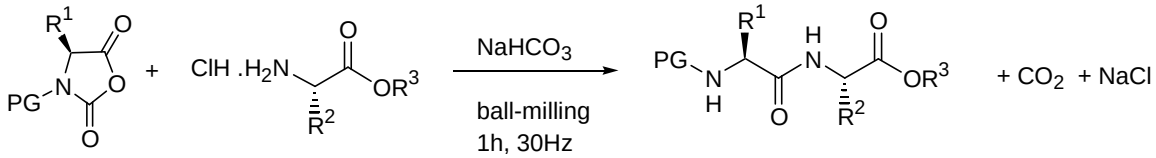
The peptide synthesis in solution was carried out using THF, DMF, toluene, DMA, NMP, acetonitrile, DMSO, glacial acetic acid and relative mixtures of these solvents.[284]



Scheme 6.2: One-pot synthesis of a tripeptide by the use of Z-protected amino acid N-carboxyanhydride.

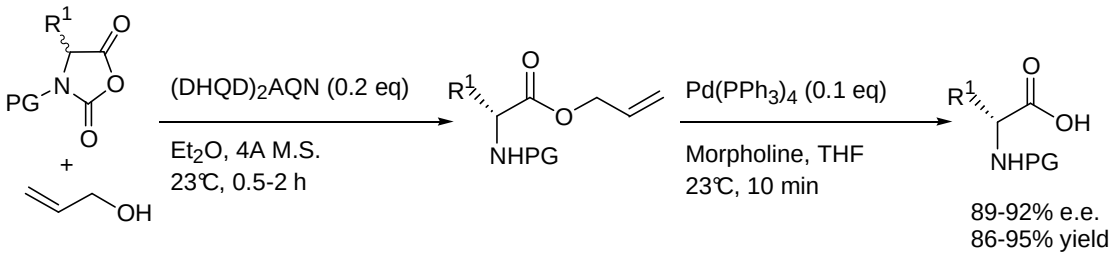
The protected tripeptides are formed in consecutive steps: the coupling the UNCAs via an aminoacid; one-pot deprotection of the dipeptide followed by coupling (coupling 2) with a new UNCA, without need to remove by-products, in most cases, the deprotecting reagents (Scheme 6.2).

New strategies were developed in order to avoid the use of solvents in the peptide synthesis. Lamaty and co-workers have improved the synthesis of dipeptides or tripeptides using a solvent free approach realized by mechanical activation (ball milling conditions) (Scheme 6.3).[283] The method showed the versatility of UNCAs in relationship with an eco-sustainable chemistry.



Scheme 6.3: Synthesis of dipeptides under solvent-free conditions.

UNCAs are used as the synthons for the asymmetric synthesis of a large number of α-aryl amino acids (Scheme 6.4). The synthesis involved by dynamic kinetic resolution of racemic α-aryl UNCAs catalyzed by modified cinchona alkaloid ($(DHQD)_2AQN$).[285, 286]



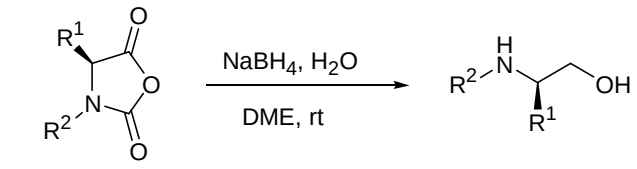
Scheme 6.4: Kinetic resolution of racemic UNCAs.

Extensive studies on the reactivity of UNCAs were developed by Martinez and coworkers. These studies point out the superb reactivity of UNCAs and their usefulness in the synthesis of aminoacid derivatives.

In particular they have described the versatility of these derivatives to access to various compounds such as β-amino alcohols, statine precursors, β-γ-dicarbonyl amino acids etc.

A convenient and attractive one-pot synthesis of β-amino alcohols by chemoselective reduction of UNCAs with sodium borohydride was reported in 1995.[287]

The UNCAs can be reduced with sodium borohydride in 1,2-dimethoxyethane in the presence of water (Scheme 6.5). The formation of *N*-protected β-amino alcohols is of much interest in organic chemistry because these families are the key intermediates for the synthesis of inhibitors of proteases and enkephalins.



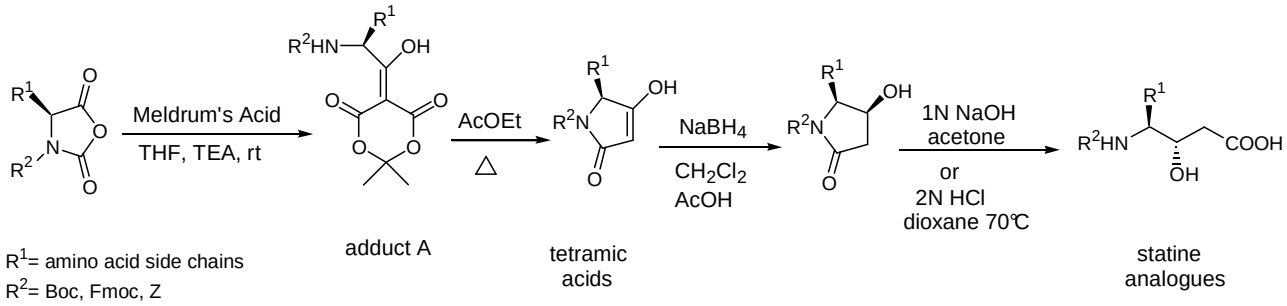
R^1= amino acid side chains
R^2= Boc, Fmoc, Z

Scheme 6.5: Synthesis of N-protected β-amino-alcohols by reduction of UNCAs by sodium borohydride.

Statine and β-hydroxy γ-amino acids have been used for the preparation of inhibitors of aspartyl proteases such as renin, a key enzyme in the renin-angiotensin system, and HIV.

By reaction of Meldrum's acid on the corresponding UNCAs in the presence of tertiary amine it was possible to obtain the adduct A that can easily be cyclized to give the corresponding

tetramic acids (Scheme 6.6). By sequential reduction and hydrolysis of tetramic acids statine analogues from UNCAs were obtained[287].

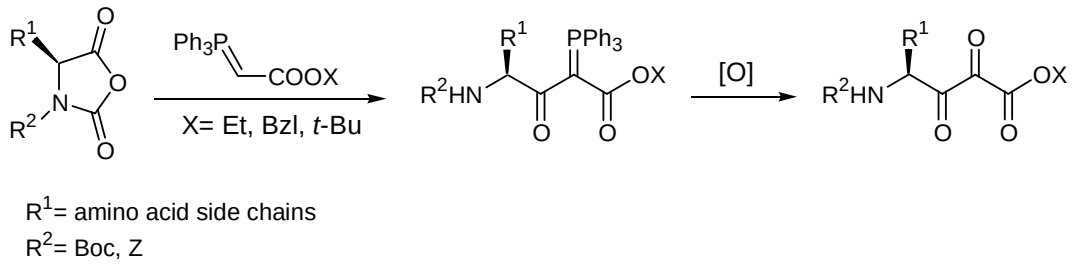


Scheme 6.6: Synthesis of statine analogues from UNCAs.

The key step of the synthesis is the diasteroselective reduction of tetramic acids, in fact only the *syn* configuration of β-hydroxy γ-amino acids (statine anologues) are recognized in their interaction with the enzymes.

An other use of UNCAs is the synthesis of vicinal tricarbonyl compounds,[287] known as potential inhibitors of serine proteases or starting materials for the synthesis of isoquinoline alkaloids, eudistomins, vicamine-related alkaloids, carbacephams and imidazoles.

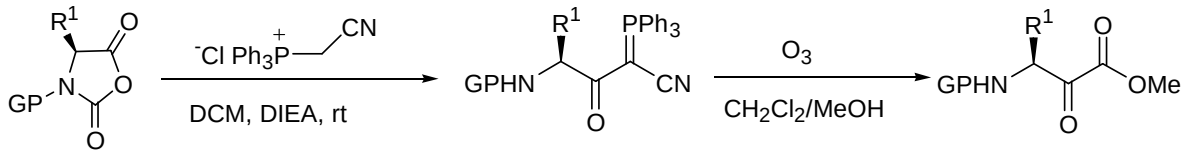
The condensation of UNCAs with triphenylphosphoranylidenes by Wittig reaction, give the corresponding keto phosphorane. These intermediates can give, by oxidation with oxone or $PhI(OAc)_2$, the vicinal tricarbonyl compounds (Scheme 6.7).



Scheme 6.7: Synthesis of vicinal tricarbonyl compounds from UNCAs

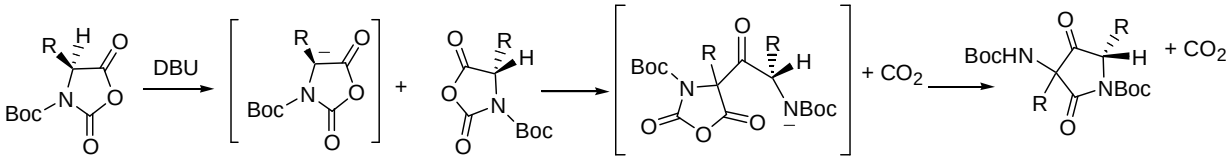
α-Keto ester and α-keto amide derivatives are inhibitors of proteolytic enzymes such as serine and cysteine proteases when these analogues are inserted in peptide sequences.

The synthesis of precursors of α-keto esters is accomplished by reaction between UNCAs and cyanomethyltriphenylphosphonium chloride, followed by ozonolysis in the presence of nucleophiles (Scheme 6.8).[288]



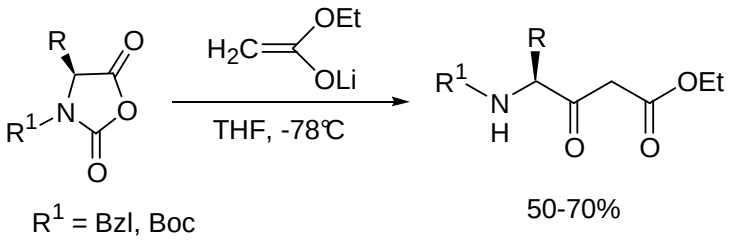
Scheme 6.8: Synthesis of β-amino-α-keto-esters from UNCAs..

Pyrrolidine-2,4-diones are considered as new aminoacid derivatives and can be useful as bioactive entities, for the introduction of biologically active moieties into pseudo-peptides and peptoids. They are also considered as heterocyclic building blocks for combinatorial chemistry.[289] The formation of N-urethane protected-3,5-dialkyl-3-amino pyrrolidine-2,4-diones as racemic *cis/trans* mixtures could be obtained using UNCAs in the presence of a base in aprotic medium (Scheme 6.9).



Scheme 6.9: Proposed mechanism of formation for pyrrolidine-diones from UNCAs.

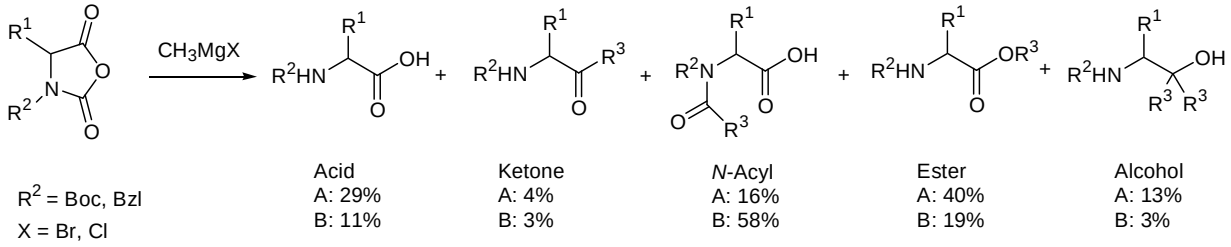
In the presence of the lithium enolate of ethyl acetate in THF at - 78°C, UNCAs led to the corresponding *N*-protected γ-amino-β-keto-ester derivatives (Scheme 6.10).[290]



Scheme 6.10: Synthesis of N-protected γ -amino-β-keto-esters from UNCAs.

The condensation of the lithium enolate is compatible with various protecting group used in peptide synthesis such as *tert*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Z) group.

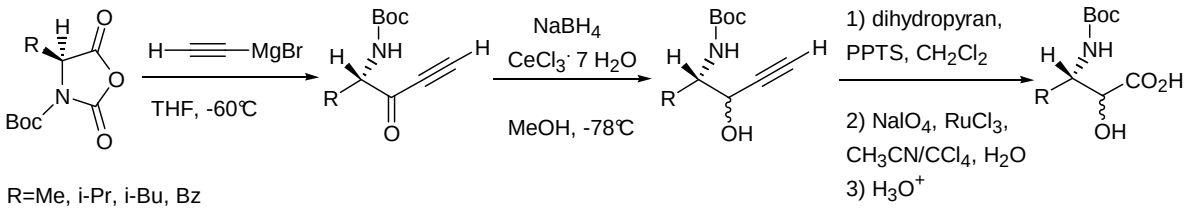
The first study on the reactivity of UNCAs with Grignard reagents was reported in 1997.[291] The addition of the UNCA to the Grignard reagent led to a mixture of products identified as *N*-protected amino acid, *N*-Acyl amino acids, α-aminoketones, alcohol compounds and ester derivatives when reaction was carried out at 0°C.



Scheme 6.11: Reaction of UNCAs with organomagnesium compounds.

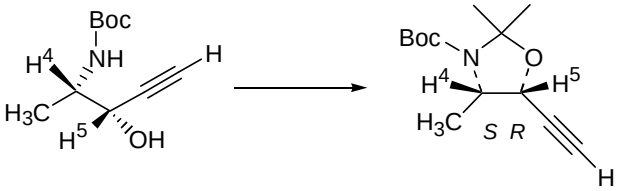
The inverse addition (addition of the Grignard reagent to the UNCA) also led to a mixture, but the major product was the *N*-protected *N*-acyl amino acid (Scheme 6.11). When lithium enolates were used the corresponding keto derivatives were obtained in good yield (50-70%).[290]

β-Amino-α-hydroxyacid moiety or norstatine derivatives could be used to be inserted into peptides known to be potent inhibitors of aminopeptidases. Furthermore, norstatine-related compounds have been reported to be HIV protease and renin inhibitors. One method to prepare β-amino-α-hydroxyacid started from urethane *N*-protected carboxyanhydrides (UNCAs); the key step of this reaction is the diastereoselective reduction of an α-amino-ynone, leading to the corresponding propargylic alcohol with *syn* diastereoselectivity (Scheme 6.12).[292]



Scheme 6.12: Alternative route to prepare norstatines from UNCAs

To confirm the supposed *syn* diastereoselectivity of the reduction leading to the (2*S*, 3*S*)-norstatines, the propargylic alcohol was converted into the corresponding oxazoline derivative (Scheme 6.13).



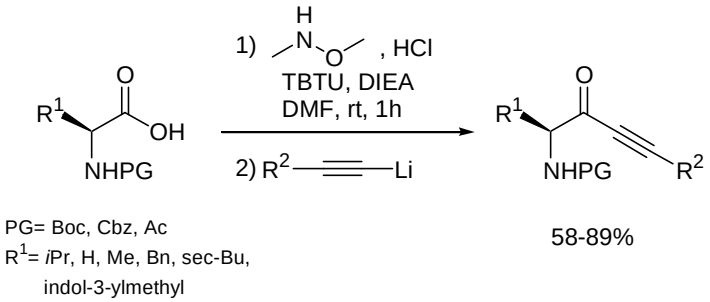
Scheme 6.13: Conversion of the propargylic alcohol into the corresponding oxazoline derivative.

The relative configuration of oxazoline derivative was assigned on the basis of the ^{1}H NMR coupling constant between H^4 and H^5. The mixture of stereoisomers was quantified by the distinguishable signals.

6.3: Results and discussion.

We became interested in the formation of α-amino-ynone derivatives that can cyclize in a metal-transition catalyzed reaction to give the corresponding pyrrolin-4-ones.

Only one method is described for the synthesis of α-amino-ynone compound: after activation as Weinreb amide (from commercially available aminoacids) the addition of various lithium acetylides gives the α-amino-ynones in good yields (Scheme 6.14).[293, 294]

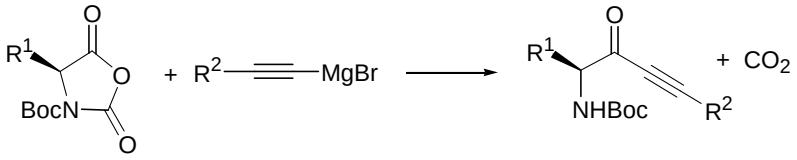


Scheme 6.14: Synthesis of the α-amino-ynones via Weinreb amide formation.

In the only example of addition of Grignard reagent to UNCAs reported (Scheme 6.15) the Grignard reagent was prepared starting from terminal alkynes, and after addition to the UNCAs, CO_2 was the only by-product.

We thought of to extending the use of this reaction using different alkynes bearing also phenyl or alkyl groups on the triple bond.

We hypothesized that it was possible to obtain mono addition of various Grignard acetylide to UNCA to give the corresponding α-amino-ynones by controlling the temperature.



Scheme 6.15: General hypothesis of addition of various Grignard acetylide to UNCAs.

The commercially available UNCA used in this study were Boc-Phe-NCA **1**, Boc-Ala-NCA **2**, Boc-Val-NCA **3** and Boc-Gly-NCA **4** (Figure 6.2).

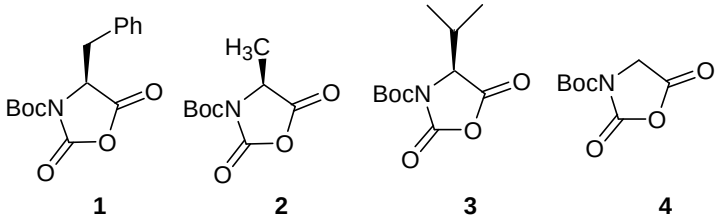
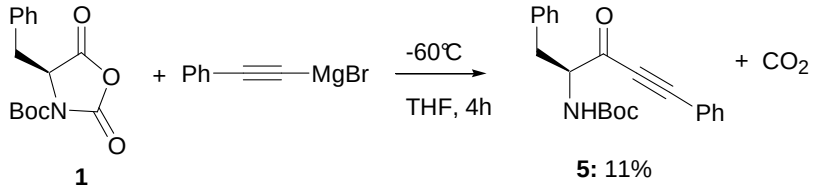


*Figure 6.2: Boc-Phe-NCA **1**, Boc-Ala-NCA **2**, Boc-Val-NCA **3** and Boc-Gly-NCA **4**.*

Before the reaction the purity of UNCAs was determined by ^{1}H NMR, the commercial batches are sometimes contaminated by the presence of the corresponding *N*-protected amino

acid, obtained after ring opening of UNCAs. In order to remove this by-product, the solid mixture was solubilized in AcOEt and washed one time with a satured solution of $NaHCO_3$. The organic phase was dried with $MgSO_4$ and the solvent was removed under vacuo.

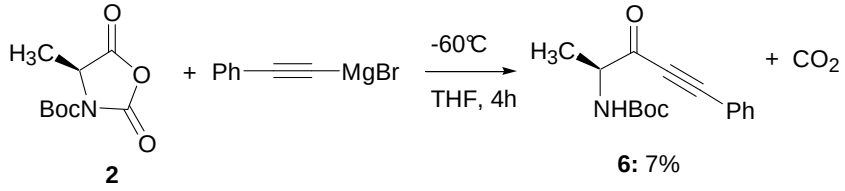
In a first experiment purified Boc-Phe-NCA **1** was treated with an equimolar amount of commercially available phenylethynylmagnesium bromide (Scheme 6.16). To a stirred solution of Grignard reagent kept at -60°C, UNCAs was added. The presence of the desired product **5** was detected by HPLC after 4h along with some by- products. The yield of α-amino-ynone **5** was very low (only 11%, Table 6.1, entry 1) after purification by column chromatography. This preliminary experiment confirmed that α-amino-ynone derivatives could be obtained using this method.



1 **5:** 11%

*Scheme 6.16: Addition of Boc-Phe-NCA **1** to phenylethynylmagnesium bromide.*

In a second attempt we changed the nature of UNCAs, testing alanine derivative **2** (Scheme 6.17).

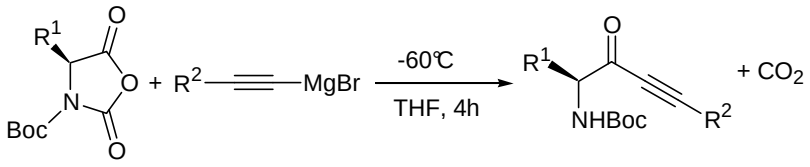


2 **6:** 7%

*Scheme 6.17: Addition of Boc-Ala-NCA **2** to phenylethynylmagnesium bromide.*

A slight excess (1.1 equivalent) of the Boc-Ala-NCA **2** was added to the Grignard reagent at -60°C confirming the complete conversion of starting material after 4h, but the yield remained poor (only 7%, Table 6.1, entry 2).

*Table 6.1: Addition of Boc-Phe-NCA **1** or Boc-Ala-NCA **2** to phenylethynylmagnesium bromide.*

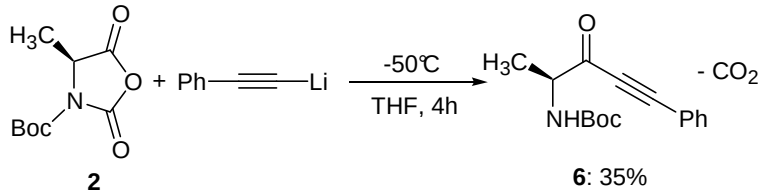


Entry	R^1	R^2	M	°C	Product	Yield (%)[a]
1	CH_2Ph	Ph	MgBr	-60	**5**	11
2	Me	Ph	MgBr	-60	**6**	7

a) isolated yield.

To increase the yield and to obtain only the mono addition, we decided to change the nature of the organometallic compound and to use a more reactive organolithium reagent.

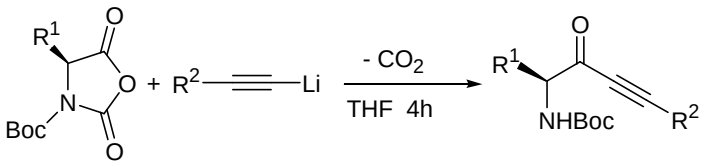
Boc-Ala-NCA **2** was added to 1.5 equivalent of phenylethynyl lithium at -50°C (Scheme 6.18). The organolithium was freshly prepared in the reaction. In this case the product **6** was obtained with a good purity albeit in low yield (35%, Table 2, entry 1).

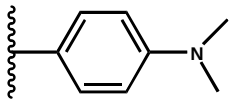


*Scheme 6.18: Addition of Boc-Ala-NCA **2** to phenylethynyllithium.*

However, the result was encouraging and the organolithium componds became the reagent of choice. An other important parameter of this reaction was to determine the enantiomeric excess of expected product. By chiral HPLC it was possible detect the two enantioners of **6** (Table 6.2, entry 1). This result suggests a partial epimerization of substrate **2** during the reaction.

Table 6.2: Addition of UNCAs to alkynyl organolithium.



Entry	R^1	R^2	°C	Product	Yield (%)[a]	e.e. (%)[b]
1	Me	Ph	-50	**6**	35	65
2	Me	Bu	-78	**7**	95	94
3	Me	Cyclopropyl	-78	**8**	80	90
4	i-Pr	Ph	-50	**9**	71	81
5	i-Pr	Ph	-60	**9**	62	97
6	i-Pr	Bu	-78	**10**	81	96
7	i-Pr	Cyclopropyl	-60	**11**	94	100
8	CH_2Ph	Ph	-78	**5**	60	10
9	CH_2Ph	Bu	-78	**12**	61	20
10	CH_2Ph	Cyclopropyl	-78	**13**	64	18
11	CH_2Ph		-78	**14**	46	95

a) isolated yield; b) e.e. determining by chiral HPLC.

Variously substituted lithium acetylides bearing an aryl or alkyl group (Table 6.2, entries 2-11) were tested.

Temperature and concentration of solvent were important factors for the control of the enantiomeric excess. When the reaction of addition of Boc-Val-NCA **3** to phenylethynyllithium to was carried out at -50°C, epimerization occured faster (Table 6.2, entries 4 and 5). Better results were achieved by carrying out the reaction at lower temperatures, between -60°C at -78°C.

α-Amino-ynones **5**, **7**-**13** were obtained exclusively in good to excellent yields (60% - 95%) while the analysis by chiral HPLC showed a moderate erosion of the enantiomeric excess for the Boc-Ala-NCA derivatives (Table 6.2, entries 1-3). Minimal decrease of the stereochemical purity for Boc-Val-NCA derivatives was observed (Table 6.2, entries 5-7)

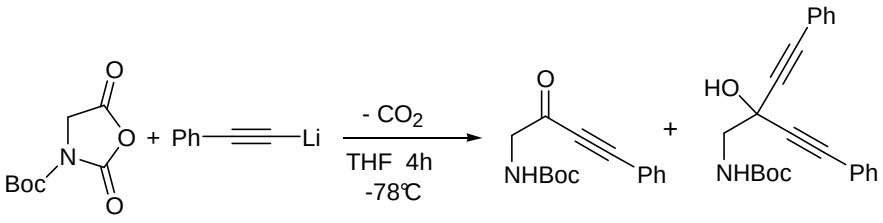
while no epimerization occurred for compound **11** presenting a cyclopropyl group on the triple bond.

Contrasting results were obtained in the case of addition of Boc-Phe-NCA **1** to organolithium reagent. For the α-amino-ynones **5**, **12**, **13** the yields of product was around 60 % but the enantiomeric excess for these derivatives was very low (Table 6.2, entry 8-10).

The only exception in this series was molecule **14** with 95% of *e.e*. (Table 6.2, entry 11). Maybe the presence of a nitrogen on the phenyl ring can produce different interaction in the transition state.

In general, the decrease of stereochemical purity could be explained by a faster epimerization when an aromatic group was present in the side chain of the amino acid derivative.[295] In all cases, the loss of enantiomeric excess could be explained by a direct enolization mechanism during the reaction of addition of UNCAs to organolithium compounds.

When Boc-Gly-NCA was the substrate, the reaction was not complete after 4 h. By LC-MS it was possible to observe that the formation of expected α-amino-ynone **15** together with the corresponding amino alcohol **16**, as a consequence of a double addition (Scheme 6.19).



4 **15** **16**

*Scheme 6.19: Addition of alkynyl organolithium to Boc-Gly-NCA **4**.*

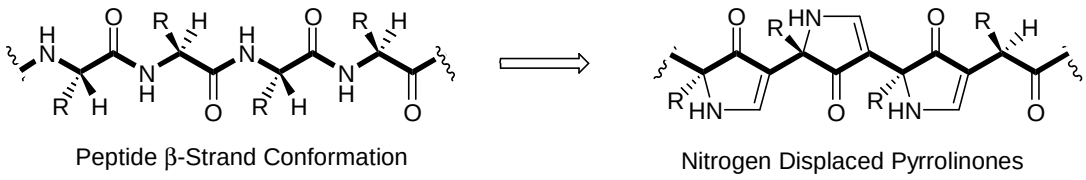
The method for the synthesis of α-amino-ynone **5-15** requires the use of commercially available UNCAs. Expected products were obtained after one reaction step, addition of UNCAs to organolithium reagent and the purification was carried out by a simple column chromatography on silica gel.

These α-aminoynones would be used as the substrates for the synthesis of pyrrolin-4-ones by metal-catalyzed cycloisomerization reaction.

6.4: Pharmacological interest and alternative synthesis of pyrrolin-4-one derivatives.

Pyrrolin-4-one derivatives are an important class of functionalized nitrogen-containing heterocycles along with useful biological activities and widely used as key building block for the development of anticancer, antithrombotic, and antimicrobial agents. Pyrrolinone mimetics present the peptide pharmacophore on a novel polypyrrolinone backbone.

Smith and Hirschmann pioneed the studies of 3,5-linked polypyrrolinone scaffold, have shown that in the pyrrolinone system, the amide backbone is "rearranged" to replace the central amide group with a 5-membered pyrrolinone ring system (Scheme 6.20).[296-299]



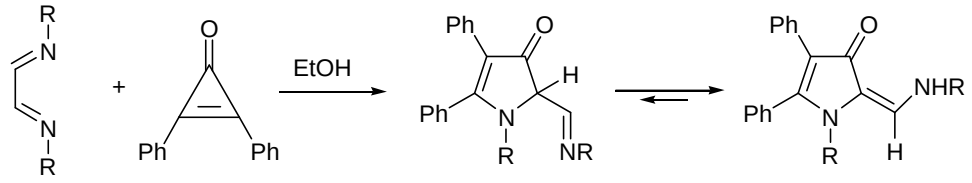
Scheme 6.20: A potential non-peptide peptidomimetic scaffold.

This transformation preserves the positioning of the side chain of the peptide while preventing the enzymatic degradation that would destroy normal peptides before they could reach their target receptors. The ring systems are highly conformationally constrained, and the internal hydrogen bonding eliminates sites for solvation. All of these features improve the potential for highly selective biological activity, metabolic stability, and bioavailability.

Mimetics based on pyrrolinones have shown potential in the development of enzyme inhibitors for example HIV protease and renin, MHC (major histocompatibility complex) Class II DR1 inhibitors, and MMP (Matrix metalloproteinases) inhibitors.

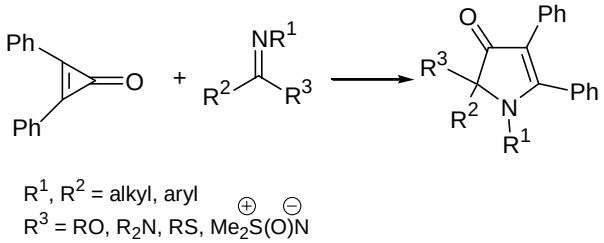
Extensive research has generated many procedures for the synthesis of pyrrolin-4-ones.

Pyrrolinones derivatives are synthesized by the reaction between *N*,*N*′-dicyclohexylethane-1,2-diylidenediamine and *N*,*N*′-diarylethane-1,2-diylidenediamines with diphenylcyclopropenone through a formal [2 + 3] cycloaddition reaction (Scheme 6.21).[300, 301]



Scheme 6.21: Formal [2 + 3] cycloaddition reaction of cyclopropenones with imine derivatives.

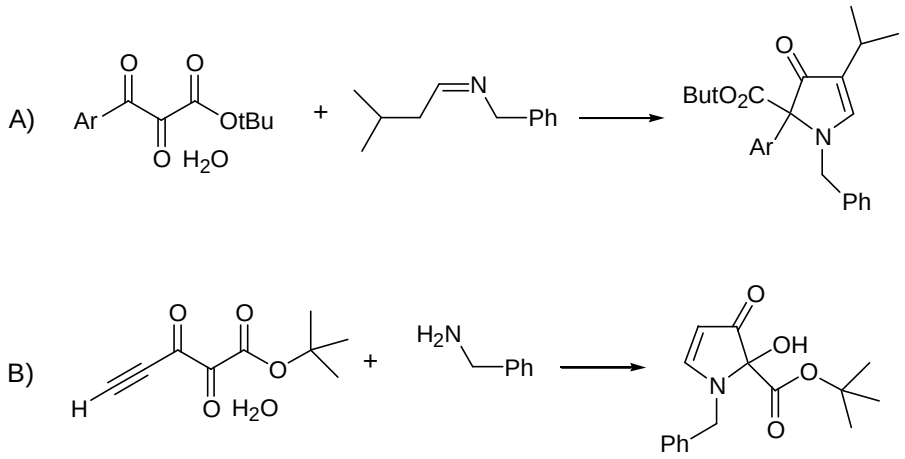
Moreover nucleophiles such as alcohols, thiocyanic acids, thiols, or acetylacetone reacted with immonium salts (Scheme 6.22) to yield 5-substituted -2-pyrrolin-4-ones.[302]



Scheme 6.22: 5-Substituted -2-pyrrolin-4-one.

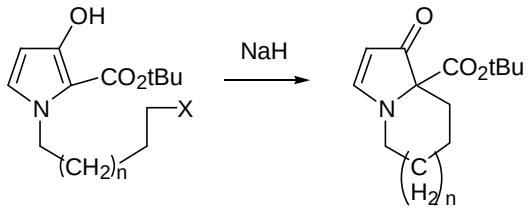
Wasserman and co-workers reported a series of reactions using tricarbonyl derivatives. Application of tricarbonyl chemistry in synthesis is illustrated by the formation of various natural products or their precursors including fused-ring beta-lactams, indole alkaloids, marine metabolites, enzyme inhibitors containing alpha-keto amides, and bioactive depsipeptides incorporating hydrated tricarbonyl units.[303]

The reactions of aryl and hetero vicinal tricarbonyl derivatives with aldehyde Schiff bases lead to pyrrolinone derivatives by benzylic acid-related rearrangements, driven, most probably, by iminium ion intermediates (Scheme 6.23, A).[304] It was also we reported that the acetylenic tricarbonyl serves as a polyelectrophile in addition reactions of primary amines substituted with nucleophilic groups (Scheme 6.23, B). [305]



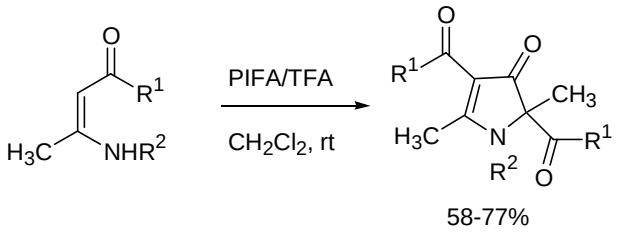
Scheme 6.23: Reaction of vicinal tricarbonyls with enamines (A) or amines (B).

The same group reported that the intramolecular alkylation of substituted 3-hydroxpyrrole-2-carboxylates (Scheme 6.24) lead to fused ring systems found in the pyrrolizidine, indolizidine, and related pyrrolidine alkaloids.[306]



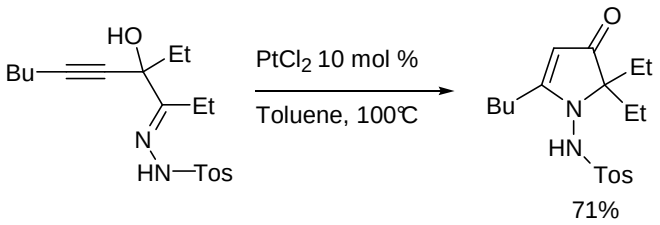
Scheme 6.24: Intramolecular alkylation of substituted 3-hydroxpyrrole-2-carboxylates

An alternative access route to substituted pyrrolin-4-ones consisted of a [phenyliodin(III) bis-(trifluoroacetate)] PIFA-mediated oxidative cyclization (Scheme 6.25).[307]



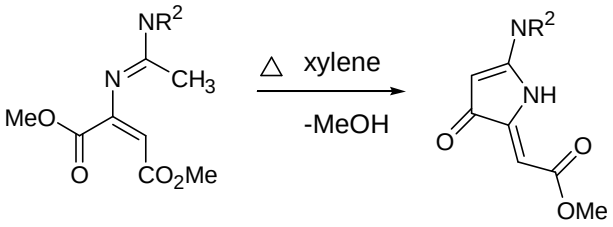
Scheme 6.25. PIFA-mediated oxidative cyclization.

Bunnelle and co-workers have hypothesized that tertiary propargylic alcohol substrates could provide a platform for heterocyclizations involving a 1,2-shift to give substituted pyrrolin-4-ones (Scheme 6.26).[308] This is the only example reported in the literature that uses platinum di-chloride as catalyst for the synthesis of these derivatives.



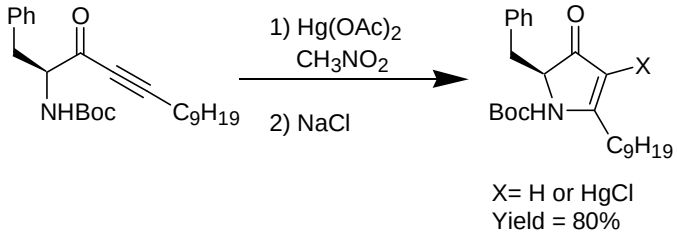
Scheme 6.26: 1,2-Shift heterocyclizations for give substituted pyrrolin-4-ones.

An other system involves an intramolecular cyclization of *N*-vinylic amidines to yield 4-pyrrolin-3-ones (Scheme 6.27). [309]



Scheme 6.27: Intramolecular cyclization of N-vinylic amidine.

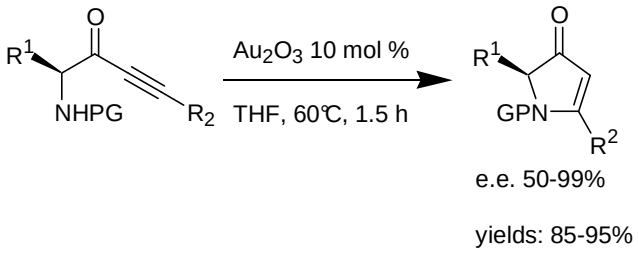
The first example of use of α-amino-ynone was reported in 1994 by Overhand and Hecht.[293] the antifungal agent (+)-preussin was synthesized in five steps from *t*-Boc-(*S*)-phenylalanine (Scheme 6.28). The key step involved by 5-*endo*-dig process Hg (II)-mediated ring closure of α-amino-ynone. This strategy required a stoichiometric amount of mercuric acetate to achieve the ring closure.



Scheme 6.28: Hg (II)-mediated ring closure of a-amino-ynone.

To find an other example on the use of α-amino-ynones, it was necessary to wait for the work of Gouault and co-workers in 2009.[294] They reported the gold-catalyzed cyclization of

various α-amino-ynone derivatives to afford the corresponding pyrrolin-4-ones. The use of gold (III) oxide as catalyst allows a moderate to total stereocontrol during the cyclization. (Scheme 6.29).



Scheme 6.29: Gold (III) oxide catalyzed cyclization of various α-amino-ynones.

6.5: Cycloisomerization reaction of α-amino-ynones in PEG under microwave activation.

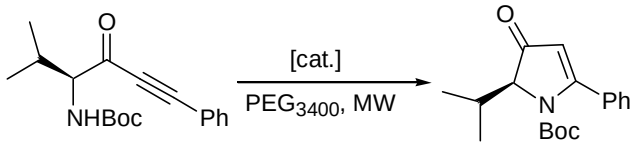
We considered to test the cycloisomerization reaction of the α-amino-ynone **9** using PEG as solvent. As previously detailed (c.f. Chapter 4), Poly (ethylene glycol) or PEG is a good solvent for this reaction under microwave irradiation.

According to the experimental conditions for the cycloisomerization reaction of diols and aminoalcohols described in Chapter 4 the first catalyst tested was platinum di-chloride.

Very interesting results were obtained reported in Table 6.3. Independently on the quantity of catalyst (1 mol % or 5 mol %) product **17** was recovered pure after the precipitation-filtration in excellent yield 99% and 95% respectively (Table 6.3, entries 1-2). However, the analysis of the chiral purity showed an epimerization, the pyrrolin-4-one **17** was obtained with only 36 % of *e.e.*

The next experiment was carried out in the absence of catalyst in order to test a possible spontaneous cyclization. The reaction mixture was heated up under microwave irradiation for 1 h. The analysis of mixture showed exclusively the presence of the substrate (Table 6.3, entry 3).

*Table 6.3: Screening of catalysts in the cycloisomerization reaction of α-amino-ynone **9**.*



9: 81% e.e. **17**

Entry	Catalyst (mol %)	PEG	°C	Time	Conv[a] (%)	Yield[a] (%)	*e.e.*[b] (%)
1	$PtCl_2$ (1)	PEG_{3400}	80	30	100	99	36
2	$PtCl_2$ (5)	PEG_{3400}	80	30	100	95	35
3	-[c]	PEG_{3400}	80	60	0	0	0
4	CuO (5)	PEG_{3400}	80	30	0	0	0
5	$CuCl_2$ (5)	PEG_{3400}	80	30	90	75	14
6	PdI_2 (2)	PEG_{3400}	80	30	31	30	-[d]
7	$PtCl_2$ (5) $AgSbF_6$ (10)	PEG_{3400}	60	30	100	84	63

a) determined by ^1H NMR using CH_2Br_2 as internal standard b) *e.e.* determined by chiral HPLC. c) reaction was carried out in the absence of catalyst. d) not calculated.

Two different copper catalysts were also tested: copper (II) oxide and copper di-chloride. When copper (II) oxide as catalyst was used, the substrate was recovered unreacted (Table 6.3, entry 4). In the case of copper di-chloride, formation of expected product was observed but the conversion of substrate was not complete (Table 6.3 entry 5).

Palladium catalysts were also explored (Table 6.3, entry 6). In comparison with the other catalysts, the reaction catalyzed by palladium di-iodine, was slower.

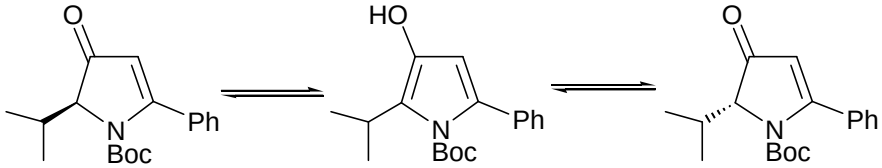
Platinum di-chloride together with an additive of silver species, silver hexafluoroantimoniate, produce a cationic platinum $Pt(SbF_6)_2$ (Equation 6.1).

$$PtCl_2 + 2\ AgSbF_6 \rightarrow Pt(SbF_6)_2 + 2AgCl$$

Equation 6.1: Complex of cationic platinum.

This cationic species is more electrophilic, allowing a more efficient activation of the substrate. Full conversion was reached after 30 minutes at 60°C (Table 6.3, entry 7). Interesting the analysis of enatiomeric excess showed a lower rate of epimerization (*e.e.* 63%).

The epimerization that occurred during the cycloisomerization could be attributed to the keto-enol equilibrium favoured by the presence of HCl released during the reaction leading to a hydroxypyrrole (Scheme 6.30)

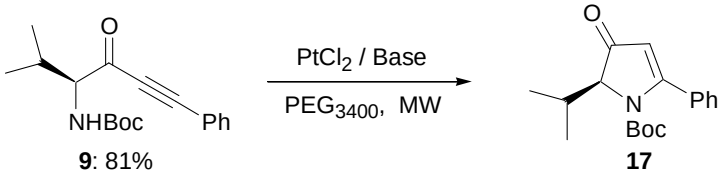


*Scheme 6.30: Keto-enol equilibrium of pyrrolin-4-one **17**.*

The use of cation platinum, $Pt(SbF_6)_2$, gave good results however, a better alternative system need to be found, in order to prevent the use of heavy metals, requiring special technique of purification.

The use of a base could be effective to neutralize the acidic conditions diminishing the epimerization extent. We start to test K_2CO_3 as base. When the base alone was used, the cyclization did not take place (Table 6.4 entry 1). Entries 2-4 of are show different results obtained using 1 mol % of $PtCl_2$ and 15% of K_2CO_3. In these set of reactions, it was possible to observe that the conversion of substrate **9** was not complete. The reaction was very slowly and suggesting that the base could inhibit the catalytic activity of metal.

Table 6.4: Screening of time and temperature for cycloisomerization.



9: 81% **17**

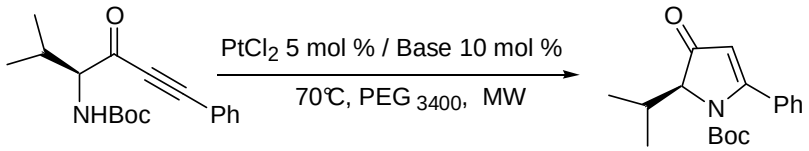
Entry	Catalyst (mol %)	Base (mol %)	°C	Time (min)	Conv. (%)[a]	Yield (%)[a]	*e.e.* (%)[b]
1	-	K_2CO_3 (15)	80	60	0	0	n.d.
2	$PtCl_2$ (1)	K_2CO_3 (15)	80	30	60	40	62
3	$PtCl_2$ (1)	K_2CO_3 (15)	80	60	74	38	n.d.
4	$PtCl_2$ (1)	K_2CO_3 (15)	60	60	50	30	67
5	$PtCl_2$ (5)	K_2CO_3 (10)	80	30	100	70	72
6	$PtCl_2$ (5)	K_2CO_3 (10)	70	30	100	80 (80)	77
7	$PtCl_2$ (5)	K_2CO_3 (10)	70	30	100	95 (94)	90[c]

a) determined by ^1H NMR using CH_2Br_2 as internal standard b) *e.e.* determined by chiral HPLC. c) e.e. of substrate **9** was 97%. In parenthesis isolated yield.

Entries 5 and 6 of Table 6.4 show the effect of temperature on the epimerization extent. A difference in the increase of enantiomeric excess was observed. When reaction was carried out at 70°C for 30 min the desired product **17** was obtained in good yield and excellent enantiomeric excess (77%). In this case, the enantiomeric excess of starting material was 81%. To validate this optimized reaction condition, the same substrate **9** but with a higher enantiomeric excess (97%) was tested (Table 6.4, entry 7).

We tried to explore the reaction in the presence of different bases. When cesium carbonate and triethylamine (Table 6.5, entries 3-4) were used, the reaction time was longer. Full conversion of substrate **9** was complete only after 60 min. However, the enantiomeric excess of product **17** decreased (47-58 % respectively).

*Table 6.5: Screening of different bases in $PtCl_2$-catalyzed cycloisomerization reaction of α-amino-ynone **9**.*



9: 81% **17**

Entry	Catalyst	Base	Time (min)	Yield (%)[a]	*e.e.* (%)[b]
1	$PtCl_2$	K_2CO_3	30	80 (80)	77
2	$PtCl_2$	$NaHCO_3$	30	87	60
3	$PtCl_2$	Cs_2CO_3	60	81	47
4	$PtCl_2$	Et_3N	60	83	58
5	$PtCl_2$	*t*-BuOK	60	54	18

a) determined by ^1H NMR using CH_2Br_2 as internal standard b) *e.e.* determined by chiral HPLC. In parenthesis isolated yield.

With potassium *tert*-butoxide a decrease of both enantiomeric excess and yield of product (Table 6.5, entry 5) were observed. The presence of a strong base can inhibit the catalytic system and destroy the product.

Under the optimized conditions, the 5-*endo*-dig intramolecular cyclization was successfully achieved using 5 mol % $PtCl_2$, 10 mol % of K_2CO_3 as the base, PEG_{3400} as solvent, for 30 minutes at 70°C under microwave activation with an initial microwave power of 400W. The yield of **17** was very good in each case and the crude product was recovered pure after a

simple precipitation-filtration of PEG without need of purification by column chromatography.

The optimal conditions were used to cyclize α-amino-ynones bearing aromatic or alkyl functions on the acetylenic moiety. Excellent yields of product were obtained in all cases, (between 80% to 98%), highlighting the general method of Pt-catalyzed cycloisomerization reaction in PEG under microwave activation (Figure 6.3).

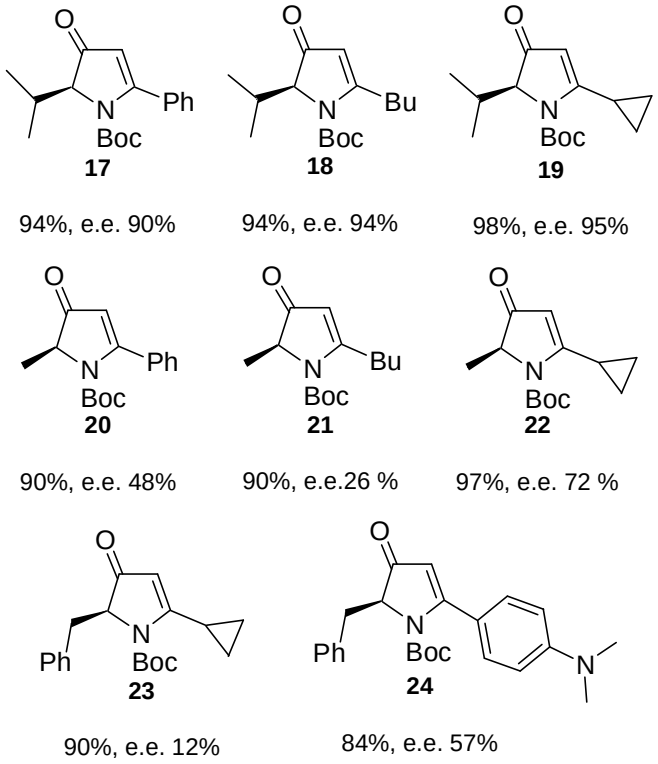


Figure 6.3: Pt-catalyzed cycloisomerization of α-amino-y-none derivatives under microwave irradiation in PEG $_{3400}$. Isolated yield.

In the case of valine-based starting materials, the reaction of cycloisomerization gave very excellent results in term of yield 94% for compound **17**, 94% and 98% for compounds **18** and **19**. Minimal epimerization occurred during reaction.

In the case of alanine-based starting materials, the cycloisomerization gave excellent results in term of yield but with loss of enantiomeric excess. Chiral purity was degraded in the case of phenylalanine-based starting material.

Alanine and phenylalanine derivatives present a moderate to strong propensity toward epimerization at the α-carbon.[295]

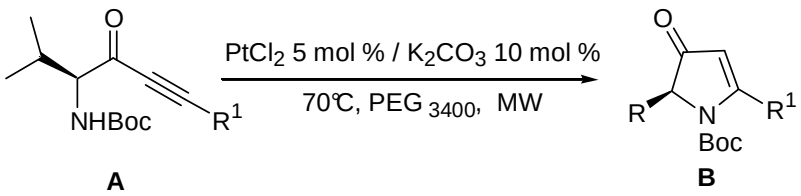
6.6: Recycle of catalytic system $PEG_{3400}/PtCl_2/K_2CO_3$.

The possibility to recycle the catalytic system constituted by $PEG_{3400}/PtCl_2/K_2CO_3$ was tested (Figure 6.4).

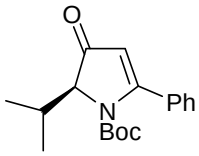
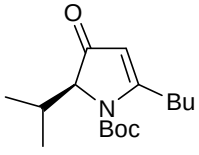
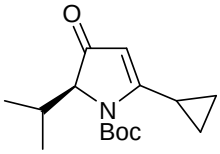
Figure 6.4: PEG_{3400} after filtration.

The precipitate recovered after the precipitation-filtration work up was used again in another reaction. The catalytic system was charged with new substrate and heated up under microwave irradiation. The activity of the catalytic system was effective for 1 or 2 runs. For a total conversion of substrate the reaction time was adjusted at each run of the recycling. Independent of reaction time in every case no epimerization reaction occurred during the recycling (Table 6.6).

Table 6.6: Results for the recycling of the catalytic system.



A **B**

Entry		Run	Time	Conv **A** (%)	*e.e.* **A** (%)[b]	Yield **B** (%)[a]	*e.e.* **B** (%)[b]
1		I	30	100	81	80	77
2		II	45	100	81	80	80
3	**17**	III	60	84[c]	81	-[d]	n.d.
4		I	30	100	96	94	94
5		II	45	100	96	94	94
6	**18**	III	60	0	96	0	n.d
7		I	30	100	100	94	95
8		II	45	100	100	96	95
9	**19**	III	60	100	100	98	95
10		IV	75	100	100	0	n.d

a) Isolated yield b) *e.e.* determined by chiral HPLC analysis. c) calculated by ^{1}H NMR using CH_2Br_2 as an internal standard. d) product not isolated.

6.7: Conclusion.

In conclusion, we propose herein an original and alternative route to the preparation of α-amino-ynone derivatives by direct addition of commercially available UNCAs to organolithium compounds. The unprecedented Pt-catalyzed 5-*endo-dig* cycloisomerization of these intermediate using PEG_{3400} as an alternative and ecofriendly solvent under microwave irradiation provided a new route to the synthesis of pyrrolin-4-ones. After a simple

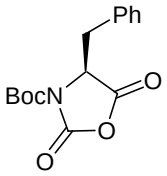
precipitation-filtration the pure product was recovered with good to excellent yields and the catalytic system $PtCl_2/K_2CO_3/PEG_{3400}$ could be also recovered and reused.

Experimental section

6.8: General remarks.

Commercially available compounds (Aldrich, Fluka, Chem, ISOCHEM) were used as received. Boc-Phe-NCA **1**, Boc-Ala-NCA **2** and Boc-Gly-NCA **3** resp. was diluted in AcOEt and washed with a saturated solution of $NaHCO_3$ to remove traces of corresponding acid derivative. The solvents were purified by distillation over a drying agent. Chemical shifts (δ) of ^1H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for ^1H and $CDCl_3$: δ = 77 ppm for ^{13}C. *J*- values are given in Hz. ^1H and ^{13}C NMR was registered on Bruker Avance-300 MHz, Bruker Avance 400 MHz. Microwave-assisted reactions were performer with a Biotage Initiator^{TM} 2.0. Instrument. Temperature was measured with an IR sensor on the surface of the reaction vial. LC-MS analysis were performed with HPLC Waters Alliance 2695 (UV Waters 2489), column Onyx C_{18}, 25 mn x 4.6 mn, flow 3 ml/min (H_2O-0.1% HCO_2H (A)/CH_3CN 0.1% HCO_2H (B)) gradient 0 to 100% in 2.5 min. HRMS analysis were performed on a Q-Tof (Waters, 2001) with ESI. Chiral HPLC analysis was performed with Beckman Coulter System Gold 126 Solvent Module and Beckman Coulter System Gold 168 Detector. Column: Chiralpak AD-H 0.46 cm x 25 cm, Chiralcel OD-H 0.46 cm x 25 cm. Chiral HPLC phase inverse: Chiralcel OD-RH 0.46 cm x 25 cm. $[\alpha]^d$ measurement were performed on a Perkin Elmer Instrument Polarimeter, model 341 Polarimeter, OROT 589 nm, 20°C, [10 mg/mL], solv: dichloromethane.

Boc-Phe-NCA (1)



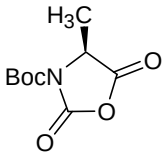
CAS Registry Number: [142955-51-9]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.37-7.34 (m, 3H), 7.13-7.10 (m, 2H), 4.95 (dd, 1H, *J* = 2.6, 5.8 Hz), 3.57 (dd, 1H, *J* = 5.8, 14.2 Hz), 3.36 (dd, 1H, *J* = 2.6, 14.2 Hz), 1.66 (s, 9H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 165.8, 147.7, 145.8, 132.3, 129.5, 129.2, 128.3, 86.1, 60.8, 35.3, 28.0.

ESIMS *m/z*: 292.0 $(M+H)^+$, 314.1 $(M+Na)^+$, 236.0 $(M+H-\text{t-Bu})^+$, 605.3 $(2M+Na)^+$.

Boc-Ala-NCA (2)

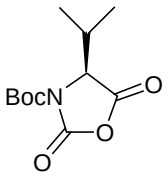


CAS Registry Number: [125814-30-4]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.67 (q, 1H, *J* = 6.9 Hz), 1.69 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 166.7, 147.4, 146.2, 86.0, 55.8, 27.9, 16.9.

Boc-Val-NCA (3)



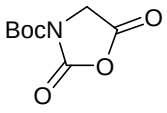
CAS Registry Number: [141468-55-5]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.56 (d, 1H, *J* = 3.5 Hz), 2.63-2.47 (m, 1H) 1.58 (s, 9H), 1.20 (d, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 164.8, 147.6, 146.6, 86.0, 64.6, 30.0, 27.9, 17.8, 15.7;

ESIMS *m/z*: 266.1 $(M+Na)^+$, 188.2 $(M+H-\text{t-Bu})^+$, 509.2 $(2M+Na)^+$.

Boc-Gly-NCA (4)



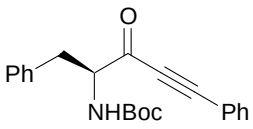
CAS Registry Number: [142955-50-8]

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.49 (s, 2H), 1.57 (s, 9H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 162.5, 147.3, 146.2, 86.3, 48.3, 27.9.

6.9: Synthesis of α-amino-ynones.

(1-Benzyl-2-oxo-4-phenyl-but-3-ynyl)-carbamic acid tert-butyl ester (5)



Yellow solid, m.p. 90-94°C, e.e. 10 %.

A solution of phenylacetylene (264 mg, 2.58 mmol) in anhydrous THF (6 mL) was added dropwise to a stirred, to solution of BuLi (1.6 mL of a 1.6 M solution in hexanes, 2.58 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (159 g, 1.82 mmol) in THF (3 mL). After 0.5 h, Boc-Phe-NCA (500 mg, 1.72 mg), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **5** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 351 mg (60 %) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.60 (d, 2H, J = 7.5 Hz), 7.52-7.50 (m, 1H), 7.43 (t, 2H, J = 7.6 Hz), 7.33- 7.23 (m, 6H), 5.15 (d, 1H, J = 7.4 Hz), 4.82 (dd, 1H, J = 6.1, 13 Hz), 3.34 Hz (dd, 1H, J = 5.8, 14.0 Hz), 3.29 (dd, 1H, J = 5.8, 14.0 Hz), 1.45 (s, 9H).

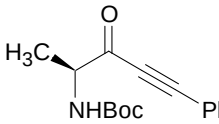
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 186.1, 155.2, 135.8, 133.4, 131.3, 129.7, 128.8, 128.7, 127.2, 119.7, 95.0, 86.6, 80.2, 62.2, 37.6, 28.5.

ESIMS *m/z*: 350.2 $(M+H)^+$, 372.3 $(M+Na)^+$, 294.2 $(M+H\text{-}t\text{-}Bu)^+$, 250.2 $(M+H\text{-}Boc)^+$, 699.4 $(2M+H)^+$.

HMRS (ESI) calcd. For C22H24NO3 $(M+H)^+$: 350.1756, found: 350.1748.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 21.267 min, t_{minor} = 17.867 min.

(1-Methyl-2-oxo-4-phenyl-but-3-ynyl)-carbamic acid tert-butyl ester (6).



CAS Registry Number:[1169845-20-8]; pale yellow solid; m.p. 65-67°C; lit[294] 64-66°C. e.e. 65 %;$[\alpha]^d$ = +0.005° (10 mg/mL CH_2Cl_2).

A solution of phenylacetylene (705 mg, 6.9 mmol) in anhydrous THF (3 mL) was added dropwise to a stirred, to solution of BuLi (4.3 mL of a 1.6 M solution in hexanes, 6.9 mmol) in anhydrous THF (5 mL) at -40°C. To the resulting mixture, maintained at -40°C, was added, with stirring, a solution of LiBr (426 g, 4.9 mmol) in THF (3 ml). After 0.5 h, Boc-Ala-NCA (1.00 g, 4.65 mmol), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **6** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 385 mg, (35%) of the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.61-7.59 (m, 2H), 7.49-7.38 (m, 3H), 5.24 (d, 1H, J = 5.7 Hz), 4.57-4.52 (m, 1H), 1.51 (d, 3H), 1.46 (s, 9H).

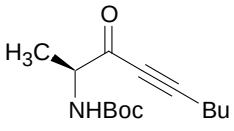
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 187.1, 155.1, 133.1, 131.0, 128.6, 119.5, 94.3, 85.8, 79.9, 56.9, 28.3, 17.8.

ESIMS *m/z* 274.2 $(M+H)^+$, 296.2 $(M+Na)^+$, 218.2 $(M+H\text{-}t\text{-}Bu)^+$, 174.0 $(M+H\text{-}Boc)^+$, 569.2 $(2M+ Na)^+$.

HMRS (ESI) calcd. For C16H20NO3 $(M+H)^+$: 274.1443, found: 274.1442.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 23.683 min, t_{minor} = 22.050 min.

(1-Methyl-2-oxo-oct-3-ynyl)-carbamic acid tert-butyl ester (2c)



Pale oil, e.e. 94%; $[\alpha]^d$ = +0.026° (10 mg/mL CH_2Cl_2)

A solution of hexyne (254 mg, 3.09 mmol) in anhydrous THF was added dropwise to a stirred, to solution of BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.09 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (190 g, 2.18 mmol) in THF (3 mL). After 0.5 h, Boc-Ala-NCA (500 mg, 2.32 mmol), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over

$MgSO_4$. After filtration, the solvent was evaporated to obtain pure product **7** to afford 560 mg (95 %) of the title compound.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.20 (d, 1H, J = 7.5 Hz), 4.42-4.35 (m, 1H), 2.40 (t, 2H, J = 6.8 Hz), 1.62-1.40 (m, 4H), 1.45 (s, 9H), 0.93 (t, 3H, J = 7.1 Hz)

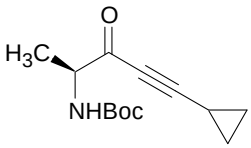
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 187.1, 155.0, 98.3, 79.8, 78.8, 57.0, 29.6, 28.3, 28.0, 22.0, 17.9, 13.5.

ESIMS *m/z* 254.1 $(M+H)^+$, 276.2 $(M+Na)^+$, 198.1 $(M+H\text{-}t\text{-}Bu)^+$, 154.1 $(M+H\text{-}Boc)^+$, 529.3 $(2M+Na)^+$.

HMRS (ESI) calcd. For C14H24N03 $(M+H)^+$: 254.1756, found: 254.1756.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 13.017 min, t_{minor} = 11.65 min.

(4-Cyclopropyl-1-methyl-2-oxo-but-3-ynyl)-carbamic acid tert-butyl ester (8)



Pale yellow solid, m.p. 62-65°C, e.e. 90 %; $[\alpha]^d$ = + 0.016° (10 mg/mL CH_2Cl_2).

A solution of cyclopropylacetylene (160 mg, 2.42 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred, to solution of BuLi (1.5 mL of a 1.6 M solution in hexanes, 2.42 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (171 mg, 1.97 mmol) in THF (1.5 mL). After 0.5h, Boc-Ala-NCA (400 mg, 1.86 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain the pure product **8** to afford 401 mg, (80 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.18 (d, 1H, J = 5.5 Hz), 4.35 (t, 1H, J = 7.2 Hz), 1.44 (s, 9H), 1.44 (m, 1H), 1.39 (d, 3H, J = 6.0 Hz), 1.05-0.98 (m, 2H), 0.97-0.91 (m, 2H)

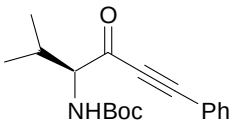
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 186.8, 155.0, 102.6, 79.8, 74.6, 56.8, 28.3, 17.9, 10.0, -0.15.

ESIMS *m/z*: 238.1 $(M+H)^+$, 260.1 $(M+Na)^+$, 182.1 $(M+H\text{-}t\text{-}Bu)^+$, 138.1 $(M+H\text{-}Boc)^+$, 475.2 $(2M+H)^+$, 497.1 $(2M+Na)^+$.

HMRS (ESI) calcd. For C13H20NO3 $(M+H)^+$ 238.1445, found: 238.1443.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 8.783 min, t_{minor} = 9.383 min.

(1-Isopropyl-2-oxo-4-phenyl-but-3-ynyl)-carbamic acid tert-butyl ester (9)



CAS Registry Number: [1169845-48-0], pale yellow solid, m.p. 102-105°C, lit[294]. 100-102°C, e.e. 81 %, $[\alpha]^d$ = + 0.030°; e.e. 97%, $[\alpha]^d$ = + 0.035°[10 mg/mL CH_2Cl_2].

A solution of phenylacetylene (315 mg, 3.09 mmol) in anhydrous THF (5 mL) was added dropwise to a stirred, to solution of BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.09 mmol) in anhydrous THF at -60° C. To the resulting mixture, maintained at -60° C, was added, with stirring, a solution of LiBr (190 g, 2.18 mmol) in THF. After 0.5 h, Boc-Val-NCA (500 mg, 2.06 mg), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **9** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 384 mg (62 %).

A solution of phenylacetylene (819 mg, 8.02 mmol) in anhydrous THF was added dropwise to a stirred, to solution of BuLi (5 mL of a 1.6 M solution in hexanes, 8.02 mmol) in anhydrous THF at -60° C. To the resulting mixture, maintained at -60° C, was added, with stirring, a solution of LiBr (557 g, 6.4 mmol) in THF. After 0.5 h, Boc-Val-NCA (1500 mg, 6.17 mg), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **9** that was purified by

column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 1.33 g (71 %) of the title compound.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.59-7.59 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.37 (m, 2H), 5.17 (d, 1H, *J* = 8.9 Hz), 4.51 (dd, 1H, *J* = 3.5, 8.9 Hz), 2.53-2.46 (m, 1H), 1.45 (s, 9H), 1.08 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 6.8 Hz).

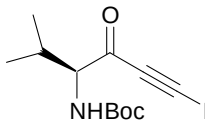
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 187.0, 155.8, 133.1, 130.1, 128.6, 119.6, 94.1, 86.7, 79.8, 65.9, 30.5, 28.3, 19.7, 16.7.

ESIMS *m/z* 302.2 $(M+H)^+$, 324.0 $(M+Na)^+$, 246.1$(M+H\text{-}t\text{-}Bu)^+$, 202.1 $(M+H\text{-}Boc)^+$.

HMRS (ESI) calcd. For C18H24NO3 $(M+H)^+$: 302.1756, found: 302.1751.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 19.95 min, t_{minor} = 17.533 min.

(1-Isopropyl-2-oxo-oct-3-ynyl)-carbamic acid tert-butyl ester (10)



Pale oil, e.e. 96 %, $[\alpha]^d$ = + 0.060° (10 mg/mL CH_2Cl_2).

A solution of hexyne (254 mg, 3.09 mmol) in anhydrous THF was added dropwise to a stirred, to solution of BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.09 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (190 g, 2.18 mmol) in THF (3 mL). After 0.5 h, Boc-Val-NCA (500 mg, 2.06 mmol), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **10** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 472 mg (81 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.08 (d, 1H, *J* = 8.6 Hz), 4.35 (dd, 1H, *J* = 3.6, 8.6 Hz), 2.39 (t, 2H, *J* = 7.0 Hz), 1.60-1.53 (m, 2H), 1.47-1.38 (m, 2H), 1.43 (s, 9H), 1.02 (d, 3H, *J* = 6.9 Hz), 0.92 (t, 3H, *J* = 7.3 Hz), 0.81 (d, 3H, *J* = 6.9 Hz)

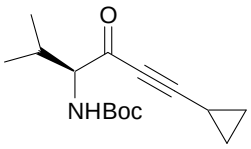
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 187.0, 155.7, 97.7, 79.7, 79.6, 65.8, 30.4, 29.6, 28.2, 21.9, 19.7, 18.7, 16.5, 13.4.

ESIMS *m/z* 282.2 $(M+H)^+$, 304.2 $(M+Na)^+$, 226.2 $(M+H\text{-}t\text{-}Bu)^+$, 182.2 $(M+H\text{-}Boc)^+$, 563.3 $(2M+H)^+$, 585.2 $(2M+ Na)^+$.

HMRS (ESI) calcd. for C16H28NO3 $(M+H)^+$: 282.2069, found: 282.2060.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 11.55 min, t_{minor} = 9.383 min.

(4-Cyclopropyl-1-isopropyl-2-oxo-but-3-ynyl)-carbamic acid tert-butyl ester (11)



White solid, m.p. 40-45°C, e.e. 100%, $[\alpha]^d$ = + 0.050° (10 mg/mL CH_2Cl_2).

A solution of cyclopropylacetylene (284 mg, 4.3 mmol) in anhydrous THF was added dropwise to a stirred, to a solution of BuLi (2.7 mL of a 1.6 M solution in hexanes, 4.3 mmol) in anhydrous THF at -60°C. To the resulting mixture, maintained at -60°C, was added, with stirring, a solution of LiBr (304 mg, 3.49 mmol) in THF (3 mL). After 0.5 h, Boc-Val-NCA (800 mg, 3.29 mmol), diluted in anhydrous THF, was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **11** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 816 mg (94 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.06 (d, 1H, *J* = 8.5 Hz), 4.31 (dd, 1H, *J* = 3.7, 8.9 Hz), 2.38-2.32 (m, 1H), 1.48-1.35 (m, 1H), 1.49 (s, 9H), 1.00 (d, 3H, *J* = 6.9 Hz), 0.98-0.90 (m, 4H), 0.80 (d, 3H, *J* = 6.9 Hz).

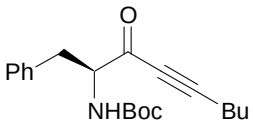
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 186.7, 155.7, 102.3, 79.6, 75.4, 65.6, 30.4, 28.2, 26.8, 19.6, 16.5, 9.9, 0.18.

ESIMS *m/z* 266.2 $(M+H)^+$, 288.2 $(M+Na)^+$, 210.1 $(M+H\text{-}t\text{-}Bu)^+$, 166.1 $(M+H\text{-}Boc)^+$, 531.3 $(2M+H)^+$, 553.3 $(2M+Na)^+$.

HMRS (ESI) calcd. For C15H24N03 $(M+H)^+$: 266.1756, found: 266.1750.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t = 18.65 min.

(1-Benzyl-2-oxo-oct-3-ynyl)-carbamic acid tert-butyl ester (12)



White solid; m.p. 30-32°C; e.e. 20 %.

A solution of hexyne (254 mg, 3.09 mmol) in anhydrous THF was added dropwise to a stirred, to a solution of BuLi (1.9 mL of a 1.6 M solution in hexanes, 3.09 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (190 g, 2.18 mmol) in THF (3 mL). After 0.5 h, Boc-Phe-NCA (600 mg, 2.06 mmol), diluted in anhydrous THF (3 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **12** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 421 mg (61 %).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.24-7.16 (m, 3H), 7.13-7.05 (m, 2H), 4.98 (d, 1H, J = 7.4 Hz), 4.58 (m, 1H), 3.18 (dd, 1H, J = 5.8, 14 Hz), 3.08 (dd, 1H, J = 5.8, 14.0 Hz), 2.33 (t, 2H, J = 6.9 Hz), 1.50-1.42 (m, 2H), 1.40-1.28 (m, 2H), 1.34 (s, 9H), 0.86 (t, 3H, J = 7.3 Hz).

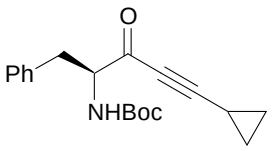
^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 185.9, 155.0, 135.8, 129.5, 128.5, 127.0, 98.7, 79.9, 65.2, 62.0, 37.4, 29.6, 28.3, 22.0, 18.8, 13.5.

ESIMS *m/z*: 330.2 $(M+H)^+$, 274.2 $(M+H\text{-}t\text{-}Bu)^+$, 230.2 $(M+H\text{-}Boc)^+$, 659.4 $(2M+H)^+$.

HMRS (ESI) calcd. For C20H28NO3 $(M+H)^+$: 330.2069, found: 330.2059.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 30.017 min, t_{minor} = 19.2 min.

(1-Benzyl-4-cyclopropyl-2-oxo-but-3-ynyl)-carbamic acid tert-butyl ester (13)



White solid; m.p. 88-90°C; e.e. 18 %.

A solution of cyclopropylacetylene (147 mg, 2.24 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred, to solution of BuLi (1.4 mL of a 1.6 M solution in hexanes, 2.24 mmol) in anhydrous THF at -78°C . To the resulting mixture, maintained at -78°C, was

added, with stirring, a solution of LiBr (158 mg, 1.82 mmol) in THF (1.5 mL). After 0.5 h, Boc-Phe-NCA (500 mg, 1.72 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **13** that was purified by column chromatography on silica gel (9:1 cyclehexane-AcOEt) to afford 343 mg (64 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.32-7.24 (m, 3H), 7.19-7.16 (m, 2H), 5.05 (d, 1H, J = 7.6 Hz), 4.63 (dd, 1H, J = 6.0, 13.7 Hz), 3.21 (dd, 1H, J = 5.9, 14.0 Hz), 3.16 (dd, 1H, J = 5.9, 14.0 Hz), 1.46-1.39 (m, 1H), 1.42 (s, 9H), 1.05-0.98 (m, 2H), 0.97-0.90 (m, 2H).

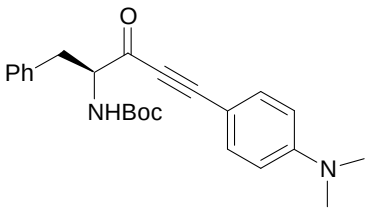
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 185.6, 155.1, 135.8, 129.5, 128.5, 127.0, 103.1, 79.9, 75.2, 61.8, 37.5, 28.3, 10.1, 10.0, -0.10.

ESIMS *m/z*: 314.1 $(M+H)^+$, 336.1 $(M+Na)^+$, 258.1 $(M+H\text{-}t\text{-}Bu)^+$, 214.1 $(M+H\text{-}Boc)^+$, 627.2 $(2M+H)^+$, 649.1 $(2M+Na)^+$.

HMRS (ESI) calcd. For C19H24NO3 $(M+H)^+$: 314.1756, found: 314.1761.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 21.383 min, t_{minor} = 15.467 min.

Tert-butyl 5-(4-(dimethylamino)phenyl)-3-oxo-1-phenylpent-4-yn-2-ylcarbamate (14)



Yellow solid; m.p. 132-134°C; $[\alpha]^d$ = -0.102° (10 mg/mL CH_2Cl_2).

A solution of 4-ethynyl-*N*,*N*-dimethylaniline (313 mg, 2.16 mmol) in anhydrous THF (1.5 mL) was added dropwise to a stirred,to solution of BuLi (1.4 mL of a 1.6 M solution in hexanes, 2.16 mmol) in anhydrous THF at -78°C. To the resulting mixture, maintained at -78°C, was added, with stirring, a solution of LiBr (153 mg, 1.76 mmol) in THF (1.5 mL). After 0.5 h, Boc-Phe-NCA (485 mg, 1.66 mmol), diluted in anhydrous THF (2.5 mL), was slowly added under nitrogen at the same temperature. The resulting mixture was stirred for additional 4h and then allowed to warm up to room temperature. After quenching with a

saturated solution of NH_4Cl, the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was evaporated to obtain crude **2l** that was purified by column chromatography on silica gel (8:2 cyclehexane-AcOEt) to afford 299 mg (46 %).

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.48 (d, 2H, J = 8.9 Hz), 7.31-7.24 (m, 5H), 6.67 (d, 2H, J = 9.0 Hz), 5.22 (d, 1H, J = 7.8 Hz), 4.82 (dd, 1H, J = 5.9, 13.5 Hz), 3.34 (dd, 1H, J = 5.9, 14.0 Hz), 3.28 (dd, 1H, 5.7, 14.0 Hz), 3.1 (s, 6H), 1.46 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 185.5, 155.2, 152.1, 136.2, 135.5, 129.8, 128.6, 127.0, 111.6, 105.0, 99.9, 87.6, 79.9, 61.9, 40.1, 37.9, 28.5.

ESIMS *m/z*: 393.1 $(M+H)^+$, 337.1 $(M+H\text{-}t\text{-}Bu)^+$, 293.1 $(M+H\text{-}Boc)^+$.

HMRS (ESI) calcd. For C24H29N2O3 $(M+H)^+$: 393.2178, found: 393.2183.

HPLC chiralpak AD-H, i-propanol/ hexane = 10/90, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 29.483 min, t_{minor} = 27.000 min.

6.10: Typical procedure for the $PtCl_2$-catalyzed heterocyclisation of α-amino-ynones.

A typical experimental procedure for the heterocyclisation of α-amino-ynones is described.

A mixture of $PtCl_2$ (1.3 mg, 0.005 mmol), K_2CO_3 (1.4 mg, 0.01 mmol), PEG_{3400} (400 mg) and substrate **9** (0.1 mmol) were placed in a microwave reactor. The resulting mixture was heated under microwave irradiation at 70°C (initial power 400W) for 30 min.

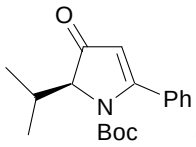
The reaction mixture was solubilized in CH_2Cl_2 (2.0 mL) and precipitated in Et_2O (250 mL). After 3h at -18°C, filtration of catalytic system (PEG_{3400}/catalyst/base) and evaporation of ether afforded pure product **17**.

6.11: Typical procedure for to recycle catalytic system.

A typical experimental procedure for the recycling of the catalytic system is described. The substrate **9** (0.1 mmol) was added to the precipitate PEG_{3400}/Metal/base obtained from first experiment after the precipitation-filtration (Table 4). The mixture was heated under microwave irradiation to give pure product **17** yield evaluated by ^{1}H NMR using CH_2Br_2 as an internal standard).

6.12: Characterization of products.

2-Isopropyl-3-oxo-5-phenyl-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (17)



CAS Registry Number: [1169845-39-9], Yellow solid, m.p. 65-68°C, lit[294]. 70-72°C e.e. 90 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.36-7.34 (m, 5H), 5.53 (s, 1H), 4.11 (d, 1H, J = 3.5 Hz), 2.54 (septuplet, 1H, J = 3.5 Hz), 1.16 (s, 9H), 1.10 (d, 3H, J = 7.0 Hz), 0.95 (d, 3H, J = 7.0 Hz).

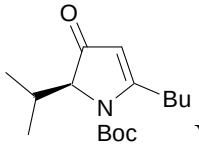
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 201.1, 172.9, 150.3, 133.1, 130.2, 128.0, 127.0, 113.6, 82.6, 71.5, 32.1, 27.6, 17.2, 17.1.

ESIMS *m/z* 302.1 $(M+H)^+$, 246.1 $(M+H\text{-}t\text{-}Bu)^+$, 603.3 $(2M+H)^+$.

HMRS (ESI) calcd. For C18H24NO3 $(M+H)^+$: 302.1756, found: 302.1748.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 9.333 min, t_{minor} = 8.417 min.

5-Butyl-2-isopropyl-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (18)



Yellow oil, e.e. 94%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.30 (s, 1H), 3.92 (d, 1H, J = 3.4 Hz), 3.02-2.70 (m, 2H), 2.52-2.36 (m, 1H), 1.62-1.34 (m, 4H), 1.49 (s, 9H), 1.12 (d, 3H, J = 7.1 Hz), 0.92 (t, 3H, J = 7.0 Hz), 0.79 (d, 3H, J = 7.0 Hz).

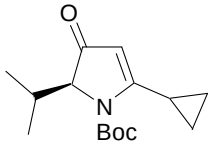
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 200.5, 177.0, 149.4, 110.1, 82.6, 70.2, 31.0, 30.6, 29.7, 28.0, 22.4, 17.3, 15.9, 13.7.

ESIMS *m/z* 282.2 $(M+H)^+$, 304.2 $(M+Na)^+$, 226.2 $(M+H\text{-}t\text{-}Bu)^+$, 563.3 $(2M+Na)^+$.

HMRS (ESI) calcd. For C16H28NO3 $(M+H)^+$: 282.2069, found: 282.2063.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 6.833 min, t_{minor} = 4.817 min.

5-Cyclopropyl-2-isopropyl-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (19)



Yellow solid, m.p. 70-72°C, e.e. 95%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.01 (s, 1H), 3.98 (d, 1H, J = 3.1 Hz), 2.74-2.65 (m, 1H), 2.52-2.42 (m, 1H), 1.53 (s, 9H), 1.17-1.13 (m, 2H), 1.14 (d, 3H, J = 7.0 Hz), 0.84-0.75 (m, 2H), 0.81 (d, 3H, J = 7.0 Hz).

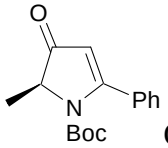
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 200.3, 179.7, 149.9, 105.0, 82.7, 70.8, 30.9, 28.2, 17.5, 16.1, 11.4, 11.3, 11.2.

ESIMS *m/z*: 266.2 $(M+H)^+$, 210.2 $(M+H\text{-}t\text{-}Bu)^+$, 531.4 $(2M+H)^+$.

HMRS (ESI) calcd. For C15H24NO3 $(M+H)^+$: 266.1756, found: 266.1761.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 12.6 min, t_{minor} = 9.083 min.

2-Methyl-3-oxo-5-phenyl-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (20)



CAS Registry Number: [1169845-42-4], Yellow solid, m.p. 80-85°C, lit[294]. 90-92°C, e.e. 48 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.46-7.41 (m, 5H), 5.58 (s, 1H), 4.24 (q, 1H, J = 7.1 Hz), 1.61 (d, 3H, J = 7.1 Hz), 1.29 (s, 9H).

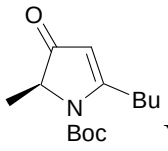
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 201.0, 172.1, 149.7, 132.8, 130.2, 127.9, 127.4, 111.2, 82.8, 63.6, 27.8, 17.6.

ESIMS *m/z* 274.2 $(M+H)^+$, 296.1 $(M+Na)^+$, 218 $(M+H\text{-}t\text{-}Bu)^+$, 174.2 $(M+H\text{-}Boc)^+$.

HMRS (ESI) calcd. For C16H20NO3 $(M+H)^+$: 274.1443, found: 274.1431.

HPLC chiralpak AD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 11.483 min, t_{minor} = 10.917 min.

5-Butyl-2-methyl-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (21)



Yellow oil, e.e. 26%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.38 (s, 1H), 4.01 (q, 1H, J = 7.0 Hz), 2.91 (m, 2H), 1.60-1.39 (m, 4H), 1.49 (s, 9H), 1.44 (d, 3H, J = 7.0 Hz), 0.95 (t, 3H, J = 7.0 Hz).

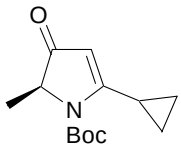
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 201.1, 176.7, 107.9, 82.7, 62.7, 30.9, 29.5, 28.2, 22.4, 17.3, 13.8.

ESIMS *m/z* 254.1 $(M+H)^+$, 276.1 $(M+Na)^+$, 198.1 $(M+H\text{-}t\text{-}Bu)^+$, 507.2 $(2M+H)^+$.

HMRS (ESI) calcd. For C14H24NO3 $(M+H)^+$: 254.1756, found: 254.1759.

HPLC chiralcel OD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 7.767 min, t_{minor} = 7.050 min.

5-Cyclopropyl-2-methyl-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (22)



Yellow oil, e.e. 72%.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 5.02 (s, 1H), 4.02 (q, 1H, J = 7.0 Hz), 2.83-2.74 (m, 1H), 1.54 (s, 9 Hz), 1.45 (d, 3H, J = 7.0 Hz), 1.21-1.16 (m, 2H), 0.87-0.82 (m, 2H).

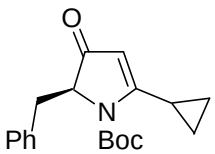
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 200.6, 179.4, 149.6, 102.4, 82.8, 63.2, 28.2, 17.3, 11.9, 11.5, 11.1.

ESIMS *m/z* 238.1 $(M+H)^+$, 260.2 $(M+Na)^+$, 182.1 $(M+H\text{-}t\text{-}Bu)^+$.

HMRS (ESI) calcd. For C13H20NO3 $(M+H)^+$: 238.1443, found: 238.1442.

HPLC chiralcel OD-H, i-propanol/ hexane = 2/98, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 10.183 min, t_{minor} = 9.083 min.

2-Benzyl-5-cyclopropyl-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (23)



Yellow oil, e.e. = 12 %.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.19- 7.17 (m, 3H), 7.07- 7.03 (m, 2H), 4.84 (s, 1H), 4.3 (dd, 1H, *J* = 2.6, 6.1 Hz), 3.44 (dd, 1H, *J* = 6.1, 13.4 Hz), 3.24 (dd, 1H, *J* = 2.6, 13.4 Hz), 2.48-2.42 (m, 1H), 1.61 (s, 9H), 1.02-0.93 (m, 1H), 0.90-0.83 (m, 1H), 0.62-0.59 (m, 1H), 0.11-0.09 (m, 1H).

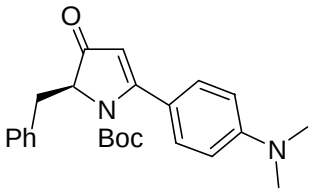
^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 199.8, 179.9, 149.5, 134.5, 129.7, 127.9, 126.8, 105.3, 82.9, 67.1, 36.8, 28.3, 11.2, 10.8, 9.8.

ESIMS *m/z* 314.1 $(M+H)^+$, 336.0 $(M+Na)^+$, 258.1$(M+H\text{-}t\text{-}Bu)^+$, 627.2 $(2M+H)^+$, 649.2 $(2M+Na)^+$.

HMRS (ESI) calcd. for C19H24NO3 $(M+H)^+$: 314.1756, found: 314.1762.

HPLC chiralcel OD-RH, CH^3CN-0.01% TFA/ H_2O-0.01% TFA = 60/40, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 22.717 min, t_{minor} = 20.5 min.

2-Benzyl-5-(4-dimethylamino-phenyl)-3-oxo-2,3-dihydro-pyrrole-1-carboxylic acid tert-butyl ester (24)



Orange oil; e.e. 57 %.

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.20-7.16 (m, 5H), 7.02 (d, 2H, *J* = 8.9 Hz), 6.58 (d, 2H, *J* = 8.9 Hz), 5.35 (s, 1H), 4.42 (dd, 1H, *J* = 2.8, 6.9 Hz), 3.54 (dd, 1H, *J* = 6.3, 13.3 Hz), 3.35 (dd, 1H, *J* = 2.8, 13.3 Hz), 2.98 (s, 6H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 199.2, 174.0, 151.9, 150.2, 135.1, 129.9, 128.0, 126.8, 118.9, 111.1, 110.5, 82.5, 67.6, 40.1, 37.5, 28.0.

ESIMS *m/z* 393.2 $(M+H)^+$, 337.1 $(M+H\text{-}t\text{-}Bu)^+$.

HMRS (ESI) calcd. for C24H29N2O3 $(M+H)^+$: 393.2178, found: 393.2168.

HPLC chiralpak AD-H, i-propanol/ hexane = 10/90, flow rate 1.0 ml/ min, λ 214 nm, t_{major} = 9.8 min, t_{minor} = 8.62 min.

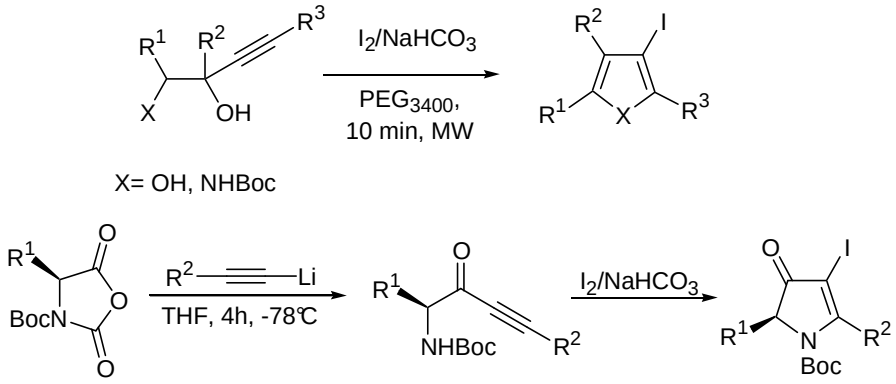
Chapter 7

Electrophilic iodo-mediated cyclization of alkynyl diols, alkynyl amino alcohols and α-amino-ynones

7.1: Introduction.

Iodocyclization is a reaction whereby the intramolecular nucleophilic group attacks the carbon-carbon double or triple bond activated by electrophilic halogenating reagent to give cyclic compounds.

After having studied the platinum or gold cycloisomerization reaction in PEG, we turned our attention to the possibility to perform an electrophilic iodo-mediated cyclization of alkynyl diols, alkynyl amino alcohols and α-aminoynones.



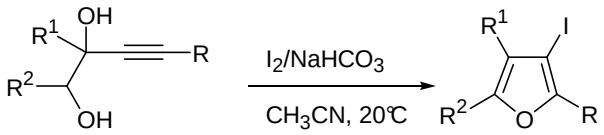
To the best of our knowledge no examples of the synthesis of α-iodopyrrolinone by direct iodocyclization have been reported.

The introduction of one atom of iodine in the aromatic ring system can be exploited to further functionalize the molecule by a palladium-catalyzed cross-coupling reactions, for example Heck, Sonogashira, Suzuki reaction.

7.2: Bibliographic section.

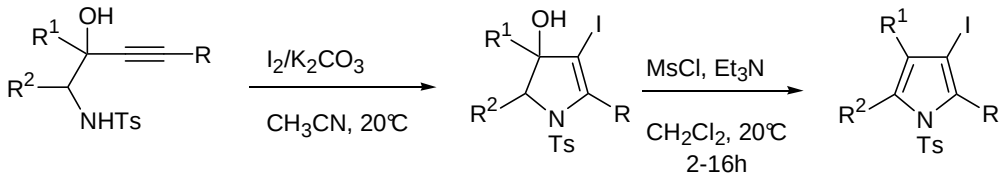
The iodocyclization of alkynyl diols or alkynyl amino alcohols in classical solvents has been already reported in the literature.

Knight and co-workers presented the 5-*endo*-dig cyclisation of 3-alkyne-1,2-diols using iodine as the electrophile, to smoothly afford the corresponding β-iodofurans.[310, 311] The reaction was carried out in acetonitrile (CH_3CN) at room temperature using molecular iodine with $NaHCO_3$ as a base (Scheme 7.1).



Scheme 7.1: Synthesis of β-iodofurans.

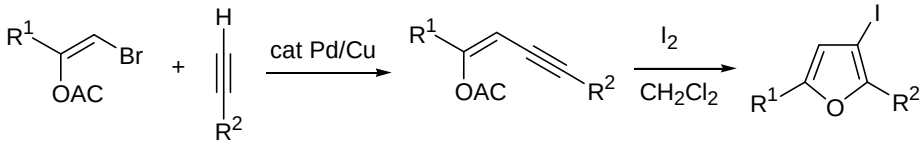
The synthesis of various iodopyrroles has also been described by the same authors starting from the 3-hydroxy-2-sulfonylamino-4-alkynes with an excess of iodine and K_2CO_3. The reaction was carried out at room temperature for 2-16 h (Scheme 7.2). The first step of the reaction involves the formation of the intermediate hydroxyl-dihydropyrroles.[312] The corresponding iodopyrroles were obtained after activation of the alcohol function towards dehydration using MsCl in basic medium.



R= H, alkynyl
R^1= alkyl, aryl
R^2= CO_2Et, Ph, Me

Scheme 7.2: Synthesis of iodopyrroles.

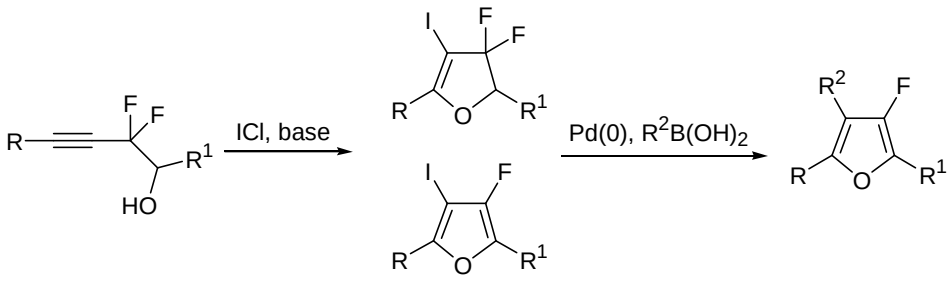
Chen and coworkers described the synthesis of 2,3,5-trisubstituted furans by iodocyclization (Scheme 7.3) starting from the (Z)-enyns acetates with molecular iodine in dichloromethane (CH_2Cl_2) at room temperature. The substrate could be obtained from (Z)-β-haloenol acetates by palladium/copper-catalyzed cross-coupling with terminal alkynes.[313]



Scheme 7.3: Iodocyclization of (Z)-β-haloenol acetates.

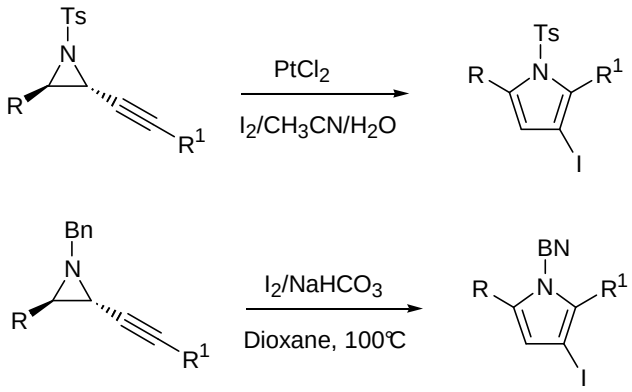
Hammond and co-workers developed the synthesis of 2,4,5-trisubstituted 3-fluorofurans via a sequential iodocyclization and cross-coupling of *gem*-difluorohomopropargyl alcohols.[314]

The iodocyclization carried out with I_2 and ICl, respectively, produced the corresponding fluorinated iodofuran analogues (Scheme 7.4). The system can be functionalized by palladium cross-coupling reaction to afford the corresponding fluoro compound.



Scheme 7.4: Synthesis of fluorinated iodofuran analogues.

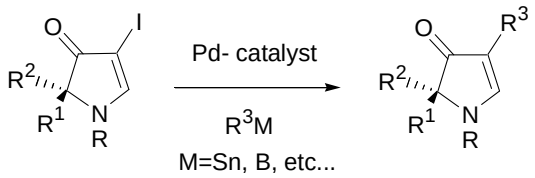
Yoshida and co-workers reported the electrophilic cyclizations of *N*-substituted propargylic aziridines. Disubstituted 3-iodopyrroles were synthesized by reacting propargylic aziridines with iodine at 100°C using $NaHCO_3$ as a base (Scheme 7.5). Whereas *N*-tosyl-substituted substrates required a platinum catalyst to promote the reaction, the iodine-promoted cycloisomerization proceeds smoothly when *N*-benzyl-substituted substrates are employed.[315]



Scheme 7.5: Iodocyclizations of N-substituted propargylic aziridines.

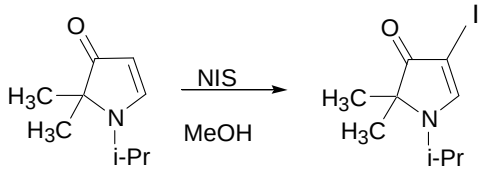
Concerning the synthesis of α-iodopyrrolinone, to the best of our knowledge no examples of this reaction by direct iodocyclization have been reported.

The existence of α-iodopyrrolinone was previously mentioned by Hirschmann and co-workers,[297] however, the synthesis was not illustrated but they used the compound as a starting material for cross-coupling reactions, such as Suzuki and Stille. However, we could find the description of the synthesis of the α-iodopyrrolinones and the conditons for the coupling reactions (Scheme 7.6).



Scheme 7.6: Pd-catalyzed functionalization of C-terminal pyrrolinones.

Two examples of indirect methods of iodination were reported. McNab and co-workers reported that pyrrolinones react readily with N-halogenosuccinimides under standard 'electrophilic' conditions (20 °C, methanol) to give the stable crystalline 4-chloro-, 4-bromo- and 4-iodo-derivatives in 91, 88 and 76% yields respectively (Scheme 7.7). Electrophilic bromination can also be carried out by molecular bromine (in methanol), but these conditions give a 1:1 mixture of product and starting material. [316, 317]

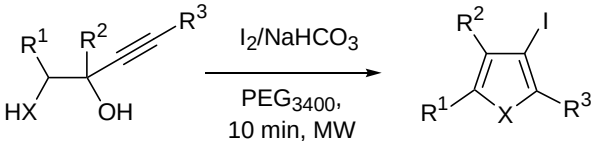


Scheme 7.7: Reaction of pyrrolinones with halogen-electrophiles.

7.3: Results and discussion.

7.3.1: Iodocyclization reaction of alkynyl diols or alkynyl amino alcohols.

We turn our interest towards the iodocyclization reaction of alkynyl diols or alkynyl amino alcohols in alternative solvent, in particular PEG(Scheme 7.8), using the substrates prepared previously (cf. Chapter 5).



1 X= NBoc, R^1= iBu, R^2= CCPh, R^3= Ph **6**
2 X= NBoc, R^1= benzyl, R^2= CCPh, R^3= Ph **7**
3 X= OH, R^1= CH3, R^2= CCPh, R^3= Ph **8**
4 X= OH, R^1= H, R^2= Ph, R^3= Ph **9**
5 X= OH, R^1= H, R^2= Ph, R^3= Cpr **10**

Scheme 7.8: Substrates using for iodocyclization reaction.

The first reaction was carried out using 3 equivalents of molecular iodine I_2, 3 equivalents of $NaHCO_3$ and 300 mg of PEG_{3400}. The mixture was heated under microwave activation for 15 min at 50°C (Table 7.11 entry 1). The reaction mixture was cooled down, dissolved in a small amount of CH_2Cl_2 and precipitated in Et_2O. The product was recovered after a precipitation-filtration work-up. The organic phase was washed with a satured solution of thiosulphate ($Na_2S_2O_3$) to neutralize the excess of iodine (Equation 7.1).

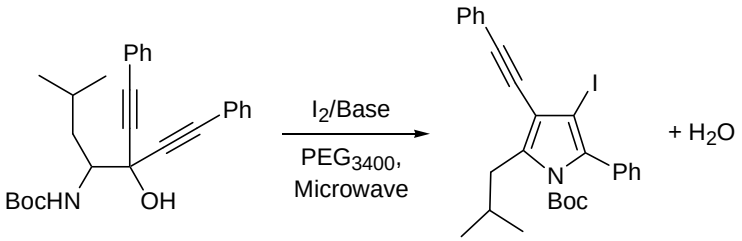
$$I_2 + 2(S_2O_3)^{2-} \rightarrow (S_4O_6)^{2-} + 2I^-$$

Equation 7.1: Neutralization of I_2.

The filtrate was analyzed by ^{1}H NMR, which confirmed the positive outcome of the reaction with a 44% yield.

In the search for a more effective conditions, the reaction time was reduced to ten minutes, however the yield was not improved (42%, entry 2). We also tried to work in more diluted conditions by increasing the quantity of solvent and reducing the amount of I_2 and $NaHCO_3$ (2 equivalents), and the reaction mixture was irradiated at 50°C under microwave irradiation to afford the expected product in 81% yield (entry 3). However, if the reaction was stopped after five minutes, the yield was decreased (69% entry 4).

*Table 7.1: Iodocyclization of **1**, screening of time and molar ratio of I_2 and base.*



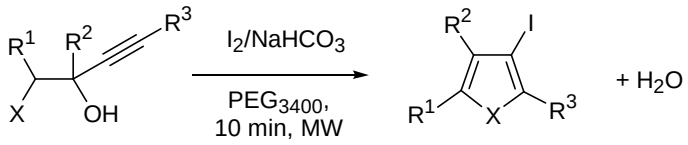
1 **6**

Entry	PEG_{3400} (mg)	Substrate (eq.)	I_2 (eq.)	$NaHCO_3$ (eq.)	Time (min)	Yield (%)[a]
1	300	1	3	3	15	44
2	300	1	3	3	10	42
3	350	1	2	2	10	81
4	350	1	2	2	5	69

a) Yield was determined by ^1H NMR using CH_2Br_2 as internal standard. All the reactions were carried out at 50°C under microwave irradiation.

In all cases the formation of dihydroiodopyrrole as a by-prodcut was not detected. With the method in the hands, the iodocyclization reaction was extended to others diols and amino alcohols. If products **7-9** were obtained in satisfying yields (63- 67%), the substrate **5** gave poor results, may be for his instability in these conditions (37%, entry 5).

Table 7.2: Synthesis of substituted iodofurans and iodopyrroles.

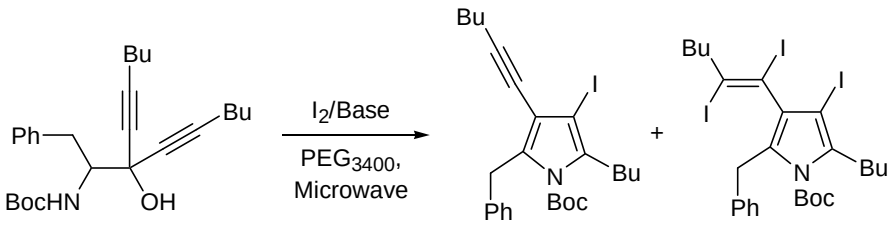


X= OH, NHBoc

Entry	X	R^1	R^2	R^3	Product	°C	Yield[a] (%)
1	NHBoc	i-butyl	-CCPh	Ph	**6**	50	81
2	NHBoc	benzyl	-CCPh	Ph	**7**	55	67
3	OH	CH_3	-CCPh	Ph	**8**	50	66
4	OH	H	Ph	Ph	**9**	55	63
5	OH	H	Ph	cyclopropyl	**10**	55	37

a) Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

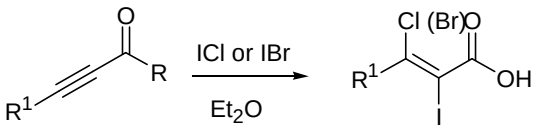
To our surprise, with the *N*-protected aminoalcohol **11** bearing butyl group onto the triple bond, the iodocyclization afforded a mixture of two different products identified respectively as the expected iodocyclized **12** and one of its derivative **13** in which the triple bond was diiodinated (Scheme 7.9).



11 **12:** 59% **13**: 39%

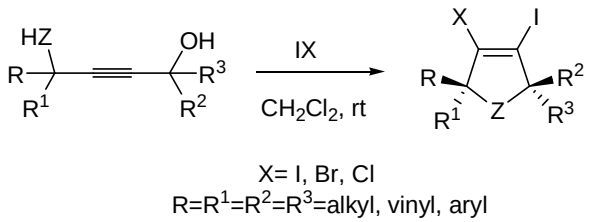
*Scheme 7.9: Iodocyclization of **11** in PEG.*

Several examples describing the double addition of iodine or halogen to alkyne was reported in the literature. For example, Langle and co-workers developed a selective *one-pot* procedure for the production of *E*-dihalo-substituted *α,β*-unsaturated alkenoic acids and derivatives from the corresponding α,β-unsaturated alkynoic acids (Scheme 7.10).[318]



Scheme 7.10: Synthesis of 2,3-dihaloalk-2-enoic acids and derivatives

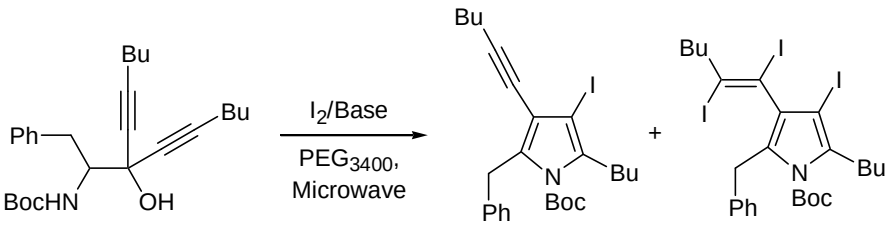
Ji and co-workers reported that 1,4-butyne-diol, 4-aminobut-2-yn-1-ol, and pent-2-yne-1,5-diol derivatives could react with different electrophiles (I_2, IBr, and ICl) at room temperature and both halogen atoms generated from electrophiles were used effectively (Scheme 7.11). Highly substituted dihalogenated dihydrofurans, dihydropyrroles, and dihydro-2*H*-pyrans bearing alkyl, vinyl, aryl, and heteroaryl moieties can be prepared[319, 320] by iodocyclization.



Scheme 7.11: Synthesis of dihalogenated dihydrofurans, dihydropyrroles.

In order to improve the selectivity of reaction we have tested different conditions and the results are summarized in Table 7.3. Iodopyrroles **12** and **13** were prepared through 5-*endo*-trig iodocyclization of the corresponding *N*-protected amino alcohol **11** with iodine (2 equivalents) in the presence or in the absence of a base. The nature of the solvent plays a peculiar role: when $PEG_{2000}(OMe)_2$ was used, the global yield was decreased (entry 2) and product **13** was the major one. The reaction proved to be completely selective towards the formation of product **12**, when K_2CO_3 was the base, even if the yield was low (entry 3).
The selectivity is completely reversed if the reaction is carried out without a base and the product **13** could be obtained in good yield and in a short time (entry 4).

*Table 7.3: Optimization iodocyclization of substrate **11**.*



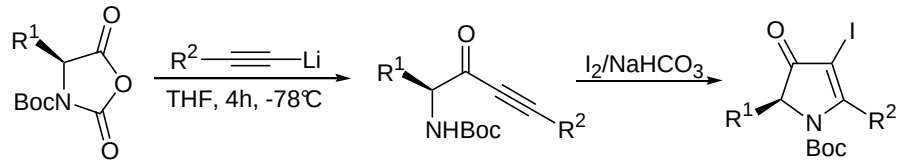
11 **12** **13**

Entry	PEG	Base (eq.)	°C	Time (min)	Yield[a] (%) **12**	Yield[a] (%) **13**
1	PEG_{3400}	$NaHCO_3$ (2)	50	10	50	39
2	$PEG_{2000}(OMe)_2$	$NaHCO_3$ (2)	55	10	18	42
3	PEG_{3400}	K_2CO_3 (2)	55	10	45	0
4	PEG_{3400}	-	55	10	0	71

a) Yields were determined by ^1H NMR using CH_2Br_2 as internal standard. All the reactions were carried out using 350 mg of PEG_{3400}, initial power 400W.

7.3.2: Iodocyclization reaction of α-amino-ynones.

After the study of platinum cycloisomerization reaction in PEG we turned our attention towards the possibility to perform an electrophilic iodo-mediated cyclization reaction of α-aminoynones (Scheme 7.12) preparated previously (c.f. Chapter 6).

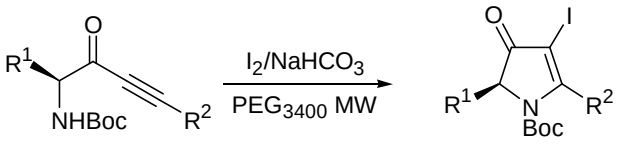


14	R^1= ipr, R^2= Ph	**22**
15	R^1= ipr, R^2= Bu	**23**
16	R^1= ipr, R^2= Cpr	**24**
17	R^1= CH_3, R^2= Ph	**25**
18	R^1= CH_3, R^2= Bu	**26**
19	R^1= CH_3, R^2= Cpr	**27**
20	R^1= Ph, R^2= Ph	**28**
21	R^1= Ph, R^2= Cpr	**29**

Scheme 7.12: α-Amino-ynones using for iodocyclization reaction.

In view of the scarcity of literature reports on the iodocyclization of α-amino-ynones, we report herein our results. We first studied the effects of PEG as the reaction solvent for the iodocyclization, using 2 equivalents of I_2 and sodium carbonate. The mixture was heated up under microwave activation for 10 min at 50°C. The reaction mixture was cooled down, dissolved in a small amount of CH_2Cl_2 and precipitate in Et_2O. The product was recovered after precipitation-filtration. The organic phase was washed with a satured solution of thiosulphate ($Na_2S_2O_3$) to neutralize the excess of iodine. The analysis of the filtrate shows partial conversion of the substrate, but the expected product **22** was obtained in a moderate yield (34%, Table 7.7 entry 1). When the reaction time was extended to 15 minutes, the quantity of iodine increased (3 equivalents) and a base used (entry 2), substrate was completely converted and the product was obtained in 65% yield (entry 2).

Table 7.4: Iodocyclization of α-amino-ynones in PEG_{3400}.



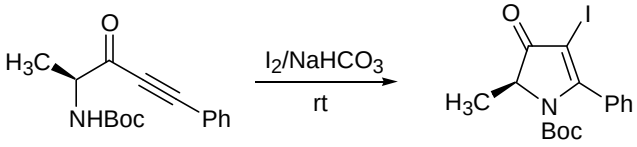
Entry	R^1	R^2	Product	I_2 (eq.)	$NaHCO_3$ (eq.)	Time (min)	Conversion[a] (%)	Yield[a] (%)
1	i-pr	Ph	**22**	2	2	10	70	34
2	i-pr	Ph	**22**	3	3	15	100	65
3	i-pr	Bu	**23**	3	3	15	100	80
4	i-pr	Cpr	**24**	3	3	15	100	64
5	CH_3	Bu	**26**	3	3	15	60	29

a) Yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard.

Different substrates were tested. A good result was obtained when the iodocyclization reaction was carried out using substrate **15** (80% of yield, entry 3). In the same conditions substrate **7** was not reactive (entry 4).

The method proved not to be general, for this reason the iodocyclization reaction was studied in the classic solvents. We tried two common solvents used in iodocyclization reaction such as CH_3CN and CH_2Cl_2 at room temperature. Using acetonitrile full conversion of substrate **17** was reached after 2h affording 67% of corresponding product **25** (Table 7.4) With dichloromethane, total conversion was reached after 75 minutes. The analysis of crude shows many signals of degradation and decomposition, the expected product **25** was recovered in only 32 % of yield.

*Table 7.5: Iodocyclization of **17** in classical solvents.*

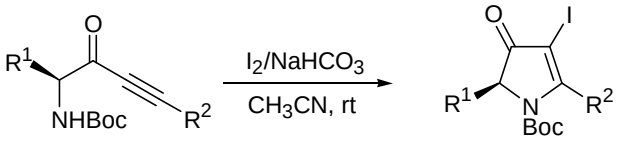


Entry	Solvent	°C	Time (min)	Yield (%)[a]
1	CH_3CN	Rt	120	67
2	CH_2Cl_2	Rt	75	32

a) Yield was determined by ^1H NMR using CH_2Br_2 as internal standard.

Consequently we have preferred to use CH_3CN as solvent for the iodocyclization reaction. The optimized conditions (2 h at rt, entry 1) were applied to various α-aminoynones bearing an aromatic or alkyl group at the end of the acetylene functionality. Excellent results were obtained in all cases (Table 7.6).

Table 7.6: Iodocyclization of α-aminoynones in CH_3CN.



Entry	R^1	R^2	Product	Time (h)	Isolated Yield (%)
1	i-Pr	Ph	**25**	2	74
2	i-Pr	Ph	**25**	1	98
3	i-Pr	Bu	**26**	2	96
4	i-Pr	Cpr	**27**	1	95
5	CH_3	Bu	**29**	2	76
6	CH_3	Cpr	**30**	2	98
7	Benzyl	Ph	**31**	2	99
8	Benzyl	Cpr	**32**	2	98

3 Equivalents of iodine in acetonitrile (CH_3CN) were found to promote iodocyclization of α-amino-ynones to afford the β-iodo pyrrolinones.

The enantiomeric excess was also verified by chiral HPLC. Less epimerization occured during the reaction (Figure 7.1).

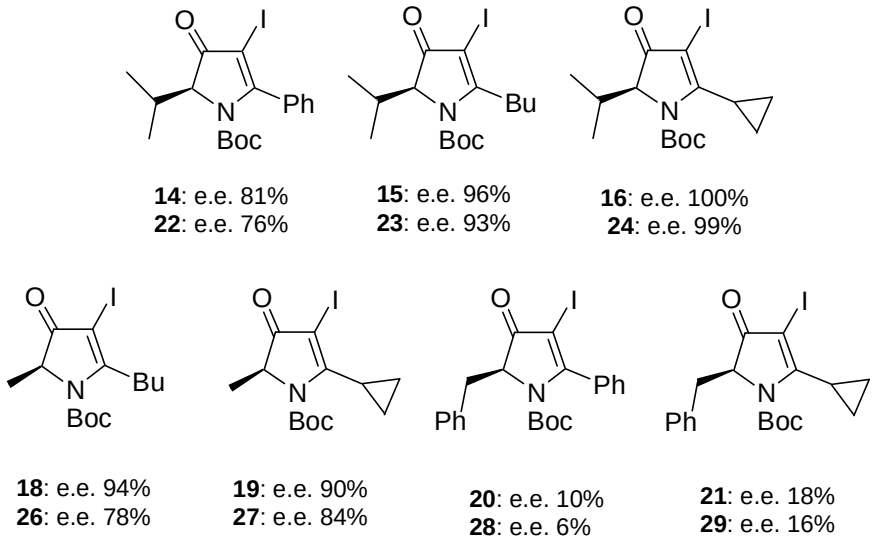
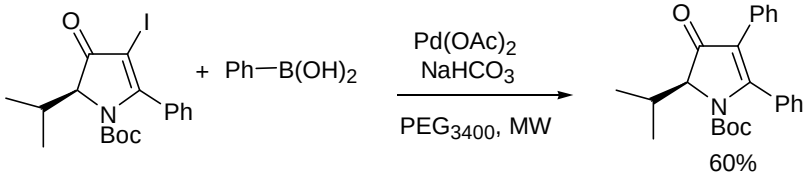


Figure 7.1: Study of loss of enantiomeric excess of iodo-pyrrolinones.

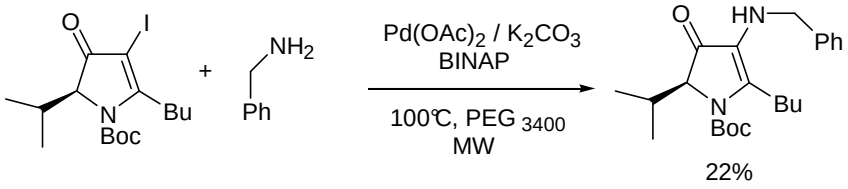
Subsequent functionalization of the resulting heterocycles by palladium-catalyzed coupling reactions led to a number of interesting five- substituted skeletons.

We have test Suzuki cross-coupling in PEG. In a preliminary experiment we carried out the reaction in PEG_{3400}, using 5 mol % of $Pd(OAc)_2$, 3 equivalents of Na_2CO_3 as base, and 1 equivalent of phenyl boronic acid. The reaction was heated under microwave activation for 2,5 h at 100°C. By ^1H NMR analysis it was possible to observe the expected product in 60% of yield.



Scheme 7.13: Suzuki cross-coupling in PEG.

Buchwald-Hartwig amination reaction was also tested. The reaction was carried out in PEG, using 2 mol% of $Pd(OAc)_2$ and BINAP as ligand, 3.5 equivalents of K_2CO_3, and 1.2 equivalent of benzylamine. After 30 min. at 100°C, the presence of the product was detected but a complex reaction mixture was obtained. Preliminary results suggest the possibility to obtain the expected product but the yield was poor.



Scheme 7.14: Buchwald-Hartwig amination reaction in PEG.

7.4: Conclusion.

The iodocyclization reaction of alkynyl diols and alkynyl amino alcohols was presented. The iodopyrroles and iodofurans were obtained in short reaction time (10 min), in a satisfying yield, using an alternative solvent (PEG) under microwave activation. It was also possible to put in evidence the formation of unprecedented compound **13**, issued of the addition of three atoms of iodine, iodination in β-position of ring system and di-iodination of the triple bond.
Direct coupling reactions to perform new carbon-carbon bond formation involving organolithium, organocopper, organozinc, organotin or metal-catalyzed cross-coupling reactions, are tested for further derivatization.

Also the iodocyclization reaction of α-amino-ynones, preparated previolusly from UNCAs, was tested. It was also possible to put in evidence the unprecedent formation of iodo-pyrrolin-4-ones in mild condition. Excellent yields (74-99%) were obtained and less epimerization occured during the reaction. Suzuki cross-coupling and Buchwald-Hartwig amination reaction were tested in PEG_{3400} under microwave activation. Preliminary results have confirmed the presence of expected products.

Experimental section

7.5: General remarks.

The solvents were purified by distillation over a drying agent. Chemical shifts (δ) of ^{1}H NMR and ^{13}C NMR spectra are reported in ppm relative to residual solvent signals ($CHCl_3$ in $CDCl_3$: δ = 7.27 ppm for ^{1}H and $CDCl_3$: δ = 77 ppm for ^{13}C. *J*- values are given in Hz. ^{1}H and ^{13}C NMR was registered on Bruker Avance-300 MHz, Bruker Avance 400 MHz. Microwave-assisted reactions were performer with a Biotage Initiator^{TM} 2.0. Instrument. Temperature was measured with an IR sensor on the surface of the reaction vial. LC-MS analysis were performed with HPLC Waters Alliance 2695 (UV Waters 2489), column Onyx C_{18}, 25 mn x 4.6 mn, flow 3 ml/min (H_2O-0.1% HCO_2H (A)/CH_3CN 0.1% HCO_2H (B)) gradient 0 to 100% in 2.5 min. HRMS analysis were performed on a Q-Tof (Waters, 2001) with ESI. Chiral HPLC analysis was performed with Beckman Coulter System Gold 126 Solvent Module and Beckman Coulter System Gold 168 Detector. Column: Chiralpak AD-H 0.46 cm x 25 cm, Chiralcel OD-H 0.46 cm x 25 cm. Chiral HPLC phase inverse: Chiralcel OD-RH 0.46 cm x 25 cm.

7.6: Typical procedure of iodocyclization in PEG.

A typical experimental procedure for the iodocyclisation is described.

A mixture of I_2 (25 mg, 0.1 mmol), $NaHCO_3$ (8.4 mg, 0.1 mmol), PEG_{3400} (350 mg) and substrate **1** (0.05 mmol) were placed in a microwave reactor. The resulting mixture was heated under microwave irradiation at 50°C (initial power 400W) for 10 min.

The reaction mixture was solubilized in CH_2Cl_2 (2.0 mL) and precipitated in Et_2O (250 mL). After 3h at -18°C, by precipitation-filtration work-up the organic phase was washed with a satured solution of thiosulphate ($Na_2S_2O_3$) to neutralize the excess of iodine and the product **6** was recovered.

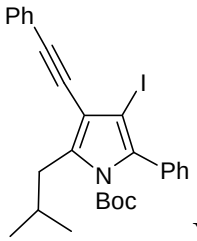
7.7: Typical procedure of iodocyclization in CH_3CN.

A typical experimental procedure for the iodocyclisation is described. In a stirred solution of substrate **14** (0.1 mmol), $NaHCO_3$ (25.2 mg, 0.3 mmol) and 0.5 mL of CH_3CN was added I_2 (76.2 mg) and 0.5 mL of CH_3CN. After 2h at r.t, the organic phase was evaporated under

vacuo. The crude was dissolved in AcOEt and washed with a satured solution of thiosulphate ($Na_2S_2O_3$) to neutralize the excess of iodine and the product **22** was recovered.

7.8: Characterization of products.

Iodo-pyrrole (6)



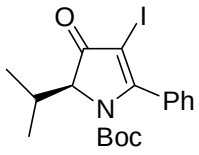
Yellow oil

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.58-7.55 (m, 2H), 7.43-7.31 (m, 8H), 3.00 (d, 2H, J = 7.1 Hz), 2.03 (septuplet, 1H), 1.18 (s, 9H), 1.04 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 148.6, 140.3, 134.8, 134.3, 128.26, 127.8, 123.8, 112.7, 93.6, 84.5, 84.4, 75.1, 36.3, 29.7, 27.0, 22.6.

HMRS (ESI) calcd. for C27H29NO2I $(M+H)^+$: 526.1243, found: 526.1245.

Iodopyrrolin-4-one (22)



yellow oil, e.e. 76%

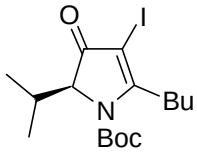
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49-7.40 (m, 5H), 4.35 (d, 1H, *J* = 3.5 Hz), 2.60 (septuplet, 1H, *J* = 3.5 Hz), 1.18 (d, 3H, *J* = 7.0 Hz), 1.16 (s, 9H), 0.95 (d, 3H, *J* = 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 197.0, 171.2, 149.3, 133.6, 130.0, 128.1, 127.8, 83.1, 80.72, 69.8, 32.2, 27.5, 17.1, 16.8.

HMRS (ESI) calcd. for C18H23NO3I $(M+H)^+$: 428.0723, found: 428.0714.

ESIMS *m/z* 427.9 $(M+H)^+$, 449.9 $(M+Na)^+$, 371.9 $(M+H-t\text{-}Bu)^+$, 327.9 (M+H-Boc).

Iodopyrrolin-4-one (23)



e.e. 93%

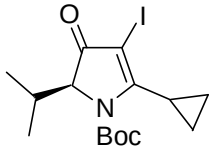
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.16 (d, 1H, *J* = 3.4 Hz), 3.24-3.17 (m, 1H), 3.00-2.96 (m, 1H), 2.45-2.39 (m, 1H), 1.67-1.44 (m, 4H), 1.47 (s, 9H), 1.15 (d, 3H, *J* = 7.1 Hz), 0.96 (t, 3H, *J* = 7.0 Hz), 0.76 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 196.0, 175.7, 148.5, 83.4, 77.2; 69.6, 32.3, 31.2, 30.1, 28.1, 22.9, 17.4, 15.9, 13.9.

HMRS (ESI) calcd. for C16H27NO3I $(M+H)^+$: 408.1036, found: 408.1030.

ESIMS *m/z* 408.0$(M+H)^+$, 429.2 $(M+Na)^+$, 352.0 (M+H-*t*-Bu)$^+$, 837.1 $(2M+Na)^+$.

Iodopyrrolin-4-one (24)



e.e. 99%

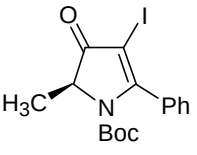
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.13 (d, 1H, *J* = 3.1 Hz), 2.45-2.39 (m, 1H), 2.28-2.21 (m, 1H), 1.51 (s, 9H), 1.33-1.1 (m, 4H), 1.03 (d, 3H, *J* = 7.0 Hz), 0.74 (d, 3H, *J* = 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 197.2, 173.8, 149.3, 83.1, 77.4, 69.6, 31.5, 28.1, 17.2, 16.2, 13.9, 10.6, 9.5.

HMRS (ESI) calcd. for C15H23NO3I $(M+H)^+$: 392.0723, found: 392.0721.

ESIMS *m/z* 392.0 $(M+H)^+$, 414.0 $(M+Na)^+$, 336.0 (M+H-*t*-Bu)$^+$.

Iodopyrrolin-4-one (25)



e.e. 64%

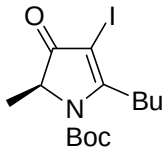
^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.49-7.47 (m, 3H), 7.39-7.36 (m, 2H), 4.41 (q, 1H, *J* = 7.04 Hz), 1.64 (d, 3H, *J* = 7.04 Hz), 1.20 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 197.3, 170.8, 148.7, 133.3, 130.0, 128.1, 127.8, 83.3, 78.0, 61.8, 27.6, 17.8.

ESIMS *m/z* 400.0$(M+H)^+$, 422.1 $(M+Na)^+$, 344.1 $(M+H\text{-}t\text{-}Bu)^+$, 300.0 (M+H-Boc), 821.1 $(2M+Na)^+$.

HMRS (ESI) calcd. For C16H19NO3I $(M+H)^+$: 400.0410, found: 400.0407.

Iodopyrrolin-4-one (26)



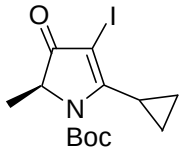
e.e. 78%

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.20 (q, 1H, *J* = 7.0 Hz), 3.16-3.03 (m, 2H), 1.68-1.44 (m, 4H), 1.49 (s, 9H), 1.44 (d, 3H, *J* = 7.0 Hz), 0.98 (t, 3H, *J* = 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 196.7, 175.3, 148.3, 83.5, 76.8, 76.0, 61.8, 32.0, 29.8, 28.1, 22.8, 17.8, 13.9.

HMRS (ESI) calcd. For C14H23NO3I $(M+H)^+$: 380.0723, found: 380.0731.

Iodopyrrolin-4-one (27)



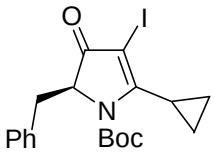
e.e. 84%

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 4.12 (q, 1H, *J* = 7.0 Hz), 2.32-2.24 (m, 1H), 1.47 (s, 9 Hz), 1.45 (d, 3H, *J* = 7.0 Hz), 1.18-1.10 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 197.6, 172.9, 148.9, 83.2, 73.9, 61.6, 28.2, 17.8, 13.4, 10.3, 9.9.

HMRS (ESI) calcd. for C13H19N03I $(M+H)^+$: 364.0410, found: 364.0407

Iodopyrrolin-4-one (28)



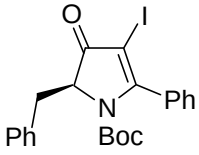
e.e. 16%

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.27- 7.16 (m, 3H), 6.96-6.93 (m, 2H), 4.41 (dd, 1H, *J* = 2.6, 6.1 Hz), 3.42 (dd, 1H, *J* = 6.1, 13.4 Hz), 3.28 (dd, 1H, *J* = 2.6, 13.4 Hz), 1.91-1.81 (m, 1H), 1.59 (s, 9H), 0.99-0.88 (m, 1H), 0.90-0.83 (m, 1H), 0.45-0.38 (m, 1H), 0.21-0.17 (m, 1H).

HMRS (ESI) calcd. for C19H23NO3I $(M+H)^+$: 440.0723, found: 440.0715.

ESIMS *m/z* 440.0 $(M+H)^+$, 462.1 $(M+Na)^+$, 383.9 $(M+H\text{-}t\text{-}Bu)^+$, 901.0 $(2M+Na)^+$.

Iodopyrrolin-4-one (29)



e.e. 6%

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.28-7.18 (m, 7H), 7.04-7.00 (m, 2H), 4.56 (dd, 1H, *J* = 2.8, 6.9 Hz), 3.55 (dd, 1H, *J* = 6.3, 13.3 Hz), 3.39 (dd, 1H, *J* = 2.8, 13.3 Hz), 1.11 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 196.6, 172.1, 148.6, 134.1, 133.3, 129.7, 128.1, 127.9, 127.3, 83.1, 80.1, 65.5, 37.6, 27.6.

HMRS (ESI) calcd. For C22H23NO3I $(M+H)^+$: 476.0723, found: 476.0719.

ESIMS *m/z* 475.9 $(M+H)^+$, 497.9 $(M+Na)^+$, 419.9 $(M+H\text{-}t\text{-}Bu)^+$, 375.9 (M+H-Boc), 973.0 $(2M+Na)^+$.

Chapter 8

Formation of Isoquinolines by Pd-Catalyzed Oxidative Carbonylation of (2-Alkynyl)benzylideneamines.

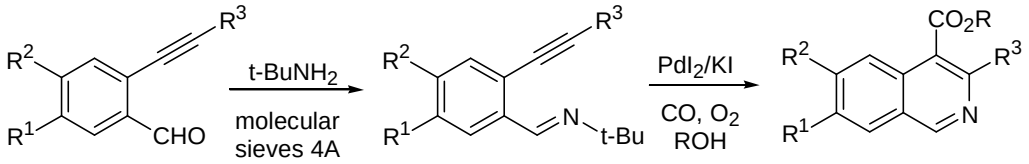
8.1: Introduction.

The syntheses catalyzed by PdI_2-based systems promote different kind of oxidative carbonylations under mild conditions to afford important carbonyl derivatives with high selectivity and efficiency.

Isoquinoline carboxylic derivatives are important family of heterocycle derivatives endowed with biological activities.

Due to the importance of isoquinoline derivatives in organic chemistry, the progress of new synthetic approaches with various reaction conditions remains an active research area.

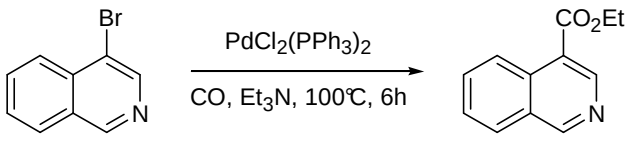
In particular, the developments towards the one-step synthesis of synthesis of isoquinoline-4-carboxylic esters starting from (2-alkynyl)benzylideneamines are described.



8.2: Bibliographic section.

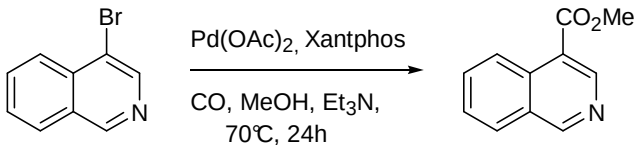
Different approaches for the synthesis of isoquinoline carboxylic derivatives are described in the literature using direct or indirect carbonylative methods and we are presenting some examples.

Palladium-catalyzed alkoxycarbonylation of heterocyclic halides such as pyridine, pyrimidine and isoquinolines, leads to the synthesis of heterocyclic esters (Scheme 8.1).[321]



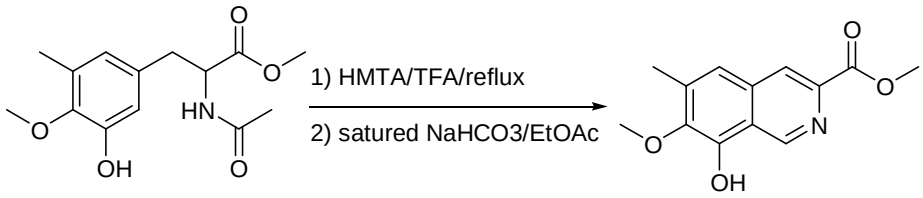
Scheme 8.1: Palladium catalyzed alkoxycarbonylation of aryl bromides.

A method for the Pd-catalyzed carbonylation of aryl bromides has been developed using Xantphos as the ligand.[322] This method is effective for the direct synthesis of Weinreb amides, 1° and 2° benzamides, and methyl esters from the corresponding aryl bromides at atmospheric pressure (Scheme 8.2).



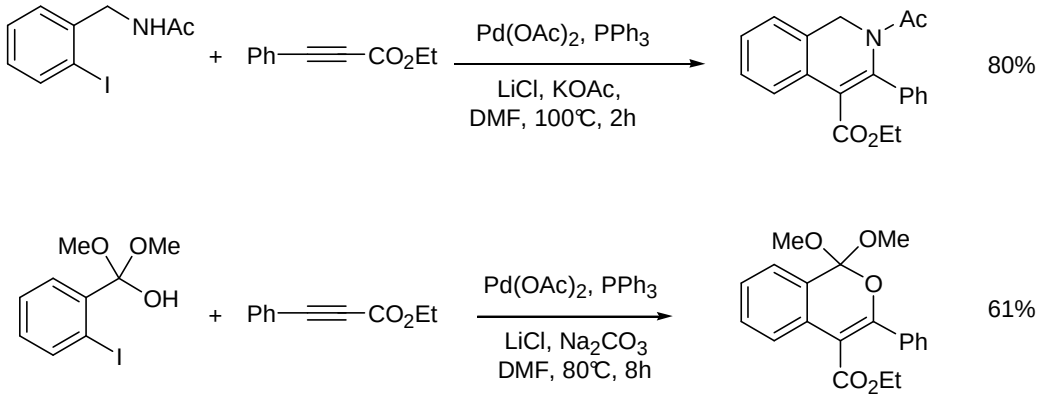
Scheme 8.2: Synthesis of isoquinolines methyl esters via Pd-catalyzed alkoxycarbonylation.

Isoquinoline-3-carboxylates constitute a wide spectrum of compounds attracting much interest, due to their various biological activities. Liu and co-workers have reported the synthesis of isoquinoline-3-carboxylate framework through formylation of 2' position of *N*-acetyl-(3'-hydroxy-4'-methoxy-5'-methyl)phenylalanine methyl ester by Duff reaction (Scheme 8.3).[323]



Scheme 8.3: Synthesis of isoquinoline-3-carboxylate framework by Duff reaction.

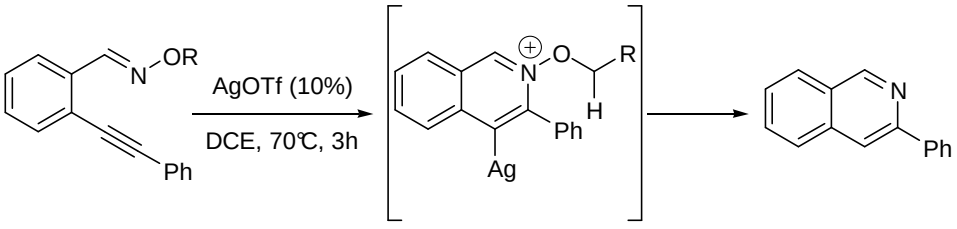
Larock and co-worker have reported the synthesis of aromatic heterocycles via palladium-catalyzed annulation of internal alkynes.[324] This strategy allows the access to a wide variety of heterocycles, including 1,2-dihydroisoquinolines, benzofurans, benzopyrans, and isocoumarins (Scheme 8.4).



Scheme 8.4: Synthesis of isoquinolines and isochromenes via palladium-catalyzed annulation of internal alkynes.

Shin and co-workers have reported that under AgOTf and Brønsted acid co catalysis, *O*-alkyl *o*-alkynylbenzaldoxime derivatives undergo a cyclization- induced N–O cleavage to produce isoquinolines with the simultaneous oxidation of *O*-alkyl group.[325]

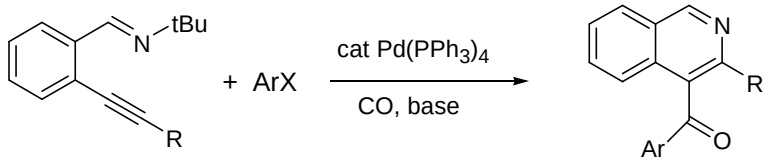
This redox-based method provides a general access to diverse isoquinoline derived heterocycles that are simple, efficient, and tolerant of various functional groups from readily available and hydrolytically stable oxime precursors (Scheme 8.5).



Scheme 8.5: Isoquinoline synthesis via redox reactions of O-alkyl oximes.

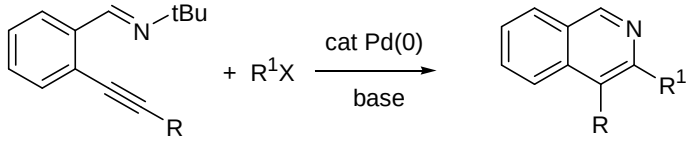
Larock and co-workers have reported an efficient synthetic approach for the carbonylative cyclization of *N-tert*-butyl-2-(1-alkynyl)benzaldimines and aryl halides to the corresponding 3-substituted 4-aroylisoquinolines in the presence of CO and a palladium catalyst (Scheme

8.6). Synthetically, the methodology provides a simple and convenient route to isoquinolines containing an aryl, alkyl, or vinylic group at C-3 and an aroyl group at C-4 of the isoquinoline ring. The reaction is believed to proceed via cyclization of the alkyne containing a proximate nucleophilic center promoted by an acylpalladium complex.[326]



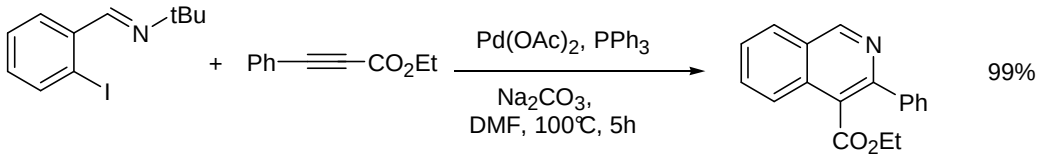
Scheme 8.6 Synthesis of 3-substituted 4-aroylisoquinolines.

The same group have also reported, the palladium-catalyzed synthesis of 3,4-disubstituted isoquinolines from readily available *N*-*tert*-butyl-2-(1-alkynyl)arylaldimines and various organic halides (Scheme 8.7).[327, 328]



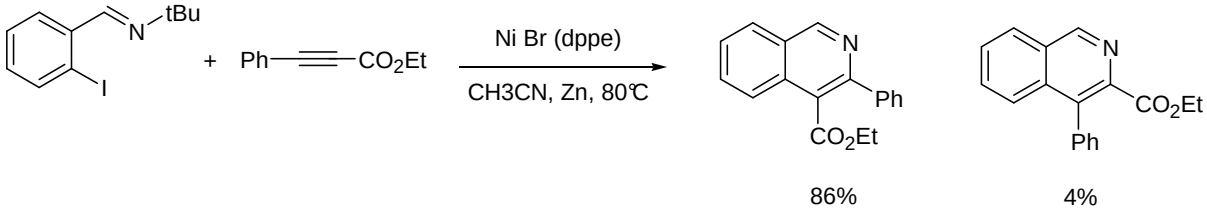
Scheme 8.7: Synthesis of 3,4-disubstituted isoquinolines.

A wide variety of substituted isoquinolines, tetrahydroisoquinolines, 5,6-dihydrobenz[*f*]isoquinolines, pyrimidines, and pyridine heterocycles have been prepared in good to excellent yields via annulation of internal acetylenes with the *tert*-butylimines of *o*-iodobenzaldehydes and 3-halo-2-alkenals in the presence of a palladium catalyst. The best results were obtained by employing 5 mol % of $Pd(OAc)_2$, an excess of the alkyne, 1 equiv of Na_2CO_3 as a base, and 10 mol % of PPh_3 in DMF as the solvent (Scheme 8.8). This annulation methodology is particularly effective for aryl- or alkenyl-substituted alkynes.[329, 330]



Scheme 8.8: Synthesis of isoquinolines by the palladium-catalyzed annulation of internal alkynes.

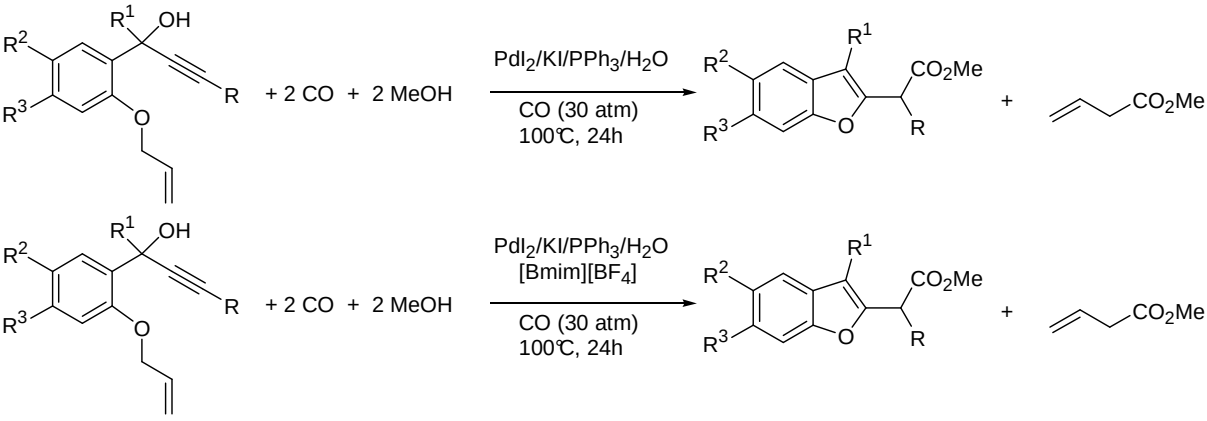
Cheng and co-workers have reported that a wide range of substituted isoquinolines were synthesized via a highly efficient nickel-catalyzed annulation of the tert-butyl imines of 2-iodobenzaldehydes and various alkynes (Scheme 8.9). The examination of the regiochemistry of isoquinolines synthesized indicates that there are two different alkyne insertion pathways for the catalytic reactions with asymmetric alkyne.[331]



Scheme 8.9: Ni-catalyzed annulation reactions.

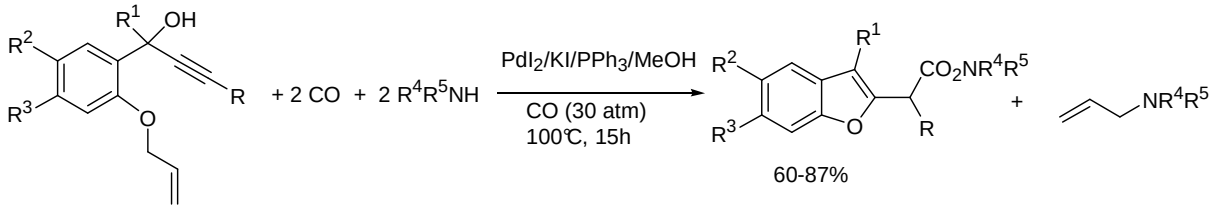
In the laboratory, different studies in the field of carbonylation reactions were developed. Gabriele and co-workers have found that PdI_2, in conjunction with an excess of iodide anions, constitutes an exceptionally efficient, selective and versatile catalyst for promoting a variety of oxidative carbonylation processes, leading to important acyclic as well as heterocyclic carbonyl compounds.[79, 80] Here some just recent examples are described.

The synthesis of benzofuran-2-acetic esters starting from 1-(2-allyloxyphenyl)-2-yn-1-ols by sequential Pd (0)-catalyzed deallylation Pd (II)-catalyzed carbonylative heterocyclization was reported (sequential homobimetallic catalysis). The transformation takes place in classical solvent[332] and in IL[333] as reaction medium (Scheme 8.10).



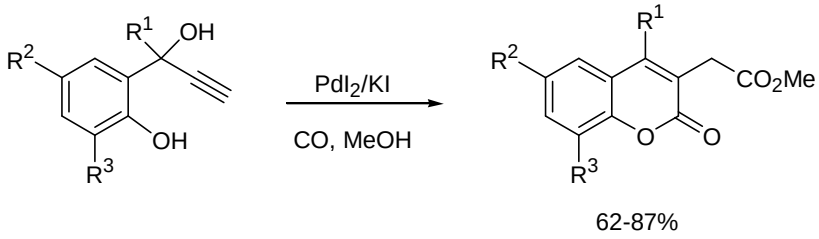
Scheme 8.10: Sequential homobimetallic catalysis.

The synthesis of 2-benzofuran-2-ylacetamides was also undertaken, starting from readily available 1-(2-allyloxyaryl)-2-yn-1-ols, amines, and CO (Scheme 8.11). Carbonylation reactions are carried out under relatively mild conditions and in the presence of a PdI_2-based catalytic system.[334]



Scheme 8.11: Synthesis of 2-benzofuran-2-ylacetamides by sequential homobimetallic catalysis.

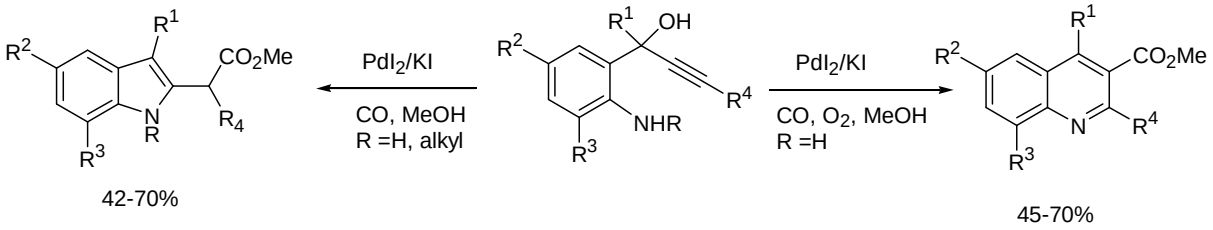
Synthesis of 3-[(alkoxycarbonyl)methyl]coumarins starting from readily available 2-(1-hydroxyprop-2-ynyl)phenols, based on palladium-catalyzed dicarbonylation process was reported (Scheme 8.12). Reactions were carried out in the presence of catalytic amounts of PdI_2 in conjunction with an excess of KI in MeOH as the solvent at room temperature and under 90 atm of CO, to give coumarin derivatives in good to high yields.[335]



Scheme 8.12: Synthesis of coumarine derivatives by Pd-carbonylation reaction.

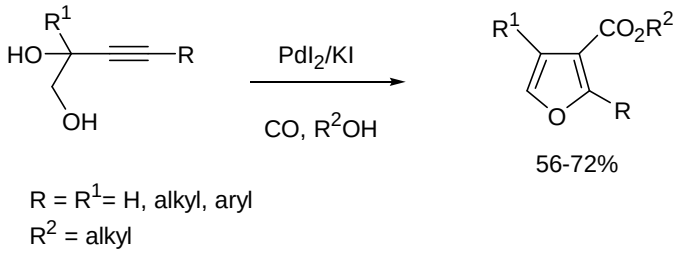
1-(2-Aminoaryl)-2-yn-1-ols were subjected to carbonylative conditions in the presence of the PdI_2-KI catalytic system.[336] Under oxidative conditions 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group were selectively converted into quinoline-3-carboxylic esters in fair to good yields ensuing from 6-*endo*-dig cyclization followed by dehydration and oxidative methoxycarbonylation. Under nonoxidative conditions, 1-(2-aminoaryl)-2-yn-1-ols bearing either a primary or secondary amino group and substituted with a bulky group on the triple

bond were converted into indol-2-acetic esters, deriving from 5-*exo*-dig cyclization followed by dehydrating methoxycarbonylation (Scheme 8.13).



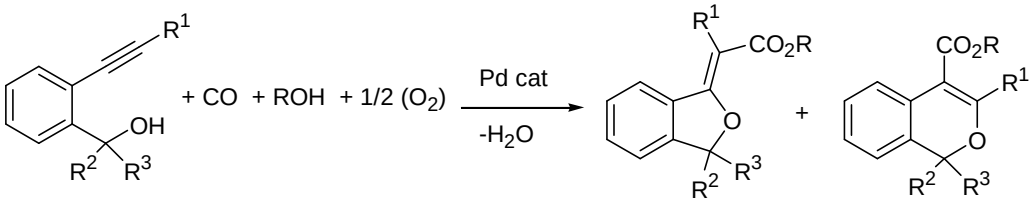
Scheme 8.13: Palladium-catalyzed carbonylation of 1-(2-aminoaryl)-2-yn-1-ols.

The synthesis of furan-3-carboxylic esters was presented, based on palladium-catalyzed direct oxidative carbonylation of readily available 3-yne-1,2-diols (Scheme 8.14). The process, corresponding to a sequential combination between a 5-*endo*-dig heterocyclodehydration step and an oxidative alkoxycarbonylation stage, is catalyzed by PdI_2 in conjunction with an excess of KI under relatively mild conditions.[337]



Scheme 8.14: Palladium-catalyzed oxidative heterocyclodehydration-alkoxycarbonylation of 3-yne-1,2-diols.

1,3-Dihydroisobenzofurans containing an (alkoxycarbonyl)methylene chain and 4-(alkoxycarbonyl)benzo[*c*]pyrans have been easily obtained by PdI_2/KI-catalysed oxidative cyclization/alkoxycarbonylation of readily available 2-alkynylbenzyl alcohols (Scheme 8.15).[338]

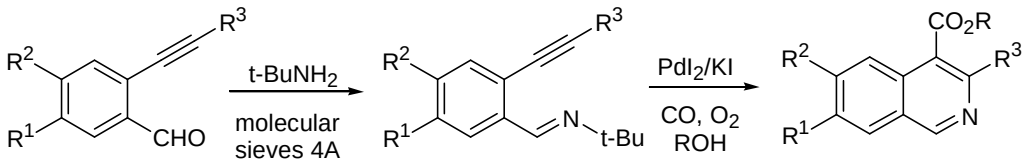


Scheme 8.15: Oxidative carbonylation of 2-alkynylbenzyl alcohols.

8.3: Results and discussion.

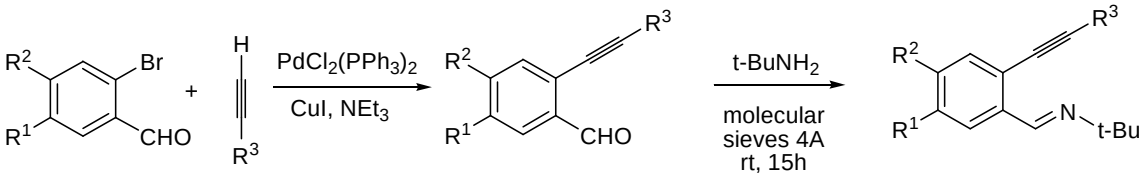
In this work we have tested the possibility to obtain isoquinoline-4-carboxylic esters by readily available *tert*-butyl-(2-alkynylbenzylidene)amines (Scheme 8.16) via a direct PdI_2-catalyzed oxidative heterocyclization-alkoxycarbonylation.[339]

The hypothesis of PdI_2-catalyzed heterocyclization-alkoxycarbonylation processes for the synthesis of isoquinoline-4-carboxylic esters can be explained by different studies in the field of carbonylation reactions developed in the laboratory and detailed before.



Scheme 8.16: Synthesis of isoquinoline-4-carboxylic esters by PdI_2-catalyzed oxidative heterocyclization-alkoxycarbonylation.

The substrates **10**-**14** were prepared in two steps reaction: Sonogashira coupling reaction followed by condensation of *tert*-butylamine (Scheme 8.17).



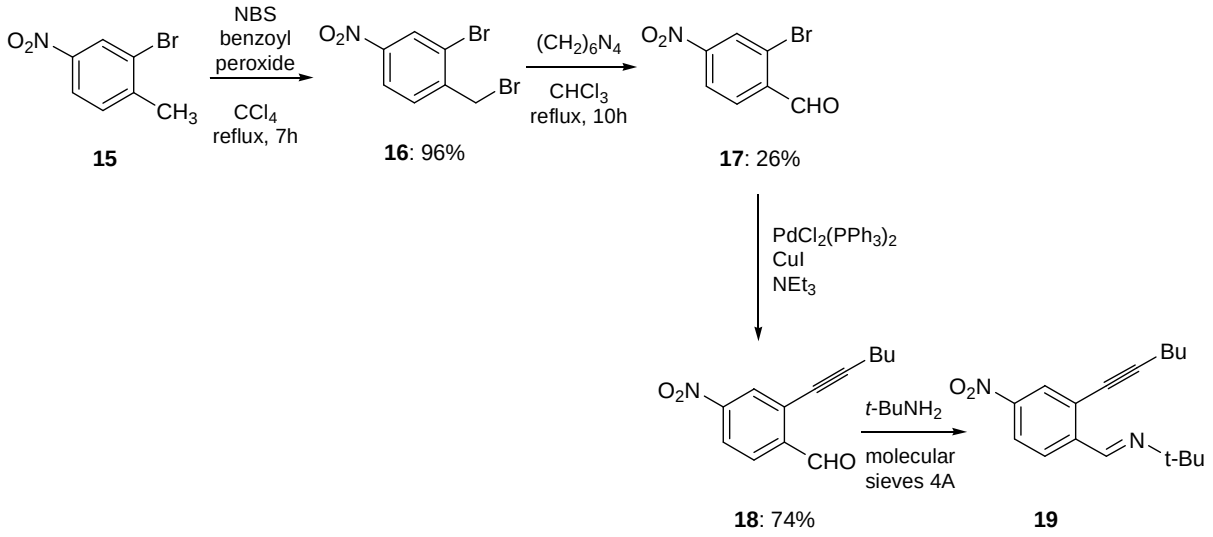
1 R^1= R^2= H
2 R^1= NO_2, R^2= H
3 R^1= H, R^2= CH_3
4 R^1= OCH_3, R^2= H

5 R^1= R^2= H, R^3= Bu, 85%
6 R^1= R^2= H, R^3= CH_2OTHP, 85%
7 R^1= NO_2, R^2= H, R^3= Bu, 52%
8 R^1= H, R^2= CH_3, R^3= Bu, 98%
9 R^1= OCH_3, R^2= H, R^3= Bu, 73%

10 R^1= R^2= H, R^3= Bu
11 R^1= R^2= H, R^3= CH_2OTHP
12 R^1= NO_2, R^2= H, R^3= Bu
13 R^1= H, R^2= CH_3, R^3= Bu
14 R^1= OCH_3, R^2= H, R^3= Bu

*Scheme 8.17: Preparation of (2-alkynylbenzylidene)(tert-butyl)-amines **10**-**14**.*

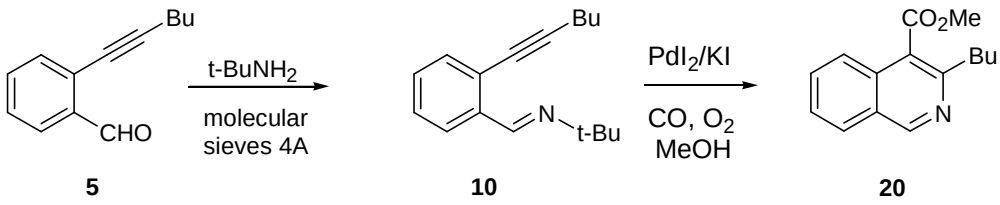
2-Bromo-4-nitrobenzaldehyde **17** was not commercially available, for this reason other two steps were required (Scheme 8.18) for its synthesis. 2-Bromo-4-nitrobenzoyl bromide **16** was obtained by reaction with 2-bromo-4-nitrotoluene **15** (commercially available), *N*-bromosuccimide and benzoyl peroxide. The compound **16** was transformed in **17** by formylation reaction using hexamethylenetetramine.



*Scheme 8.18: Preparation of 2-nitro-tert-butyl-(2-hex-1-ynylbenzylidene)amine **19**.*

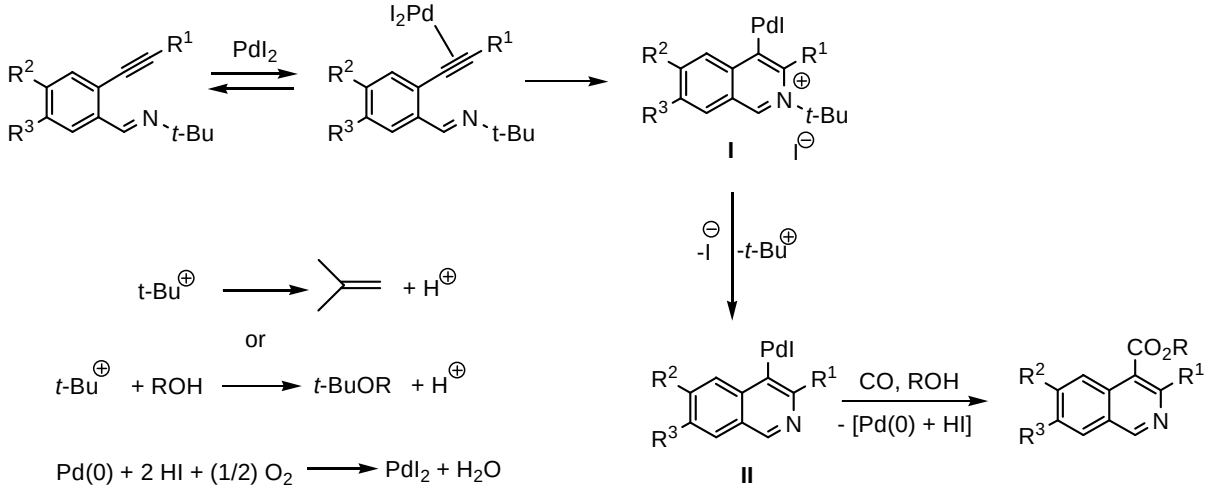
Owing to their instability to hydrolysis, the *tert*-butyl-(2-alkynylbenzylidene)amines **10**-**14** and **19** were directly used, without further purification for the second step.

The first test was carried out using *tert*-butyl-(2-hex-1-ynylbenzylidene)amine **10**, obtained by the condensation of 2-(2-hex-1-ynyl)benzaldehyde **5** with *tert*-butylamine (Scheme 8.19).



*Scheme 8.19: Synthesis of tert-butyl-(2-hex-1-ynylbenzylidene)amine **10**.*

The hypothetical reaction mechanism of PdI_2/KI-catalyzed oxidative carbonylation conditions can in principle involves: (a) an intramolecular 6-*endo*-dig nucleophilic attack of the imine nitrogen to the triple bond coordinated to Pd (II), to give the ionic intermediate **I**; (b) elimination of the *t*-butyl carbocation to give the (4-isoquinolinyl)palladium complex **II**; (c) alkoxycarbonylation of the latter to give the desired isoquinoline-4-carboxylic ester (Scheme 8.20).



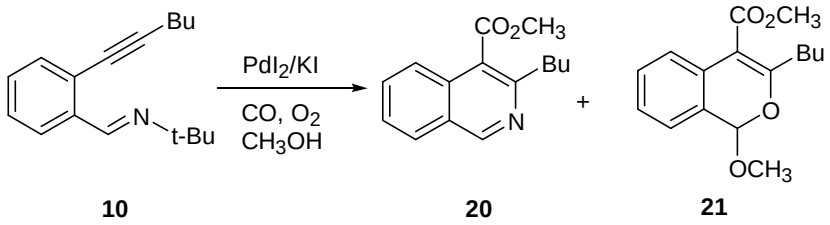
Scheme 8.20: Possible formation of isoquinoline-4-carboxylic ester by PdI_2-catalyzed oxidative carbonylation.

The oxidative carbonylation of **10** was initially carried out using MeOH as the solvent and the nucleophile (Scheme 8.21). The concentration of substrate was 0.2 mM. The autoclave was charged with a mixture of carbon monoxide (CO) and air 4:1 to a total amount of 20 atm.
These conditions (16 atm of CO together with 5 atm total of air, considering that the autoclave was loaded under 1 atm of air) corresponded to 76.2% of CO in air and were outside the explosion limits for CO in air (ca. 16–70% at 18–20 °C and atmospheric pressure, 14.8–71.4% at 100 °C and atmospheric pressure). At higher total pressure, the range of flammability decreases: for example, at 20 atm and 20 °C the limits are ca. 19% and 60%.[39]

The catalytic system is a combination of 2 mol % of PdI_2 in conjunction with an excess of KI (KI : PdI_2 molar ratio = 1/10). The mixture was heated up at 80°C. After 4h the GLC analysis showed the partial conversion of **10** and the presence of desired carbonylated isoquinoline **20**

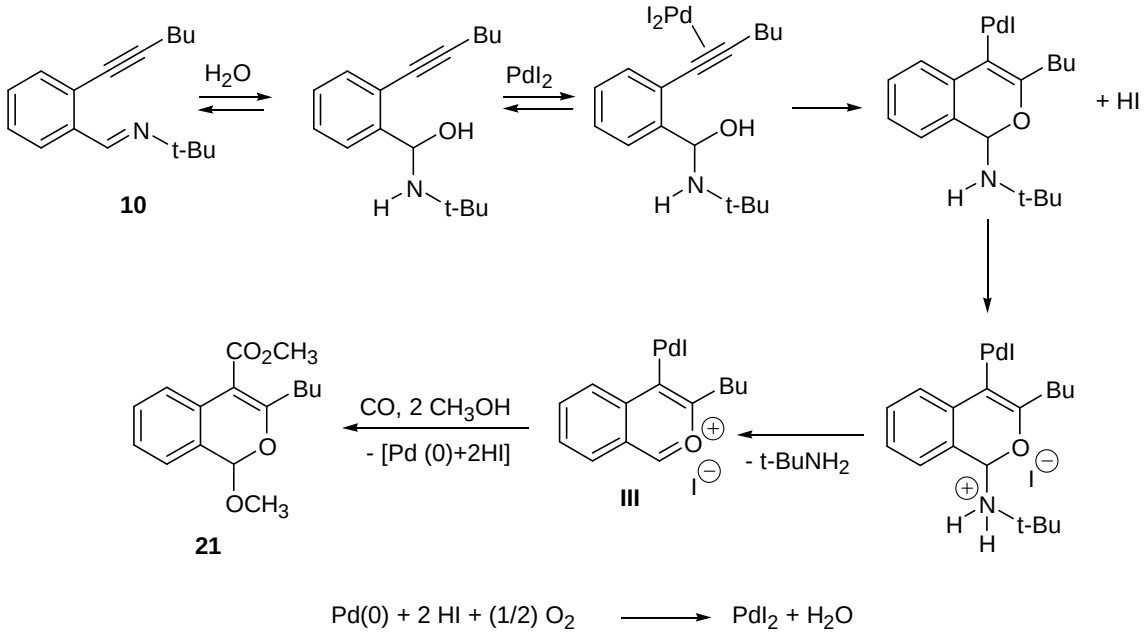
in 10 % GLC yield based on starting **10** (Table 8.1, entry 1). The formation of **20**, although in low yield, confirmed the possibility to realize the carbonylation reaction.

Also in the reaction mixture was observed small amount of by-product identified in methyl 2-butyl-1-methoxy-1-*H*-isochromene-4-carboxylated **21** (Scheme 8.21).



*Scheme 8.21: Formation of isoquinolines methyl ester **20** and isochromenes methyl ester **21** by carbonylation reaction.*

Formation of **21** can be due to water attack to the imino group of **10**, followed by 6-*endo*-dig *O*-cyclization, HI-promoted elimination of *tert*-butylamine to give the oxonium cation **III**, MeOH attack to **III** and methoxycarbonylation (Scheme 8.22).



*Scheme 8.22: Plausible mechanism for the formation of isochromene **21**.*

In the case of particularly water-sensible oxidative carbonylation processes, a dehydrating agent has proven to be necessary to achieve acceptable catalytic efficiencies and/or product yields. Several systems have been envisaged to eliminate water, such as acetals, enol ethers, orthoformates, etc.[79]

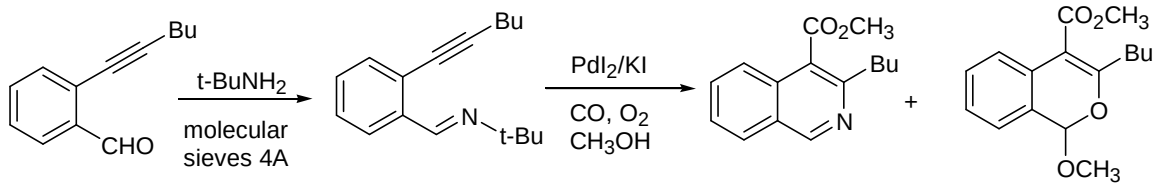
In order to remove water and improve the initial result, the next experiments were carried out in presence of trimethyl orthoformate $HC(OMe)_3$ as mild dehydrating agent. In presence of water methyl formate was formed, simply removed from the reaction mixture under vacuum, (b.p. 32°C) and methanol.

When reaction was carried out using $HC(OMe)_3$ as solvent only traces of product were observed (4% of yield) and the unidentified products due to the substrate instability in these conditions (Table 8,1, entry 5).

Different proportions between MeOH and dehydrating agent were studied, in particular the volume ratio 1:2, 1:3, 1:4 (Table 8.1, entries 2-4). In these series the best result, in terms of selectivity of formation of isoquinoline was observed using 1 part of solvent and 3 parts of trimethyl orthoformate (entry 3).

An increase of the temperature from 80°C to 100°C provides a total conversion of substrate **15** after 8h and formation of isoquinoline-4-carboxylic ester and isochromene-4-carboxylic ester (entry 7). Increase of pressure from 20 atm to 40 atm (32/8 = CO/air) reduces the yield of product **20** (entry 8). A decrease of molar ratio PdI_2 / KI produces also a decrease of activity of catalytic system (entry 9).

*Table 8.1: Reactions of (tert-butyl)[2-(hex-1-ynyl)benzylidene]amine **10** with CO, O_2, and MeOH in the presence of the PdI_2/KI catalytic system.*



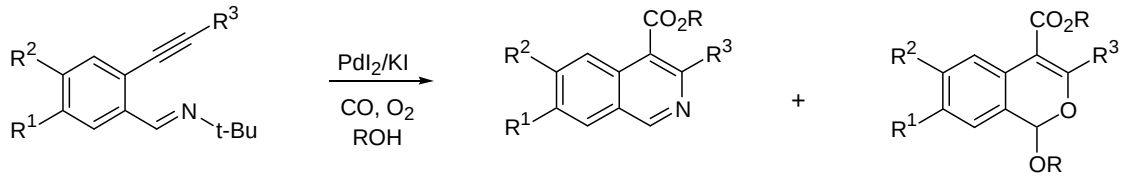
5 **10** **20** **21**

Entry	Solvent	°C	Conversion of **10**[a]	Yield of **20**[a]	Yield of **21**[a]
1	MeOH	80	40	10	6
2	MeOH/$HC(OMe)_3$ (1:2, v/v)	80	74	30	5
3	MeOH/$HC(OMe)_3$ (1:3, v/v)	80	59	31	3
4	MeOH/$HC(OMe)_3$ (1:4, v/v)	80	70	21	3
5	$HC(OMe)_3$	80	43	4	0
6	MeOH/$MeC(OMe)_3$ (1:2, v/v)	80	58	20	3
7	MeOH/$HC(OMe)_3$ (1:2, v/v)	100	100	43	18
8[b]	MeOH/$HC(OMe)_3$ (1:2, v/v)	80	92	23	10
9[c]	MeOH/$HC(OMe)_3$ (1:2, v/v)	80	88	24	7

a) Yields and conversion determinated by GLC. b) The reaction was carried out under 40 atm (at 25 °C) of a 4:1 mixture CO/air. c) The reaction was carried out with a PdI_2/KI/**5** molar ratio of 1:5:50. All reactions were carried out with a substrate concentration of 0.2 mmol of **5** per mL of solvent (1 mmol scale based on **5**) for 4 h in the presence of PdI_2 and KI (PdI_2/KI/**5** molar ratio = 1:10:50) under 20 atm (at 25 °C) of a 4:1 mixture of CO/air.

The substrate conversion reached 100 % after 8 h, with isolated yields of **20** and **21** (based on starting **5**) in 58 % and 8 %, respectively (Table 8.2, entry 1). The process is also effective in EtOH, even though it was necessary to work at 100 °C for 15 h in order to achieve complete substrate conversion (Table 8.2, entry 2).

The reaction was very efficient when the substituent of the triple bond was an alkyl group (Scheme 8.23).



10 R^1= R^2= H, R^3= Bu
11 R^1= NO_2, R^2= H, R^3= Bu
12 R^1= H, R^2= CH_3, R^3= Bu
13 R^1= OCH_3, R^2= H, R^3= Bu
14 R^1= R^2= H, R^3= CH_2OTHP
19 R^1= H, R^2= NO_2, R^3= Bu

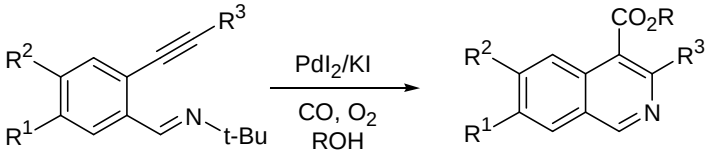
20 R= Me, R^1= R^2= H, R^3= Bu
22 R= Et, R^1= R^2= H, R^3= Bu
24 R= Me, R^1= NO_2, R^2= H, R^3= Bu
25 R= Me, R^1= H, R^2= CH_3, R^3= Bu
26 R= Me, R^1= OCH_3, R^2= H, R^3= Bu
27 R= Me, R^1= H, R^2= NO_2, R^3= Bu
28 R= Me, R^1= R^2= H, R^3= CH_2OTHP

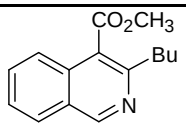
21 R= Me, R^1= R^2= H, R^3= Bu
23 R= Et, R^1= R^2= H, R^3= Bu

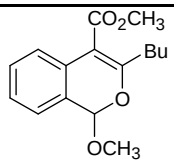
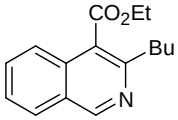
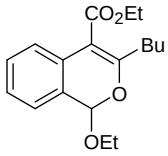
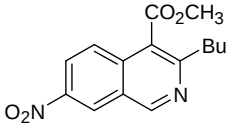
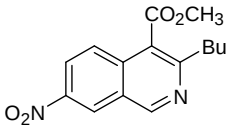
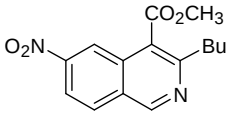
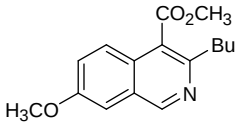
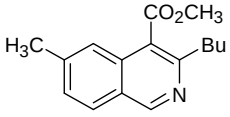
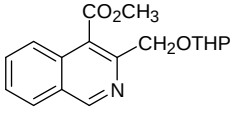
Scheme 8.23: General Pd-catalyzed oxidative carbonylation of (2-alkynyl)benzylideneamine derivatives.

Interestingly with substrates **11**-**14** and **19** the process turned out to be selective toward the formation of isoquinolines **24-28**, since no formation of carbonylated isochromenes as by-products was observed (Table 8.2, entries 3-8).

Table 8.2: Synthesis of isoquinoline-3-carboxylic esters by PdI_2/KI-catalyzed oxidative heterocyclization/alkoxycarbonylation of (2-alkynylbenzylidene)(tert-butyl)amines.



Entry	Time (h)	Mol (%) PdI_2	Product	Isolated yield (%)[a]
1	8	2	 **20**	58

			 **21**	8
2	15	2	 **22**	59
			 **23**	13
3	8	2	 **24**	52
4	8	5	 **24**	66
5	8	5	 **27**	60
6	15	5	 **26**	53
7	15	5	 **25**	50
8	15	5	 **28**	51

a) Isolated yield. all reactions were carried out at 80 °C in a 1:3 mixture (v/v) of ROH/$HC(OR)_3$ with a substrate concentration of 0.2 mmol of 1 per mL of solvent in the presence of PdI_2 and KI (PdI_2/KI molar ratio = 1:10) under 20 atm (at 25 °C) of a 4:1 mixture of CO/air.

8.4: Conclusion.

In summary, we have reported a versatile approach to isoquinoline-4-carboxylic esters based on PdI_2-catalyzed oxidative carbonylation of readily available (2-alkynyl)benzylideneamine derivatives, carried out in alcoholic media at 80-100 °C and under 20-80 atm (at 25 °C) of a 4:1 mixture of CO-air. In particular, isoquinolines, deriving from *N*-cyclization, were selectively obtained starting from *tert*-butyl-(2-alk-1-ynylbenzylidene)amines and working in the presence of a dehydrating agent, such as a $HC(OR)_3$.

Experimental Section

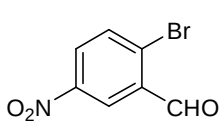
8.5: General consideration.

Solvents and chemicals were of reagent grade and were used without further purification. All reactions were analyzed by TLC (silica gel 60 F_{254}) or by GLC [capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5)]. Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C with a Bruker DPX Avance 300 spectrometer in CDCl3 solutions at 300 MHz and 75 MHz, respectively, with Me4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were recorded with a JASCO FTIR 4200 spectrometer. GC–MS data were obtained with a Shimadzu QP-2010 GC–MS apparatus operating at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Model 1106.

8.6: Preparation of starting materials and characterization

2-Bromo-5-nitrobenzaldehyde (2)

To a stirred, cooled (5-10 °C) mixture of fuming HNO_3 (4.5 mL) and concentrated H_2SO_4 (34 mL), was added dropwise 2-bromobenzaldehyde 1 (10.0 g, 54.1 mmol). The resulting mixture was warmed to room temperature with stirring and then poured into ice/water. Crude 2-bromo-5-nitrobenzaldehyde 2 was recovered by extracting the aqueous phases with Et_2O (3 x 50 mL), washing the combined organic phases with water until neutrality, and drying the organic phases with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by column chromatography (SiO_2; hexane/acetone, 95:5).



Colorless solid, 37%

IR (KBr): ν = 1685 (s), 1606 (w), 1536 (m), 1384 (s), 1352 (m), 1188 (w), 1039 (m), 915 (w), 846 (w), 817 (w), 737 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.39 (s, 1 H), 8.72 (d, *J* = 2.8 Hz, 1 H), 8.30 (dd, *J* = 8.7, 2.8 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1 H).

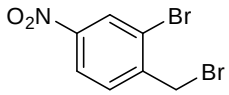
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 189.4, 147.7, 135.3, 134.4, 133.0, 128.8, 124.7.

GC–MS: *m*/*z* (%) = 231 (22) $[M + 2]^+$, 230 (25) $[M + 1]^+$, 229 (28) $[M]^+$, 215 (4), 199 (5), 183 (7), 157 (12), 145 (7), 119 (8), 103 (12), 76 (37), 75 (100), 63 (11).

Anal. calcd for C7H4BrNO3 (230.02): calcd. C 36.55, H 1.75, Br 34.74, N 6.09; found C 36.51, H 1.76, Br 34.78, N 6.07.

2-Bromo-4-nitrobenzyl bromide (16)

To a stirred, heated (80°C) solution of 2-bromo-4-nitrotoluene (10.0 g, 46.3 mmol) and *N*-bromosuccinimide (8.24 g, 46.2 mmol) in anhydrous carbon tetrachloride (12 mL) was added, under nitrogen, benzoyl peroxide (168 mg, 0.69 mmol), and the resulting mixture was heated to reflux for 7 h. After cooling to room temperature, the mixture was diluted with Et_2O, water was added, and the phases were separated. The aqueous layer was extracted with Et_2O, and the combined organic phases were dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by column chromatography (SiO_2; hexane/AcOEt, 7:3).



Yellow solid, 96 % of yield.

M.p. 63–65 °C.

IR (KBr): ν = 1523 (s), 1384 (m), 1346 (s), 1116 (m), 1037 (w), 896 (m), 808 (m), 715 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.44 (d, *J* = 2.3 Hz, 1 H), 8.17 (dd, *J* = 8.5, 2.3 Hz, 1 H), 7.66 (d, *J* = 8.5 Hz, 1 H), 4.62 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.9, 144.0, 131.7, 128.4, 124.6, 122.9, 31.1.

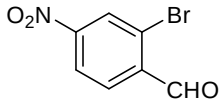
GC–MS: *m*/*z* (%) = 295 (14) $[M + 2]^+$, 293 (8) $[M]^+$, 249 (1), 216 (87), 214 (86), 186 (8), 170 (11), 168 (11), 143 (2), 117 (3), 105 (54), 89 (100), 77 (34), 63 (69).

Anal. calcd for C7H5Br2NO2 (294.93): calcd. C 28.51, H 1.71, Br 54.19, N 4.75; found C 28.55, H 1.71, Br 54.13, N 4.76.

2-Bromo-4-nitrobenzaldehyde (17)

The 2-bromo-4-nitrobenzyl bromide **16** thus obtained was added to a stirred solution of hexamethylenetetramine (9.3 g, 66.6 mmol) in $CHCl_3$ (65 mL). The mixture was heated to reflux for 15 h and then cooled to room temperature to precipitate the ammonium salt, which was

recovered by filtration and washed with cold Et2O. After drying, the salt was suspended in aqueous acetic acid (60% v/v; 100 mL), and the resulting mixture was heated to reflux for 1.5 h. After cooling, the solution was added to 3 n aqueous HCl (140 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude product was purified by column chromatography (SiO_2; hexane/AcOEt, 95:5).



Yellow solid, 26 % of yield.

M.p. 98–99 °C

IR (KBr): ν = 1689 (m), 1596 (m), 1526 (m), 1384 (s), 1350 (m), 1197 (m), 1038 (w), 911 (w), 812 (m), 740 (m) cm^{-1}.

^{1}H NMR (300 MHz, CDCl3): δ (ppm) = 10.44 (d, *J* = 0.9 Hz, 1 H), 8.54 (d, *J* = 2.4 Hz, 1 H, 3-H), 8.28 (ddd, *J* = 8.5, 2.1, 0.9 Hz, 1 H), 8.09 (distorted d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl3): δ (ppm) = 190.0, 150.9, 137.3, 130.8, 129.1, 126.8, 122.8.

GC–MS: *m*/*z* = 231 (28) $[M + 2]^+$, 230 (35) $[M + 1]^+$, 229 (37) $[M]^+$, 215 (3), 183 (7), 181 (8), 157 (9), 155 (12), 149 (12), 119 (5), 103 (19), 76 (47), 75 (100), 74 (53).

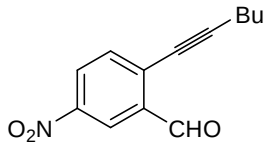
Anal. calcd for C7H4BrNO3 (230.02): calcd. C 36.55, H 1.75, Br 34.74, N 6.09; found C 36.59, H 1.75, Br 34.70, N 6.08.

Preparation of 2-Alkynylbenzaldehydes 5-9, 18.

To a stirred solution of the 2-bromobenzaldehyde derivative (8.06 mmol); 2-bromobenzaldehyde **1**, 2-bromo-5-nitrobenzaldehyde **2**, 2-bromo-4-methylbenzaldehyde **3**, 2-bromo-5-methoxybenzaldehyde **4** or 2-bromo-4-nitrobenzaldehyde **17** in NEt_3 (30 mL), were added under nitrogen, the 1-alkyne (9.67 mmol; 1-hexyne, 2-(prop-2-ynyl)tetrahydropyran, phenylacetylene, 0.161 mmol of $PdCl_2(PPh_3)_2$ and 0.081 mmol of CuI in this order. The reaction mixture was stirred under nitrogen at 50 °C for 4 h. After cooling, the solution was filtered, and the solid was washed several times with diethyl ether.

2-(Hex-1-ynyl)-5-nitrobenzaldehyde (7)

Purified by column chromatography on silica gel (hexane/acetone, 95:5).



Yellow solid. 52 % of yield.

M.p. 39–41 °C.

IR (KBr): ν = 2216 (w), 1696 (s), 1600 (m), 1516 (s), 1384 (s), 1347 (s), 1181 (w), 917 (w), 844 (m), 745 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.53 (s, 1 H), 8.70 (distorted d, *J* = 2.4 Hz, 1 H), 8.35 (dd, *J* = 8.5, 2.4 Hz, 1 H), 7.67 (d, *J* = 8.5 Hz, 1 H), 2.56 (t, *J* = 7.1 Hz, 2 H), 1.72–1.44 (m, 4 H), 0.98 (t, *J* = 7.1 Hz, 3H).

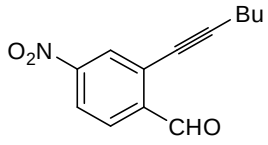
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 189.8, 146.9, 136.7, 134.5, 133.5, 127.5, 122.3, 104.4, 75.5, 30.3, 22.1, 19.6, 13.6.

GC–MS: *m*/*z* (%) = 231 (4) $[M]^+$, 213 (6), 202 (18), 190 (23), 189 (100), 167 (10), 156 (18), 143 (24), 128 (22), 115 (67), 102 (22), 89 (21), 77 (18), 75 (19), 63 (22).

Anal. calcd for C13H13NO3 (231.25): calcd. C 67.52, H 5.67, N 6.06; found C 67.56, H 5.68, N 6.04.

2-(Hex-1-ynyl)-4-nitrobenzaldehyde (17)

Purified by column chromatography on silica gel (hexane/AcOEt, 95:5).



Yellow oil. 74% of yield.

IR (film): ν = 2227 (w), 1703 (s), 1610 (w), 1533 (s), 1467 (w), 1386 (m), 1350 (s), 1183 (m), 904 (w), 812 (m), 741 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.58 (d, *J* = 0.9 Hz, 1 H), 8.34 (d, *J* = 2.1 Hz, 1 H), 8.18 (distorted ddd, *J* = 8.5, 2.1, 0.9 Hz, 1H), 8.04 (distorted d, *J* = 8.5 Hz, 1 H), 2.54 (t, *J* = 7.0 Hz, 2 H), 1.72–1.44 (m, 4 H), 0.98 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 190.4, 150.6, 139.4, 129.1, 128.39, 128.36, 122.4, 101.5, 74.8, 30.3, 22.1, 19.4, 13.6.

GC–MS: *m*/*z* (%) = 231 (5) $[M]^+$, 216 (6), 202 (18), 190 (24), 189 (100), 172 (16), 159 (20), 156 (24), 143 (40), 131 (19), 128 (29), 115 (85), 102 (19), 89 (37), 77 (19), 75 (25), 63 (36).

Anal. calcd for C13H13NO3 (231.25): calcd. C 67.52, H 5.67, N 6.06; found C 67.48, H 5.67, N 6.08.

Preparation of Crude (2-Alkynylbenzylidene)(*tert*-butyl)-amines 10-14, 19.

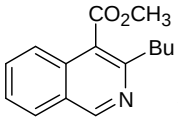
A mixture of aldehyde (1.58 mmol of 2-(hex-1-ynyl)-benzaldehyde **5**, 2-[3-(tetrahydropyran-2-yloxy)-prop-1-ynyl]benzaldehyde **6**, 2-(hex-1-ynyl)-5-nitrobenzaldehyde **7**, 2-(hex-1-ynyl)-4-methylbenzaldehyde **8**, 2-(hex-1-ynyl)-5-methoxybenzaldehyde **9**, 2-(hex-1-ynyl)-4-nitrobenzaldehyde **18**, *tert*-butylamine (4.74 mmol) and water (400 μL), was stirred at room temp. under nitrogen for 15 h. The excess *tert*-butylamine was removed under reduced pressure, then water (5 mL) was added, and the resulting mixture was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried with $MgSO_4$. After filtration and evaporation of the solvent, the crude *tert*-butylimines 10-14, 19 were used for the carbonylation reaction.

8.7: General procedure for carbonylation reaction.

A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2, KI and crude (2-alkynylbenzylidene)(*tert*-butyl)amine (1.58 mmol) dissolved in 8 mL of a 3:1 mixture of $HC(OR)_3$ and anhydrous ROH (R = Me or Et). The autoclave was sealed and, while stirring, the autoclave was pressurized with CO (16 atm) and air (up to 20 atm). After stirring at 80 or 100 °C for 15 h, the autoclave was cooled, degassed and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel.

8.8: Characterization of products.

Methyl 3-butylisoquinoline-4-carboxylate (20)



Yellow oil.

IR (film): ν = 2952 (m), 2931 (m), 1735 (s), 1622 (m), 1576 (m), 1497 (m), 1435 (m), 1379 (m), 1278 (m), 1229 (s), 1139 (m), 1037 (m), 869 (w), 757 (m) cm^{-1}.

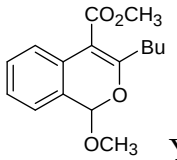
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.25 (s, 1H), 7.96 (dd, J = 8.1, 1.2, 1H), 7.81 (distorted dd, J = 8.5, 1.2, 1H), 7.71 (distorted ddd, J = 8.5, 6.9, 1.2, 1H), 7.57 (distorted ddd, J = 8.1, 8.9, 1.2, 1H), 4.06 (s, 3H), 2.99-2.89 (m, 2H), 1.86-1.74 (m, 2H), 1.49-1.35 (m, 2H), 0.95 (t, J = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.1, 153.6, 153.5, 133.2, 131.4, 127.9, 126.9, 126.4, 123.8, 122.9, 52.4, 36.2, 32.3, 22.7, 13.9.

GC-MS: *m/z* 243 (1) $[M]^+$, 228 (22), 214 (17), 201 (100), 186 (65), 184 (62), 168 (17), 167 (13), 154 (15), 143 (81), 129 (19), 128 (15), 127 (16), 115 (36), 101 (9), 89 (10), 77 (11).

Anal. calcd for $C_{15}H_{17}NO_2$ (243.30): C 74.05, H 7.04, N 5.76; found C 74.03; H, 7.05, N 5.74.

Methyl 3-butyl-1-methoxy-1*H*-isochromene-4-carboxylate (21)



Yellow oil.

IR (film): *v* 1715 (s), 1609 (m), 1492 (w), 1434 (m), 1381 (w), 1337 (m), 1210 (m), 1121 (w), 1085 (w), 1039 (s), 967 (m), cm^{-1}.

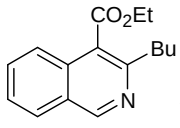
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.60 (dd, *J* = 8.1, 1.2, 1H), 7.36 (distorted ddd, *J* = 8.1, 7.1, 1.8, 1H), 7.30-7.23 (m, 1 H), 7.21 (distorted dd, *J* = 7.4, 1.8, 1H), 5.92 (s, 1H), 3.99 (s, 3H), 3.56 (s, 3H), 2.74-2.52 (m, 2H), 1.74-1.61 (m, 2H), 1.48-1.34 (m, 2H), 0.94 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.8, 161.3, 129.4, 127.9, 126.5, 126.2, 125.6, 123.5, 107.6, 99.9, 55.5, 51.4, 32.8, 30.0, 22.5, 13.8.

GC-MS: *m/z* 276 (31) $[M]^+$, 245 (100), 244 (30), 229 (3), 219 (11), 215 (55), 203 (7), 185 (8), 174 (10), 171 (15), 167 (13), 161 (17), 145 (13), 143 (11), 133 (14), 131 (11), 129 (13), 128 (11), 115 (26), 103 (17), 89 (26), 77 (11).

Anal. calcd for $C_{16}H_{20}O_4$ (276.33): C 69.54, H 7.30; found C 69.50; H, 7.33.

Ethyl 3-butylisoquinoline-4-carboxylate (22)



Yellow oil.

IR (film): *v* 2958 (m), 2929 (m), 1725 (s), 1622 (w), 1577 (m), 1497 (w), 1466 (m), 1378 (m), 1280 (m), 1226 (s), 1139 (m), 1037 (m), 867 (w), 757 (m) cm^{-1}.

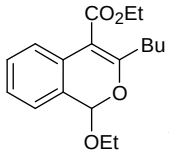
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.24 (s, 1 H), 7.99-7.93 (m, 1 H), 7.87-7.80 (m, 1H), 7.71 (distorted ddd, *J* = 8.5, 6.9, 1.6, 1H), 7.58 (distorted ddd, *J* = 8.1, 6.9, 1.2, 1H), 4.55 (q, *J* = 7.3, 2H), 3.00-2.90 (m, 2H), 1.87-1.75 (m, 2H), 1.50-1.36 (m, 2H), 1.47 (t, *J* = 7.3, 3H), 0.96 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.7, 153.5, 153.2, 133.2, 131.3, 127.9, 126.8, 126.4, 123.7, 123.2, 61.7, 36.3, 32.3, 22.8, 14.3, 14.0.

GC-MS: *m/z* 257 (1) $[M]^+$, 228 (13), 215 (11), 200 (8), 186 (51), 184 (23), 168 (13), 154 (21), 143 (100), 130 (19), 115 (34), 102 (16), 89 (11), 77 (10), 76 (10), 63 (19).

Anal. calcd for $C_{16}H_{19}NO_2$ (257.33): C 74.68, H 7.44, N 5.44; found C 74.63; H, 7.45, N 5.44.

Ethyl 3-butyl-1-ethoxy-1*H*-isochromene-4-carboxylate (23)



Yellow oil.

IR (film): *v* 1711 (s), 1607 (m), 1493 (w), 1378 (m), 1331 (m), 1220 (m), 1125 (m), 1084 (m), 1038 (s), 967 (m), 754 (m) cm^{-1}.

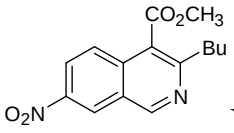
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.65 (dd, *J* = 8.1, 1.2, 1H), 7.34 (distorted ddd, *J* = 8.1, 6.5, 1.8, 1H), 7.28-7.22 (m, 1 H), 7.19 (distorted dd, *J* = 7.7, 1.8, 1 H), 6.01 (s, 1H), 4.35 (q, *J* = 7.3, 2H), 4.03-3.91 (m, 1H), 3.83-3.70 (m, 1H), 2.74-2.62 (m, 1H), 2.61-2.49 (m, 1H), 1.73-1.58 (m, 2H), 1.47-1.33 (m, 2H), 1.37 (t, *J* = 7.3, 3H), 1.24 (t, *J* = 7.3, 3H), 0.94 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.4, 161.1, 129.2, 127.9, 126.5, 126.3, 125.5, 123.4, 107.6, 98.3, 63.9, 60.6, 32.9, 30.0, 22.5, 15.1, 14.3, 13.9.

GC-MS: *m/z* 304 (21) $[M]^+$, 259 (100), 258 (44), 229 (68), 213 (8), 201 (6), 188 (9), 173 (25), 171 (15), 147 (14), 145 (11), 131 (11), 118 (15), 115 (19), 91 (18), 89 (20), 77 (11).

Anal. calcd for $C_{18}H_{24}O_4$ (304.38): C 71.03, H 7.95; found C 71.10; H, 7.96.

Methyl 3-butyl-7-nitroisoquinoline-4-carboxylate (24)



Yellow solid .

M.p. 55-56°C.

IR (KBr): *v* 1724 (s), 1625 (m), 1534 (m), 1384 (s), 1347 (s), 1223 (m), 1091 (w), 1032 (w), 840 (m), 731 (w) cm^{-1}.

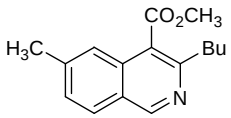
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.44 (s, 1 H), 8.92 (d, *J* = 2.3, 1 H), 8.46 (dd, *J* = 9.2, 2.3, 1H), 8.00 (d, *J* = 9.2, 1H), 4.10 (s, 3H), 3.05-2.95 (m, 2H), 1.88-1.75 (m, 2H), 1.51-1.36 (m, 2H), 0.96 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.0, 158.0, 155.1, 145.8, 135.8, 126.1, 125.0, 124.5, 124.4, 123.0, 52.9, 36.6, 32.1, 22.7, 13.9.

GC-MS: *m/z* 288 (absent) $[M]^+$, 273 (20), 259 (14), 246 (100), 231 (58), 229 (52), 213 (14), 199 (10), 188 (50), 185 (22), 167 (10), 142 (17), 128 (10), 115 (15), 101 (6), 91 (6).

Anal. calcd for $C_{15}H_{16}N_2O_4$ (288.30): C 62.49, H 5.59, N 9.72; found C 62.40; H, 5.58, N 9.75.

Methyl 3-butyl-6-methylisoquinoline-4-carboxylate (25)



Yellow oil.

IR (film): *v* 1728 (s), 1628 (w), 1497 (w), 1437 (m), 1232 (m), 1147 (w), 1036 (m), 805 (m) cm^{-1}.

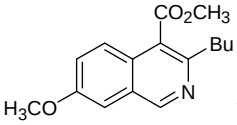
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.17 (s, 1 H), 7.85 (d, *J* = 8.5, 1H), 7.57-7.53 (m, 1H), 7.41 (dd, *J* = 8.5, 1.6, 1 H), 4.06 (s, 3H), 2.96-2.87 (m, 2H), 2.54 (s, 3H), 1.85-1.71 (m, 2H), 1.49-1.34 (m, 2H), 0.94 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.4, 153.4, 153.1, 142.0, 133.4, 129.2, 127.7, 124.9, 122.6, 122.4, 52.4, 36.3, 32.3, 22.7, 22.4, 13.9.

GC-MS: *m/z* 257 (1) $[M]^+$, 256 (2), 242 (21), 228 (16), 226 (11), 215 (100), 200 (66), 198 (50), 182 (14), 157 (90), 142 (13), 129 (13), 128 (13), 115 (18), 102 (4), 89 (3), 77 (8).

Anal. calcd for $C_{16}H_{19}NO_2$ (257.33): C 74.68, H 7.44, N 5.44; found C 74.62; H, 7.42, N 5.45.

Methyl 3-butyl-7-methoxyisoquinoline-4-carboxylate (26)



Yellow solid.

M.p. 65-67°C.

IR (KBr): *v* 1727 (s), 1579 (m), 1501 (m), 1385 (w), 1221 (s), 1161 (w), 1135 (w), 1028 (m), 833 (m), 746 (s) cm^{-1}.

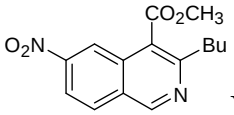
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.15 (s, 1 H), 7.73 (d, *J* = 8.9, 1H), 7.36 (dd, *J* = 8.9, 2.4, 1H), 7.21 (distorted d, *J* = 2.4, 1H), 4.04 (s, 3H), 3.94 (s, 1H), 2.96-2.88 (m, 2 H), 1.85-1.72 (m, 2 H), 1.49-1.35 (m, 2 H), 0.95 (t, *J* = 7.3, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 169.3, 158.1, 152.1, 151.6, 128.8, 127.7, 125.5, 124.4, 122.8, 105.0, 55.5, 52.4, 36.1, 32.4, 22.7, 13.9.

GC-MS: *m/z* 273 (5) $[M]^+$, 258 (16), 244 (12), 231 (100), 216 (56), 214 (44), 198 (6), 187 (6), 173 (74), 158 (15), 141 (6), 130 (11), 128 (11), 115 (10), 102 (6), 89 (5), 77 (5).

Anal. calcd for $C_{16}H_{19}NO_3$ (273.33): C 70.31, H 7.01, N 5.12; found C 70.39; H, 7.03, N 5.10.

Methyl 3-butyl-6-nitroisoquinoline-4-carboxylate (27)



Yellow solid

M.p. 68-71°C.

IR (KBr): *v* 1725 (s), 1585 (m), 1535 (s), 1384 (m), 1348 (s), 1239 (m), 1092 (w), 1033 (w), 842 (m) cm^{-1}.

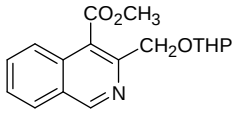
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.41 (s, 1 H), 8.81-8.78 (m, 1 H), 8.35 (dd, *J* = 9.1, 2.1, 1H), 8.16 (distorted d, *J* = 9.1, 1 H), 4.13 (s, 3H), 3.07-2.97 (m, 2H), 1.90-1.75 (m, 2H), 1.52-1.36 (m, 2H), 0.96 (t, *J* = 7.3, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 167.8, 156.4, 153.7, 149.0, 132.7, 129.9, 127.7, 123.8, 120.7, 120.5, 53.0, 36.4, 32.1, 22.7, 13.9.

GC-MS: *m/z* = 288 (absent) $[M]^+$, 273 (20), 259 (13), 246 (100), 231 (62), 229 (65), 213 (15), 199 (11), 188 (39), 185 (17), 158 (10), 142 (17), 128 (13), 115 (16), 114 (16), 101 (8), 88 (6), 77 (9).

Anal. calcd for $C_{15}H_{16}N_2O_4$ (288.30): C 62.49, H 5.59, N 9.72; found C 62.52; H, 5.57, N 9.73.

Methyl 3-(tetrahydropyran-2-yloxymethyl)-isoquinoline-4-carboxylate (28)



Yellow oil

IR (film): *v* 2948 (m), 1730 (s), 1685 (m), 1576 (w), 1437 (m), 1363 (m), 1221 (s), 1121 (m), 1065 (m), 1033 (m), 975 (w), 905 (w), 755 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 9.26 (s, 1 H), 7.90 (d, br, *J* = 7.9, 1H), 7.85 (distorted dd, *J* = 8.5, 0.9, 1H), 7.66 (distorted ddd, J = 8.5, 7.0, 1.5, 1H), 7.54 (distorted ddd, *J* = 7.9, 7.0, 0.9, 1H), 5.03 (distorted d, *J* = 12.9, 1H), 4.83 (distorted d, *J* = 12.9, 1 H), 4.63 (t, *J* = 3.2, 1H), 4.04 (s, 3H), 3.86-3.72 (m, 1H), 3.50-3.40 (m, 1H), 1.65-1.36 (m, 6H).

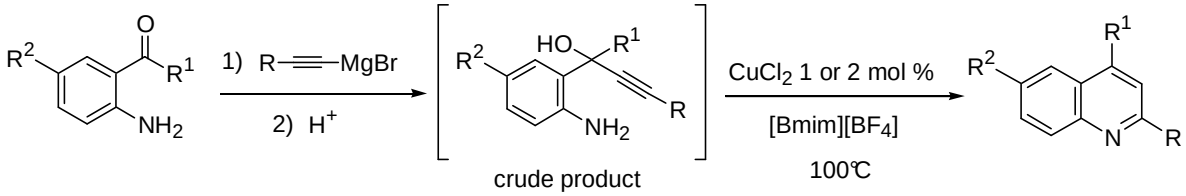
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 168.4, 153.4, 149.6, 133.3, 131.5, 127.9, 127.6, 127.4, 124.0, 123.7, 98.2, 69.2, 62.0, 52.5, 30.3, 25.4, 19.1.

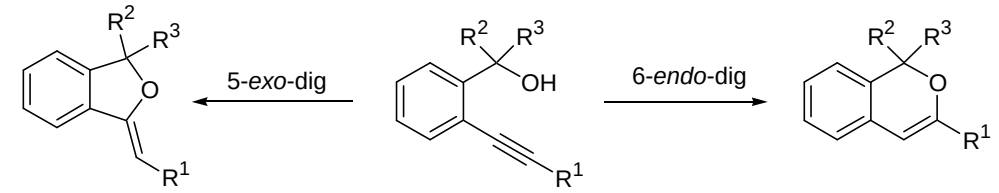
GC-MS: *m/z* 301 (2) $[M]^+$, 270 (1), 244 (6), 216 (10), 201 (100), 200 (94), 186 (52), 170 (15), 157 (14), 156 (18), 143 (58), 142 (26), 128 (23), 115 (25), 101 (7), 85 (37).

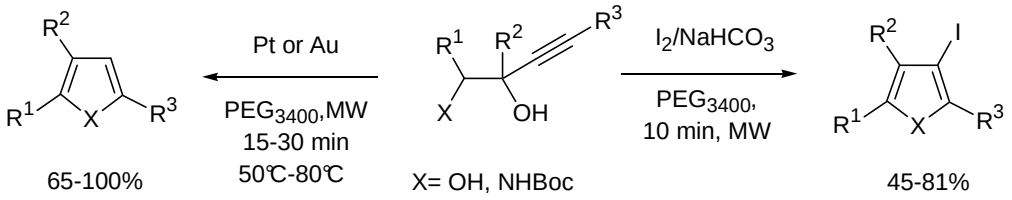
Anal. calcd for $C_{17}H_{19}NO_4$ (301.34): C 67.76, H 6.36, N 4.65; found C 67.70; H, 6.35, N 4.64.

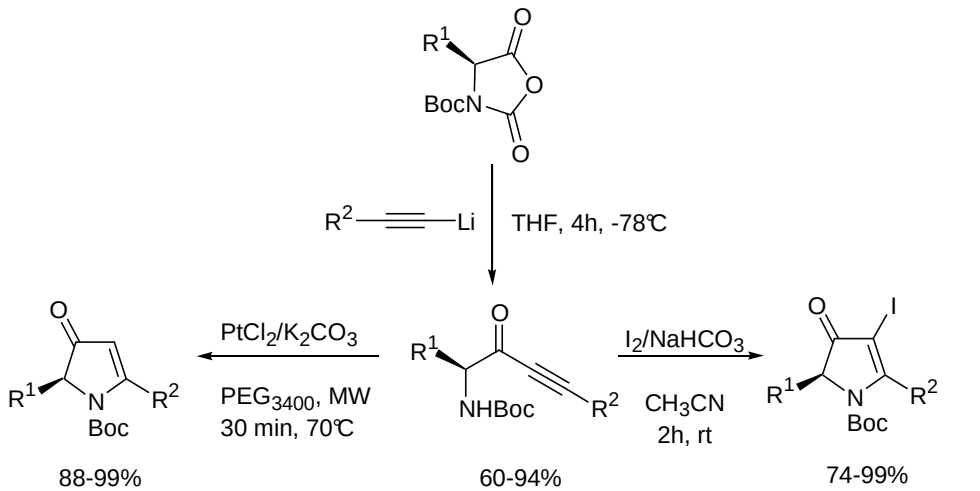
General Conclusion

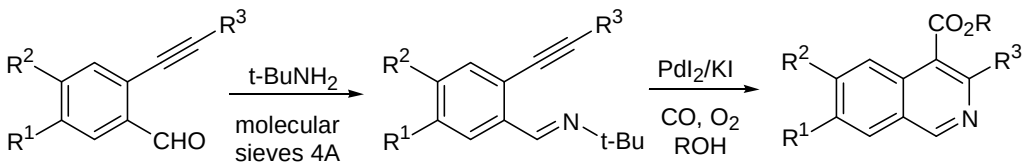
Chemical Abstract











Catalysis, alternative solvents and atom economy represent key areas for the sustainable development of versatile strategies in organic chemistry.
The objectives of this research project, developed in collaboration between University of Calabria and University of Montpellier in the context of a cotutelle of thesis, were to found new synthetic methodology strategies for the preparation of *N*- or *O*- heterocycles.

We have developed a copper-catalyzed cycloisomerization reaction for the synthesis of quinolines in [BMIM][BF_4] ionic liquid (IL). The possibility to recycle the catalytic system, constituted by Cu/IL was also tested.

We have performed extensive screening experiments for the cycloisomerization reaction of alkynylbenzyl alcohols using palladium, copper, gold and platinum as catalyst, or a base in order to obtain 5-*exo*-dig or 6-*endo*-dig cyclization route. Depending on the mechanism of nucleophilic attack of the OH group, it was possible to obtain (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and/or 1*H*-isochromenes.

A successfully synthesis of furans and pyrroles was achieved by platinum or gold-catalyzed cycloisomerization reaction of diols or *N*-protected aminoalcohols in Poly(ethylene glycol) (PEG) under microwave irradiation. The heterocyclic systems were recovered after a simple precipitation-filtration work-up. The same substrates are used for the iodo-mediated cyclization reactions in PEG under microwave activation to obtain the corresponding β-iodofuran and β-iodopyrrole derivatives.

A general method for the preparation of substituted α-amino-ynones by addition of organolithium reagents to *N*-protected carboxyanhydrides of amino acids (UNCAs) is described. Monoaddition was achieved selectively with good to excellent yields (60-94%). Chiral purity was preserved in most cases. The platinum-catalyzed 5-*endo*-dig cycloisomerization of these α-amino-ynones under microwave irradiation using PEG as solvent provided the corresponding pure pyrrolin-4-ones in excellent yields (80% - 99%) and retention of enantioselectivity after a straightforward precipitation-filtration procedure for isolation and purification. Unprecedented iodo-mediated cyclization reaction was carried out using α-amino-ynones. The corresponding β-iodopyrrolin-4-ones were obtained in excellent yield and chiral purity was preserved.

A versatile approach to isoquinoline-4-carboxylic esters based on PdI_2-catalyzed oxidative carbonylation of readily available (2-alkynyl)benzylideneamine derivatives, carried out in alcoholic media at 80-100 °C and under 20-80 atm (at 25 °C) of a 4:1 mixture of CO-air was reported.

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Abstract

Catalysis, alternative solvents and atom economy represent key areas for the sustainable development of versatile strategies in organic chemistry. Fused heterocycles, such as substituted quinolines by a cycloisomerization reaction using a recyclable catalytic system copper/ionic liquids and isoquinoline-4-carboxylic esters based on PdI_2-catalyzed oxidative carbonylation were prepared. A selective 5-*exo*-dig or 6-*endo*-dig cyclization route to obtain 1,3-dihydroisobenzofurans and/or 1H-isochromenes was tested by metal transition cycloisomerization reaction of alkynylbenzyl alcohols in PEG. Five membered ring heterocycles such as furans, pyrroles and pyrrolin-4-ones were successfully obtained by a novel platinum or gold-catalyzed cycloisomerization reaction of diols, aminoalcohols or α-amino-ynones in poly(ethylene glycol) (PEG) under microwave irradiation. The heterocyclic systems were recovered pure after a simple precipitation-filtration work-up. The catalytic systems were studied by using the TEM and XPS techniques. The chiral α-amino-ynone substrates were prepared by an original method starting from N-protected carboxyanhydrides of amino acids (UNCAs). Also unprecedented results are reported in the area of iodocyclization to obtain chiral iodopyrrolin-ones.

Key words: Heterocycles, platinum, gold, cycloisomerization, microwave, poly(ethylene glycol), ionic liquids, UNCAs, oxidative carbonylation, iodocyclization, TEM , XPS.

Résumé

La catalyse, les solvants alternatifs et l'économie d'atome font partie des clés pour le développement de nouvelles stratégies durables de synthèse. Des hétérocycles comme les quinoléines substituées, par réaction de cycloisomérisation catalysée par le cuivre en utilisant les liquides ioniques, et les isoquinoléines carbonylées par réaction de carbonylation oxydante catalysée par le palladium dans le méthanol ont été synthetiseés. La formation sélective de 1,3-dihydroisobenzofuranes et/ou 1*H*-isochromènes a été tentée par réaction de cycloisomérisation catalysée par différent métaux de transition. La synthèse d'hétérocycles à cinq chaînons, par exemple furanes, pyrroles et pyrrolin-4-ones à été mise au point par nouvelle réaction de cycloisomérisation catalysée par de sels de platine ou d'or en utilisant des diols, des amino alcools ou des α-amino-ynones dans le PEG sous activation micro-ondes. Les produits sont récupérés pur après une simple étape de précipitation-filtration. Les α-amino-ynones chiral sont synthétisée à partir de *N*-protégé carboxyanhydrides des aminoacides (UNCAs). Une réaction de iodocyclisation a été aussi développée pour obtenir de nouvelles structures hétérocycliques.

Mots clés: Hétérocycles, platine, or, cycloisomérisation, micro-ondes, poly(éthylène glycol), liquides ionic, UNCAs, carbonylation oxydante, iodocyclisation, TEM, XPS.

Resoconto

La catalisi, l'uso di solventi alternativi e l'economia di atomi rappresentano tre punti chiave per lo sviluppo di nuove strategie sintetiche in chimica organica. Attraverso la reazione di cicloisomerizzazione catalizzata dal rame sono state ottenute chinoline sostituite usando i liquidi ionici come solvente, altresi isochinoline carbonilate sono state sintetizzate mediante reazione di carbonilazione ossidativa catalizzata dal palladio nel metanolo. E' stata inoltre valutata la possibilità di ottenere selettivamente la formazione di derivati 1,3-diidroisobenzofuranici e 1*H*-isocromenici attraverso la reazione di cicloisomerizzazione catalizzata da metalli di transizione in PEG. La sintesi di furani, pirroli e pirrolin-4-oni é stata largamente studiata. I substrati, come dioli, ammino alcoli ed α-ammino-inoni sono stati ciclizzati mediante reazione di cicloisomerizzazione catalizzata da sali di platino e d'oro usando il PEG come solvente alternativo sotto attivazione microonde. I prodotti sono recuperati puri dopo una semplice tappa di precipitazione-filtrazione. Gli α-ammino-inoni chirali sono stati sintetizzati partendo dagli UNCAs, *N*-protetti carbossianidridi degli aminoacidi. Infine la reazione di iodociclizzatione ha portato alla sintesi di nuove strutture eterocicliche.

Parole chiavi: Eterocicli, platino, oro, cicloisomerizzazione, microonde, poli (etilene glicole), liquidi ionici, UNCAs, carbonilazione oosidativa, iodociclizzazione, TEM, XPS.

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