Università della Calabria

Doctorate Course:

"Methodologies for the Development of Molecules of Pharmacological Interest"

(MDMP, *cicle XXII*)

Innovative Syntheses of Heterocycles via Transition-Metal or Organic Catalysis

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… al destino ed al libero arbitrio

…ed a tutte le occasioni che ci offrono

"Don't go away
Say what you say
But say that you'll stay
Forever and a day
In the time of my life "

(Oasis – Don't gio away)

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Chapter 1

General Introduction

1.1 General importance of heterocycles

Heterocycles form, by far, the largest of the classical divisions of organic chemistry. Moreover, they are of immense importance not only biologically and industrially but also to the functioning of any developed human society as well. Their importance in a wide range of areas can hardly be overemphasized. Many molecules, active in the cellular metabolism present in their structure an heterocyclic moiety. Same example are here reported: precursors of coenzymes and vitamins (such as Thiamine, Riboflavin, Nicotinic Acid, Adenine and Vitamin B12 and E); photosynthetic pigments (Chlorophyll) and oxygen-delivering molecules (Hemoglobin); Purine and pyrimidine bases, amino-acids (Histidine, Tryptophan, Proline) and Hormones (Serotonin, Histamine). Moreover among natural heterocyclic drugs the most important are purines (Caffeine), alkaloids (nicotine) and antibiotics (such as pennicilline).

A large number of heterocyclic synthetic drugs that mimic natural products have been discovered and developed starting from the molecular structure of this biological products. These synthetic drugs belong to very different pharmacological classes: Hypnotics (barbiturates), anticonvulsive, antihistamines, antithyroid, fungicides. Other important practical applications of these compounds can also be cited; for instance, their use as additives and modifiers in a wide variety of industries including cosmetics, reprography, information storage, plastics, solvents, antioxidants, and vulcanization accelerators. Finally, as an applied science, heterocyclic chemistry is an inexhaustible resource of novel compounds. A vast number of combinations of carbon, hydrogen, and heteroatoms can be designed, providing compounds with the most different physical, chemical, and biological properties. Among the approximately 20 million chemical compounds identified by the end of the second millennium, more than two-thirds are fully or partially aromatic, and approximately one-half are heteroaromatic. It is, therefore, easy to understand why both the development of new methods and the strategic utilization of known methods for the synthesis of complex heterocyclic compounds continue to drive the field of synthetic organic chemistry.

Organic chemists have been engaged in extensive efforts to produce these heterocyclic compounds by developing new and efficient synthetic transformations. Among them,

catalytic reactions are the most attractive methodologies for synthesizing heterocyclic compounds using both metallic or organic catalysts.

Such protocols are hugely important as they may offer distinct advantages such as improved atom utilization or atom economy by avoidance of common derivation procedures; decreased byproduct formation and, hence, decreased waste resulting from purification procedures required to separate the desired product from impurities; in many cases, reduced energy utilization both in the reaction and purification stages. Further improvements can be provided by the utilization of alternatives more eco-friendly solvents.

The magnitude of these advantages is clear when considering the 12 Green Chemistry Principles and the international tendency to develop green and sustainable chemical processes, with lesser generation of toxic and nontoxic waste.

During my PhD course some innovative methodologies for the synthesis of different and important classes of heterocyclic compounds using metal or organic catalysts have been developed; five experimental projects will be presented and discussed. All of them involve the use of efficient catalytic systems for the synthesis of different heterocycles also in non conventional media such as supercritical carbon dioxide. Three of these projects (concerning the use of catalytic systems based on Pd or Cu), were carried out at the Department of Chemistry of the University of Calabria under supervision of Prof. G. Salerno and B. Gabriele, while the last (concerning use of organic catalyst in $scCO_2$), have been carried out at the Department of Organic and Industrial Chemistry of the University of Parma, under supervision of Prof. M. Costa and in the framework of a collaboration between Prof. Mirco Costa and professors Giuseppe Salerno and Bartolo Gabriele .

An introduction will be provided focusing on general aspects and on the most interesting and recent applications of catalysis.

1.2. Trends in heterocycles synthesis

The attention for environmental and energetic problems, such as greenhouse effect and other pollution-related issues, and the need of new energy and raw materials sources,

have been constantly growing during the last years. It is now widely acknowledged that the solutions for these problems can be provided with innovation in technology, which can lead to a more sustainable progress without affecting the economical and human development and the level of quality of life.

It is more and more diffuse conviction that scientific research can play a leading role in this field. Chemistry in particular is among the most involved disciplines, and a great effort is being made by many research groups in the world towards a "greener" chemistry. These works try to provide low-waste, low-energy consumption, low-hazard methods as candidates for replacing the traditional industrial processes.

The development of efficient catalytic systems and the use of alternative reaction media are powerful tools to reach the target of a sustainable chemistry in terms of both economy and ecology.

This thesis describes some examples of how the use of a combination of highly efficient catalysts and alternative reaction media can strongly improve the environmental impact of many processes that in several cases have proved to become also more efficient and economically advantageous than their conventional analogues also leading in some cases to new important products.

Many examples of catalysis in non-conventional media have been published in the latest years. The following chapter focuses on the general aspects of this matter and reviews some of the most interesting examples.

1.2.1 Towards a greener chemistry: the problem of waste

Traditional industrial chemistry processes are usually focused on optimizing reaction efficiency and chemical yield. Due to the increasingly strict legislative regulations and the growing awareness in the scientific community and in the public opinion of the problems that arise from the intensive production of toxic and polluting waste, it is now widely acknowledged that the production of waste and/or the use of hazardous chemicals must be taken into account when estimating the efficiency of a process, and a trend has established towards a more sustainable technology or "green chemistry".

A general definition of "green chemistry" has been proposed by Roger Sheldon as follows: "green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products."

Waste is defined as "everything produced in the process, except the desired product". From the data reported in literature, it comes out clear that the amount of waste produced increases strongly going downstream from bulk to specialty chemicals, reaching values of over 100 kg waste / kg product in the pharmaceutical industry.

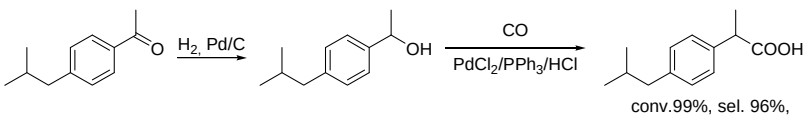
The production of waste derives from different sources. The most important ones are considered in the following paragraphs.

1.2.1.1 Inorganic salts

Inorganic salts come from the use of stoichiometric amounts of inorganic reagents; for instance, Friedel-Crafts reactions that use stoichiometric amounts of Lewis Acids ($AlCl_3$) and Bronsted Acids (H_2SO_4); reductions with metal hydrides ($LiAlH_4$, $NaBH_4$); oxidations with potassium permanganate, etc.

The solution to this problem is switching to catalytic atom-efficient methodologies that employ molecules like H_2, CO, CO_2, O_2, H_2O_2, H_2O and NH_3 as direct sources of H, C, O and N for the organic synthesis. The above listed compounds can be obtained from renewable sources such as biomass, process exhausts, water and air. This switch might be a major challenge for the chemical industry of the future; nevertheless, several processes based on catalytic hydrogenation, hydroformylation, carbonylation, oxidation have been developed and applied in the industry during the past years.

An elegant example is the Hoechst-Celanese process for the synthesis of ibuprofen, a common pharmaceutical product presently manufactured in over 8000 t/y (scheme 1).[1]



Scheme 1

The synthesis is accomplished in a two-step 100% atom efficient catalytic process; however, the reagent is still obtained via a Friedel-Crafts acetylation of isopropylbenzene, so leaving space for a further optimization of the process.

1.2.1.2 Undesired byproducts

Many processes are still affected by the production of non negligible amounts of byproducts. The problem consists in a lack of selectivity and can be avoided by developing new highly efficient catalytic systems.
For instance, most fine chemicals (pharmaceuticals, herbicides, etc.) require a high optical purity. Traditional organic processes often involve the production of a racemate and the consequent enantioseparation, thus wasting the undesired enantiomer or having it to undergo expensive and waste-producing recovery and racemization steps. An elegant way to avoid enantioseparation is the development of asymmetric catalyst suitable for producing only the desired enantiomer in high yields and purity. Many example of asymmetric catalysis are available in literature and have already gained widespread application in industry. Pioneers in these fields such as Noyori, Sharpless and Knowles gained the Nobel Prize in 2001 for their works in this field[2].

1.2.1.3 Solvents

Solvents are a major issue in the production of chemicals. Glaxo-Smith-Kline researchers[3] have pointed out that about 85% of the total mass of chemicals involved in pharmaceutical production is constituted by solvents. Although solvents are recovered after each step, the recovery efficiencies generally range from 80% to 50%. This means that the environmental impact of specialty chemicals processes is dramatically affected by the problem of solvents.
- **Volatility**. Solvents are usually chosen for their separation properties and for the solubility of substrates. Unfortunately, these are the same properties that affect their impact on environment. Most conventional solvents are highly volatile. This makes

easier their separation from the product by distillation, but on the other hand volatility leads to losses by evaporation and spillage, therefore polluting the atmosphere and exposing workers to their vapors. VOCs (Volatile organic Compounds) for these reasons are now subjected to severe regulations in most developed countries.

- Toxicity and regulations. Moreover, some of the formerly most common solvents for organic synthesis such as benzene or chlorinated hydrocarbons have proved to be major carcinogenics and their use has been banned or restricted in several countries.

- Disposal and contamination. Some polar aprotic solvents such as DMF or DMSO are scarcely volatile and they are usually separated by washing the product with water. This leads to contaminated aqueous effluents that are difficult to treat and dispose of.

- Flammability. The vast majority of conventional solvents are highly flammable. This implies that they need special care in handling and stocking, these precautions also contributing to increase the cost of the overall process.

- Non renewability. Presently almost every available organic solvent is derived from oil processing. In the future, together with the shift to renewable energy sources, also raw materials including those for chemicals will be obtained from renewable sources such as biomass or atmosphere. Solvents like lower alcohols, natural esters etc., which can be easily obtained form natural sources and are biodegradable, are going to be privileged also in the choice of solvents for chemical manufacture.

1.2.4 Catalysis in non conventional media as a solution

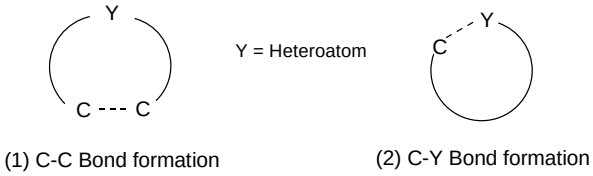
From the above considerations, it comes out clear that a major role on the road towards a more sustainable chemistry can be played by a combination of highly efficient catalysts and green solvents. Homogeneous catalysis has several advantages, including higher selectivities and activities, milder reaction conditions, efficient heat transfer, and minor mass transfer problems. Nevertheless, heterogeneous catalysis is usually preferred in the industry because of a single but essential reason: the easier separation and reuse of the catalyst.

In the next chapters a summary of some of the most important catalytic processes and the main alternative solvents presently available for the synthesis of heterocyclic compounds will be described.

1.3. Metal-catalyzed synthesis of heterocycles

1.3.1 Introduction

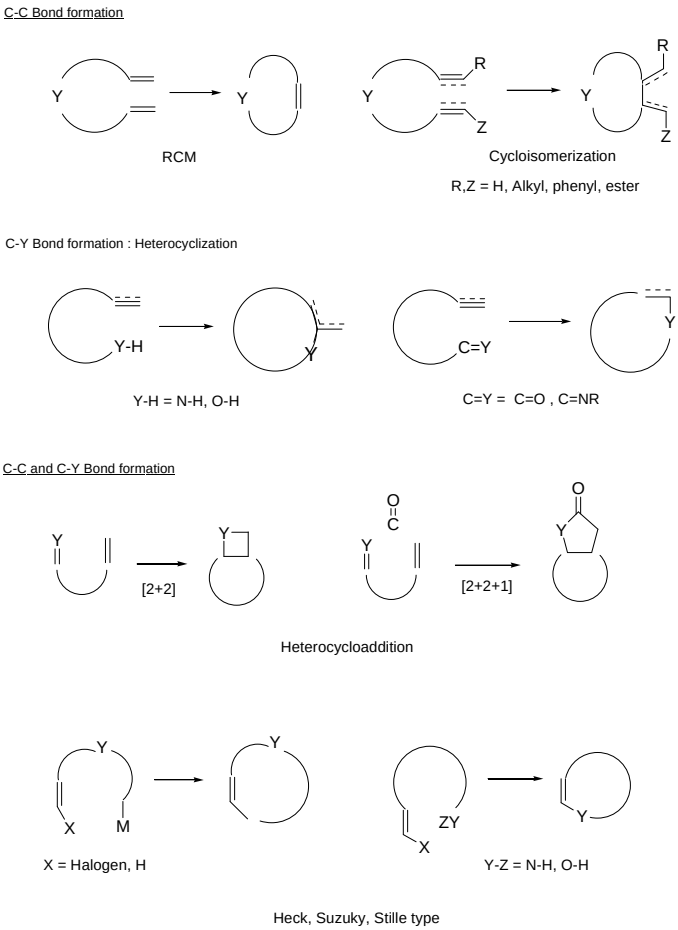
Among a variety of new synthetic transformations, transition-metal-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since a transition- metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions. The catalytic construction of heterocyclic skeletons is classified into two major processes, as shown in Scheme 2: (1) C-C bond formation from the corresponding acyclic precursors and (2) C-Y bond formation from the corresponding acyclic precursors.



Scheme 2

The synthesis of heterocycles via the olefin metathesis reaction (RCM, ring closing metathesis,) and via the cycloisomerization of dienes, diynes, and enynes belongs to category 1 (Scheme 3). The cyclization of alkenes, allenes, and alkynes bearing Y-Z at an appropriate position of the carbon chain is classified under category 2. The two processes, C-C and C-Y bond formation, take place together in the intra- and intermolecular hetero-cycloaddition of alkenes and alkynes bearing a hetero-unsaturated bond at an appropriate position of the carbon chain; four-, five- or six-membered heterocycles can be synthesized, depending on the partner of the intra- and

intermolecular reaction. The intramolecular reaction of aryl and vinyl halides via Heck-, Suzuki-, and Stille-type reactions proceeds through the C-C bond formation and that via the coupling with a heteroatom proceeds through the C-Y bond formation.



Scheme 3

As can be seen from Scheme 3, all the starting materials possess C-C and/or C-heteroatom unsaturated bond(s) in (a) certain position(s) of their structural framework and those functional groups become a reactive site for making a new C-C and/or C-heteroatom bond (C-Y bond). This is a logical outcome, since, the formation of a complex between a transition metal and C-C (or C-Y) unsaturated bond plays an

important role in the transition-metal catalyzed reaction and often triggers a key reaction for producing heterocycles.

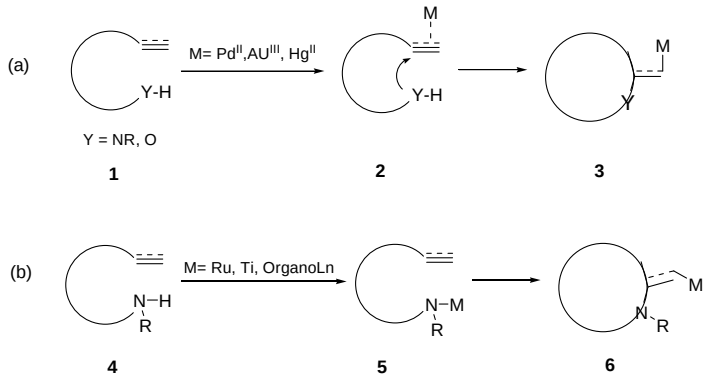
Compared to the traditional organic transformations leading to heterocycles, the transition-metal catalyzed transformation seems to be not straightforward and not easily understandable in many cases. This is presumably due to the fact that sequential processes often are involved in the catalytic transformation, which makes it difficult to understand at a glance the conversion from a starting substrate to a final product.

An important feature in the modern heterocycle synthesis with transition-metal catalysts is that asymmetric catalytic synthesis is becoming very popular and attracting interest of a wide range of organic chemists.

Among all the important methodologies used for the synthesis of heterocyclic compounds I will emphasized the ones that constituted my background and led me to obtain the results show later in this thesys.

1.3.2 Intramolecular Reaction of Alkenes and Alkynes Bearing N-H, O-H, C=O, and C=N Groups: Heterocyclization

Transition-metal-catalyzed intramolecular reactions of carbon-carbon unsaturated compounds tethered with N-H, O-H, C=O, and C=N groups have been extensively studied and have become a powerful tool for the synthesis of heterocycles. Alkenes and alkynes have been utilized as a carbon-carbon unsaturated compound, and a wide variety of transition-metal complexes, such as palladium, platinum, gold, copper, titanium, tungsten, and organolanthanides, have been used as a catalyst. In these reactions the heterocyclic compounds are produced via carbon-heteroatom (C-Y) bond formation (see Scheme 3). The transition-metal catalyzed intramolecular addition reaction of Y-H to the C-C unsaturated bonds is classified into two major groups, as illustrated in Scheme 4.



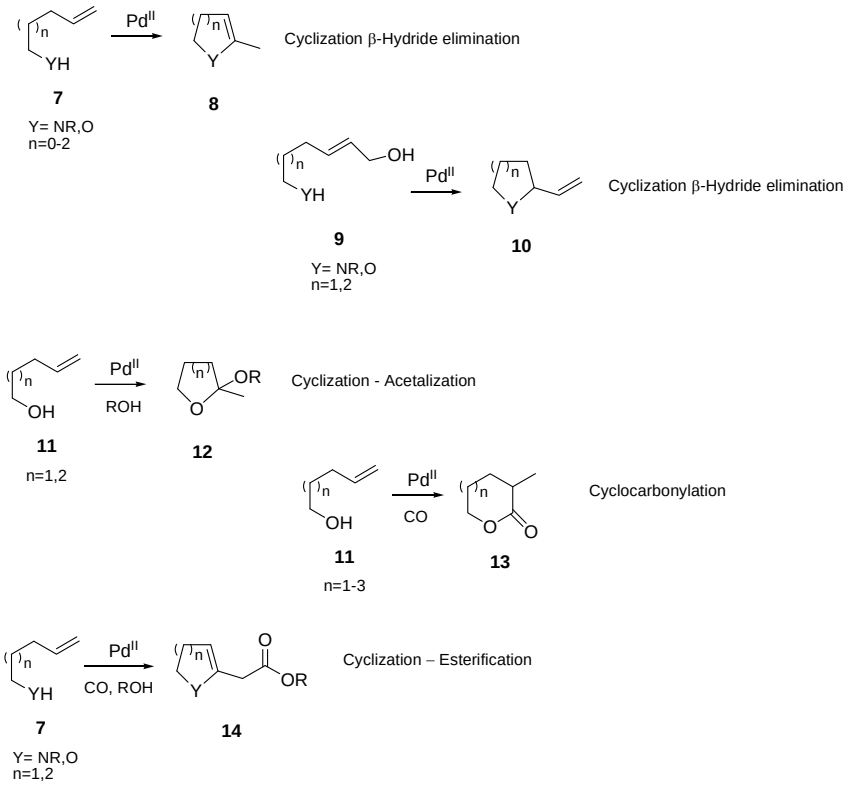
Scheme 4

In the presence of a higher valent transition-metal catalyst, such as Pd^{II}, Au^{III}, and Hg^{II}, the reaction of **1** having a Y-H group is initiated by the formation of the π-olefin complex **2** through the coordination of the carbon-carbon unsaturated bond to the transition metal. Subsequent intramolecular nucleophilic attack of the heteroatom to the electron-deficient unsaturated bond produces the new heterocyclic organometallics **3**. On the other hand, the ruthenium, titanium, and organolanthanide-catalyzed reaction of the amine derivatives **4** starts from the formation of the metal-amido complex **5**, and the following intramolecular aminometalation of the C-C unsaturated bond produces the new heterocyclic organometallics **6**. The organometallic compounds **3** and **6** undergo either β-elimination or the reaction with electrophiles to give the corresponding heterocyclic products.

1.3.2.1 Alkenes

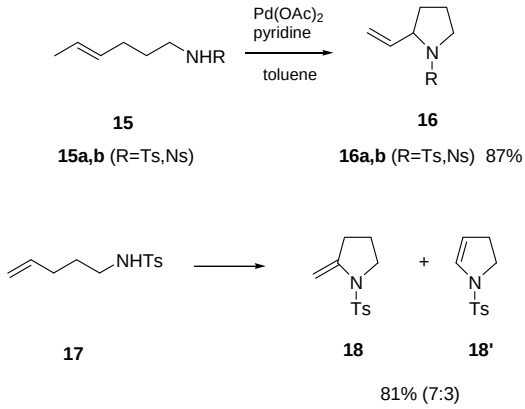
Higher valent palladium(II)-catalyzed reaction of alkenylamines and alkenyl alcohols have been widely investigated, and these reactions are categorized into the five different reaction patterns, as shown in Scheme 5. The cyclization of the alkenylamines or alcohols **7** followed by β-hydride elimination gives the cyclic enamines or enols **8** .[4a,b,5] The reaction of the substrates **9** having an allyl alcohol moiety proceeds through the cyclization, and the subsequent β-hydroxy elimination gives the heterocycles **10** bearing a vinyl group .[4b,6] The reaction of the alkenols **11** with an external alcohol produces the

cyclic acetals **12** .[4b,7] The cyclocarbonylation of **11** with carbon monoxide gives the lactones **13** .[4c,8] The reaction of the alkenylamines or alkenyl alcohols **7** with carbon monoxide and an alcohol proceeds through the cyclization−esterification to give **14** .[4d,9] In these reactions the carbon−carbon double bond of substrates coordinates to the Lewis acidic palladium(II) complex and intramolecular nucleophilic attack of a heteroatom takes place as shown in Scheme 3.



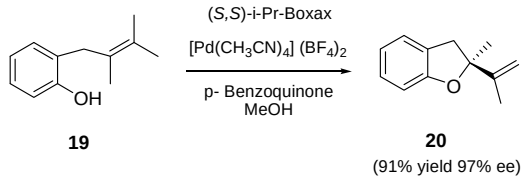
Scheme 5

Fix et al. reported the palladium-catalyzed oxidative cyclization of aminoalkenes.[5b] The reaction of the aminoalkenes **15** having a methyl group on the olefin moiety gave the 2-vinylpyrrolidines **16**, while the reaction of the aminoalkene **17** having a terminal olefin gave a mixture of the cyclic enamines **18** and **18**‘ (Scheme 6).



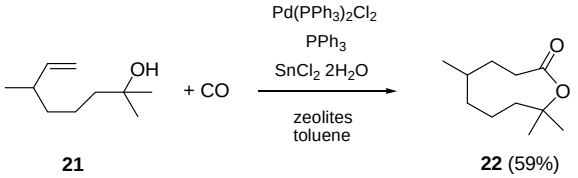
Scheme 6

Uozumi et al. reported the palladium-catalyzed asymmetric heterocyclization. The reaction of the *o*-allylphenol **19** in the presence of $[Pd(CH_3CN)_4](BF_4)_2$ and (*S*,*S*)-*i*-Pr-boxax gave the dihydrobenzofuran **20** in 91% yield with 97% ee (Scheme 7).[5c]



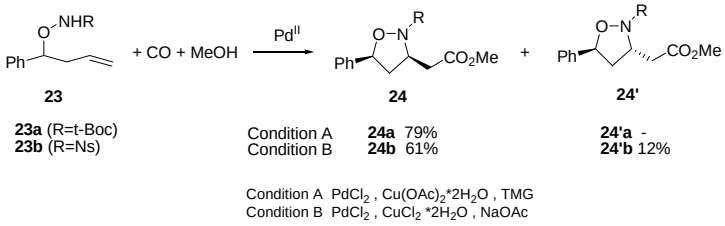
Scheme 7

Lenoble et al. reported the cyclocarbonylation of the alkenyl alcohol **21** with carbon monoxide in the presence of palladium, phosphine, and tin catalysts gave the nine-membered lactone **22** selectively (Scheme 8).[8c]



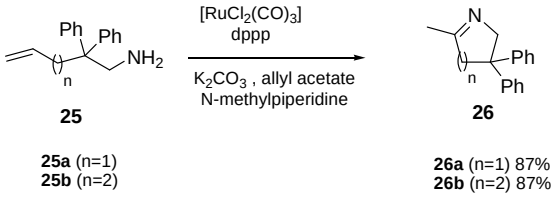
Scheme 8

Bates and Sa-Ei demonstrated that the reaction of *O*-homoallylhydroxyamines **23** with carbon monoxide and methanol in the presence of a palladium catalyst gave the isooxazolidine in good yields.[9a] The reaction of the carbamate **23a** gave only the cis-isomer 2**4a** diastereoselectively, while the reaction of the sulfonamide **23b** gave a 5:1 mixture of the cis−trans diastereomers (Scheme 9).



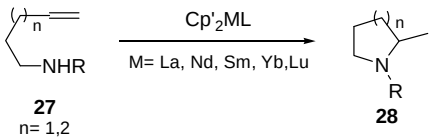
Scheme 9

Mitsudo et al. reported that the ruthenium-catalyzed intramolecular oxidative amination of the aminoalkenes **25** gave the cyclic imines **26** in high yields (Scheme 10).[10]



Scheme 10

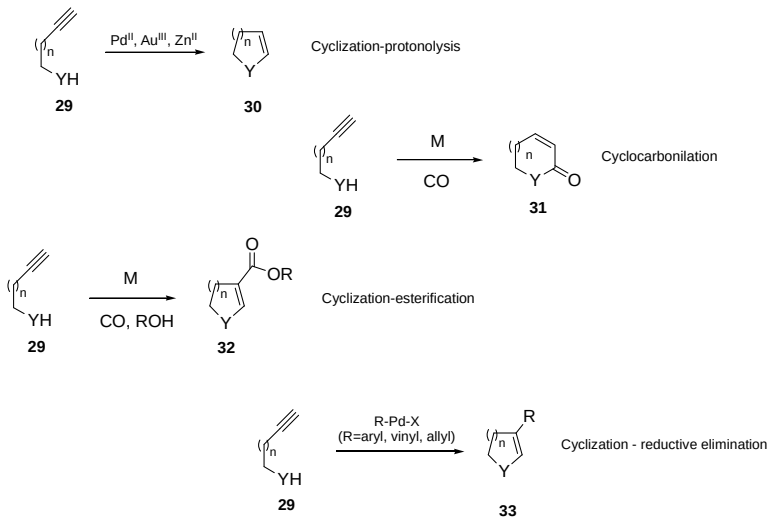
The organolanthanide-catalyzed intramolecular hydroamination of the aminoalkenes **27** is one of the most useful processes for constructing the nitrogen heterocycles **28**, whose skeletons are often found in naturally occurring alkaloids (Scheme 11).[11,12]



Scheme 11

1.3.2.3 Alkynes

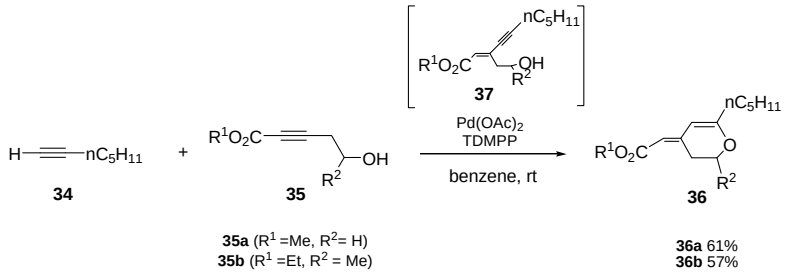
The Lewis acidic metal complexes, such as Pd^{II}, Au^{III}, Zn^{II}, and $W(CO)_6$, promote the intramolecular reaction of an alkyne with an amine, amide, alcohol, and carboxylic acid. These reactions are classified into four types, as shown in Scheme 12. The cyclization of **29** and subsequent protonolysis gives the heterocycles **30** having a carbon-carbon double bond .[4,11,13] The cyclocarbonylation of **29** occurs under carbon monoxide atmosphere to give the lactones and lactams **31**.[4,14] The reaction of the alkynylamines or alkynyl alcohols **29** with carbon monoxide and an alcohol gives the heterocycles **32** having an α,β-unsaturated ester moiety.[4,15] In the presence of organopalladium species R-Pd-X, the reaction of **29** proceeds through the cyclization promoted by the Lewis acidic R-Pd-X, and subsequent reductive elimination of Pd(0) from the resulting cycloalkenylpalladium(II)X complex gives **33**.[16]



Scheme 12

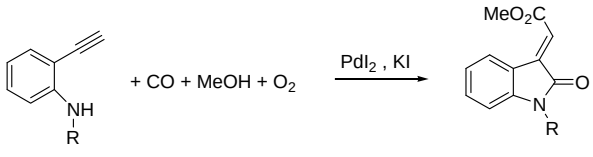
Trost and Frontier reported that the tandem palladium-catalyzed reaction of 1-heptyne **34** with the alkynols **35** produced the dihydropyrans **36** in good yields (Scheme 13).[13h] The reaction proceeds through the palladium-catalyzed coupling of 1-heptyne and the

alkynols **35**, followed by subsequent palladiumcatalyzed 6-endo-dig cyclization of the resulting enynols **37**.

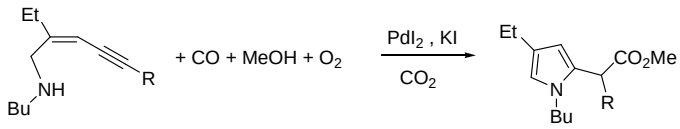


Scheme 13

Gabriele et al. reported that the palladium-catalyzed reaction of the *o*-ethynylanilines **38** with carbon monoxide, methanol, and oxygen gave the 1,3-dihydroinol-2-one derivatives **39** in good yields (Scheme 14).[14b] The reaction proceeds through the cyclocarbonylation-esterification (see Scheme 12). On the other hand, the reaction of the (*Z*)- (2-en-4-ynyl)amines **40** with carbon monoxide, methanol, and oxygen under CO_2 atmosphere gave the pyrroles **41**, derived from cyclization-esterification, in good yields (Scheme 15).[15e]



Scheme 14



40

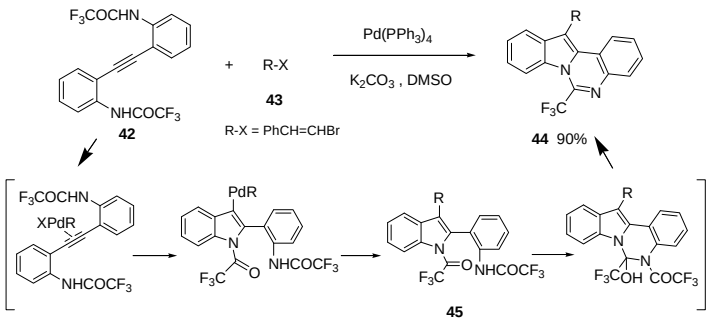
40a (R=Bu)
40b (R=TMS)

41

41a 70%
41b 72% (R=H)

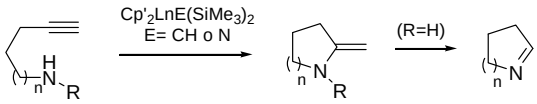
Scheme 15

Arcadi et al. reported that the palladium-catalyzed cyclization of bis(*o*-trifluoroacetamidophenyl)acetylene **42** with aryl and vinyl halides **43** gave the indole[1,2-*c*]quinazolines **44** in high yields (Scheme 16).[16h] The reaction proceeds through aminopalladation- reductive elimination. The cyclization of the resulting 3-arylinodole derivatives **45** gives the tetracyclic heterocycle **44**.



Scheme 16

The organolanthanide-catalyzed hydroamination of the aminoalkynes **46** gives the nitrogen-containing heterocycles **47** or **48** (in the case of R = H).[17] The reaction of primary amines produces the cyclic imines **48**, while the reaction of secondary amines gives the cyclic enamines **47** (Scheme 17). The organolanthanide- catalyzed bicyclization of the aminodiynes, aminoenynes, and aminodienes **49** produces the pyrrolizidine and indolizidine derivatives **50** in a single reaction (Scheme 18).[18]

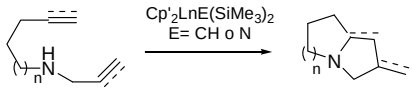


46
n=1-3

47

48

Scheme 17

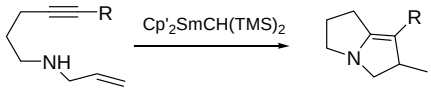


49
n=1,2

50

Scheme 18

Li and Marks reported that the reaction of the aminoenynes **51** in the presence of an organolanthanide catalyst gave the pyrrolizines **52** in good yields (Scheme 19).[18]



51

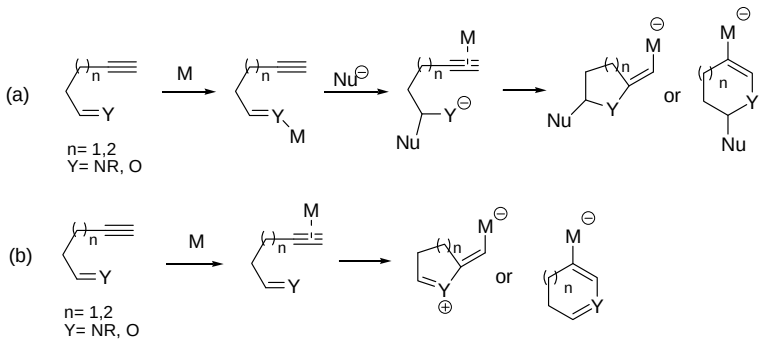
51a (R=Ph)
51b (R=Me)

52

52a 68%
52b 75%

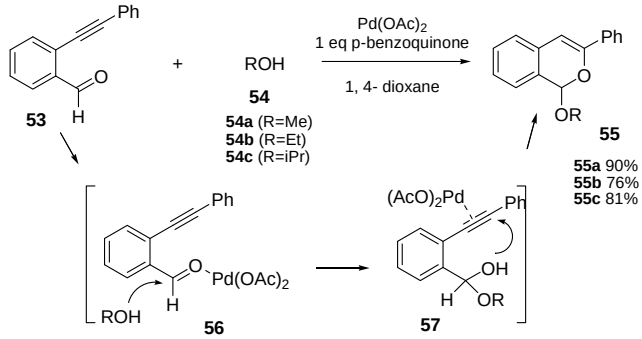
Scheme 19

Heterocyclization of alkynyl aldehydes and imines proceeds through two different mechanistic pathways (Scheme 20, routes a and b). A Lewis acidic transition metal is coordinated by a heteroatom of C=Y, the nucleophilic addition of Nu- to the electron-deficient carbon of C=YM takes place first, and then the resulting Y^- attacks an electron-deficient carbon of the alkyne coordinated to M (type a). It should be noted that the M acts simultaneously as a Lewis acid and as a typical transition-metal catalyst, that is to say, as a dual-role catalyst. Alternatively, the triple bond coordinates first to a transition-metal catalyst M, and then the nucleophilic attack of a heteroatom of C=Y takes place (type b).



Scheme 20

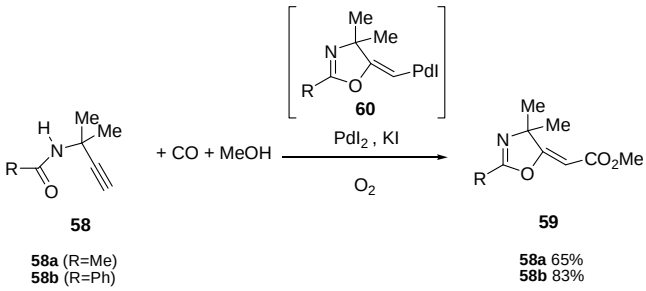
Yamamoto reported that the palladium-catalyzed reaction of *o*-alkynylbenzaldehyde **53** with the alcohols **54** gave the alkenyl ethers **55** in good to high yields (Scheme 21).[19] This reaction proceeds through formation of the hemiacetal **57** and subsequent nucleophilic attack of the OH group on the electron- deficient alkyne coordinated by palladium(II). In this reaction, $Pd(OAc)_2$ acted simultaneously as a Lewis acid and as a transition-metal catalyst; the carbonyl group is activated by a Lewis acidic Pd(II) (**56**) to make facile addition of ROH, and the alkynyl moiety is activated by Pd(II), having a typical transition metal characteristic, as shown in **57**, to produce the cyclized alkenyl palladium(II) intermediate that undergoes protonation.



Scheme 21

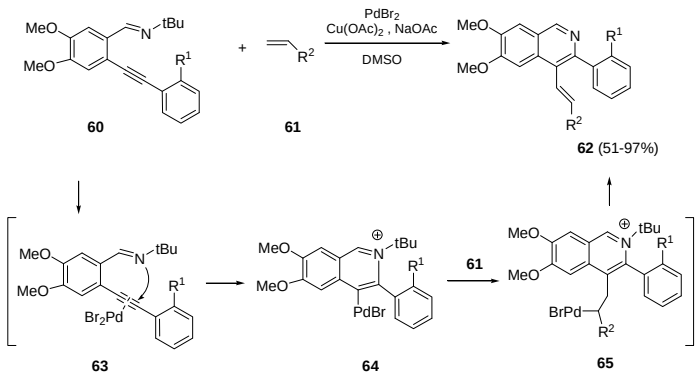
Bacchi et al. reported the efficient and general synthesis of the 5-(alkoxylcarbonyl)methylene-3-oxazolines **59** by the palladium-catalyzed oxidative

carbonylation of the pro-2-ynylamides **58** (Scheme 22).[20] This reaction is initiated by nucleophilic attack of an oxygen atom of an amide group on an alkyne coordinated by palladium(II), forming the vinylpalladium intermediate **60**. The insertion of CO into the C-Pd bond of **60**, followed by methanolysis of the resulting acylpalladium complex, affords the esters **59** and Pd(0) catalyst. The Pd(0) is oxidized to Pd(II) by molecular oxygen, and thus the catalytic cycle operates well.



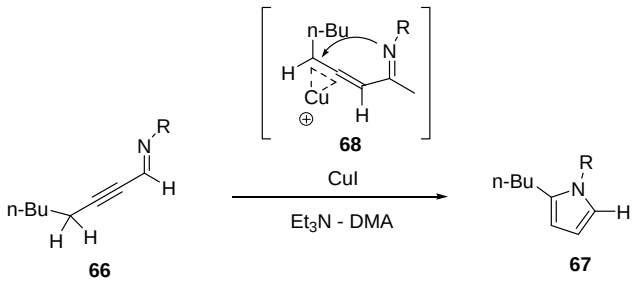
Scheme 22

Huang and Larock reported that palladium-catalyzed cyclization/olefination reaction of the *o*-alkynylbenzaldimines **60** with the olefins **61** produced the isoquinolines **62** in good to high yields (Scheme 23).[21] The reaction proceeds through the nucleophilic attack of the nitrogen atom on electron-deficient alkyne **63**, the formation of the alkenylpalladium intermediate **64**, the insertion of the alkenes **61** into the C-Pd bond **65**, and β-hydride elimination. They reported many examples of this type of reactions.[22]

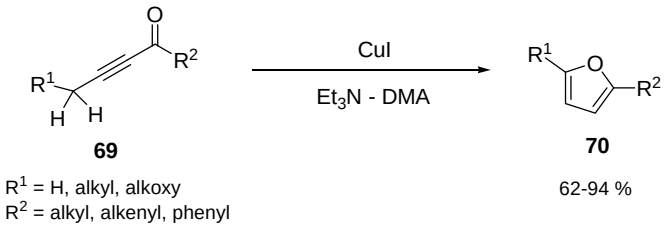


Scheme 23

Kel'in et al. reported that the copper-assisted cycloisomerization of the alkynyl imines **66** gave the pyrroles **67** in high yields (Scheme 24).[169] Mechanistic studies revealed that this reaction proceeded via the propargyl-allenyl isomerization of **66** to an allenyl imines and through the nucleophilic attack of the nitrogen atom of imine on the electrondeficient carbon **68**. The cycloisomerization of alkynyl ketones **69** gave 2,5-disubstituted furans **70** (Scheme 25).[24]



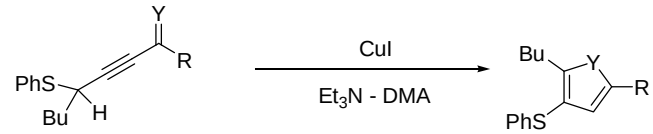
Scheme 24



R^1 = H, alkyl, alkoxy
R^2 = alkyl, alkenyl, phenyl

Scheme 25

The 3-thiofurans and pyrroles **72** were synthesized similarly by the copper-catalyzed cycloisomerization of the keto- and iminopropargyl sulfides **71** (Scheme 26).[25] The reaction proceeds through the copper-catalyzed isomerization of alkyne to the corresponding allenes, followed by the thermal or Cu-mediated 1,2-migration of the thio group.



71

71a (Y= O,R =Ph)
71b (Y= N-Tr, R=H)

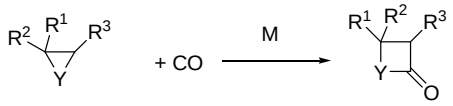
72

72a 91%
72b 85%

Scheme 26

1.3.3 Synthesis of heterocycles via carbonylation methodologies

The transition-metal catalyzed carbonylation reaction has been extensively investigated, and especially the carbonylative ring expansion reaction of strained heterocycles has been shown to be a useful and efficient procedure to synthesize lactams, lactones, and thiolactones.[26] The carbonylation of epoxides and aziridines **73** is a powerful tool to construct the β-lactone and β-lactam skeletons **74** (Scheme 27).[27] This type of reactions can be regarded as a hetero-[3 + 1]-cycloaddition.

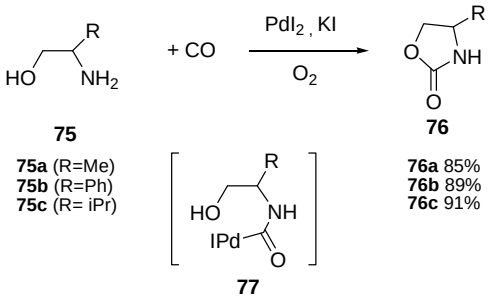


73
Y = O, NR

74

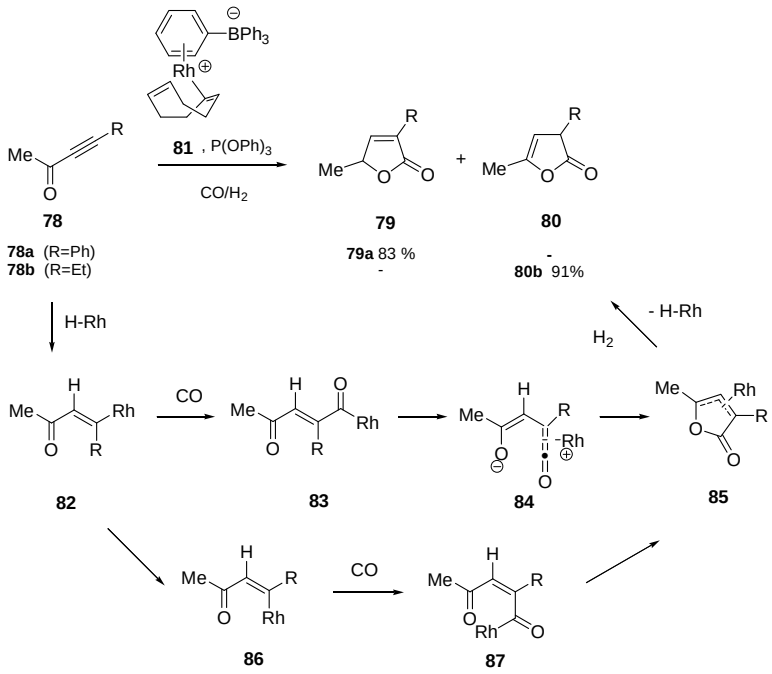
Scheme 27

Gabriele et al. reported that the 2-oxazolidinones **76** were synthesized by the palladium-catalyzed oxidative carbonylation of the 2-amino-1-alkanols **75** (Scheme 28).[28] The aminocarbonyl palladium complex **77** is formed as an intermediate, and subsequent ring closure gives **76**.



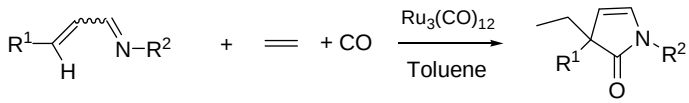
Scheme 28

Van den Hoven et al. reported that the zwitterionic rhodium complex **81**-catalyzed chemo- and regioselective cyclohydrocarbonylation of the α-keto alkynes **78** afforded either the furanone **79** or **80**, depending on the substituent R (Scheme 29).[28] The reaction of **78a** with R = Ph gave the 2(*3H*)-furanone **79a** in 83% yield, while the reaction of **78b** with R = alkyl afforded 2(*5H*)-furanone **80b** in high yield. The reaction proceeds via hydrorhodation of the triple bond of ynones **78**. The insertion of CO into the C-Rh bond of **82**, rearrangement from **83** to the zwitterionic ketene **84**, and subsequent cyclization of **84** give **85**. Alternatively, the *E-Z* isomerisation of **82** to **86**, CO insertion to the sp2 C-Ru bond of the alkenylruthenium **87**, and intramolecular acylrhodation of the carbonyl moiety of **87** give the same intermediate **85**. The reduction of the ruthenium complex **85** with H_2 gives **79** or **80**.



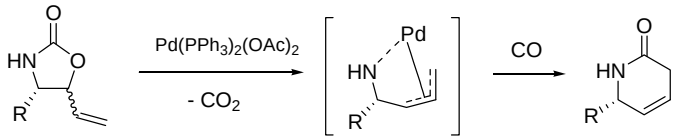
Scheme 29

Imhof et al. and Chatani et al. independently reported that the ruthenium-catalyzed reaction of the α,β-unsaturated imines **88** with alkenes and carbon monoxide gave the β,γ-unsaturated γ-butyrolactams **89** (Scheme 30).[29]



Scheme 30

Knight et al. reported that the palladium-catalyzed decarboxylative carbonylation of amino acid-derived 5-vinyloxzolidin-2-ones **90** gave the corresponding δ-lactams, 3,6-dihydro-1*H*-pyridin-2-ones **91**, in good to high yields (Scheme 31).[30] This reaction proceeds through release of carbon dioxide, forming the π-allylpalladium intermediate **92**, followed by insertion of CO.



90

90a (R=iPr)
90b (R=Bn)
90c (R=Ph)

91

92

92a 87%
92b 78%
92c 58%

Scheme 31

1.3.4 Conclusions

Heterocycles are especially important in chemical and pharmaceutical industries. It seems that industrial people have been using mostly the traditional and conventional transformations for the synthesis of heterocycles, perhaps because those reactions are reliable and robust and proceed generally at low cost.

However, it is also true that some of those reactions are accompanied with waste byproducts. In this sense, transition-metal catalyzed reactions minimize such waste and are in general environmentally friendly. Heterocycles having a complicated structure with many labile functional groups can be synthesized often from rather simple starting materials through sequential catalytic processes.

1.4. Non conventional solvents

All the problems associated with the use of solvents can be overcome if the reaction can be run without the need of any solvent. However, in scientific literature and industrial applications there are only few examples of solvent-free systems, which are limited by the necessity of liquid reagents and products, concentration issues, and catalyst solubility.

If a solvent is needed, the ideal green solvent should be non volatile, non toxic, non hazardous, cheap, easy to recover, immiscible with water.

Several proposals have been made in the latest years; some of them have been applied with success in industrial production.

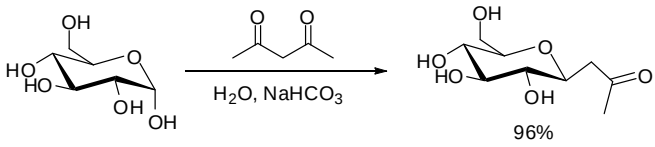
1.4.1 Water

Water is the most abundant, inexpensive and less dangerous solvent available. Traditionally it has not been intensively used in organic chemistry because of the lack of solubility of most organic compounds and catalysts and of its possible reactivity. It is also to be taken into account that conducting a reaction in water implies that effluents should be conveniently purified; in fact, release of wastewater contaminated by traces of, for instance, heavy metals can be a serious environmental issue, thus invalidating the "greenness" of the whole process.

However, studies have shown that the unique properties of water as a reaction medium can be exploited to improve reaction performances, or to explore completely new reactivity of organic compounds.

Bulk water is in fact a system of small, highly polar molecules in a network of intermolecular hydrogen bonds, thus providing hydrophobic effects that can enhance the reactivity, and the low solubility of oxygen gas allows running in water air-sensitive organometallic catalyzed reactions.[31]

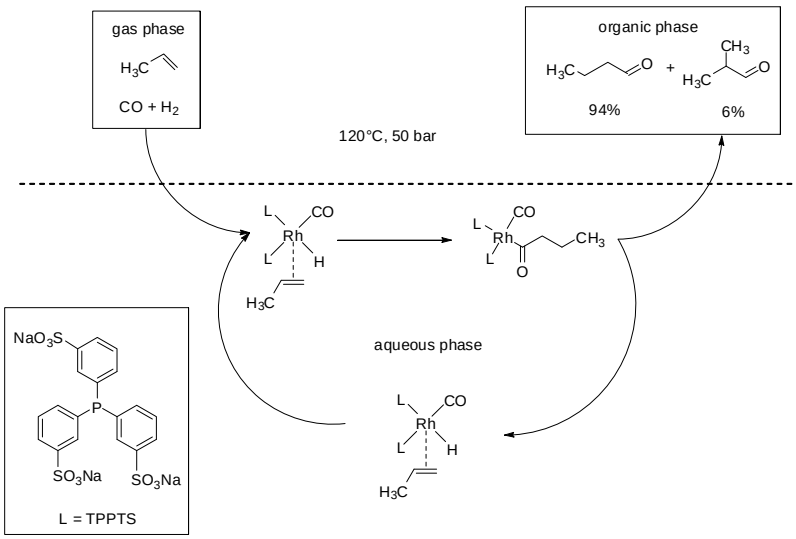
Moreover, being living systems essentially aqueous environments, water is a perfect solvent for many reactions that involve natural products. For instance, carbohydrates can be caused to react without further derivatization (that would be necessary for the use of organic solvents). Carbohydrates are common building blocks for the total syntheses of many natural products. An elegant example is the synthesis of β-C-glycosidic ketone that has been carried out in water in a single step with high yield. (Scheme 32). The same product had previously been obtained in seven steps via conventional organic reactions[32].



Scheme 32

Several examples are available of transition metal catalysis in water. In contrast, traditionally water was avoided in transition metal catalyzed reactions because it may attack metal-carbon bonds or compete with chosen ligands for coordination on the metal centre, thus modifying the desired reaction pathway. In recent times it was demonstrated that the above mentioned properties can have a positive effect or be minimized by opportunely developing the catalytic system. Thus, transition metal catalysis in water has become a widely studied field.

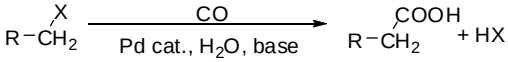
New ligands and catalysts have been designed for this application, and presently several examples are available both in industry and in scientific literature. The most famous is the Rhone-Paulenc / Ruhrchemie hydroformylation process (scheme 33). This process is now reported to produce over 10% of the world's C4-C5 aldehyde capacity[34].



Scheme 33

The water soluble ligands is widely used in homogeneous catalysis. Other suitable ligands for the preparation of water-soluble metal complexes include anionic phosphines bearing carboxylate groups and phosphonate groups, cationic phosphines such as AMPHOS, neutral phosphines bearing alkylhydroxilic groups[35], sulphonated and carboxylated diphosphines[36]. Less common are water soluble non-phosphorous containing ligands, such as bypyridines, EDTA, dithiolates and calixarenes[37].
Metal-catalyzed reactions with water soluble catalysts are sometimes affected by problems due to the low solubility in water of some organic substrates (e.g., higher olefins in hydroformylation). This problem has been solved by preparing special surfactant-based phosphines[38].

A different approach is the direct coordination of water molecules to the metal center. This allows to use less expensive metal complexes and to avoid the sometimes difficult and expensive synthesis of dedicated ligands. Although less studied, this field presents several examples of highly efficient catalyzed reactions in water. The most common catalysts used are hydrate late transition metal salts such as $[RhCl_n(H_2O)_{6-n}]_{3-n}$ and $[RuCl_n(H_2O)_{6-n}]_{3-n}$. which were first used in 1966 for the hydrogenation of maleic and fumaric acids[39].
Several carbonylation reactions in water have been reported in literature. In most cases, they involve the use of allylic or aromatic halides and the use of a Pd catalyst such as $Pd(OAc)_2$ or $Pd(TPPTS)_2Cl_2$. Scheme 34 provides the general equation for the reaction[40].

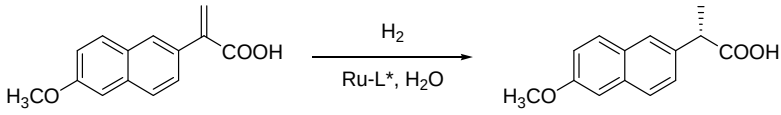


X = Cl, Br, I
R = aromatic or allylic

Scheme 34

Finally, asymmetric syntheses have been successfully performed in water. These reactions combine the efficient chiral catalysts developed for “classic “ asymmetric hydrogenations with water soluble moieties. This approach allows to elegantly solving

the problem of recycling the expensive chiral catalysts via a simple extraction and recovery of the aqueous phase. The aqueous phase can be recycled several times without significant loss of activity and enantioselectivity. Scheme 35 reports an example, studied by Davies and coworkers, which allows the synthesis of Naproxen utilizing a sulphonated Ru(BINAP) catalyst[41].



Scheme 35

1.4.2 Supercritical fluids and carbon dioxide

TABLE 1 Critical points of some common substances.

Substance	T_c °C	P_c Bar
Ethylene	9.3	50.4
Xenon	16.6	58.4
CO_2	31.1	73.8
Ethane	32.2	48.8
Propane	96.7	42.5
NH_3	132.5	112.8
Butane	152.1	38
Pentane	196.5	33.7
Methanol	239.5	81
Toluene	318.6	41.1
H_2O	374.2	220.5

Supercritical fluids (SCFs) are also an attractive alternative to standard solvents. Their main limitation are the technically challenging conditions required to reach the supercritical state for most compounds. Actually, the only supercritical fluid that has found a quite extensive application is carbon dioxide, due to its relatively low critical pressure (74 bar) and temperature (31°C). Most other molecules have critical points too high to be industrially attractive as reaction media. A list of critical points of common substances is given in Table 1.

Studies have suggested possibilities for the utilization also of supercritical water (P_c = 220 bar, T_c = 374°C), hydrocarbons and fluorocarbons. A relevant application

in this field is the industrial polymerization of ethylene, an homogeneously catalyzed process in which the supercritical fluid acts as both solvent and reagent.

However, supercritical carbon dioxide ($scCO_2$) is by far the most interesting and the most studied SCF so far. It is non toxic, non flammable, abundant and cheap. It is also non pollutant, as long as it is recycled from industry exhausts, since its use gives no further contribution to greenhouse effect. $scCO_2$ has a number of uses in fields other than synthetic chemistry, such as extraction solvent in food industry (with a very relevant role in caffeine extraction from coffee), in environmental decontamination, and as solvent or antisolvent for several industrial processes in the field of polymer manufacturing.

The reason of this success in separation technologies can be found in the fact that a supercritical fluid possesses the advantages of both liquids and gases. In fact, density is comparable to that of liquids, thus giving SCFs appreciable solvent capability, while viscosity and diffusivity are more similar to those of gases, thus overcoming most of mass transfer problems.

It is now widely acknowledged that these unique properties can be successfully exploited when a supercritical fluid is used as solvent. It is worth of note that some compounds can be soluble in a supercritical fluid and not in the corresponding liquid, or the opposite. This provides a potential way to separate catalyst and / or products from the reaction mixture just by a temperature or pressure change. Interestingly, SCF density is strongly correlated to pressure and temperature.

Several researchers, including Noyori[42], Jessop[43], and Leitner[44] have reported that reactions involving gas reagents have been found to be faster in supercritical media, probably because mass transfer problems between different phases can be avoided. In fact, reactions of gaseous with liquid reagents with homogeneous catalysts dissolved in a liquid phase are usually limited by the mass transport at the interphase. The use of homogeneous catalyst systems in supercritical reaction media constitutes an elegant way to solve mass transport problems; in fact, supercritical fluids are in several cases able to dissolve both the gas and the liquids reagents thus forming an homogeneous mixture and then the reaction can be run with the fast kinetics typical of homogeneous catalysis. Moreover, in some cases, such as oxidations or hydrogenation, the use of non-

flammable $scCO_2$ allows to reduce or avoid problems connected with flammability and explosion hazards.

Summarizing, SCFs allow potential advantages on several aspects of a catalytic reaction, including better yields and selectivities, easy recycle and longer lifetime of catalysts, enhanced mass and heat transfer.

1.4.2.1 Catalysis in SCF

Supercritical fluids have been discovered in 1822, and their first application in catalysis (in the polymerization of ethylene) dates back to 1913[45], but it was not until the mid 1990s that extensive studies were made about catalysis in SCFs. Since then, however, the field has been constantly and very rapidly growing. Reactions of almost any kind in both homogeneous- and heterogeneous- catalysis in $scCO_2$ have been attempted and published.

A recent comprehensive review from Philip Jessop[46] lists more than 150 different kind of homogeneous catalysis reactions published up to date in supercritical or liquid CO_2. Solubility of catalysts and/or reagents can be an issue in the development of a homogeneous reaction in $scCO_2$. Common aromatic ligands also are usually insoluble in $scCO_2$. However, several reactions have proved to proceed well even in these semi-heterogeneous conditions. Else, it is possible to develop CO_2-soluble catalysts or ligands, which are sometimes able to enhance the dissolution of the catalyst in the reaction media. Common strategies include the use of trialkylphosphines, the attachment of perfluorurated chains on the aromatic rings, or even the use of a cosolvent.

Heterogeneous catalysis in $scCO_2$ is also being intensively studied. A review published by Alfons Baiker in 1999[47] lists about 30 different applications of SCFs in heterogeneous catalysis.

Some of the most recent and interesting examples of catalysis in $scCO_2$ will be here described.

As already pointed out the use of $scCO_2$ can be particularly useful in reactions involving gaseous reagents, allowing a liquid-gas system, whose performance is limited by mass transport at the interphase, to become an homogeneous phase.

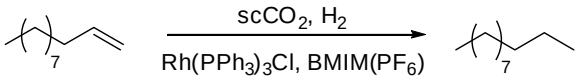
Thus, several examples are available both in academic research and industrial applications in the fields of oxidation and hydrogenation.

For instance, pilot plants or small scale industrial productions for the hydrogenation of various substances including fatty acids in supercritical fluids have been started some years ago[48].

On the side of oxidation, efforts have been made in the development of process capable of efficiently producing epoxides, in particular propylene oxide, in $scCO_2$ using oxygen or H_2O_2 as oxidant. Several researchers have been working in this area[49-51], although no economically competitive processes involving air as only oxidant have been described yet.

Supercritical carbon dioxide has also been extensively studied and applied in industry for the production and manufactory of advanced materials, such as polymers and nanoparticles[52], as well as a solvent for a number of organic reactions including, among others, Friedel-Crafts chemistry[53], enzymatic catalysis[54], C-C couplings[55-57].

An interesting application of $scCO_2$ is its use as a second phase in a biphasic catalysis system; particularly in the case of using another green solvent as the first phase, it is clear that such a system would potentially allow recovering the catalyst and separating the product without the use of any organic solvent. Water and ionic liquids (ILs) are the most common phases chosen to dissolve the catalyst, while CO_2 is commonly used to extract the reaction products. An example is the work of Liu et al.[58], which shows that olefins such as 1-decene and cyclohexene could be hydrogenated by Wilkinson's catalyst dissolved in a ionic liquid phase and the product could be obtained via separation of the supercritical phase, allowing the recycle of the IL/catalyst phase for several times (scheme 36)



Scheme 36

Eckert and coworkers have developed a new concept of multiphase catalysis involving "tunable solvents". Their work is aimed at coupling organic reactions with product separation, with considerable benefits for the sustainability of the whole process. The idea is to exploit the limited, but not negligible, solubility of CO_2 even at low pressures in organic media to alter the organic solvent properties, such as polarity, dielectric constants, and gas solubility.

It is thus possible, by adding and releasing CO_2 pressure, to "switch" the solvent between two different states, and exploit its different properties under different conditions to separate catalyst and products due to their different solubility.

Several techniques have been developed to take advantage of this effect[59]. One of the most elegant examples consists in the hydrogenation of styrene with a modified Wilkinson catalyst[60]. This reaction, similar to that described in the previous paragraph, takes advantage of a different approach. In this case, the notorious CO_2-philicity of highly fluorinated hydrocarbons was exploited. A modified silica gel bearing fluorocarbon tails was used as the mean of separating the catalyst, a fluorinated version of Wilkinson's complex, $[RhCl\{P(C_6H_4\text{-}p\text{-}CH_2CH_2(CF_2)_6F)_3\}_3]$. The reagent was dissolved in a standard organic solvent, cyclohexane. Upon addition of CO_2 to the system, the catalyst was solubilized in the organic phase and the reaction took place homogeneously. After CO_2 pressure release, the catalyst was captured on the fluorinated silica gel beads and the liquid phase, containing the products, could be easily separated and recycled (figure 1).

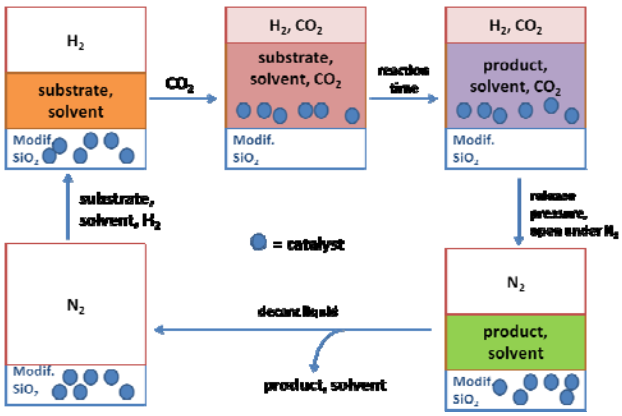


Figure 1

1.4.3 Ionic liquids

Ionic liquids (ILs) are commonly defined as salts with a melting point lower than 100°C. ILs that are liquid at ambient temperature are the most widely used because of their easiness of handling. Over their melting points, ILs can be viewed as liquids composed entirely of ions.

ILs have received a great attention in recent years. They are usually non-volatile, easy to recover, and have a broad (300°C) liquid range. The interest of researchers in this field has exponentially grown in the last decade, and they are now recognized as one of the most attractive alternatives to conventional organic solvents. However, although academic research has produced a great number of works in which ILs are used as solvents, cosolvents and/or catalysts, they have not found an application in industry yet, mainly because of their usually very high cost, and secondarily for their, still to be determined, adverse effects and biodegradability.

The reason for the relatively low melting point of this salts is the low energy of their crystalline network. They are usually composed of a bulky and asymmetric organic cation (generally ammonium or phosphonium) with low charge density and low tendency to intermolecular interactions and an inorganic anion. However, carboxylate-based ionic liquids have been also synthesized in latest years.

The most common cations are 1,3-dialkylimidazolium salts, but 1,4-dialkylpyridinium and 1,1-dialkylpyrrolidinium salts are commonly used as well. The most common anions include BF_4^-, PF_6^-, $Al_2Cl_7^-$, RSO_3^-. The chemical, physical and solvent properties of the ILs depend on both the cation and the anion. Thus it is possible to design new ionic liquids with the desired properties by opportunely choosing the cation and the anion. Some of the most common anions and cations are reported in figure 2.

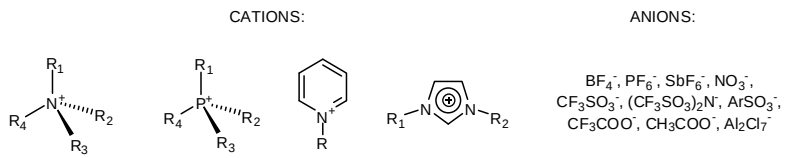
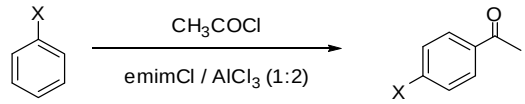


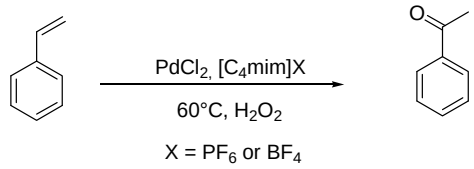
Figure 2

One of the most interesting features of ILs is the opportunity of using them as both solvent and catalyst. Some examples of this kind have been reported by Seddon and coworkers, in the ionic liquid-catalyzed Friedel-Crafts acylation of substituted aromatics[61] (scheme 37).



Scheme 37

In other cases the ionic liquid acts as a cocatalyst, for instance in the Pd-catalyzed Wacker oxidation of styrene to acetophenone (scheme 38)[62]. It has been reported that in this case the imidazolium cation activates the H_2O_2 which, in turn, reoxidizes palladium(0) to palladium(II) to complete the reaction cycle.



Scheme 38

Obviously there are also several examples in which ILs act simply as a solvent without interacting in the reaction mechanism[63].

It is worth noticing that ILs are also a good reaction medium for biocatalyzed transformations, in which they have several advantages over conventional organic solvents, including higher stabilities and enantioselectivity of the reaction system[64-65].

1.4.4 Final remarks

A quick review of the most important alternative reaction media has been presented. Although only catalytic reactions were taken in consideration as examples, since they match the subject of this thesis, it is not to underestimate the great potential these

substances have also for replacing organic solvents in organic synthesis and in other technologies (e.g. extraction, purification, etc.). The number of papers and patents that came out in the last years (figure 3) in this field is growing fast and some commercial applications have already shown to be not only environment-friendly but also economically competitive. In perspective, these applications should replace a large part of the existing chemical processes in order to achieve a more sustainable chemical industry.

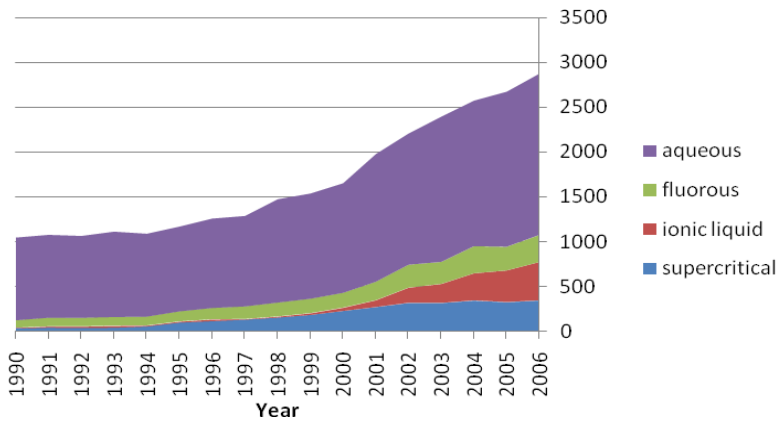


Figure 3

1.5 REFERENCES

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Chapter 2

Novel Synthesis of Substituted Quinolines by Copper- or Palladium Catalyzed Cyclodehydration of 1-(2-aminoaryl)-2-yn-1-ols*

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2.1 Introduction

The transition metal-catalyzed 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 from relatively simple acyclic subunits containing ene and yne fragments.

Among a range of transition metal complexes capable of catalyzing cycloisomerizations, copper and palladium complexes are particularly important as they are capable of delivering a diverse array of cyclic products that are produced under mild conditions, in many cases with excellent chemoselectivity and high synthetic efficiency.

While the pioneering work in this area goes back to the 1970s, there has been an explosive increase of interest in Cu and Pd catalysis during the last years.

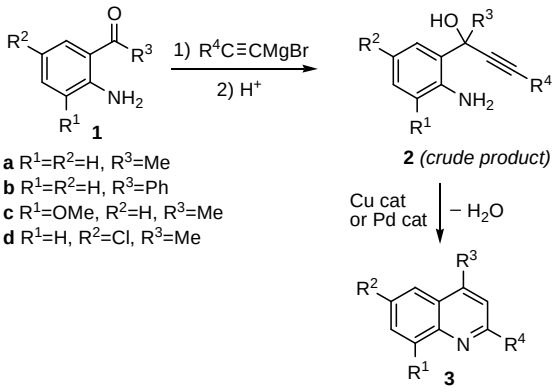
The diversity of cyclic structural motifs that can be efficiently accessed from a common yne precursor is remarkable. The process can furnish a six-membered or alternatively a five-membered heterocyclic products. The substitution pattern of the starting yne, as well as the nature of the catalyst, influences significantly the outcome of the cycloisomerization process.

2.2 General importance of quinolines

Quinolines are a very important class of heterocyclic compounds. The quinoline core is present in many biologically active natural products, in particular alkaloids. Moreover, substituted quinolines are known to display a wide range of pharmacological activities, such as anti-inflammatory,[1] antibacterial,[2] antiprotozoan,[3] antimalarial,[4] antiasthmatic,[5] antituberculosis,[6] anti-Alzheimer,[7] antihypertensive,[8] anthelmintic,[9] anti-HIV,[10] and anti-cancer activity.[11] In view of the remarkable importance of this class of heterocyclic compounds, during the last years many efforts have been devoted to the development of new regioselective synthetic methodologies for their production.[12] In particular, new synthetic strategies based on metal-catalyzed heteroannulation of acyclic precursors have attracted considerable attention, owing to the possibility to construct the quinoline

ring with the desired substitution pattern in one step under mild conditions starting from readily available starting materials.[13]

We have developed a general and convenient synthesis of substituted quinolines **3** through copper or palladium-catalyzed 6-*endo-dig* heteroannulation-dehydration of 1-(2-aminoaryl)-2-yn-1-ols **2**,[14,15] easily obtained by the Grignard reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones **1** (Scheme 1). The intermediates **2** deriving from the first step could be used without further purification for the second step, thus facilitating the synthetic procedure.



1

a R^1=R^2=H, R^3=Me
b R^1=R^2=H, R^3=Ph
c R^1=OMe, R^2=H, R^3=Me
d R^1=H, R^2=Cl, R^3=Me

2 *(crude product)*

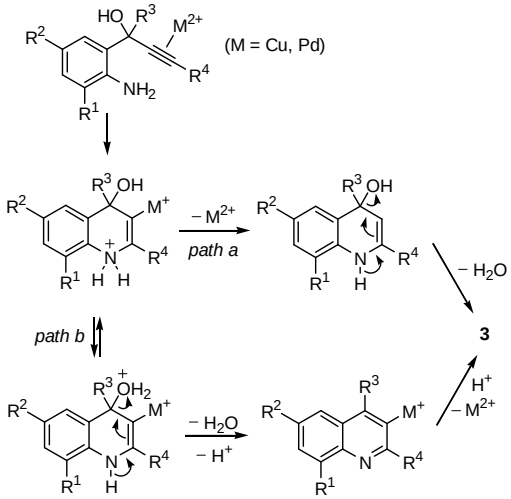
3

aa R^1=R^2=H, R^3=Me, R^4=Bu: 80%
ba R^1=R^2=H, R^3=Ph, R^4=Bu: 80%
ca R^1=OMe, R^2=H, R^3=Me, R^4=Bu: 76%
da R^1=H, R^2=Cl, R^3=Me, R^4=Bu. 81%
ab R^1=R^2=H, R^3=Me, R^4=Ph: 73%
bb R^1=R^2=H, R^3=R^4=Ph: 68%
cb R^1=OMe, R^2=H, R^3=Me, R^4=Ph: 90%
db R^1=H, R^2=Cl, R^3=Me, R^4=Ph: 78%
ac R^1=R^2=H, R^3=Me, R^4=*t*-Bu: 75%
bc R^1=R^2=H, R^3=Ph, R^4=*t*-Bu: 70%
cc R^1=OMe, R^2=H, R^3=Me, R^4=*t*-Bu: 77%

Scheme 1

2.3 Results and discussion

In the laboratory where I developed my work several examples of copper or palladium-catalyzed cycloisomerization reactions leading to heterocyclic derivatives starting from suitably functionalized alkyne derivatives have been reported.[16] In particular, we have reported a general methodology for the regioselective synthesis of substituted furans,[17] thiophenes,[18] and pyrroles[19] starting from (*Z*)-2-en-4-yn-1-ols, (*Z*)-2-en-4-yne-1-thiols, and (*Z*)-(2-en-4-ynyl)amines, respectively, through 5-*exo*-*dig* heteroannulation-aromatization promoted by PdX_2 in conjunction with KX (X = Cl, I) or by $CuCl_2$ as the catalytic system. A divergent synthesis of (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and 1*H*-isochromenes by PdI_2/KI-catalyzed 5-*exo*-*dig* or 6-*endo*-*dig*, respectively, cycloisomerization of 2-alkynylbenzyl alcohols has also been reported.[20] On the basis of these results, we have investigated the possibility to synthesize substituted quinolines starting from 1-(2-aminoaryl)-2-yn-1-ols, through a metal-promoted 6-*endo*-*dig* cyclodehydration route, based on intramolecular nucleophilic attack of the $–NH_2$ group to the triple bond coordinated to the metal center followed by protonolysis and dehydration (Scheme 2, path *a*) or vice versa (path *b*).



Scheme 28

The first substrate we used was 2-(2-aminophenyl)oct-3-yn-2-ol **2aa** ($R^1 = R^2 = H$, $R^3 =$ Me, $R^4 =$ Bu) obtained in ca. 60% isolated yield by the reaction between commercially available 2-aminoacetophenone **1a** and 1-hexynylmagnesium bromide. The reactivity of **2aa** was initially tested at 60 °C in MeOH as the solvent in the presence of 2 mol % of different catalytic systems, based on zinc, palladium, and copper. The results obtained are shown in Table 1:

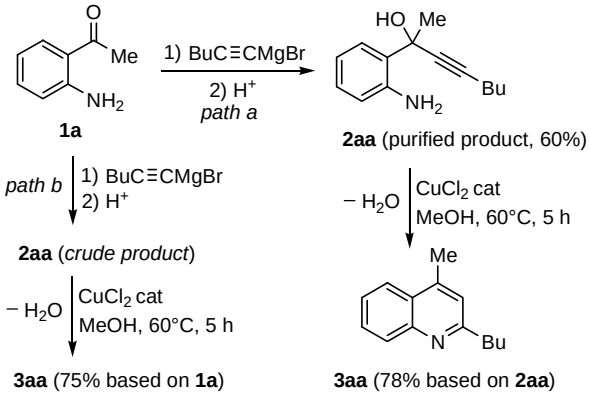
TABLE 1. Cyclodehydration reactions of 2-(2-aminophenyl)oct-3-yn-2-ol 2aa in MeOH to give 2-butyl-4-methylquinoline 3aa in the presence of different catalytic systems[a]

Entry	Catalyst	t (h)	Conversion of **2aa** (%)[b]	Yield of **3aa** (%)[c]
1	$ZnCl_2$	1	43	35
2	ZnI_2	1	50	45
3	$PdCl_2$+10KCl	1	54	48
4	PdI_2+10KI	1	58	46
5	CuCl	1	75	72
6	CuI	1	75	63
7	CuI	5	93	78
8	$CuCl_2 \cdot 2H_2O$	1	86	75
9	$CuCl_2 \cdot 2H_2O$	5	100	82
10	$CuCl_2$	1	79	76
11	$CuCl_2$	3	90	80
12	$CuCl_2$	5	100	85 (78)
13	None	5	100	0[d]

[a] All reactions were carried out in MeOH at 60 °C with a substrate concentration of 0.22 mmol of **2aa** per mL of MeOH in the presence of 2 mol % of catalyst. [b] Based on starting **2aa**, by GLC. [c] GLC yield (isolated yield) based on **2aa**. [d] Unidentified chromatographically immobile materials were formed under these conditions.

As can be seen, 2-butyl-4-methylquinoline **3aa** was selectively formed in all cases (entries 1-12), thus confirming the validity of this metodology. The best results in terms of substrate conversion rate and product selectivity were obtained with $CuCl_2$ as the catalyst: after 5 h reaction time, **3aa** was formed in 85% GLC yield at total substrate conversion (78% isolated, entry 12 and Scheme 3, path *a*). The reaction did not occur in the absence of the metal catalyst, as confirmed by blank experiments (decomposition of

the starting material to give unidentified chromatographically immobile materials was observed under these conditions, entry 13).



Scheme 3

Using $CuCl_2$ as the catalyst, has been next tested the reactivity of **2aa** in different solvents. The results, shown in Table 2, entries 14-19 (to be compare with entry 10 of Table 1),clearly indicate MeOH as the solvent of choice for the reaction.

TABLE 2. Cyclodehydration reactions of 2-(2-aminophenyl)oct-3-yn-2-ol 2aa in different solvents to give 2-butyl-4-methylquinoline 3aa in the presence of $CuCl_2$ as the catalyst[a]

Entry	Solvent	t (h)	Conversion of **2aa** (%)[b]	Yield of **3aa** (%)[c]
14	Dioxane	1	45	39
15	DME	1	54	43
16	DME	5	70	56 (46)
17	MeCN	1	44	39
18	DMA	1	80	60
19	DMA	5	100	65 (58)

[a] All reactions were carried out at 60 °C with a substrate concentration of 0.22 mmol of **2aa** per mL of MeOH in the presence of 2 mol % of $CuCl_2$. [b] Based on starting **2aa**, by GLC. [c] GLC yield (isolated yield) based on **2aa**.

One drawback of this synthetic approach was related to the instability of **2aa** during the purification procedures, which in several cases caused its partial decomposition after column chromatography. However, I have found that the cyclization reaction worked nicely even on the crude product, which also facilitated the synthetic protocol. Thus, when crude **2aa** was let to react under the same conditions of entry 12, quinoline **3aa** was obtained in 75% isolated yield based on starting 2-aminoacetophenone **1a** (Table 3), entry 20, and Scheme 3, path *b*). It is worth noting that this yield was considerably higher with respect to the overall yield obtained using pure **2aa** (47% isolated yield based on **1a**, Scheme 3, path *a*).

The generality of the process was then verified by varying the nature of substituents R^1 and R^2 (on the aromatic ring), R^3 (at the benzylic position), and R^4 (on the triple bond) (Scheme 1). The results are shown in Table 3. As can be seen, in most cases, better results in terms of product yield were obtained by working in a Schlenk flask at 100° C rather than 60°C. The benzylic position and the triple bond could be substituted with an alkyl as well as an aryl substituent, while electron-withdrawing as well as π-donating groups could be present on the aromatic ring.

Interestingly, in the case of 2-(2-aminophenyl)-5,5-dimethylhex-3-yn-2-ol **2ac** ($R^1 = R^2 = H$, R^3= Me, R^4 = *tert*-Bu), the reaction, carried out under the same conditions of entry 20, led to 2-(1-methoxy-1,4,4-trimethylpent-2-ynyl)phenylamine **4ac** as the main reaction product (30% isolated yield based on starting 2-aminoacetophenone **1a**), together with smaller amounts of the expected 2-*tert*-butyl-4-methylquinoline **3ac** (20% isolated yield based on **1a**, entry 35 and Scheme 4).

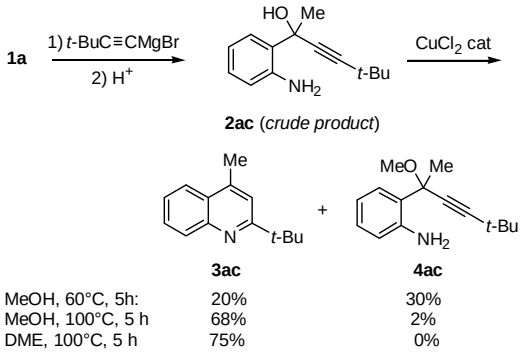
Clearly, this undesired reaction becomes competitive owing to the diminished reactivity of the sterically hindered triple bond. However, when the same reaction was carried out at 100 °C rather than 60°C, quinoline **3ac** became the main reaction product (68% isolated yield based on **1a**), **4ac** being formed in less than 2% isolated yield based on **1a** (entry 36 and Scheme 4). In a non-nucleophilic solvent such as 1,2-dimethoxyethane (DME), **3ac** was selectively obtained with a 75% isolated yield based on **1a** (entry 37 and Scheme 4). Under the same conditions of entry 36, other substrates bearing a *t*-butyl group on the triple bond, such as 1-(2-aminophenyl)-4,4-dimethyl-1-phenylpent-2-yn-1-

ol **2bc** (R^1 = R^2 = H, R^3 = Ph, R^4 = *t*-Bu), and 2-(2-amino-3-methoxyphenyl)-5,5-dimethylhex-3-yn-2-ol **2cc** (R^1 = OMe, R^2 = H, R^3 = Me, R^4 = *t*-Bu) afforded the corresponding quinolines **3bc** and **3cc**, respectively, in good isolated yield (70% and 77%, respectively) after 2-5 h reaction time (entries 38 and 39).

TABLE 3. **Synthesis of substituted quinolines 3 by cyclodehydration of crude 1-(2-aminophenyl)-2-yn-1-ols 2, obtained by the reaction between $R^4C{\equiv}CMgBr$ and 2-aminoaryl ketones 1, in the presence of $CuCl_2$ as the catalyst**[a]

Entry	**1**	R^1	R^2	R^3	R^4	**2**	*T* (°C)	**3**	Yield of **3** (%)[b]
20	**1a**	H	H	Me	Bu	**2aa**	60	**3aa**	75
21	**1a**	H	H	Me	Bu	**2aa**	100	**3aa**	80
22	**1b**	H	H	Ph	Bu	**2ba**	60	**3ba**	80
23	**1c**	OMe	H	Me	Bu	**2ca**	60	**3ca**	60
24	**1c**	OMe	H	Me	Bu	**2ca**	100	**3ca**	76
25	**1d**	H	Cl	Me	Bu	**2da**	60	**3da**	81
26	**1d**	H	Cl	Me	Bu	**2da**	100	**3da**	69
27	**1a**	H	H	Me	Ph	**2ab**	60	**3ab**	65
28	**1a**	H	H	Me	Ph	**2ab**	100	**3ab**	73
29	**1b**	H	H	Ph	Ph	**2bb**	60	**3bb**	63
30	**1b**	H	H	Ph	Ph	**2bb**	100	**3bb**	68
31	**1c**	OMe	H	Me	Ph	**2cb**	60	**3cb**	72
32	**1c**	OMe	H	Me	Ph	**2cb**	100	**3cb**	90
33	**1d**	H	Cl	Me	Ph	**2db**	60	**3db**	78
34	**1d**	H	Cl	Me	Ph	**2db**	100	**3db**	74
35	**1a**	H	H	Me	*t*-Bu	**2ac**	60	**3ac**	20[c]
36	**1a**	H	H	Me	*t*-Bu	**2ac**	100	**3ac**	68[d]
37[e]	**1a**	H	H	Me	*t*-Bu	**2ac**	100	**3ac**	75
38	**1b**	H	H	Ph	*t*-Bu	**2bc**	100	**3bc**	70
39[f]	**1c**	OMe	H	Me	*t*-Bu	**2cc**	100	**3cc**	77

[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1** per mL of MeOH, 9 mmol scale based on **1**) for 5 h in the presence of 2 mol % of $CuCl_2$. Conversion of **2** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] The reaction also led to the formation of 2-(1-methoxy-1,4,4-trimethylpent-2-ynyl)phenylamine **4ac** (30% isolated yield based on starting 2-aminoacetophenone **1a**). [d] The reaction also led to the formation of **4ac** (2% isolated yield based on starting **1a**). [e] The reaction was carried out in 1,2-dimethoxyethane (DME). [f] Reaction time was 2 h.



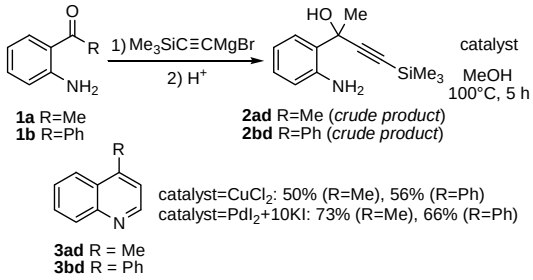
Scheme 4

The cyclodehydration reaction could also be successfully applied to substrates bearing a trimethylsilyl group on the triple bond, such as 2-(2-aminophenyl)-4-trimethylsilanylbut-3-yn-2-ol **2ad** ($R^1 = R^2 = H$, $R^3 = Me$, $R^4 = TMS$). Under the same conditions of entry 21, this substrate was converted into 4-methylquinoline **3ad** ($R^1 = R^2 = R^4 = H$, $R^3 = Me$), ensuing from loss of the TMS group under the reaction conditions, in 50% isolated yield (Table 4, entry 40, and Scheme 5). Interestingly, a higher selectivity toward **3ad** (69-73%) could be obtained working in the presence of PdX_2 + 10 KX (X = Cl, I) as the catalytic system (entries 41 and 42 and Scheme 5). Similar results were observed in the case of 1-(2-aminophenyl)-1-phenyl-3-trimethylsilanylprop-2-yn-1-ol **2bd** ($R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = TMS$) to give 4-phenylquinoline **3bd** ($R^1 = R^2 = R^4 = H$, $R^3 = Ph$) (entries 43-45 and Scheme 5).

TABLE 4. Synthesis of 4-substituted quinolines 3ad and 3dd by Cu- or Pd-catalyzed cyclodehydration-desilylation of crude 1-(2-aminophenyl)-2-yn-1-ols 2ad and 2dd, obtained by the reaction between TMS-C≡C-MgBr and 2-aminophenyl ketones 1a and 1d[a]

Entry	**1**	R^1	R^2	R^3	R^4	**2**	Catalyst	**3**[b]	Yield of **3** (%)[c]
40	**1a**	H	H	Me	TMS	**2ad**	$CuCl_2$	**3ad**	50
41	**1a**	H	H	Me	TMS	**2ad**	$PdCl_2$ + 10 KCl	**3ad**	69
42	**1a**	H	H	Me	TMS	**2ad**	PdI_2 + 10 KI	**3ad**	73
43	**1b**	H	H	Ph	TMS	**2bd**	$CuCl_2$	**3bd**	56
44	**1b**	H	H	Ph	TMS	**2bd**	$PdCl_2$ +10 KCl	**3bd**	66
45	**1b**	H	H	Ph	TMS	**2bd**	PdI_2 +10 KI	**3bd**	66

[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1** per mL of MeOH, 9 mmol scale based on **1**) at 100 °C for 5 h with a substrate concentration of in the presence of 2 mol % of catalyst. Conversion of **2** was quantitative in all cases. [b] R^3 = H in the final product **3**. [c] Isolated yield based on starting **1**.



Scheme 5

2.4 Conclusions

We have developed a novel and practical synthesis of substituted quinolines through a two-step procedure involving Grignard addition of alkynylmagnesium bromides to 2-aminoaryl ketones followed by regioselective copper– or palladium–catalyzed 6-*endo-dig* cyclodehydration of the corresponding 1-(2-aminophenyl)-2-yn-1-ols. The latter intermediates could be used without further purification for the subsequent cyclization

step, thus further facilitating the synthetic procedure. The generality of the process has been verified by varying the nature of substituents on the aromatic ring as well as at the benzylic position and on the triple bond.

2.5 Experimental Section

2.5.1 Cyclodehydration of 2-(2-Aminophenyl)oct-3-yn-2-ol 2aa to 2-Butyl-4-methylquinoline 3aa (Tables 1 and 2).

In a typical experiment, the catalyst ($5.28 \cdot 10^{-2}$ mmol) [in conjunction with KX ($5.28 \cdot 10^{-1}$ mmol) in the case of PdX_2, X = Cl or I] was added under nitrogen to a solution of pure **2aa** (574.0 mg, 2.64 mmol) in the anhydrous solvent (12.0 mL) (see Tables 1 and 2) in a Schlenk flask. The resulting mixture was stirred under nitrogen at the temperature and for the time indicated in Tables 1 and 2. Solvent was evaporated, and the crude product purified by column chromatography on silica gel using 95:5 hexane-AcOEt as the eluent to give **3aa** as a yellow oil. The yields obtained in each experiment are reported in Tables 1 and 2.

2.5.2 General Procedure for the Synthesis of Quinolines 3 (Tables 3 and 4).

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-Amino ketone **1** (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 ($R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Bu$; $R^1 = OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = Bu$; $R^1 = H$, $R^2 = Cl$, $R^3 = Me$, $R^4 = Bu$), 2 h ($R^1 = OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = Ph$; $R^1 = H$, $R^2 = Cl$, $R^3 = Me$, $R^4 = Ph$; $R^1 = OMe$, $R^2 = H$, $R^3 = Me$, $R^4 = t$-Bu; $R^1 = H$, $R^2 = Cl$, $R^3 = Me$, $R^4 = t$-Bu; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Ph$; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = t$-Bu; $R^1 = R^2 = H$, $R^3 = Me$, $R^4 = TMS$; $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = t$-Bu; $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = TMS$) or 3 h ($R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Bu$; $R^1 = R^2 = H$, $R^3 = R^4 = Ph$), the mixture was cooled to room temperature. Saturated NH_4Cl was added with stirring to achieve 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 (3 × 30 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 **2** used as such for the next step. $CuCl_2$ (24.0 mg, $1.79 \cdot 10^{-1}$ mmol) [or PdX_2 ($1.79 \cdot 10^{-1}$ mmol) in conjunction with KX (1.79 mmol), X = Cl or I, see Tables 3 and 4] was added to a solution of crude **2** in anhydrous MeOH (40.5 mL) or DME (40.5 mL) see Tables 3 and 4 in a Schlenk flask. The resulting mixture was stirred at the temperature and for the time indicated in Tables 3 and 4. Solvent was evaporated and the crude product purified by column chromatography on silica gel: **3aa** (yellow oil, 95: 5 hexane-AcOEt); **3ba** (yellow oil, 95:5 hexane-AcOEt); **3ca** (yellow oil, 95:5 hexane-acetone); **3da** (yellow oil, 90:10 hexane-acetone); **3ab** (yellow solid, mp 65-67 °C, 95:5 hexane-AcOEt); **3bb** (yellow solid, mp 107-108 °C, 95:5 hexane-AcOEt); **3cb** (yellow solid, mp 96-97 °C, 90:10 hexane-acetone); **3db** (yellow solid, mp 89-90 °C, 99:1 hexane-acetone); **3ac** (yellow oil, 95:5 hexane-AcOEt); **3bc** (colorless solid, mp 86-87 °C, 95:5 hexane-acetone); **3cc** (yellow oil, 95:5 hexane-acetone); **3ad** (yellow oil, 90:10 hexane-acetone); **3bd** (yellow solid, mp 61-62 °C, 90:10 hexane-acetone). The yields obtained in each experiment are reported in Tables 3 and 4.

2.5.3 Characterization Data of Products

2-Amino-3-methoxyacetophenone (1c) : Yellow solid, mp 59-61 °C (1.41 g, 75% starting from 2.22 g, 11.4 mmol of 2-nitro-3-methoxyacetophenone). IR (KBr): ν = 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}; ^1H NMR (500 MHz): δ = 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 = 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).

2-Amino-5-chloroacetophenone (1d) : Yellow solid, mp 63-64 °C (3.97 g, 45% based on 5-chloro-2-nitroacetophenone). IR (KBr): ν = 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}; ^1H NMR (500 MHz): δ = 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).

2-(2-Aminophenyl)oct-3-yn-2-ol (2aa) : Yellow oil (1.16 g, 60% based on **1a**). IR (film): ν = 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}; ^1H NMR (300 MHz): δ = 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 = 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).

2-Butyl-4-methylquinoline (3aa). Yield: 1.42 g, starting from 1.20 g of 2-aminoacetophenone **1a** (80%) (Table 1, entry 21). Yellow oil. IR (film): ν = 2955 (m), 2929 (s), 2869 (m), 1604 (s), 1561 (w), 1465 (m), 1379 (w), 1259 (w), 1123 (w), 861 (w), 758 (m) cm^{-1}; ^1H NMR (300 MHz): δ = 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): δ = 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 $C_{14}H_{17}N$ (199.29): C, 84.37; H, 8.60; N, 7.03; found C, 84.41; H, 8.59; N, 7.00.

2-Butyl-4-phenylquinoline (3ba). Yield: 1.86 g, starting from 1.76 g of 2-aminobenzophenone **1b** (80%) (Table 1, entry 22). Yellow oil. IR (film): ν = 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}; ^1H NMR (300 MHz): 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): δ = 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 $C_{19}H_{19}N$ (261.36): C, 87.31; H, 7.33; N, 5.36; found C, 87.39; H, 7.31; N, 5.30.

2-Butyl-8-methoxy-4-methylquinoline (3ca). Yield: 1.55 g, starting from 1.47 g of 3-methoxy-2-aminoacetophenone **1c** (76%) (Table 1, entry 24). Yellow oil. IR (film): ν = 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}; ^1H NMR (500 MHz): 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, 3 H), 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): δ = 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 $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11; found C, 78.66; H, 8.33; N, 6.09.

2-Butyl-6-chloro-4-methylquinoline (3da). Yield: 1.69 g, starting from 1.51 g of 5-chloro-2-aminoacetophenone **1d** (81%) (Table 1, entry 25). Yellow oil. IR (film): ν = 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}; ^1H NMR (300 MHz): 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): δ = 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 $C_{14}H_{16}ClN$ (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-Methyl-2-phenylquinoline (3ab). Yield: 1.42 g, starting from 1.20 g of 2-aminoacetophenone **1a** (73%) (Table 1, entry 28). Yellow solid, 65-67 °C, lit.[7] 64-64.5 °C. IR (KBr): ν = 3060 (m), 1597 (s), 1551 (m), 1509 (w), 1495 (w), 1451 (m), 1348 (m), 1079 (w), 1029 (w), 861 (w), 769 (s), 694 (s) cm^{-1}; ^1H NMR (300 MHz): δ = 8.20-8.10 (m, 3 H), 7.97-7.92 (m, 1 H), 7.69 (ddd, *J* = 8.4, 6.9, 1.5, 1 H), 7.68-7.65 (m, 1 H), 7.54-7.39 (m, 4 H), 2.71 (d, *J* = 1.0, 3 H); ^{13}C NMR (75 MHz): δ = 157.0, 148.1, 144.8, 139.8, 130.2, 129.3, 129.2, 128.7, 127.5, 127.2, 126.0, 123.6, 119.7, 19.0; GC-MS: *m/z* = 219 (100) [M^+], 218 (42), 217 (23), 216 (8), 205 (13), 204 (71), 109 (12); anal. calcd for $C_{16}H_{13}N$ (219.28): C, 87.64; H, 5.98; N, 6.39; found C, 87.58; H, 5.99; N, 6.43.

2,4-Diphenylquinoline (3bb). Yield: 1.70 g, starting from 1.76 g of 2-aminobenzophenone **1b** (68%) (Table 1, entry 30). Yellow solid, mp 107-108 °C, lit.[8] 105-106 °C. IR (KBr): ν = 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}; ^1H NMR (300 MHz): 8.24 (ddd, *J* = 8.5, 1.1, 0.6, 1 H), 8.20-8.14 (m, 2 H), 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): δ = 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 $C_{21}H_{15}N$ (281.35): C, 89.65; H, 5.37; N, 4.98; found C, 89.71; H, 5.35; N, 4.94.

8-Methoxy-4-methyl-2-phenylquinoline (3cb). Yield: 2.00 g, starting from 1.47 g of 2-amino-3-methoxyacetophenone **1c** (90%) (Table 1, entry 32). Yellow solid, mp 96-97°C. IR (KBr): ν = 1600 (m), 1552 (w), 1493 (m), 1468 (s), 1407 (w), 1350 (w), 1257 (s), 1160 (m), 1045 (m), 906 (m), 773 (w), 744 (m), 708 (m) cm^{-1}; ^{1}H NMR (500 MHz): δ = 8.19-8.15 (m, 2 H), 7.72 (s, 1 H), 7.55-7.39 (m, 5 H), 7.04 (d, *J* = 7.7, 1 H), 4.07 (s, 3 H), 2.71 (s, 3 H); ^{13}C NMR (126 MHz): δ = 156.0, 155.8, 144.7, 140.1, 139.9, 129.0, 128.7, 128.4, 127.6, 126.1, 120.2, 115.5, 107.8, 56.1, 19.5; GC-MS: *m/z* = 249 (92) [M^+], 248 (100), 220 (51), 219 (28), 218 (17), 217 (12), 204 (15), 115 (10), 77 (17); anal. calcd for $C_{17}H_{15}NO$ (249.31): C, 81.90; H, 6.06; N, 5.62; found C, 81.98; H, 6.05; N, 5.60.

6-Chloro-4-methyl-2-phenylquinoline (3db). Yield: 1.76 g, starting from 1.51 g of 2-amino-5-choroacetophenone **1d** (78%) (Table 1, entry 33). Yellow solid, mp 89-90 °C, lit.[9] 92-93 °C. IR (KBr): ν = 1599 (s), 1545 (w), 1491 (m), 1446 (w), 1436 (w), 1384 (s), 1348 (s), 1283 (w), 1091 (m), 1028 (w), 881 (m), 777 (m), 698 (s), 684 (m) cm^{-1}; ^{1}H NMR (500 MHz): δ = 8.15-8.10 (m, 3 H), 7.94 (d, *J* = 2.2, 1 H), 7.71 (s, br, 1 H), 7.65 (dd, *J* = 9.3, 2.2, 1 H), 7.54-7.44 (m, 3 H), 2.72 (d, *J* = 1.1, 3 H); ^{13}C NMR (126 MHz): δ = 157.0, 145.8, 144.9, 138.6, 132.1, 131.3, 130.6, 129.8, 128.9, 128.0, 127.6, 122.8, 120.6, 19.0; GC-MS: *m/z* = 255 (33) [M^+ + 2], 254 (27), 253 (100) [M^+], 252 (22), 240 (15), 238 (46), 218 (10), 217 (24), 216 (14), 203 (11), 109 (23); anal. calcd for $C_{16}H_{12}ClN$ (253.73): C, 75.74; H, 4.77; Cl, 13.97; N, 5.52; found C, 75.81; H, 4.76; Cl, 13.95; N, 5.48.

2-*tert*-Butyl-4-methylquinoline (3ac). Yield: 1.33 mg, starting from 1.20 g of 2-aminoacetophenone **1a** (75%) (Table 1, entry 37). Yellow oil. IR (film): ν = 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}; ^1H NMR (300 MHz): δ = 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): δ = 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 $C_{14}H_{17}N$ (199.29): C, 84.37; H, 8.60; N, 7.03; found C, 84.33; H, 8.62; N, 7.05.

2-*tert*-Butyl-4-phenylquinoline (3bc). Yield: 1.63 g, starting from 1.76 g of 2-aminobenzophenone **1b** (70%) (Table 1, entry 38). Colorless solid, mp 86-87 °C, lit.[10] 85-88 °C. IR (KBr): ν = 3060 (m), 1590 (s), 1554 (m), 1488 (m), 1447 (m), 1407 (m), 1363 (m), 1252 (m), 1106 (m), 1027 (m), 886 (m), 839 (w), 779 (m), 762 (s), 707 (s) cm^{-1}; ^1H NMR (300 MHz): 8.13 (ddd, *J* = 8.4, 1.2, 0.6, 1 H), 7.84 (ddd, *J* = 8.4, 1.5, 0.6, 1 H), 7.64 (ddd, *J* = 8.4, 6.9, 1.5, 1 H), 7.51-7.43 (m, 6 H), 7.39 (ddd, *J* = 8.4, 6.9, 1.2, 1 H), 1.49 (s, 9 H); ^{13}C NMR (75 MHz): δ = 168.7, 148.1, 147.9, 138.8, 129.8, 129.6, 128.9, 128.4, 128.1, 125.7, 125.3, 125.0, 118.4, 38.1, 30.1; GC-MS: *m/z* = 261 (44) [M^+], 260 (28), 247 (20), 246 (100), 220 (10), 219 (48), 205 (13), 204 (18); anal. calcd for $C_{19}H_{19}N$ (261.36): C, 87.31; H, 7.33; N, 5.36; found C, 87.26; H, 7.35; N, 5.39.

2-*tert*-Butyl-8-methoxy-4-methylquinoline (3cc). Yield: 1.57 g, starting from 1.47 g of 3-methoxy-2-aminobenzophenone **1c** (77%) (Table 1, entry 39). Yellow oil. IR (film): ν = 2959 (s), 2866 (m), 1598 (m), 1588 (m), 1557 (m), 1494 (m), 1409 (s), 1362 (m), 1336 (w), 1258 (s), 1202 (w), 1048 (m), 932 (w), 870 (w), 731 (m) cm^{-1}; ^1H NMR (500 MHz): 7.50 (distorted d, *J* = 8.2, 1 H), 7.41-7.36 (m, 2 H), 7.01 (d, *J* = 7.7, 1 H), 4.05 (s, 3 H), 2.65 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (126 MHz): δ = 167.7, 155.8, 143.6, 139.2, 127.8, 125.4, 119.6, 115.5, 108.2, 56.5, 38.2, 30.2, 19.5; GC-MS: *m/z* = 229 (99) [M^+], 228 (100), 215 (12), 214 (73), 213 (17), 212 (20), 210 (12), 200 (63), 199 (73), 198 (47), 197 (10), 196 (33), 187 (11), 185 (13), 184 (32), 183 (15), 173 (23), 169 (10), 115 (17), 107 (11), 77 (10); anal. calcd for $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11; found C, 78.62; H, 8.33; N, 6.10.

4-Methylquinoline (3ad). Yield: 0.93 g, starting from 1.20 g of 2-aminoacetophenone **1a** (73%) (Table 2, entry 42). Yellow oil. IR (film): ν = 1596 (m), 1580 (m), 1524 (s), 1452 (s), 1310 (m), 1251 (m), 841 (m), 757 (s) cm^{-1}; ^1H NMR (300 MHz): 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): δ = 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 $C_{10}H_9N$ (143.19): C, 83.88; H, 6.34; N, 9.78; found C, 83.75; H, 6.36; N, 9.89.

4-Phenylquinoline (3bd). Yield: 1.20 g, starting from 1.76 g of 2-aminobenzophenone **1b** (66%) (Table 2, entry 45). Yellow solid, mp. 61-62 °C, lit.[11] 61 °C. IR (KBr): ν = 1584 (m), 1508 (w), 1491 (m), 1391 (m), 1277 (w), 1030 (w), 851 (m), 769 (s), 704 (s), 612 (m) cm^{-1}; ^1H NMR (300 MHz): 8.94 (d, *J* = 4.4, 1 H), 8.18 (ddd, *J* = 8.5, 1.1, 0.6, 1 H), 7.94-7.89 (m, 1 H), 7.71 (ddd, *J* = 8.5, 7.0, 1.5, 1 H), 7.55-7.44 (m, 6 H), 7.32 (d, *J* = 4.4, 1 H); ^{13}C NMR (75 MHz): δ = 149.9, 148.7, 148.6, 138.0, 129.8, 129.6, 129.3, 128.6, 128.4, 126.8, 126.6, 125.9, 121.3; GC-MS: *m/z* = 205 (100), 204 (97), 203 (10), 178 (13), 177 (12), 176 (30), 151 (12), 102 (14), 88 (12); anal. calcd for $C_{15}H_{11}N$ (205.25): C, 87.77; H, 5.40; N, 6.82; found C, 87.83; H, 5.38; N, 6.79.

2-(1-Methoxy-1-methylhept-2-ynyl)phenylamine (4ac). Yield: 620 mg, starting from 1.20 g of 2-aminoacetophenone **1a** (30%) (Table 1, entry 35). Yellow oil. IR (film): ν = 3470 (m), 3371 (m), 2969 (s), 2934 (m), 2221 (vw), 1614 (s), 1492 (m), 1459 (m), 1364 (w), 1310 (w), 1263 (m), 1085 (s), 1048 (w), 859 (w), 750 (m) cm^{-1}; ^1H NMR (300 MHz): δ = 7.57 (dd, *J* = 7.7, 1.5, 1 H), 7.08 (ddd, *J* = 7.9, 7.3, 1.5, 1 H), 6.70 (ddd, *J* = 7.7, 7.3, 1.2, 1 H), 6.58 (dd, *J* = 7.9, 1.2, 1 H), 4.45 (s, br, 2 H), 3.24 (s, 3 H), 1.78 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR (75 MHz): δ = 144.7, 129.2, 128.8, 124.4, 117.3, 116.5, 96.7, 78.6, 78.5, 51.9, 31.1, 27.7, 27.6; GC-MS: *m/z* = 231 (38) [M^+], 216 (28), 200 (21), 199 (63), 198 (16), 185 (19), 184 (100), 170 (17), 169 (39), 168 (26), 167 (13), 158 (42), 157 (17), 156 (11), 154 (15), 144 (23), 143 (21), 142 (11), 131 (13), 130 (34), 115 (9), 106 (6), 91 (9), 77 (10); anal. calcd for $C_{15}H_{21}NO$ (231.33): C, 77.88; H, 9.15; N, 6.05; found C, 77.86; H, 9.13; N, 6.02.

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Chapter 3

Versatile Synthesis of Quinoline-3-Carboxylic Esters and Indol-2-Acetic Esters by Palladium-Catalyzed Carbonylation of 1-(2-Aminoaryl)-2-Yn-1-Ols *

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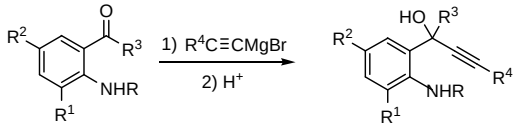
3.1 Introduction

Quinoline and indole derivatives are particular important classes of heterocyclic derivatives, with many important applications.[1-3]

During the last years, the intramolecular nucleophilic attack to a triple bond coordinated to Pd(II) followed by alkoxycarbonylation has proved to be one of the most important and powerful methodologies for the direct synthesis of carbonylated heterocycles starting from acyclic precursors.[4] In this area, our the research group has shown that PdI_2 in conjunction with an excess of KI is a very useful and versatile catalyst for achieving several convenient syntheses of carbonylated heterocycles starting from suitably functionalized alkynes, under oxidative as well as nonoxidative conditions.[4,5] In this part of my thesis I will show my investigation of the reactivity of 1-(2- aminoaryl)-2-yn-1-ols under carbonylative conditions in the presence of the PdI_2-KI catalytic system to develop new and selective synthetic approaches to carbonylated nitrogen heterocycles.

3.2 Results and Discussion

1-(2-Aminoaryl)ketones **1-5** were reacted with an excess of alkynylmagnesium bromides to give the corresponding (2-aminoaryl)-2-yn-1-ols, according to Scheme 1. The crude products **6-19** thus obtained could be used as substrates for the subsequent carbonylation reactions without further purification (as already pointed out in Chapter 2 about this kind of substrates).



1 R=R^1=R^2=H, R^3=Me
2 R=R^2=H, R^1= OMe, R^3=Me
3 R=R^1=H, R^2=Cl, R^3=Me
4 R=R^1=R^2=H, R^3=Ph
5 R=R^3=Me , R^1=R^2=H

6 R=R^1=R^2=H, R^3=Me, R^4=Bu
7 R=R^2=H, R^1=OMe, R^3=Me, R^4=Bu
8 R=R^1=H, R^2=Cl R^3=Me, R^4=Bu
9 R=R^1=R^2=H, R^3=Me, R^4=Ph
10 R=R^2=H, R^1=OMe, R^3=Me, R^4=Ph
11 R=R^1=H, R^2=Cl, R^3=Me,R^4=Ph
12 R=R^1=R^2=H, R^3=Me, R^4=t-Bu
13 R=R^2=H, R^1=OMe, R^3=Me, R^4=t-Bu
14 R=R^1=H, R^2=Cl, R^3=Me, R^4=*t*-Bu
15 R=R^1=R^2=H, R^3=Ph, R^4=*t*-Bu
16 R=R^1=R^2=H, R^3=Me, R^4=TMS
17 R=R^2=H, R^1=OMe, R^3=Me, R^4=TMS
18 R=R^1=R^2=H, R^3=Ph, R^4=TMS
19 R=R^3=Me, R^1=R^2=H, R^4=tBu

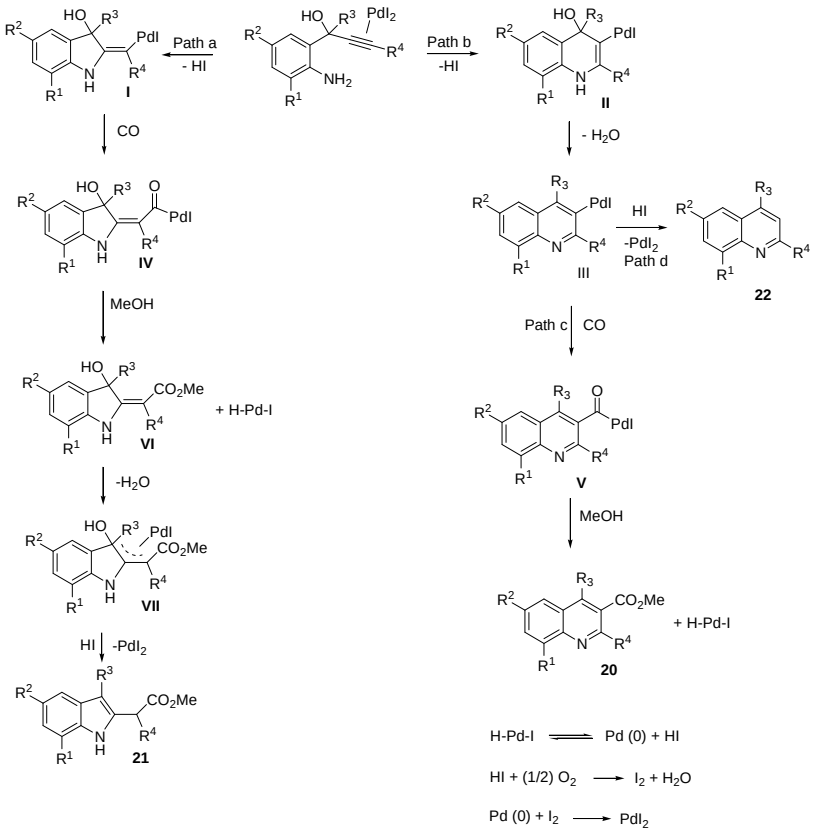
Scheme 1

In principle, different reaction pathways can be followed when 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group (R= H) are reacted in the presence of the PdI_2/KI catalytic system under carbonylative conditions (Scheme 2, anionic iodide ligands are omitted for clarity). In fact, the initial intramolecular attack by the amino group to the coordinated triple bond can occur in a 5-*exo*-*dig* (path a) or a 6-*endo*-*dig* (path b) cyclization mode, leading to isomeric vinylpalladium intermediates **I** and **II**, respectively, with formal elimination of HI.

In contrast to intermediate **I**, however, complex **II** can easily undergo loss of water with simultaneous aromatization to give the 3-quinolinylpalladium species **III**. Under CO pressure, both complexes **I** and **III** can insert carbon monoxide, to give the corresponding acylpalladium intermediates **IV** and **V**, respectively. Eventually, nucleophilic displacement by an external alcohol should afford the corresponding heterocyclic derivatives **VI** and **20**, respectively, with elimination of H-Pd-I [which is known to be in equilibrium with Pd(0)+HI].[6] Because intermediate **VI** still contains an allyl alcoholic function, it can react further with H-Pd-I, according to a known reactivity,[7,8] to give the allylpalladium complex **VII**. Protonolysis of the latter by HI would then lead to the indol-2-acetic ester **21** with regeneration of the catalytically active species PdI_2. On the other hand, the process leading to the quinoline-3-carboxylic

ester **20** (path c) may become catalytic only in the presence of an external oxidant, such as oxygen, able to reoxidize Pd(0) to PdI_2.[9] However, in the absence of an oxidant, a catalytic cycle is possible also starting with a 6-*endo-dig* cyclization mode, because intermediate **III** may undergo protonolysis by HI to give the noncarbonylated quinoline **22** with simultaneous regeneration of PdI_2 (path d).[10]

On the basis of these mechanistic hypotheses, we have studied the reactivity of 1-(2-aminoaryl)-2-yn-1-ols bearing a primary amino group (R = H), such as **6-18**, with CO and MeOH in the presence of the PdI_2/KI catalytic system under oxidative (using oxygen as the oxidant) as well as nonoxidative conditions to verify the possibility to find novel approaches to important carbonylated heterocyclic derivatives **20** and **21**, starting from readily available substrates.



Scheme 2

The first substrate we tested was 2-(2-aminophenyl)oct-3-yn-2-ol **6** (R =R^1 = R^2= H, R^3 = Me, R^4 = Bu). Crude **6**, obtained by the reaction between commercially available 1-(2-aminophenyl)ethanone **1** and 1-hexynylmagnesium bromide, was already suitable as substrate for the subsequent reactions without further purification .

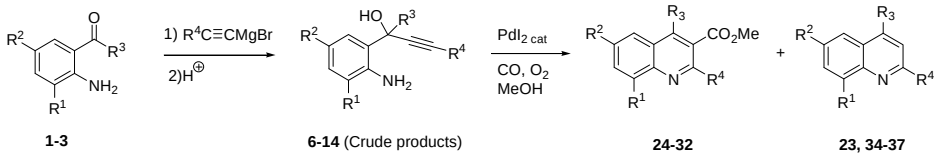
Substrate **6** was initially reacted under oxidative conditions, in MeOH as the solvent (0.22 mmol of substrate per mL of MeOH) at 100 °C and under 20 atm of a 4:1 mixture of CO/air, and in the presence of PdI_2 (2 mol %) and KI as the catalyst (KI: PdI_2 = 10). The substrate conversion was complete after 2 h, and the main reaction product turned out to be 2-butyl-4-methylquinoline **23** (79% isolated yield, based on starting **6**), whereas the carbonylated quinoline **24** was formed only in traces (Table 1, entry 1). This result shows that, under the above conditions, **6** selectively undergoes 6-*endo-dig* cyclization (Scheme 2, path b) followed by dehydration and protonolysis (path d) rather than carbonylation (path c).

Because it is known that protonolysis by HI is slowed down working under less concentrated conditions, we next tried the reaction at 0.02 rather then 0.22 mmol of **6** per mL of MeOH. As expected, the quinoline-3-carboxylic ester **24** was now obtained in appreciable yield (33% isolated), quinoline **23** still being the main reaction product (62% isolated yield, Table 1, entry 2). This result did not significantly change working under more diluted conditions.

In order to improve the selectivity toward **24**, the reaction was then carried out under a higher CO pressure, which was expected to favor the carbon monoxide insertion with respect to protonolysis. Indeed, under the same conditions of entry 2, but under 80 atm of a 4:1 mixture of CO/air, **24** was the main reaction product (69% isolated yield), quinoline **23** being formed in only 24% yield (Table 1, entry 3).

Under the same conditions of entry 3, other 1-(2-aminoaryl)-2-yn-1-ols **7**-**14**, bearing different substituents on the triple bond and on the aromatic ring, were converted into the corresponding quinoline-3-carboxylic esters **25**-**32** in fair to good yields, thus allowing a general synthesis of this class of heterocyclic compounds (Table 1, entries 4-11).

TABLE 1. Reactions of 1-(2-aminoaryl)-2-yn-1-ols 6-14 with CO, O_2 and MeOH in the presence of the PdI_2-KI catalytic system [a]



1-3 **6-14** (Crude products) **24-32** **23, 34-37**

Entry			R^1	R^2	R^3	R^4		Yield[b] (%)		Yield[b] (%)
1[c,d]	**1**	**6**	H	H	Me	Bu	**24**	Traces	**23**	79
2[d]	**1**	**6**	H	H	Me	Bu	**24**	33	**23**	62
3	**1**	**6**	H	H	Me	Bu	**24**	69	**23**	24
4	**2**	**7**	OMe	H	Me	Bu	**25**	65	**33**	28
5	**3**	**8**	H	Cl	Me	Bu	**26**	60		
6	**1**	**9**	H	H	Me	Ph	**27**	45	**34**	30
7	**2**	**10**	OMe	H	Me	Ph	**28**	63	**35**	25
8	**3**	**11**	H	Cl	Me	Ph	**29**	65		
9	**1**	**12**	H	H	Me	t-Bu	**30**	69	**36**	13
10	**2**	**13**	OMe	H	Me	t-Bu	**31**	70	**37**	10
11	**3**	**14**	H	Cl	me	t-Bu	**32**	58		

[a] Crude substrate **6-14** were directly used as substrates without need for further purification.Unless otherwise noted, all reactions were carried out in MeOH as the solvent (0.22 mmol of **1-3** per mL of MeOH) for 2 h in the presence of PdI_2 and KI (**1-3**/PdI_2/KI molar ratio 50:1:10) at 100°C and under 80 atm of a 4:1 mixture of CO-Air. Substrate conversion was quantitative in all cases . [b] Isolated yield based on starting **1-3** [c]Substrate concentration was 0.22 mmol/mL di MeOH. [d]The reaction was carried out under 20 Atm of a 4:1 mixture CO-Air.

Minor amounts of noncarbonylated quinolines **33-37** were obtained in some cases (entries 4, 6, 7, 9, 10).

The reaction worked well also with substrates bearing a *tert*butyl group on the triple bond, such as **30-32**, which led to the corresponding quinolines in 58-70% isolated yields based on starting amino ketones **1-3** (Table 1, entries 9-11). In the case of **12**, the formation of small amounts (7%) of 3,3-dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl ester **38**, deriving from path a (Scheme 2), was observed (Table 1, entry 9). Thus, under oxidative conditions, the reaction pathway beginning with a 6-*endo-dig* cyclization (Scheme 2, path b) is preferentially followed with respect to that beginning with a 5-*exo-dig* cyclization (Scheme 2, path a), even in the presence of a bulky

substituent on the terminal *sp* carbon. This apparently unusual result can be explained as follows.

The pathway beginning with a 6-*endo*-*dig* cyclization is particularly favored by the stabilization ensuing from the subsequent aromatization with formation of the quinoline ring. On the other hand, the pathway beginning with a 5-*exo*-*dig* cyclization can lead to aromatization only after the reaction between intermediate **VI** and the H-Pd-I species; however, this latter reaction is hindered by the fact that, under oxidative conditions, H-Pd-I is readily reconverted to PdI_2,[4,9] which may begin a new catalytic cycle leading to **20**.

It was interesting at this point to test the reactivity of 1-(2- aminoaryl)-2-yn-1-ols under nonoxidative conditions. I found that substrates not bearing a bulky group on the triple bond preferentially underwent 6-*endo*-*dig* rather than 5-*exo*-*dig* cyclization.

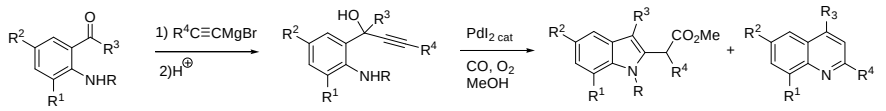
For example, the reaction of 2-(2-aminophenyl)-4- phenylbut-3-yn-2-ol **9** (bearing a phenyl group on the triple bond), carried out under the same conditions of entry 3 (Table 1) but under 60 atm of CO and in the absence of oxygen, selectively led to 4-methyl-2-phenylquinoline **34** (59% isolated yield, Table 2, entry 12), ensuing from 6-*endo*-*dig* cyclization (Scheme 2, path b) followed by aromatization and protonolysis (Scheme 2, path d). This result shows that, for a substrate bearing a phenyl on the triple bond, the route leading to indoles **21** (Scheme 2, path a) it is not competitive with the pathway leading to quinolines **22**. As expected, other substrates bearing a phenyl or a butyl group on the triple bond, such as **10**, **11**, and **8**, behaved similarly, leading to the corresponding noncarbonylated quinolines **35**, **39**, and **40** in 39-49% yields, as shown by the results reported in Table 2, entries 13-15.

On the basis of these results and observations, the next logical step was to test the reactivity of substrates bearing a bulky *tert*butyl or TMS group on the triple bond, under nonoxidative conditions. In this case, in fact, the 5-*exo*-*dig* pathway leading to indoles **21** was expected to become competitive with the 6-*endo*-*dig* route leading to quinolines **22** (Scheme 2) for steric reasons. Indeed, the reaction of 2-(2-aminophenyl)-5,5-dimethylhex-

3-yn-2-ol **12** (R4) *tert*-butyl) carried out under the same conditions as those of entries 12-15 (Table 2) led to 3,3- dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl

ester **38** in 66% isolated yield [based on starting 1-(2-aminophenyl) ethanone **1**], 2-*tert*-butyl-4-methylquinoline **36** being formed as byproduct (36% isolated yield based on **1a**, Table 2, entry 16). The selectivity toward **38** could be improved working under a higher CO pressure: at 90 atm, the yields of **38** and **36** were 75 and 6%, respectively, based on **1** (entry 17, Table 2). Under these latter conditions, other substrates bearing a *tert*-butyl group on the triple bond, such as **13-15**, led to the corresponding indoles **41-43** with good yields and selectivities (entries 18-20, Table 2). Minor amounts of noncarbonylated quinolines **37** and **44** were obtained from substrates **13** and **15**, respectively (entries 18 and 20).

TABLE 2. Reactions of 1-(2-aminoaryl)-2-yn-1-ols 8-19, 49 with CO and MeOH in the presence of the PdI_2-KI catalytic system [a]



1-5 **8-19, 49** (Crude products) **38, 41-43, 45-47, 50** **34-37, 39, 40, 44, 48**

Entry			R	R^1	R^2	R^3	R^4		Yield[b] (%)		Yield[b] (%)
12[c]	**1**	**9**	H	H	H	Me	Ph			**34**	59
13[c]	**2**	**10**	H	OMe	H	Me	Ph			**35**	54
14[c]	**3**	**11**	H	H	Cl	Me	Ph			**39**	39
15[c]	**3**	**8**	H	H	Cl	Mr	Bu			**40**	49
16[c]	**1**	**12**	H	H	H	Me	t-Bu	**38**	66	**36**	36
17	**1**	**12**	H	H	H	Me	t-Bu	**38**	75	**36**	6
18	**2**	**13**	H	OMe	H	Me	t-Bu	**41**	45	**37**	30
19	**3**	**14**	H	H	Cl	Me	t-Bu	**42**	68		
20	**4**	**15**	H	H	H	Ph	t-Bu	**43**	60	**44**	22
21	**1**	**16**	H	H	H	Me	TMS	**45**[d]	88		
22	**2**	**17**	H	OMe	H	Me	TMS	**46**[d]	42		
23	**4**	**18**	H	H	H	Ph	TMS	**47**[d]	63	**48**[d]	14
24[e]	**5**	**49**	Me	H	H	Me	Bu				
25	**5**	**19**	Me	H	H	Me	t-Bu	**50**	44		

[a] Crude substrate **8-18** were directly used as substrates without need for further purification.Unless otherwise noted, all reactions were carried out in MeOH as the solvent (0.22 mmol of **1-4** per mL of MeOH) for 2 h in the presence of PdI_2 and KI (**1-4**/PdI_2/KI molar ratio 50:1:10) at 100°C and under 90 atm of CO. Substrate conversion was quantitative in all cases . [b] Isolated yield based on starting **1-4** [c]Reaction was carried out under 60 Atm of CO. [d]R^4=H in the final product. [e]Decomposition of the substrate, with formation of unidentified chromatographically immobile materials, was observed

As we have already observed in other PdI_2-catalyzed cyclization and oxidative carbonylation reactions,[4,5,10] in the case of substrates bearing a trimethylsilyl substituent on the triple bond, such as **16**-**18**, the TMS group was lost in the course of the process, thus allowing the synthesis of R-unsubstituted indol-2-acetic esters **45**-**47** (entries 21-23, Table 2).4-Phenylquinoline **48** was obtained as byproduct in the case of the reaction of **18** (entry 23).

We also tested the reactivity of 1-(2-alkylaminoaryl)-2-yn-1-ols bearing a secondary rather than a primary amino group. Clearly, for these substrates, bearing only one hydrogen bonded to nitrogen, paths c and d (Scheme 2) could not be followed, thus the possibility to obtain quinoline derivatives **20** or **22** was prevented. The reaction of 2-(2-methylaminophenyl)-oct-3-yn-2-ol **49** (substituted with a butyl group on the triple bond), carried out under nonoxidative conditions, similar to those reported in entry 17 (Table 2), led to decomposition of the starting material, with formation of unidentified chromatographically immobile materials (Table 2, entry 24). This is conceivable, because, as we have seen, if the substituent on the triple bond is not sterically demanding, the 5-*exo*-*dig* cyclization (path a, Scheme 2) is not favored and, as a consequence, the substrate preferentially undergoes decomposition. On the other hand, the reaction of 5,5-dimethyl-2-(2-methylaminophenyl)-hex-3-yn-2- ol **19**, bearing a *tert*-butyl group on the triple bond, did afford the corresponding indol-2-acetic derivative **50**, even though in moderate yield [44% isolated, based on starting 1-(2-methylaminophenyl) ethanone **5**, Table 2, entry 25].

3.3 Conclusions

In conclusion, we have demonstrated that 1-(2-aminoaryl)-2-yn-1-ols **6**-**19** [used as crude products deriving from the Grignard reaction between 1-(2-aminoaryl)ketones **1**-**5** and alkynylmagnesium bromides] may follow different reaction pathways when let to react in the presence of the PdI_2-KI catalytic system under oxidative or nonoxidative carbonylation conditions, depending on the nature of the substrate and on reaction conditions.

In particular, 1-(2-aminoaryl)-2-yn-1-ols, bearing a primary amino group, such as **6**-**14**, selectively undergo 6-*endo*-*dig* cyclization when allowed to react under oxidative conditions, with selective formation of quinoline-3-carboxylic esters **24**-**32** in fair to good yields [45-70% isolated, based on starting 1-(2-aminoaryl)ketones **1**-**3**]. On the other hand, indol-2-acetic esters **38**, **41**-**43**, **45**-**47**, and **50**, deriving from 5-*exo*-*dig* cyclization, are obtained in moderate to good yields [42-88%, based on starting 1-(2-aminoaryl)ketones **1**-**5**] under nonoxidative conditions, when the starting material is substituted with a bulky group on the triple bond, as in the case of **12**-**19**. In this latter case, a primary as well as a secondary amino group can be present in the substrate, and R-unsubstituted indol-2-acetic esters are formed from substrates bearing a TMS group on the triple bond, ensuing from loss of the TMS group in the course of the process.

The present methodology represents a simple and direct approach to the synthesis of functionalized quinolines and indoles starting from readily available starting materials.[11-14]

3.4 Experimental Section

3.4.1 General Procedure for the Synthesis of Quinoline-3-carboxylic Esters 24-32 (Table 1, entries 3-11)

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, then it was maintained at 40 °C (R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = *t*-Bu) or 50 °C (R = R^1 = R^2 = H, R^3 = Me, R^4 = Bu; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = Bu; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 =

Bu; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = Ph; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = Ph; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = Ph; R = R^1 = R^2 = H, R^3 = Me, R^4 = *t*-Bu) for 2 h, and used as such at the same temperature for the next step. 1-(2-Aminoaryl)ketone **1-3** (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) under nitrogen. After stirring at 40 °C for 1.5 h (R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = *t*-Bu), 50 °C for 1 h (R = R^1 = R^2 = H, R^3 = Me, R^4 = Bu; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = Bu; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = Bu) or 50 °C for 2 h (R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = Ph; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = Ph; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = Ph; R = R^1 = R^2 = H, R^3 = Me, R^4 = *t*-Bu), the mixture was cooled to room temperature. Saturated NH4Cl was added with stirring to achieve 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 (3 × 30 mL), and the collected organic layers were washed with brine to ca. neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude products **6-14** were diluted with MeOH and transferred into a volumetric flask (50 mL). To 7.0 mL of the solution (formally deriving from 1.25 mml of **1-3**) were added 55.5 mL of MeOH (to adjust the substrate concentration to 0.02 mmol / mL of MeOH), and the resulting solution was transferred to an autoclave, previously loaded with PdI_2 (9.0 mg, 2.5 × 10-2 mmol) and KI (41.5 mg, 0.25 mmol). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (64 atm) and air (up to 80 atm). After being stirred at 100 °C for 2 h, the autoclave was cooled, degassed, and opened. The solvent was evaporated, and products **24-32** and **23**, **33-37** were purified by column chromatography on silica gel using 99:1 hexane-acetone as eluent. Non-carbonylated quinolines **23**, **33-37** were eluted first in all cases; in the case of the reaction mixture deriving from **12**, small amounts of 3,3-dimethyl-2-(3-methyl-1*H*-indol-2-yl)butyric acid methyl ester **38** were also isolated (order of elution: **36**, **38**, **30**): **24** [yellow oil, 221.3 mg, 69% based on starting 1-(2- aminophenyl)ethanone **1**]; **23** (yellow oil, 60.3 mg, 24% based on starting **1**); **25** [yellow oil, 233.7 mg, 65% based on starting 1-(2-amino-3-

methoxyphenyl)ethanone **2**]; **33** (yellow oil, 79.5 mg, 28% based on starting **2**); **26** [yellow oil, 220.2 mg, 60% based on starting 1-(2-amino-5- chlorophenyl)ethanone **3**]; **27** (yellow solid, mp 58-59 °C, 156.6 mg, 45% based on starting **1**); **34** (yellow oil, 81.8 mg, 30% based on starting **1**); **28** (yellow solid, mp 100-101 °C, 241.2 mg, 63% based on starting **2**); **35** (yellow solid, mp 97-98 °C, 77.3 mg, 25% based on starting **2**); **29** (yellow oil, 254.2 mg, 65% based on starting **3**); **30** (yellow oil, 222.9 mg, 69% based on starting **1**); **38** (yellow solid, mp 115-117 °C, 23.1 mg, 7% based on starting **1**); **36** (yellow oil, 31.5 mg, 13% based on starting **1**); **31** (yellow solid, mp 65-67 °C, 252.3 mg, 70% based on starting **2**); **37** (yellow oil, 30.0 mg, 10% based on starting **2**); **32** (yellow oil, 213.3 mg, 58% based on starting **3**).

3.4.2 General Procedure for the Synthesis of Indol-2-acetic Esters 38, 41-43, 45-47, 50 (Table 2, entries 17-23, 25)

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, then it was maintained at 40 °C (R = R^2 =H, R^1 = OMe, R^3 = Me, R^4 = TMS; R = R^3 = Me, R^1 = R^2 = H, R^4 = *t*-Bu; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = *t*-Bu) or 50 °C (R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = TMS; R = R^1 = R^2 = H, R^3 = Ph, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Ph, R^4 = TMS) for 2 h, and used as such at the same temperature for the next step. 1-(2-Aminoaryl)ketone **1-5** (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) under nitrogen. After stirring at 40 °C C for 1.5 h (R = R^1 = H, R^2 =

Cl, R^3 = Me, R^4 = *t*-Bu; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = TMS), at 40 °C for 2 h (R = R^3 = Me, R^1 = R^2 = H, R^4 = *t*-Bu), 50 °C for 2 h (R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Me, R^4 = TMS; R = R^1 = R^2 = H, R^3 = Ph, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Ph, R^4 = TMS), the mixture was cooled to room temperature. Saturated NH_4Cl was added with stirring to achieve 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 (3 × 30 mL), and the collected organic layers were washed with brine to ca. neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude products **12-19** were diluted with MeOH and transferred into volumetric flask (50 mL). To 7.0 mL of the solution (formally deriving from 1.25 mml of **1-5**) were added 55.5 mL of MeOH (to adjust the substrate concentration to 0.02 mmol / mL of MeOH), and the resulting solution was transferred to an autoclave, previously loaded with PdI_2 (9.0 mg, 2.5×10^{-2} mmol) and KI (41.5 mg, 0.25 mmol). The autoclave was sealed, purged at room temperature several times with CO with stirring (10 atm) and eventually pressurized at 90 atm of CO. After being stirred at 100 °C for 2 h, the autoclave was cooled, degassed, and opened. The solvent was evaporated, and products **38, 41-43, 45-47, 50** and **36**, **37, 44, 48** were purified by column chromatography on silica gel using hexane-acetone from 99:1 to 95:5 (R = R^1 = R^2 = H, R^3 = Me, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Ph, R^4 = *t*-Bu; R = R^1 = R^2 = H, R^3 = Ph, R^4 = TMS; R = R^1 = H, R^2 = Cl, R^3 = Me, R^4 = *t*-Bu) or hexane-AcOEt from 99:1 to 95:5 as eluent (R = R^1 = R^2 = H, R^3 = Me, R^4 = TMS; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = *t*-Bu; R = R^2 = H, R^1 = OMe, R^3 = Me, R^4 = TMS; R = R^3 = Me, R^1 = R^2 = H, R^4 = *t*-Bu). Non-carbonylated quinolines **36**, **37, 44, 48** were eluted first in all cases: **38** (yellow solid, mp 115-117 °C, 244.7 mg, 75% based on starting **1**); **36** (yellow oil, 15.2 mg, 6% based on starting **1**); **41** (colorless solid, mp 83-85 °C, 163.9 mg, 45% based on starting **2**); **37** (yellow oil, 86.8 mg, 30% based on starting **2**); **42** (yellow solid, mp 101-103 °C, 250.6 mg, 68% based on starting **3**); **43** (yellow solid, mp 174-176 °C, 240.9 mg, 60% based on starting **4**); **44** (colorless solid, 77-78 °C, 72.4 mg, 22% based on starting **4**); **45** [yellow solid, mp 78-79 °C (lit.3 77-78 °C), 224.8 mg, 88% based on starting **1**); **46** (yellow oil, 122.3 mg, 42% based on starting **2**); **47** (yellow solid, mp 83-

84 °C, 210.1 mg, 63% based on starting **4**); **48** (yellow oil, 36.4 mg, 14% based on starting **4**); **50** (yellow solid, mp 86-88 °C, 149.4 mg, 44% based on starting **5**).

3.4.3 Characterization data of products

Quinolines **23**, **33**, **34**, **35**, **36**, **37**, **39**, **40**, **44**, and **48** were characterized by comparison with literature data.[97] Complete characterization data for all the other products are given below.

2-Butyl-4-methylquinoline-3-carboxylic acid methyl ester (24). Yield: 221.3 mg, 69% based on starting 1-(2-aminophenyl)ethanone **1a** (Table 1, entry 3). Yellow oil. IR (film): ν = 1731 (s), 1588 (m), 1456 (m), 1435 (m), 1290 (m), 1235 (s), 1161 (w), 1056 (w), 759 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08-8.05 (m, 1 H), 8.01-7.96 (m, 1 H), 7.70 (ddd, *J*= 8.3, 6.9, 1.4, 1 H), 7.53 (ddd, *J* = 8.3, 6.9, 1.4, 1 H), 3.99 (s, 3 H), 2.96-2.88 (m, 2 H), 2.63 (s, 3 H), 1.85-1.72 (m, 2 H), 1.44 (sext, *J* = 7.4, 2 H), 0.95 (t, *J* = 7.4, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 158.3, 147.3, 141.6, 130.0, 129.5, 127.7, 126.3, 125.7, 124.0, 52.4, 37.1, 31.8, 22.9, 15.9, 13.9 ; GC-MS: *m/z* = 257 (6) [M+], 242 (17), 228 (23), 226 (11), 216 (16), 215 (100), 200 (53), 198 (10), 171 (10), 167 (12), 158 (13), 157 (88), 143 (10), 115 (13); anal. calcd for $C_{16}H_{19}NO_2$ (257.33): C,74.68; H, 7.44; N, 5.44. Found C, 74.76; H, 7.46; N, 5.43

2-Butyl-8-methoxy-4-methylquinoline-3-carboxylic acid methyl ester (25). Yield: 233.7 mg, 65% based on starting from **1b** (Table 1, entry 4). Yellow oil. IR (film): ν = 1732 (s), 1567 (w), 1494 (w, 1471 (m), 1436 (m), 1399 (w), 1274 (m), 1257 (m), 1158 (s), 1047 (m), 748 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (distorted dd, *J* = 8.4, *J* = 1.2, 1 H), 7.45 (dd, *J*= 8.4, 7.8, 1 H), 7.07 (distorted dd, *J* = 7.8, 1.2, 1 H), 4.07 (s, 3 H), 3.99 (s, 3 H), 3.01-2.94 (m, 2 H), 2.60 (s, 3 H), 1.84-1.71 (m, 2 H), 1.47 (sext, *J* = 7.4, 2 H), 0.94 (t, *J* = 7.4, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 157.2, 155.4, 141.5, 139.3, 128.2, 126.9, 126.2, 115.7, 108.4, 56.3, 52.4, 37.4, 32.1, 22.9, 16.4, 13.9 ; GC-MS: *m/z* = 287 (5) [M+], 286 (10), 272 (11), 258 (22), 246 (13), 245 (100),

230 (39), 228 (13), 227 (12), 212 (11), 187 (66), 172 (17), 115 (16); anal. calcd for $C_{17}H_{21}NO_3$ (287.35): C, 71.06; H, 7.37; N, 4.87. Found C, 71.17; H, 7.36; N, 4.86.

2-Butyl-6-chloro-4-methylquinoline-3-carboxylic acid methyl ester (26). Yield: 220.2 mg, 60% based on starting **1c** (Table 1, entry 5). Yellow oil. IR (film): ν= 1732 (s), 1588 (m), 1487 (m), 1275 (m), 1227 (s), 1095 (m), 832 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (distorted d, *J* = 8.8, 1 H), 7.93 (d, *J* = 2.2, 1 H), 7.62 (dd, *J* = 8.8, 2.2, 1 H), 4.00 (s, 3 H), 2.94-2.85 (m, 2 H), 2.58 (s, 3 H), 1.84-1.71 (m, 2 H), 1.43 (sext, *J* = 7.5, 2 H), 0.95 (t, *J* = 7.4, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 158.6, 145.7, 140.7, 132.1, 131.1, 130.7, 128.4, 126.5, 123.1, 52.5, 37.0, 31.6, 22.8, 15.8, 13.9; GC-MS: *m/z* = 293 (0.2) [M++2], 291 (0.7) [M+], 276 (12), 262 (21), 251 (34), 250 (16), 249 (100), 236 (14), 234 (45), 232 (11), 193 (25), 192 (11), 191 (73), 167 (12), 154 (13), 115 (10) ; anal. calcd for $C_{16}H_{18}ClNO_2$ (291.77): C, 65.86; H, 6.22; Cl, 12.15; N, 4.80. Found C, 65.98; H, 6.18; Cl, 12.08; N, 4.83

4-Methyl-2-phenylquinoline-3-carboxylic acid methyl ester (27). Yield: 156.6 mg, 45% based on starting **1a** (Table 1, entry 6). Yellow solid, mp 58-59 °C. IR (KBr): ν = 1721 (s), 1494 (w), 1436 (w), 1293 (m), 1230 (s), 1114 (m), 1054 (w), 770 (m), 757 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.21-8.15 (m, 1 H), 8.11-8.05 (m, 1 H), 7.81-7.73 (m, 1 H), 7.73-7.65 (m, 2 H), 7.65-7.57 (m, 1 H), 7.51-7.41 (m, 3 H), 3.67 (s, 3 H), 2.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 156.1, 147.3, 142.9, 140.5, 130.4, 130.3, 128.8, 128.5, 128.3, 127.8, 127.0, 126.0, 124.1, 52.4, 15.8; GCMS: *m/z* = 277 (24) [M+], 263 (18), 262 (100), 246 (34), 217 (20), 108 (15); anal. calcd for $C_{18}H_{15}NO_2$ (277.32): C, 77.96; H, 5.45, N, 5.05. Found C, 78.08; H, 5.46; N, 5.06

8-Methoxy-4-methyl-2-phenylquinoline-3-carboxylic acid methyl ester (28). Yield: 241.2 mg, 63% based on starting **1b** (Table 1, entry 7). Yellow solid, mp 100-101°C. IR (KBr): ν= 1726 (s), 1560 (w), 1467 (m), 1437 (w), 1398 (w), 1246 (w), 1259 (m), 1160 (s), 1043 (w), 767 (w) (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73-7.67 (m, 2 H), 7.62 (distorted dd, *J* = 8.4, 1.1, 1 H), 7.51 (dd, *J* = 8.4, 7.8, 1 H), 7.45-7.38 (m, 3 H), 7.10 (dd, *J* = 7.8, 1.1, 1 H), 4.05 (s, 3 H), 3.67 (s, 3 H), 2.71 (s, 3 H); ^{13}C NMR (75

MHz, $CDCl_3$): δ = 169.9, 155.9, 154.7, 142.6, 140.7, 139.3, 128.6, 128.5, 128.3, 127.8, 127.2, 127.1, 115.7, 108.7, 56.2, 52.4, 16.3; GC-MS: *m/z* = 307 (100) [M+], 306 (77), 278 (38), 277 (22), 274 (13), 246 (16), 217 (18), 216 (13), 204 (12), 77 (13); anal. calcd for $C_{19}H_{17}NO_3$ (307.34): C, 74.25; H, 5.58; N, 4.56. Found C, 74.18; H, 5.59; N, 4.58

6-Chloro-4-methyl-2-phenylquinoline-3-carboxylic acid methyl ester (29). Yield: 254.2 mg, 65% based on starting from **1c** (Table 1, entry 8). Yellow oil. IR (film): ν= 1719 (s), 1291 (m), 1226 (s), 1117 (m), 1090 (w), 833 (m), 716 (w), 698 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13-8.01 (m, 2 H), 7.73-7.64 (m, 3 H), 7.52-7.41 (m, 3 H), 3.68 (s, 3 H), 2.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 156.3, 145.7, 142.1, 140.1, 132.9, 131.9, 131.3, 129.0, 128.5, 128.2, 127.9, 126.8, 123.2, 52.5, 15.8; GC-MS: *m/z* = 313 (15) [M++2], 311 (34) [M+], 298 (32), 297 (16), 296 (100), 282 (17), 281 (19), 280 (44), 253 (13), 217 (28), 216 (28), 114 (14), 77 (13), 75 (11), 73 (33); anal. calcd for $C_{18}H_{14}ClNO_2$ (311.76): C, 69.35; H, 4.53; Cl, 11.37; N, 4.49. Found C, 69.47; H, 4.54; Cl, 11.38, N, 4.50.

2-*tert*-Butyl-4-methylquinoline-3-carboxylic acid methyl ester (30). Yield: 222.9 mg, 69% based on starting **1a** (Table 1, entry 9). Yellow oil. IR (film): ν = 1729 (s), 1634 (m), 1384 (s), 1305 (s), 1196 (w), 1182 (w) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.85-8.80 (m, 1 H), 8.29-8.24 (m, 1 H), 8.07 (ddd, *J* = 8.5, 7.1, 1.3, 1 H), 7.91 (ddd, *J*= 8.5, 7.1, 1.3, 1 H), 4.07 (s, 3 H), 2.86 (s, 3 H), 1.72 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 162.7, 155.1, 137.7, 135.7, 130.5, 128.0, 126.5, 124.7, 122.5, 53.5, 39.8, 29.5, 17.5; GC-MS: *m/z* = 257 (25) [M+], 243 (18), 242 (100), 226 (13), 224 (12), 215 (34), 210 (20), 200 (16), 182 (11), 167 (21), 157 (21), 143 (37), 115 (19), 90 (11); anal. calcd for $C_{16}H_{19}NO_2$ (257.33): C, 74.68; H, 7.44; N, 5.44. Found C, 74.59; H, 7.42; N, 5.45

2-*tert*-Butyl-8-methoxy-4-methylquinoline-3-carboxylic acid methyl ester (31). Yield: 252.3 mg,70% based on starting **1b** (Table 1, entry 10). Yellow solid, mp 65-67°C. IR (KBr): ν= 1726 (s), 1467 (m), 1279 (w), 1260 (m), 1246 (w), 1204 (w), 1081

(s), 1043 (m), 796 (w), 767 (w), 742 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (distorted dd, *J* = 8.4, 1.0, 1 H), 7.43 (dd, *J* = 8.4, 7.8, 1 H), 7.05 (dd, *J* = 7.8, 1.0, 1 H), 4.06 (s, 3 H), 3.96 (s, 3 H), 2.55 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 161.7, 155.8, 152.0, 141.5, 138.4, 127.1, 126.5, 115.5, 109.0, 56.6, 52.2, 40.2, 30.1, 16.2; GC-MS: *m/z* = 287 (49) [M+], 286 (37), 273 (18), 272 (100), 258 (13), 257 (13), 256 (16), 254 (21), 245 (18), 212 (17), 198 (13), 187 (16), 173 (33), 158 (12), 115 (11); anal. calcd for $C_{17}H_{21}NO_3$ (287.35): C, 71.06; H, 7.37; N, 4.87. Found C, 71.13; H, 7.36; N, 4.86

2-*tert*-Butyl-6-chloro-4-methylquinoline-3-carboxylic acid methyl ester (32). Yield: 213.3 mg, 58% based on starting **1c** (Table 1, entry 11). Yellow oil. IR (film): ν = 1733 (s), 1577 (w), 1482 (m), 1223 (s), 1123 (m), 1092 (m), 1056 (m), 832 (m), 803 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ= 7.96 (distorted d, *J* = 8.8, 1 H), 7.93 (d, *J* = 2.2, 1 H), 7.61 (distorted dd, *J*= 8.8, 2.2, 1 H), 3.96 (s, 3 H), 2.52 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 163.4, 144.8, 140.7, 132.2, 131.8, 130.4, 128.3, 126.0, 122.6, 52.3, 40.0, 30.0, 15.7; GC-MS: *m/z* = 293 (5) [M++2], 291 (25) [M+], 278 (34), 277 (16), 276 (100), 260 (16), 258 (12), 251 (17), 249 (43), 244 (19), 234 (21), 216 (11), 193 (12), 191 (32), 181 (10), 180 (12), 179 (11), 177 (33), 140 (12), 115 (10), 90 (12); anal. calcd for $C_{16}H_{18}ClNO_2$ (291.77): C, 65.86; H, 6.22; Cl, 12.15; N, 4.80. Found C, 65.95; H, 6.20; Cl, 12.13, N, 4.79.

3,3-Dimethyl-2-(3-methyl-1*H*-indol-2-yl)acetic acid methyl ester (38). Yield: 244.7 mg, 75% based on starting **1a** (Table 2, entry 17). Yellow solid, mp 115-117 °C. IR (KBr): ν = 3401 (s), 1727 (s), 1460 (w), 1340 (w), 1151 (m), 741 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (s, br, 1 H), 7.56-7.48 (m, 1 H), 7.36-7.28 (m, 1 H), 7.21-7.03 (m, 2 H), 3.80 (s, 1 H), 3.69 (s, 3 H), 2.25 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 135.2, 129.0, 128.4, 121.6, 118.9, 118.4, 110.7, 109.7, 52.3, 51.7, 36.9, 28.0, 9.2 ; GC-MS: *m/z* = 259 (53) [M+], 203 (45), 202(45), 172 (14), 171 (100), 170 (92), 144 (27), 143 (28), 142 (16), 116 (10), 115 (30); anal. calcd for $C_{16}H_{21}NO_2$ (259.34): C, 74.10; H, 8.16; N, 5.40. Found C, 74.21; H, 8.14; N, 5.38.

2-(7-Methoxy-3-methyl-1*H*-indol-2-yl)-3,3-dimethylbutyric acid methyl ester (41). Yield: 163.9 mg, 45% based on starting **1b** (Table 2, entry 18). Colorless solid, mp 83-85°C. IR (KBr): ν = 3457 (s), 1713 (s), 1582 (w), 1456 (w), 1329 (w), 1259 (m), 1228 (m), 1156 (m), 1047 (w), 723 (w) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (s, br, 1 H), 7.12 (d, *J* = 7.8, 1 H), 7.00 (t, *J* = 7.8, 1 H), 6.60 (d, *J* = 7.8, 1 H), 3.93 (s, 3 H), 3.78 (s, 1 H), 3.69 (s, 3 H), 2.24 (s, 3 H), 1.05 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 146.1, 130.0, 128.9, 126.1, 119.4, 111.4, 110.3, 102.1, 55.3, 52.6, 51.5, 36.8, 28.1, 9.4 ; GC-MS: *m/z* = 289 (50) [M+], 233 (33), 232 (47), 202 (14), 201 (100), 200 (87), 174 (13); anal. calcd for $C_{17}H_{23}NO_3$ (289.37): C, 70.56; H, 8.01; N, 4.84. Found C, 70.67; H, 8.03; N, 4.82.

2-(5-Chloro-3-methyl-1*H*-indol-2-yl)-3,3-dimethylbutyric acid methyl ester (42). Yield: 250.6 mg, 68% based on starting **1c** (Table 2, entry 19). Yellow solid, mp 101-103 °C. IR (KBr): ν = 3410 (s), 2950 (m), 1715 (s), 1469 (m), 1445 (m), 1348 (w), 1196 (w), 1157 (w), 605 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, br, 1 H), 7.49-7.46 (m, 1 H), 7.24 (distorted d, *J* = 8.6, 1 H), 7.10 (distorted dd, *J* = 8.6, 2.2, 1 H), 3.78 (s, 1 H), 3.72 (s, 3 H), 2.21 (s, 3 H), 1.04 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 133.9, 133.5, 130.7, 129.5, 124.6, 121.8, 117.9, 111.7, 52.2, 51.8, 37.0, 28.0, 9.1 ; GC-MS: *m/z* = 295 (6) [M++2], 293 (22) [M+], 239 (12), 238 (15), 237 (34), 236 (30), 207 (34), 206 (25), 205 (100), 204 (44), 178 (17), 177 (15), 141 (10), 140 (12); anal. calcd for $C_{16}H_{20}ClNO_2$ (293.79): C, 65.41; H, 6.86; Cl, 12.07; N, 4.77. Found C, 65.49; H, 6.88; Cl, 12.09; N, 4.76.

Dimethyl-2(3-phenyl-1*H*-indol-2-yl)butyric acid methyl ester (43). Yield: 240.9 mg, 60% based on starting **1d** (Table 2, entry 20). Yellow solid, mp 174-176 °C. IR (KBr): □ = 3406 (s), 1713 (s), 1435 (w), 1350 (w) 1256 (w), 1196 (m), 1155 (m), 738 (m), 705 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.06 (s, br, 1 H), 7.61-7.55 (m, 1 H), 7.51-7.37 (m, 5 H), 7.37-7.28 (m, 1 H), 7.20 (ddd, *J* = 8.2, 7.1, 1.2, 1 H), 7.09 (ddd, *J* = 7.9, 7.1, 1.2, 1 H), 4.09 (s, 1 H), 3.75 (s, 3 H), 0.88 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 135.2, 135.1, 130.2, 129.4, 128.7, 127.4, 126.3, 122.1, 119.8, 119.1, 117.6, 110.9, 51.92, 51.85, 36.7, 27.9; GC-MS: *m/z* = 321 (36) [M+], 266 (10), 265 (49), 264

(23), 234 (14), 233 (77), 206 (18), 205 (29), 204 (100), 203 (11); anal. calcd for $C_{21}H_{23}NO_2$ (321.41): C, 78.47; H, 7.21; N, 4.36. Found C, 78.52; H, 7.20; N, 4.35.

(**3-Methyl-1*H*-indol-2-yl)acetic acid methyl ester (45).** Yield: 224.8 mg, 88% based on starting **1a** (Table 2, entry 21). Yellow solid, mp 78-79°C (lit.3 77-78 °C). IR (KBr): ν = 3359 (s), 1720 (s), 1460 (w), 1435 (w), 1307 (m), 1240 (m), 1163 (w), 1006 (w), 746 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, br, 1 H), 7.51-7.45 (m, 1 H), 7.24-7.19 (m, 1 H), 7.15-7.05 (m, 2 H), 3.69 (s, 2 H), 3.67 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.1, 135.8, 129.0, 126.3, 121.8, 119.2, 118.5, 110.7, 109.0, 52.1, 31.7, 8.3 ; GC-MS: *m/z* = 203 (45) [M+], 145 (11), 144 (100), 143 (23), 115 (9); anal. calcd for $C_{12}H_{13}NO_2$ (203.24): C, 70.92; H, 6.45; N, 6.89. Found C, 71.15; H, 6.47; N, 6.87

(7-Methoxy-3-methyl-1*H*-indol-2-yl)acetic acid methyl ester (46). Yield: 122.3 mg, 42% based on starting **1b** (Table 2, entry 22). Yellow oil. IR (film): ν = 3373 (s), 1734 (s), 1575 (w), 1463 (m), 1335 (w), 1259 (s), 1171 (m), 1047 (m), 1002 (m), 773 (w), 716 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (s, br, 1 H), 7.11 (distorted d, *J* = 7.7, 1 H), 7.00 (t, *J* = 7.7, 1 H), 6.60 (d, *J* = 7.7, 1 H), 3.92 (s, 3 H), 3.75 (s, 2 H), 3.70 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 145.8, 130.1, 126.0, 125.8, 119.6, 111.3, 109.5, 101.9, 55.3, 52.2, 31.8, 8.7 ; GC-MS: *m/z* = 233 (60) [M+], 175 (12), 174 (100), 172 (11), 160 (10), 159 (29), 158 (10), 144 (10), 131 (19), 130 (16), 103 (10); anal. calcd for $C_{13}H_{15}NO_3$ (233.26): C, 66.94; H, 6.48; N, 6.00. Found C, 67.06; H, 6.47; N, 6.01.

(3-Phenyl-1*H*-indol-2-yl)acetic acid methyl ester (47). Yield: 210.1 mg, 63% based on starting **1d** (Table 2, entry 23). Yellow solid, mp 83-84 °C. IR (KBr): ν = 3356 (s), 3336 (m), 1724 (s), 1431 (w), 1256 (m), 1140 (m), 1011 (w), 748 (m), 695 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (s, br, 1 H), 7.65 (d, br, *J* = 7.7, 1 H), 7.52-7.41 (m, 4 H), 7.35 (distorted d, *J* = 8.1, 1 H), 7.34-7.28 (m, 1 H), 7.20 (td, *J* = 7.7, 1.0, 1 H), 7.11 (td, *J* = 8.1, 1.0, 1 H), 3.88 (s, 2 H), 3.73 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =

171.2, 136.0, 134.7, 129.8, 128.7, 127.6, 126.8, 126.4, 122.4, 120.2, 119.4, 116.6, 110.9, 52.3, 32.1; GC-MS: *m/z* = 265 (90) [M+], 207 (18), 206 (100), 205 (34), 204 (44), 179 (32), 178 (24); anal. calcd for $C_{17}H_{15}NO_2$ (265.31): C, 76.96; H, 5.70; N, 5.28. Found C, 77.12; H, 5.68; N, 5.29.

2-(1,3-Dimethyl-1*H*-indol-2-yl)-3,3-dimethylbutyric acid methyl ester (50). Yield: 149.4 mg, 44% based on starting **1e** (Table 2, entry 25). Yellow solid, mp 86-88°C. IR (KBr): ν = 3457 (m, br), 1741 (s), 1471 (m), 1331 (w), 1202 (w), 1144 (s), 1040 (w), 1021 (w), 743 (m) cm1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57-7.51 (m, 1 H), 7.30-7.18 (m, 2 H), 7.15-7.07 (m, 1 H), 3.75 (s, 1 H), 3.71 (s, 3 H), 3.60 (s, 3 H), 2.31 (s, 3 H), 1.13 (s, 9 H); GC-MS: *m/z* = 273 (99) [M+], 218 (10), 217 (66), 216 (99), 214 (180), 186 (30), 185 (99), 184 (100), 182 (11), 169 (12), 168 (15), 167 (11), 158 (65), 157 (26), 156 (26), 154 (10), 144 (16), 128 (10), 115 (13); anal. calcd for $_{C17H23NO2}$ (273.37): C, 74.69; H, 8.48; N, 5.12. Found C, 74.61; H, 8.49; N, 5.13.

3.5 References

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Chapter 4

New synthesis of 5 and 6 membered cyclic carbonates by Pd-catalyzed oxidative carbonylation of diols *

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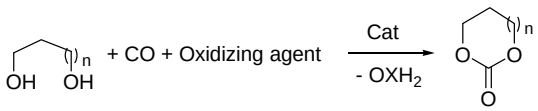
4.1 Introduction

Cyclic carbonates are a very important class of carbonyl compounds, with many important applications in various fields. They are usually used as solvents and chemical intermediates [1,2,3] and find many applications as additives in fuels and hydraulic fluids, precursors for biomedical applications and as protecting group in carbohydrate chemistry[1-5].

They are usually prepared either by carboxylation (with CO_2 or its derivatives as carboxylating agents) of suitable substrates (such as diols, epoxides, and olefins) or by indirect carbonylation (with phosgene or its derivatives, including acyclic carbonates, as carbonylating agents) of diols.[6]

These last reactions in particular are not very attractive in terms of environmental impact because the use of poisonous or polluting chemicals.

Surprisingly, however, the direct, phosgene-free oxidative carbonylation of diols with carbon monoxide (Scheme 1) has so far received limited attention, in spite of the large availability of CO and the attractiveness of the process in view of its high atom economy[7] and ecofriendliness.

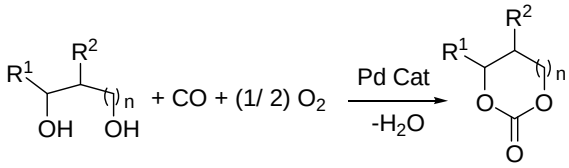


Scheme 1

The stoichiometric oxidative carbonylation of 1,2-diols to give [1,3]dioxolan-2-ones was reported by Tam to be promoted by $PdCl_2$ in conjunction with 2 equiv of AcONa.[8,9] Tam also reported a catalytic version of his reaction [carried out in the presence of 10% of $PdCl_2$, $CuCl_2$ as the oxidant (2 equiv with respect to the substrate) and AcONa or Et_3N as the base (2 equiv with respect to the substrate)], which, however, was limited to the conversion of 1-phenyl-1,2-ethanediol into 4-phenyl-[1,3]dioxolan-2-one (with a catalytic turnover of 10) and of 1-(N-phenylamino)propane-2,3-diol into a ca. 3:1

mixture of 4-phenylamino-[1,3]dioxolan-2-one and 5-hydroxymethyl-3-phenyloxazolidin-2-one (with a total catalytic turnover of 7.4).[8,10]

Starting from the well known reactivity of PdI_2 with an excess of KI as simple and excellent catalyst in oxidative carbonylation reactions[11] (see also Chapter 3 of this thesis), we have used it to obtain the conversion of 1,2-diols into 5-membered cyclic carbonates, with unprecedented catalytic efficiencies for this kind of reaction (up to ca. 190 mol of product per mol of PdI_2) (Scheme 2, n = 0). Moreover using the same catalyst, 6-membered cyclic carbonates have been obtained for the first time through the direct catalytic oxidative carbonylation of 1,3-diols (Scheme 2, n = 1).



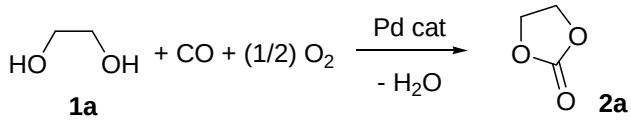
Scheme 2

4.2 Results and discussion

We started the study of this synthetic methodology with a screening of reaction parameters using 1,2- ethandiol as substrate. Results are shown in Table 1:

This screening allowed to optimize the reaction conditions as follows (Table 1, Entry 10): *N*,*N*-dimethylacetamide (DMA) as the solvent; 100°C of temperature; a molar ratio KI/PdI_2 of 200 and a pressure of 20 bar of a 4/1 CO/air mixture.

TABLE 1. **Oxidative carbonylation reactions of 1,2-ethanediol 1a to give [1,3]dioxolan-2-one in the presence of PdI_2 in conjunction with an excess of KI**[a]



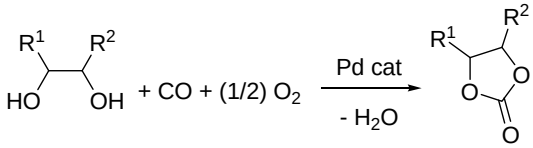
1a **2a**

Entry	KI/PdI_2 Molar ratio	T (°C)	Solvent	Conc. of **1a**[b]	P_{co} (atm)	P_{air} (atm)	Conv. of **1a** (%)[c]	Yield of **1a** (%)[d]
1	10	100	DME	0.5	16	4	68	56
2	10	100	DME	1.0	16	4	70	67
3	10	100	DME	0.25	16	4	56	42
4	100	100	DME	0.5	16	4	55	39
5	50	100	DME	0.5	16	4	42	30
6	2	100	DME	0.5	16	4	60	41
7	10	90	DME	0.5	16	4	54	34
8	10	100	DME	0.5	32	8	62	52
9	10	100	Dioxane	0.5	16	4	10	Traces
10	10	100	DMA	0.5	16	4	78	70

[a]All reactions were carried out for 5 h in the presence of 0.5 mol % of PdI_2. [b]Mmol of **1a** per mL of solvent. [c]Determined by GLC. [d]isolated yield based on starting **1a**

These oxidative carbonylation reaction condition were applied to variously substituted 1,2-diols (n = 0) and conversions and yields are presented in Table 2:

TABLE 2. **Synthesis of 5-membered cyclic carbonates 2a-e by PdI_2/KI-catalyzed oxidative carbonylation of 1,2-diols 1a-e**[a]



1a-e **2a-e**

Entry	n	R^1	R^2	**1**	1 : PdI_2 molar ratio	Time (h)	Conv. of **1** (%)[b]	2	Yield of **2** (%)c
1	0	H	H	**1a**	200	15	100	**2a**	84
2	0	Me	Me	**1b**	200	15	100	**2b**	65[d]
3	0	Et	H	**1c**	200	15	100	**2c**	94
4	0	Ph	H	**1d**	200	15	100	**2d**	94
5	0	Ph	Ph	**1e**	200	24	100	**2e**	70

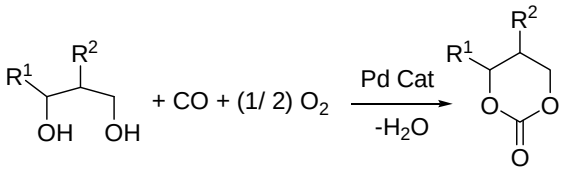
[a]All reactions were carried out in DMA(substrate concentration = 0.5 mmol of 1/mL of DMA)at 100 °Cunder 20 atm of a 4:1 mixture of CO-air in the presence of PdI_2 in conjunction with 10 equiv of KI. [b]Determined by GLC. [c]isolated yield based on starting **1a** [d]racemic mixture (44+21 %)

Under these conditions, after 15 h, 1,2-ethanediol **1a** ($R^1 = R^2 = H$) was converted into [1,3]dioxolan-2-one **2a** in 84% isolated yield (Table 2, entry 1). To the best of our knowledge, this reaction represents the first example of oxidative carbonylation of 1,2-ethanediol to give **2a** with catalytic turnover. The other 1,2-diols, bearing one o two alkyl or phenyl groups as substituent, such as butane-2,3-diol **1b** ($R^1 = R^2 = Me$), butane-1,2-diol **1c** ($R^1 = Et$, $R^2 = H$), 1-phenylethane-1,2-diol **1d** (n = 0, $R^1 = Ph$, $R^2 = H$) and 1,2-diphenylethane-1,2-diol **1e** ($R^1 = R^2 = Ph$)**,** behaved similarly, with formation of the corresponding cyclic carbonates **2b–c** with isolated yields from 65 to 90% (Table 2, entries 2 and 5).

This method has been successfully also applied to the first direct catalytic oxidative carbonylation of 1,3-diols (Table 3), such as 1,3-propanediol **1f** (n = 1, $R^1 = R^2 = H$), 1,3-butanediol **1g** (n = 1, $R^1 = Me$, $R^2 = H$), and 2-methylpropane-1,3-diol **1h** (n = 1, $R^1 = H$, $R^2 = Me$) to give the corresponding [1,3]dioxan-2-ones **2f-h** in good yields (Table

3, entries 1-3). As expected in view of their higher conformational mobility, 1,3-diols turned out to be less reactive with respect to 1,2-diols: thus, the reaction of **1f**, carried out under the same conditions as previously employed for 1,2-diols **1a–e** (Table 2, entries 1-5), led to a substrate conversion of 80%, with an isolated yield of [1,3]dioxan-2-one **2f** of 42% (Table 2, entry 1). Better results were however obtained by working with a lower substrate-to-catalyst molar ratio: with 1 mol % of PdI_2, the substrate conversion was quantitative after 15 h, and the yield of **2f** increased to 74% (Table 2, entry 2). Under the same conditions, the reactions of **1g** and **1h** were slightly slower: the substrate conversion reached 100% after 24 h, with isolated yields of the corresponding 6-membered cyclic carbonates **2g** and **2h** of 66% and 68%, respectively (Table 2, entries 3 and 4).

TABLE 3. **Synthesis of 6-membered cyclic carbonates 2f-h by PdI_2/KI-catalyzed oxidative carbonylation of 1,3-diols 1f-h**[a]



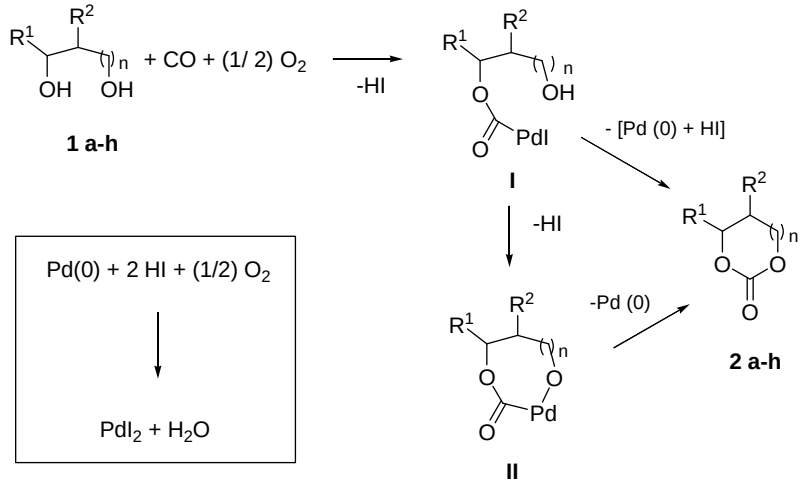
1f-h **2 f-h**

Entry	n	R^1	R^2	**1**	1 : PdI_2 molar ratio	Time (h)	Conv. of **1** (%)[b]	2	Yield of **2** (%)c
1	1	H	H	**1f**	200	15	80	**2f**	42
2	1	H	H	**1f**	100	15	100	**2f**	74
3	1	Me	H	**1g**	100	24	100	**2g**	66
4	1	H	Me	**1h**	100	24	100	**2h**	68

[a]All reactions were carried out in DMA(substrate concentration = 0.5 mmol of 1/mL of DMA)at 100 °Cunder 20 atm of a 4:1 mixture of CO-air in the presence of PdI_2 in conjunction with 10 equiv of KI. [b]Determined by GLC. [c]isolated yield based on starting **1a**

On the basis of what is already known on PdI_2-catalyzed oxidative carbonylation reactions, formation of **2a-h** may be interpreted as occurring as shown in Scheme 3

(anionic iodide ligands are omitted for clarity). Thus, formation of the alkoxycarbonylpalladium species I takes place through the reaction between the alcoholic function of the substrate, CO, and PdI_2, with elimination of HI. Complex **I** may then undergo intramolecular nucleophilic displacement by the second hydroxyl group, with formation of the cyclic carbonate and elimination of Pd(0) and HI. Alternatively, intermediate **I** may convert into palladacycle derivative **II** with elimination of HI. Reductive elimination eventually leads to the final product and Pd(0). In any case, Pd(0) is then reoxidized to PdI_2 according to a mechanism[12] involving initial oxidation of HI by O_2 to give I_2 followed by oxidative addition of the latter to Pd(0).



Scheme 3

4.3 Conclusions

In conclusion, we have developed the first general method for the catalytic direct oxidative carbonylation of both 1,2- and 1,3- diols, to give the corresponding cyclic carbonates in good to excellent yields (65–94%) and high catalytic efficiencies (up to

ca. 190 mol of product per mol of palladium). The present phosgene-free, atom-economical approach for the preparation of cyclic carbonates thus represents a valuable alternative to the currently known methods for their production.

4.4 Experimental section

4.4.1 General procedure for the synthesis of cyclic carbonates (2a-h, Table 1, 2)

The 1,2- or 1,3 diol (4 mmol) were transferred in a stainless steel 125 mL autoclave in the presence of PdI_2 (0.5 mol % for substrates **1a-e**, 1 mol % for substrates **1f-h**) in conjunction with 10 equiv. of KI and *N*,*N* – dimethylacetamide (DMA), as solvent (8 mL, [sub]= 0.5mmol per mL of DMA). The autoclave was pressurized under stirring with 20 bar of a gaseous mixture of 16 bar of CO and 4 bar of air at room temperature. After being stirred at 100°C for 15h (**1a-d, f**), or 24h (**1e,g,h**), the autoclave was cooled, degassed, and opened. The products were recovered using 15 ml of methanol; the solvent was evaporated at low pressure pump. The products were purified by column chromatography on silica gel using hexane-acetone from 95:5 to 7:3. **2a** (Yellow oil; 288.6 mg, 82%, Table 2, Entry 1), **2b** (Yellow oil; Yield: 301.6 mg, 65%, Table 2, Entry 2), **2c** (Yellow oil; 436.1 mg, 94%, Table 2, Entry 3), **2d** (White solid, mp 52.2 – 54.3; 616.6 mg, 94%, Table 2, Entry 4), **2e** (White solid, mp 118 – 120; 672 mg, 70%, Table 2, Entry 5), **2f** (Yellow solid, mp 47 – 48 °C; 302 mg, 74%, Table 3, Entry 2), **2g** (Yellow oil; 306.2 mg, 66%, Table 3, Entry 3), **2h** (Yellow oil; 315.5 mg, 68%, Table 3, Entry 4).

4.4.2 Characterization data

1,3-Dioxolan-2-one (2a): $C_3H_4O_3$ (PM 88). Yellow oil; Yield: 288.6 mg, 82%, Table 2, Entry 1. IR (film): ν = 2929 (w), 1962 (w), 1800 (s), 1773 (s), 1480 (m), 1392 (m), 1164 (s), 1072 (s) 937 (m), 894 (w), 774 (m), 716 (m) cm-1; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 4.5 (s, 4H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 60.3. GC-MS: *m/z* = 88(M^+, 88), 87 (99), 72 (89), 58 (10), 56 (11), 45 (99), 44 (99), 43 (100), 42 (93), 41 (13).

4,5-Dimethyl-1,3-dioxolan-2-one (2b): $C_5H_8O_3$ (PM 116.05). Yellow oil; Yield: 301.6 mg, 65%, Table 2, Entry 2. IR (film): ν = 2994 (m), 2942 (w), 1801 (s), 1561 (w), 1389 (m), 1369 (s), 1321 (w), 1212 (s), 1155 (m), 1077 (s), 889 (w), 775 (s) cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 – 1.37 (m, 6H, 2 CH_3) , 4.84 – 4.89 (m, 2H, 2 –CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.6, 76.1, 14.3. GC-MS: *m/z* = 116(M^+, 2), 57 (10), 45 (21), 44 (23), 43 (100), 41 (10).

4-Ethyl-1,3-dioxolan-2-one (2c): $C_5H_8O_3$ (PM 116.05). Yellow oil; Yield: 436.1 mg, 94%, Table 2, Entry 3. IR (film): ν = 2973 (m), 2939 (w), 2883 (w), 2352 (w), 1794 (s), 1483 (m), 1463 (m), 1376 (s), 1301 (w), 1176 (s), 1126 (m), 1110 (m), 1060 (s), 1012 (w), 982 (w), 775 (s) cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (t, *J*= 7.02, 3H, -CH_3), 1.74 – 1.87 (m, 2H, -C<u>H</u>$_2$$CH_3$) , 4.08 – 4.13 (m, 1H, –C<u>H</u>H), 4.53 – 4.58 (m, 1H, -CH), 4.64 – 4.72 (m, 1H, -CH<u>H</u>) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.3, 78.2, 69.1, 26.9, 8.5. GC-MS: *m/z* = 116(M^+, 9), 87 (17), 86 (100), 85 (60), 71 (18), 58 (10), 57 (51), 55(12), 44 (71), 43 (99), 42 (99), 41 (91), 40 (14).

4-Phenyl-1,3-dioxolan-2-one (2d) : $C_9H_8O_3$ (PM 164.05). White solid, mp 52.2 – 54.3; Yield: 616.6 mg, 94%, Table 2, Entry 4. IR (KBr): ν = 3447 (m), 3067 (w), 3037 (w), 2980 (w), 2925 (w), 2343 (w), 1960 (w), 1814 (s), 1778 (s), 1458 (m), 1392 (m), 1358 (s), 1326 (m), 1210 (m), 1185 (s), 1169 (s), 1066 (s), 1055 (s), 961 (m), 906 (m), 777 (s), 759 (s), 720 (s), 699 (s) cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 4.29 – 4.34 (m, 1H, -C<u>H</u>H), 4.76 – 4.81 (m, 1H, -CH<u>H</u>), 5.67 (t, *J*= 7.8, 1H, -C<u>H</u>) , 7.33 – 7.38 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.9, 135.9, 129.6, 129.2, 125.9, 78.0, 71.2. GC-MS: *m/z* = 164(M^+, 59), 119 (12), 105 (34), 92 (14), 91 (79), 90 (100), 89 (40), 78 (96), 77 (32), 65 (29), 63 (20), 52 (10), 51(41), 50 (18).

4,5-Diphenyl-1,3-dioxolan-2-one (2e) : $C_{15}H_{12}O_3$ (PM 240.1). White solid, mp 118 – 120; Yield: 672 mg, 70%, Table 2, Entry 5. IR (KBr): ν = 3031 (w), 2923 (w), 1966 (w), 1834 (w), 1786 (s), 1768 (m), 1452 (m), 1384 (w), 1337 (m), 1221(w), 1172 (s), 1046 (s), 778 (m), 747 (m), 724 (m), 699 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (s, 2H, 2 -CH), 6.92 – 7.24 (m, 10H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.8, 133.2, 128.8, 128.2, 126.2, 82.1. GC-MS: *m/z* = 240 (M^+, 28), 196 (12), 195 (18), 178 (13), 167 (44), 165 (13), 152 (10), 118 (10), 105 (29), 91 (13), 90 (100), 89 (58), 77 (33), 63 (15), 51(21).

1,3-dioxan-2-one (2f) : $C_4H_6O_3$ (PM 102). Yellow solid, mp 47 – 48 °C; Yield: 302 mg, 74%, Table 3, Entry 2. IR (KBr): ν = 3460 (m), 2923 (w), 1898 (w), 1739 (s), 1634 (w), 1478 (m), 1417 (s), 1250(s), 1179 (s), 1146 (s), 1048 (s), 768 (m), 747 (m), 676 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (t, *J*= 6.1, 2H, -CH_2), 4.46 (t, *J*= 6.1, 4H, 2 -CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 68.1, 21.8. GC-MS: *m/z* = 102 (M^+, 20), 58 (10), 57 (100), 44 (11), 43 (44).

4-Methyl-1,3-dioxan-2-one (2g) : $C_5H_8O_3$ (PM 116). Yellow oil; Yield: 306.2 mg, 66%, Table 3, Entry 3. IR (KBr): ν = 3471 (w), 2983 (m), 2936 (m), 1898 (w), 1743 (s), 1482 (m), 1408 (s), 1242 (s), 1190 (s), 1114 (s), 950 (w), 769 (m), 668 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.44 (d, *J*= 7, 3H, -CH_3), 1.89 – 1.99 (m, 1H, -C<u>H</u>H), 2.10 – 2.16 (m, 1H, -CH<u>H</u>), 4.40 – 4.45 (m, 2H, CH_2), 4.62 – 4.67 (m, 1H, -CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.0, 75.8, 66.9, 28.7, 21.1. GC-MS: *m/z* = 116 (M^+, 2), 45 (10), 44 (24), 43 (100), 42 (78), 41 (32).

5-Methyl-1,3-dioxan-2-one (2h) : $C_5H_8O_3$ (PM 116). Yellow oil; Yield: 315.5 mg, 68%, Table 3, Entry 4. IR (KBr): ν = 3471 (w), 2973 (m), 2916 (m), 1744 (s), 1474 (m), 1409 (s), 1360 (w), 1235 (s), 1190 (s), 1124 (s), 1087 (m), 1033 (w), 896 (w), 796 (m), 759 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (d, *J*= 6.7, 3H, -CH_3), 2.36 – 2.45 (m, 1H, -CH), 4.05 – 4.12 (m, 2H, CH_2), 4.38 – 4.44 (m, 2H, -CH_2); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 148.4, 75.6, 26.4, 11.9. GC-MS: *m/z* = 116 (M^+, 4), 71 (10), 57 (15), 44 (22), 43 (47), 42 (100), 41 (70), 40 (12).

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Chapter 5

Innovative synthesis of linear and cyclic carbonates,carbamates and ureas from variously substituted propargylic alcohols and amines in the presence of supercritical CO_2 and a non-metallic catalyst

5.1 Introduction

In the perspective of developing a "sustainable" or "green" chemistry, an easily accessible and renewable source of carbon is carbon dioxide being non-toxic, abundant and cheap; indeed synthesis of chemicals based on carbon dioxide has gained growing interest. However, the activation and incorporation of carbon dioxide into organic substrates remains a difficult goal to achieve due to the chemical inertia of this molecule. From an environmental point of view research for the identification of suitable molecules that can act as effective agents of fixation of carbon dioxide and convert them into important chemicals is of primary importance.

Carbonates and carbamates are important intermediates in organic synthesis. They find wide application as solvents, as effective protecting groups for alcohols and diols involved in important synthesis of biological compounds, in the preparation of industrial products, polymers, pharmaceuticals and agrochemicals[1]. Their synthesis was classically achieved by processes using phosgene, an highly toxic pollutant.
Ureas are one of the most studied classes of compounds and there is a wide literature about them; they are used as chemical intermediate, pharmaceutical, agrochemical and in the chemical industry. The use of $scCO_2$ for the synthesis of this kind of molecules has found scant application in the literature so far.[2,3]

Propargylic alcohols and amines can be advantageously used as starting materials for the synthesis of functionalized carbonates, carbamates and cyclic oxalkylcarbonates and -carbamates in combination with CO_2. This strategy is based on the "in situ" formation and subsequent cyclization of species propargylcarbonate $HC{\equiv}CC(R_2)OCO_2^-$ or propargylcarbamate $HC{\equiv}CC(R_2)N(R^1)CO_2^-$ to the corresponding cyclic α-alkylidencarbonate or α-alkylidencarbamate in the presence of different catalysts. With propargyl alcohols, methods based on the use of transition metals (such as Ru[4], Co[5], Pd[6], Cu[7], Fe[8]), phosphines [9], inorganic bases (K_2CO_3) in the presence of crown ethers[10], or organic bases such as DBU coupled to Ag salts[11] have been developed. Several

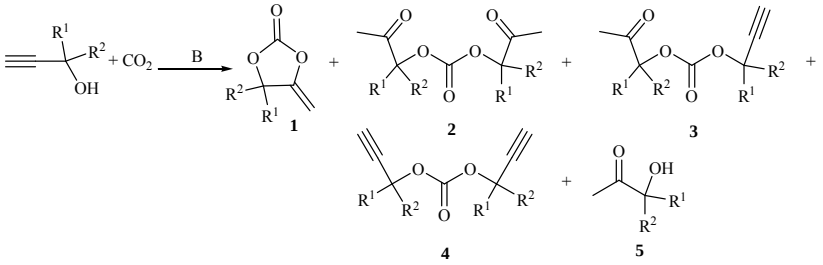
reaction media have been used, such as conventional polar aprotic solvents, $scCO_2$, and ionic liquids in the presence of copper metal salts[12]. With propargyl amines, catalysts based on Ru[4], Pd[6] and guanidine bases [13,14], alkylphosphine [15], in conventional solvents as well as $scCO_2$, have also been used with success. In $scCO_2$ the cyclization to oxazolidinones may occur spontaneously in the absence of catalysts [16].

During my PhD, I worked on the development of a phosgene-free and metal-free one-step synthesis of linear and cyclic carbonates or carbamates through direct incorporation of carbon dioxide into propargyl alcohols or amines. This work was carried out at the Department of Industrial and Organic Chemistry of the University of Parma, in the framework of a collaboration between the research group of Professor Mirco Costa and my supervisors. The catalytic system used is based on an organic base, in particular a guanidine, whose good activity had already been shown in the formation of unsatured oxazolidinones starting from secondary propargyl amines.[14] These previous experiments showed the importance of the strength of the base [14] (bases with ^{CH_3CN} $pK_A < 24$ showed in fact low catalytic activity) and steric effects on the progress of these reactions carrying them out in acetonitrile or in aqueous medium.

5.2 Results and discussions

Our objective has been the study of reactions of carboxylation of propargyl alcohols and amines, carried out in $scCO_2$ in the absence of solvents and in the presence of different catalytic systems to evaluate yields and selectivity of products.

The first studies were carried out on the carboxylation of propargyl alcohols in $scCO_2$. The reaction of different propargyl alcohols, carried out in the presence of different bases, led to the formation of a mixture of products (Scheme 1):



Scheme 1

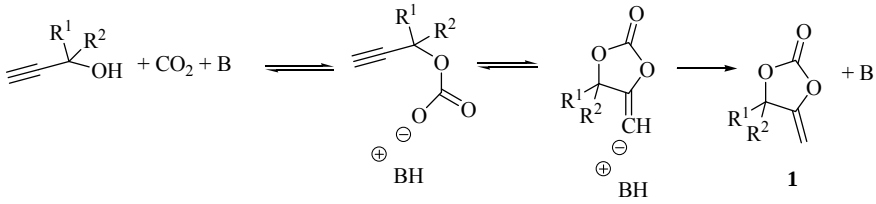
Reaction conditions were as follows: propargyl alcohol (5 mmol) were charged in a stainless steel 125 mL autoclave using a catalytic amount (10 mol%) of catalyst, in presence of CO_2 (44 g of liquid CO_2 at room temperature) in the absence of air at 100 ° C for 24 h under magnetic stirring. The results obtained are shown in Table 1:

TABLE 1. **Catalytic reactions of propargyl alcohols in $scCO_2$ in the presence of different catalytic systems**[a]

Entry	R^1	R^2	Catalyst	Conversion [b] %	Yield[c] % 1 2 3 5	Products
1	Me	Me	MTBD[f]	99	25 60 5	**1a, 2a, 5a**
2	Me	Me	TBD – pol[g]	93	45 30	**1a, 2a**
3	Me	Me	TBD[h]	-	-	**1a**
4	Me	Me	NBu_4BF_4+ KF[i]	21	15	**1a**
5	Me	Me	NBu_4F	14	10	**1a**
6	Me	$-CH_2=CH_2$	MTBD	40	20	**1b**
7	$-(CH_2)_5-$		MTBD	97	35 38 6	**1c, 2c, 5c**
8	$-(CH_2)_5-$		TBD – pol	93	36 36	**1c, 2c**
9	$-(CH_2)_5-$		TBD	-	-	**1c**
10	$-(CH_2)_5-$		MTBD+CH_3CN	97	41 30	**1c, 2c**
11	$-(CH_2)_5-$		DBU[f]	60	16 26	**1c, 2c**
12	$-(CH_2)_5-$		NBU_4F	26	21	**1c**
13	$-(CH_2)_5-$		-	14	9	**1c**
14	Me	Ph	MTBD	-	-	**1d**
15	Me	H	MTBD	85	45[d] 33[e]	**1e, 3e**
16	H	H	MTBD	-	-	**1f**

[a]Reaction conditions: alcohol 5 mmol, base 0.5 mmol, conc. Base 0.033 M, temp. 100 ° C, liquid CO_2 44 g at room temperature, time 24h. [b]referred to starting alcohol. [c]Determined by GC and based on the conversion of starting alcohol to the indicated product.[d] Mixture of two isomers in molar ratio 2.7:1. [e]Mixture of diastereoisomers in 1.2:1 molar ratio. [f]MTBD= 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene ;[g] TBD-pol = 1,5,7- triazabicyclo[4.4.0]dec-5-ene supported on polystyrene;[h] TBD=1,5,7-triazabicyclo [4.4.0]dec-5-ene;[i] NBu_4BF_4= tetrabutylammoniumtetrafluoroborate

The mechanism by which carbon dioxide is introduced into propargylic alcohols to form the cyclic carbonate **1**can be considered similar to that already reported in literature[14] and is shown in Scheme **2**:



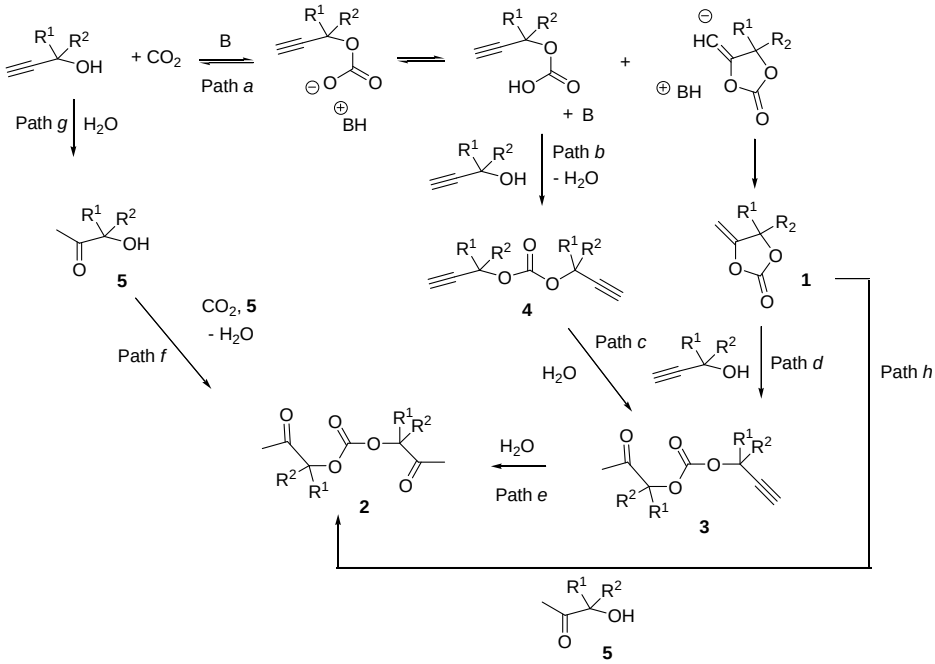
Scheme 2

The key step of the reaction is the equilibrium formation of carbonate anion; at this step the strength of the base and the pressure of CO_2 plays a key role in shifting the equilibrium to the right.

In the second step there is the nucleophilic attack of the oxygen atom on the internal carbon of the triple bond. In this ring closure process critical points are the polarizability of the counterions, which allows to the carbonate anion to be relatively free without affecting too much its nucleophilic reactivity towards the triple bond, the steric and structural effects that determine a solvation by one or more hydrogen bonds, and the conformational effects associated with substituents on the methylene group.

In the last step, the protonated base give back the proton to the carbanion which is formed by the previous intramolecular reaction.

In the same reaction compound **5** derives from hydration of the triple bond of the substrate (Scheme 3, path *g*). Product **4** is the acyclic carbonate deriving from carboxylation of the substrates followed by the attack of another molecule of propargyl alcohol (Scheme 3, path *b*), while products **2** and **3** may derive from hydration of the triple bond(s) of **4** (Scheme 3, path *c* and *e*) or by attack of the propargyl alcohol on product **1** (Scheme 3, path *d* and *e*). The reaction between **1** and **5** (Scheme 3, path *h*), may also directly lead to product **2** :



Scheme 3

Reactions of propargyl alcohols (Table 1) carried out in $scCO_2$ in the presence of MTBD, TBD and DBU led mainly to the formation of mixtures of products **1** and **2**, without showing a relevant selectivity toward the condensation product **2** with respect to cyclic carbonate **1** (Entries 1, 2, 7, 8, 10,11 and 15). The condensation product **2** is probably formed by a nucleophilic attack of the oxygen of a second molecule of alcohol to the carbonyl carbon of the cyclic carbonate **1** (Scheme 3, path *e*), promoted by the presence of strong bases such as guanidine and DBU. Other catalytic systems such NBu_4BF_4 + KF and NBu_4F, less basic, provided low conversions and yields of **1** (Entries 4, 5 and 12); in the absence of catalyst 1-ethynilcyclohexanol provided product **1** in yield of 9% (Entry 13), 3-methylpent-1-en-4-yn-3-ol in the presence of MTBD led to **1** in modest yield (20%, Entry 6), 2-phenylbut-3-yn-2-ol and prop-2-yn-1-ol did not give products of CO_2 insertion in the presence of MTBD (Entries 14 and 16), the secondary alcohol but-3-yn-2-ol led to a mixture of two isomers of **1** in molar ratio

2.7:1 and a mixture of diastereoisomers of product **3** in molar ratio 1.2:1 (Entry 15). It is interesting to note the absence of catalytic activity of tetraalkylated guanidine **a** (such as TBD) that is unable to promote the formation of cyclic carbonate using the propargyl alcohols under the same conditions (Entries 3 and 9). Furthermore, other authors have highlighted this behaviour also in different conditions.[17] In a previous publication[10] it was noted that in aqueous phase TBD favours the formation of the hydrophobic site through the coordination of carbamic anion with two hydrogen bonds. This means that the anion is less active because this coordination reduces the nucleophilicity of the anion by a strong stabilization effect by the protonated guanidine. On the other hand the pentaalkylated guanidine (**b**) coordinates the carbamate by a single hydrogen bond allowing a greater nucleophilic reactivity of O^- leaving at the latter the possibility to give the intramolecular nucleophilic attack on the triple bond (Figure 1):

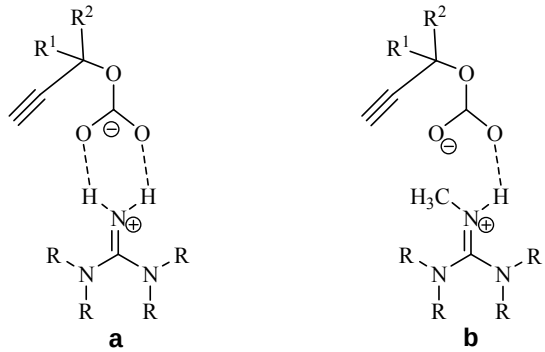


Figure 1

The low selectivity toward the cyclic carbonate **1** using $scCO_2$ led us to further investigate the reaction in order to improve yields and selectivities. The next choice of using a homogenous mixture of acetonitrile and gaseous CO_2 in the presence of a catalytic amount of 7-methyl-1,5,7-triazabicyclo[4.4.0] dec-5-ene (MTBD) (molar ratio alcohol / base = 10 / 1) was made on the basis of the good results previously obtained in the synthesis of oxazolidinones in homogeneous phase.[14] The pentaalkylated guanidine MTBD favours the ring closure forming the carbonate by nucleophilic attack on the

triple bond while the attack by a second molecule of alcohol to the carbonyl carbon of the cyclic carbonate **1** does not occur in CH_3CN (Scheme 3, Path *d* and *e*).

Thus, various propargylic alcohols (5 mmol) were made to react in a stainless steel autoclave at 100 ° C with CO_2 (40 bar at room temperature) for 24 h under magnetic stirring in the presence of MTBD (0.5 mmol, concentration of base 0.03 M) in CH_3CN. The results obtained are shown in Table 2.

TABLE 2. Catalytic reactions of propargyl alcohols with gaseous CO_2 in CH_3CN in the presence of MTBD[a]

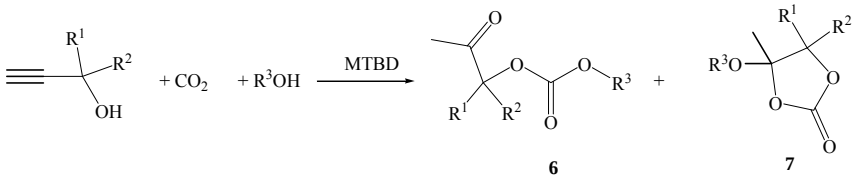
Entry	R^1	R^2	Conversion[b] %	Yield[c] % **1**	**2**	**3**	**4**	**5**	Products
17	Me	Me	99	82	6	4		2	**1a, 2a, 3a, 5a**
18	Me	-CH=CH_2	76	55				8	**1b, 5b**
19	-$(CH_2)_5$-		75	61				5	**1c, 5c**
20	Me	Ph	97	71				10	**1d, 5d**
21	Me	H	85	15[d]		66[e]			**1e, 3e**
22	H	H	18				12		**4f**
23	Me	Et	78	64				5	**1g, 5g**
24	Ph	Ph	28	14					**1h**

[a]Reaction conditions: alcohol 5 mmol, base 0.5 mmol, conc. Base 0.033 M, temp. 100 ° C, CO_2 44 bar at room temperature,time 24h. [b]Referred to starting alcohol. [c]Determined by GC and based on the conversion of starting alcohol to the indicated product. [d]Mixture of two isomers in molar ratio 2.7:1. [e]Mixture of diastereoisomers in 1.2:1 molar ratio.

The results generally show good yields in cyclic carbonates **1** whose formation is strongly influenced by the nature of the groups R^1 and R^2, the best yields and selectivity being obtained in the case of tertiary propargyl alcohols. In fact, the reaction works well using substrates substituted with two alkyl groups (Entries 17,19,23) and with an alkyl and phenyl or vinyl groups (Entries 18,20); the only exception was the substrate bearing two phenyl substitutents, whose reaction turned out to be very slow, even if the selectivity was quite good (Entry 24). On the other hand the reaction of an α-monosubstituted alcohol led mainly to product **3**, while the corresponding cyclic carbonate **1** was obtained with a yield of 15% (Entry 21). Finally, using an α-unsubstituted substrate, the reaction was very slow and led to the formation of product **4** (Entry 22).

The formation of products **2** (particularly in the case of reactions carried out in $scCO_2$, see Table 1), led us to investigate the reaction of propargyl alcohols with $scCO_2$ in the presence of a second nucleophile such as an alcohol or an amine using MTBD as a catalyst, in order to obtain the direct synthesis of oxoalkylcarbonates (**6**) or carbamates (**8** and **9**, respectively). It is worth noting that the synthesis of β-oxopropyl carbonates was reported by Dixneuf et al.[18,19], in a reaction of preformed α-methylene cyclic carbonates with alcohols in the presence of catalytic amounts of 2-hydroxypyridine and KCN or DBN, with good yields under mild conditions .

Therefore we carried out the reaction using a tertiary propargyl alcohols in $scCO_2$ in the presence of an equimolar amount of saturated primary, secondary or tertiary aliphatic alcohol, allyl alcohol, propargyl alcohol, benzyl alcohol and phenol (Scheme 4).



Scheme 4

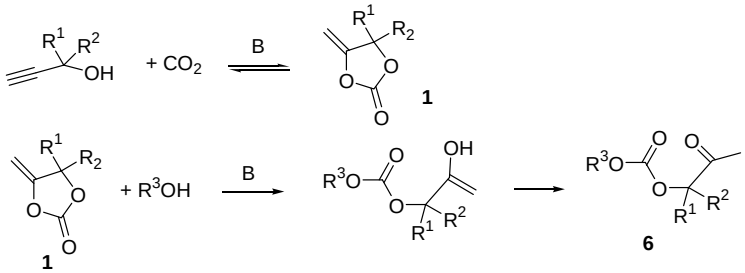
The results obtained using 2-methyl-3-butyn-2-ol, ethynylcyclohexanol and 2-phenyl-3-butyn-2-ol as starting materials are shown in Table 3. As can be seen, good yields of product **6** were achieved in reactions conducted using MTBD, TBDpol and DBU and an aliphatic primary alcohol (such as methanol and *n*-buthanol) or allyl alcohol as the external nucleophile (Entries 1-3, 5, 10, 11, 14, and 17). Yields in product **6** decreased using NBu_4F as base (Entries 4, 12) or a secondary alcohol such as butan-2-ol (Entry 6). Interestingly, some particular combinations between the substrate and the external nucleophile led to a reaction more selective toward the formation of product **7** (Entries 7-9, 15, 16, 19). We refrain, however, to propose a rationalization of this unexpected result, which would require further investigation.

TABLE 3. Catalytic reactions of propargyl alcohols with CO_2 in sc CO_2 in the presence of a second alcohol [a]

Entry	R^1	R^2	External Alcohol	Catalyst	Conversion[b] %	Yield[c] % 6	Yield[c] % 7	Products
1	Me	Me	MeOH	MTBD	90	73		**6a**
2	Me	Me	BuOH	MTBD	99	81		**6b**
3	Me	Me	BuOH	TBD –pol	99	84[d]		**6b**
4	Me	Me	BuOH	NBU_4F	70	51		**6b**
5	Me	Me	BuOH	DBU	95	81		**6b**
6	Me	Me	Butan-2-ol	MTBD	65	42		**6c**
7	Me	Me	Allyl Alcohol	MTBD	90		81	**7a**
8	Me	Me	Propargyl Alcohol	MTBD	86		68	**7b**
9	Me	Me	PhOH	MTBD	80		63	**7c**
10	-$(CH_2)_5$-		BuOH	MTBD	99	70		**6d**
11	-$(CH_2)_5$-		BuOH	TBD –pol	99	79[e]		**6d**
12	-$(CH_2)_5$-		BuOH	NBU_4F	80	62		**6d**
13	-$(CH_2)_5$-		BuOH	DBU	85	60		**6d**
14	-$(CH_2)_5$-		Allyl Alcohol	MTBD	95	86		**6e**
15	-$(CH_2)_5$-		PhOH	MTBD	70		43	**7d**
16	-$(CH_2)_5$-		PhOH	TBD –pol	60		31	**7d**
17	Me	Ph	BuOH	MTBD	99	87		**6f**
18	Me	Ph	Allyl Alcohol	MTBD	50	22	21	**6g, 7e**
19	Me	Ph	PhOH	MTBD	99		84	**7f**

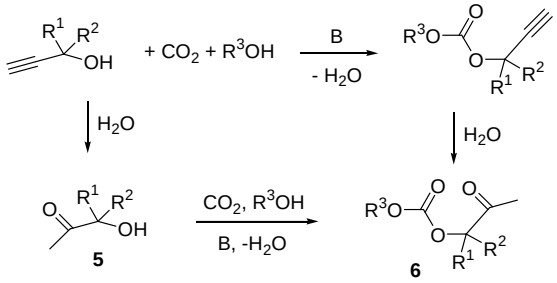
[a]Reaction conditions: alcohol 5 mmol, added alcohol 5 mmol, base 0.5 mmol, conc. Base 0.033 M, temp. 100 ° C, liquid CO_2 44 g at room temperature, time 24h. [b]referred to starting alcohol. [c]Determined by GC and based on the conversion of starting alcohol to the indicated product. [d]3 recycles [e] 2 recycles

The formation of product **6** can be rationalized according to the mechanism shown in Scheme 5. The initially formed cyclic carbonate can undergo nucleophilic attack by the external alcohol with ring opening and tautomerization (Scheme 5):



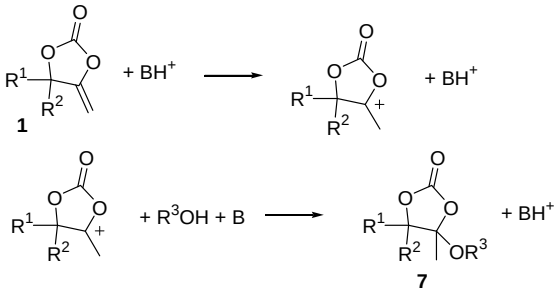
Scheme 5

Alternatively, formation of the mixed acyclic carbonate occurs, followed by water addition, or vice versa (Scheme 6):



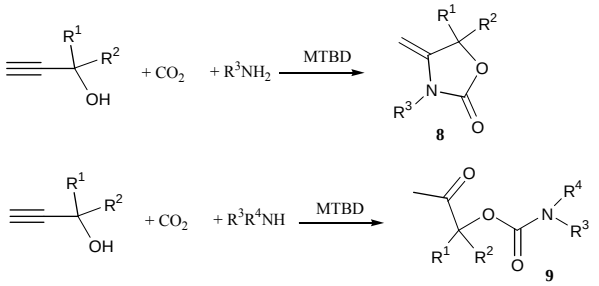
Scheme 6

Product **7** derives from alcohol addition to the vinylethereal bond of **1** (Scheme 7):



Scheme 7

Under the same reaction conditions, we have studied the reactivity of various primary and secondary amines as external nucleophiles in $scCO_2$ in presence of MTBD. Interestingly, primary amines led to α-methylenoxazolidinones **8**, while acyclic carbamate **9** were obtained in the case of secondary amines (Scheme 8).



Scheme 8

The results obtained using different tertiary propargyl alcohols and various amines are reported in Table 4.

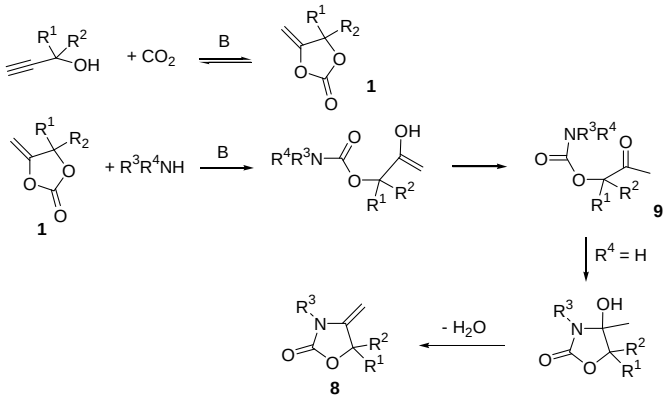
TABLE 4. Catalytic reactions of propargyl alcohols with CO_2 in $scCO_2$ in the presence of a primary or secondary amine [a]

Entry	R^1	R^2	Added Amine	Catalyst	Conversion[b] %	Yield[c] % **8**	**9**	Products
1	Me	Me	$BuNH_2$	MTBD	90	78		**8a**
2	Me	Me	Butan-2-amine	MTBD	95	72		**8b**
3	Me	Me	*t*-$BuNH_2$	MTBD	-	-		**8c**
4	Me	Me	$AllylNH_2$	MTBD	93	72		**8d**
5	Me	Me	$BzNH_2$	MTBD	87	67		**8e**
6	Me	Me	$PhNH_2$	MTBD	50	38		**8f**
7	Me	Me	Pyrrolidine	MTBD	99		79	**9a**
8	Me	Me	Bu_2NH	MTBD	99		79	**9b**
9	Me	Me	N-MeAniline	MTBD	80		53	**9c**
10	$-(CH_2)_5-$		$BuNH_2$	MTBD	90	69		**8g**
11	$-(CH_2)_5-$		$PhNH_2$	MTBD	51	33		**8h**
12	$-(CH_2)_5-$		Pyrrolidine	MTBD	99		81	**9d**
13	$-(CH_2)_5-$		Bu_2NH	MTBD	99		82	**9e**
14	Me	Ph	$BuNH_2$	MTBD	88	72		**8i**
15	Me	Ph	$PhNH_2$	MTBD	40	15		**8j**
16	Me	Ph	Pyrrolidine	MTBD	99		78	**9f**
17	Me	Ph	Bu_2NH	MTBD	99		77	**9g**

[a]Reaction conditions: alcohol 5 mmol, added amine 5 mmol, base 0.5 mmol, conc. Base 0.033 M, temp. 100 ° C, liquid CO_2 44 g at room temperature, time 24h. [b]Referred to starting alcohol. [c]Determined by GC and based on the conversion of starting alcohol to the indicated product

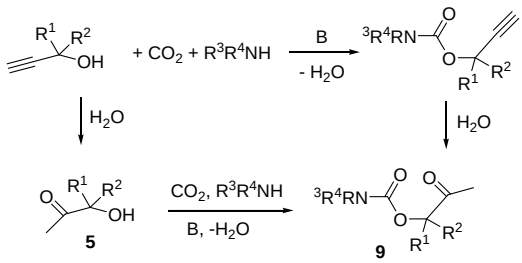
The yields of products **8** and **9** were generally high using primary alkyl, allyl and benzyl primary and alkyl or aromatic secondary amines (Entries 1, 2, 4, 5, 7, 8, 9, 10, 12, 13, 14, 16 and 17). Aromatic primary amines, such as aniline (Entries 6, 11 and 15) led to lower yields while no reaction occurred with *t*-butylamine, probably for steric reasons (Entry 3).

The formation of oxazolidinones and oxalkylcarbamates had previously been explained by Dixneuf et al.[18], for the reaction of the preformed cyclic α-metylencarbonate conducted in the presence of PBu_3 as a catalyst: the cleavage of the carbonyl bond by the external amine gave the oxopropylcarbamate **9** and then **8** through elimination of water (Scheme 9):



Scheme 9

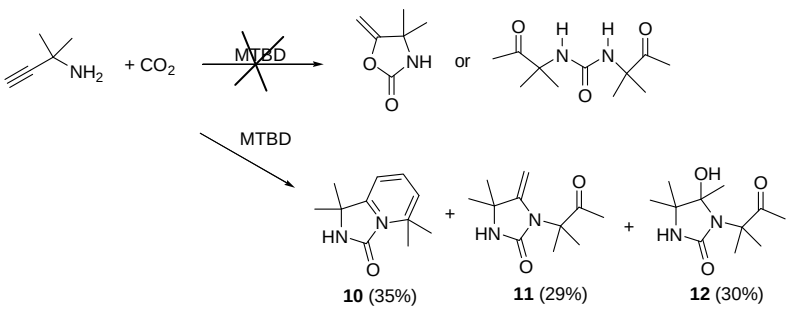
Alternatively, compound **9** can be directly formed by the reaction between propargyl alcohol, CO_2 and the amine (Scheme 10):



Scheme 10

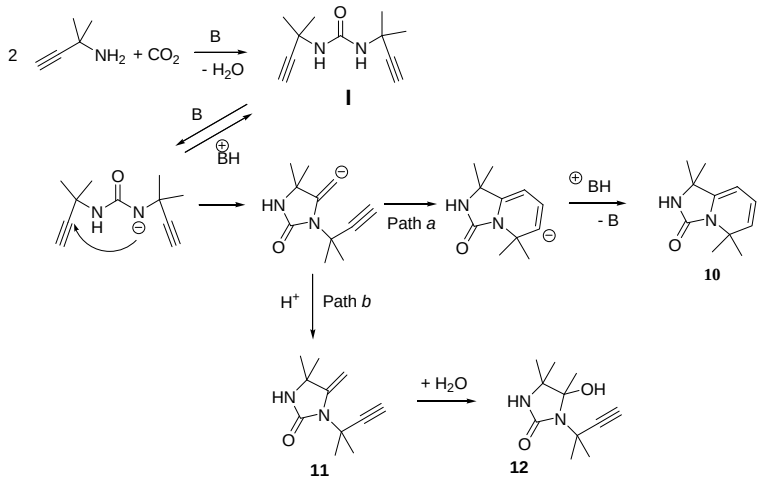
Finally, the reaction of propargylic amines for the synthesis of cyclic and linear ureas, using the same reaction conditions applied in the case of propargylic alcohols ($scCO_2$ and MTBD), led to some surprisingly and really interesting results.

The first substrate studied was 2-methylbut-3-yn-2-amine. This propargyl amine was made to react in $scCO_2$ in the presence of MTBD as base and catalyst. This reaction led to products **10**, **11** and **12** (Scheme 11) in 35% , 29% and 30% of yields, respectively, without any formation of the expected oxazolidinone derivative, possibly deriving from carboxylation of the amine group followed by cyclization, or the linear urea, possibly deriving from the attack by a second molecule of propargyl amine on the oxazolidinone, in analogy with the behaviour of propargyl alcohol (Scheme 11).



Scheme 11

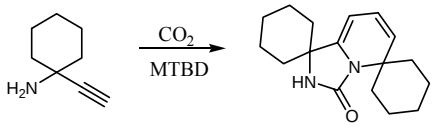
A possible rationalization of the formation of ureas **10, 11** and 12 is given in Scheme 12:



Scheme 12

The reaction between propargyl amine and CO_2 leads to the formation of the urea intermediate **I** from which all products **10**, **11** and **12** can derive. In fact, in presence of a very strong base, one of the NH group can be deprotonated so it is possible to have an intramolecular *5-exo-dig* nucleophilic attack on the internal carbon atom of the triple bond that leads to a cyclic anion. Protonation of the latter affords product **11**, from which **12** can be obtained by water addition to the vinylethereal double bond (Scheme 12, Path *b*). Alternatively, a nucleophilic attack of the anion to the external carbon atom of the second triple bond leads to the dihydrotetramethylimidazopyridinone derivative **10** (Scheme 12, Path *a*).

A similar product was obtained when the reaction was carried out using a different propargyl amine, such as 1-ethynylcyclohexanamine (Scheme 13):

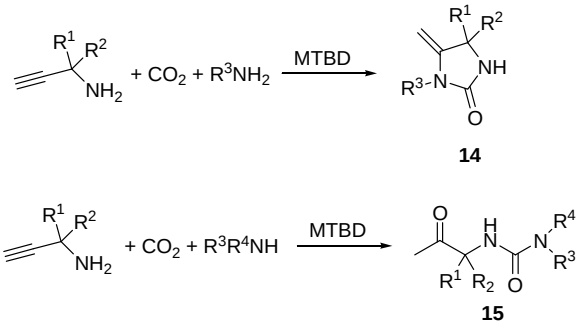


13 42%

Scheme 13

Formation of **13** occurs through the same mechanism shown in Scheme 12, in which intermediate **I** selectively follows path *a*.

We have also tried to synthesize cyclic and linear ureas from the reaction between propargyl amines and another nucleophilic primary or secondary amine (Scheme 14).



Scheme 14

The results obtained and shown in Table 5 but further investigation is still in progress to generalize the process.

TABLE 5. Catalytic reactions of propargyl amines $scCO_2$ in the presence of a primary or secondary amine [a]

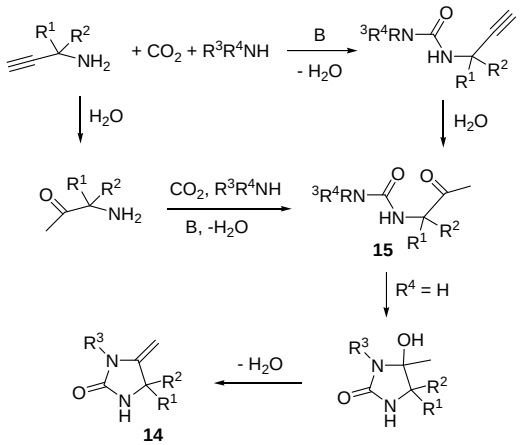
Entry	R^1	R^2	Added Amine	Catalyst	Conversion[b] %	Yield[c] % **14**	**15**	Products
1	Me	Me	$BuNH_2$	MTBD	99	40[c]		**14a**
2	Me	Me	$PropargylNH_2$	MTBD	99	25[c]		**14b**
3	Me	Me	Pyrrolidine	MTBD	99		-	**15a**
4	Me	Me	Aniline	MTBD	99	23[c]		**14c**
5	$-(CH_2)_5-$		$BuNH_2$	MTBD	99	69[c]		**14d**
6	$-(CH_2)_5-$		$PropargylNH_2$	MTBD	99	-		**14e**
7	$-(CH_2)_5-$		Pyrrolidine	MTBD	99		58	**15b**

[a]Reaction conditions: propargyl amine 5 mmol, added amine 5 mmol, base 0.5 mmol, conc. Base 0.033 M, temp. 80 ° C, liquid CO_2 44 g at room temperature, time 24h. [b]Referred to starting alcohol. [c]Propargyl amine not leading to the formation of product 10 or 11 react with CO_2 to give product **10**, **11** and **12**

As expected, the reactions between a propargyl amine and a primary amine lead to the formation of cyclic ureas **14**, while in the case of secondary amines the products are linear ureas **15**.

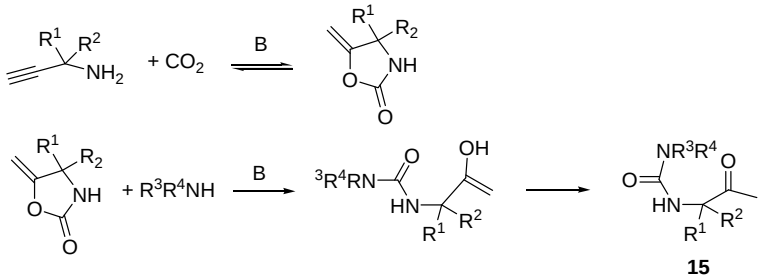
The yields, especially in the case of 2-methylbut-3-yn-2-amine (Entries 1-4), are affected by the high reactivity of the propargyl amines to react with themselves not allowing the nucleophilic attack by the external alkyl, propargyl or aromatic amine.

The suggested reaction mechanism for the formation of compounds **14** and **15** (Scheme 15) is similar to that shown in Scheme 10:



Scheme 15

An alternative mechanism, involving the initial formation of the α-methyleneoxazolidinone (similar to that shown in Scheme 9, see Scheme 16), appears to be less likely, since the formation of α-methyleneoxazolidinone derivatives was not observed with propargyl amines in the absence of external amines (see Scheme 11).



Scheme 16

5.3 Conclusions

In conclusion, a new synthetic way for the preparation of cyclic and linear carbonates, carbamates and ureas has been found, starting from simple and commercially available substrates.

This new methodology represents an important improvement for the synthesis of these very important classes of molecules from an environmental and chemical point of view. The advantages are due to the use of green and non conventional solvents such as $scCO_2$, to the absence of metal-based catalysts, that are replaced by an organic base, and last but not least, to the possibility to obtain a direct one-pot synthesis of these compounds previously synthesized in two steps. This also means less purification processes and waste and minor loss of atoms, a very important feature in designing an atom economical chemical process.

5.4 Experimental section

5.4.1 General procedure for the synthesis of carbonates ((1-5)a-f, Table 1) and ureas (10-13, Scheme 11,12) in $scCO_2$

The propargyl alcohols or amine (5 mmol) were transferred in a stainless steel 125 mL autoclave with a catalytic amount (10 mol%) of catalyst. The autoclave was sealed and purged at room temperature several times with CO_2 under stirring (10 bar). Then was pressurizzed with 44 g of liquid CO_2 at room temperature weighting it before and after the pressurization. After being stirred at 100°C for 24h the autoclave was cooled, degassed, and opened. The products were recovered using 15 mL of methanol and then were purified by column chromatography on silica gel using hexane-acetone from 9:1 to 7:3. Cyclic carbonates and ureas were eluted first in all cases: **1a** (white solid, mp 27.5-28.3 °C, 160 mg, 25% Table1, Entry 1); **2a** (yellow oil, 690 mg, 60% Table 1, Entry 1); **5a** (colorless oil, 25.5 mg, 5% Table 1, Entry 1); **1b** (colorless liquid, 140 mg, 20% Table 1, Entry 6); **1c** (colorless liquid, 294.2 mg, 35% Table 1, Entry 7); **2c** (white solid, mp 100.1-101.3 °C, 589.4 mg, 38% Table 1, Entry 7); **5c** (colorless oil, 42.6 mg,

6% Table 1, Entry 7); **1e (**colorless liquid, 256.7 mg, 45% Table 1, Entry 15); **3e** (colorless oil, 303.7 mg, 33% Table 1, Entry 15), **10** (White solid, mp 132,4 – 133,5; 336.1 mg, 35%, Scheme 11), **11** (White solid, mp 116.1 – 118.9; 305 mg, 29%, Scheme 11), **12** (Colorless oil; 342.2 mg, 30%, Scheme 11), **13** (White solid, mp 139,4 – 140.2; 571.6 mg, 42%, Scheme 12).

5.4.2 General procedure for the synthesis of carbonates in gaseous CO_2 and CH_3CN ((1-5)a-h, Table 2)

The propargyl alcohols (5 mmol) were transferred in a stainless steel 125 mL autoclave with a catalytic amount (10 mol%) of catalyst and 15 mL of CH_3CN (concentration of base 0.03 M). The autoclave was sealed and purged at room temperature several times with CO_2 under stirring (10 bar). Then was pressurizzed with 40 bar of gaseous CO_2 at room temperature. After being stirred at 100°C for 24h the autoclave was cooled, degassed, and opened. The products were recovered using 15 ml of methanol and then were purified by column chromatography on silica gel using hexane-acetone from 9:1 to 7:3. Cyclic carbonates were eluted first in all cases: for carbonates **1a, 2a, 5a, 1b, 1c, 2c, 5c,1e, 3e** see chapter 5.4.1. **3a** (Colourless oil, 42.4 mg, 4% Table 2, Entry 1); **1d** (white solid, mp 29.7 – 30.9 °C, 674.8 mg, 71% Table 2, Entry 20), **4f** (yellow oil, 82.9 mg, 12% Table 2, Entry 22), **1g** (colorless liquid, 455 mg, 64% Table 2, Entry 23), **1h** (colorless oil, 106.5 mg, 14% Table 2, Entry 24)

5.4.3 General procedure for the synthesis of carbonates, carbamates and ureas in $scCO_2$ in presence of an external nucleophile (6-9 14-15, Table 3, 4, 5)

The propargyl alcohols or amine (5 mmol) were transferred in a stainless steel 125 mL autoclave with a catalytic amount (10 mol%) of catalyst and an alcohol or an amine (5 mmol), acting as external nucleophile. The autoclave was sealed and purged at room temperature several times with CO_2 under stirring (10 bar). Then was pressurizzed with 44 g of liquid CO_2 at room temperature weighting it before and after the pressurization.

After being stirred at 100°C for 24h the autoclave was cooled, degassed, and opened. The products were recovered using 15 mL of methanol and then were purified by column chromatography on silica gel using hexane-acetone from 9:1 to 7:3. Cyclic carbonates were eluted first in all cases: **6a** (Colorless liquid, 584 mg, 73%, Table 3, Entry 1),**6b** (Colorless liquid, 818.1 mg, 81%, Table 3, Entry 2),**6c** (Yellow liquid, 424.2 mg, 42%, Table 3, Entry 6), **6d** (Colorless liquid, 847 mg, 70%, Table 3, Entry 10), **6e** (Colorless liquid 971.8 mg, 86%, Table 3, Entry 14), **6f** (Yellow solid, mp 50.4-51.3, 1148.4 mg, 87%, Table 3, Entry 17),**6g** (Yellow Oil, 272.8 mg, 22%, Table 3, Entry 18)**, 7a** (Colorless liquid, 753.3 mg, 81%, Table 3, Entry 7), **7b** (Yellow liquid, 625.6 mg, 68%, Table 3, Entry 8), **7c** (Yellow liquid, 699.3 mg, 63%, Table 3, Entry 9), **7d** (White solid, mp 74.8-75.5, 563.3 mg, 43%, Table 3, Entry 15), **7e** (Yellow liquid, 260.4 mg, 21%, Table 3, Entry 18), **7f** (Yellow liquid, 1192.8 mg, 84%, Table 3, Entry 19), **8a (**Colorless liquid, 714.2 mg, 78%, Table 4, Entry 1), **8b** (Yellow oil, 659.3 mg, 72%, Table 4, Entry 2), **8d** (Colorless oil, 601.5 mg, 72%, Table 4, Entry 4), **8e** (Yellow liquid; 727.3 mg, 67%, Table 4, Entry 5), **8f** (Yellow solid, mp 119.2 – 120.1; 437.2 mg, 38%, Table 4, Entry 6), **8g (**White solid, mp 89.7 – 90.5; 770 mg, 69%, Table 4, Entry 10), **8h** (solid, mp 160.7 – 161.6; 386.3 mg, 69%, Table 4, Entry 11), **8i (**Colorless liquid; 882.5 mg, 72%, Table 4, Entry 14), **8j (**Yellow liquid; 198.8 mg, 15%, Table 4, Entry 15), **9a (**Colorless liquid; 786.5 mg, 79%, Table 4, Entry 7), **9b** (Yellow liquid; 1071.3 mg, 79%, Table 4, Entry 8), **9d** (White solid, mp 62.1 – 63.0; 968.5 mg, 81%, Table 4, Entry 12), **9e** (Yellow oil; 1217.7 mg, 82%, Table 4, Entry 13), **9f** (White solid, mp 123.9 – 124.7; 1018.4 mg, 78%, Table 4, Entry 16), **9g** (Yellow oil; 1228.9 mg, 77%, Table 4, Entry 17), **14a** (Colorless oil; 364.2 mg, 40%, Table 5, Entry 1), **14b** Colorless oil; Yield: 205.1 mg, 25%, Table 5, Entry 2), **14d** (Yellow oil; Yield: 766.5 mg, 69%, Table 5, Entry 5), **15b** (White solid, mp 73.2 – 74.0; Yield: 690.7 mg, 58%, Table 5, Entry 7)

5.4.4 Characterization data of products

4,4-Dimethyl-5-methylene-1,3-dioxolan-2-one (1a). $C_6H_8O_3$ PM (128,05). White solid, mp 27.5-28.3 °C. Yield: 160 mg, 25% (Table 1, Entry 1). IR (KBr): ν = 2988

(m), 2939 (w), 1834 (s), 1689 (s), 1374 (m), 1316 (m), 1275 (s), 1175 (s), 1087 (s), 1036 (s), 856 (s), 770 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 6H, 2 CH_3), 4.28 (d, , *J*= 3.9 Hz, 1H =C<u>H</u>H), 4.74 (d, , *J*=3.9, 1H =CH<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1, 149.2, 84.2, 74, 31 ; GC-MS: *m/z* = 128 (M^+, 2), 113 (1), 84 (8), 69 (9), 56 (72), 43 (36), 42 (47), 41 (100)

Di-1,1-dimethyl-2-oxopropyl carbonate (2a) $C_{11}H_{18}O_5$ PM (230,12). Yellow oil. Yield: 690 mg, 60%. Table 1, Entry 1. IR (film): ν = 2987 (m), 1740 (s), 1724 (s), 1674 (m), 1653 (w), 1457 (w), 1369 (w), 1305 (s), 1150 (m), 1112 (s), 920 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 12H, 4 CH_3), 2.18 (s, 6H, 2 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206, 152.6, 85.8, 23.6, 23.2; GC-MS: *m/z* = 230 (M^+, 1), 187 (14), 147 (3), 129 (2), 126 (1), 101 (1), 86 (25), 85 (100), 71 (12), 57 (57), 43 (72)

1,1-Dimethyl-2-oxopropyl-1',1'-dimethylprop-2'-ynil carbonate (3a) $C_{11}H_{16}O_4$ PM (212,1). Colourless oil Yield: 42.4 mg, 4% Table 2, Entry 1. IR (film): ν = 3281 (m), 2156 (w), 1743 (s), 1736 (s), 1252 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (s, 6H, $2CH_3$), 1.57 (s, 6H, $2CH_3$), 2.18 (s, 3H, CH_3), 2.55 (s, 1H, CH acetylenic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210, 155.3, 90.2, 87,5, 73.1, 69.2, 29.2, 25.1 , 21.4. GC-MS: *m/z* = 212 (M^+, 1), 169 (1), 125 (2), 111 (1), 95 (1), 85 (10), 67 (100), 65 (17), 57 (16), 43 (87), 41 (35)

2-Hydroxy-2-methylbutan-3-one (5a) $C_5H_{10}O_2$ PM (102,07). Colourless oil Yield: 25.5 mg, 5% Table 1, Entry 1. IR (film): ν = 3449 (s), 2976 (s), 1816 (w), 1620 (s), 1162 (m), 1104 (m), 971 (m), 818 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 6H, $2CH_3$), 2.35 (s, 3H, CH_3), 4.02 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 91.6, 73.2, 66, 29.5. GC-MS: *m/z* = 102 (M^+, 1), 87 (5), 69 (2), 59 (100), 44(3), 43 (73), 41 (30)

4,4-Dimethyl-5-methylene-1,3-dioxolan-2-one (1b) : $C_7H_8O_3$ PM (140,05). Colorless liquid; Yield: 140 mg, 20% Table 1, Entry 6. IR (film): ν = 3434 (s), 2989 (w), 2935 (w), 1832 (s), 1746 (s), 1727 (m), 1684 (m), 1448 (w), 1373 (m), 1277 (s), 1234 (m),

1181 (w), 1078 (w), 1029 (s), 935 (w), 857 (w), 766 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3), 4.33 (d, *J*= 3.9, 1H, H ethynil), 4.86 (d, *J*= 3.9, 1H, H ethynil), 5.29 – 5.50 (m, 2H, CHC$\underline{H}_2$ Vynil), 5.9 (q, J_1 = 10.8, J_2 = 17.1, 1H, C$\underline{H}$CH$_2$ vynil) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156, 151, 136, 117, 87, 85, 25. GC-MS: *m/z* = 140 (M^+, 2), 122 (2), 114 (2), 107 (3), 97 (25), 79 (73), 77 (40), 71 (21), 63 (8), 53 (18), 43 (100), 41 (11

4-Methylen-1,3-dioxaspiro[4.5]-decan-2-one (1c): $C_9H_{12}O_3$ PM (168,1). Colorless liquid, Yield: 294.2 mg, 35% Table 1, Entry 7. IR (film): ν = 2940 (s), 2864 (m), 1841 (s), 1814 (s), 1685 (s), 1450 (m), 1311 (m), 1271 (m), 1201 (m), 1129 (m), 1060 (s), 1023 (s), 852 (m), 769 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56-1.79 (m, 6H, 3CH$_2$), 1.97-2.02 (m, 4H, 2 CH$_2$), 4.27 (d, *J*= 3.8 Hz, 1H, =C$\underline{H}$H), 4.75 (d, *J*=3.8 Hz, 1H, CH$\underline{H}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159, 147, 90.7, 79.3, 38.1, 28.4, 19.9. GC-MS: *m/z* = 168 (M^+, 1), 140 (1), 126 (1), 109 (1), 99 (100), 87 (2), 81 (64), 79 (10), 69 (3), 55 (5), 43 (5)

Di-1-dicyclohexyl-2-oxopropyl carbonate (2c) : $C_{17}H_{26}O_5$ PM (310,2). white solid, mp 100.1-101.3 °C; Yield: 589.4 mg, 38% Table 1, Entry 7. IR (KBr): ν = 2950 (m), 2861 (m), 1738 (s), 1715 (s), 1450 (m), 1354 (m), 1312 (s), 1281(w), 1269 (m), 1243(s), 1204 (m), 1153 (w), 1130 (s), 1050 (m), 933 (s), 896 (m), 827 (w), 794 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.28 (m, 2H, Cyclohexane), 1.53-1.71 (m, 14H, cyclohexane), 2.05-2.09 (m, 4H, cyclohexane), 2.13 (s, 6H, COC$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206, 152.6, 87.1, 30.6, 24.7, 23.7, 20.7. GC-MS: *m/z* = 310 (M^+ ,1), 267 (12), 223 (1), 169 (2), 153 (4), 141 (6), 126 (15), 125 (98), 109 (9), 99 (58), 81 (38), 67 (21), 55 (10), 43 (100).

1-(1-hydroxycyclohexyl)Ethanone (5c) : $C_8H_{14}O_2$ PM (142,07). Colorless oil; Yield: 42.6 mg, 6% Table 1, Entry 7. IR (film): ν = 3449 (s), 2976 (s), 1816 (w), 1620 (s), 1450 (m),1271 (m), 1201 (m),1162 (m), 1104 (m), 971 (m), 818 (w), 780 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37–1.52 (m, 6H, Cyclohexane), 1.67- 1.74 (m, 2H, cyclohexane), 1.90-1,98 (m, 2H, cyclohexane), 2.03 (s, 1H, OH), 2.13 (s, 3H, COC$\underline{H}_3$);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210, 89.3, 35.3, 28.3, 22.5, 19.1. GC-MS: *m/z* = 142 (M^+, 1), 127 (40), 124 (23), 99 (15), 72 (100), 70 (10), 56 (19), 43 (73), 42 (35)

4-Phenyl-4-methyl-5-methylen-1,3-dioxolan-2-one (1d): $C_{11}H_{10}O_3$ PM (190,1). White solid, mp: 29.7 – 30.9 °C; Yield: 674.8 mg, 71% Table 2, Entry 20. IR (KBr): ν = 2985 (m), 1820 (s), 1686 (s), 1449 (w), 1297 (w), 1225 (m), 1122 (m), 1063 (m), 1022 (s),698 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H, CH_3), 4.45 (d, *J*= 4.0 Hz, 1H, =CHH), 4.94 (d, *J*=4.0 Hz, 1H,CHH), 7.25-7.50 (m, 5H, Aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 148, 144.1, 129.5, 125.4, 90.6, 87.4, 26.9. GC-MS: *m/z* = 190 (M^+, 1), 146 (15), 131 (17), 118 (100), 117 (86), 103 (45), 91(17), 77 (40), 63 (8), 51 (26), 43 (8)

4-Methyl-5-methylen-1,3-dioxolan-2-one (1e): $C_5H_6O_3$ PM (114,1). Colorless liquid; Yield: 256.7 mg, 45% Table 1, Entry 15. IR (film): ν = 2983 (m), 1820 (s), 1680 (s), 1374 (m), 1322 (m), 1275 (s), 1184 (s), 1087 (s), 855 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (d, *J*= 6.5 Hz, 3H, CH3), 4.40 (d, *J*= 3.9 Hz, 1H, =CHH), 4.84 (d, *J*=3.9 Hz, 1H, CHH), 5.31 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155, 147.5, 91.4, 71.9, 19.7 . GC-MS: *m/z* = 114 (M^+, 3), 86 (2), 70 (2), 55 (16), 53 (7), 50 (6), 44 (7), 43 (100), 41 (36)

1-Methyl-2-oxopropyl-1'-methylprop-2'-ynil carbonate (3e) : $C_9H_{12}O_4$ PM (184,1). Colourless liquid; Yield: 303.7 mg, 33% Table 1, Entry 15. IR (film): ν = 3270 (m), 2150 (w), 1750 (s), 1730 (s), 1260 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (d, *J*= 6.0 Hz, 3H, CH_3), 1.63 (d, *J*=6.0 Hz, 3H, CH_3), 2.23 (s, 3H, CH_3CO), 2.73 (d, *J*=2.6, 1H, CH acetylenic), 5.15 (m, 1H, CH), 5.45 (q, *J*=6 Hz, 1H, CHCCH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207, 155, 85.3, 79.3, 69.7, 69.4, 24.6, 20.8, 13.3 . GC-MS: *m/z* = 184 (M^+, 1), 142 (1), 114 (1), 97 (1), 83 (1), 71 (6), 53 (100), 45 (20), 43 (95)

Di-prop-2-ynil carbonate (4f) : $C_7H_6O_3$ PM (138,1). Yellow oil; Yield: 82.9 mg, 12% Table 2, Entry 22. IR (film): ν = 3293 (m), 2963 (s), 2131 (w), 1814 (w), 1761 (s), 1440 (w), 1392 (w), 1262 (s), 1097 (s), 1022 (m), 800 (m) cm-1; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 2.53 (t, *J*= 2.5 Hz, 2H, CH), 4.76 (d, *J*= 2.5, 4H, CH2) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207, 155, 85.3, 79.3, 69.7, 69.4, 24.6, 20.8, 13.3 . GC-MS: *m/z* = 139 ($(M+1)^+$, 1), 99 (15), 93 (1), 79 (2), 76(5), 65 (39), 55 (100), 53 (10), 45 (3), 44 (3)

4-Ethyl-4-methyl-5-methylen-1,3-dioxolan-2-one (1g): $C_7H_{10}O_3$ PM (142,1). Colorless liquid; Yield: 455 mg, 64% Table 2, Entry 23. IR (film): ν = 2979 (m), 1832 (s), 1688 (s), 1457 (w), 1382 (w), 1299 (s), 1235 (m), 1148 (m), 1097 (m), 1047 (s), 1021 (m), 856 (w), 769 (m) cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, *J*= 7.2 Hz, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.76 (dq, *J*=7.4 Hz, *J*= 7.2 Hz, 1H, CHH), 1.91 (dq, *J*=7.4 Hz, *J*= 7.2 Hz, 1H, CHH), 4.25 (d, *J*= 3.9 Hz, 1H, =CHH), 4.81 (d, *J*=3.9 Hz, 1H, CHH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.4, 149.1, 87.6, 86.1, 34.2, 24.7, 9.1. GC-MS: *m/z* = 142 (M^+, 1), 127 (1), 113 (2), 98 (2), 83 (5), 70 (7), 56 (100), 55 (30), 43 (31), 41 (39)

4,4-Diphenyl-5-methylen-1,3-dioxolan-2-one (1h): $C_{16}H_{12}O_3$ PM (152,1). colorless oil; Yield: 106.5 mg, 14% Table 2, Entry 24. IR (film): ν = 2970 (m), 1832 (s), 1674 (s), 1441 (w), 1278 (m), 1201 (m), 1133 (s), 1045 (m), 1009 (s),735 (m), 698 (w) cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 4.45 (d, *J*= 3.8 Hz, 1H, =CHH), 5.18 (d, *J*=3.8 Hz, 1H, CHH), 7.01-7.60 (m, 5H, 2 Aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 146.2, 143.4, 129.5, 128, 125.1, 92.6, 90.2. GC-MS: *m/z* = 252 (M^+, 1), 183 (2), 165 (2), 152 (2), 105 (9), 77 (34), 63 (3), 51 (15), 43 (100)

Methyl 2-methyl-3-oxobutan-2-yl carbonate (6a): $C_7H_{12}O_4$ PM (160.07). Colorless liquid; Yield: 584 mg, 73%, Table 3, Entry 1. IR (film): ν = 3665 (w), 3479 (w), 3432 (w), 2992 (s), 2960 (s), 2856 (m), 1809 (s), 1747 (s), 1725 (s), 1639 (w), 1443 (s), 1384 (s), 1368 (s), 1292 (s), 1157 (m), 1124 (m), 1028 (m), 947 (s), 860 (s), 795 (m)cm-1; ^1H NMR (300 MHz, $CDCl_3$): δ 1.37(s, 6H, 2 CH_3), 2.03 (s, 3H, CH_3CO), 3.64 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 154.2, 85.2, 54.6, 23.2, 22.9. GC-MS: *m/z* = 202 (M^+, 1), 159 (9), 118 (1), 104 (1), 85 (15), 69 (4), 59 (100), 57 (35), 43 (48), 41 (33)

Butyl 2-methyl-3-oxobutan-2-yl carbonate (6b) : $C_{10}H_{18}O_4$ PM (202). Colorless liquid; Yield: 818.1 mg, 81%, Table 3, Entry 2. IR (film): ν = 2962 (m), 2876 (m), 1742 (s), 1726 (s), 1467 (m), 1385 (m), 1285 (s), 1157 (s), 1124 (s), 1094 (m), 966 (w), 916 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.8 (t, *J*= 7.3, 3H, CH_3 butyl), 1.11-1.56 (m, 4H, -CH_2CH_2-), 1.36 (s, 6H, CH_3), 2.01 (s, 3H, COC$\underline{H}_3$), 3.99 (t, *J*= 6.6, 2H, -OCH_2-); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206, 153.8, 85, 67.7, 30.4, 23.2, 22.9, 18.6, 13.3. GC-MS: *m/z* = 202 (M^+, 1), 159 (9), 118 (1), 104 (1), 85 (15), 69 (4), 59 (100), 57 (35), 43 (48), 41 (33)

Sec-butyl 2-methyl-3-oxobutan-2-yl carbonate (6c) : $C_{10}H_{18}O_4$ PM (202). Yellow liquid; Yield: 424.2 mg, 42%, Table 3, Entry 6. IR (film): ν = 2980 (s), 2941 (s), 2882 (m), 1738 (s), 1458 (m), 1383 (s), 1338 (s), 1286 (s), 1207 (w), 1158 (s), 1111 (s), 1026 (m), 992 (m), 967 (m), 919 (m), 901 (m), 863 (w), 827 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (t, *J*= 7.3, 3H, CH_3 butyl), 1.25 (d, *J*= 6.2, 3H, C$\underline{H}_3$CH-), 1.48 (s, 6H, 2 CH_3), 1.45-1.70 (m, 2H, CHC$\underline{H}_2$), 2.14 (s, 3H, COC$\underline{H}_3$), 4.63-4.7 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6, 153.5, 85.1, 68, 30.5, 28.6, 23.1, 19.2, 9.4. GC-MS: *m/z* = 202 (M^+, 1), 159 (8), 116 (1), 104 (2), 85 (42), 71 (3), 59 (100), 57 (99), 43 (74), 41 (40)

1-Acetylcyclohexyl butyl carbonate (6d) : $C_{13}H_{22}O_4$ (PM 242). Colorless liquid; Yield: 847 mg, 70%, Table 3, Entry 10. IR (film): ν = 3422 (w), 2939 (s), 2866 (s), 1807 (m), 1743 (s), 1451 (s), 1393 (s), 1353 (s), 1246 (s), 1201 (m), 1139 (s), 1054 (m), 1031 (w), 932 (s), 895 (w), 829 (w), 795 (m), 738 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82(t, *J*= 7.2, 3H, $CH_2C\underline{H}_3$), 1.25 – 1.60 (m, 12H, -$C\underline{H}_2C\underline{H}_2CH_3$ + 8H cyclohexyl), 1.93 – 1.97 (m, 2H, cyclohexane), 2.01 (s, 3H, CH_3CO), 4.03 (t, *J*= 6.6, 2H, OCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.6, 153.7, 86.4, 67.7, 30.4, 29.7, 24.7, 23.2, 20.8, 18.6, 13.3. GC-MS: *m/z* = 242(M^+, 1), 199 (4), 125 (6), 109 (3), 99 (100), 81 (45), 67(10), 57 (32), 55 (21), 43 (94), 41 (52)

1-Acetylcyclohexyl allyl carbonate (6e) : $C_{12}H_{18}O_4$ (PM 226). Colorless liquid; Yield: 971.8 mg, 86%, Table 3, Entry 14. IR (film): ν = 3421 (w), 3087 (w), 2939 (s), 2864 (s), 1743 (s), 1649 (m), 1451 (s), 1367 (s), 1246 (s), 1201 (s), 1139 (s), 1053 (w), 1031 (w), 934 (s), 895 (m), 830 (w), 794 (m)cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 – 1.28 (m, 6H, cyclohexyl), 1.46 – 1.69 (m, 2H, cyclohexyl), 2.02 – 2.09 (m, 2H, Cyclohexyl), 2.10 (s, 3H, CH_3CO), 4.57 – 4.60 (m, 2H, OCH_2), 5.23 – 5.37 (m, 2H, $=CH_2$), 5.84 – 5.95 (m, 1H, CH allyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.9, 153.6, 131.3, 119, 86.4, 68.4, 30.6, 24.8, 23.5, 20.9. GC-MS: *m/z* = 226(M^+, 1), 183 (10), 139 (34), 125 (8), 109 (3), 99 (16), 81 (20), 69 (9), 67(5), 55 (13), 43 (76), 41 (100)

Butyl 3-oxo-2-phenylbutan-2-yl carbonate (6f) : $C_{15}H_{20}O_4$ (PM 264). Yellow solid, mp 50.4-51.3; Yield: 1148.4 mg, 87%, Table 3, Entry 17. IR (KBr): ν = 2961 (w), 2874 (w), 1733 (s), 1581 (w), 1497 (m), 1450 (w), 1301 (m), 1220 (m), 1133 (m), 1067 (s), 961 (s), 900 (s), 793 (s), 774 (s), 795 (m), 703 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, *J*= 7.4, 3H, $CH_2C\underline{H}_3$), 1.35 – 1.47 (m, 2H, $C\underline{H}_2CH_3$), 1.63 – 1.75 (m, 2H, $CH_2C\underline{H}_2CH_2$) 1.86 (s, 3H, CH_3), 1.97 (s, 3H, CH_3CO), 4.15 – 4.21 (m, 2H, OCH_2), 7.27– 7.45 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 203.5, 153.8, 138.1, 128.6, 128.1, 124.7, 88.7, 68.2, 30.6, 23.4, 22.6, 18.8, 13.6. GC-MS: *m/z* = 264(M^+, 1), 221 (7), 147 (15), 121 (91), 105 (19), 91 (10), 77 (22), 65(3), 57 (30), 43 (100), 41 (36)

Allyl 3-oxo-2-phenylbutan-2-yl carbonate (6g) : $C_{14}H_{16}O_4$ (PM 248). Yellow Oil; Yield: 272.8 mg, 22%, Table 3, Entry 18. IR (film): ν = 3434(w), 3061 (w), 3007 (m), 2945 (m), 1751(s), 1649 (w), 1583 (w), 1495 (s), 1449 (m), 1368 (m), 1212 (s), 1132 (m), 1097 (m), 1061 (m), 950 (m), 887 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (s, 3H, $C\underline{H}_3CPh$), 2.00 (s, 3H, $C\underline{H}_3CO$,), 4.66 – 4.70 (m, 2H, -CH_2 allyl), 5.29 – 5.44 (m, 2H, $=CH_2$ allyl), 5.90- 6.03 (m, 1H, CH allyl), 7.25 – 7.46 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 203.5, 153.5, 138, 131.2, 128.7, 128.2, 124.7, 119.5, 89, 68.8, 23.6, 22.5. GC-MS: *m/z* = 248(M^+, 1), 163 (7), 147 (13), 121 (71), 104 (100), 91 (12), 78 (20), 77 (19), 43 (48).

4-(allyloxy)-4,5,5-Trimethyl-1,3-dioxolan-2-one (7a) : $C_9H_{14}O_4$ (PM 186). Colorless liquid; Yield: 753.3 mg, 81%, Table 3, Entry 7. IR (film): ν = 3433 (w), 3089 (w), 2988 (m), 2945 (w), 1745 (s), 1726 (s), 1649 (w), 1453 (m), 1385 (w), 1368 (m), 1281 (s), 1156 (s), 1123 (s), 1090 (w), 996 (w), 953 (m), 857 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H, CH_3), 1.43 (s,3H, CH_3), 1.51 (s, 3H, CH_3), 4.07-4.22 (m, 2H, -CH_2-), 5.1-5.15 (m, 1H, CHCHH), 5.20-5.27 (m, 1H, CHCHH), 5.77-5.9 (m, 1H, CHCHH) ; ^{13}C NMR (75 MHz, $CDCl_3$): 153, 133.5, 116.4, 108, 87.6, 64.1, 24.2, 20.1, 16.2. GC-MS: *m/z* = 186 (M^+, 1), 143 (12), 99 (18), 85 (15), 69 (3), 59 (10), 57 (13), 43 (60), 41 (100).

4,4,5-Trimethyl-5-(prop-2-ynyloxy)-1,3-dioxolan-2-one (7b) : $C_9H_{12}O_4$ (PM 184). Yellow liquid; Yield: 625.6 mg, 68%, Table 3, Entry 8. IR (film): ν = 3582 (w), 3291 (s), 2988 (s), 2942 (s), 2881 (w), 2337 (w), 2128 (m), 1809 (s), 1564 (w), 1462 (m), 1395 (m), 1379 (m), 1287 (m), 1161 (m), 1121 (m), 1066 (m), 998 (s), 916 (w), 873 (s), 783 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s,3H, CH_3), 1.43 (s, 3H, CH3), 1.55 (s, 3H, CH_3), 2.43 (t, *J*= 2.1, 1H, CH), 4.29 (t, *J*= 2.1, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 108.1, 87.7, 79.1, 74.7, 51.6, 24.3, 19.9, 16.2. GC-MS: *m/z* = 185 (M^++1, 1), 139 (1),125 (8), 99 (19), 85 (15), 83(8), 79 (5), 69 (8), 59 (10), 57 (19), 43 (100), 41 (20).

4,4,5-Trimethyl-5-phenoxy-1,3-dioxolan-2-one (7c) : $C_{12}H_{14}O_4$ (PM 222). Yellow liquid; Yield: 699.3 mg, 63%, Table 3, Entry 9. IR (film): ν = 3445 (m), 2988 (m), 2942 (w), 1808 (s), 1592 (m), 1492 (s), 1455 (w), 1395 (s), 1387 (m), 1276 (s), 1210 (s), 1166 (m), 1148 (m), 1122 (s), 1065 (s), 1012 (s), 938 (m), 886 (w), 774 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.47 (s, 6H, 2 CH_3), 1.63 (s, 3H, CH_3), 7.09-7.33 (m, 5H, Aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 152.8, 152.6, 129.6, 125, 122.3, 121, 87.9, 24.2, 20.5, 16.8. GC-MS: *m/z* = 222 (M^+, 2), 163 (6), 145 (3), 135 (12), 107 (3), 95 (10), 94 (100), 85 (4), 77 (13), 65 (12), 57 (15), 51 (8), 43 (35), 41 (20).

4-Methyl-4-phenoxy-1,3-dioxaspiro[4.5]-decan-2-one (7d) : $C_{15}H_{18}O_4$ (PM 262). White solid, mp 74.8-75.5; Yield: 563.3 mg, 43%, Table 3, Entry 15. IR (KBr): ν =

2945 (w), 2859 (w), 1795 (s), 1758 (m), 1597 (w), 1589 (w), 1494 (s), 1395 (m), 1378 (w), 1302 (m), 1266 (m), 1228 (m), 1216 (s), 1105 (s), 1028 (w), 1003 (s), 945 (s), 910 (w), 873 (s), 752 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 – 1.68 (m, 8H, cyclohexyl), 2.15 (s, 3H, CH_3), 2.41 – 2.46 (m, 2H, cyclohexyl), 6.82 – 6.93 (m, 3H, aromatic), 7.08 – 7.29 (m, 3H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 155.6, 152.57 , 129.5, 124.9, 122.5, 115.2, 89.0, 32.64, 28.7, 20.9. GC-MS: *m/z* = 262 (M^+, 3), 201 (1), 175 (10), 125 (25), 109 (3), 94 (95), 81 (14), 77 (10), 67 (8), 65 (18), 55 (13), 43 (100), 41 (10).

4-(allyloxy)-4,5-Dimethyl-5-phenyl-1,3-dioxolan-2-one (7e) : $C_{14}H_{16}O_4$ (PM 248). Yellow liquid; Yield: 260.4 mg, 21%, Table 3, Entry 18. IR (film): ν = 3462(s), 3434(w), 3061 (w), 3007 (m), 2945 (m), 1809 (s), 1751(s), 1583 (w), 1495 (s), 1449 (m), 1368 (m), 1357 (w), 1291 (m), 1261 (s), 1132 (m), 1097 (m), 1061 (m), 950 (m), 887 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.65 (s, 3H, C<u>H</u>$_3$CO), 1.77 (s, 3H, C<u>H</u>$_3$CPh,), 3.99 – 4.05 (m, 2H, OCH_2), 4.77 – 4.94 (m, 2H, $=CH_2$), 5.55 – 5.64 (m, 1H, CH allyl), 7.25 – 7.38 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 152.8, 137.2, 122.9, 128.0, 124.8, 115.7, 108.7, 90.3, 63.7, 25.5, 17.5. GC-MS: *m/z* = 284M^+, 3), 240 (1), 198 (6), 197 (38), 147 (100), 131 (13), 119 (66), 104 (19), 103 (21), 93 (70), 91 (61), 78 (14), 77 (29), 65 (28), 51 (18), 43 (54), 41 (25).

4,5-Dimethyl-4-phenoxy-5-phenyl-1,3-dioxolan-2-one (7f) : $C_{17}H_{16}O_4$ (PM 284). Yellow liquid; Yield: 1192.8 mg, 84%, Table 3, Entry 19. IR (film): ν = 3462(s), 3063 (w), 3039 (w), 2985 (w), 2936 (w), 1809 (s), 1712(s), 1593 (m), 1492 (s), 1449 (s), 1391 (m), 1357 (w), 1291 (m), 1261 (s), 1213 (m), 1126 (s), 1097 (m), 1067 (s), 1028 (w), 998 (s), 945 (m), 914 8w), 897 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (s, 3H, C<u>H</u>$_3$CPh), 1.82 (s, 3H, C<u>H</u>$_3$CO,), 6.82 – 6.86 (m, 3H, aromatic), 7.09 – 7.48 (m, 7H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 152.6, 152.4, 137.3, 129.3, 128.7, 128.2, 128, 124.8, 122.8, 109.8, 90.8, 25.2, 17.5. GC-MS: *m/z* = 284M^+, 3), 240 (1), 198 (8), 197 (44), 147 (100), 131 (10), 119 (78), 104 (11), 103 (16), 93 (61), 91 (75), 78 (14), 77 (36), 65 (21), 51 (18), 43 (70), 41 (22).

3-Butyl-5,5-dimethyl-4-methyleneoxazolidin-2-one (8a) : $C_{10}H_{17}NO_2$ (PM 183.13); Colorless liquid; Yield: 714.2 mg, 78%, Table 4, Entry 1. IR (film): ν = 3391 (s), 1961 (s), 2935 (s), 2874 (m), 1816 (w), 1739 (s), 1446 (s), 1412 (s), 1273 (m), 1202 (m), 1089 (s), 1035 (w), 934 (w), 773 (m), 736 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*= 3.6, 3H, C<u>H</u>$_3$ butyl), 1.21 – 1.35 (m, 2H, C<u>H</u>$_2$CH$_3$), 1.42 (s, 6H, CH_3), 1.47-1.57 (m, 2H, CH_2C<u>H</u>$_2$$CH_2$), 3.37 (t, *J*= 7.2, 2H, NCH*2*), 3.93 (d, *J*= 2.8, 1H, =C<u>H</u>H), 4.02 (d, *J*=2.8, 1H, =CH<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): 155.5, 150.8, 81.8, 79, 41, 28.2, 27.8, 19.8, 13.6. GC-MS: *m/z* = 183 (M^+, 21), 168 (15), 141 (30), 128 (73), 112 (10), 97 (58), 96 (84), 84 (41), 82 (57), 68 (28), 67 (23), 57 (35), 56 (30), 43 (29), 41 (100).

3-sec-Butyl-5,5-dimethyl-4-methyleneoxazolidin-2-one (8b) : $C_{10}H_{17}NO_2$ (PM 183.13); Yellow oil; Yield: 659.3 mg, 72%, Table 4, Entry 2. IR (film): ν = 3393 (s), 3058 (w), 2980 (s), 2937 (s), 2877 (m), 1714 (s), 1553 (w), 1453 (s), 1349 (s), 1298 (m), 1194 (s), 1154 (s), 1090 (m), 1037 (m), 989 (w), 962 (w), 896 (m), 776 (m), 738 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*= 7.2, 3H, C<u>H</u>$_3$ ethyl), 1.23 – 1.40 (m, 3H, CH_3), 1.46 (s, 6H, CH_3), 1.58-1.75 (m, 2H, C<u>H</u>$_2$CH$_3$), 3.78 – 3.85 (m, 1H, CH), 3.96 (d, *J*= 1.7, 1H, =C<u>H</u>H), 4.16 (d, *J*=1.7 1H, =CH<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): 155.2, 150.4, 81.1, 79.9, 51.4, 28.0, 24.9, 16.8, 11.0. GC-MS: *m/z* = 183 (M^+, 15), 168 (8), 128 (100), 112 (15), 110 (16), 96 (7), 84 (23), 82 (15), 68 (16), 57 (12), 41 (20).

3-Allyl-5,5-dimethyl-4-methyleneoxazolidin-2-one (8d) : $C_9H_{13}NO_2$ (PM 167.09); Colorless oil; Yield: 601.5 mg, 72%, Table 4, Entry 4. IR (film): ν = 3393 (s), 3086 (w), 2985 (s), 2935 (m), 1742 (s), 1681 (m), 1427 (m), 1404 (s), 1342 (w), 1280 (w), 1127 (m), 967 (m), 934 (w), 736 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (s, 6H, CH_3), 3.97 (d, *J*=2.9, 2H, NC<u>H</u>$_2$), 4.02 – 4.06 (m, 2H, =CH_2), 5.13 – 5.20 (m, 2H, =CH_2), 5.65 – 5.78 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): 155.2, 150.3, 130.4, 117.4, 82.0, 79.9, 43.6, 27.8. GC-MS: *m/z* = 167 (M^+, 68), 122 (100), 108 (94), 94 (15), 82 (59), 69 (21), 68 (20), 67 (26), 55 (88), 41 (96).

3-Benzyl-5,5-dimethyl-4-methyleneoxazolidin-2-one (8e) : $C_{13}H_{15}NO_2$ (PM 217.11); Yellow liquid; Yield: 727.3 mg, 67%, Table 4, Entry 5. IR (film): ν =3446 (w), 3033 (w), 2981 (w), 2931 (w), 1766 (s), 1681 (s), 1498 (m), 1406 (m), 1381 (s), 1370 (s), 1272 (w), 1212 (m), 1111 (w), 1066 (m), 972 (s), 815 (s), 712 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (s, 6H, CH_3), 3.95 (d, *J*=2.9, 1H, C<u>H</u>H), 4.02 (d, *J*= 2.9, 1H, =CH<u>H</u>), 4.64 (s, 2H, C<u>H</u>$_2$Ph), 7.23 – 7.33 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 155.8, 150.2, 128.64, 127.7, 127.2, 82.2, 80.0, 45.1, 27.8. GC-MS: *m/z* = 217 (M^+, 43), 172 (15), 158 (10), 91 (100), 82 (12), 65 (14), 41 (10).

5,5-Dimethyl-4-methylene-3-phenyloxazolidin-2-one (8f) : $C_{12}H_{13}NO_2$ (PM 203.09); Yellow solid, mp 119.2 – 120.1; Yield: 437.2 mg, 38%, Table 4, Entry 6. IR (KBr): ν =3353 (m), 3062 (w), 2985 (w), 2943 (w), 1733 (s), 1648 (m), 1558 (m), 1497 (w), 1393 (s), 1232 (w), 1146 (s), 1089 (w), 1064 (m), 974 (w), 892 (m), 754 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (s, 6H, CH_3), 4.03 (d, *J*=2.9, 1H, C<u>H</u>H), 4.13 (d, *J*= 2.9, 1H, =CH<u>H</u>), 7.26 – 7.50 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): 154.4, 151.7, 134.0, 129.4, 128.2, 126.9, 82.4, 81.1, 27.8. GC-MS: *m/z* = 203 (M^+, 71), 158 (98), 144 (90), 118 (21), 104 (100), 91 (12), 77 (61), 56 (32), 51 (25), 41 (17).

3-Butyl-5-cyclohexyl-4-methyleneoxazolidin-2-one (8g) : $C_{13}H_{21}NO_2$ (PM 223.16). White solid, mp 89.7 – 90.5; Yield: 770 mg, 69%, Table 4, Entry 10. IR (KBr): ν = 3337 (m), 2931 (m), 2860 (m), 1726 (s), 1673 (s), 1450 (m), 1411 (s), 1378 (s), 1352 (m), 1283 (m), 1221 (s), 1192 (w), 1138 (s), 1079 (s), 1066 (m), 1033 (m), 843 (w), 807 (s), 663 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82(t, *J*= 7.2, 3H, CH_2C<u>H</u>$_3$), 1.17 – 1.75 (m, 14H, -C<u>H</u>$_2$C<u>H</u>$_2$$CH_3$ + 10H cyclohexyl), 3.32 (t, *J*= 6.8, 2H, -C<u>H</u>$_2$$CH_2$), 3.85 (d, *J*=2.9, 1H, C<u>H</u>H), 3.97 (d, *J*= 2.9, 1H, =CH<u>H</u>) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.6, 150.7, 83.4, 79.1, 40.8, 36.7, 28.2, 24.5, 21.5, 19.7, 13.5. GC-MS: *m/z* = 223(M^+, 30), 208 (10), 181 (54), 168 (100), 137 (31), 135 (28), 124 (13), 122 (33), 112 (40), 106 (30), 96 (22), 94 (28), 82 (20), 79 (24), 67(20), 55 (36), 43 (31), 41 (78)

5-Cyclohexyl-4-methylene-3-phenyloxazolidin-2-one (8h) : $C_{15}H_{17}NO_2$ (PM 243.13). White solid, mp 160.7 – 161.6; Yield: 386.3 mg, 69%, Table 4, Entry 11. IR

(KBr): ν = 3377 (m), 2931 (m), 2856 (w), 1747 (s), 1598 (w), 1502 (m), 1404 (s), 1286 (w), 1150 (m), 1123 (m), 1079 (w), 958 (m), 910 (w), 758 (m), 701 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 – 1.75 (m, 10H, cyclohexyl), 1.81 (d, *J*=2.9, 1H, C<u>H</u>H), 2.07 (d, *J*= 2.9, 1H, =CH<u>H</u>), 7.20 – 7.35 (m, 5H, aromatic) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 150.7, 134.7, 128.8, 127.7, 127.4, 122.5, 119.4, 91.8, 86.8, 33.2, 28.5, 24.9, 21.7, 20.4. GC-MS: *m/z* = 243(M^+, 35), 202 (16), 198 (51), 188 (40), 170 (18), 156 (18), 144 (12), 130 (20), 118 (36), 117 (37), 108 (20), 104 (44), 91 (18), 82 (33), 77 (100), 67(19), 51 (30), 41 (25)

3-Butyl-5-methyl-4-methylene-5-phenyloxazolidin-2-one (8i) : $C_{15}H_{19}NO_2$ (PM 245.14). Colorless liquid; Yield: 882.5 mg, 72%, Table 4, Entry 14. IR (film): ν = 3406 (s), 3056 (m), 2962 (s), 2874 (m), 1816 (w), 1740 (s), 1676 (m), 1496 (w), 1448 (s), 1407 (s), 1266 (s), 1062 (s), 1029 (w), 765 (s), 702 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, *J*= 7.1, 3H, $CH_2C\underline{H}_3$), 1.25 – 1.37 (m, 2H, -$CH_2C\underline{H}_2CH_3$), 1.52 – 1.62 (m, 2H, -$C\underline{H}_2CH_2CH_3$), 1.84 (s, 3H, CH_3), 3.40 – 3.52 (m, 2H, -$C\underline{H}_2CH_2$-), 4.08 (d, *J*= 2.8, 1H, =CH<u>H</u>), 4.20 (d, *J*= 2.8, 1H, =C<u>H</u>H), 7.30 – 7.45 (m, 5H, aromatic) ;^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 149.5, 141.2, 128.5, 128.3, 124.7, 84.1, 81.9, 41.2, 28.2, 27.4, 19.8, 13.6. GC-MS: *m/z* = 245(M^+, 15), 200 (13), 190 (15), 172 (10), 159 (71), 158 (98), 144 (100), 129 (30), 118 (36), 104 (24), 103 (35), 97 (81), 91 (20), 78 (32), 77 (62), 51 (22), 41 (63).

5-Methyl-4-methylene-3,5-diphenyloxazolidin-2-one (8j) : $C_{17}H_{15}NO_2$ (PM 265.11). Yellow liquid; Yield: 198.8 mg, 15%, Table 4, Entry 15. IR (film): ν = 3447 (s), 3063 (m), 2986 (w), 2933 (m), 1772 (s), 1675 (m), 1653 (s), 1506 (m), 1394 (m), 1272 (s), 1153 (m), 1059 (m), 981 (m), 827 (w), 760 (s), 699 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.00 (s, 3H, CH_3), 4.19 (d, *J*=2.7, 1H, C<u>H</u>H), 4.29 (d, *J*= 2.7, 1H, =CH<u>H</u>), 7.21 – 7.59 (m, 5H, aromatic) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 150.6, 141.1, 133.9, 129.5, 128.6, 128.5, 128.3, 127.0, 124.8, 84.7, 84.1, 27.6. GC-MS: *m/z* = 265(M^+, 25), 221 (59), 220 (100), 206 (25), 118 (62), 117 (24), 103 (14), 77 (23), 51 (18)

2-Methyl-3-oxobutan-2-yl pyrrolidine-1-carboxylate (9a) : $C_{10}H_{17}NO_3$ (PM 199.12). Colorless liquid; Yield: 786.5 mg, 79%, Table 4, Entry 7. IR (film): ν = 3426 (m), 3057 (w), 2983 (m), 2881 (m), 1697 (s), 1421 (s), 1269 (m), 1227 (w), 1159 (s), 1122 (s), 1098 (m), 1028 (w), 922 (w), 771 (m), 737 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (s, 6H, $2CH_3$), 1.96 – 2.05 (m, 4H, pyrrolidine), 2.24 (s, 3H, CH_3), 3.44 – 3.54 (m, 4H, pyrrolidine) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.9, 148.1, 77.1, 40.4, 20.0, 19.2, 18.0, 17.8. GC-MS: *m/z* = 199(M^+, 2), 156 (15), 114 (14), 98 (100), 70 (17), 56 (23), 55(42), 43 (61), 41 (32).

2-Methyl-3-oxobutan-2-yl dibutylcarbamate (9b) : $C_{14}H_{27}NO_3$ (PM 257.2). Yellow liquid; Yield: 1071.3 mg, 79%, Table 4, Entry 8. IR (film): ν = 3523 (w), 3427 (w), 2926 (s), 2874 (s), 1729 (s), 1544 (w), 1421 (m), 1363 (m), 1259 (w), 1230 (m), 1075 (w) 924 (s), 854 (w), 772 (s), 748 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.7 – 0.8 (m, 6H, 2 -$CH_2C\underline{H}_3$, 1.28 (s, 6H, $2CH_3$), 1.13 – 1.38 (m, 8H, CH_2 butyl), 1.95 (s, 3H, CH_3), 3.06 – 3.08 (m, 4H, $NC\underline{H}_2$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.2, 154.8, 82.6, 46.7, 46.4, 23.3, 23.0, 19.7, 13.6. GC-MS: *m/z* = 271 (M^+, 1), 258 (3), 214 (14), 172 (18), 156 (80), 100 (23), 86 (25), 57 (100), 43 (38), 41 (30).

1-Acetylcyclohexyl pyrrolidine-1-carboxylate (9d) : $C_{13}H_{21}NO_3$ (PM 239.15). White solid, mp 62.1 – 63.0; Yield: 968.5 mg, 81%, Table 4, Entry 12. IR (KBr): ν = 2976 (m), 2937 (s), 2862 (m), 1689 (s), 1450 (m), 1411 (s), 1356 (w), 1276 (w), 1252 (s), 1179 (w), 1121 (m), 1096 (s), 1049 (w), 972 (m), 945 (m), 831 (w), 774 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 – 1.19 (m, 6H, cyclohexyl), 1.35 – 1.59 (m, 4H, pyrrolidine), 1.73 - 1.85 (m, 2H, cyclohexyl), 1.85 – 1.88 (m, 2H, cyclohexyl), 2.00 (s, 3H, CH_3), 3.25 – 3.40 (m, 4H, pyrrolidine) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.2, 153.4, 83.9, 45.9, 45.8, 30.9, 25.6, 25.0, 24.7, 23.5, 21.3. GC-MS: *m/z* = 239(M^+, 2), 196 (21), 114 (10), 98 (100), 81 (10), 70 (14), 56 (23), 55(44), 43 (41).

1-Acetylcyclohexyl dibutylcarbamate (9e) : $C_{17}H_{31}NO_3$ (PM 297.2). Yellow oil; Yield: 1217.7 mg, 82%, Table 4, Entry 13. IR (film): ν = 3417 (w), 2932 (s), 2862 (s),

1768 (w), 1718 (s), 1473 (m), 1379 (w), 1306 (w), 1254 (w), 1224 (m), 1140 (m), 1052 (m) 937 (m), 893 (m), 771 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.8 – 0.9 (m, 6H, 2 -$CH_2C\underline{H}_3$, 1.22 – 1.67 (m, 14H, CH_2), 2.00 – 2.06 (m, 4H, 2 -$C\underline{H}_2$ cyclohexyl), 2.07 (s, 3H, CH_3), 3.11 – 3.29 (m, 4H, $NC\underline{H}_2$) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 154.6, 84.2, 47.0, 46.9, 31.0, 30.9, 30.1, 25.1, 23.4, 21.4, 20.0, 19.8, 13.8, 13.7. GC-MS: *m/z* = 297(M^+, 2), 254 (14), 172 (10), 156 (100), 125 (10), 100 (20), 86 (17), 57 (93), 43 (85), 41 (26).

3-Oxo-2-phenylbutan-2-yl pyrrolidine-1-carboxylate (9f) : $C_{15}H_{19}NO_3$ (PM 261.14). White solid, mp 123.9 – 124.7; Yield: 1018.4 mg, 78%, Table 4, Entry 16. IR (KBr): ν = 2995 (w), 2975 (w), 2882 (w), 1723 (s), 1696 (s), 1492 (m), 1415 (s), 1352 (m), 1134 (s), 1090 (m), 878 (w), 766 (s), 708 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 – 2.03 (m, 4H, pyrrolidine), 1.85 (s, 3H, CH_3), 1.97 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 3.42 – 3.67 (m, 4H, pyrrolidine), 7.25 – 7.47 (m, 5H, aromatic) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.5, 153.2, 139.6, 128.5, 127.8, 124.7, 86.7, 46.2, 46.1, 25.7, 24.8, 23.8, 23.6. GC-MS: *m/z* = 262($M+1^+$, 1), 219 (27), 218 (19), 160 (10), 107 (25), 98 (100), 77 (14), 56 (22), 55 (59), 43 (36).

3-Oxo-2-phenylbutan-2-yl dibutylcarbamate (9g) : $C_{19}H_{29}NO_3$ (PM 319.2). Yellow oil; Yield: 1228.9 mg, 77%, Table 4, Entry 17. IR (film): ν = 3430 (w), 3060 (w), 2959 (s), 2933 (s), 2874 (m), 1724 (s), 1700 (s), 1494 (m), 1472 (s), 1423 (s), 1368 (m), 1296 (w), 1230 (w), 1212 (m), 1159 (m), 1103 (m) 907 (w), 763 (s), 737 (m), 699 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 – 1.0 (m, 6H, 2 -$CH_2C\underline{H}_3$), 1.27 – 1.69 (m, 8H, CH_2), 1.82 (s, 3H, $C\underline{H}_3$), 1.94 (s, 3H, CH_3), 3.21 – 3.45 (m, 4H, $NC\underline{H}_2$), 7.29 – 7.44 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.3, 154.5, 139.6, 128.6, 128.3, 127.8, 124.6, 86.9, 47.3, 47.0, 30.9, 30.1, 23.7, 23.5, 20.0, 19.9, 13.9, 13.8. GC-MS: *m/z* = 319(M^+, 2), 277 (20), 190 (15), 172 (10), 156 (100), 147 (18), 119 (10), 105 (27), 86 (13), 57 (48), 43 (19), 41 (15).

1,2-Dihydro-1,1,5,5-tetramethylimidazo[1,5-a]pyridin-3(5H)-one (10) : $C_{11}H_{16}N_2O$ (PM 192.1). White solid, mp 132,4 – 133,5; Yield: 336.1 mg, 35%, Scheme 11. IR

(KBr): ν = 3367 (w), 3272 (w), 2988 (s), 2919 (m), 2849 (m), 1706 (s), 1640 (s), 1556 (s), 1468 (w), 1380 (m), 1361 (m), 1285 (s), 1222 (m), 1194 (m), 1163 (m), 1159 (m), 1130 (m), 971 (m), 874 (w), 781 (m), 709 (m), 675 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 6H, 2 C$\underline{H}_3$), 1.55 (s, 6H, 2 C$\underline{H}_3$), 4.66 (d, *J*= 5.7, 1H, CH), 4.88 (d, *J*= 5.7, 1H, CH), 5.64 – 5.69 (m, 1H, CH), 5.74 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 147.6, 125.9, 118.3, 88.9, 56.2, 55.0, 28.8, 27.9. GC-MS: *m/z* = 192 (M^+, 10), 177 (29), 134 (100), 118 (10), 106 (13), 92 (11), 77 (12), 65 (16), 51 (6), 42 (10).

4,4-dimethyl-1-(2-methyl-3-oxobutan-2-yl)-5-methyleneimidazolidin-2-one (11) : $C_{11}H_{18}N_2O_2$ (PM 210.1). White solid, mp 116.1 – 118.9; Yield: 305 mg, 29%, Scheme 11. IR (KBr): ν = 3362 (w), 3275 (m), 2980 (s), 2897 (m), 2846 (w), 1714 (s), 1651 (s), 1557 (s), 1355 (w), 1343 (s), 1290 (s), 1211 (w), 1187 (s), 1162 (w), 1149 (m), 976 (w), 860 (m), 776 (s), 709 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 6H, 2 CH_3), 1.41 (s, 6H, 2 CH_3), 2.03 (s, 3H, CH_3), 4.02 (d, *J*= 2.7, 1H, C$\underline{H}$H), 4.09 (d, *J*= 2.7, 1H, CH$\underline{H}$), 7.53 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.2, 156.5, 152.5, 80.5, 63.8, 53.4, 28.9, 22.9, 21.5. GC-MS: *m/z* = 210(M^+, 10), 177 (11),167 (100), 134 (10), 124 (84), 111 (19), 106 (10), 96 (11), 82 (15), 68 (31), 58 (36), 43 (40), 42 (43), 41 (45).

5-hydroxy-4,4,5-trimethyl-1-(2-methyl-3-oxobutan-2-yl)imidazolidin-2-one (12) : $C_{11}H_{20}N_2O_3$ (PM 228.15). Colorless oil; Yield: 342.2 mg, 30%, Scheme 11. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 6H, 2 CH_3), 1.69 (s, 3H, CH_3), 2.18 (s, 6H, 2 CH_3), 2.24 (s, 3H, CH_3), 5.29 (s, 1H, OH), %.61 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5, 156.2, 92.6, 66.6, 60.5, 53.4, 26.0, 24.3, 23.7, 21.3. GC-MS: *m/z* = 210(M^+-18, 10), 185 (11), 177 (10), 167 (14), 151(10), 134 (10), 124 (9), 110 (19), 94 (11), 84 (12), 58 (100), 43 (31), 42 (34), 41 (27).

1,2-Dihydro-1,5-dicyclohexylimidazo[1,5-a]pyridin-3(5H)-one (13) : $C_{17}H_{24}N_2O$ (PM 272.2). White solid, mp 139,4 – 140.2; Yield: 571.6 mg, 42%, Scheme 12. IR (KBr): ν = 3214 (m), 2933 (s), 2861 (m), 1713 (s), 1667 (s), 1595 (m), 1415 (m), 1393 (w), 1320 (m), 1284 (m), 1124 (w), 718 (m), 675 (w) cm-1; ^{1}H NMR (300 MHz,

$CDCl_3$): δ 1.27 – 1.60 (m, 12H, cyclohexyl), 1.66 – 1.96 (m, 8H, cyclohexil), 4.70 (d, *J*=4.3, 1H, CH), 5.39 (s, 1H, NH), 5.56 (d, *J*= 4.3, 1H, CH), 5.74 – 5.79 (m, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.4, 148.3, 120.89, 119.1, 90.1, 48.0, 38.3, 34.8, 25.2, 25.0, 22.2, 21.3. GC-MS: *m/z* = 272 (M^+, 25), 229 (100), 216 (10), 200 (11), 186 (86), 173 (23), 144 (11), 130 (10), 91 (11), 77 (12), 65 (13), 41 (10).

1-Butyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (14a) : $C_{10}H_{18}N_2O$ (PM 182.1). Colorless oil; Yield: 364.2 mg, 40%, Table 5, Entry 1. IR (film): ν = 3271 (s), 2961 (s), 2931 (s), 2873 (m), 1722 (s), 1664 (s), 1566 (w), 1459 (m), 1421 (m), 1297 (w), 1126 (m), 1043 (w), 922 (w) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J*= 3.5, 3H, C<u>H</u>$_3$ butyl), 1.17 – 1.29 (m, 2H, C<u>H</u>$_2$CH$_3$), 1.32 (s, 6H, CH_3), 1.34-1.60 (m, 2H, CH_2C<u>H</u>$_2$$CH_2$), 3.37 (t, *J*= 7.4, 2H, NCH*2*), 3.88 (d, *J*= 2.4, 1H, =C<u>H</u>H), 3.94 (d, *J*=2.4, 1H, =CH<u>H</u>), 5.59 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 157.8, 153.6, 77.3, 56.1, 39.6, 29.6, 28.5, 27.8, 19.4, 13.7. GC-MS: *m/z* = 182 (M^+, 12), 167 (31), 154 (15), 153 (10), 152 (12), 139 (32), 125 (100), 97 (26), 57 (40), 55 (19), 43 (69).

4,4-Dimethyl-5-methylene-1-(prop-2-ynyl)imidazolidin-2-one (14b) : $C_9H_{12}N_2O$ (PM 164.1). Colorless oil; Yield: 205.1 mg, 25%, Table 5, Entry 2. IR (film): ν = 3238 (s), 2974 (m), 2359 (s), 2120 (m), 1716 (s), 1676 (s), 1642 (w), 1616 (m), 1558 (w), 1438 (s), 1330 (m), 1283 (m), 1181 (w), 1144 (w), 931 (m), 907 (s), 809 (s), 761 (m) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 6H, CH_3), 3.11 (s, 1H, acetilenic), 3.36 (s, 2H, CH_2), 4.03 (d, *J*= 2.3, 1H, =C<u>H</u>H), 4.11 (d, *J*=2.3, 1H, =CH<u>H</u>), 7.5 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 155.4, 152.1, 78.4, 77.9, 73.3, 55.5, 39.3, 29.0, 28.6. GC-MS: *m/z* =164 (M^+, 6), 149 (15), 139 (22) , 135 (10), 134 (12), 125 (21), 111 (17), 96 (100), 95 (42), 83 (30), 68 (15), 57 (26),53 (12), 41 (43).

1-butyl-4-cyclohexyl-5-methyleneimidazolidin-2-one (14d) : $C_{13}H_{22}N_2O$ (PM 222.17). Yellow oil; Yield: 766.5 mg, 69%, Table 5, Entry 5. IR (film): ν = 3469 (w), 3302 (w), 3187 (w), 3057 (w), 2939 (s), 2874 (m), 1775 (s), 1665 (s), 1469 (s), 1456 (s), 1408 (s), 1357 (m), 1312 (m), 1266 (m), 1114 (w), 1071 (s), 994 (s), 943 (m), 840 (s), 738 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, *J*= 7.1, 3H, CH_2C<u>H</u>$_3$), 1.11 – 1.69

(m, 14H, -C<u>H</u>$_2$C<u>H</u>$_2$CH$_3$ + 10H cyclohexyl), 3.32 (t, *J*= 7.6, 2H, -NC<u>H</u>$_2$-), 4.42 (d, *J*=3.0, 1H, C<u>H</u>H), 4.63 (d, *J*=3.0, 1H, =CH<u>H</u>) 5.26 (s, 1H, NH) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 154.3, 87.5, 59.0, 39.8, 34.3, 33.9, 31.6, 23.9, 21.2, 20.9, 20.1, 13.6. GC-MS: *m/z* = 222(M^+, 10), 193 (15), 179 (18), 165 (31), 151 (10), 123, (21), 95 (61), 70 (41), 57 (38), 43 (100), 42 (23).

N-(1-acetylcyclohexyl)pyrrolidine-1-carboxamide (15b) : $C_{13}H_{22}N_2O_2$ (PM 238.17). White solid, mp 73.2 – 74.0; Yield: 690.7 mg, 58%, Table 5, Entry 7. IR (KBr): ν = 3218 (m), 3110 (w), 2932 (m), 2869 (m), 1720 (s), 1662 (s), 1576 (s), 1450 (s), 1421 (s), 1349 (m), 1333 (w), 1246 (w), 1165 (w), 1066 (s), 932 (m), 818 (w), 796 (m), 783 (s) cm-1; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 – 1.36 (m, 3H, 3 –C<u>H</u>H cyclohexyl), 1.57 – 1.67 (m, 7H, 3 –CH<u>H</u> cyclohexyl + 2 CH_2 pyrrolidine), 1.86 - 1.90 (m, 4H, 2 CH_2 cyclohexyl), 2.13 (s, 3H, CH_3), 3.25 – 3.40 (t, *J*= 6.6, 4H, CH_2 pyrrolidine), 4.5 (s, 1H, NH) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.5, 155.4, 62.6, 45.5, 31.5, 25.5, 25.2, 24.2, 21.5. GC-MS: *m/z* = 238(M^+, 2), 195 (21), 168 (12), 140 (33), 113 (10), 98 (100), 83 (23), 81 (10), 70 (14), 56 (23), 55 (44), 43 (41).

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APPENDIX

List of publications

1. Bartolo Gabriele, Raffaella Mancuso, Giuseppe Salerno, Giuseppe Ruffolo, Pierluigi Plastina. *"Novel and Convenient Synthesis of Substituted Quinolines by Copper - or Palladium- Catalyzed Cyclodehydration of 1-(2-Aminoaryl)-2-yn-1-ols" J. Org. Chem.* **2007**, 72, 6873-6877

2. Bartolo Gabriele, Raffaella Mancuso, Giuseppe Salerno, Elvira Lupinacci, Giuseppe Ruffolo , Mirco Costa *"Versatile Synthesis of Quinoline-3-Carboxylic Esters and Indol-2-Acetic Esters by Palladium-Catalyzed Carbonylation of 1-(2-Aminoaryl)-2-Yn-1-Ols" J. Org. Chem.* **2008**, 73, 4971-4977

3. Bartolo Gabriele, Raffaella Mancuso, Giuseppe Salerno, Giuseppe Ruffolo, Mirco Costa, Angela Dibenedetto. "*A novel and efficient method for the catalytic direct oxidative carbonylation of 1,2- and 1,3-diols to 5-membered and 6-membered cyclic carbonates*" *Tetrahedron Lett.* **2009**, *50*, 7330-7332

Education – Overview of training activities

Meetings

1. International School "Bernardino Telesio": Residential School On Applied Mass Spectrometry and Related Topics (ISSOC2006) **2006**, Rende (Cs).
2. XV Congresso Nazionale di Catalisi-GIC **2007**, Tirrenia (Pisa)
3. XXXI Convegno Nazionale della Divisione di Chimica Organica della Soc. Chim. Italiana **2007**, Rende (Cs)
4. VII SAYCS (Sigma Aldrich Young Chemists Symposium) **2007**, Riccione (RN)
5. Dmitri Mendeleev, 140 anni dalla presentazione del sistema periodico **2009**, Roma

Workshops & Seminars

Workshop: "La Chimica incontra la natura"
Workshop: "Drug delivery systems"
Workshop: "Le Piu' Recenti Innovazioni Della Spettrometria Di Massa Nel Settore Agro-Alimentare, Ambientale e Farmaceutico"
Workshop: Prof. Himo "Enzymatic Reaction Mechanisms: Oxidation and Reduction"
Workshop: "Qualità e salubrità degli alimenti. Il contributo della spettrometria di massa"
Workshop: "Human and vegetable proteomics"

Prof. Casciaro, "Numerical post-buckling analysis"
Dr. K. Hopmann "Preliminary study on the working mechanism of PAL enzyme"
Dr. F. Lucas "Theoretical calculations on the enzyme pyruvate formate lyase"
Prof. Ragno "I farmaci di automedicazione, vantaggi e limiti"
Dott.ssa Ioele "Sistemi di stabilizzazione di farmaci fotosensibili"
Dott.ssa Maiuolo "L'uso di Lantanidi nella catalisi in chimica organica"

Dott.ssa. Trombino "Attività antiossidante di composti naturali e loro veicolazione per applicazioni in campo farmaceutico"
Dott.ssa. Maiuolo "Reazioni pericicliche: cicloaddizioni, sigmatropiche e elettrocicliche"
Prof Garofalo "Enzimi (recettori catalitici): aspetti chimico-farmaceutici (Parte I)"
Dott.ssa Trombino "Direzionamento di famaci al Sistema Nervoso Centrale"
Dott.ssa Iemma "Polimeri per applicazioni farmaceutiche (Parte I)"
Prof. Bortolini "Epossidazione di Substrati Organici (Parte I)"
Prof. Bortolini "Epossidazione di Substrati Organici (Parte II)"
Prof. Menichini "Aspetti fitochimici nella ricerca sulle piante medicinali"
Prof Garofalo "Enzimi (recettori catalitici): aspetti chimico-farmaceutici (Parte II)"
Prof. Serge Carreau "Roles of estrogens in spermatogenesis"
Prof. Salerno "Sintesi di derivati carbo- ed eterociclici mediante catalisi organometallica
Prof. Menichini "Valutazione dell'attività biologica di principi attivi di origine naturale"
Dott.ssa Muzzalupo "Strategie utilizzate per superare le problematiche inerenti alla veicolazione di principi attivi
Prof. Gabriele "Sintesi di eterocicli PdI_2-catalizzata"
Prof. Nouri Neamati, "Design and discovery of novel small-molecules drugs with anticancer and antiviral activities"
Prof. Takashi Oshima, "Mechanism of action of a novel anticancer agent"
Prof. Porto "Controllo dei Parametri necessari per la validazione dei metodi di analisi"
Dott.ssa Fazio "Le ciclodestrine nella chimica degli alimenti"
Prof De Nino "Le reazioni multicomponente (MCRs)"
Prof De Nino "L'evoluzione dei modelli per la reazione di addizione al Carbonile"
Prof. Picci "Nuove strategie di rilascio controllato di farmaci"
Dr. Tagarelli "Mass Spectrometry Basics"
Dott.ssa Ioele "Farmaci utilizzati nella terapia pediatrica"
Dott.ssa Leggio "Peptidomimetici"
Prof Liguori "Chimica degli steroidi"
Prof Liguori "Sintesi di amminoacidi e peptici modificati"
Dott.ssa Napoli "Mass Spectrometry Advanced"
Dott.ssa Di Gioia "Tecniche di sintesi su supporto solido"
Prof. Picci "Nuove strategie di rilascio controllato di farmaci (Parte II)"
Prof. Siciliano "Analisi NMR di biomolecole: la terza dimensione"
Prof. Siciliano "L'analisi strutturale NMR nella progettazione e preparazione di analoghi di biomolecole aventi potenzialità farmaceutiche"
Dott.ssa Aiello "Drug-like properties and the causes of poor solubility and poor permeability"
Prof. R. C. Larock "Adventures in bioplastics, iodine, palladium and aryne Chemistry"
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Prof. Zanotti "Reactions of bridging C_3 ligands in diiron complexes: unconventional routes to new functionalized organic frames"
Prof B. Silvi and M. Curie "Electronic reaction mechanisms from molecular geometry"
Prof. I. Andreu "Photosensitisation of lipids by diaryl-ketones in model dyads"
Prof. L. Coitino "Targeting DNA by metallic complexes useful in therapy and early of human diseases with in silico approaches"

Prof Ragno “Sistemi farmaceutici anticoncezionali”
Prof. A. Caruso “Effetti dell’oleuropeina su colture primarie di endoteli umani: Attività antinfiammatoria e antivirale”
Dott.ssa Trombino “Principali tecniche per la clonazione animale”
Dr.C. Athanassopoulos “Total syntheses of medicinally interesting polyamine analogues”