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**TITOLO TESI**

# $PdI_2$ Catalyzed Oxidative Carbonylation of Amine Derivatives Leading to Macrolactam, Urea, Oxamide, Oxazolidinone and Benzoxazolone Derivatives

**Settore Scientifico Disciplinare** Chim/06 (Chimica Organica)

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**Chapter 1 Introduction**

# Chapter 1

# General Introduction

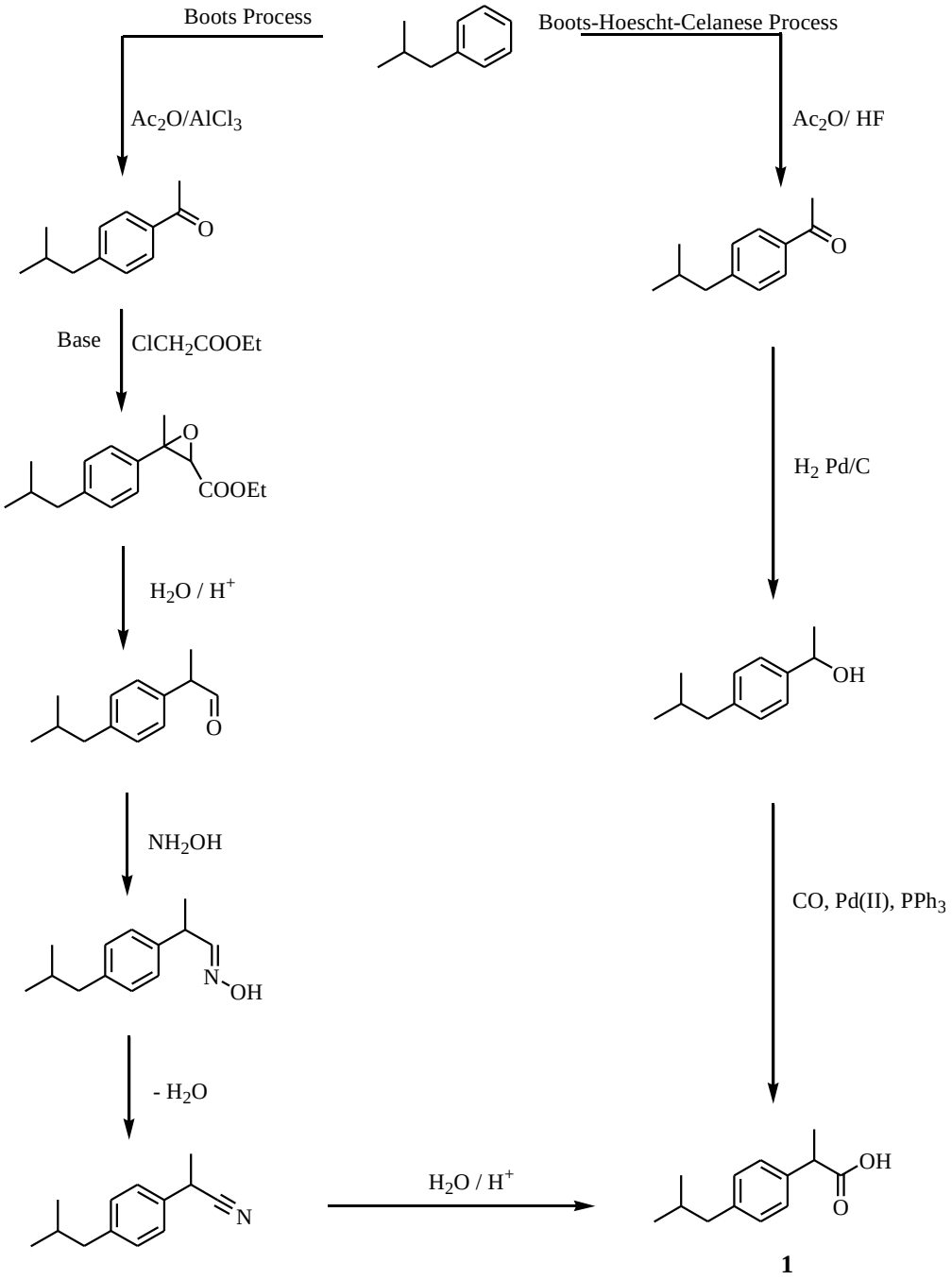
## 1.1 General Introduction to Carbonylation reactions:

Carbonylation, the incorporation of carbon monoxide into an organic substrates such as olefins, alkynes and alkylic, vinylic, arylic species is now widely recognized as a very important tool in industrial and organic chemistry[1]. It allows the direct synthesis of carbonyl compounds starting from the simplest C-1 unit, which also meets the requirements of "atom economy"[2], step economy[3] and "green chemistry"[4]. The distinguishable advantages of carbonylation reactions are, the carbon chain can be easily increased after the insertion of carbon monoxide; carbonyl-containing compounds are important synthetic intermediates in organic synthesis, which hold imperative applications in advanced materials, dyes, pharmaceuticals, and so on; Being a fundamental and promising transformation, the carbonylation process introduces a new approach for constructing synthetically versatile cyclic-acyclic carbonylated derivatives with high efficiency and selectivity[5]. This growing importance of carbonylation methods in organic synthesis is attested to by the increasing number of publications dealing with this topic, including reviews[1].

Carbon monoxide (CO) was discovered in the 18th century by de Lassone who reacted zinc oxide with coke. Since then first application of CO in chemical industry 80 years ago, academic and industrial laboratories have broadly explored CO's use in chemical reactions[6]. Today organic chemists routinely employ CO as an inexpensive and easily available C1 source to synthesize all kinds of carbonyl compounds. Dramatic increase in global fuel consumption and the resulting emissions of enormous quantities of CO and $CO_2$ are contemporary energy and environmental issues. Since the utilization of CO and $CO_2$ as the C1 building block for fuels and chemicals is one of the most promising strategies to solve both issues, reduction and utilization of $CO_2$ and CO in carbonylative processes has been extensively investigated[5]. Among the different catalytic reactions, carbonylation is of particular importance, which represents industrial core technologies for converting various bulk chemicals into a diverse set of useful products of our daily life. In fact, today the largest applications of homogeneous catalysis in bulk chemical industry (regarding scale) are carbonylation reactions, especially hydroformylations. The most successful example of industrial carbonylation process is the synthesis of acetic acid via carbonylation of methanol (by

Rh catalysis Monsanto process or Ir catalysis Cativa process)[7]. Not only carboxylic acids, esters and amides are accessible by carbonylation, but anhydrides, acid fluorides, aldehydes, and ketones can also be easily synthesized. Which of these products are obtained depends on the nucleophile: water (hydroxycarbonylation), alcohols (alkoxycarbonylation), amines (aminocarbonylation), carboxylate salts, fluorides, hydrides, or organometallic reagents can be used. A variety of carbonylation products can be prepared from the same aromatic substrate simply by changing the nucleophile, an advantage with respect to biologically active compound libraries. In addition to intermolecular carbonylations, intramolecular reactions are also possible, which allow for the synthesis of heterocycles. A prominent example is the intramolecular alkoxy- or aminocarbonylation (cyclocarbonylation) of hydroxy- or amino-substituted aryl/vinyl halides which enables the synthesis of lactones, lactams, oxazoles, thiazoles, imidazoles, and other heterocycles.[5]

An elegant example of carbonylative approach is the Hoechst-Celanese process for the synthesis of non-steroid anti-inflammatory drug, ibuprofen[8] **1** a common pharmaceutical product presently manufactured in over 8000t/y (Scheme 1.1)[8b]. Two routes for the production of ibuprofen, via the common intermediate, p-isobutylacetophenone, are compared. The classical route, developed by the Boots Pure Drug Company entails six steps with stoichiometric reagents, relatively low atom efficiency and substantial inorganic salt formation. In contrast, the elegant alternative, developed by the Boots Hoechst-Celanese (BHC) Company, involves only three catalytic steps. Acetylation, hydrogenation and carbonylation, in which last two steps are 100% atom efficient. It represents a benchmark in environmental excellence in chemical processing technology that revolutionized bulk pharmaceutical production and became a source of inspiration for other pharmaceutical manufacturers for utilization of direct carbonylative protocols.




(Scheme 1 Synthesis of Ibuprofen **1**, Classical route Vs carbonylative approach )

Although, until the early sixties carbonylation chemistry was little considered as a synthetic method for the preparation of fine organic chemicals, but in recent years, there has been a dramatic change in this picture, mostly brought about by the discovery of stable but extremely active catalysts based on organophosphine complexes of Palladium and Rhodium. Many carbonylations can now be carried out below 100°C at atmospheric pressure, using very small quantities of non-volatile, air-stable catalyst precursors, such as $[Pd(PPh3)_2CI_2]$ or $[RhCI(CO)(PPh_3)_2]$ and $K_2PdI_4$

[1a-e], which are converted to the active catalytic species *in situ.* Moreover, the scope and understanding of carbonylation has grown to such an extent that it can now be regarded, like catalytic hydrogenation, as one of the more generally useful techniques of synthetic organic chemistry, with a well-developed set of guidelines for choice of catalyst and reaction conditions. In most cases the functional group tolerances of catalysts and reaction conditions have been examined and selectivities between different functional groups established, so that reactions using new substrates can be carried out with a degree of confidence impossible a few years ago.

Different kinds of carbonylation reactions can be defined; depending on the particular type of process under consideration four types of carbonylation processes are possible.

1) Substitutive Carbonylation

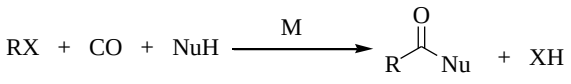
2) Additive Carbonylation

3) Reductive carbonylation

4) Oxidative Carbonylation

### 1.1.1 Substitutive Carbonylation

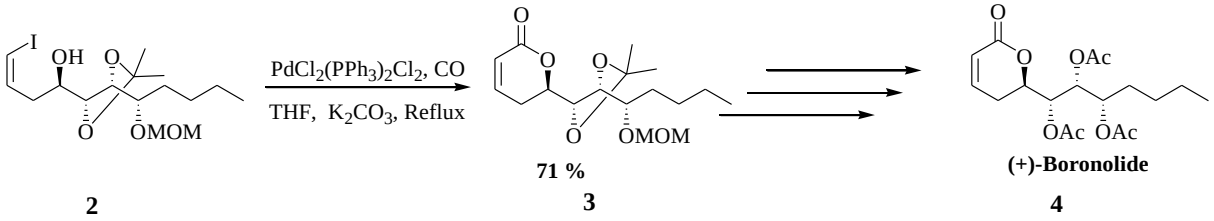
"Substitutive carbonylation" is a process in which a certain functional group (Generally aryl halides), such as a C–X bond (X = I, Br, Cl, OTf or another possible leaving group) is formally substituted with a NuH moiety (Scheme 1.2) [NuH usually corresponding to an OH, OR, NHR, or $R^1NHR^2$group.] This is a particularly versatile type of reaction providing a wide range of 'acyl anion equivalents', which allow the synthesis of many carboxylic acid derivatives from organic halides. Substitutive carbonylation of aliphatic halides is also possible, but generally requires more vigorous conditions[1e].




X = I, Br, Cl, O $SO_2R$,... NuH = $H_2O$, R'OH, $R^1NHR^2$,.....

(Scheme 1.2)

Natural product (+)-Boronolide **4** isolated from Tetradenia fruticosa Benth having anti-malarial activity was synthesized starting from **2** by intramolecular cyclization process to obtain **3** via substitutive carbonylative approach[9] (Scheme 1.3)

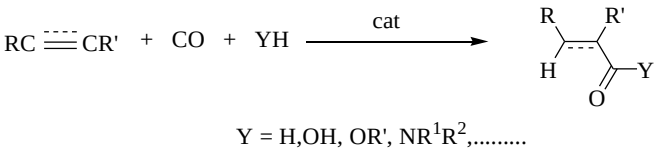



**2** **71 %** **3** **4**

(Scheme 1.3)

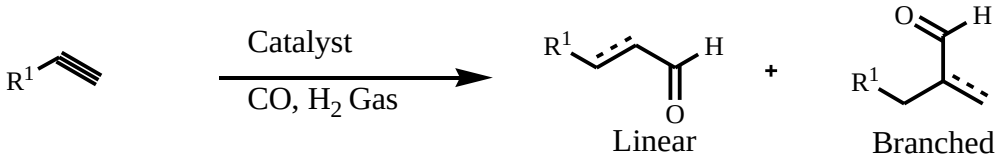
### 1.1.2 Additive Carbonylation

"Additive carbonylation" is a reaction in which a W–COY moiety (W usually corresponding to H; Y = H, OH, OR, NHR, $NR_2$, or some other nucleophilic group) formally adds to an unsaturated bond[1e] (Scheme 1.4).




(Scheme 1.4)

This type of carbonylation reaction mainly includes hydroformylation reaction Hydroformylation, also known as the oxo-process, refers to the addition of synthesis gas ("syngas"), a mixture of CO and $H_2$, to olefins in the presence of a catalyst under the formation of aldehydes. Hydrogen ("hydro") and a formyl group (H−C═O) are added in an atom-economical manner (Scheme 1.5).

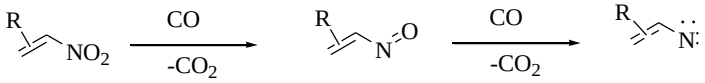



(Scheme 1.5)

Today, this transformation represents one of the largest homogeneously catalyzed reactions in industry[6]. Formed aldehydes are valuable final products and intermediates in the synthesis of bulk chemicals like alcohols, esters, and amines which has end application in preparations of detergents, surfactants, solvents, lubricants and chemical intermediates[10].

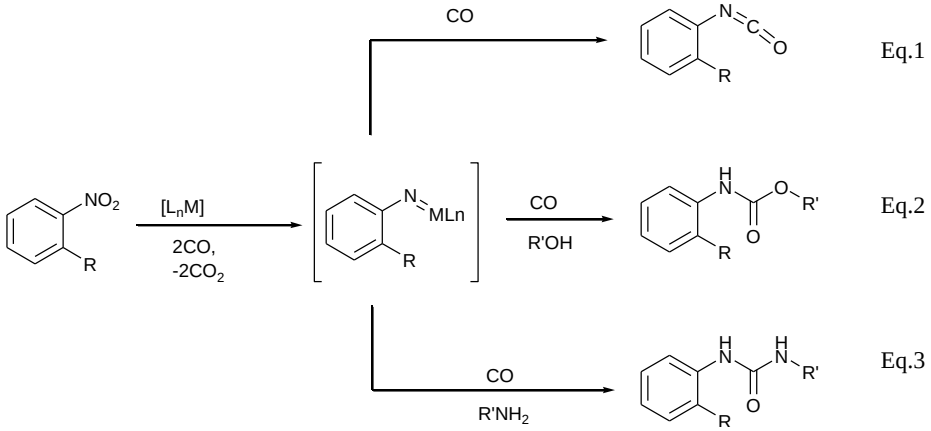
### 1.1.3 Reductive Carbonylation:

When carbonylation process takes place with reduction of the starting material(s), termed as reductive carbonylation[1e]. Metal catalyzed reductive carbonylation of nitroarenes to nitroso and/or nitrene is well known process of reductive carbonlylation[11] (Scheme 6) in which CO is oxidized to $CO_2$.




(Scheme 1.6)

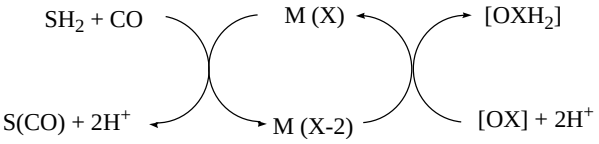
In recent years reductive carbonylation has been recognized one of the important process for phosgene free direct conversion of nitroarene to phenylisocyanates (Eq.1) phenylcarbamate (Eq.2), and urease (Eq.3) derivatives1[20a-c] (Scheme 7).




(Scheme 1.7)

### 1.1.4 Oxidative Carbonylations

An oxidative carbonylation process can be defined as a process in which carbon monoxide is inserted into an organic substrate under the action of a suitable metal species undergoing a reduction of its oxidation state [The reduction M(X) to M(X– 2) being the most common case]. Usually an oxidative carbonylation process is promoted by a metal in a relatively high oxidation state, [most commonly M(II)], in the presence of an external oxidant. In order to achieve a catalytic process, the reduced metal must be reoxidized to its original oxidation state through the action of a suitable external oxidant (Scheme 1.8).




(Scheme 1.8)

**[**Scheme12. The principle of oxidative carbonylation. M (X) = metal catalyst promoting the process; [$SH_2$] = organic substrate; [OX] = oxidant; [S(CO)] = carbonylated product; [$OXH_2$] = reduced oxidant.]

Oxidative carbonylation is an important and powerful tool for the direct synthesis of carbonylated heterocycles[1a-e]. A wide variety of chemically and functionally distinct heterocyclic compounds were synthesized with the application of oxidative carbonylative approach by several research groups. Several oxidative carbonylative processes tends to undergo alkoxycarbonylation, aminocarbonylation and hydroxy carbonylation with respect to external nucleophile as Alcohol, amine and water. Synthesis of several heterocyclic compounds by Gabriele catalyst ($PdI_2$ in conjunction with KI) via Oxidative carbonylation will be discussed deeply in the next part.

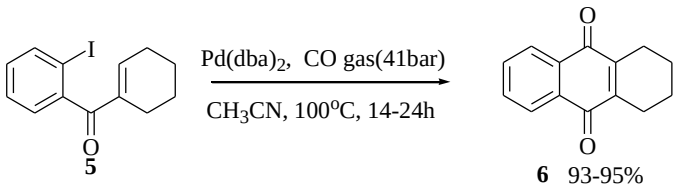
### 1.1.5 Carbonylative coupling reactions

C-C bond forming coupling reaction are routinely applied in the synthesis wide variety of organic compounds. Since Heck and co-worker reported the firstly the use of CO for heck coupling, new era of carbonylative cross coupling reactions started. Several examples of Heck coupling, Stille coupling, Suzuki coupling, Sonogashira coupling and so on has been published in last two decades. Cross-coupling reactions have become reliable transformations for all kinds of complex natural product syntheses. Moreover, the advancements in cross-coupling chemistry have made it possible that some carbonylations of aryl halides are efficient enough to be run in industry on a ton scale. Carbonylative coupling reactions can works under mild conditions such as ambient or low pressure, which also increased their interest in academia too.

#### 1.1.5.1 Carbonylative Heck Coupling Reaction

In 1974 Heck and co-workers described palladium-catalyzed alkoxy, hydroxy, and aminocarbonylation of aryl iodides and bromides, which is referred as ‘Heck carbonylation Reaction[13]. To date many carbonylative heck coupling reactions were

reported of aryl halide[14b], vinyl halide[14c], aryl triflates[14d] with alkene and allenes[15a-c] to form cyclic acyclic derivatives. Negishi and his group reported first palladium catalyzed intramolecular synthesis of various quinines[14a] **5** from o-iodoaryl cyclohexenylketones (Scheme 1.9) as starting material**4**. in good yields with 100% regioselectivity.

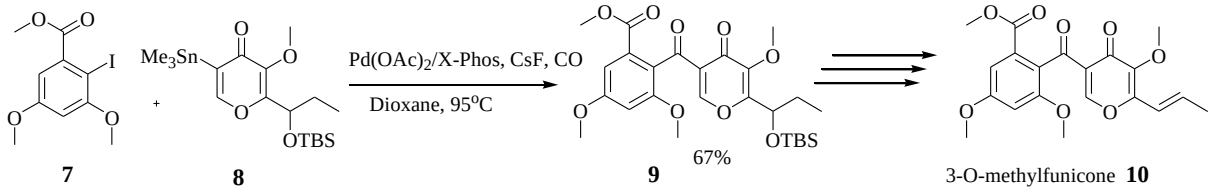



(Scheme 1.9)

### 1.1.5.2 Carbonylative Stille Coupling Reaction

The carbonylative Stille reaction between organic halides (or pseudohalides), carbon monoxide, and stannanes has been extensively studied in the past 20 years. In spite of the toxicity of the tin compounds, the Stille carbonylation has found many applications in organic synthesis because of its functional group tolerance and versatility.

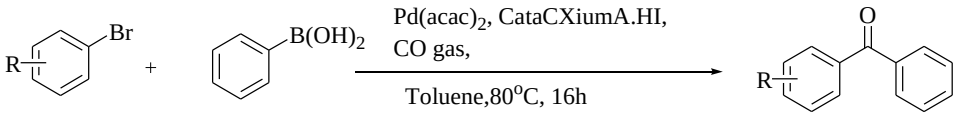
Antiproliferative and antifungal3-O-methylfunicone **10** was synthesized by carbonylative stille cross coupling. Intermediate **9** was synthesized by Carell et al by carbonylative stlle cross coupling[16] of organohalide **7** with organostannate **8** under stille condition yielded coupling product **9** in moderate yield. (Scheme 1.10)




(Scheme 1.10)

### 1.1.5.3 Carbonylative Suzuki Coupling Reaction

In 1993 first carbonylative Suzuki cross coupling was reported by A. Suzuki and co-workers[17]. Since then extensive work has been done to make the transformation more efficient and to widen its substrate scope[18]. Several diaryl and heteoaryl ketone[19] derivatives**13** unsymmetrical biaryl ketones[17] were synthesized by carbonylative cross coupling of aryl halide **11** with aryl boronic acids **12** (Scheme 1.11).

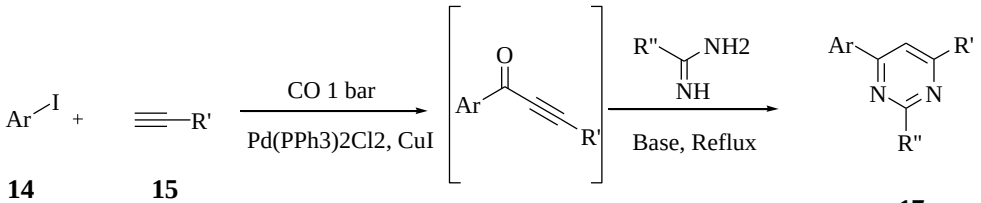



**11** **12** **13**
62-90%

(Scheme 1.11)

### 1.1.5.4 Carbonylative Sonogashira Coupling Reactions

The carbonylative three-component cross-coupling of aryl halides with terminal alkynes in the presence of amines as the base to give alkynyl ketones is known as the carbonylative Sonogashira reaction. Carbonylative Sonogashira reactions have been successfully employed in natural product syntheses. For example Bhanage et al reported the synthesis of 2,4,6-trisubstituted pyrimidines[20] **17** by a consecutive four-component carbonylative reaction sequence in one pot. (Scheme 1.12) Starting from carbonylative Sonogashira coupling between (hetero)aryl iodides **14** and alkynes **15** to obtain in situ intermediate **16** which then underoes alkynylation/cyclocondensation with amidines to yield trisubstituted pyrimidine **17.**




**14** **15** **16** **17**

(Scheme 1.12)

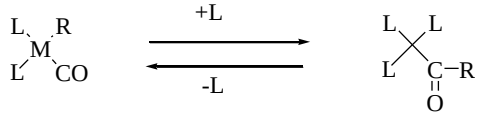
## 1.2 Transition metals in Carbonylation reactions:

Transition metal catalysis dominates the organic synthesis and the fine chemical industry. Specifically, there are numerous procedures in industrial and fine chemical companies that require transition metals as their key catalysts[21]. Stoichiometric and catalytic transition-metal reactions have attracted great interest for their many applications in industrial and synthetic processes. Transition-metal reactions are critical in many thermodynamically feasible processes because they accelerate the reaction by opening a lower activation energy pathway, often one that was symmetry forbidden. These metal-centred reactions consists of one or more elementary reactions such as substitution, oxidative addition, reductive elimination, migratory insertion, hydrogen exchange, α-hydrogen transfer, σ-bond metathesis and nucleophilic addition.

First use of transition metal catalyst in carbonylation reaction as Cobalt ($HCo(CO)_4$) for hydroformylation of alkene with Carbon monoxide and hydrogen gas was reported in 1938 known as Roelen Reaction.[22] and in 1953 Reppe's first catalytic carbonylation process converted acetylene, CO, and water to acrylic acid ( Hydroxycarbonylation) using $Ni(CO)_4$ as catalyst.[23] This was most fascinating examples of carbonylation reactions involving the interaction of a π-system with a transition metal. Since then carbonylation, "an insertion of Carbon monoxide in organic substrate under the action of suitable metal catalyst (preferably transition metal) became an important synthetic tool for the synthesis of carbonylated derivatives. Continuous research progress in this area has led broader applications in the synthesis of a wide variety of simple carbonyl compounds to more complex organic molecules.

Synthetic organic reactions involving carbonylation of alkenes, alkynes such as hydroformylation and hydroesterification, amino and alkoxy carbonylation are catalyzed by the complexes of late transition metals such as Se[24],Tl[25], Hg[26] Mn[27] Fe[28] Co[29,] Ni[30], Cu[31], Ru[32], Rh[33], Pd[34], $PdI_2$[35], W[36], Pt,[37],Ir [38] and Au[39]. In most cases metal carbonyl complexes have been used or assumed as catalyst. e.g. $HCo(CO)_4$, $HRh(CO)(PR_3)_3$ , $Ni(CO)_4$. In general these reactions involve activation of CO molecule by transition metal complexes as the key step; CO coordinates to the metal

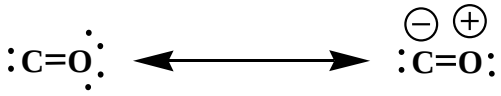
center, giving the carbonyl-metal intermediates, and migratory insertion of the CO ligand into the M-C bond takes place as shown in (scheme 13). Subsequent decomposition of the acyl-metal complex by reaction with a nucleophilic substance having an active hydrogen (H-Y) results into final nucleophilic displacement to yield product respect to the nucleophile.




(Scheme 1.13)

### 1.2.1 Chemistry of Carbon monoxide

Carbon monoxide (CO) is a colourless, odourless, and tasteless gas that is slightly less dense than air. It is highly toxic to humans and animals when encountered in higher concentrations. CO is relatively inert molecule, although it reacts with carbocations and carbanions, it is relatively non-reactive toward organic compounds without the intervention of metal catalyst. So generally all kind of carbonylation reactions were carried out under the action of suitable metal catalyst.




"carbene like" "dinitrogen like"

Carbon monoxide has a molar mass of 28.0, which consists carbon and oxygen bonded by triple bond, which is formed of two covalent bonds and one dative covalent bond with one pair of electron shared by oxygen. CO is the simplest oxo-carbon, and iso-electronic with the cyanide ion and molecular nitrogen. The bond length between the carbon atom and the oxygen atom is 112.8 pm. The bond dissociation energy of 1072 kJ/mol which is stronger than that of $N_2$ (942 kJ/mol) and represents the strongest chemical bond known. The ground electronic state of carbon monoxide is a singlet state since there are no unpaired electrons.

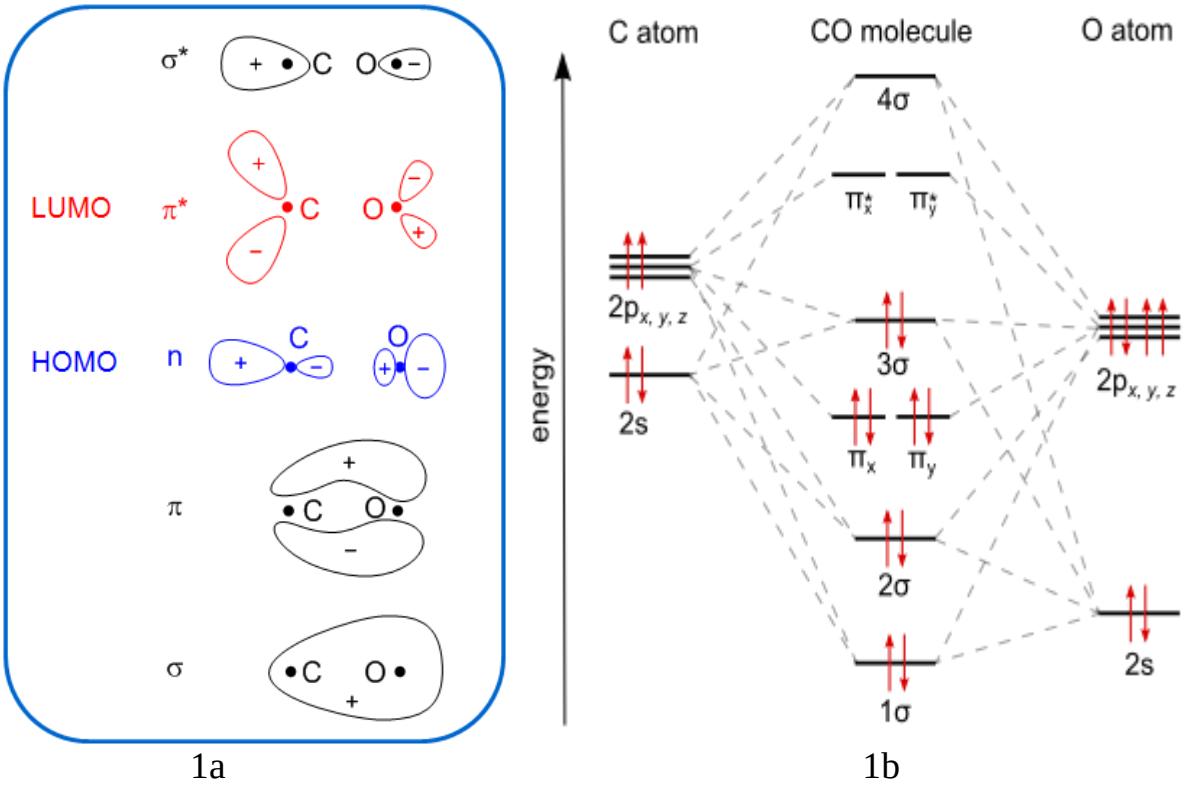



Fig. 1 energy level diagram of CO molecule

The qualitative molecular orbital description of CO is described with special emphasis on hybridization of ***σ*** and ***π*** orbitals. The MOT principle states that orbitals combining to form a strong bond must have comparable energies or two atomic orbitals can form a strong bond only if their energies are fairly close[40]. Inspection of Fig. lb, which describes the energy level diagram, shows that this criterion of similar energies in CO can only meet if $\sigma_1$ of carbon interacts with $\sigma_2$ of oxygen to form the sigma bond. As a result, the lone pair of the carbon atom in :C≡O: will be in $\sigma_2$ oribital and have largely $p_z$, character and the lone pair of the oxygen atom will be in $\sigma_1$ and have largely ***s*** character. Thus the ionization potential of the carbon lone pair is quite low and makes it a relatively basic lone pair which is available for π back-donation while the ionization potential of the oxygen lone pair is relatively high and these electrons are unavailable chemically. Sahni et al[41]. estimated from the data of set of "localized" CO orbital, that the lone pair orbital localized predominantly on the oxygen atom has approximately 22 per cent ***p*** character while on the orbital localized predominantly on carbon approximately 68 per cent ***p*** character. Thus in carbon monoxide carbon has predominantly ***p*** character which makes CO as nucleophile and

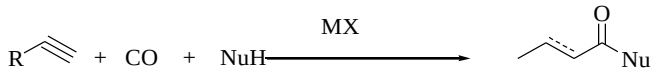
directional at carbon end while orbital localized predominantly on Oxygen has ***s*** character and is not strongly directional.

The energy level diagram of CO further serves to explain the reactivity of carbon monoxide toward nucleophilic reagents (e.g. $RO^-$) as well as the unusual ability of carbon monoxide to accept back-donation from filled *d* orbitals in transition metal carbonyls. The lowest unoccupied orbital is a π* orbital (Ccpπc-Copπo). Inspection of the MO diagram shows that this orbital lies much closer to the pπ orbitals of the isolated carbon atom than those of the isolated oxygen atom, and hence receives a predominant contribution from the carbon Pπ orbital and a much smaller contribution from the corresponding oxygen orbital, i.e. Cc > Co. Accordingly, nucleophilic attack occurs exclusively on carbon, and overlap of the π* orbital with a dπ orbital of a metal is favorable because in the

$\int d\pi_{metal}\pi_{co}{}^{*}d_T = \int d\pi_{metal}(c_c p\pi_c - c_o p\pi_o)\ d_T = c_c\int d\pi_{metal}\, p\pi_c\ d_T - c_o\int d\pi_{metal}\ p\pi_o d_T$ the last integral is small and multiplied by a small coefficient, and $\int d\pi_{metal}\ p\pi_o d_T$ is large and multiplied by a large coefficient. The relatively low energy of the π* orbital further contributes to its acceptor ability and electrophilic character.

### 1.2.2 General Mechanistic Approach of Transition Metals in Carbonylation:

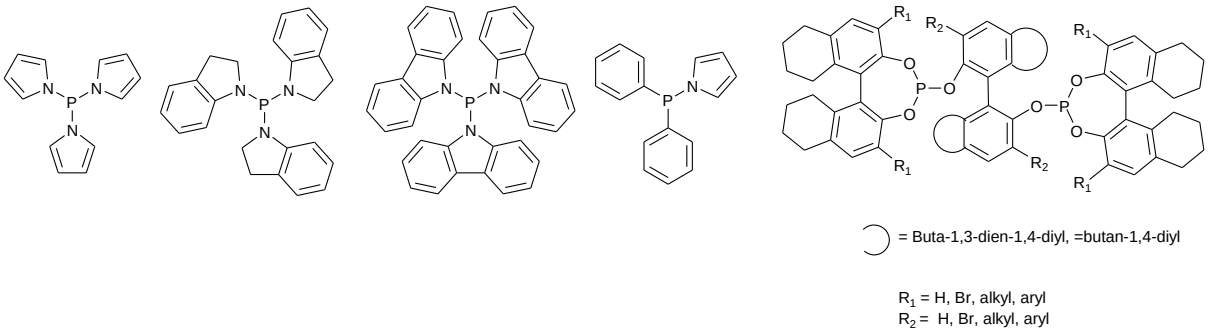
In general transition metal catalyzed carbonylation of olefins/acetylenes with nucleophiles such as alcohol, amine, hydrogen gas or water yields respected carbonylated derivatives (Scheme 1.14)




(Scheme 1.14)

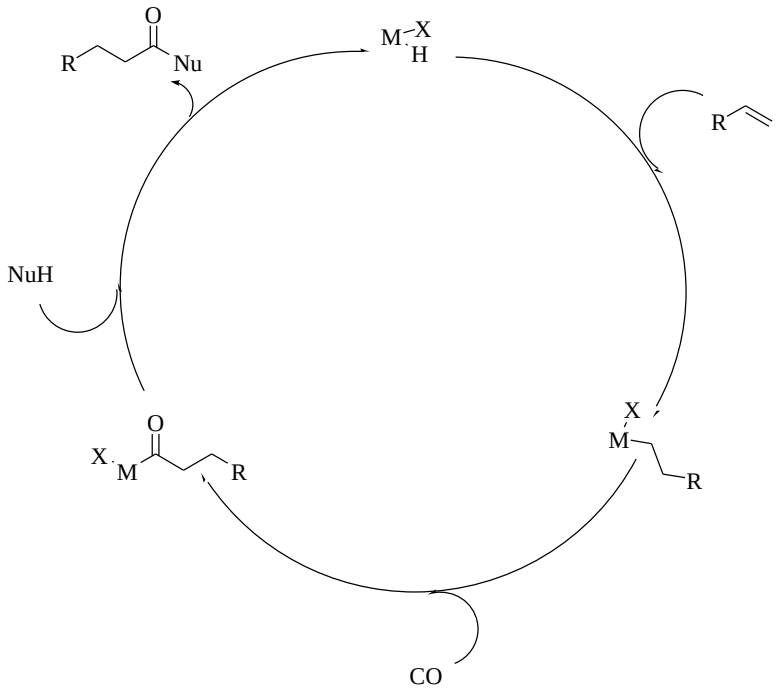
At the beginning of industrial homogeneous catalysis, nickel and cobalt catalysts prevailed in alkoxycarbonylations and hydroformylations. Later on there was tremendous increase in interest to develop less expensive and more selective catalysts based on transition metal for these reactions. Till date catalyst based on Rh, Pd, Ru, Pt, Ir, Fe, Ni, Mo, Cu has been discovered and developed by several research groups. Due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylation) and palladium (for alkoxycarbonylations) as base metals[6]. Due to the advancements in organometallic

chemistry and organic ligand synthesis, now a days a plethora of ligands -N, -P and recently C-ligands is theoretically available (10.000 to 1000.000). These ligands are extremely important in determining the reactivity, productivity and selectivity of a homogeneous metal catalyst, In fact, "ligand-tailoring" constitutes an extremely powerful tool to control all kinds of selectivity in a given catalytic reaction and to influence catalyst stability and activity[42]. Some representative examples of –N, -P ligands are shown in Scheme 15.




(Scheme 1.15)

Despite the differences in the Organometallic catalyst, substrates or nucleophile carbonylation reaction follows general mechanism (Scheme 1.16)




NuH = $H_2$, alcohol, amine, water

(Scheme 1.16)

The reaction starts with the corresponding metal-hydride species, which is primarily formed by the reaction of the pre-catalyst with acid additives (TsOH, HBF4, etc.) or from the reaction of a suitable acyl metal complex with nucleophiles during the catalytic cycle. Subsequent coordination, insertion of the unsaturated substrates, followed by further insertion of carbon monoxide leads to the acyl metal complex. Finally, the catalytic cycle is finished by the nucleophilic attack of the nucleophile on the acyl-metal species and the metal-hydride is regenerated.

As mentioned above due to the improved activities and selectivities since the 1970s, catalyst developments focused especially on rhodium (for hydroformylation) and palladium (for alkoxycarbonylations) as base metals[6] and other metals used scarcely for these kinds of reactivities except cobalt considering as cost effective catalyst. Rhodium, Cobalt and Palladium catalyzed carbonylation will be discussed here.

### 1.2.3 Rhodium Catalyzed Carbonylation Reactions:

Rhodium (Rh) catalysts can be up to 1000 times more reactive than Co complexes. These features have also been recognized by the chemical industry. Thus, in 1980 less than 10% of hydroformylation was conducted with rhodium; by 1995 this had increased to ~80%. Rhodium catalyzed isomerization and hydroformylation reactions of internal olefins provide straightforward access to higher value aldehydes. Catalytic hydroaminomethylations offer an ideal way to synthesize substituted amines and even heterocycles directly.

Rh catalyzed hydroformylations can yields into formation of linear and branched aldehyde product. Linear aldehydes are of great interest in chemical industry and so mostly the research was focused on improvement of the regioselectivity. In order to obtain excellent regioselectivity, organometallic complex of Rh catalyst were designed and synthesized with chelating bulky phosphites or phospines as ligands on the basis of conclusion made on the observations.

* Rate of isomerisation of internal olefins must be faster than the hydroformylation reaction.

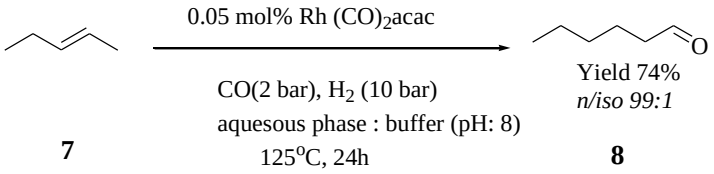
* Catalyst should be highly *n* selective for the hydroformylations.

* Rhodium species coordinated with less electron-rich ligands exhibit significant activity toward isomerization of the substrate.

* Regioselectivity of the hydroformylation is influenced by π-acceptor and σ-donor properties of the respective ligand, so electronic properties of heterocyclic phosphine ligands can influence the *n / iso* regioselectivity.

Keeping in mind the above conclusions several group especially M. Beller and co-worker reported several bulky phosphine and phosphite based ligands for Rh catalysis. Such as pyrrolyl, indolyl, carbazoyl, Bisphosphite 1a, BINAS 1b,(Scheme1.15)

M. Beller et al reported the highly selective water-soluble rhodium-catalyzed hydroformylation of pentene[43] **7** by the use of Sulfonated Naphos (so-called BINAS). Apart from the ligand tailoring, also the pH value and CO partial pressure are important factors for the success of this reaction. The product was obtained n-selectivities exceeded in good yields and the catalyst was easily reused several times without decrease of product yield and selectivities (Scheme 1.17).




(Scheme 1.17)

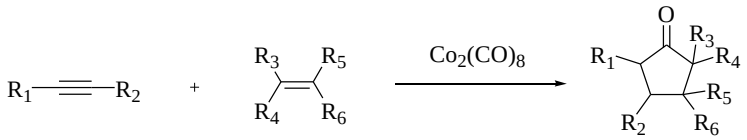
### 1.2.4 Cobalt catalyzed carbonylation reactions:

As mentioned earlier in introduction, on apart from rhodium and palladium, other metals have only been scarcely applied in carbonylative transformations so far. The main reasons for this were the low activity of the corresponding metal carbonyl complexes as well as the tendency to undergo increased side reactions such as hydrogenations. On the other hand, the fact of the lower costs and toxicity of cobalt catalysts in comparison with other transition metals, ecological and economical cobalt-mediated transformations have received continuous ever-growing attention during the two last decades that leads to exciting and fruitful research. Moreover, cobalt has a high affinity to carbon−carbon π-bonds, carbon−nitrogen π-bonds, and carbonyl groups that was used to develop the Nicholas reaction [2+2+1] cycloaddition, Pauson− Khand reaction, [2+2+2] cycloadditions. [45] The cobalt

carbonyls mainly $Co_2(CO)_8$ and cobalt hydrocarbonyl, $HCo(CO)_4$ play important roles in the catalysis[46].

### 1.2.4.1 Pauson–Khand reaction

Pauson–Khand reactions are the most representative reactions with the organocobalt compounds used in organic synthesis[47]. These reactions involve the cyclization of one acetylene**9**, one olefin**10** and a cobaltcarbonyl (as a carbon monoxide source, e.g. octacarbonyldicobalt) and yield cyclopentenone**11** by the [2 + 2 + 1] cyclization addition, as shown in (Scheme 1.18). In these reactions, $Co_2(CO)8$ reacts with acetylene at room temperature for several hours to form a stable acetylene $\pi$-complex, then an olefin reacts with the complex under a nitrogen or carbon monoxide atmosphere with heating. Generally, a stoichiometric amount of the metal is required to achieve an acceptable yield because the cobalt carbonyl compound is used as the carbon monoxide source[48].




**9** **10** **11**

(Scheme 1.18)

### 1.2.5 Palladium catalyzed carbonylation reactions:

Palladium-catalyzed coupling reactions are well known; also carbonylation reactions have experienced impressive improvements since the first work of R. Heck and co-workers in 1974. Palladium catalysed carbonylation reactions are now widely recognized as a very important tool in industrial and organic chemistry Palladium metal based catalytic system has been routinely employed in carbonylation reactions preferably for oxidative carbonylation and carbonylative coupling reactions than hydroformylation reactions. Palladium catalyzed oxidative carbonylation reactions require the coupling of organic nucleophiles or electrophiles in the presence of CO and an oxidant to prepare various carbonyl-containing compounds[49]. Under oxidative carbonylation conditions palladium can leads to the formation of mono and double carbonylated products[50]. Most commonly Pd(II) catalyst reacts with the organic

substrates of electron-rich species, such as olefins, alkynes, and arenes[51]. Numerous Pd(II) complexes of the type $L_2PdX_2$ can be easily formed from PdCl2 and the appropriate ligand L. The well known Pd(II) complexes[52] are $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, and $PdCl_2(RCN)_2$ and $PdI_2$[1a-e, 53]. Various carbonylation reactions catalyzed by palladium metal have been reported in literature.

### 1.2.5.1 Palladium catalyzed oxidative carbonylation:

Under palladium catalyzed oxidative carbonylation conditions amines (mostly primari), diols and aminoalcohols undergoes mono-carbonylation process results into the formation of ureas[54] (Eq.1), carbamate, cyclic carbonates[55] and Oxazolidinone[56] (Eq.2) derivatives (Scheme 1.19).

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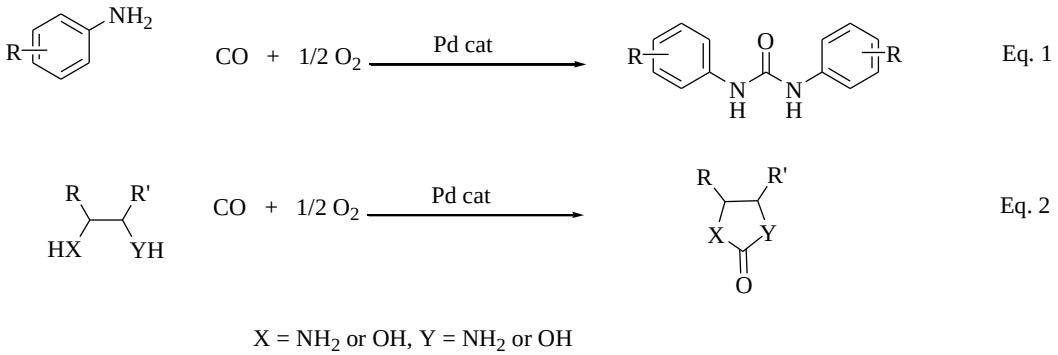
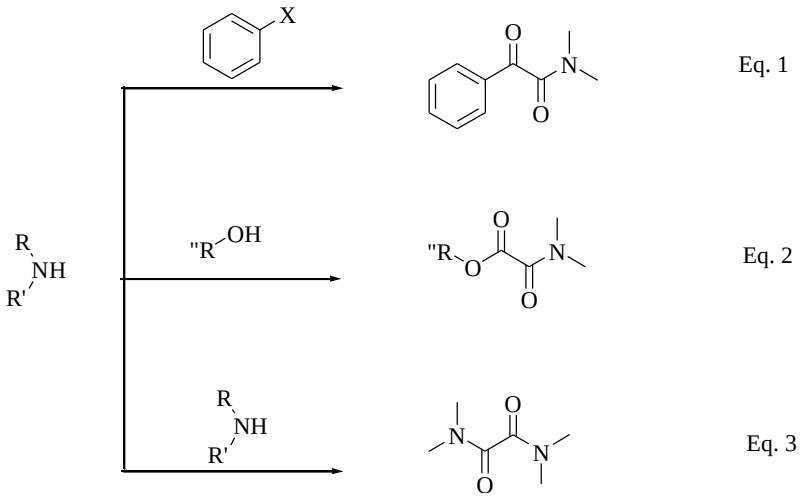



X = $NH_2$ or OH, Y = $NH_2$ or OH

(Scheme 1.19)

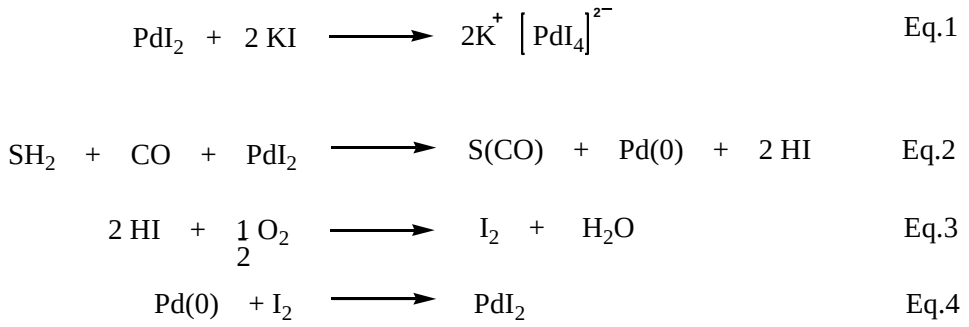
Palladium catalysed double carbonylation of amines and aryl halides is an important reaction for the synthesis of a-keto amides[57] oxamides[58] and oxamates[59] (Scheme 1.20)




(Scheme 1.20)

### 1.2.5.2 Gabriele Catalyst: $PdI_2$ in conjunction with KI

The Gabriele Catalyst, $PdI_2$ in conjunction with KI was introduced by Prof. Gabriele about 20 years ago[53], now this catalytic system has been established as one of the most versatile and efficient catalysts for the oxidative carbonylation of simple and functionalized alkynes.[1a-e] Gabriele catalyst in conjunction with an excess of iodide anions from KI, constitutes an exceptionally efficient, selective and versatile catalyst for promoting a variety of oxidative carbonylation processes, leading to important acyclic as well as heterocyclic carbonyl compounds under mild conditions and with high selectivity. The main characteristics of this system are its simplicity, the only ligands for Pd(II) being electron rich iodide anions which also provides efficient mechanism of re-oxidation of Pd(0) to Pd(II) by the use of oxygen directly as the external oxidant. $PdI_4^{2-}$ formed in situ (Eq.1 Scheme 1.21) from the reaction between $PdI_2$ and KI is an active species to carry out the effective carbonylation process, also responsible for solubility of catalyst in the solvent which tends to perform carbonylation under homogeneous catalytic conditions. General mechanism for $PdI_2$/KI catalyzed carbonylation can be described as (in the following schemes anionic iodide ligands are omitted for clarity), Carbonylation of organic substrate ($SH_2$) results into formation of carbonylated product and reduced Pd(0) species along with liberated two moles of HI (Eq.2; Scheme 1.21). Reaction of HI with oxygen present in gas mixture occurs along with production of water as product (Eq.3; Scheme 1.21). Pd(0) reoxidation occurs through oxidative addition of $I_2$ (Eq.4; Scheme 1.21)



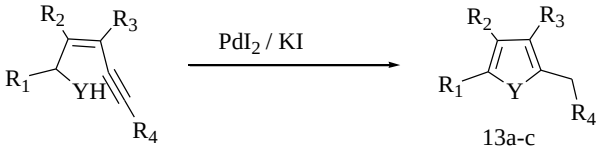

(Scheme 1.21. Mechanism of Pd(0) reoxidation in $PdI_2$/KI-catalysed oxidative carbonylation reactions. Anionic iodide ligands are omitted for clarity. $SH_2$ = organic substrate; S (CO) = carbonylated product.)

$PdI_4^{2-}$ was generally a more active catalyst species than $PdCl_4^{2-}$, which was, in turn, more active than neutral complexes, such as $(PhCN)_2PdCl_2$ or $Pd(OAc)_2$. These results indicates that the active catalytic species is stabilized by halide ligands. Moreover, the better results obtained with iodide rather than chloride can be interpreted in view of the higher electron-releasing power of $I^-$ compared with $Cl^-$, which tends to favour the final protonolysis step leading to the heterocyclic ring.

Gabriele catalytic system is able to promote different heterocyclization reactions under mild conditions and with high selectivity. The synthetic protocols leading to heterocycles mainly grouped into two classes of reactions: (a) cycloisomerization; and (b) oxidative carbonylations. Cycloisomerization and oxidative carbonylations will be discussed and explained below.

### 1.2.5.2.1 $PdI_2$-Catalyzed Cycloisomerization Reactions:

The synthesis of substituted furans (Oxygen heterocycles), thiophenes (sulphur heterocycles), and pyrroles (nitrogen heterocycles) by transition metal-catalyzed heterocyclization reactions has recently attracted great interest in view of the possibility of constructing the heterocyclic ring with the desired substitution pattern in a one-step procedure[60]. From the point of view of atom economy[2], the ideal approach is clearly represented by a simple cycloisomerization process[61]. $PdI_2$ is an excellent catalyst for carrying out the cycloisomerization (Scheme 1.22) of (*Z*)-2-en-4-yn-1-ols (**12a**), (*Z*)-2-en-4-yne-1-thiols (**12b**), and (*Z*)-(2-en-4-ynyl)amines (**12c**) into the corresponding furans,[62] thiophenes,[63] and pyrroles[64] (**13a**–**c**), respectively has been reported by Gabriele research group.



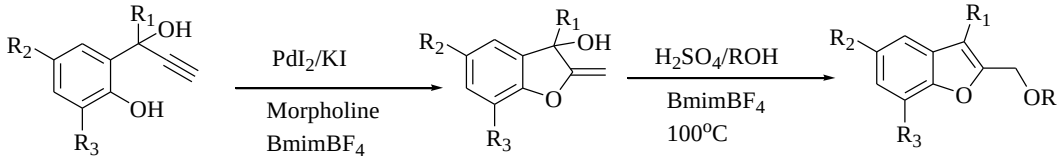

12a = Y = O
12b = Y = S
12c = Y= NR

13a-c

(Scheme 22)

Cycloisomerization reactions leading to furans, thiophenes, and pyrrols have been performed under mild conditions in classical organic solvents, either dipolar aprotic (such as *N*,*N*- dimethylacetamide (DMA), dimethylsulfoxide (DMSO), or MeCN), apolar or slightly polar (such as toluene, THF, or $CH_2Cl_2$), or protic ones (such as MeOH). However, recenly these processes were carried out successfully in unconventional solvents, such as ionic liquids (ILs). This has allowed the easy and convenient recycling of the reaction medium and/or of the catalyst[63b].

Recyclable approach for $PdI_2$ catalyzed synthesis of 2-methylene-2,3-dihydrobenzofuran-3-ols**15** by cycloisomerization of 2-(1-hydroxyprop-2-ynyl)phenols **14** in an ionic liquid medium (BmimBF4)[65] (Scheme 1.23) published recently by Gabriele research group. The recyclable process takes place under relatively mild conditions (100 °C, 5 h) in the presence of catalytic amounts (2 mol %) of $PdI_2$ in conjunction with KI (5 equiv with respect to $PdI_2$) and an organic base, such as morpholine (1 equiv with respect to **14**), to give **15** in high yields (70%–86%), and catalytic system was recycled up to six times. Moreover, conversion of products **15** into 2-hydroxymethylbenzofurans **16** (52%–71%) and 2-methoxymethylbenzofurans **17** (52%–80%) based on **14** was achieved in a one-pot fashion via acid-catalyzed allylic isomerization or allylic nucleophilic substitution.




**14** **15**

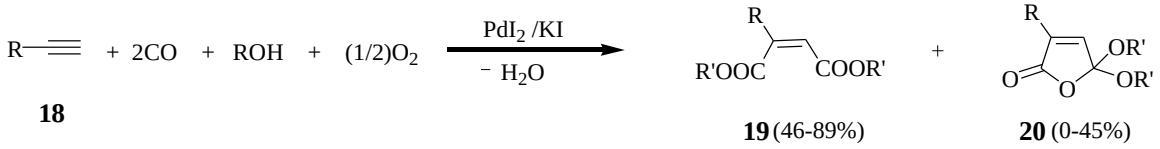
**16** = R=H
**17**= R =OMe

(Scheme 1.23)

### 1.2.5.2.2 $PdI_2$ Catalyzed Oxidative Carbonylation Reactions:

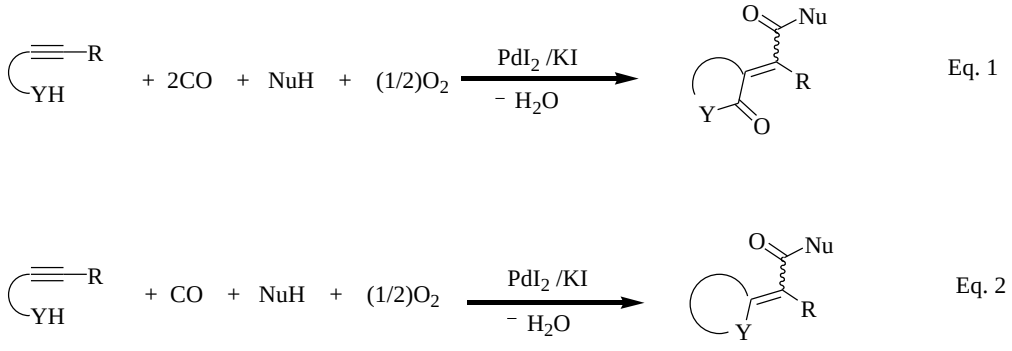
$PdI_2$/KI-catalyzed oxidative carbonylation of simple/substituted alkyl- or arylacetylenes, as well as of propynyl alcohol and propynyl acetate **18**, carried out in alcoholic solvents under mild conditions (15–25 atm of CO, 4–9 atm of air, 25–80

◦C), led to the formation of maleic derivatives**19** (together with small amounts of fumaric derivatives) and 5,5-dialkoxyfuran-2(5*H*)-ones**20**, in high yields and with unprecedented catalytic efficiencies for this kind of reaction (up to ca. 4000 mol of product per mol of Pd) (Scheme 1.24)[1d]. The furanone derivatives were easily converted into maleic esters by acid-promoted alcoholysis. The process could also be applied to the synthesis of maleic acids or maleic anhydrides[66] working in DME-H2O or water-containg dioxane, respectively, under appropriate conditions.




(Scheme 1.24)

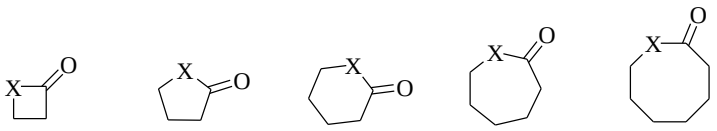
Alkynes bearing a nucleophilic group in suitable position for cyclization are excellent substrates for different kinds of oxidative carbonylation reactions leading to functionalized heterocyclic derivatives. $_{PdI2}$ catalyzed oxidative carbonylation process can leads to two different pathways a) oxidative Cyclocarbonylation (with incorporation of CO into the cycle) (Eq. 1; Scheme 1.25) and oxidative cyclization–carbonylation (without incorporation of CO ino the cycle) are possible (Eq.2; Scheme 10).




(Scheme 1.25)

**a) Oxidative Cyclocarbonylation:**

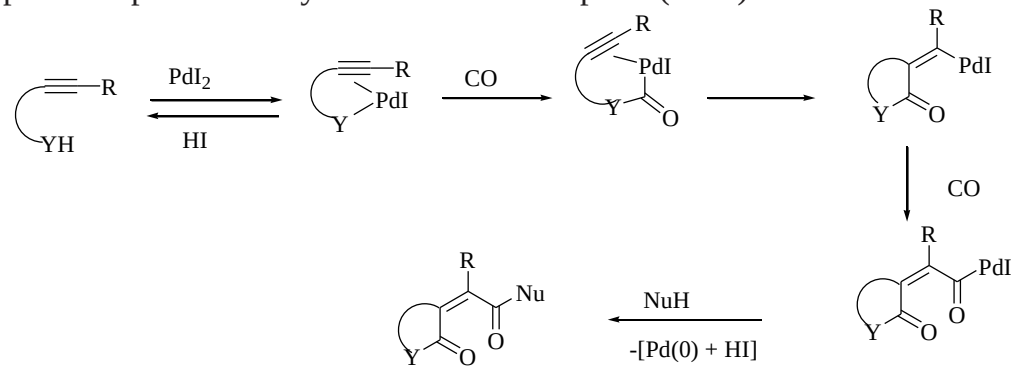
Synthesis of saturated or unsaturated heterocyclic compounds consisting carbonyl group in the ring such as lactones, lactams, and pyrrolidinones from small to large size can be achieved by direct oxidative cyclocarbonylation approach (Fig. 2) in single step[5].



X = O, -NH, -NR

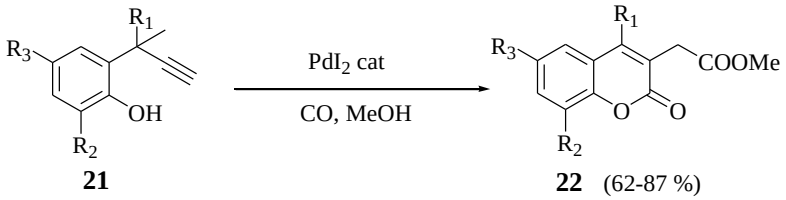
(Fig. 2 lactones and lactams of different size).

Cyclocarbonylative pathway (Scheme 1.26) proceeds via formation of an alkoxycarbonylpalladium (or carbamoylpalladium) intermediate[1e] through the reaction between the nucleophilic function of the substrate –YH (Y = O, NR), CO and $PdI_2$, followed by intramolecular *syn* insertion of the triple bond, CO insertion and nucleophilic displacement by an external nucleophile (NuH).



(Scheme 26)

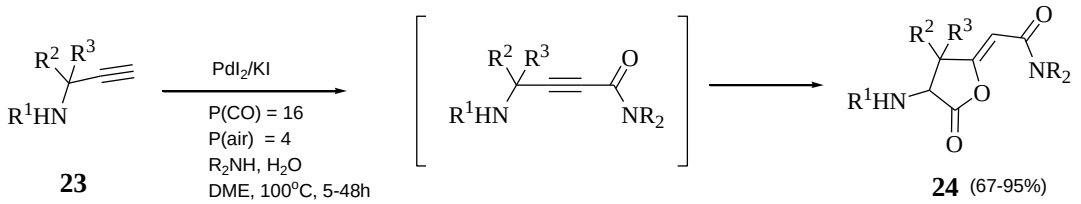
Synthesis of coumarin starting from readily available 2-(1-hydroxyprop-2-ynyl) phenols, under oxidative carbonylation conditions catalyzed by $PdI_2$/KI catalytic system[67] follows the cyclocarbonylative pathway (Scheme 1.27). Starting from readily available 2-(1-hydroxyprop-2- ynyl) phenols**21**, palladium-catalyzed cyclocarbonylative-dicarbonylation process in MeOH as the solvent in the presence of catalytic amounts of $PdI_2$ in conjunction with an excess of KI in at room temperature and under 90 atm of CO to gave 3-[(methoxycarbonyl)- methyl coumarins**22** in good to high isolated yields (62-87%).



(Scheme 1.27)

Gabriele et al, reported water and secondary amine mediated sequential oxidative aminocarbonylation/cyclocarbonylation process of α,α-disubstituted 2-ynylamines**23** (Scheme 1.28), leading to oxazolidin-2-ones **24**[68]**.** Via two sequential catalytic

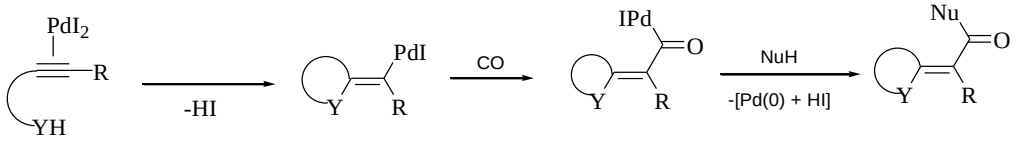
processes, both catalysed by $PdI_2$. The first corresponded to the oxidative aminocarbonylation of the triple bond of the substrate, with formation of the corresponding 2-ynamide derivative, and the second was a cyclocarbonylation, resulting from *N*-palladation, carbon monoxide insertion, water attack on the resulting carbamoylpalladium intermediate, intramolecular conjugate addition and [Pd0 + HI] elimination.




(Scheme 1.28)

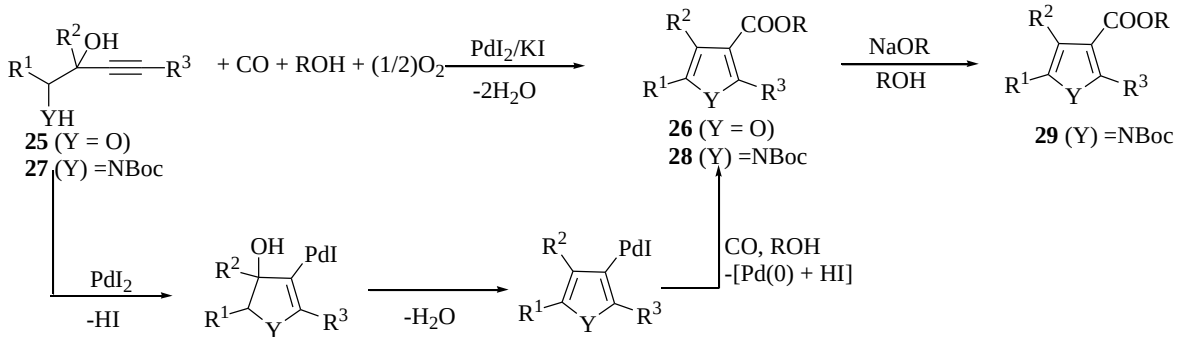
**b) Oxidative cyclization–carbonylation:**

This reaction pathway is also known as oxidative heterocyclization-carbonylation ,In this reaction pathway *anti* intramolecular nucleophilic attack[1e] by the –YH (Y= -O,-NH, -NR) group on the triple bond coordinated to $_{PdI2}$ occurs. Depending upon the substituted group on the nucleophile or the carbon chain, the cyclization mode either *exo* or *endo(* only the *exo* mode is shown in Scheme 1.29), followed by CO insertion and nucleophilic displacement by an external nucleophile (NuH).




(Scheme 1.29)

Gabriele catalyst catalyzed hetero-cyclization-carbonylation of 3-Yne-1,2-diols **25** or N-Boc-1-amino-3-yn-2-ols**27** leading to Furan-3-carboxylic Esters[69] **26** and Pyrrole-3-carboxylic Esters[70] **28** respectively has been reported (Scheme 1.30). Both the process undergoes $PdI_2$/KI-catalyzed *5-endo-dig* heterocyclodehydration-alkoxycarbonylation approach. Reactions were carried out in alcoholic solvents at 80−100 °C and under 20 atm (at 25 °C) of a 4:1 mixture of CO−air, in the presence of the $PdI_2$−KI catalytic system (2−5 mol % of $PdI_2$, KI/$PdI_2$ molar ratio = 10) resulted into formation Furan-3-carboxylic acid ester derivatives**26** in 56-72% yield, while Pyrrole-3-carboxylic acid esters**28** in 55-75% yields.




(Scheme 1.30)

The Gabriele catalyst ($PdI_2$/KI), has proved particularly efficient for oxidative carbonylation of acetylenic substrates bearing nucleophile groups in suitable positions for cyclization. A key characteristic of this system is the efficiency of the metal reoxidation process, which occurs with use only of oxygen as the oxidant and with production of water as co- product, making the $PdI_2$/KI-catalysed oxidative carbonylation reactions very attractive from the points of view of atom economy and sustainability. Another very important facet of this catalyst relates to its versatility, because it is able not only to promote different mechanistic pathways in the case of acetylenic substrates, but also to catalyse the oxidative carbonylation of different kinds of organic substrates, such as alkynes, amines, β-amino alcohols and diols.

## 1.3 Green and Sustainable Chemistry:

In a world with a continuously increasing population and limited resources, the idea of a sustainable development is of major importance for the future in the 21st century. Chairman of "The World Commission for Environment and Development" founded by the United Nations defined the term sustainable development[71] as, "Meeting the needs of the present generation without compromising the ability of future generations to meet their own needs." Only research and innovation will allow the development of economic and social networks and processes that fulfil the requirements of sustainability. Sustainability in science and technology begins when we start thinking how to solve a problem or how to turn science into technology. The original concept of sustainability emphasized the needs to combine social objectives (health, quality of life, employment) to the management of scarce resources (energy and raw materials) and the preservation of the natural bases for life, for example, the need to adopt all actions such as cleaner processes, recycle waste, reduce pollutant emissions necessary to preserve bio-diversification. Chemistry, as the science of matter and its transformation, plays a central role in this process and is the bridge between physics, material sciences and life sciences. Only chemical processes, which have reached a maximum in efficiency, will lead to more sustainable products and production. Sustainability through chemistry is thus an approach that starts from green chemistry concepts and goes on to a vision for the future sustainability of society.

### 1.3.1 Introduction to Green Chemistry:

The term 'Green Chemistry' was first coined in the early 1990s by Anastas and colleagues of the US Environmental Protection Agency (EPA). The term green chemistry[72] has been defined as *"the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances".* The main objective of green chemistry is to obtain safer, cleaner, and energy-efficient chemical processes and, to this end, twelve principles of Green Chemistry have been formulated by Anastas and Zimmerman[72] for benign by design of both products and processes. The concept of their 12 Principles which can be paraphrased or summarized as:

1. Waste prevention instead of remediation
2. Atom efficiency
3. Less hazardous/toxic chemicals
4. Safer products by design
5. Innocuous solvents and auxiliaries
6. Energy efficient by design
7. Preferably renewable raw materials
8. Shorter syntheses (avoid derivatization)
9. Catalytic rather than stoichiometric reagents
10. Design products for degradation
11. Analytical methodologies for pollution prevention
12. Inherently safer processes

More recently, a mnemonic, "PRODUCTIVELY" was proposed by Poliakoff[74] et al which captures the spirit of the twelve principles of green chemistry:

P – Prevent wastes
R – Renewable materials
O – Omit derivatisation steps
D – Degradable chemical products
U – Use of safe synthetic methods
C – Catalytic reagents
T – Temperature, Pressure ambient
I – In-Process monitoring
V – Very few auxiliary substrates
E – E-factor, maximise feed in product
L – Low toxicity of chemical products
Y – Yes, it is safe

Alternatively, the green chemistry definition[74] reduced into a single sentence. *"Green chemistry efficiently utilises (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."*

Scientists and engineers, who invent, develop and optimize such processes, their awareness, creativity and looking ahead is needed to bring reactions and chemical processes to maximum efficiency. Also eliminating waste at source, i.e. it is primary pollution prevention rather than waste remediation, as described by the first principle of green chemistry: prevention is better than cure. In the last fifteen years the concept of green chemistry has been widely embraced in both industrial and academic circles. One could say that sustainability is our ultimate common goal and green chemistry is a means to achieving it.

The most widely accepted measures of the environmental impact of chemical processes are the *E factor*[75], the mass ratio of waste produces to the desired product and the *atom economy*[2]**,** "a percentage conversion of the molecular weights of all substances reacted to the molecular weight of the desired product."

Having defined what Green Chemistry is we need to be able to compare processes (and products) on the basis of their greenness. There is no absolute greenness, one process is greener than another, and however considering green measurements is an essential task for the genuine examination of greenness. Green chemistry meshes with the important issues such as waste generation, and so in twelve principles it suggest use of less toxic/hazardous material and/or use them as in catalytic amount not in stoichiometric to avoid the waste generation. Although best catalyst is no catalyst and best solvent is no solvent. Use of toxic, volatile solvents in the synthesis is also an important issue in green chemistry.

### 1.3.2 Solvents for sustainable chemical processes:

Solvents are major issue in the production of chemicals. Glaxo-Smith-kline researchers[76] 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 in range from 80%-50%, which clearly indicates that, the environmental impact of bulk and fine chemical processes is dramatically affected by the problem of solvents.

Green Chemistry aims to change the use of toxic solvents with greener alternatives, with replacement and synthetic techniques, separation and purification

which do not need the use of solvents. Green solvents can have been characterised for their low toxicity, higher low solubility in water (low miscibility), easily biodegradable under environmental conditions, high boiling point (not very volatile, low odour, health problems to workers) and easy to recycle after use.

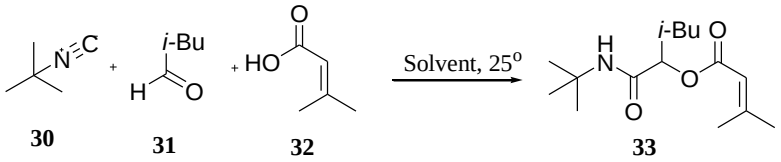
Various non-conventional reaction media have been intensely studied in recent years, including water[77], supercritical $CO_2$[78], fluorous biphasic[79] and ionic liquids[80] alone or in liquid–liquid biphasic combinations

### 1.3.2.1 Water

In principle, water is the ideal green chemistry solvent: it is benign, non-toxic, non-flammable, has a very low odour, has a high specific heat capacity to absorb energy from reactions, is available at a low cost, and is sustainable[81]. The use of water as solvent features many benefits such as improving reactivities and selectivities, simplifying the workup procedures, enabling the recycling of the catalyst and allowing mild reaction conditions and protecting-group free synthesis in addition to being benign itself. In addition, exploring organic chemistry in water can lead to uncommon reactivities and selectivities complementing the organic chemists' synthetic toolbox in organic solvents. Studying chemistry in water also allows insight to be gained into Nature's way of chemical synthesis[82].

The emergence of the use of water as a solvent for organic reactions was probably impulsed by the work of Breslow in the 1980s on the substantial rate enhancement of Diels–Alder reactions conducted in water compared to in other organic solvents[83]. In his studies, he observed that the cycloaddition of butenone and cyclopentadiene was 740 times faster in water than in isooctane and that an increased selectivity could be obtained with water (endo/exo = 21.4) compared to the same reaction in cyclopentadiene (endo/exo = 3.85). It was all the more remarkable that the use of protic polar solvents like methanol or ethanol led to similar results to those obtained with hydrocarbon solvents. These observations were rationalized by the hydrophobic effect[85]. This property of water comes from the repulsive interactions between hydrophobic molecules and water, which leads to the formation of hydrophobic aggregates that allow reducing the contact surface between them. To maintain the

network of hydrogen bonds (related to its high cohesive energy density), water wraps itself around these aggregates, thus acting as an internal pressure, which accelerates reactions with negative activation volume, likes in Diels–Alder reactions. In some cases, the rate enhancements may also originate from interfacial interactions between the organic molecules (notably the transition states) and some free hydroxyl groups of water.[85] Ugi and Passerini reactions.[86] Indeed, as multicomponent reactions consist of the reaction of three or more starting materials to form a single product, they involve transition states resulting from the condensation of several molecules and are therefore predicted to have negative activation volumes. They initially studied the Passerini reaction of 3-methylbut-2-enoic acid**32**, 3-methylbutanal**31** and 2-isocyano-2-ethylpropane**30** in several solvents (Scheme 1.31). They reported that dichloromethane allowed the formation of the product with a 50% yield after 18 h, whereas no product was obtained in methanol and only a 15% yield was observed in dimethylformamide. In contrast, the use of water furnished the expected product **33** quantitatively within 3.5 h.



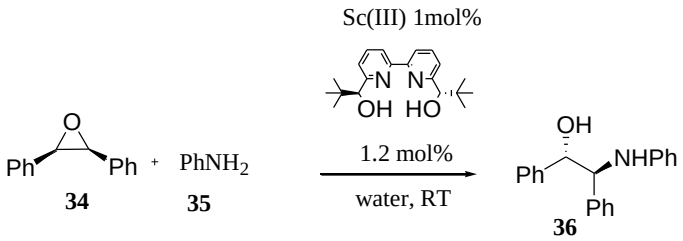

**30** **31** **32** **33**

| Solvent | Time (h) | Conversion |
|---|---|---|
| Dichloromethane | 18 | 50 |
| Dimethylformamide | 24 | 15 |
| Methanol | 24 | 0 |
| Water | 3.5 | 100 |

(Scheme 1.31, Influence of solvent on Passarini reaction)

In 2005, the group of Kobayashi studied the asymmetric desymmetrization of meso-epoxides with amines catalyzed by a chiral scandium complex[87].They showed that the reaction of aromatic epoxides with anilines led to a higher enantiomeric excess in water compared to dichloromethane or THF/water mixtures (Scheme 1.32). In addition, the use of scandium tris(dodecylsulfate) instead of scandium triflate resulted in a better yield and enantiomeric excess, and these conditions were consequently

successfully applied to a wide range of substrates, though the reaction is limited to aromatic amines.



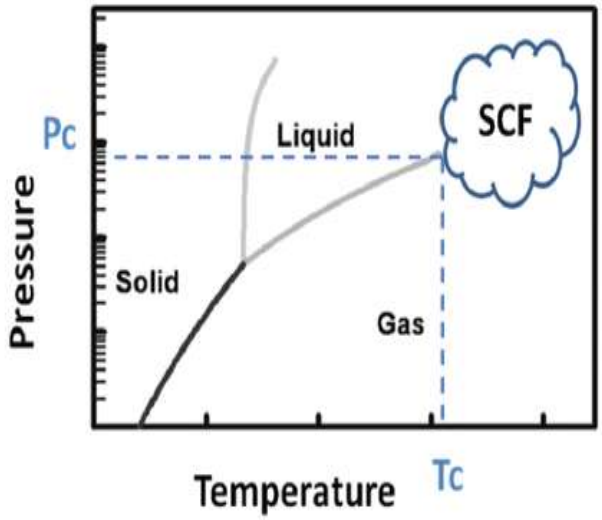

**34** **35** **36**

| Solvent | Sc(III) | Yield (%) | ee (%) |
|---|---|---|---|
| Dichloromethane | $Sc(OTf)_3$ | 85 | 74 |
| THF/Water(9:1) | $Sc(OTf)_3$ | 5 | 71 |
| Water | $Sc(OTf)_3$ | 15 | 85 |
| Water | $Sc(OSO_3C_{12}H_{25})_3$ | 89 | 91 |

(Scheme 1.32, Effect of the solvent on Sc. catalyzed asymmetric desymmetization of epoxide)

### 1.3.2.2 Supercritical Fluids:

Supercritical fluids (SCFs) are also an attractive alternative to standard solvents. A SCF is a fluid at conditions slightly above its critical temperature (Tc) and pressure (Pc). **Fig. 2** shows a generalized temperature–pressure graph which illustrates the supercritical region.[88] As the temperature and accompanying pressure are increased the liquid becomes less dense and the vapour becomes denser. At the critical point they converge to ultimately become identical. The compressibility is the slope of the isotherm, and it is infinite at the critical point. In fact, all of the special properties of SCF's occur in the region of very high compressibility. Their main limitations are the technically challenging conditions required to reach the supercritical state for most compounds. Two well-known yet very different fluids are water (Tc 373 °C; Pc 22.1 MPa) and carbondioxide (Tc31°C; Pc7.4 MPa). Supercritical carbon dioxide (scCO2) has been found useful with extensive applications in green chemistry. Being a potential replacement for volatile organic compound, $scCO_2$ could be one aspect of a significant and necessary movement towards green chemistry. As a solvent, $ScCO_2$ is non-toxic, cheap, non-flammable, readily available, recyclable, and unrestricted by the US Environmental Protection Agency (EPA).[89] In addition, $scCO_2$ exhibits high selectivity as a result of low viscosity, high diffusivity and liquid-like density[90]




General phase diagram for supercritical fluids.

(Fig.2)

As supercritical $CO_2$ ($scCO_2$) is non-toxic so could potentially be used for the production of consumable products, such as pharmaceutical and food products[91] as well as already being an established system for numerous processes, including extractions,[92] extraction of heavy metals,[93] nanoparticle production and modification[94] and polymer processing[95]

Several researchers including Noyori[96a,] Jessop[96b] and Leitner[96c] have reported that reactions involving gas reagents have been found to be faster in supercritical media, probably because mass transfer problem between different phases can be avoided. In fact, reactions of gaseous with liquid reagents with homogeneous catalyst 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 problem; in fact supercritical fluids are in several cases able to dissolve both the gas and liquid reagents thus forming a 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 catalyst, enhanced ass and heat transfer.

### 1.3.2.3 Deep Eutectic Solvents (DES):

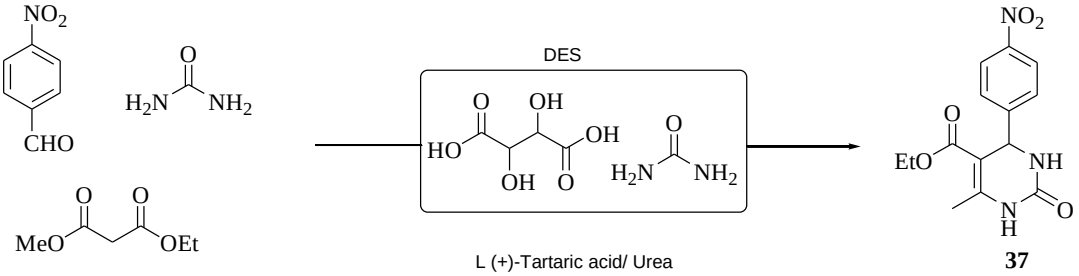
New family of ionic fluids so-called Deep Eutectic Solvents (DES) is now days rapidly emerging in the current literature as green media for reactions. A DES is a fluid generally obtained by mixing two naturally occurring components, namely, hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD), which can be associated with each other by means of hydrogen bond interactions. DESs usually have much lower melting point than the individual components mainly due to the formation of intermolecular hydrogen bonds. DESs were firstly introduced[97] by Abbott et al., who highlighted the solvent properties of sustainable and biodegradable eutectic mixtures of urea and a range of quaternary ammonium salts. DESs are promising and economically viable alternatives to traditional volatile organic solvents since they are easily prepared starting from natural compounds, and purification steps are not necessary. Being much cheaper and environmentally friendlier, DESs are now of growing interest in many fields of research.[98]

Similar to ILs, DESs are chemically tailorable solvents since they can be designed by properly combining various quaternary ammonium salts (e.g. ChCl) with different hydrogen bond donors (HBD). Hence, task-specific DESs with different physicochemical properties such as freezing point, viscosity, conductivity, and pH, among others, can be prepared.

Due to high polarity DES has wide application in the fields of in electrochemistry as electrolytes[99a] for electro deposition[99b] of metal, as solvents[99c] for electrochemistry reaction and for electro polishing (metal dissolution), etc. In the dissolution of several poorly soluble drugs including benzoic acid, griseofulvin, danazol, itraconazole and N-[4-[[6-[4-(trifluoromethyl)phenyl]- 4-pyrimidinyl]oxy]-2-benzothiazolyl]acetamide (AMG517) in ChCl/urea and ChCl/malonic acid DESs[99d].

Moreover, it is noteworthy that recently the DESs have also been proven to be promising anhydrous solvents for nucleic acids. Hud and coworkers39 showed that the nucleic acids can form several secondary structures that are reversibly denatured upon heating in DESs. In our opinion, this work definitely provides a new concept to widen the scope of DESs for life science[99e]

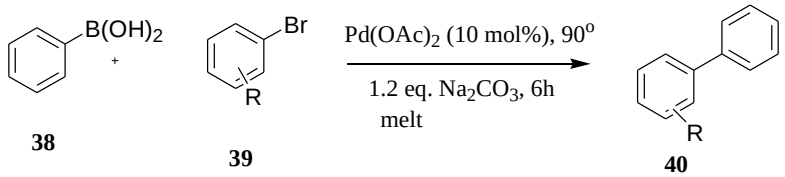
In this context, Gore et al. reported the multicomponent synthesis of valuable biologically active dihydropyrimidinone (DHPM) **37** in acidic DESs[100]. This work aims at by-passing the traditional use of Bronsted and Lewis acids which dramatically impact the economical and ecological footprint of this reaction. DHPM was synthesized from urea, aldehyde and b-ketoesters (Biginelli reaction, Scheme 1.33). Hence, urea was used in this example not only as a reactant but also as a component of the DES. For instance, in a citric acid/DMU (2:3) DES, p-4-nitrobenzaldehye, ethylacetoacetate and DMU were selectively assembled at 65 1C to the desired DHPM which was obtained with 90% yield. An even higher yield (96%) was reported in a L-(+)-tartaric acid/DMU (3:7) DES.




Biginelli reaction in DES [L (+)-Tartaric acid/ Urea]

(Scheme 1.33)

In 2006, Konig and co-workers investigated the palladium-catalyzed Suzuki coupling[101] of phenyl boronic acid with aryl bromides in different carbohydrates–urea–inorganic salts eutectic mixtures. In all tested melts, quantitative conversion was observed and biarylated products were isolated with 78–98% yields (Scheme 1.34). At the end of the reaction, products were isolated by liquid–liquid phase extraction with pentane (after dilution in water).

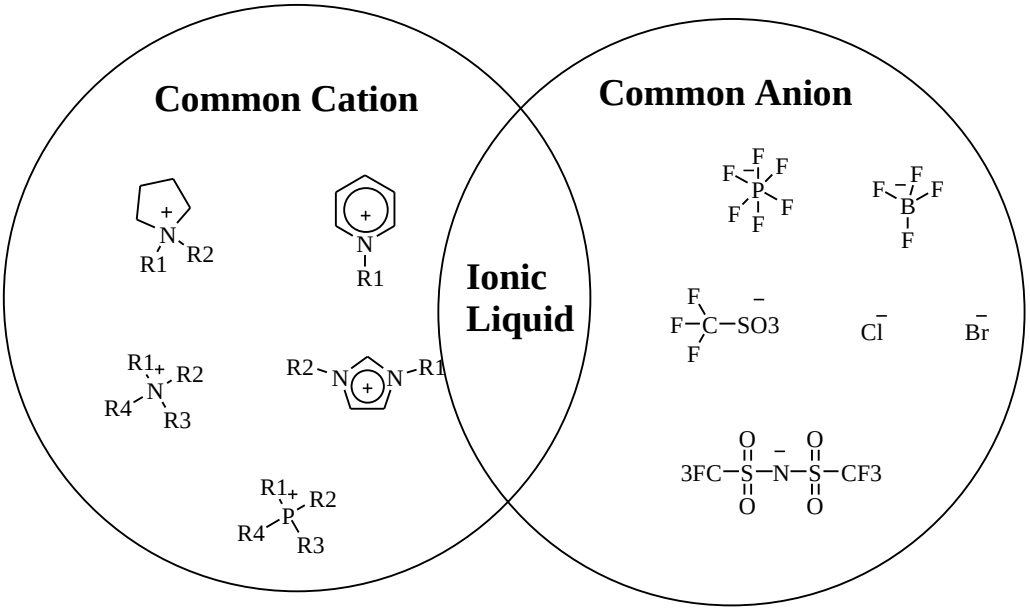



(Scheme 1.34, Palldium catalyzed Suzuki coupling in DES)

### 1.3.2.4 Ionic Liquids:

Ionic Liquids (ILs) are coordinated compounds composed of organic cations and inorganic or organic anions. In contrast to high-temperature molten salts ILs are liquid

at room temperature, so they also termed as Room Temperature Ionic Liquids[102] (RTILs). ILs are made of positively and negatively charged ions (Fig. 3), whereas water and organic solvents, such as toluene and dichloromethane, are made of molecules. The structure of ILs is similar to the table salt such as sodium chloride which contains crystals made of positive sodium ions and negative chlorine ions, not molecules. Since these conventional molten salts exhibit high melting points (400-800$^{o}$C), their use as solvents in applications is severely limited. Researchers explained that ILs remain liquid at room temperature due to the reason that their ions do not pack well.[103] The low melting points of ILs are a result of the chemical composition. The combination of larger asymmetric organic cation and smaller inorganic counterparts (anion) lower the lattice energy and hence the melting points of the resulting ionic liquid medium are lower.[104]




**(Fig. 3)**

Bearing characteristics as non volatile, non toxic, non flammable, high thermal stability, high re-use potential, miscible or immiscible in water (depending upon the nature of the anions), high viscosity, high conductivity, and high solvent power for organic and inorganic compounds has qualified ILs as green solvents which excited both the academia and the chemical industries.[105]

As solvents, ILs posses several advantages over conventional organic solvents, which make them environmentally compatible[106]

• ILs have the ability to dissolve many different organic, inorganic and organometallic materials.

• ILs are highly polar.

• ILs consist of loosely coordinating bulky ions.

• ILs do not evaporate since they have very lowvapor pressures.

• ILs are thermally stable, approximately up to 300 ◦C.

• Most of ILs have a liquid window of up to 200 ◦C which enables wide kinetic control.

• ILs have high thermal conductivity and a large electrochemical window.

• ILs are immiscible with many organic solvents.

• ILs are nonaqueous polar alternatives for phase transfer processes.

• The solvent properties of ILs can be tuned for a specific application by varying the anion cation combinations.

The possibility to modify chemical and physical properties by changing the cationic moiety with a large choice of anions offers chemists a broad range of ILs. Thus the solvent properties can be changed significantly by changing the nature of the ions such as melting point, solubility, viscosity, density, conductivity, and refractivity. For instance, in 2009, Seddon and co-workers have reported that $10^{18}$ different ILs can be theoretically produced, 250 of them being already commercialized.

The most commonly used cations in room-temperature ionic liquids are alkylammonium, alkylphosphonium, *N*,*N*′- dialkylimidazolium ([RR'IM]), and *N*alkylpyridinium ([RPy]) cations (**Figure 1**). The most commonly utilized alkyl chains are methyl, ethyl, butyl, hexyl, octyl, and decyl. The most commonly investigated IL anions are shown in **Table 1**.

**Table 1**

| Typical Cations | Typical anions |
|---|---|
| • Imidazolium<br>• Ammonium<br>• Morpholinium<br>• Phosphonium | • Halides<br>• Phosphates<br>• Sulphates<br>• Sulphonates |

| | |
|---|---|
| • Piperidinium<br>• Pyridinium<br>• Pyrrolidinium<br>• Quartenary ammonium salt<br>• Oxazolium<br>• Thiazolium | • Thiocyanates<br>• Borates<br>• Sugar analogues |

Due their unique properties, ILs considered being a relatively magical chemical; they have a large variety of applications in all areas of the chemical industries. The areas of application include electrolyte in batteries, lubricants, plasticizers, solvents and catalysis in synthesis, matrices for mass spectroscopy, solvents to manufacture nano-materials, extraction, gas absorption agents.[105] Another advantage of ILs in catalysis is the immobilization of the catalyst. Besides the tunable solubility to most organic chemicals, ILs are also able to dissolve a wide range of inorganic and organometallic compounds, and therefore large numbers of catalysts having polar or ionic character can be immobilized in ILs, which can greatly facilitate the separation and subsequent reuse of the catalyst. In addition, the technological integration of ILs with other advanced technologies, including supercritical fluids, electrochemistry, biocatalysis, and nanotechnology, *etc.*, with great potential for growth, has received more and more attention in green catalysis.

**1.4 Conclusion:**

Catalytic carbonylation reactions continue to be important in bulk processes for the manufacture of commodity chemicals, as well as being a valuable tool in organic synthesis. This is exemplified by the range of important reactions covered in this chapter. Oxidative carbonylation is an excellent methodology for the direct synthesis of carbonyl compounds starting from simple building blocks. When applied to suitably functionalized substrates, the process can occur with concomitant heterocyclization, thus leading to carbonylated heterocycles in one-step fashion. The $PdI_2$/KI catalytic system, has proved particularly efficient for oxidative carbonylation of acetylenic substrates bearing nucleophile groups in suitable positions for cyclization. A key characteristic of this system is the efficiency of the metal

reoxidation process, which occurs with use only of oxygen as the oxidant and with production of water as co- product, making the $PdI_2$/KI-catalysed oxidative carbonylation reactions very attractive from the points of view of atom economy and sustainability. An effective increase in the rate of introduction of new cleaner and safer processes could derive only from a change of perspective, in which greener technologies are not only seen as a strategy to improve the image of chemistry but as a novel business strategy for the innovation. Green and sustainable chemistry are thus not synonymous but instead green chemistry is the core around which a new strategy for chemistry should be built up.

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# Chapter 2

# $PdI_2$-Catalyzed Carbonylative Approach to (*Z*)-(6-Oxo-5,6-dihydro-12-Oxa-5-azadibenzo[*a*,*d*]cycloocten-7-ylidine)acetate ester Derivatives

## 2.1 Importance of Heterocyclic Compounds

The importance of heterocycles in many fields of science including organic, inorganic, bioorganic, agricultural, industrial, pharmaceutical, and medicinal chemistry, as well as material science can hardly be overemphasized and justifies a long-lasting effort to work out new synthetic protocols for their production[1]. Heterocyclic substances perform a very unique role in drug design and discovery. The majority of pharmaceuticals and biologically active agrochemicals are heterocyclic while countless additives and modifiers used in industrial applications ranging from cosmetics, reprography, information storage and plastics are heterocyclic in nature.

Heterocycles form the largest of classical divisions of organic chemistry and are of immense importance biologically and industrially. For more than a century, heterocycles have constituted one of the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Among the approximately 20 million chemical compounds identified by the end of the millennium, more than two thirds are fully or partially aromatics and approximately one half are heteroatomic. The presence of heterocycles in all kinds of organic compounds of interest in electronics, biology, optics, pharmacology, material sciences and so on is very well known. Between them, sulphur[2] and nitrogen-containing heterocyclic compounds[3] have maintained the interest of researchers through decades of historical development of organic synthesis. However, heterocycles with other heteroatoms such as oxygen[4], phosphorus[5] and selenium[6] also appears. Many natural drugs[7] such as papaverine, theobromine, quinine, emetine, theophylline, atropine, procaine, codeine, reserpine and morphine are heterocycles. Almost all the compounds we know as synthetic drugs such as diazepam, chlorpromazine, isoniazid, metronidazole, azidothymidine, barbiturates, antipyrine, captopril and methotrexate are also heterocycles. Some dyes (e.g. mauveine), luminophores, (e.g. acridine orange), pesticides (e.g. diazinon) and herbicides (e.g. paraquat) are also heterocyclic in nature. All these natural and synthetic heterocyclic compounds can and do participate in chemical reactions in the human body. Furthermore, all biological processes are chemical in nature. Such

fundamental manifestations of life as the provision of energy, transmission of nerve impulses, sight, metabolism and the transfer of hereditary information are all based on chemical reactions involving the participation of many heterocyclic compounds, such as vitamins, enzymes, coenzymes, nucleic acids, ATP and serotonin[8]. Why does nature utilize heterocycles? The answer to this question is provided by the fact that heterocyles are able to get involved in an extraordinarily wide range of reaction types. Depending on the pH of the medium, they may behave as acids or bases, forming anions or cations. Some interact readily with electrophilic reagents, others with nucleophiles, yet others with both. Some are easily oxidized, but resist reduction, while others can be readily hydrogenated but are stable toward the action of oxidizing agents. Certain amphoteric heterocyclic systems simultaneously demonstrate all of the above-mentioned properties. The ability of many heterocycles to produce stable complexes with metal ions has great biochemical significance. The presence of different heteroatoms makes tautomerism ubiquitous in the heterocyclic series. Such versatile reactivity is linked to the electronic distributions in heterocyclic molecules. Evidently, all the natural products and the synthetic drugs mentioned above are good examples of nature's preference for heterocycles whose biological activity cannot be determined by one or a combination of two or three of the above mentioned properties. Synthetic heterocycles have widespread therapeutic uses[8] such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV activity, antileishmanial agents, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, antiinflammatory, muscle relaxants anticonvulsant, anticancer and lipid peroxidation inhibitor, hypnotics, antidepressant, antitumoral, anthelmintic and insecticidal agents. There are larger number of synthetic heterocyclic compounds with other important applications such as fungicides, herbicides, anticorrosive agents, photostabilizers, agrochemicals, dyestuff, copolymer,photographic developers, fluorescent whiteners, sensitizers, booster agent, antioxidant in rubber and flavouring agent[9]. Pyrimidine(cytosine, thymine and uracil) and purine (adenine and guanine) derivatives are monocyclic and bicyclic heterocycles with two and four nitrogen atoms, respectively. They are key components of the deoxyribonucleic acid (DNA) molecules and participate directly in the encoding of genetic information. They also pass

information to the related ribonucleic acid (RNA) molecules that control, in protein synthesis, the sequence of amino acids[10]. The need for minute quantities of accessory dietary factors, the vitamins is well-known. Vitamins in the B group thiamine, folic acid, riboflavin, cyanocobalamine, are nitrogen-containing heterocycles[10c] and function either as coenzymes or their precursors. Other vitamins such as ascorbic acid (vitamin C) and $\alpha$-tocopherol (vitamin E) are oxygen heterocycles.

The essential amino acid proline, histidine and tryptophan[11], photosynthesizing pigment chlorophyll; the oxygen transporting pigment haemoglobin[11b], the hormones kinetin, heteroauxin, cytokinins[11c], neurotransmitter serotonin, histamine respectively are successful application of heterocyclic compounds.

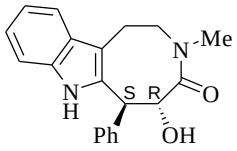
In conclusion, it can be questioned why it is specifically appropriate to emphasize the role of heterocycles, since analogies to the roles of other classes of organic compounds are easily found. In fact, dyes, luminophores, herbicides, pesticides and drugs do not necessarily have to be heterocyclic in structure. In a similar fashion there are many common features in chemistry and physics between such related compounds as pyrrole and aniline, or between pyridine and nitrobenzene. Nevertheless, nature selected the heterocycles pyrrole and pyridine and not the homocycles aniline and nitrobenzene, as the basis of most essential biological systems. We now know the reason for this: the introduction of a heteroatom into a cyclic compound imparts new properties. Heterocycles are chemically more flexible and better able to respond to the many demands of biochemical systems. The constantly accelerating rate of research and development in heterocyclic chemistry suggested that , enormous numbers of heterocyclic systems are well known and this number is increasing very rapidly.

It is therefore easy to understand why both the development of new methods and strategic utilization of known methods for the synthesis of complex heterocyclic compounds continue to drive in the field of synthetic organic chemistry.

## 2.2 Importance of Medium Ring Lactam (Macrolactam)

Medium ring lactams found widespread use in organic chemistry as key intermediates[12] in synthesis of more complex structures ranging from organic synthesis to polymer chemistry, as core structures in natural and unnatural products possessing wide and diverse medicinal and biological applications. Also they constitutes a very important class of compounds with high potential in drug,[13] materials,[14] and catalysis[15] research. Simple lactams such as ε-caprolactam, azocin-2-one and azonin-2-one showed significant CNS activity[16]. Especially medium ring lactam of an eight-membered heterocycle (Azocan-2-ones) have attracted extensive synthetic interest in recent years due to their presence in a large number of naturally occurring molecules.

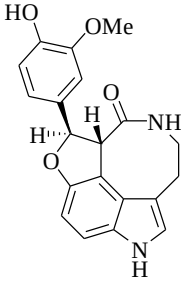
Eight-membered lactam-containing alkaloid (+)-balasubramide **41** was isolated from *Clausena indica* which grows in the central montane rainforests in Sri Lanka[17]




(-)-(5R,6S)-Balasubramide

**41**

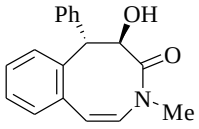
Serotobenine**42**, which is a pentacyclic indole alkaloid, was initially isolated from safflower seeds (Carthamus tinctorius L.) by Sato and co-workers in 1985.[18] The unique heterocyclic structure of Serotobenine, which includes an indole, dihydrobenzofuran, and eight-membered lactam and should be a significant structure in medicinal chemistry[18b] while its racemic analogue decursivine has strong anti-malarial activity.




Serotobenine

**42**

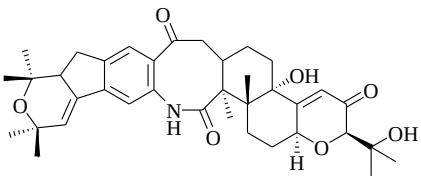
((±)-ξ-Clausenamide[19] **43** was isolated from hot water extract of leaves of Rutaceae *Clausena lansium.* Rutaceae *Clausena lansium* (Lour.) Skeels is a fruit tree widely distributed in southern China, and its fruits and leaves are used for the treatment of influenza, gastrointestinal disorders, viral hepatitis, and dermatological diseases in folk medicine.



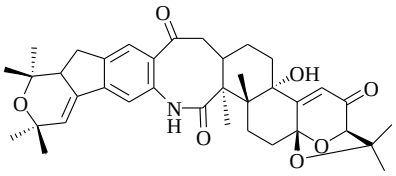

(+/-) - Clausenamide

**43**

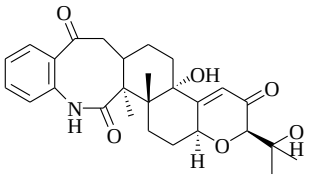
Eight different analogues of Shearinine **44** was isolated firstly from organic extracts of scleretiod ascostromata of Eupencillium Shearii[20] by James B Gloer in 1995 and later by Minjua Xu et al[20b] in 2007from endophytic fungus Penicillium sp. isolated from the mangrove plant Aegiceras corniculatum consisting eight membered lactam core. Bilogical testing of these molecules showed, in vitro blocking activity on large-conductance calcium- and voltage-activated potassium (BKCa) channels[20b]




Shearinine A




Shearinine -B




Shearinine C

**44**

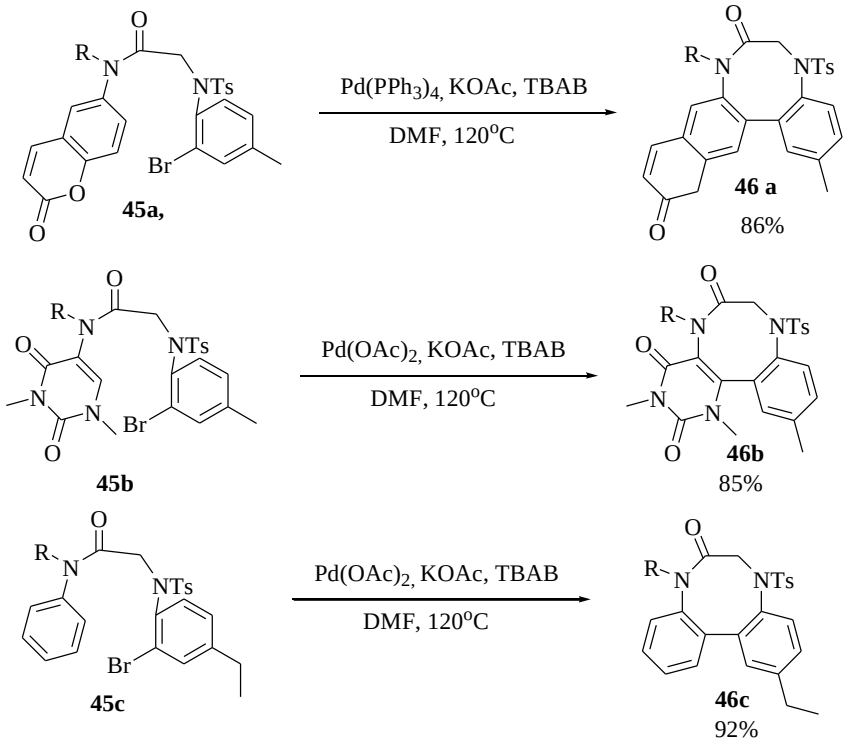
Many peptides with promising biological activities *in vitro* have been discovered. However, peptides assembled from the natural amino acids are generally of limited use as medicinal agents due to both their high conformational flexibility and fast proteolytic degradation. Utilization of rigid cyclic building blocks of heterocyclic nature (such as chiral lactams, pyrrolizidines, etc.) in the synthesis of peptide mimetics is one of the widely accepted solutions to the above-mentioned problems. A large number of cyclic peptides, which exhibit a range of biological activities, have been found in nature. The reason of cyclic peptides that attracted worldwide attention and made them extensively studied, is their enhanced metabolic stabilities, biological specificities, bioavailability, and conformational constrained structural feature, which make them important leads for drug discovery, and as actual drugs. Many cyclic peptides show very promising biological activities, including anticancer, antibacterial, antiviral, antifungal, anti-inflammatory, and anti-clotting or anti-atherogenic

properties. Peptide cyclization becomes an effective and commonly employed strategy for peptide modifications. During the past several decades, great efforts have been made to develop more efficient methods for the synthesis of cyclic peptides and peptidomimetics. Until now, the generation of such rings is still a challenge in organic synthesis. During the past decade as increasing interest has focused on the generation of cyclic peptides as well as hairpin and β-turn mimics and medium-sized lactam rings were thought to present suitable fragments. Furthermore, a range of complex natural products is characterized by such lactam structure and their total synthesis is a broad field for organic chemists to test new strategies and to develop new methods.

### 2.2.1 Trends in the synthesis of Medium ring lactam:

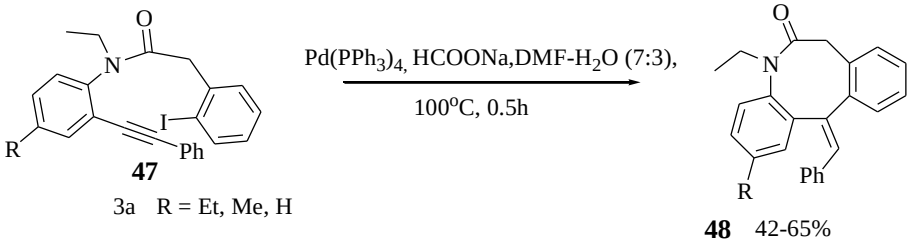
The synthesis of seven- to nine-membered medium rings has posed a significantly greater challenge in comparison to the construction of their five- and six-membered or large ring counterparts. In principle, such ring systems can be constructed by three distinct approaches *viz*. intramolecular cyclization, annulations and ring expansion. However, all of the above synthetic strategies are hampered by unfavourable transannular interactions leading to large enthalpies of activation. Moreover, ring closure by cyclization is also hindered by entropic factors. Direct closure by lactamization proceeds in high yields only if appropriate substituents on the chain induce a conformation to the linear precursor molecule that brings the terminal groups in closeproximity. [20] However, the efficient and general synthesis of eight-membered lactams is still a challenging task.[21]As I worked in the synthesis of eight membered lactam, I will discuss the synthetic protocol reported by fragmentation, ring expansion, cyclization and some miscellaneous pathways

K.C. Majumdar and co-worker reported the synthesis of benzodiazocine derivatives[22a] via intramolecular Heck reaction. Substrates 1a-c derived from coumarine**45a**, uracil**45b** and N methyl aniline**45c** was subjected to optimized Heck reaction conditions [10 mol% $Pd(PPh_3)_4$/ $Pd(OAc)_2$, KOAc, TBAB, DMF, 120$^oC$, 4–6 h] to give eight membered lactum dibenzoazocine **46a-c** in 85-92% yields. (Scheme 2.1)




(Scheme 2.1)

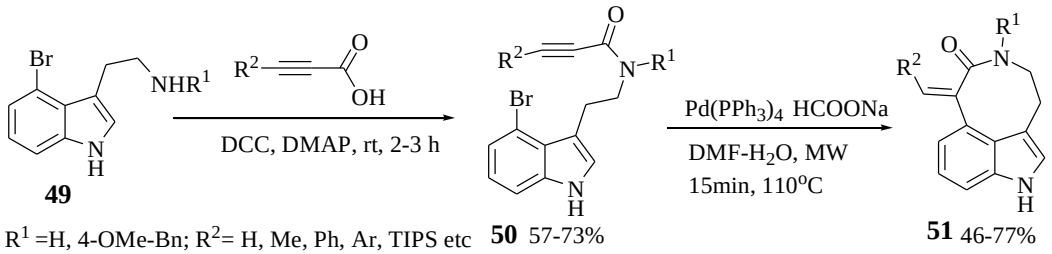
Same research group reported the synthesized of different dibenzoazocine and azocinone[22b] frameworks through palladium-mediated Mizoroki–Heck cyclization strategy. The optimal conditions for the reductive Mizoroki–Heck cyclization were established with the amide 47 under the conventional heating condition at 100°C (Pd(PPh3)4, DMF/H2O (7:3), HCOONa) for about 30 min produce the 8-exo cyclized products**48** in 42–65% yields (Scheme2.2)




(Scheme 2.2)

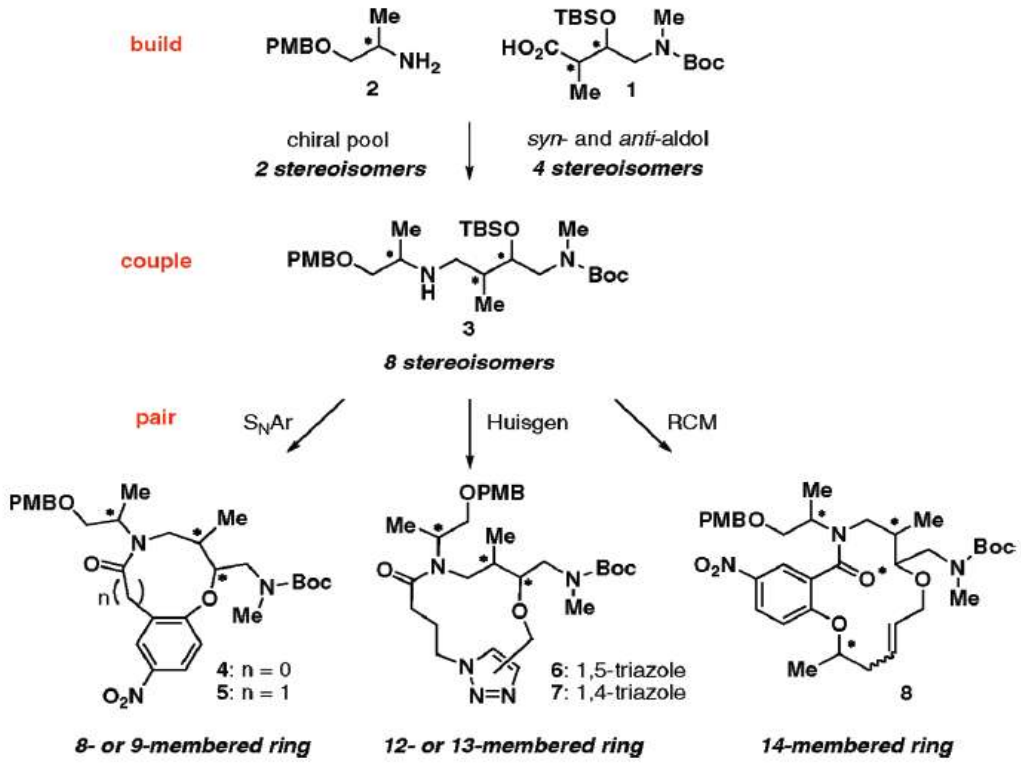
V. A. Peshkov and co-worker reported microwave assisted, Pd-catalyzed, stereo- and regioselective intramolecular acetylene hydroarylation reaction for accessing the highly interesting azocino[c,d]indole[23] **51**framework (Scheme 2.3), which is often found in naturally occurring compounds like decursivine and serotobenine.[23c] Precursors**50** for the intramolecular cyclizations were generated by the DCC-mediated amidation of suitably functionalized 4-bromotryptamines **49** and a variety of propiolic

acid derivatives. The microwave-assisted cyclizations were then carried out in a 3 : 1 mixture of DMF and water at 110 1C for 15 min using a reagent mixture of Pd(PPh3)4 (3 mol%) and HCOONa (1.5 equiv.). The desired azocino[c,d]indole**51** derivatives were isolated in good to high yields of 46–77%.



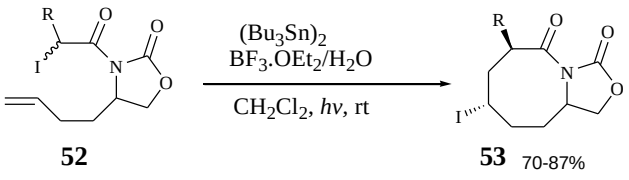

(Scheme 2.3)

Lisa A. Marcaurelle and co-worker applied the Aldol build/couple/pair (BCP) strategy for the synthesis of medium and large ring macrolactams.[24] with this strategy a diverse collection of skeletal frameworks each with a complete set of stereoisomers was achieved in excellent yields. In the initial phase (the *build* phase) the asymmetric synthesis of chiral building blocks was done followed coupling of the chiral building blocks (*couple* phase) through a variety of intermolecular bond-forming reactions to provide all possible stereochemical combinations. And finally intramolecular cyclizations (the *pair* phase) to join functional groups to create a variety of ring systems. Synthesis of 8-14 membered lactam ring was achieved with respect to final pairing. Nucleophilic aromatic substitution (SNAr) for (8-9 membered), Huisgen [3+2] cycloaddition (12-13 membered), or ring-closing metathesis (RCM) (14 memebered (Scheme 2.4)




(Scheme 2.4)

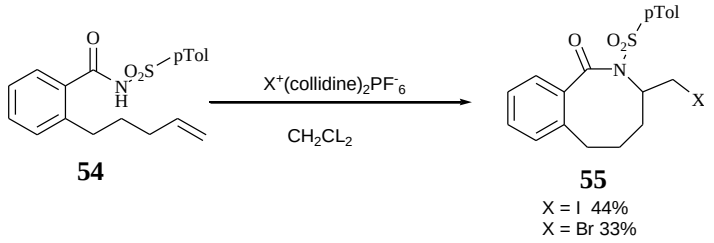
Chaozhong Li reported the efficient regio- and stereoselective formation of eight membered lactam**53** via 8-*Endo c*yclization of α-carbamoyl radicals[25]. Under the optimized reaction conditions as 30 mol % of $(Bu_3Sn)_2$, 400 mol % $BF_3{\cdot}OEt_2$ (freshly distilled), and 20 mol % $H_2O$, *under sunlamp for* 1 h obtained high yields of 8 endo product with excellent regio and stereoselectivity. Assuming that substrate *N*-Acyloxazolidinone **52** would exist exclusively in the *E*-conformation to avoid the steric interaction between the olefinic chain and the iodoethyl moiety in its *Z*-conformation which allows direct the 8-*endo* radical cyclization to proceed via the fixed *E*-conformational TS. (Scheme 2.5)




(Scheme 2.5)

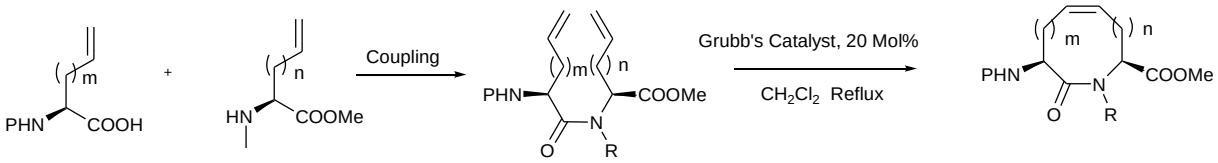
In 1998, Fadi Homsi and Gerard Rousseau reported the case of electrophilic cyclization of N- protected benzamide**54** bearing carbon chain suitable for cyclization with terminal C=C bond.[26] Under the conditions fulfilled for electrophilic cyclization as an introduction of conformational constraint to the chain obtain satisfactory yields and the reagent used must be highly electrophilic with an un-reactive counter anion.

Reaction of these amides in methylene chloride in the presence of 1.3 equiv of bis(collidine)iodine(I) hexafluorophosphate **1** led to the formation of eight members halo lactams **55** in moderate yields. (Scheme 2.6)




(Scheme 2.6)

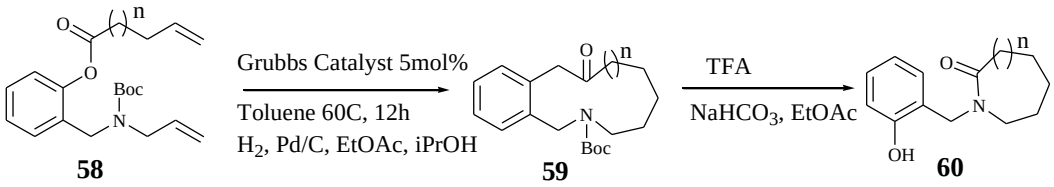
William D. Lubell and co-worker reported the synthesis of macrocyclic dipeptide 8-10 membered rings by ring-closing metathesis[27] (RCM). Dipeptide allylic substrates **56** were syntheisized through several steps to obtain allylglycine and homoallylglycine methyl ester salts and as amine components and *N*-(Boc)allyl and *N*-(Boc)homoallylglycines and as acid components. These two dipeptidyl components was the coupled using TBTU as the coupling agent. Macrocycles of eight and nine members **57** were synthesized from dipeptides by using Grubbs catalyst via RCM in hig yields. (Scheme 2.7)




(Scheme 2.7)

Inspired from octalactin-A natural product consisting of an eight membered ring skeleton having potent antitumor activity chemically and functionally distinct, library of 163 medium ring lactam compounds were syntheiszed by Neil Brown and his research group by using similar concept of RCM.[27b] Similar work with changed substitutions at precursors was reported by Allen B. Reitz and co-worker[27c] by Grubbs catalyst catalyzed RCM.

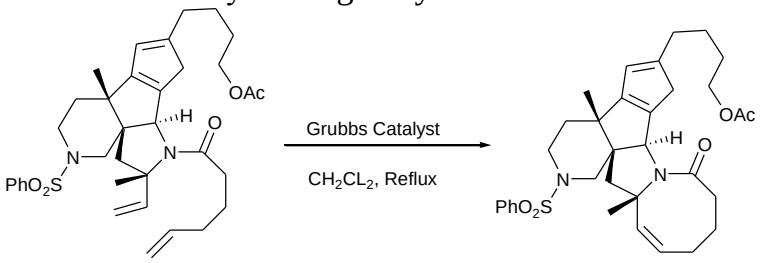
J.H. Van Marseveen research group reported the synthesis of medium-sized lactams**60** based on an auxiliary-mediated combined tethered/templated strategy.[27d] Substrate **58** was prepared starting from salicylaldehyde, was then subjected to RCM by the use of Grubbs catalyst to yield lactone **59**. Under acidic conditions 2 undergoes Boc deprotection followed by ring-contracting lactamization to yield the final product as Macrolactam3. (Scheme 2.8).




**58** **59** **60**

(Scheme 2.8)

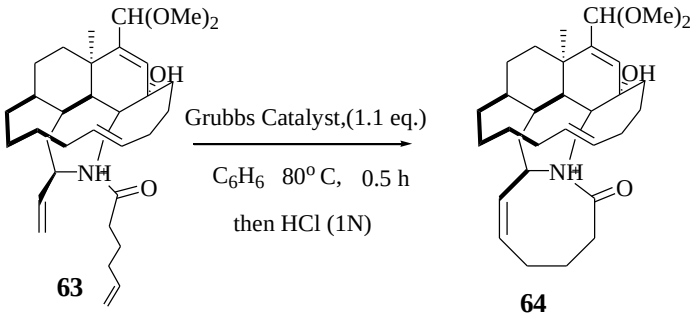
Nishida and co-worker reported the synthesis of an enantiomer of the unusual marine natural product, nakadomarin A[27e], which is, believed to belong to the manzamine family. Their approach exploited RCM reactions to construct the eight- and the fifteen- membered azacycles present in this natural product. The authors observed that lactamization of the advanced intermediate 1 (Scheme 2.9) proceeded best with the second generation Grubbs' catalyst 4 in good yield.




**61** **62**

(Scheme 2.9)

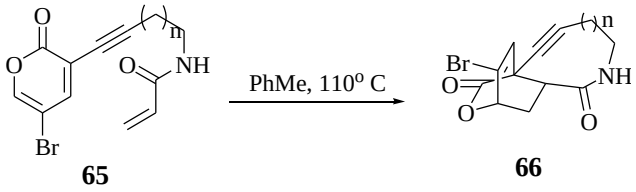
Martin's group later reported that the RCM of the tetracyclic amide [27f] (Scheme 2.10) gave the pentacyclic amide with 1.1 equiv of the Grubbs catalyst. The desired product**64** was obtained in low yield (26%), even with an equivalent of the catalyst, possibly because of the tertiary amino group. The product thus obtained was elaborated into the natural product, ircinal A.




**63** **64**

(Scheme 2.10)

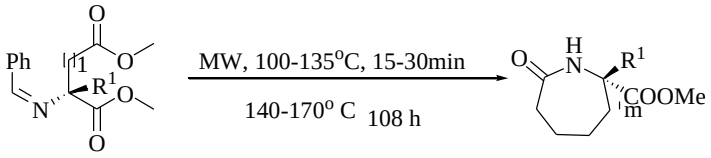
Cheon-Gyu Cho et al reported intramolecular Diels–Alder cycloaddition[28] (IMDA). Intermediate **65** with dienyl character undergoes IMDA cycloaddition reaction with both electron-rich and electron-poor dienophiles. The precursors 1 with variable carbon chain proceeded IMDA cycloadditions to the corresponding 8, 9, 10 and 11-membered lactams **66** in fair yields, when heated in toluene. Subsequent opening of the bridgehead lactone would furnish the structurally novel macrocycle 3. (Scheme 2.11)




**65** **66**

(Scheme 2.11)

Zradni and co-workers have explored the microwaveassisted, solvent-free intramolecular cyclization of a-iminoester derivatives, leading to the synthesis of a number of seven, eight and ten membered lactams[29] (Scheme 2.12). The authors carried out a detailed investigation on the cyclization of these iminoesters, providing comparisons of microwave-assisted and conventional heating conditions in the synthesis of these medium-sized ring lactams. A dramatic shortening of the reaction times from days to merely 15–30 min was observed during the microwave-assisted cyclizations, furnishing the desired products in good to excellent yields of 76–85% in comparison with the 40–80% yield obtained under conventional heating (Scheme 2.12)

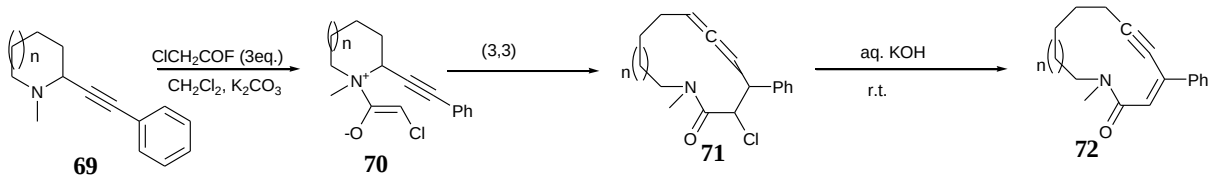



**67** **68**

(Scheme 2.12 Microwave assisted intramolecular cyclization of eight membered lactams)

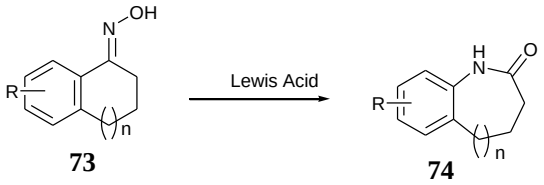
Udo Nubbemeyer and co-worker reported the first synthesis of medium-sized ring allenyl lactams[30]. Starting from readily available pyrrolidone (*n* = 0), piperidone (*n* = 1), or azepinone (*n* =2) synthesis of allenyl lactams of seven, eight, nine membered macrolactam was done via zwitterionic aza-Claisen rearrangement. Starting from pyrrolidone **69a** (*n* = 0), piperidone **69b** (*n* = 1), or azepinone **69c** (*n* =2), phenylethynyllithium addition in the presence of BF3·OEt2 delivered the intermediate iminium salt**70**, which was immediately reduced with LiAlH4 to give propargylamine product **71a**, **71b**, or **71c** in 52–72% yield overall (Scheme 2).[13] In several runs, *N*-methylpyrrolidine, -piperidine, or -azepine was formed as the major side product, indicating incomplete or reversible alkyne addition. First ring expansion reactions of these propargylamines were carried out by using the in situ formed Lewis acid

activated chloroketene. Treatment of 2-alkynylpiperidine **71b** and -azepane **71c** with chloroacetyl fluoride[14,15] and trimethylaluminum[16] in the presence of solid potassium carbonate smoothly delivered allenyl lactams **72b** and **72c** in 77 and 70% yield, respectively (Scheme 2.13)




(Scheme 2.13, Synthesis of allenyl lactams by zwitteionic aza-claisen fragmentation)

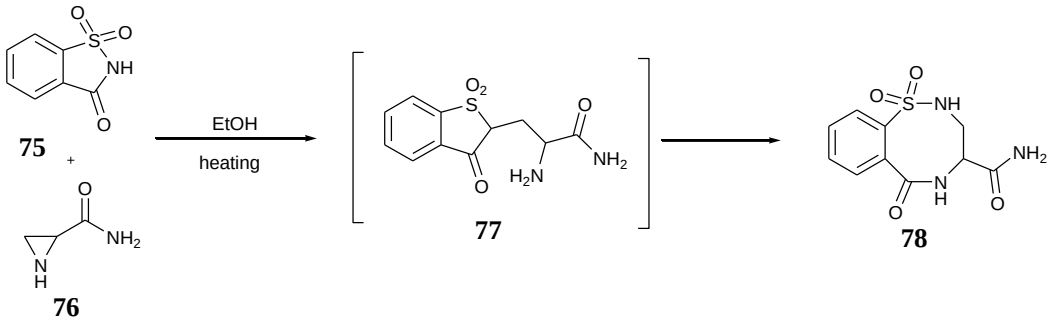
Ring expansion of cyclic ketones by nitrogen insertion has attracted significant attention as a method for the synthesis of medium-ring lactams. One commonly used nitrogen-insertion process is the Beckmann rearrangement of cyclic oximes. Usually acidic and harsh conditions are required for such transitions. But several lewis acid catalyzed mild conversions also reported. Kaur et al reported Bismuth Chloride catalyzed [31a] ring expansion under microwave irradiation, while Jayne L. Kenwright et al reported Tosyl Chloride catalyzed[31b] Beckmann rearrangement under basic conditions in under conventional heating. (Scheme 2.14)




(Scheme 2.14)

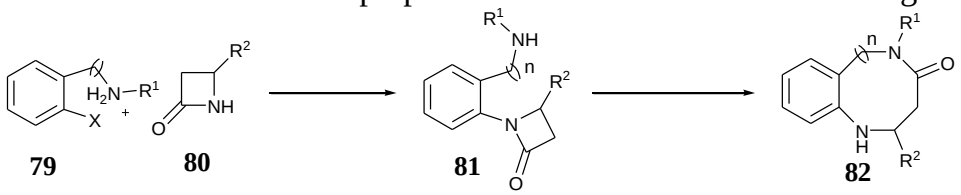
R. Zalubovskis et al reported an example of ring expansion strategy[32a] for one pot conversion of saccharin**75** to eight membered ring. The reaction can be considered as a domino process, in which the first stage is of *N*-alkylation of saccharin with opening of the aziridine ring to give the intermediate compound **77**. The latter undergoes an intramolecular nucleophilic substitution at the carbonyl carbon atom with expansion

of the ring to yield the eight membered medium ring lactam**78** (Scheme 2.15)



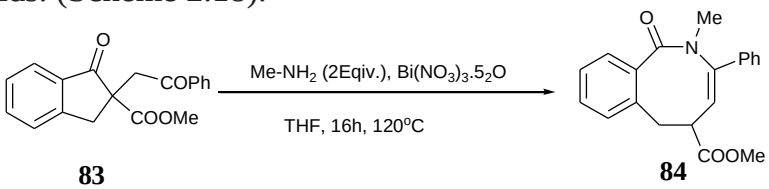

(Scheme 2.15)

Buchwald et al reported the Cu(I) catalyzed domino process for the synthesis of medium-sized benzo-fused azalactams ring via *β*-lactam ring-expansion process[32b]. Starting from 2-bromobenzylamine**79** and 2-azetidinone**80** as the coupling partners the desired eight-membered heterocycle **82** was obtained in 88-96% yield and none of the *N*-arylated *β*-lactam **81** was observed, indicating a facile domino process involving the copper-catalyzed aryl amidation reaction and subsequent ring expansion. Product was obtained in toluene at 80 °C (Scheme 2.16). The C-N coupling-ring-expansion reaction could also be extended to preparation of 9- and 10-membered rings.




(Scheme 2.16)

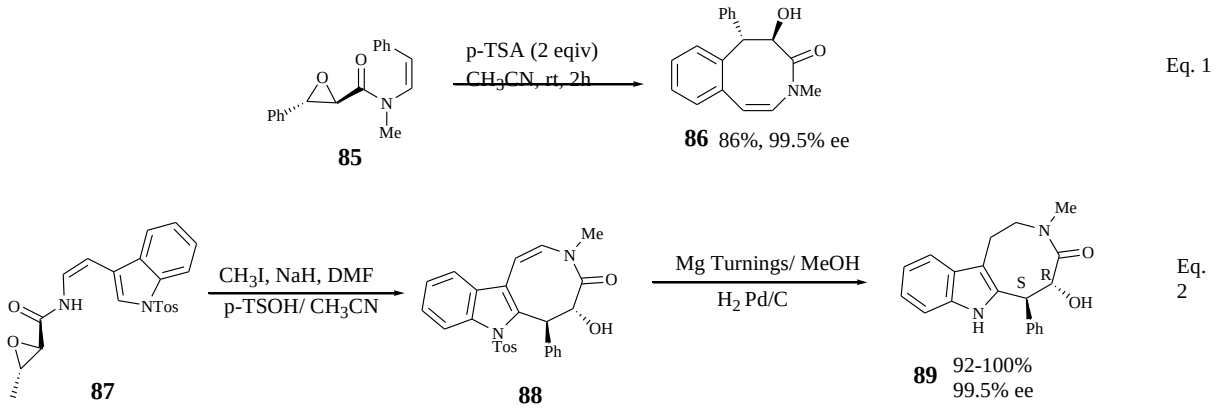
Jens Christoffers et al reported the bismuth-catalyzed ring-enlargement reaction of β-oxo esters **83** with primary amines ring expansion that furnishes eight-membered ring lactams[32c]**84**. Reaction of B oxo ester **83** with an excess of $MeNH_2$ and stoichiometric amounts (0.1 equiv.) of hydrated bismuth nitrate at an elevated temperature (120 °C) to achieved full conversion. The formation of compound 3 could be anticipated to occur through cleavage of the central C–C bond of the intermediate 2 by a retro-Claisen reaction. Intermediate formed as a result of MeNH2 addition to both carbonyl groups of the 1,4-diketone moiety of the starting material . Total conversion resulted in moderate yields. (Scheme 2.18).




(Scheme 2.17)

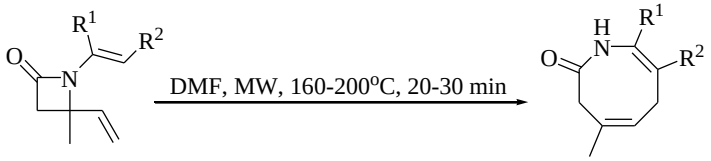
Mei-Xiang Wang et al reported the synthesis of important natural products ((±)-ξ-Clausenamide and (-)-(5R,6S)-Balasubramide **89** which consists eight membered lactum as core structure[33]. Ring expansion and cyclization took place through the unprecedented intramolecular 8-endo-epoxy-arene cyclization of (Z)-N-(phenylvinyl)oxiranecarboxamides (Scheme 2.19). Precursor **85** was subjected for

aryl-epoxide cyclization in presence of p-TSA in acetonitrile yielded eight membered ring product Clausenamide **86**b via the 8-*endo*-epoxy-arene cyclization. Precursor 2a on *p*-TSA-promoted 8-*endo*-indole-epoxide cyclization gave indole-fused eight-membered lactam 2b in 50-62% yield. Deprotection of the tosyl group in the presence of magnesium turnings followed by catalytic hydrogenation of 15 yielded an almost quantitative yield of (-)-(5*R*,6*S*)-balasubramide 16 (Eq. 2 Scheme 2.19). The exclusive formation of 88**, 89** is most probably due to the synergetic electronic and steric effects, i.e., the conjugation of an enamide with a benzene ring and the folded conformation of **88, 89**. In other words, both the delocalization of enamideelectrons into the benzene ring and the perfectly predisposed conformational structure of **89** dictate the 8-*endo*-epoxy-arene cyclization.




(Scheme 2.18)

Yudin and co-workers have investigated a microwave assisted ring-expansion of N-vinyl β-lactams**90** as an easy way for accessing eight-membered ring lactams[34]**91**. The eight membered products have been formed by a [3,3]-sigmatropic rearrangement between two strategically placed alkenes on a β-lactam (Scheme 2.20). The microwave assisted rearrangement was carried out in DMF at 160–200$^{o}$C for 20–30 min, and the desired eight membered lactams were isolated in good yields of 48–86% (Scheme 2.20)



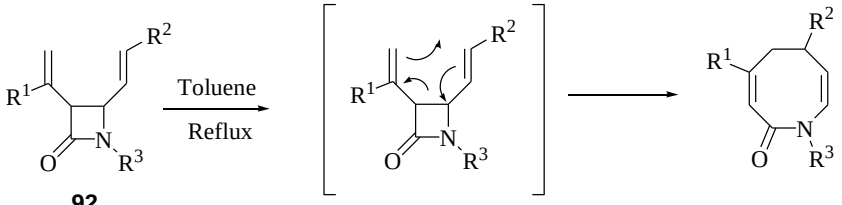

$R^1$ = H, Me

$R^2$ = Ph, (4-Cl)Ph, (4-$NO_2$)Ph

(Scheme 2.19 Microwave assisted synthesis of eight membered ring enamide via [3,3] sigma tropic rearrangement)

A clean protocol for the synthesis of eight-membered lactams (tetrahydroazocinones) via a concerted C3-C4 bond breakage of the β-lactam nucleus has been published**.** The authors reasoned that the presence of alkenyl groups attached to adjacent ring positions (C3 and C4) of the β-lactam ring might provide an opportunity to use a

thermal [3,3] sigmatropic rearrangement for the synthesis of eight-membered lactams through C3-C4 bond breakage[35a]. Starting from 2-azetidinone-tethered 1,5-dienes a stereoselective synthesis of tetrahydroazocinones was developed. This is the first example of a Cope rearrangement in which the C3- C4 bond of the β-lactam nucleus is the central bond of the 1,5-hexadiene system (Scheme 2.20). Of particular interest were the reactions of enantiomerically pure substrates **92a**-α and **92b**-β, which cleanly rearranged to the corresponding optically pure products **93a**-α and **93b**-β. The high stereospecificity of these Cope rearrangements may be interpreted via a boat-like transition state.

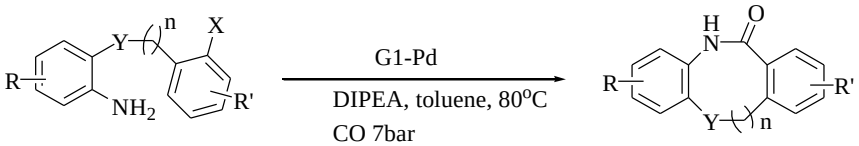



**92** **93**

(+)-92a-α = $R^1$ = Me, $R^2$=Ph, $R^3$= (R)-CH(Me)Ph
(-)-92a-β = $R^1$ = Me, $R^2$=Ph, $R^3$= (R)-CH(Me)Ph

(Scheme 2.20)

Lu and Alper developed a more general and efficient method for the synthesis of oxygen-, nitrogen-, or sulfur-containing medium ring-fused heterocycles with recyclable palladium complexed dendrimers on silica as catalysts. Their process tolerates a wide array of functional groups, including halide, ether, nitrile, ketone, and ester. The dendritic catalysts showed high activity, affording the heterocycles in excellent yields (Scheme 86). Importantly, these catalysts were easily recovered by simple filtration in air and could be reused up to the eight cycles with only a slight loss of activity.




**94** **95**

X = I, Br
Y = O, S, NR
n = 0,1

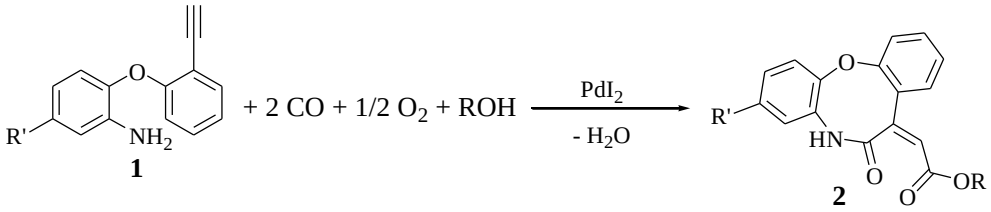
(Scheme 2.21, Carbonylative synthesis of macroactam)

In summary, as the formation of medium ring compounds are valuable form the point of view of their use in various scientific fields, and also their anti cancer activities increased their importance in medicinal and pharmaceutical research too. In order to make synthetic process economic by avoiding expensive catalytic system and use of available cheap source is required. Carbonylation reaction will be the better solution.

### 2.3 Result and Discussion

When acetylenic substrates bearing a nucleophilic group suitably placed for cyclization reacted in presence of Gabriele Catalyst under oxidative alkoxy carbonylative process, two different kinds of reactivity's can be predicted as oxidative cyclocarbonylation alkoxycarbonylation with insertion of carbonyl group into the ring and/or oxidative heterocyclization alkoxycarbonylation without insertion of carbonyl group into the ring.

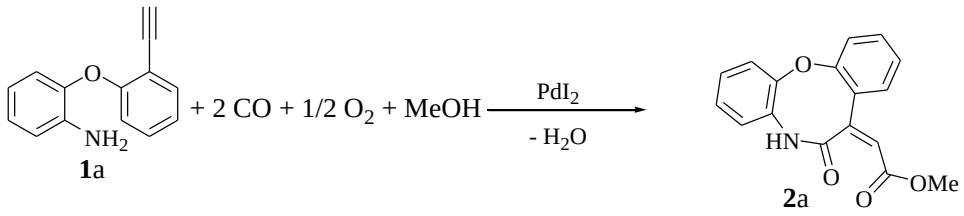
Substituted 2-(2-Ethynyl phenoxy) aniline **1** was reacted under oxidative carbonylation conditions in alcoholic solvent, under pressuer of 4:1 gas mixture of CO and air in presence of $PdI_2$ (in conjuction with KI) as catalytic system in, reaction proceeds via cyclocarbnylative approach resulted into Eight memebered tricyclic lactam **2** with 42-57 % isolated yields (Scheme 2.22). Structure of the product was confirmed by NMR and x-ray chrystallography.




(Scheme 2.22) 42%-57%

Here we are reporting a full account of the Gabriele catalyst catalyzed a new regioselective macrolactamization process leading to oxidative cyclocarbonylation-alkoxycarbonylation of readily available 2-(2-Ethynyl phenoxy) Aniline derivatives **1** to *8-exo-dig* to give (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[*a*,*d*]cycloocten-7-ylidene)acetate esters **2**

Starting from readily available 2-(2-Ethynyl phenoxy) Aniline derivatives **1a** (R = H), bearing nucleophilic primary amino group, synthesized from 2-(2 Iodo phenoxy) aniline by sonogashira coupling with alkyne, was chosen as model substrate to test the reactivity under oxidative carbonylation conditions in the presence of catalytic amounts of $PdI_2$/KI. In the first attempt reactionwas carried at 100 °C in MeOH as a solvent (**1a** Molar concentration = 0.05 mmol per mL of MeOH, 1a : KI : $PdI_2$ molar ratio = 50:10:1) under 20 atmospheric pressure of a 4:1 mixture of CO-air. Under these conditions desired Macrolactam derivative (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[*a*,*d*]cycloocten-7-ylidene) acetate esters **2**a (33% isolated yield) was obtained at a substrate conversions of 100%. (Scheme 2.23)




(Scheme 2.23) (33%)

In order to improve this initial result, we then did the screening of the reaction parameters with respect to Change in temperature, pressure conditions, catalytic ratio of with respect to substrate and ratio between $PdI_2$ and KI and the molar concentration of the substrate in the solvent. Results obtained from screening of reaction parameters are shown in Table 2.1 through entries 2-7, as can be seen from Table 2.1. An increase in the molar concentration of 1a to 0.2M reduced the yields with incomplete conversion of the substrate 1a (entry 2). Even more increase in the concentration to 0.1M (entry 3), no product observed. Lowering temperature conditions (Entry 4) also lowered yield and the conversion of the substrate. Also decreased co-catalyst ratio decreased both yield and substrate conversion (entry 5). When pressure conditions were increased to 40 (32CO, 8 air) (entry 6), an improvement in the total yield of **2**a was observed, but even more increase in the pressure to 60 (48 CO, 12air) again reduced yield of **2**a (entry 7). By carrying out the reaction under the optimized conditions (1a:KI:$PdI_2$ molar ratio = 50:10:1, at 100 °C, 32 atm of CO, 8 atm of air, 1a

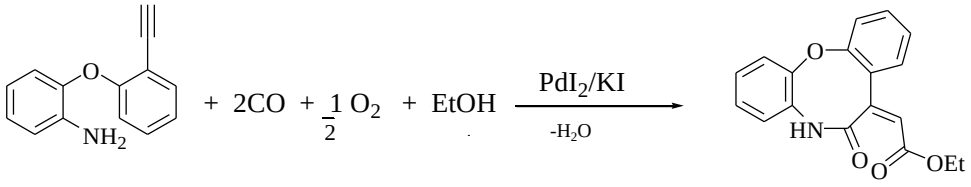
concentration = 0.05 mmol per mL of MeOH), (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[*a*,*d*]cycloocten-7-ylidene) acetic acid methyl ester **2**a was obtained moderate yield 42% (isolated yield), Table 2.2, entry 6). as shown In table 2.1

**Table 2.1**

| Run | $PdI_2$/KI/Sub | T ($^oC$) | $P_{co}$ /$P_{air}$ | Molar conc. (mmol/mL) | Conversion | Yields (%)[b] |
|---|---|---|---|---|---|---|
| **1** | **1/10/50** | **100** | **16/4** | **0.05** | **100** | **33** |
| **2** | **1/10/50** | **100** | **16/4** | **0.2** | **29** | **12** |
| **3** | **1/10/50** | **100** | **16/4** | **0.1** | **25** | **-** |
| **4** | **1/10/50** | **80** | **16/4** | **0.05** | **77** | **6** |
| **5** | **1/5/50** | **100** | **16/4** | **0.05** | **51** | **19** |
| **6** | **1/10/50** | **100** | **32/8** | **0.05** | **100** | **42** |
| **7** | **1/10/50** | **100** | **48/12** | **0.05** | **100** | **32** |

[a] Carbonylation reactions were carried out at 100°C in MeOH (0.05 mmol of substraten per mL of MeOH) using a **1a**:$PdI_2$:KI molar ratio of 50:1:10, under 32 atm of CO and 8 atm of air (at 25 °C) for 24 h.

The generality of the process was then verified by testing the reactivity of other differently substituted 2-(2-Ethynyl phenoxy) Aniline, bearing a substituents at C-3 position to amino group. As can be seen from the results reported in Table 2.2, (entries 1-5)

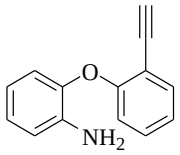
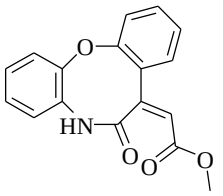
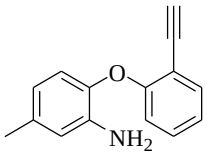
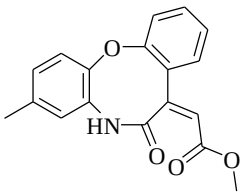
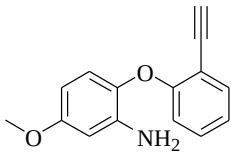
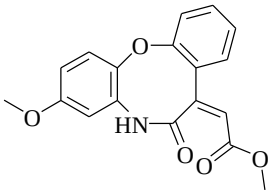
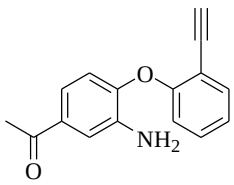
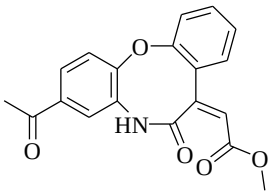
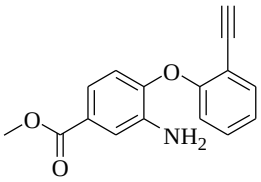
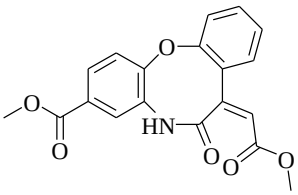
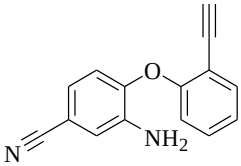
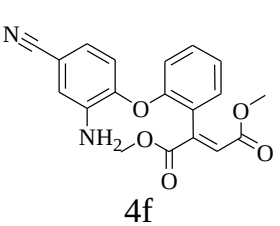



(Scheme 2.24) 52%

The generalized process was then tested by changing nucleophilc solvent to Ethanol. When 2-(2-Ethynyl phenoxy) Aniline was reacted under generalized conditions (1a:KI:$PdI_2$ molar ratio = 50:10:1, at 100 °C, 32 atm of CO, 8 atm of air, 1a concentration = 0.05 mmol per mL of EtOH), the product 3b (*Z*)-(6-oxo-5,6-dihydro-

12-oxa-5-aza-dibenzo[*a*,*d*]cycloocten-7-ylidene) acetic acid ethyl ester **3b** was obtained in enlarged yield 52% (isolated yield) (Scheme 2.24)

**Table 2.2**

| Entry | Substrate 1 | R | Product 2 | Yields (%) |
|---|---|---|---|---|
| 1 |  1a | Me |  2a | 42 |
| 2 |  1b | Me |  2b | 51 |
| 3 |  1c | Me |  2c | 42 |
| 4 |  1d | Me |  2d | 42 |
| 5 |  1e | Me |  2e | 47 |
| 6 |  1f | Me |  4f | 45 |

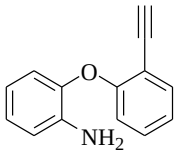
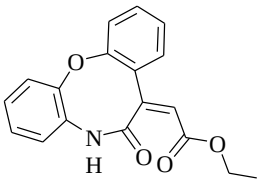
[a] Carbonylation reactions were carried out at 100°C in MeOH (0.05 mmol of substraten per mL of MeOH) using a **1a**:$PdI_2$:KI molar ratio of 50:1:10, under 32 atm of CO and 8 atm of air (at 25 °C) for 24 h.

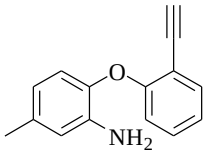
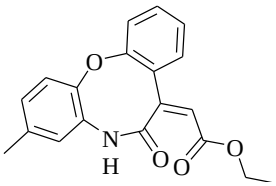
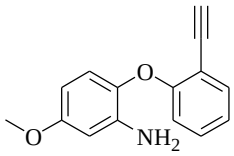
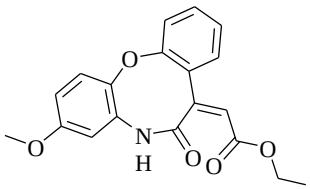
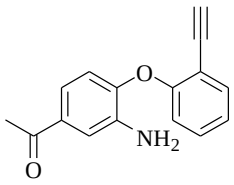
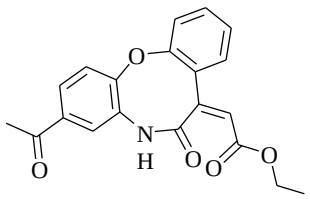
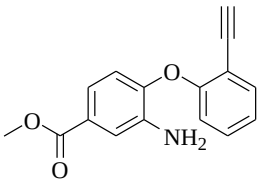
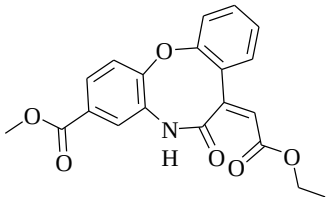
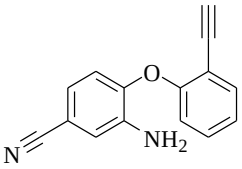
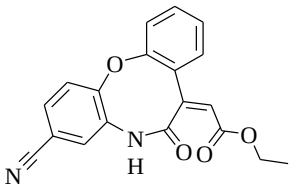
The generality of the process was then verified by testing the reactivity of other differently substituted 2-(2-Ethynyl phenoxy) Aniline $1_{a\text{-}f}$, bearing a substituents at C-3 position to amino group, As can be seen from the results reported in Table 2.3, (entries 1-6).

Macrolactamization of the substrates under oxidative carbonylation conditions tolerable disregards to electronic effect of substituents and worked well with both substrates consisting electron donating and electron withdrawing group. Surprisingly nucleophilicity of the solvent played an important role especially in case of substrate with –CN as substituent 1f. In Methanol as solvent and external nucleophilic solvent, ring opening was observed of the product which resulted into the formation of malonate derivative. Surprisingly, in case of substrate 1d and 1e the products remained unaffected.

From the observations of yields obtained from methanol as nucleophilic solvent are lesser than the yields obtained from ethanol as nucleophilic solvent. Generally, all carbonylation reactions work well with higher yields in methanol as a solvent, Nucleophilicity of the solvents may be the cause for the reactivity towards the macrolactamization. Methanol is more nucleophilic compared to ethanol. In methanol rate of formation of product is more, but as due to increased nucleophilicity, second mole of methanol may attacks the carbonyl function of amide which results into ring opening of the product to form malonate ester. If it is the case, strength of Electron withdrawing group at the C-3 position of the amine may help for this mechanism. So, the case is observed in case of **1f** having -C≡N group which caused the ring opening of the product to form malonate ester **4f** instead of **2f** as Macrolactam ring.

Table 2.3

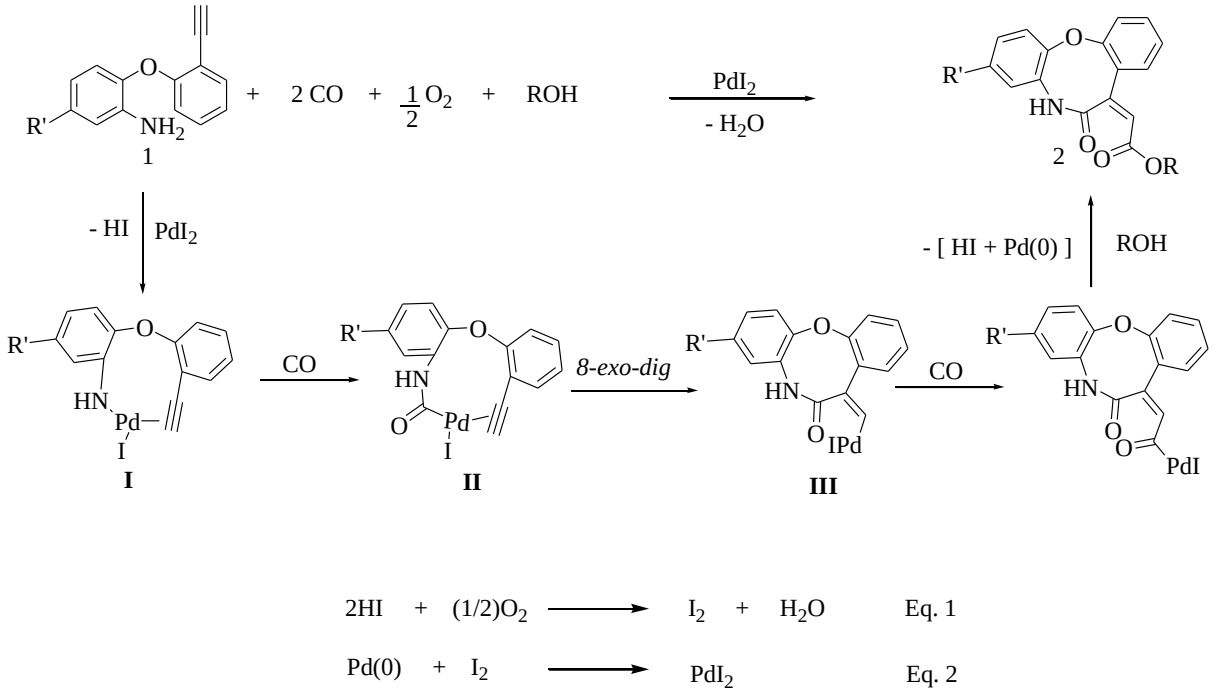
| Entry | Substrate 1 | R | Product 2 | Yields (%) |
|---|---|---|---|---|
| 1 |  1a | Me |  3a | 52 |

| | | | | |
|---|---|---|---|---|
| 2 |  1b | Me |  3b | 57 |
| 3 |  1c | Me |  3c | 53 |
| 4 |  1d | Me |  3d | 47 |
| 5 |  1e | Me |  3e | 53 |
| 6 |  1f | Me |  3f | 42 |

[a] Carbonylation reactions were carried out at 100°C in MeOH (0.05 mmol of substraten per mL of MeOH) using a **1a**:$PdI_2$:KI molar ratio of 50:1:10, under 32 atm of CO and 8 atm of air (at 25 °C) for 24 h.

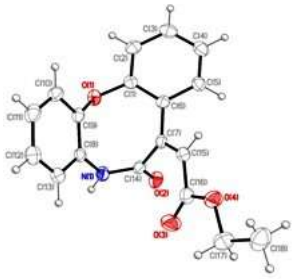
The formation of (*Z*)-(6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)acetates **2** can be interpreted as occurring as shown in Scheme 5 (anionic iodide ligands are omitted for clarity). Reaction of the amino group of **1** with $PdI_2$ leads to form complex **I** with liberation of one mole of HI, in which the triple bond is coordinated to the metal center. Carbon monoxide insertion results into the formation of carbamoylpalladium intermediate **II.** Intramolecular *syn 8-exo-dig* insertion of triple bond into the Pd-C bond gives cyclic vinyl-palladium intermediate **III** with *Z* stereochemistry. A second carbon monoxide insertion

followed by nucleophilic displacement by ROH eventually affords the final product **2** and Pd(0) with liberation of second mole of hydroiodic acid. These liberated two molecules then oxidized by oxygen present in gas mixture to form Iodine [Scheme 5 (eq.1)] which is then undergoes oxidative addition to Pd(0) to regenerate $PdI_2$. [Scheme 5 (eq.2)]




(Scheme 2.25)

The structure and the stereochemistry at the double bond has been confirmed by X-ray crystallography (Figure 5)



(Figure 5)

## 2.4 Conclusion

In summary, medium ring lactam scaffold holds great potential, along with their natural occurance, they represent an important class of therapeutic, medicinal sciences and material sciences as well. Macrolactamization has thus evolved into an extremely useful and powerful reaction tool in organic synthesis. Although, entropic and enthalpic factors are the main obstacle in medium ring synthesis, there are numerous routes and methodologies leading to the construction of medium ring macrolactams via ring closing metathesis, ring expansion, ring contraction and rearrangement. In regards to environmental factor, atom economy and cost effective strategies continuous research and development of the synthetic routes are in progress. Transition metal catalyzed carbonylation method can be a great solution for this. Herein we reported new $PdI_2$ catalyzed macrolactamization process to form medium ring lactams via oxidative carbonylation. Catalytic efficiency and versatility of Gabriele catalyst here once again proved. Initial studies of some molecules, tested against MCF-7 cell lines, showed selective inhibition activity towards cancer cells. Further deep studies are in progress. may these compounds will give therapeutic solution to fight against Breast cancer.

## 2.5 Experimental:

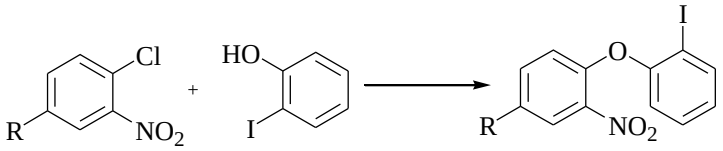
### 2.5.1 General:

Melting points were taken on a Reichert Thermovar apparatus and are uncorrected. 1H-NMR and 13C-NMR spectra were recorded at 25 °C in CDCl3 solutions with a Bruker DPX Avance 300 spectrometer operating at 300 MHz and 75 MHz, respectively, with Me4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with a JASCO FT-IR 4200 spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analyzed by TLC on silica gel 60 F254 (Merck) or on neutral alumina (Merck) and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with

polymethylsilicone + 5% polyphenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh) or neutral alumina 90 (Merck, 70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

### 2.5.1.1 Preparation of Substrates:

#### 2.5.1.1.1 Synthesis of substituted 2(2-iodo phenoxy) nitro benzene [37]

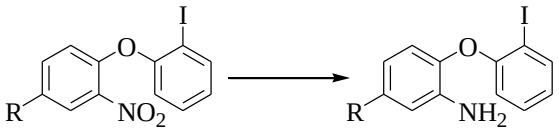



| | |
|---|---|
| R=H | MW = 341.10 |
| R=OMe | MW = 371.13 |
| R=CN | MW = 366.11 |
| R=COMe | MW = 383.14 |
| R=COOMe | MW = 399.14 |
| R=Me | MW = 355.12 |

To the mixture of 2-Iodo phenol 4.545 mmol (1g) and substituted 1-Chloro-2-nitrobenzene 4.545 mmol (R=H 716.1mg; R=OMe 852.5mg; R=CN 829.7mg; R=COMe 907.1mg; R=COOMe 979.8mg; R=Me 779.8mg) in dry DMSO (10 mL) was added $K_2CO_3$ (1.25g; 9.09 mmol) and reaction mixture was heated (at 100°C R=H; R=C≡N; R=COMe; R=COOMe, at 120°C R=OMe; R=Me) for 15h. Diluted and extracted with diethyl ether (50mL X 3 times). Organic layer was then washed with brine & water, dried over sodium sulphate and evaporated. Purified by crystallisation in EtOAc (R =-H, -CN, -COMe, -COOMe) and by column chromatography (R =-OMe, -Me) using silica gel as stationary phase and EtOAc: Hexane in proportion 5:95 to 80:20 as eluent.

Obtained in Yields, R=H, grey solid, 1.48g, 95%; R = OMe, Brown solid, 1.26g, 75%; R= CN yellow solid, 1.49g, 96% R= COMe Brown Solid, 1.42g, 82%, R= COOMe Yellow solid, 1.43g, 79%, R= Me Pale yellow solid, 1.22g, 76%

### 2.5.1.1.2 Synthesis of 2-(2-Iodo-phenoxy)-phenylamine[38]

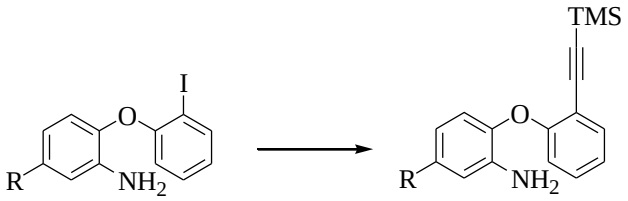



| | |
|---|---|
| R=H | MW = 311.12 |
| R=OMe | MW = 341.14 |
| R=CN | MW = 336.13 |
| R=COMe | MW = 353.16 |
| R=COOMe | MW = 369.15 |
| R=Me | MW = 325.14 |

To the solution of substituted 2-(2-Iodo-phenoxy)-nitrobenzene 4mmol (R= H, 1.36g; R= OMe 1.48g; R= CN 1.46g, R=COMe 1.53g; R=COOMe 1.59g; R=Me 1.42g ) in Ethyl acetate (20mL) was cooled to 0°C - 5°C and added $SnCl_2.2H_2O$ 20mmol (4.51g). Reaction mixture was then stirred for 15h at room temperature. After completion reaction mixture was neutralized by 2N NaOH solution (50 mL). Neutralization results into formation of white solid, which was removed by filtration through celite. Filtrate was then extracted with EtOAc (50mL X 3 times) Organic layer was washed with brine & water, dried over sodium sulphate and purified by column chromatography using Silica gel (80-200 mesh) as stationary phase and EtOAc:Hexane in proportion 5:95 to 25:75 as eluent.

Yields obtained are R=H, grey solid, 0.971g, 78%; R=OMe Brown oil, 1.141g ,84%; R=CN, white solid, 0.981g, 73%; R=COMe Brown Solid 1.16g, 82%; R= COOMe Yellow solid 1.24g, 84%; R=Me Pale yellow solid 0.98g, 76%;

### 2.5.1.1.3 Synthesis of substituted 2-(2-Trimethylsilanylethynyl-phenoxy)-phenylamine

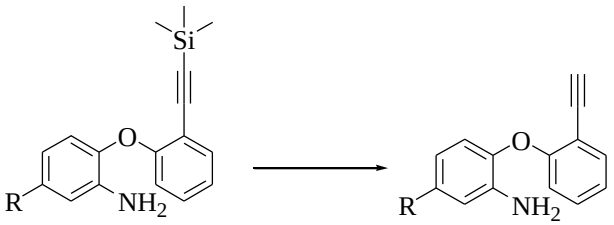



R=H MW = 281.42
R=OMe MW = 311.46
R=CN MW = 306.43
R=COMe MW = 323.46
R=COOMe MW = 339.46
R=Me MW = 295.45

To the solution of substituted 2-(2-Iodo-phenoxy)-phenylamine 1.6 mmol (R=H 497.8mg; R=OMe 545.8mg; R=CN 537.8mg; R=COMe 565mg; R=COOMe 590.6mg; R=Me 520.2mg) in dry THF (5 mL) was added Dry Triethylamine 3.2 mmol ( 0.45 mL ) and then $PdCl_2(PPh_3)_2$ 0.032mmol (12.8 mg) and CuI 0.16 mmol (30.4 mg ) and finally Ethynyltrimethylsilane 2.4mmol (0.37 mL). Reaction mixture was stirred for 8h at RT. Reaction mixture was quenched with saturated solution of Ammonium chloride (10mL), extracted with EtOAc (15mL X 3 times), washed with brine, dried over sodium sulphate, evaporated and purified by column chromatography using Silica gel (80-200 mesh) as stationary phase and with EtOAc:Hexane in proportion to 70:30 as eluent.

Pure compounds were obtained as R=H grey-brown solid, 0.342 mg, 76%; R=OMe Brown oil, 0.418g, 84%; R=CN, white solid, 0.981g, 73%; R=COMe Brown Solid, 0.439g, 85%; R= COOMe Yellow solid 0.47g, 88%; R=Me Pale yellow solid 0.34g, 72%;

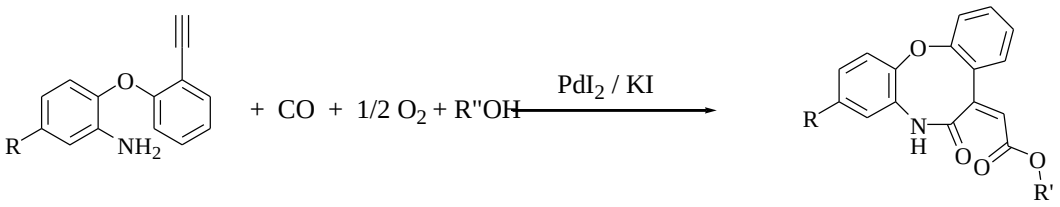
### 2.5.1.1.4 Deprotection of trimethylsilane




R=H MW = 209.24
R=OMe MW = 239.27
R=CN MW = 234.25
R=COMe MW = 251.28
R=COOMe MW = 267.28
R=Me MW = 223.27

To the solution of 2-(2-Trimethylsilanylethynyl-phenoxy)-phenylamine 1.5mmol (R=H 422.1mg; R=OMe 467.1mg; R=CN 459.6mg; R=COMe 485.2mg; R=COOMe 509.2mg; R=Me 443.2mg) in dry Methanol (5 mL) was added dry $K_2CO_3$ 4.5mmol (622mg) and it was stirred for 6h at RT. After completion of reaction, reaction mixture was filtered through celite to remove $K_2CO_3$, washed with excess of Methanol (50mL). It was then evaporated till dryness. Crude product was then solubilised in Dichloromethane (50mL) and washed with brine and water, dried over sodium sulphate, purified by column chromatography using silica gel (80-200 mesh) as stationary phase and EtOAc:Hexane in proportion from 95:5 to 70:30 as eluent. Pure compounds obtained as. R= H grey-white solid in 0.244mg 78%; R=OMe Brown oil, 0.301g, 84%; R=CN, white solid, 0.295g, 73%; R=COMe Brown Solid 0.376g, 81%; R= COOMe Yellow solid 0.336g, 84%; R=Me yellow liquid 0.254g, 76%

### 2.5.1.1.5 Synthesis of 5H,7H-12-oxa-5-aza-dibenzo[a,d]cycloocten-6-one derivatives (Carbonylation process)

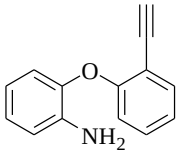



| | | |
|---|---|---|
| R=H | R'=OMe | MW = 295.29 |
| | R'=EtOH | MW = 309.32 |
| R=OMe | R'=OMe | MW = 325.32 |
| | R'=EtOH | MW = 339.34 |
| R=CN | R'=OMe | MW = 352.34 |
| | R'=EtOH | MW = 334.33 |
| R= COMe | R'=OMe | MW = 337.33 |
| | R'=EtOH | MW = 351.35 |
| R= COOMe | R'=OMe | MW = 353.33 |
| | R'=EtOH | MW = 367.35 |
| R= Me | R'=OMe | MW = 309.32 |
| | R'=EtOH | MW = 323.34 |

In typical procedure for the oxidative carbonylation of 5 substituted 2-(2-Ethynyl-phenoxy)-phenylamine was added in 250 mL stainless steel autoclave charged in the presence of air with $PdI_2$ (2.5 mg, $6.94x10^{-3}$ mmol ), KI (11.5 mg, $6.94 \times 10^{-2}$ mmol), and a solution of 5 substituted 2-(2-Ethynyl-phenoxy)-phenylamine $3.47x\ 10^{-1}$mmol (R=H 72.6mg; R=OMe 83.02mg; R=CN 81.2mg; R=COMe 87.2mg; R=COOMe 92.7mg; R=Me 77.4mg) in ROH (R = Me or Et, 6.94 mL; 0.05M). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (8 atm). After being stirred at $100^{o}$C for 15h (R=MeOH) and 24h (R= EtOH), the autoclave was cooled, degassed, and opened. The solvent was evaporated, and the products were purified by column chromatography on silica gel (80-200mesh) (eluent: 6:4 Hexane–EtOAc for R"=MeOH and 65:35 hexane–EtOAc for R''=EtOH)
All pure compounds were obtained as R=H, (R'=OMe, Yellow solid, 43mg, 42%); (R'=EtOH, White solid, 55.8mg, 52%); R=OMe (R'=OMe, Yellow solid, 47.4mg, 42%) (R'=EtOH, yellow- brown solid, 62.4mg, 53%); R=CN (R'=OMe, yellow oil, 55mg, 45%) (R'=EtOH White solid, 48.7mg, 42) R= COMe (R'=OMe, White solid 49.1mg, 42%); (R'=EtOH, Yellow solid, 57.3mg, 47); R= COOMe (R'=OMe Yellow solid, 57.6mg, 47%); (R'= EtOH, Yellow solid, 67.5mg, 53%); R= Me (R'=OMe yellow solid, 54.7mg, 51%); (R'=EtOH, Yellow solid, 63.9mg 57%)

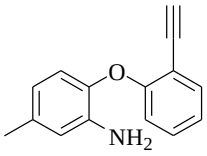
## 2.6 Characterization Data:

All the substrates prepared using reported methods and characterization data was matched with the previously reported characterization data.



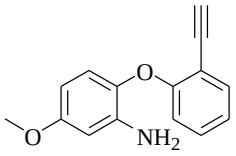
$C_{14}H_{11}NO$
Mol. Wt.: 209.24
C, 80.36; H, 5.30; N, 6.69; O, 7.65

**2-(2-Ethynylphenoxy)aniline (1a).** Grey-White solid, 78% yield; mp 64-65$^{o}$C; IR (KBr) $\nu_{max}$ = 3281(s, br), 2106(m), 1619(s), 1509(s), 1443(s), 1231(s), 886(m), 748(s) cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.52 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.23 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.02_6.97 (m,2H), 6.89 (dd, *J* = 1.5, 7.5 Hz, 1H), 6.82_6.76 (m, 2H), 6.72 (dt, *J* = 1.5, 8.0 Hz, 1H), 3.83 (ws, 2H), 3.30 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 158.56, 142.60, 138.63, 134.09, 130.18, 125.26, 122.42, 120.52, 118.62, 116.46, 115.88, 122.68, 81.82, 79.32; MS (EI) *m/z* 209 [M+]; HRMS Calcd. for $C_{14}H_{11}NO$ 209.0841, found 209.0822.



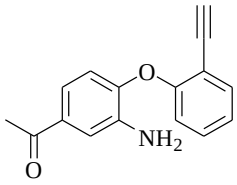
$C_{15}H_{13}NO$
Mol. Wt.: 223.27
C, 80.69; H, 5.87; N, 6.27; O, 7.17

**5-Methyl-2-(2-ethynylphenoxy)aniline (1b).** yellow liquid 76% yield; IR (Neat) $\nu_{max=}$ 3376(m), 3280(m), 2106(m), 1620(m), 1509(s), 1481(s), 1232(s), 862(s), 754(s) cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.52 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.21 (dt, *J* = 1.5, 8.5 Hz, 1H), 6.98 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 6.53 dd, *J* = 2.0, 8.0 Hz, 1H), 3.75 (ws, 2H), 3.31 (s, 1H), 2.27 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 158.97, 140.21, 138.41, 135.60, 134.05, 130.18, 122.12, 120.75, 119.28,17.14, 115.34, 112.31, 81.79, 79.48, 20.98; MS (EI) *m/z* 223 [M+]; HRMS Calcd. For $C_{15}H_{13}NO$ 223.0997, found 223.0975.



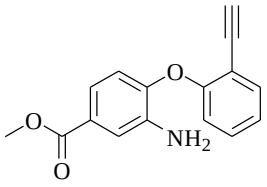
$C_{15}H_{13}NO_2$
Mol. Wt.: 239.27
C, 75.30; H, 5.48; N, 5.85; O, 13.37

**5-Methoxy-2-(2-ethynylphenoxy)aniline (1c).** Brown oil**,** 84% yield; IR (KBr) $\nu_{max}$= 3376(m), 3278(m,br), 2104(m), 1622(m), 1509(s), 1481(s), 1231(s), 1208(s), 1208(m), 754(m), 630(m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.50 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.20 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.96 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 3.81 (ws, 2H), 3.71 (s, 3H), 3.33 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 159.17, 157.41, 143.57, 139.78, 136.03, 134.04, 129.67, 121.94, 114.67, 111.88, 103.42, 101.24, 81.80, 79.53, 55.35; MS (EI) *m/z* 239 [M+]; HRMS Calcd. for $C_{15}H_{13}NO_2$ 239.0946, found 239.0925.



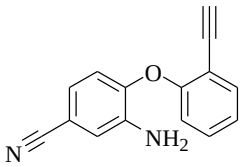
$C_{16}H_{13}NO_2$
Mol. Wt.: 251.28
C, 76.48; H, 5.21; N, 5.57; O, 12.73

**1-[3-Amino-4-(2-ethynylphenoxy)phenyl]ethanone (1d).** Brown solid 81% yield; mp 91-93 $^oC$; IR (neat) $\nu_{max}$= 3365(m), 3281(m, br), 2103(m), 1673(s), 1585(m), 1301(s), 1225(s), 1194(s), 754(m) $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.53 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.30_7.25 (m, 2H), 7.10 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.05 (ws, 2H), 3.21 (s, 1H), 2.51 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 197.29, 156.91, 147.83, 137.85, 134.30, 133.28, 130.34, 123.93, 119.57, 118.53, 117.21, 115.45, 114.34, 82.27, 78.56, 26.41; MS (EI) *m/z* 251 [M+]; HRMS Calcd. for $C_{16}H_{13}NO_2$- 251.0946, found 251.0939.



$C_{16}H_{13}NO_3$
Mol. Wt.: 267.28
C, 71.90; H, 4.90; N, 5.24; O, 17.96

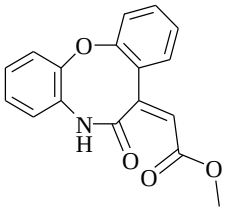
**3-Amino-4-(2-ethynyl-phenoxy)-benzoic acid methyl ester (1e)** Yellow solid 84% Yield; mp. 63.2-64.1$^{o}$C, IR (KBr) $\nu_{max}$ = 3434(m), 2111(s), 1724(s), 1620(m), 1592(s), 1445(s), 1302(s), 1117(m), 916(m), 749(s), 608(m), $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.2(t, 1H, aromatic), 7.13(s, 1H aromatic), 7.1-6.78(m, 5H, aromatic), 4.05 (ws, 2H,), 3.88(s, 3H, $CH_3OCO$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 167, 159.7, 147, 135.4, 131.8, 127.9, 124.4, 121.2, 119.4, 118, 116.9, 116, 111.1, 84.6, 78.3, 50. GC-MS: *m/z* = 267(100), 236(33), 208(33.3), 207(20), 195(22), 183(22), 180(32), 152(24), 89.9(12), 75(12.5), 63(12), 51.9(14), 44(39), 39.9(34).



$C_{15}H_{10}N_2O$
Mol. Wt.: 234.25
C, 76.91; H, 4.30; N, 11.96; O, 6.83

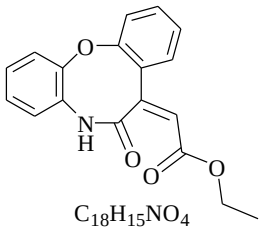
**3-Amino-4-(2-ethynylphenoxy)benzonitrile (1f).** white solid 73% yield; IR (neat) $\nu_{max}$ = 3468(m), 3360(m), 2225(s), 1618(m), 1507(s), 1235(s), 989(m), 755(m) cm$^{-1}$; $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.54 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.33 (dt, *J* = 1.5, 8.0 Hz, 1H), 7.14 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.94_6.90 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 4.18 (ws, 2H), 3.19 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 156.20, 147.54, 138.36, 134.41, 130.47, 124.51, 122.58, 119.21, 119.13, 118.35, 117.30, 114.76, 106.98, 82.52, 78.37; MS (EI) *m/z* 234 [M+]; HRMS Calcd. for C15H10N2O 234.0793, found 234.0778.

**Characterization of products:**



$C_{17}H_{13}NO_4$
Mol. Wt.: 295,29
C. 69,15; H. 4,44; N. 4,74; O. 21,67

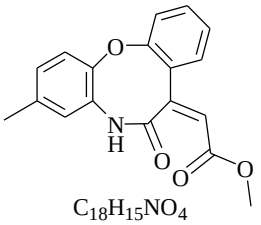
**(*z*)(6-Oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid methyl ester(2a).** Yellow solid; 42% yield; mp 222-225$^{o}$C; IR (KBr) $\nu_{max}$ = 3378(w,br), 2951(m), 1723(s), 1622(s), 1482(m), 1435(m), 1216(m), 754(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.88 (s br, 1H, NH), 7.58-7.48 (m, 1H, aromatic), 7.45-7.38 (m, 1H, aromatic), 7.35-7.0 (m, 6H, aromatic), 5.78 (s, 1H, C=CH), 3.74 (s, 3H, OMe); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 168.9, 164.3, 152.4, 149.9, 131.7, 130.5, 126.4, 126.3, 125.5, 125.1, 123.2, 123.0, 121.3, 120.0, 119.0, 51.6; GC-MS: *m/z* = 296 ($M^+$, 11), 295 (58), 278 (12), 263 (97), 235 (100), 207 (29), 190 (14), 180 (36), 165 (28), 152 (35), 139 (6), 103 (10), 89 (17), 75 (13), 63 (15), 51 (18);anal. calcd for $C_{17}H_{13}NO_4$ (295.29): C, 69.15; H, 4.44; N, 4.74; found C, 81.26; H, 4.56; N, 9.01.



$C_{18}H_{15}NO_4$
Mol. Wt.: 309.32
C, 69.89; H, 4.89; N, 4.53; O, 20.69

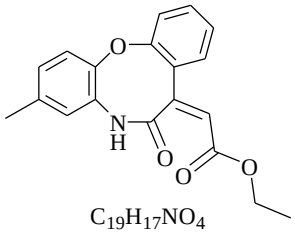
**(*z*)(6-Oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid ethyl ester(3a).** White solid, 52% yield, mp231-233$^{o}$C, IR (KBr) $\nu_{max}$= 3290(w,br), 2981(m), 1716(s), 1673(s), 1446(s), 1383(m), 1190(m), 754(s) cm$^{-1}$, GCMS: *m/z* = 309(37), 263(72), 236(100), 207(20), 190(8), 180(26), 165(18),152(21), 89(7), 77(7), 63(6), 51(8), $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90 (s br, 1H, NH), 7.45-7.37 (m, 1H, aromatic), 7.36-7.32 (m, 1H, aromatic), 7.30-7.10 (m, 6H, aromatic), 5.80 (s, 1H, C=CH), 4.19 (q, J=7.1, 2H, $CH_2CH_3$), 1.29 (t, J=7.1, 3H, $CH_2CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 169.2,163.8, 156.6, 151.9, 149.3, 131.7, 130.4, 129.2, 126.7, 126.3, 126.0, 125.0, 123.1, 121.2, 120.3, 60.8, 14.1; GC-MS: *m/z* = 309 (37), 281 (6),

263 (73), 236 (100), 219 (6), 207 (21), 190 (8), 180 (26), 165 (18), 152 (22), 89 (8), 77 (7), 63 (6), 51 (8); anal. calcd for $C_{18}H_{15}NO_4$ (309.32): C, 69.89; H, 4.89; N, 4.53; found C, 81.26; H, 4.56; N, 9.01.



$C_{18}H_{15}NO_4$
Mol. Wt.: 309.32
C, 69.89; H, 4.89; N, 4.53; O, 20.69

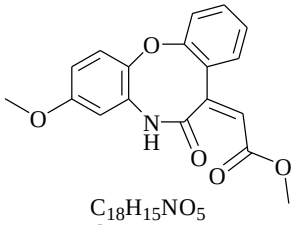
**(*z*)(3-Methyl-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid methyl ester (2b).** Yellow solid, 51% yield, mp 205-207$^{o}$C, IR (KBr) $\nu_{max}$= 3307(br), 2949(m), 1721(s), 1672(s), 1478(m), 1384(s), 1211(s), 1172(s), 756(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.87 (s br, 1H, NH), 7.45-7.38 (m, 1H, aromatic), 7.35-7.28 (m, 2H, aromatic), 7.20-7.11 (m, 1H, aromatic), 7.08-6.92 (m, 3H, aromatic), 5.80 (s, 1H, C=CH), 3.75 (s, 3H, OMe), 2.30 (s, 3H, Me); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 169.0, 164.4, 157.1, 150.0, 136.4, 131.7, 130.5, 129.8, 126.5, 125.6, 125.0, 122.8, 121.3, 120.0, 118.9, 51.6, 20.8; GCMS: *m/z* = 309(11.4), 277(12.8), 250(12), 249(11), 221(4), 207(11), 193(6), 179(3), 51(4), 44(100).



$C_{19}H_{17}NO_4$
Mol. Wt.: 323.34
C, 70.58; H, 5.30; N, 4.33; O, 19.79

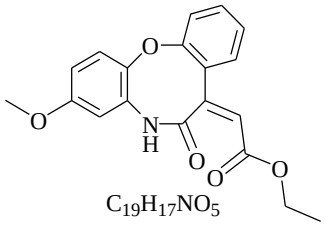
**(*z*)(3-Methyl-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid ethyl ester (3b).** Yellow solid; 57% yield; mp 219-222$^{o}$C, IR (KBr) $\nu_{max}$= 3395(br), 2992(m), 1712(s), 1673(s), 1501(m) 1477(m), 1384(m), 1180(s), 757(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.32 (s br, 1H, NH), 7.57-7.38 (m, 1H, aromatic), 7.35-7.25 (m, 2H, aromatic), 7.20-7.12 (m, 1H, aromatic), 7.05-6.95 (m, 3H, aromatic), 5.80 (s, 1H, C=CH), 4.21 (q, J=7.1, 2H, $CH_2CH_3$), 2.29 (s, 3H, Me), 3.76 (s, 3H, OMe), 1.30 (t, J=7.1, 3H, $CH_2CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 169.0, 163.9, 157.1, 150.2, 149.7, 136.4, 131.9, 131.6, 130.5, 129.7, 125.2, 126.5, 124.9,

122.8, 121.6, 120,4, 60.8, 20.8, 14.2; GCMS: *m/z* = 323(38.7), 294(5), 277(66), 250(100), 249(79), 221(17), 207(13), 193(18), 179(15), 165(11), 101(6), 77(8), 51(9),



$C_{18}H_{15}NO_5$
Mol. Wt.: 325.32
C, 66.46; H, 4.65; N, 4.31; O, 24.59

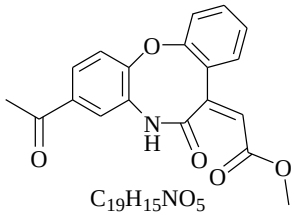
**(*z*)(3-Methoxy-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid methyl ester(2c).** Yellow solid, 42% yield, mp241-245$^{o}$C, IR (KBr) $\nu_{max}$= 3290(w,br), 2981(m), 1716(s), 1673(s), 1446(s), 1383(m), 1190(m), 754(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.88 (s br, 1H, NH), 7.58-7.48 (m, 1H, aromatico), 7.45-7.38 (m, 1H, aromatico), 7.35-7.0 (m, 6H, aromatici), 5.78 (s, 1H, C=CH), 3.74 (s, 3H, OMe); 3.71 (s, 3H, OMe); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 168.9, 164.3, 152.4, 149.9, 131.7, 130.5, 126.4, 126.3, 125.5, 125.1, 123.2, 123.0, 121.3, 120.0, 119.0, 51.6; GCMS: *m/z* = 325.1(67.8), 266(100), 265(71.6), 250(41), 222(30.5), 167(22.5), 139(13), 101(8.7), 51(11.6)



$C_{19}H_{17}NO_5$
Mol. Wt.: 339.34
C, 67.25; H, 5.05; N, 4.13; O, 23.57

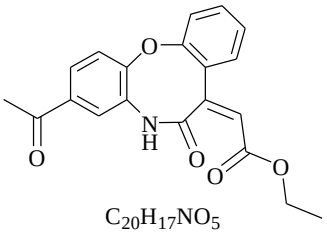
**(*z*)(3-Methoxy-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid ethyl ester(3c).** Grey solid; 53% yield; mp 218-221$^{o}$C; IR (KBr) $\nu_{max}$= 3293(w,br), 2927(m), 1712(s), 1675(s), 1482(m), 1477(m), 1502(s), 1308(m), 1208(s), 1180(s), 1031(s), 759(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, $CDCl_3$: $\delta$ = 7.91 (s br, 1H, NH), 7.50-7.30 (m, 3H, aromatic), 7.20-7.11 (m, 1H, aromatic), 7.05-7.00 (m, 1H, aromatic), 6.85-6.70 (m, 2H, aromatic), 5.80 (s, 1H, C=CH), 4.20 (q, J=7.0, 2H, C$H_2$CH$_3$), 3.76 (s, 3H, OMe), 1.30 (t, J=7.0, 3H, CH$_2$C$H_3$); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ =168.8, 164.0, 157.8, 157.3, 149.7, 146.2, 132.8, 131.5, 130.5, 127.1, 124.9, 123.6, 121.1, 120.3, 115.1, 111.1, 60.8, 56.0, 14.2; GC-MS: *m/z* = 340 (M$^{+}$,

12), 339 (52), 311 (8), 293 (42), 278 (17), 266 (100), 265 (68), 250 (37), 238 (22); 222 (23), 207 (13), 195 (15), 167 (23), 152 (8), 139 (11), 101 (9), 89 (7), 75 (7), 63 (7), 51 (11); anal. calcd for $C_{19}H_{17}NO_5$ (339.34): C, 67.25; H, 5.05; N, 4.13; found C, 81.26; H, 4.56; N, 9.01.



$C_{19}H_{15}NO_5$
Mol. Wt.: 337.33
C, 67.65; H, 4.48; N, 4.15; O, 23.72

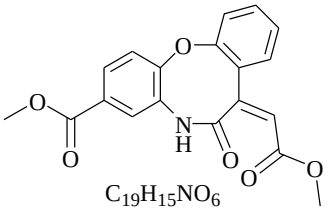
**(*z*)(3-Acetyl-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid methyl ester (2d).** White solid; 42% yield; mp 265-267$^{o}$C; IR (KBr) 3378(w,br), 2951(m), 1723(s), 1622(s), 1482(m), 1435(m), 1216(m), 754(s) cm$^{-1}$, GCMS: *m/z* = 295(58.8), 278(12),263(97), 235(100), 190(13), 180(34), 165(27),152(35), 103(10), 75(13), 51(18), $^{1}$H NMR (300 MHz, DMSO): $\delta$ = 10.4 (s br, 1H, NH), 8.30 (s, 1H, aromatic), 7.92-7.80 (m, 1H, aromatic), 7.68-7.61 (m, 1H, aromatic), 7.60-7.40 (m, 2H, aromatic), 7.38-7.24 (m, 2H, aromatic), 5.89 (s, 1H, C=CH), 3.64 (s, 3H, OMe), 2.30 (s, 3H, C(O)Me); $^{13}$C NMR (75 MHz, DMSO): $\delta$ = 196.4, 167.6, 163.6, 155.3, 154.0, 149.3, 134.7, 133.2, 132.0, 130.3, 128.9, 126.4, 125.4, 124.5, 123.2, 121.1, 119.2, 51.5, 26.6; GC-MS: *m/z* = 338[M+1](10.1), 337.1(47.5), 306(11), 305(47.6), 279(100), 278(65.3), 263(36), 262(41), 261(31), 249(12), 236(19.7), 235(21.5), 234(17.8), 223(14), 222(15), 206(20), 178(13.6), 166(10), 152(16), 151(17.8), 139(15), 89(10.5), 44(56), 43(87).



$C_{20}H_{17}NO_5$
Mol. Wt.: 351.35
C, 68.37; H, 4.88; N, 3.99; O, 22.77

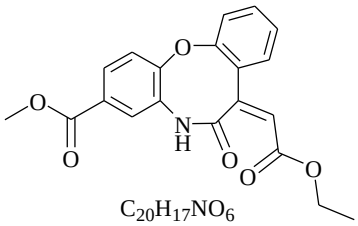
**(*z*)(3-Acetyl-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid ethyl ester(3d).** Yellow oil; 47% yield; IR (KBr) $\nu_{max}$= 3342(w,br), 2982(m), 1723(s), 1682(s), 1595(s), 1431(m), 1389(s), 1263(s), 1207(s), 1126(m) 758(s) cm$^{-1}$, $^{1}$H NMR (300 MHz, DMSO): $\delta$ = 10.4 (s br, 1H, NH), 7.92-7.85 (s, 1H,

aromatic), 7.70-7.62 (m, 1H, aromatic), 7.56-7.46 (m, 2H, aromatic), 7.45-7.42 (m, 1H, aromatic), 7.37-7.31 (m, 1H, aromatic), 7.31-7.23 (m, 1H, aromatic), 4.51 (q, J=7.1, 2H, C*H*$_2$CH$_3$), 2.55 (s, 3H, C(O)Me), 1.20 (t, J=7.1, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (75 MHz, DMSO): $\delta$ = 196.3, 167.6, 163.2, 155.3, 154.0, 149.0, 134.7, 133.3, 131.9, 130.3, 129.0, 126.4, 125.4, 124.5, 123.2, 121.0, 119.6, 60.2, 38.6, 13.9; GCMS: *m/z* = 352[M+1](8.8), 351(39.5), 278(45), 277(16.5), 262(25), 237(17.5), 236(100), 207(11), 165(30), 152(11), 44(39), 43(72.4).



$C_{19}H_{15}NO_6$
Mol. Wt.: 353.33
C, 64.59; H, 4.28; N, 3.96; O, 27.17

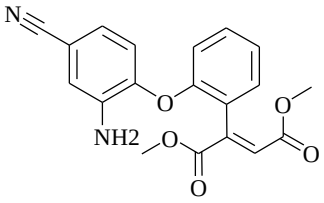
**(*z*)7-Methoxycarbonylmethylene-6-oxo-6,7-dihydro-5H-12-oxa-5-aza-dibenzo[a,d]cyclooctene-3-carboxylic acid methyl ester(2e)** White solid; 47% yield; mp 243-246$^o$C; IR (KBr) $\nu_{max}$= 3448(w,br), 3182(w), 2920(m), 1721(s), 1674(s), 1625(m), 1398(s), 1279(m), 1201(s), 1100(m), 760(m), 554(m,w) cm$^{-1}$, $^1$H NMR (300 MHz, DMSO): $\delta$ =7.98-7.92 (m, 1H, NH), 7.92-7.85 (m, 1H, aromatic), 7.50-7.40 (m, 1H, aromatic), 7.40-7.30 (m, 2H, aromatic), 7.28-7.40 (m, 3H, aromatic), 5.83 (s, 1H, C=CH), 3.91 (s, 3H, PhC(O)Ome), 3.77 (s, 3H, C=CC(O)OMe); $^{13}$C NMR (75 MHz, DMSO): $\delta$ = 169.0, 165.5,164.1, 156.0, 155.1, 149.0, 132.1, 132.0, 130.5, 130.4, 128.4, 127.3, 126.6, 125.5, 123.3, 121.3, 120.4, 52.4, 52.0; GCMS: *m/z* = 353, 321, 294(100), 262, 235, 206, 178, 151, 131, 114, 89, 59.



$C_{20}H_{17}NO_6$
Mol. Wt.: 367.35
C, 65.39; H, 4.66; N, 3.81; O, 26.13

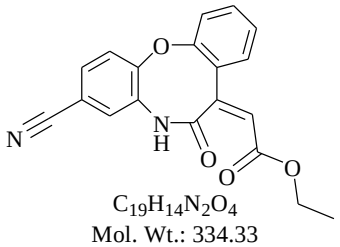
**(*z*)7-Ethoxycarbonylmethylene-6-oxo-6,7-dihydro-5H-12-oxa-5-aza-dibenzo[a,d]cyclooctene-3-carboxylic acid methyl ester(3e)** White solid; 53% yield; mp 220-222$^o$C; IR (KBr) *v max* = 3206(m, w), 2928(m), 1714(s), 1682(s), 1652(s), 1383(m), 1313(s), 1288(s), 1161(m), 758(m) cm$^{-1}$; $^1$H NMR (300 MHz,

DMSO): $\delta$ =7.98-7.92 (m, 1H, NH), 7.92-7.85 (m, 1H, aromatic), 7.50-7.40 (m, 1H, aromatic), 7.40-7.30 (m, 2H, aromatic), 7.28-7.40 (m, 3H, aromatic), 5.83 (s, 1H, C=CH), 3.91 (s, 3H, PhC(O)Ome), 4.19 (q, 3H, C=CC(O)OMe); 1.30 (t, 3H, C=CC(O)OMe); $^{13}$C NMR (75 MHz, DMSO): $\delta$ = 169.0, 165.5,164.1, 156.0, 155.1, 149.0, 132.1, 132.0, 130.5, 130.4, 128.4, 127.3, 126.6, 125.5, 123.3, 121.3, 120.4, 59.6, 52.4, 13.7; GCMS: *m/z* = 367, 339, 321, 294(100), 262, 235, 206, 178, 152, 131, 114, 89, 63.




$C_{19}H_{16}N_2O_5$
Mol. Wt.: 352.34
C, 64.77; H, 4.58; N, 7.95; O, 22.70

**2-[2-(2-Amino-4-cyano-phenoxy)-phenyl]-but-2-enedioic acid dimethyl ester (4f).** Yellow oil, 45% yield, IR (KBr) *v max* = 3375(m), 2951(m), 2226(s), 1725(s), 1622(m), 1508(m), 1484(m), 1267(m), 1216(s), 856(m), 757(s) cm$^{-1}$, $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 7.26(t, 1H aromatic), 7.13(s, 1H C=C), 6.67(s, 1H aromatic), 6.83-6.93(m, 5H aromatic), 4.1(s, 2H $NH_2$), 3.76(s, 6H $CH_3$-OCO); $^{13}$C NMR (75MHz, $CDCl_3$), 165, 165, 153.8, 148.1, 147.0, 136.2, 127.4, 125.9, 123.7, 124.9, 121.7, 118.8, 117.2, 116.5, 106.4 GCMS: *m/z* = 352(15.9), 293(18), 289(13), 275(6), 261(100), 234(12), 219(27), 205(15), 105(8), 191(5), 59(23), 44(26),




$C_{19}H_{14}N_2O_4$
Mol. Wt.: 334.33
C, 68.26; H, 4.22; N, 8.38; O, 19.14

**(*z*)(3-Cyano-6-oxo-5,6-dihydro-12-oxa-5-aza-dibenzo[a,d]cycloocten-7-ylidene)-acetic acid ethyl ester(3f).** White solid; 42% yield; mp 248-251$^o$C; IR (KBr) *v max* = 3396(w,br), 3281(m), 2290(m), 2233(m,s), 1712(s), 1670(s), 1477(m), 1384(s), 1197(s), 1025(s), 1004(m), 766(m), 566(m) cm$^{-1}$, $^1$H NMR (300 MHz, DMSO): $\delta$ = 10.4 (s br, 1H, NH), 7.48-7.40 (m, 1H, aromatic), 7.62-7.58 (m, 1H, aromatic), 7.57-7.49 (m, 2H, aromatic), 7.57-7.49 (m, 2H, aromatic), 7.32-7.23 (m, 1H, aromatic),

5.89 (s, 1H, C=CH), 4.15 (q, J=7.1, 2H, C$H_2$CH$_3$), 1.23 (t, J=7.1, 3H, CH$_2$C$H_3$); $^{13}$C NMR (75 MHz, DMSO$d_6$): $\delta$ = 167.4, 163.2, 155.2, 154.0, 148.3, 134.6, 132.5, 131.9, 130.1, 129.1, 126.6, 125.6, 124.6, 121.1, 120.4, 117,4, 109.2, 60.4, 13.9;GCMS: *m/z* = 334(15.7), 288(67), 261(100), 247(10), 232(22), 177(18), 151(20), 101(17), 89(23), 75(26),

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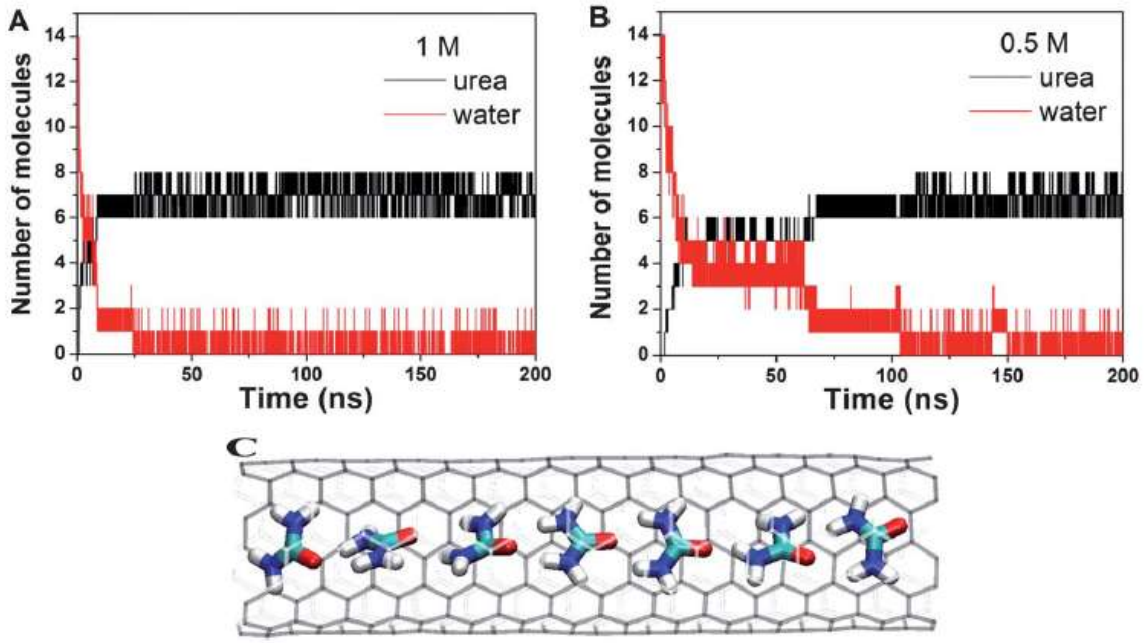
# Chapter 3

## $PdI_2$-Catalyzed Oxidative Carbonylation of Amines in Ionic Liquids: A Recyclable Synthesis of Oxamides, Ureas, Oxazolidinones,and Benzoxazolones

## 3.1 General Importance of Ureas, Oxamide, 2-Oxazolidinone and Benzoxazolone:

### 3.1.1 Importance of Ureas:

Ureas are a very important class of carbonyl compounds. Due to their strong, and tuneable hydrogen bonding abilities[1] and their relatively easy synthesis, which facilitates their use in both simple and complex systems.[2] Their occurrence in natural products made them valuable.[1g] They find extensive application as agrochemicals, dyes for cellulose fibres, antioxidants in gasoline, resin precursors, and synthetic intermediates[3] especially for the production of carbamates and isocyanates.[4] Their importance both in industrial and academic fields is well known such as in production of light coloured natural rubber,[5a] as plasticizer for production of cellulose film[5b] in thin film formation,[5c] as additives to petroleum compounds and polymers[5d], recently their use to form deep eutectic solvent (DES) tremendously increased their value in the field of organo-synthesis and catalysis as green solvent.[5e] Moreover, many ureic derivatives have displayed a wide spectrum of biological activity.[6a-i] In particular, several substituted ureas have recently been shown to possess a marked inhibiting effect on HIV protease enzyme.[6b] CCK-B receptor antagonists,[6c-d] and endothelin antagonists.[6i] Recently, interesting application of ureas were reported by Peng Xiu et al, They performed molecular dynamics simulations of narrow single-walled carbon nanotubes (SWNTs) where they observed spontaneous and continuous filling of SWNT with a one-dimensional urea wire[7] (Fig. 3.1). Furthermore, author found that the stronger dispersion interaction of urea with SWNT than water. These unique properties of molecular urea wires confined within both artificial and biological nanochannels, and are expected to have practical applications such as the electronic devices for signal transduction and multiplication at the nanoscale.




[Fig. 3.1 (A and B) Number of urea (shown in black; KBFF urea model is used) and water (shown in red) molecules within the 336-carbon (6,6) SWNT (with a length of 3.32 nm) as a function of simulation time, at 1 M (A) and 0.5 M (B) urea concentrations, respectively. (C) Representative snapshot to show a ‘‘perfect’’ urea wire at 1 M urea concentration.]

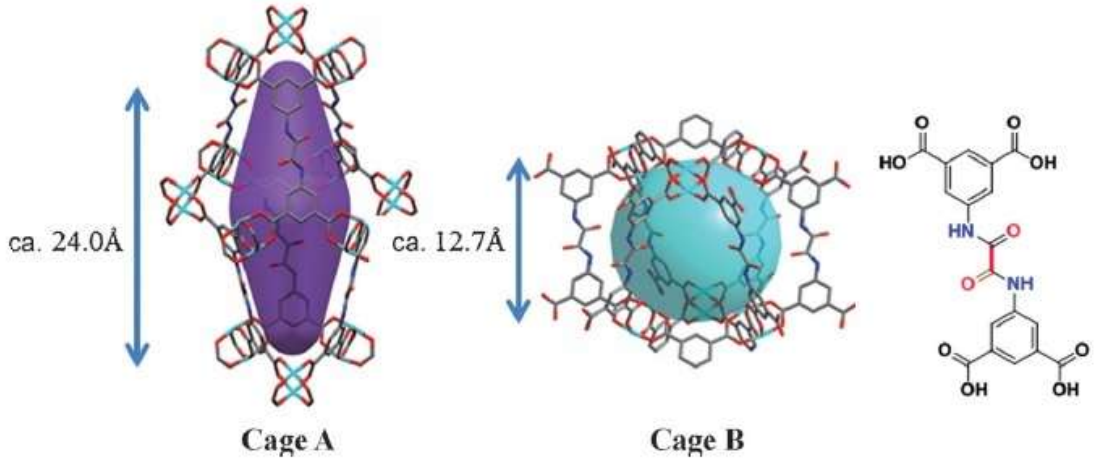
### 3.1.2 Importance of Oxamide:

Oxamides are well known for their coordination properties,[8] the Oxamide dianion acts as a bidentate ligand and, like the oxalate dianion, which is also capable of coordinating as a bridging ligand to give many kinds of mononuclear, dinuclear or polynuclear metal complexes.[8c] The binuclear copper(II) complexes formed by the oxamide dianions are more stable than those formed by the oxalate dianion, owing to the high extent of magnetic interaction between two metal ions, especially in the N, N’-bis(coordinating group substituted)oxamides. It is hoped that the binuclear complexes formed by the N, N’-bis(coordinating group substituted) oxamides will lead to the development of a new field of coordination chemistry.

Their property to form coordination complexes with metals has wide applications in material and physical sciences. Oxamides coordinated with nitrito groups “oxamidato ligands” are able to mediate a strong antiferromagnetic

interaction[9a]. Oxamides (*N*_,*N*_-bis (2-aminophenyl) oxamide) can coordinate selectively with copper ions, which helped physicist to enhance "Light Scattering" signals, which has wide application in analytical detection[9b-c].

Recently, Martin Shroder et al reported the application of substituted Oxamide derivatives in Metal Organic Frameworks[10] (MOF), MOFs (Fig.3.3) are crystalline, porous materials with exceptionally high internal surface areas and tunable functional pore has great promising applications in gas storage and separation, notably in $CO_2$ gas storage.



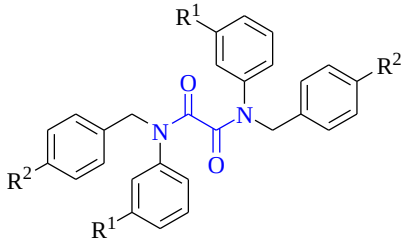

(Fig.3.2 MOFs of substituted Oxamide derivatives)

Also oxamides complexes with different transition metals[8c] (Fig.3.3) showed antimicrobial activity which indicates the bright future of oxamide complexes in biological sciences too.


(Fig. 3.3 Metal complexes of Oxamide)

S.M. Okarvi et al revealed that terminal oxamide derivatives of mercapto-acetyl-triglycine can help in renal excretions process.[11] Shi Hao Cui[11b] and Man Jiang[11c] et al, reported the DNA-binding properties , and cytotoxic activities of copper complexes

with Oxamides, K.O Yerleden et al, evaluated different derivatives of Oxamides[Fig. **3.4**] as acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitors[11d] against Alzheimer's disease (AD).



$R^1$ =$CH_3$, $CF_3$, $C_2H_5$, $OCH_3$, $OC_2H_5$, F, Cl,Br, I
$R^2$ = H, $OCH_3$

(Fig. 3.4)

Timothy E Long et al reported synthesis and use of poly-trioxamide and poly-ureaoxamide derivatives in the segmented thermoplastic elastomers[12a]. Hard segment structures of the compounds resulted due to ordered hydrogen bonding interactions with thermal dissociation profiles of poly-oxamide {Fig.3.5 (a)} and poly-urea{ Fig. 3.5 (b)}, which provides the desired segmented copolymers displaying thermoplastic elastomeric behaviour.

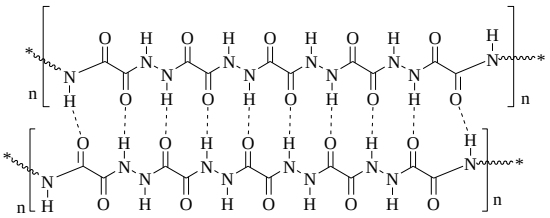


Fig.3.5 (a)

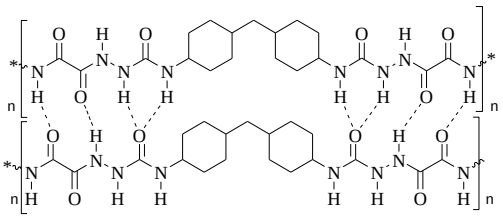


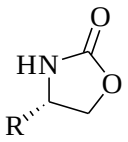
Fig. 3.5 (b)

(Fig.3.4 hydrogen bonding interactions of (a) PPG-Ox, (b) PPG-UOx)

Similarly, Tian yin et al provided a convenient method to synthesize aliphatic polyesteramides[12b] mainly composed of alternating diester diamide units by polycondensation and chain extension. These kinds of polyesteramide prepolymers found thermostability upto 298$^oC$ with high tensile strength. Predicted reason for the thermostabilty and strength of polyesteramide is the presence of strong boding between diester oxamide alternating units.

### 3.1.3 Importance of Oxazolidin-2-one:

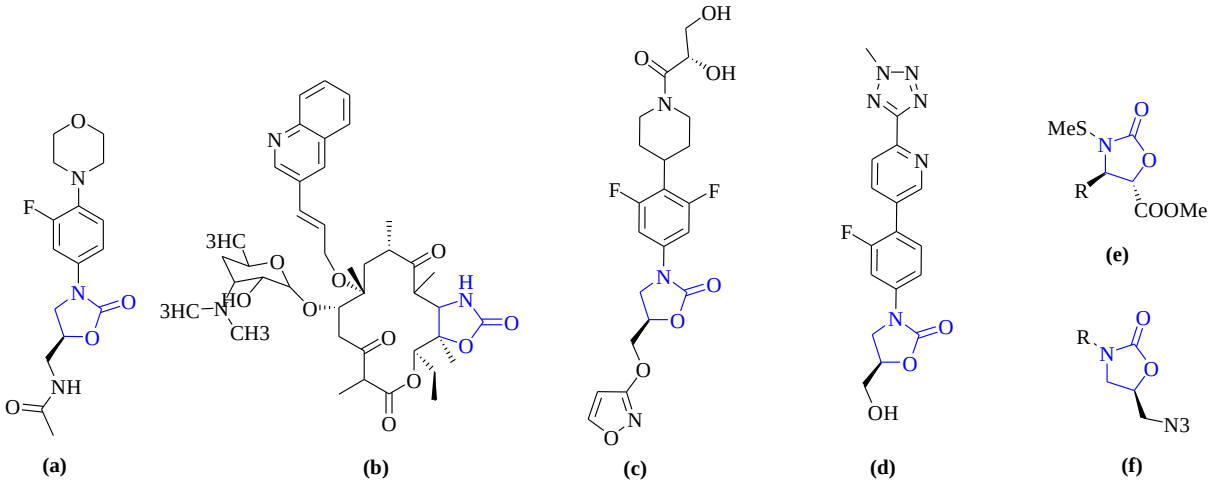
Oxazolidin-2-ones are important compounds in both pharmaceutical[13a] and synthetic organic chemistry. They are widely used as chiral auxiliaries[14] (Evan's Auxiliary Fig. 3.6) in numerous asymmetric syntheses and are applied in the synthesis of a number of valuable natural products, antibiotics, and on the other hand they are synthetic new class of five-member heterocyclic ring exhibiting potential medicinal properties with preferential antibacterial activity against gram positive bacteria, which inhibits protein synthesis via binding to a distinct region of 23*S*-RNA near the peptidyl transferase center of the 50*S*-ribosomal subunit in prokaryotes[13b]. Due to the emergence of resistance to known antibiotics such as sulphonamides and β-lactam class to various organisms, for example, Staphylococcus, Streptococcus, Enterococci, and Pseudomonas there is a renewed interest in the discovery of new antibiotics. Since 1970's several antibiotics have been brought to market, but only four of these new chemical scaffolds found useful against drug resistance[13c]. Among them one is the Oxazolidinone. Oxazolidinone, a totally synthetic class of novel antibacterials, possess activity against drug-resistant Gram-positive pathogens, especially MRSA. Linezolid, the first approved drug from this class, has shown a great promise in saving lives of many patients by acting against drug-resistant Gram-positive organisms. After the successful launch of linezolid, Oxazolidinone class of antibacterials got considerable interest from various research institutions, including pharmaceutical industries [13d] Some of the examples of oxazolidinone class antibiotics (Fig.3.7) such as Linezolid (a), cethromycin(b), Posizolid (c) and Tedizolid (d) and continuous development through derivatization of side chains in order to achieve selective antibacterial activity in progress in several research groups.[13e] Turos *et al.* recently reported the discovery of the compounds with *N*-thiolated 2-oxazolidinone[13f] rings (Fig. 3.7 (e)) as a new family of antibacterial agents, many of these *N*-thiolated derivatives showed potent antibacterial activity against methicillin-resistant *Staphylococcus aureus*[13g] (MRSA).




1 R= Bn
2 R= i-Pr

(Fig. 3.6)

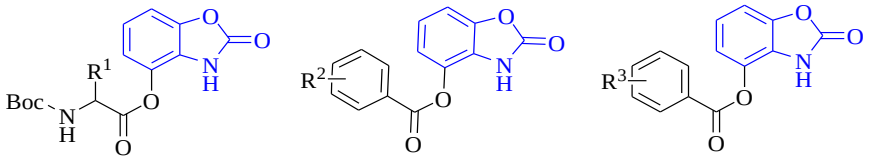
G. Madhusudhan et al. reported new class of oxazoline based compounds (R)- and (S)-5-azidomethyl- 2-oxazolidinones[13h] (Fig. 3.7 (f)) synthesized from (S)-epichlorohydrin, which showed potent anti bacterial activity.




(Fig. 3.7)

### 3.1.4 Importance of Benzoxazolone:

Benzoxazolones and its methoxy analogues widely found in natuaral products.[15a] Also benzoxazolinones are secondary metabolites found mainly in the plant family of the Poaceae, and, to a lesser extent, in the Acanthaceae, Ranunculaceae and Scrophulariaceae. They can act as "chemical weapons" both in defense against microorganisms and herbivores, and in attack, against susceptible plant competitors[15b]. Because of this property, their use in agriculture has been proposed as "bioherbicides" or "Biopesticides"[15c]. Recently, synthetic analogues of benzoxazolones revealed novel application as enzyme inhibitors. Sánchez-Moreiras et al proposed a new series of benzoxazolone derivatives[15d] as potential cholinesterase inhibitors, while Qing-Shan Li et al, reported novel 4-substituted benzoxazolone derivatives[15e] as human soluble epoxide hydrolase (sEH) inhibitors and anti-inflammatory agents (Fig. 3.8). Also structure–activity relationship (SAR) studies of novel benzoxazolone derivatives with various substituents at the amide part and C-5 position exhibited anxiolytic effect.[15f] While their property to bind Selectively to 18 kDa translocator protein (TSPO) ligands[15g] are expected to be therapeutic agents with a wide spectrum of action on psychiatric disorders.



$R^1$ = -H, $-CH_3$, $CH(CH_3)_2$, $-CH_2Ph$, $CH_2$,$CH_2SCH_3$

$R^2 = R^3$ = -H, o-Cl, m-Cl, p-Cl, o-$NO_2$, o-$CH_3$, p-$CH_3$

(Fig. 3.8)

**3.2 General Synthesis of Urea, Oxamide, Oxazolidinone and Benzoxazolone.**

Ureas (2a-g), Oxamide (4a-f), 2-Oxazolidinone (6a-b) and Benzoxazolinone (8a-c) has wide applications in agricultural, fine chemicals, material science, polymer science, pharmaceutical science and medicinal sciences. This makes them more valuable. Classical synthesis of these N-containing carbonyl compounds are mainly conducted by phosgenation of the corresponding amino compounds with toxic phosgene or its derivatives such as carbodiimidazole (CDI), triphosgene or S,S-dimethyl dithiocarbonate[16] (DMDTC). However, phosgene is toxic and phosgene derivatives are undesirable from the standpoint of environmental pollution, equipment corrosion, expense, waste minimization[17a] and atom economy.[17b] There is a great demand for finding some efficient and environmentally benign methods in place of such toxic and dangerous reagents.

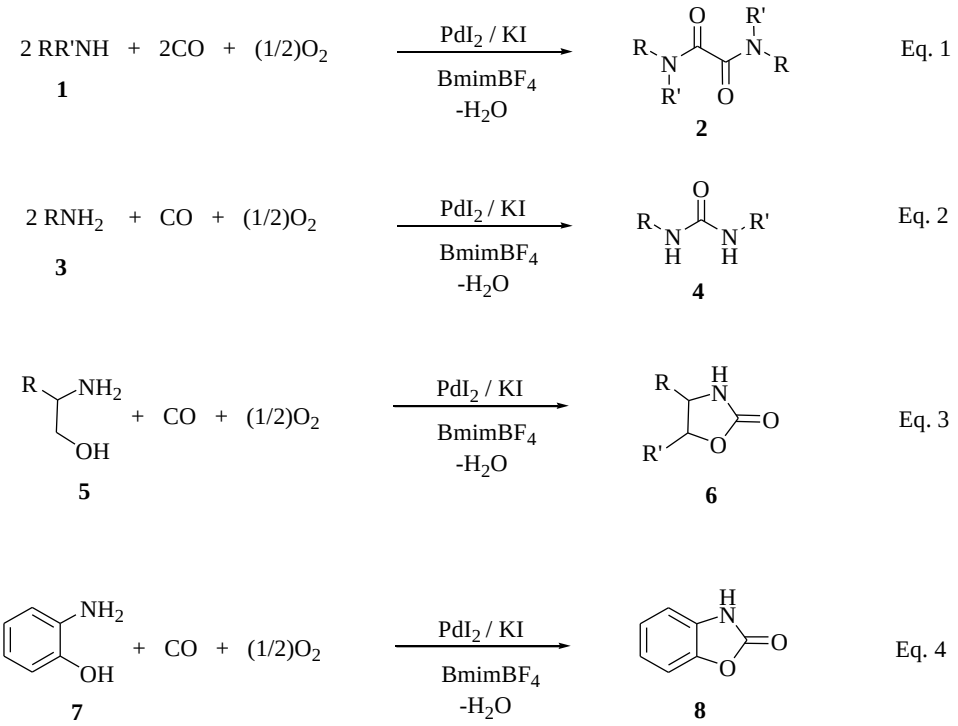
Transition metal-catalyzed oxidative carbonylation of amines[18a] provides an alternative to phosgene and phosgene derivatives. Many metals including Pd, Ru, Rh, Au, Co, Ni and W have been employed as catalysts in the carbonylation reaction.[18b], there are also problems with metal catalysts including the expense of noble metal complexes and the possibility of heavy metal contamination in the products. Sulfur[19a] and selenium[19b] catalyzed systems are also known and avoid some of the drawbacks associated with metal catalysis. These systems, however, produce the volatile and toxic by products, $H_2S$ and $SeH_2$, respectively. Also, acid or base-catalyzed hydration of cyanamides;[20a-c] reaction of amines with KOCN in aqueous solution of HCl under MW irradiation;[20d] reaction of S,S-dimethyl dithiocarbonate with ammonia in water-dioxane[20e] and hydration of cyanamides by acetaldoxime and $InCl_3$ in toluene as a toxic solvent.[20f] However, these procedures suffer from certain disadvantages such as environmentally unpleasant use of organic solvents, toxic and hazardous reagent or catalysts, high temperature and/or long reaction times, harsh reaction conditions

including the use of HF-pyridine complex, $H_2SO_4$, $H_2O_2$/NaOH and HCl, expensive and complex catalysts or reagents, many tedious isolation steps and low yields of the products.[19-20] As a result, these drawbacks have limited their large scale applications in industry. Therefore, it is desirable to develop more efficient and convenient methods for the synthesis of N-containing carbonyl compounds under mild conditions and avoiding organic solvents, corrosive and toxic reagents such as acids, phosgene and isocyanates or expensive catalysts.

Today, catalyst–product separation techniques, catalyst recoverability and catalyst reusability are the central issues to achieve an economical and environmentally friendly approach from sustainable and industrial viewpoints. Several techniques, such as biphasic catalysis, supported metal catalysis, polymer anchored catalysis and metal leaching re-deposition, have been developed in recent years. The catalysts can be easily separated, repeatedly used and, consequently, these methods provide an efficient and economical way to perform carbonylative coupling reactions. Such catalysts avoid the use of phosphines and because of this they are not air sensitive and they show moisture stability. They afford the coupling products in high yields at short reaction times.

### 3.3 Result and Discussion

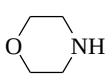
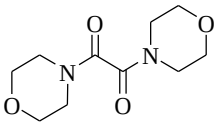
Recently, the combination ionic liquids with transition metal complexes, as versatile and recyclable reaction media have resulted in many diverse and flexible 'platforms' to establish highly effective and easily separable catalytic system[22]. With our continuous research in oxidative cyclocarbonylation, here in this work we are reporting an attractive and environmentally benign method for the direct synthesis of oxamides **2**, ureas **4**, 2-oxazolidinones **6**, and benzoxazolones **8** by $PdI_2$-KI catalyzed direct oxidative carbonylation of secondary amines **1**, primary amines **3**, β-amino alcohols **5**, and 2-aminophenols **7**, respectively, carried out in an ionic liquid (IL), such as $BmimBF_4$, as the solvent (Scheme 3.1, equations 1-4). The catalyst and the IL medium could be recycled up to six times without appreciable loss of activity and selectivity.




(Scheme 3.1)

Entrapping the $PdI_2$-KI catalytic system into an ionic liquid (IL) may allow an easy separation of products and the reuse of the catalyst. In this work, we have used this catalyst dissolved in an IL, such as $BmimBF_4$, for the direct and recyclable oxidative carbonylation of secondary amines, primary amines, β-amino alcohols, and 2-aminophenols to selectively yield oxamides, ureas, 2-oxazolidinones, and benzoxazolones, respectively, in excellent yields. As shown in Table 1 experiments were carried out in for six recycles in order to check the reactivity and sustainability of the catalytic system and reaction media.

**Table 1**

| Entry | Substrate | Product | Yield (%) |
|---|---|---|---|
| 1 |  1a |  2a | 87 |

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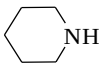
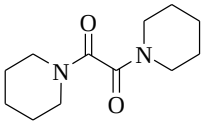
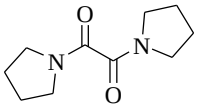
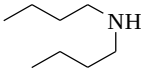
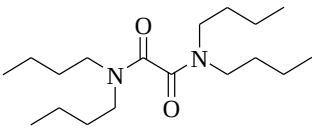
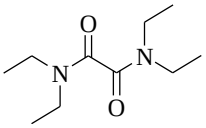
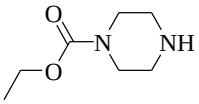
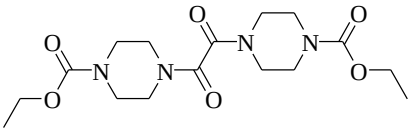
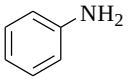
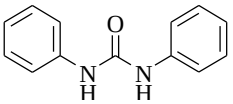
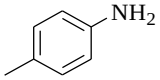
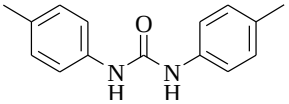
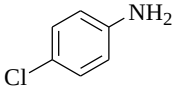
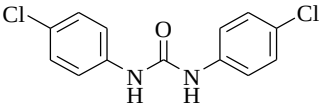
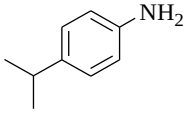
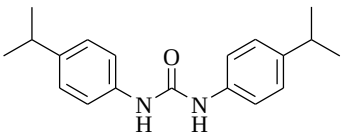
| 2 |  1b |  2b | 92 |
| 3 |  1c |  2c | 91 |
| 4 |  1d |  2d | 85 |
| 5 |  1e |  2e | 92 |
| 6 |  1f |  2f | 97 |
| 7 |  3a |  4a | 94 |
| 8 |  3b |  4b | 87 |
| 9 |  3c |  4c | 91 |
| 10 |  3d |  4d | 92 |

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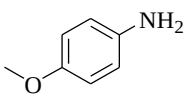
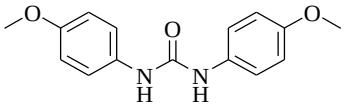
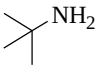
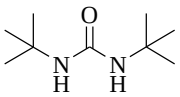
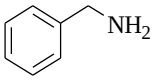
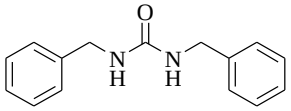
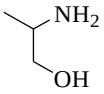
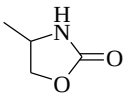
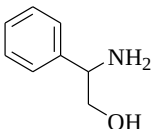
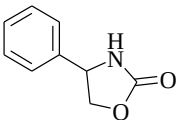
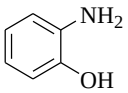
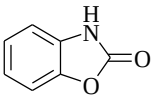
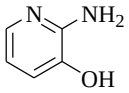
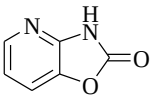
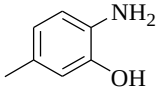
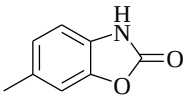
| 11 |  3e |  4e | 88 |
| 12 |  3f |  4f | 97 |
| 13 |  3g |  4g | 98 |
| 14 |  5a |  6a | 94 |
| 15 |  5b |  6b | 80 |
| 16 |  7a |  8a | 98 |
| 17 |  7b |  8b | 90 |
| 18 |  7c |  8c | 92 |

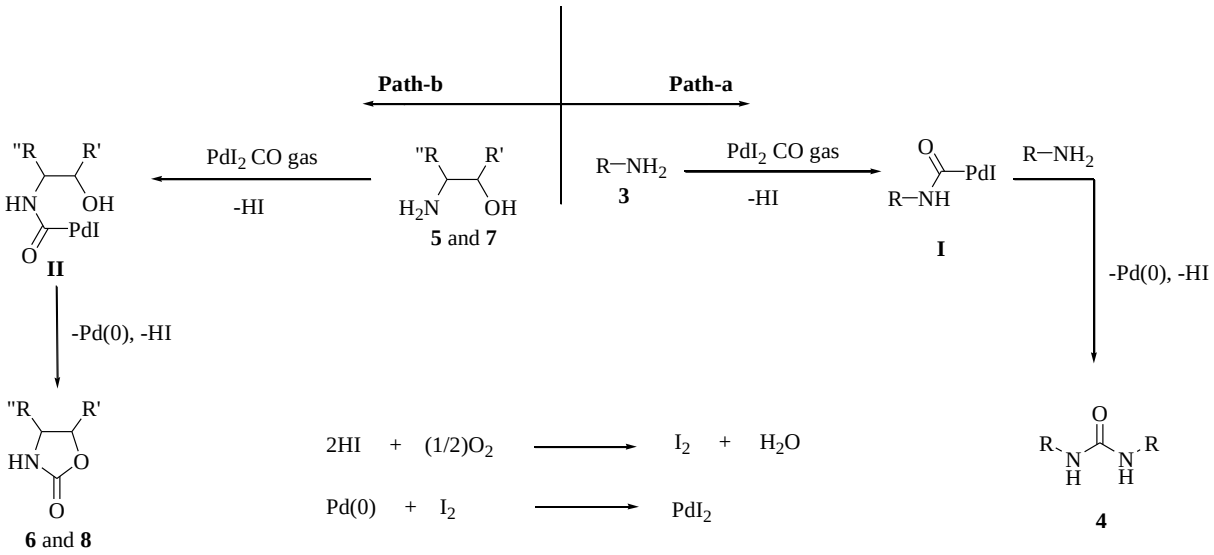
*All carbonylation reactions were carried out at 100°C in $BmimBF_4$ (0.5 mmol of substrate per mL of $BmimBF_4$) using a substrate:$PdI_2$:KI molar ratio of 100:1:10, under 16 atm of CO and 4 atm of air (at 25 °C) for 24 h. Yields are isolated from six extractions.*

From the results listed in Table 1, $PdI_2$/KI in ionic liquid $BMImBF_4$ catalytic system exhibited excellent catalytic activity to almost all the employed substrates secondary amines **(1)**, primary amines **(3)**, β-aminoalcohols **(5)** and 2-aminophenols **(7)** under the same reaction conditions, providing the corresponding Oxamides **(2)**, Ureas **(4)**, 2-oxazolidinones **(6)** and Benzoxazolones **(8)** with excellent yield and selectivity. These above mentioned results suggest that the $PdI_2$/KI catalytic system in ionic liquid $BMImBF_4$ was a robust and efficient catalytic system for the oxidative carbonylation of amine derivatives.

The formation of products follows i) mono-carbonylative and ii) double-carbonylative pathway under $PdI_2$/KI catalyzed oxidative carbonylative conditions.

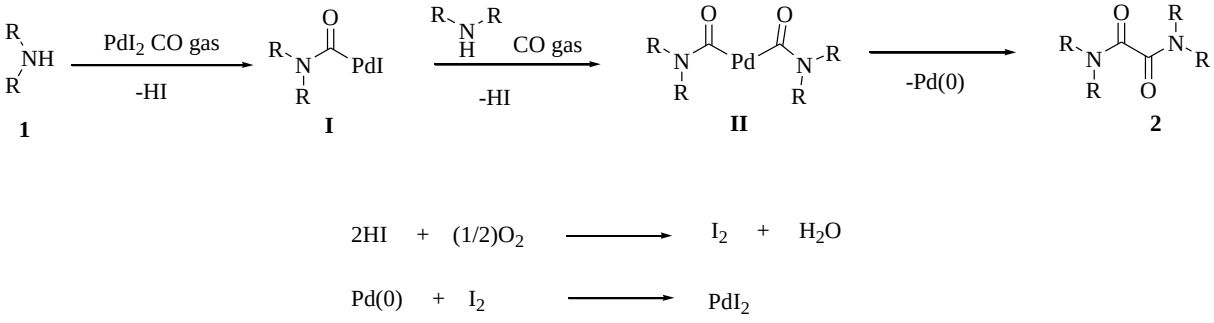
**i) mono-carbonylation of amines:** As shown in Scheme 3.2, the formation of products ureas **(4**), 2-oxazolidinones **(6)**, and benzoxazolones **(8)** proceeds via monocarbonylative reaction pathway.[23] (Anionic iodide ligands are omitted for clarity). As shown in Scheme 3.2, Primary amine follows path-a, while β-amino alcohols and 2-aminophenols follows path-b. Initial reaction of the amino group of the Primary amines**(3)** with $PdI_2$ followed by carbon monoxide insertion results into the formation of carbamoylpalladium intermediate **I**, and then reaction of intermediate **I** with second mole of primary amine resulted into formation of the product **(4),** while in path-b initial reaction of $PdI_2$ with β-amino alcohols**(5)** and 2-aminophenols**(7)** leads to the formation of carbamoylpalladium intermediate **II,** which then undergoes intramolecular cyclization and reacts with β-hydroxyl group to form the cyclic product **6** and **8** with respect to the reacting substrates **5** and **7.** Pd(0) formed during the course of the reaction is reoxidized back to $PdI_2$ by oxidative addition of $I_2$, which formed in its turn, by oxidation of HI with $O_2$ (Scheme 3.2). As in the Path-b formation of cyclic products resulted via intramolecular cyclization with insertion of carbonyl group into the ring, the process also recognized as Oxidative cyclocarbonylation.[24]

**ii) Double carbonylation of amines:** Double carbonylative pathway can be described as shown in scheme 3.3. Initial reaction of $PdI_2$ with secondary amines **(1)** leads to the




(Scheme 3.2)

formation of intermediate **I,** which then reacts with second mole of secondary amine followed by CO insertion results into the formation of intermediate **II** in which palladium metal is directly coordinated two carbamoyl species. As it is clear from the mechanism metal catalyst perform carbonylation by direct insertion of two carbonyl functions at the same time defines the term double carbonylation.[25] Finally formation of double carbonylated product **(2)** with two carbonyl groups takes place with removal of reduced palladium metal species Pd(0), which is then reoxidized back to $PdI_2$ by oxidative addition of $I_2$ which is formed in its turn by oxidation of HI with $O_2$ (Scheme 3.3).




(Scheme 3.3)

### 3.4 Conclusion:

In conclusion, we are reporting the $PdI_2$/KI in Ionic liquid $BmimBF_4$ has been proved as an efficient and versatile catalytic system for the oxidative carbonylation of

differently substituted amine derivatives (1, 3, 5, 7) to respective products (2,4,6,8) in excellent yields. Also recycling of catalyst and reaction media up to six re-cycles without appreciable loss of activity provides an green protocol for the synthesis of these carbonyl derivatives who's importance in all scientific field is very well known.

### 3.5 Experimental

#### 3.5.1 Carbonylation process:

In 100mL clean stainless steel autoclave was introduced secondary amine **1** ($R_2NH$) 1.11mmol (R= Morpholine 96.79mg; R=Piperidine 94.60mg; R=Pyrrolidine 79.01 mg; R= Piperazine-1-carboxylic acid ethyl ester 175.76 mg; R= Diethylamine 81.26mg; R= Dibutylamine 143.5mg), primary amine **3** ($RNH_2$) 1.11mmol (R= t-Butylamine 81.25mg; R= Aniline 103.46mg; R= p-Toluidine 119.06mg; R=4-Chloroaniline 141.73mg; R=p-Anisidine 136.81mg; R= 4iso-propyl Aniline 150.21mg; R= Benzylamine 119.04mg), β-amino alcohols **5** (R=2-Amino-2-phenyl-ethanol 152.4mg; R= 2-Amino-propan-1-ol 83.44mg ) and 2-aminophenols **7** (R= 2-Amino-5-methyl-phenol 136.81mg; R= 2-Amino-pyridin-3-ol 122.34mg; R= 2-Amino-phenol 121.24mg;), $PdI_2$ $1.11\times10^{-2}$mmol (4mg) and KI $1.11\times10^{-1}$mmol (18.42mg) in $BMImBF_4$ (BMIm = 1-butyl-3-methylimidazolium) 0.5M (2.22ml) as reaction media. Stainless steel autoclave was then sealed and charged with CO gas (16atm) and air (4atm) under stirring conditions at room temprature. It was then attached to hot oil flow preheated at 100$^{o}$C for 24h. The apparatus was then cooled to ambient temperature and the remaining gas was evacuated. Crude reaction mixture was transferred to RBF (Round Bottom Flask) and later extraction of product 2,4,6,8 was done through organics solvent.

#### 3.5.2 Extraction process:

To the RBF containing IL with product **2**, **6** and **8** was added Diethylether (5mL). It was stirred for 15 minutes. After that, reaction mixture was allowed to stand without magnetic stirring for 15 min to form two layers of Upper solvent and lower IL. Upper layer of Diethylether containing product was decanted. Again fresh 5mL of Diethylether was added in IL and same process was repeated for next 4 times. To the

RBF containing IL with product **4** was diluted with $CH_2Cl_2$ (5ml), and then Diethylether (10mL) was added. Mixture was then set for stirring for 1min and allowed to stand for 15 min. to form the two layers. Upper layer containing white precipitate of Urea was decanted. Solvent was the evaporated till dryness. Again fresh $CH_2Cl_2$ (5ml) and Diethylether (10ml) was added and the process was repeated for next 5 times.

**3.5.3 Crystallisation Process:**

Collected solvent phase **(**Diethylether layer) containing product was evaporated (~80%) under reduced pressure and solvent was recovered for next cycles. Product in minimum amount of Diethyl Ether was left at-20$^oC$ for 15h-24h for crystallization. After crystallization remaining amount of solvent was recovered distilled and reused for extraction processes.

**3.5.4 Ionic liquid recycle process:**

IL was attached to vacuum pump for 5h in order to remove the traces of solvent and moisture. Then it was again introduced to Stainless steel autoclave and used for next reaction cycles. Same process was repeated for next 4 cycles.

**3.5.5 Preparation of BmimCl**

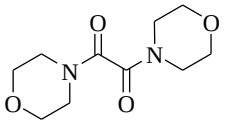
A mixture of 1-methylimidazole (40 mL, 41.2 g, 502 mmol) and toluene (50 mL) maintained at 0$^oC$ under nitrogen was stirred for 10 min. 1-Chlorobutane (58 mL, 51.4 g, 555 mmol) was quickly added at 0$^oC$ and the resulting mixture was vigorously stirred for 15 min at the same temperature. The solution was allowed to warm up to room temperature and then heated at 110$^oC$ for 24 h with stirring. After cooling to room temperature, the mixture was refrigerated (-20$^oC$) and allowed to stand for 24 h. After this time, two phases separated; toluene was removed by decantation, while the residue was taken up with MeCN. The solvent was removed under vacuum and MeCN (ca. 30 mL) and THF (ca. 30 mL) were added. The resulting mixture was cooled with the aid of an ice-water bath, to give, on standing, BmimCl as a whitish solid. The mixture was then cooled at -20$^oC$ overnight. After decantation and removal of the solvent, the residue was washed with cold THF and eventually dried in vacuo to give pure BmimCl as a whitish solid, which was stored at -20$^oC$ under nitrogen (77.6 g, 89%).

### 3.5.6 Preparation of $BmimBF_4$

$NaBF_4$ (5.7 g, 51.9 mmol) was added to 9.0 g (51.8 mmol) of BmimCl maintained at 80°C under vigorous stirring. The mixture was allowed to stir at 80°C for 8 h and then at room temperature for 15 h. $CH_2Cl_2$ (ca. 30 mL) was added with stirring, and the solution was cooled to -20°C and allowed to stand at this temperature overnight. The precipitate (NaCl) was removed by filtration, and the solvent was removed under vacuum to give pure BmimBF4, which was stored under nitrogen at room temperature (9.3 g, 80%).

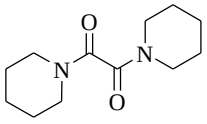
## 3.6 Characterization data

### i) Oxamides:



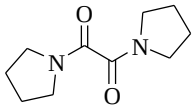
$C_{10}H_{16}N_2O_4$
Mol. Wt.: 228.25
C, 52.62; H, 7.07; N, 12.27; O, 28.04

***1,2-Di-morpholin-4-yl-ethane-1,2-dione(2a).*** White solid; 87% Yield, mp 162-181°C. IR (KBr) 2915(m), 2864(s), 1638(s), 1433(m), 1274(m), 1113(s), 759(m) $cm^{-1}$, $^1H$ NMR (300MHz, $CDCl_3$) 3.45 (t, 4H, *J*=4.8 Hz), 3.66 (t, 4H, *J*=4.8 Hz), 3.71-3.74 ppm (m, 8H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 162.8, 66.9, 66.6, 46.6, 41.5 ppm. MS *m/z*: 228.1(4.74), 185(6.9), 114(69), 86(100), 70(86), 56(14), 42(32).



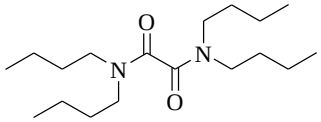
$C_{12}H_{20}N_2O_2$
Mol. Wt.: 224.30
C, 64.26; H, 8.99; N, 12.49; O, 14.27

***1,2-Di-piperidin-1-yl-ethane-1,2-dione(2b),*** White-Yellowish Solid, 92% yield, mp. 82.1-82.7°C IR (KBr) 2937(m, br), 2857(m), 1642(s), 1429(s), 1250(m), 1213(m), 957(m), 540(m) $cm^{-1}$, $^1H$ NMR (300MHz, $CD_3OD$): δ 3.46 (t, 4H, *J*=5.4 Hz), 3.65-3.67 (t, 4H, *J*=5.4 Hz), 1.42-1.60 ppm (m, 12H); $^{13}C$ NMR (75MHz, $CD_3OD$): δ 164.8, 42.7, 27.3, 26.3, 25.2 MS *m/z*: 224.15(10.43), 112(77), 84(100), 69(62), 56(19), 41(35).



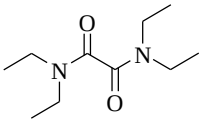
C10H16N2O2
Mol. Wt.: 196.25
C, 61.20; H, 8.22; N, 14.27; O, 16.31

***1,2-Di-pyrrolidin-1-yl-ethane-1,2-dione(2c).*** White solid; 91% yield, mp 72−79 °C; IR (KBr) 2950(m), 1725(s), 1609(m), 1450(m), 1213(s), 754(s)$cm^{-1}$, $^{1}H$ NMR (300MHz, $CDCl_3$) δ 3.49−3.42 (m, 8H), 1.90−1.83 (m, 8H); $^{13}C$ NMR (75MHz, $CDCl_3$) δ 163.1, 46.8, 45.0, 25.8, 24.1; MS *m/z*: 196.1(2.14), 168(8), 98(66), 70(100), 56(42), 55(89). HRMS (EI) m/z (M+) calcd for $C_{10}H_{16}N_2O_2$ 196.1212, found 196.1199.



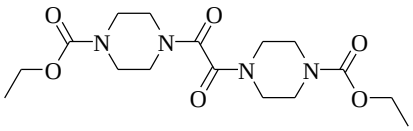
C18H36N2O2
Mol. Wt.: 312.49
C, 69.18; H, 11.61; N, 8.96; O, 10.24

***$N^1$,$N^1$,$N^2$,$N^2$-Tetrabutyloxalamide(2d).*** Colorless oil, 85% yield; IR (Neat) 2959(s), 2798(m, br), 1591(m), 1464(m), 1053(s), 754(s) $cm^{-1}$; $^{1}H$ NMR (300MHz, $CDCl_3$) δ 3.38−3.13 (m,8H), 1.63−1.50 (m, 8H), 1.39−1.21 (m, 8H), 0.95−0.88 (m, 12H); $^{13}C$ NMR (75MHz, $CDCl_3$) δ 165.0, 47.7, 43.5, 30.5, 29.2, 20.1, 20.0, 13.7, 13.6; GCMS *m/z*: 312(6), 255(6), 156(51), 128(100), 100(22), 57(79), 41(15). HRMS (EI) m/z (M+) calcd for $C_{18}H_{36}N_2O_2$ 312.2777, found 312.2766



C10H20N2O2
Mol. Wt.: 200.28
C, 59.97; H, 10.07; N, 13.99; O, 15.98

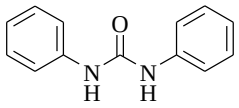
***$N^1$,$N^1$,$N^2$,$N^2$-Tetraethyl-oxalamide(2e).*** Yellowish-White Solid, 92% yield, 26-28$^{o}$C, IR (Neat) 2975(s), 2938(m), 1637(s), 1423(s), 1257(s), 1117(s), 786(m), 609(m) $cm^{-1}$, $^{1}H$ NMR (300MHz, $CD_3OD$): δ 3.24-3.47 (m, 8H), 1.08-1.28 ppm (m, 12H); $^{13}C$ NMR (75MHz, $CD_3OD$): δ 166.1, 43.7, 39.6, 14.1, 12.7 ppm. MS *m/z*: 200(3.6), 100(94), 72(100), 44(25).



C16H26N4O6
Mol. Wt.: 370.40
C, 51.88; H, 7.08; N, 15.13; O, 25.92

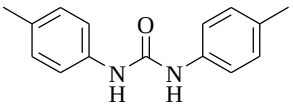
***1,2-Di-piperazin(1-carboxylic acid ethyl ester)-1-yl-ethane-1,2-dione(2f)*** white solid, 97% yield, mp. 134.9-136.9$^{o}$C, IR (KBr) 2969(m), 1698(s), 1644(s), 1428(s), 1233(s), 1051(s, br), 767(s), 521(m), $^{1}$H NMR (300MHz, $CDCl_3$) δ 3.22(*m*, 16H), 4.12(*q*, 4H), 1.3(*t*, 4H), $^{13}$C NMR(75MHz, $CDCl_3$) δ 158.4, 155.7, 57.2, 50.4, 48.8, 13.3. GCMS *m/z*: 370.25(69.75), 325(13), 256(12), 185(58), 157(92), 156(52), 141(43), 130(40), 128(56), 113(90), 111(33), 70(64), 56(100), 44(37), 42(45)..

**ii) Urea:**



C13H12N2O
Mol. Wt.: 212.25
C, 73.56; H, 5.70; N, 13.20; O, 7.54

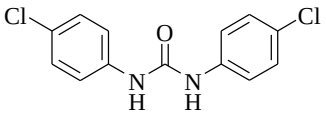
***1,3-Diphenylurea (4a)*.** Colorless solid, 94% yield, mp 240–241 °C. IR (KBr) 1649 (s), 1595 (m), 1559 (s), 1448 (w), 1315 (w), 1234 (m), 754 (m), 698 (m) cm$^{-1}$; $^{1}$H NMR (300MHz, DMSO-$d_6$) δ 8.69 (s, 2H, 2NH), 7.53–7.14 (m, 4H on phenyl rings), 7.33–7.23 (m, 4H on phenyl rings), 7.01–6.93 (m, 2H on phenyl rings); $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 152.5, 139.7, 128.7, 121.7, 118.1; MS *m/z* 212 (M+, 18), 119 (12), 94 (7), 93 (100), 92 (9), 91 (7), 77 (10), 66 (11), 65 (12). Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70, N, 13.20. Found C, 73.44; H, 5.71, N, 13.23.



C15H16N2O
Mol. Wt.: 240.30
C, 74.97; H, 6.71; N, 11.66; O, 6.66

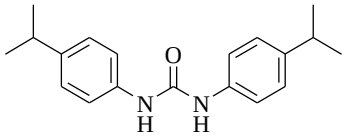
***1,3-Bis-(4-methyphenyl)-urea(4b),*** White-Brown solid, 87% Yield, mp 225-232$^{o}$C. IR (KBr) 3321 (m), 2959 (m), 1651 (s), 1592 (m), 1555 (s), 1514 (m), 1427 (w), 1309 (m), 1279 (w), 1236 (m), 825 (m) cm$^{-1}$ $^{1}$H NMR (300MHz, DMSO-$d_6$) δ 8.46 (s, 2H), 7.30 (d, J = 8.1 Hz, 4H), 7.04 (d, J = 7.6 Hz, 4H), 2.21 (s, 6H). $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 155.71, 140.31, 133.58, 132.24, 121.29, 23.43 GCMS *m/z:* 240,

133(100), 104(35), 9(13), 78(15), 52(12), 39(10), HRMS (ESI): calcd. for $C_{15}H_{16}N_2O$: 240.3115; found: 240.3118.



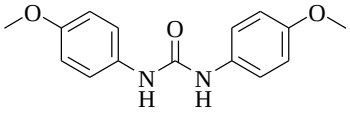
C13H10Cl2N2O
Mol. Wt.: 281.14
C, 55.54; H, 3.59; Cl, 25.22; N, 9.96; O, 5.69

***1,3-Bis-(4-chlorophenyl)urea (4c).*** Grey solid, 91% yield, mp 266-269°C. IR (KBr) 3296 (m), 1633 (s), 1591 (s), 1557 (s), 1492 (s), 1397 (w), 1299 (w), 1237 (m), 1085 (m), 1013 (w), 823 (m), 639 (s), 507 (m) $cm^{-1}$; $^1H$ NMR (300MHz, DMSO-$d_6$) δ 8.88 (s, 2H, 2NH), 7.55–7.48 (m, 4H on phenyl rings), 7.37–7.30 (m, 4H on phenyl rings); $^{13}C$ NMR (75MHz, DMSO-$d_6$) δ 152.3, 138.5, 128.6, 125.5, 119.8; MS *m/z* 282 (M+ + 2, 8), 280 (M+, 11), 153 (13), 129 (32), 127 (100), 92 (8), 90 (7), 75 (5), 65 (10). Anal. Calcd for $C_{13}H_{10}C_{l2}N_2O$: C 55.54; H, 3.59; Cl, 25.22; N, 9.96. Found C, 55.63; H, 3.60; Cl, 25.20; N, 9.95.



C19H24N2O
Mol. Wt.: 296.41
C, 76.99; H, 8.16; N, 9.45; O, 5.40

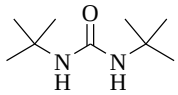
***1,3-Bis-(4-isopropylphenyl)urea (4d).*** Grey-White solid, 92% Yield, mp 207–208°C. IR (KBr) 3311 (m), 2959 (m), 1651 (s), 1597 (m), 1555 (s), 1514 (m), 1417 (w), 1309 (m), 1285 (w), 1236 (m), 832 (m) $cm^{-1}$; $^1H$ NMR (300MHz, DMSO-$d_6$) δ 8.54 (s, 2H, 2NH), 7.41–7.34 (m, 4H on phenyl rings), 7.18–7.10 (m, 4H on phenyl rings), 2.82 (heptuplet, *J* = 6.8, 2H, 2 C*H*Me2), 1.18 (d, *J* = 6.8, 12H, 4Me); $^{13}C$ NMR (75MHz,DMSO-$d_6$) δ 152.6, 141.6, 137.4, 126.4, 118.2, 32.7, 24.0; MS *m/z* 296 (M+, 23), 161 (4), 146 (12), 135 (34), 133 (9), 120 (100), 103 (4), 91 (7), 77 (5). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16, N, 9.45. Found C, 76.85; H, 8.18, N, 9.46.



C15H16N2O3
Mol. Wt.: 272.30
C, 66.16; H, 5.92; N, 10.29; O, 17.63

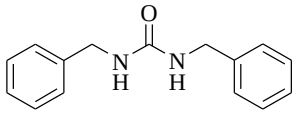
***1,3-Bis-(4-methoxyphenyl)urea (4e).*** Whitish-Grey solid, 88% yield, mp 226–236°C. IR (KBr) 3302 (m), 1634 (s), 1607 (m), 1560 (s), 1511 (s), 1245 (s), 1170 (w),1030

(w), 827 (m) $cm^{-1}$; $^{1}H$ NMR (300MHz, DMSO-$d_6$) δ 8.40 (s, 2H, 2NH), 7.42–7.33 (m, 4H on phenyl rings), 6.91-6.82 (m, 4H on phenyl rings), 3.71 (s, 6H, 2OMe); $^{13}C$ NMR (75MHz, DMSO-$d_6$) δ 154.3, 153.0, 132.9, 119.9, 113.9, 55.1; MS *m/z* 272 (M+, 44), 149 (19), 134 (11), 123 (100), 108 (91), 95 (6), 80 (12). Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92, N, 10.29. Found C, 66.28; H, 5.91, N, 10.27.



C9H20N2O
Mol. Wt.: 172.27
C, 62.75; H, 11.70; N, 16.26; O, 9.29

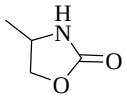
***1,3-Di-tert-butylurea (4f).*** White solid, 97% yield, mp 119.6-122°C. IR (KBr) 3355 (m), 2964 (m), 1637 (s), 1560 (s) $cm^{-1}$; $^{1}H$ NMR (300MHz, DMSO-$d_6$) δ 5.45 (s, 2H, 2NH), 1.19 (s, 18H, 2*t*-Bu); $^{13}C$ NMR (75MHz, DMSO-$d_6$) δ 157.0, 48.7, 29.3; MS *m/z* 172 (M+, 3), 157 (13), 71 (3), 61 (7), 59 (4), 58 (100), 57 (13), 56 (3). Anal. Calcd for $C_9H_{20}N_2O$: C, 62.75; H, 11.70, N, 16.26. Found C, 62.64; H, 11.72, N, 16.25.



C15H16N2O
Mol. Wt.: 240.30
C, 74.97; H, 6.71; N, 11.66; O, 6.66

***1,3-Dibenzylurea (4g).*** White solid, 98% yield, mp 164–165 °C. IR (KBr) 3320 (m), 1627 (s), 1571 (s), 697 (m) $cm^{-1}$; $^{1}H$ NMR (330MHz, DMSO-$d_6$) δ 7.34–7.18 (m, 10 H on phenyl rings), 6.48 (t, *J* = 5.9, 2H, 2NH), 4.24 (d, *J* = 5.9, 4H, 2 $CH_2$); $^{13}C$ NMR (75MHz, DMSO-$d_6$) δ 158.1, 140.8, 128.1, 126.9, 126.5, 42.9; MS *m/z* 240 (M+, 27), 149 (16), 106 (100), 91 (43), 79 (15). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71, N, 11.66. Found C, 75.11; H, 6.72, N, 11.62.

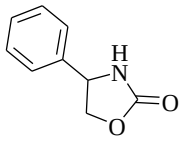
**iii) Oxazolidinone:**



C4H7NO2
Mol. Wt.: 101.10
C, 47.52; H, 6.98; N, 13.85; O, 31.65

***4-Methyl-oxazolidin-2-one(6a),*** Yellow oil. 94% yield, IR (Neat) = 3320(m), 1740(s), 1260(m) 750(m) $cm^{-1}$; $^{1}H$ NMR (300MHz, $CDCl_3$): $\delta$ = 1.42 (*d*, *J* = 6.2 Hz, 3H), 3.18 (t, *J* = 7.9Hz, 1H), 3.68 (t, *J* = 8.4 Hz, 1H), 4.78–4.69 (m, 1H), 6.52 (br., 1H). $^{13}C$

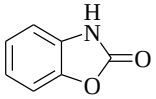
NMR (75MHz, $CDCl_3$) $\delta$ = 20.9, 47.8, 73.9, 160.9, MS (EI): *m/z* = 101(20.6), 86(100), 58(8), 56(4), 44(16), 43(25), 42(70), 40(9).



C9H9NO2
Mol. Wt.: 163.17
C, 66.25; H, 5.56; N, 8.58; O, 19.61

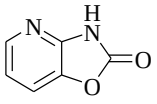
***4-Phenyl-oxazolidin-2-one(6b).*** White solid, 80% yield, mp. 115-126$^{o}$C, IR (KBr) 3243(s,br), 3144(m), 1743(s), 1705(s), 1616(m), 1487(m), 1401(s), 1236(s), 1097(s), 923(s), 697(s,br). $^{1}$H NMR (300MHz, DMSO-$d_6$) δ 4.00 (t, 1H), 4.67 (t, 1H), 4.94 (t, 1H), 7.31– 7.42 (m, 5H), 8.23 (br, 1H). $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 55.3, 71.6, 126.2, 128.2, 128.9, 141.1, 159.2; MS (EI): *m/z* = 163(44), 162(14), 133(100), 106(6.14), 105(76.1), 104(93), 91(34), 89(8), 78(26), 77(27), 65(9), 51(25), 50(10), 42(9).

**iv) Benzoxazolone:**



C7H5NO2
Mol. Wt.: 135.12
C, 62.22; H, 3.73; N, 10.37; O, 23.68

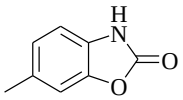
***H-Benzooxazol-2-one(8a).*** Brown solid; 98% yield, m.p. 140–141$^{o}$C; IR (KBr) 3233(m), 1774(s, br), 1748(s, br), 1480(s), 1440(m), 1151(m), 943(m), 683cm$^{-1}$. $^{1}$H NMR (300MHz, $CDCl_3$) δ = 10.0 (br s, 1H), 7.24–7.11 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ =156.3, 143.9, 129.4, 124.3, 122.8, 110.3, 110.2; GCMS *m/z*: 135(100), 91(34), 78(3.7), 53(4.1), 52(28.9), 50(5), HRMS: m/z calcd for [M + H]+ $C_7H_6NO_2$: 136.0399; found: 136.0400.



C6H4N2O2
Mol. Wt.: 136.11
C, 52.95; H, 2.96; N, 20.58; O, 23.51

***3H-Oxazolo[4,5-b]pyridin-2-one (8b).*** Brown solid, 90% yield, mp 152-153$^{o}$C; IR (KBr) 3000(m), 2900(m), 1750(s), 1610(s), 842(m) cm$^{-1}$; $^{1}$H NMR (300MHz, DMSO-

$d_6$)δ 6 7.13 (*dd*, 1H, J = 8.2,5.1 Hz), 7.63 (*dd*, 1H, J = 8.2, 1.0 Hz), 8.05 (*dd*, 1H, H, J = 5.1, 1.0 Hz), 11.9 (br 8, 1H, NH), 13C NMR (75MHz, DMSO $d_6$) δ 154.8, 150.4, 143.6, 140.3, 114.3, 125.8 GCMS *m/z*: 136.1(100), 109(8), 93(22), 65(23), 53(14), 39(4).




C8H7NO2
Mol. Wt.: 149.15
C, 64.42; H, 4.73; N, 9.39; O, 21.45

***6-Methyl-3H-benzooxazol-2-one(8c)*.** Red-Brown solid; 92% yield, m.p. 137–143$^{o}$C; IR (KBr) 3290(m), 1737(s), 1499(s), 1400(s), 1268(s), 931(s), 676(s). $^{1}$H NMR (300MHz, CDCl3) δ = 9.88 (br s, 1H), 7.03–6.95 (m, 3H), 2.38 (s, 3H); $^{13}$C NMR (75MHz, CDCl3) δ = 156.6 (s), 144.0 (s), 132.8 (s), 127.0 (s), 124.6 (d), 110.7 (d), 109.8 (d), 21.4 (q); GCMS *m/z*: 149(100), 148(20), 104(17), 93(21), 78(16), 77(8), 66(12), 51(10), 40(4). HRMS: m/z calcd for [M + H]+ C8H8NO2: 150.0555; found: 150.0551.

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**ALLEGATO B - Dnyaneshwar RAUT**

Il candidato/a ha usufruito di una borsa aggiuntiva di dottorato di ricerca MIUR – Bando Fondo Sostegno Giovani. Il Collegio dei Docenti ha valutato l'attività di ricerca del/della candidato/a che si è sviluppata nel campo della sintesi di derivati carbonilici mediante reazioni di carbonilazione palladio-catalizzate, e ha preso in esame i risultati conseguiti, riportati in n° 2 lavori in corso di stampa su riviste internazionali con referee a buon IF medio, n° 4 comunicazioni in congressi internazionali e n° 4 comunicazioni in congressi nazionali.

Il Collegio ha inoltre valutato:

- l'attività formativa del candidato che si è realizzata attraverso la partecipazione a n° 2 Scuole Internazionali (9th International School of Organometallic Chemistry e XXXIX "A. Corbella" International Summer School On Organic Chemistry-ISOS2014) e n° 2 Convegni nazionali (XXXV Convegno della Divisione di Chimica Organica della Società Chimica Italiana e XXV Congresso Nazionale della Società Chimica Italiana)
- l'attività formativa del candidato/a che si è realizzata a seguito della assidua frequenza all'attività didattica proposta dalla Scuola di Dottorato.

Con riferimento a quanto sopra richiamato, il Collegio dei Docenti del corso di Dottorato di Ricerca in *Scienza e Tecnica – Curriculum OMPI (Organic Materials of Pharmaceutical Interest)*, giudica l'attività del candidato **Dnyaneshwar RAUT** ampiamente positiva e lo presenta con piena soddisfazione al giudizio della Commissione.

IL COORDINATORE OMPI
(PROF. B. GABRIELE)