UNIVERSITÀ DELLA CALABRIA

Department of Chemistry and Chemical Technology

Doctorate School
Science and Technique "Bernardino Telesio"

"Organic Materials of Pharmacological Interest" (OMPI)

XXVIII Cycle

New Palladium Catalyzed Carbonylation Processes for the Synthesis of Molecules of Applicative Interest

Ph.D. Thesis

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A.A. 2014-2015

UNIVERSITÀ DELLA CALABRIA

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Scuola di Dottorato
Scienza e Tecnica "Bernardino Telesio"

Indirizzo
Sintesi di Molecole Organiche di Interesse Farmaceutico (OMPI)

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New Palladium Catalyzed Carbonylation Processes for the Synthesis of Molecules of Applicative Interest

Settore Scientifico Disciplinare Chim/06 (Chimica Organica)

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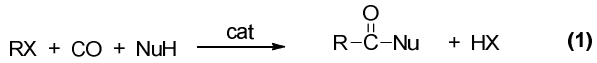
Abstract

In the present investigation we have developed new palladium-catalyzed carbonylation processes for the synthesis of molecules of applicative interest. In particular, isoindolinone and isobenzofuranimine derivatives have been synthetized starting from 2-alkynylbenzamides by a divergent PdI_2-catalyzed multicomponent carbonylative approach, depending on the nature of the external nucleophile and reaction conditions. Thus, oxidative carbonylation of 2-ethynylbenzamides, bearing a terminal triple bond, carried out in the presence of a secondary amine as external nucleophile, selectively led to the formation of 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones. On the other hand, 3-[(alkoxycarbonyl)methylene]-isobenzofuran-1(3*H*)imines were selectively obtained when the oxidative carbonylation of 2-alkynylbenzamides, bearing a terminal or an internal triple bond, was carried out in the presence of an alcohol R'OH (such as methanol or ethanol) as the external nucleophile and $HC(OR')_3$ as a dehydrating agent, necessary to avoid substrate hydrolysis. Isoindolinone derivatives were used as starting material to obtain the corresponding spiro-isoindolin isoxazolidines, able to work as inhibitors of the p53-MDM2 interaction: biological test showed that these compounds have antiproliferative activity on cancer cell lines of neuroblastoma, colorectal adenocarcinoma and hepatocarcinoma in the μM range. Isobenzofuranimine derivatives, instead, showed a strong phytotoxic effect on shoot and root systems of *Arabidopsis thaliana*, a weed which compete with crops for edaphic resources such as water and nutrients. Furo-furanone derivatives have been synthetized by PdI_2-catalyzed oxidative carbonylation starting from 4-yn-1,3-diols, substrates bearing themselves nucleophilic groups in a suitable position to give a “double” intramolecular nucleophilic attack so as to obtain functionalized bicyclic molecules. Biological assay showed that these compounds are promising anticancer agents. Finally, part of this *PhD* was spent at *Leibniz Institute for Catalysis* in Rostock University in order to develop a new heterogeneous catalyst based on palladium via immobilization and pyrolysis on activated carbon. Palladium supported on *N*-doped carbon was applied to the alkoxycarbonylation of aryl iodides to benzoates, important feedstocks and key intermediates for pharmaceuticals.

Chapter 1

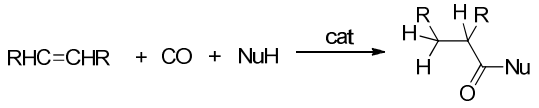
1.1 Carbonylation reactions

Carbonylation is the incorporation of carbon monoxide into organic substrates in order to obtained a functionalized compounds starting from simplest molecules[1] such as in the case of olefins hydroformylation or synthesis of carboxylic acids and esters starting from unsaturated hydrocarbons.[2] Carbon monoxide, which is a cheap and abundant material from either fossil or renewable sources, is a relatively inert molecule so carbonylations usually need to be performed under drastic conditions[3] or to be carried out in the presence of very reactive reagents or more effectively in the presence of a transition metal catalyst.[4] On the basis of the reaction mechanism, it is possible to distinguish four types of carbonylation reactions: substitutive carbonylation; additive carbonylation; reductive carbonylation and oxidative carbonylation.[5] A *substitutive carbonylation* is a process in which a certain functional group X (I, Br, Cl, or another possible leaving group) is formally substituted with a CONu moiety ("Nu" usually corresponding to an OH, OR, NHR or NR_2 group). (*Eq. 1*)

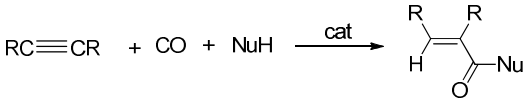


(1)

One of the most important example is the Palladium-catalyzed synthesis of carboxylic acids derivatives directly from aryl halides. Substitutive carbonylation of aliphatic halides is also possible but, in this case, a different type of catalyst such as $Pt(PPh_3)_2Cl_2$ is necessary because of the tendency of alkyl palladium complexes to undergo β-hydride elimination before carbon monoxide insertion can occur.[6] An *additive carbonylation* is a reaction in which a H-CONu moiety (Nu = H, OH, OR, NHR, NR_2 or some other nucleophilic group) formally adds to an unsaturated bond, as shown in *Eq. 2a* and *2b.*

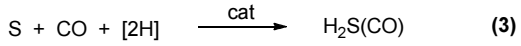


(2a)



(2b)

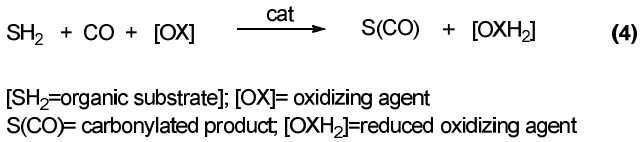
A *reductive carbonylation* is a process in which the starting material is reduced by formally addition of molecular H_2 (*Eq. 3*) such as in hydroformylation reaction, an important industrial process in which a hydrogen molecule and a CO group are added to an alkene so as to obtain aliphatic aldehyde.



(3)

[S=organic substrate]

Finally, an *oxidative carbonylation* is a process in which carbon monoxide is inserted into an organic substrate through the action of a metal species undergoing a reduction of its oxidation state [$M^{(X)}$ to $M^{(X-2)}$]; clearly, in order to achieve a catalytic process, the reduced metal must be re-oxidized to its original oxidation state through the action of a suitable external oxidant. (*Eq. 4*) Oxidative carbonylations have acquired a growing importance during the last few years, owing to the development of new and selective catalytic systems, mainly based on palladium, which are able to promote ordered sequences of transformations under mild conditions with formation of highly functionalized carbonyl compounds in one step, starting from very simple building blocks.



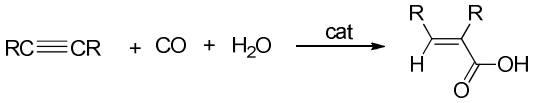
1.2 Palladium catalyzed carbonylation reactions

In the last 40 years more active and selective catalytic systems have been discovered: in particular catalysts based on palladium allow to operate under mild conditions (100 °C, atmospheric pressure) using no volatile and air stable precursors.[7] The catalytic process usually starts with the coordination of substrate to catalyst followed by metal oxidative addition with subsequent loss of two valence electrons by metal itself. Oxidative addition is a key step in many catalytic cycles and often, it is the slow rate-determining step, because a covalent bond (usually in the substrate) is broken. The electron density at the metal center is a key parameter in oxidative addition reactions: ligands that increase the electron density at the metal center, promote oxidative addition; on the contrary ligands that reduce the electron density at the metal center will slow the oxidative addition reaction. Then, an insertion or migration step involves the introduction of one unsaturated ligand into another metal–ligand bond on the same complex. Nucleophilic attack in conjunction with reductive elimination are common bond-forming final steps, just as oxidative addition is a common bond-breaking step. In many catalytic cycles, the reactant enters the cycle in an oxidative addition step, and part of it leaves the intermediate in a reductive elimination step. Finally, in a catalytic process, the excess of substrate (and thus, of product) with respect to the catalyst, but also of the solvent and sometimes of ligands, can influence rate reaction: this competition with the catalyst present in

very low amount, can enhance the rate of reaction, but also retard it: if the active site is always occupied by excess ligand, solvent, or even product, the reaction will stop.[8]

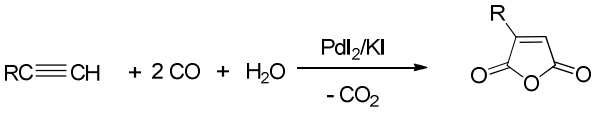
1.2.1 Palladium-catalyzed carbonylation of alkyne*s*

Hydroxycarbonylation reactions of alkynes allow to introduce into the substrate a molecules of CO and H_2O leading to the corresponding saturated carboxylic acids. The general equation related to the synthesis of acrylic acid discovered by Reppe[9] is below shown in *Equation 6*.



(6)

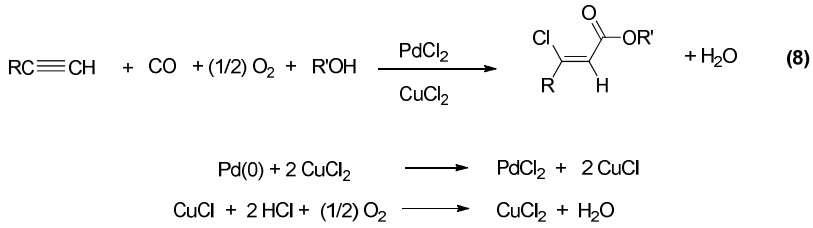
It is important to mention the pioneering work of Reppe and co-workers who discovered as early as 1938 the industrial preparation of acrylic acid by carbonylation of acetylene.[10] The reaction was conducted at 200–230 °C and 100 bar of CO and catalyzed by $Ni(CO)_4$ in the presence of a copper halide. Selectivity of 90% and 85% were reached in acrylic acid with regard to acetylene and carbon monoxide, respective. Later, Alper and his group reported that hydroxycarbonylation of alkynes can be performed under mild conditions using the cationic hydridopalladium complex $[Pd(H)(H_2O)(PCy_3)_2][BF_4]$.[11] It is worth mentioning that some precursors easily catalyze the reductive carbonylation of alkynes from the CO/H_2O couple. Here, the main role of water is to furnish hydrogen through the water-gas-shift reaction, as evidenced by the co-production of CO_2. In the presence of PdI_2/KI terminal alkynes have been selectively converted into furan-2-(5*H*)-ones. Two CO building blocks are incorporated and the cascade reactions that occur on palladium result in a cyclization together with the formation of an oxygen-carbon bond.[12] (*Eq. 7*)



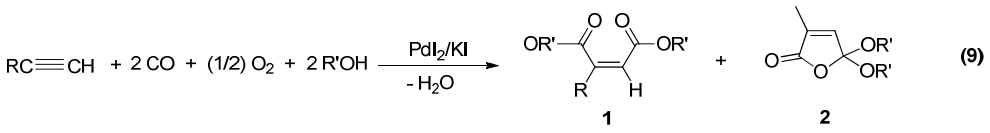
(7)

Alkoxycarbonylation of alkynes involve carbon monoxide and alcohol in order to obtain esters or lactones. The first observations, done by Tsuji et al. in 1980 on substituted acetylenes, were reinvestigated by Brandsma in 1994 and concern the alkoxycarbonylation of these substrates, not to give an acrylate moiety, but instead acetylenic esters. The catalytic system involves $PdCl_2/CuCl_2/NaOAc$. Copper chloride introduced in stoichiometric amounts is responsible for the CH activation, maintaining the triple bond.[13] Later, using the same $PdCl_2/CuCl_2$ system without added base or acid and in less polar solvents, such as benzene, Jiang and his group

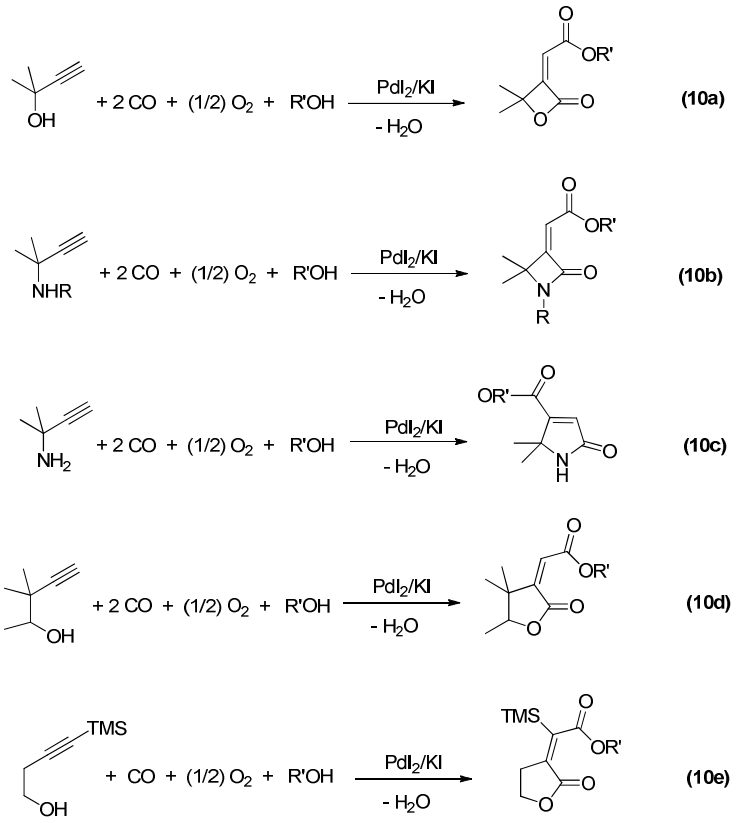
developed a method for the highly regio and stereospecific synthesis of (*Z*)-3-chloroacrylate esters from terminal alkynes (*Eq. 8*). They explained that *cis*-addition of acetylenes on $PdCl_2$ produced a *cis*-chloropalladium intermediate. Then acylation and alcoholysis steps in the catalytic cycle afforded the corresponding chloro acrylate esters.[14] In the case of $CuCl_2$, the resulting cuprous chloride has in its turn been reoxidized by oxygen.



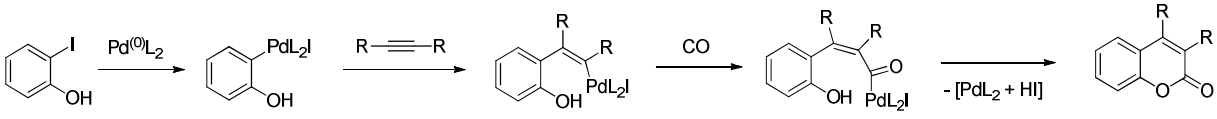
Under similar reaction conditions, γ-acetoxy-β-methoxyalkenoates are produced when propargylic acetates are carbonylated. The presence of the acetoxy moiety is indispensable because it plays the role of an ancillary ligand during the coordination of the triple bond to the palladium(II) species.[15] Incorporation of two CO building blocks can be obtained associating an oxidant to the palladium catalyst leading to the diester **1**: in fact, PdI_2 stabilized by an excess of KI transforms a terminal alkyne into the corresponding maleic esters in the presence of O_2.[16] The reaction, carried out under mild conditions (25-80 °C, 20 atm of 3:1 mixure of CO-air) in an alcoholic solvents, also leads to the formation of a new interesting heterocyclic compound **2** as by-products which can be considered as cyclic isomers of the diester **1**. (*Eq. 9*)



The application of triple bond oxidative dialkoxycarbonylation methodology to *α*-disubstituted propynyl alcohols or *α*-disubstituted *N*-alkyl propynylamines allowed a direct synthesis of β-lactone (*Eq. 10a*) and β-lactam (*Eq. 10b*) Interestingly, *N*-unsubstituted *α,α*-dialkyl propynylamines did not efford the expected β-lactam but γ-lactam derivative, formally derived from *anti* addition to the triple bond (*Eq. 10c*). On the other hand, the reaction of 3-yn-1-ols is stereoselctive to the corresponding *Z* isomer (*Eq. n10d and 10e*).[17]



In an alternative strategy functionalized phenols, such as iodophenol, were involved in palladium-catalyzed carbonylation of alkynes, producing 3,4-dialkyl-2*H*-chromen-2-one derivatives (*Scheme 1*). After oxidative addition of the iodophenol to the Pd(0) catalyst, insertion of alkynes precedes insertion of CO, affording coumarine derivatives, as reported by Larock.[18]

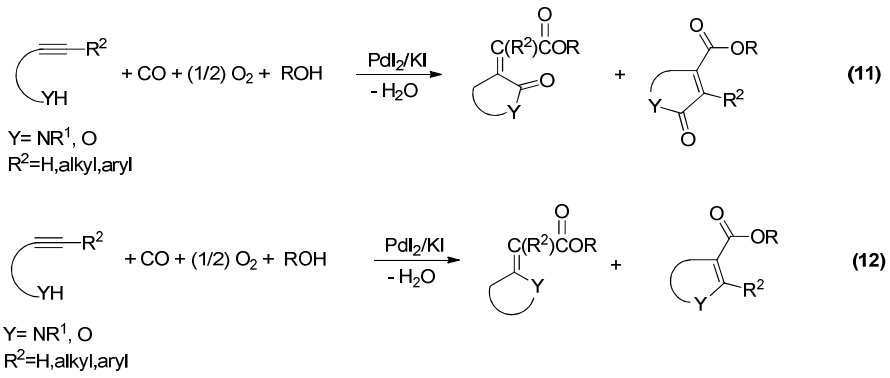


Scheme 1

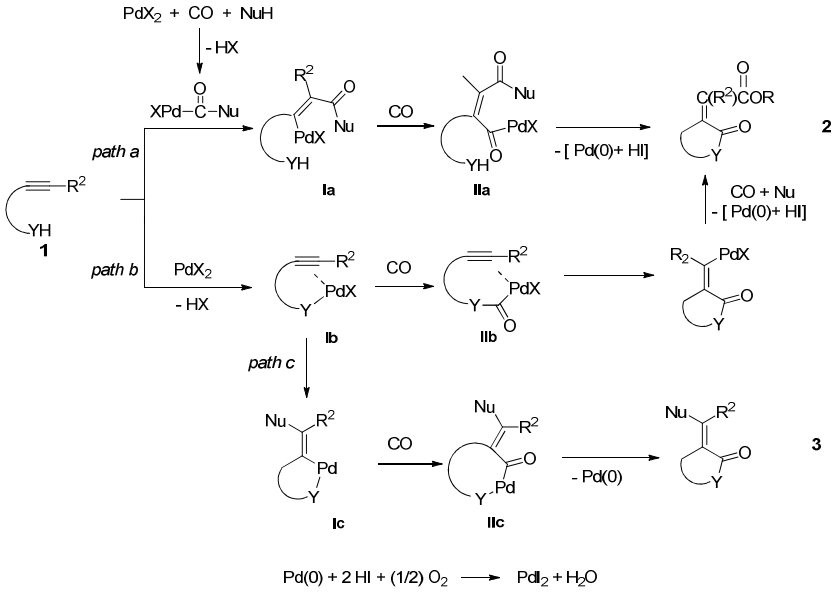
Unsaturated lactones can be obtained from alkynols and, according to the substrate or to the catalyst as well as to the reaction conditions, the double bond can be endo- or exocyclic. Norton have developed an efficient tool to carbonylate alkynols into *α*-methylene lactones under mild conditions. Different palladium precursors can be used for this reaction such as $PdI_2/PBu_3/CH_3CN$ or $PdCl_2/PPh_3/SnCl_2/CH_3CN$.[19]

1.2.2 PdI_2-catalyzed oxidative carbonylation of functionalized alkynes to heterocycles

The direct and selective synthesis of functionalized heterocyclic molecules by a one-step, atom-economical procedure is particularly attractive. Alkynes bearing a nucleophilic group in suitable position for cyclization are excellent substrates for different kinds of oxidative carbonylation reactions leading to functionalized heterocyclic derivatives. Both oxidative carbonylation with incorporation of CO into the cycle (*Eq. 11*) and oxidative cyclization-carbonylation without incorporation of CO in the cycle (*Eq. 12)* are possible.

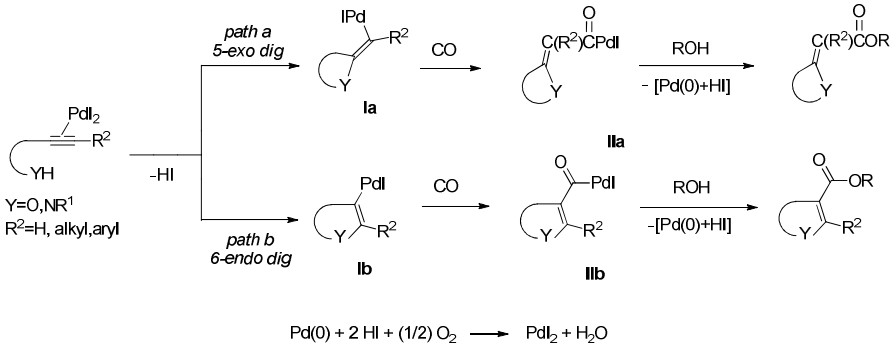


In the case of incorporation of CO into the cycle, the reaction begin with the addition of the X–Pd–CONu intermediate (formed from the reaction between PdI_2, CO and NuH) to the triple bond, followed by CO insertion and intramolecular nucleophilic displacement by YH on the acylpalladium intermediate **IIa** (*Scheme 2*, path a). Another possibility is the formation of the Y-PdX intermediate **Ib** stabilized by triple bond coordination (*Scheme 2*, path b), which in its turn may undergo either CO insertion followed by triple bond insertion, further carbonylation and nucleophilic displacement by NuH or external attack by NuH (with formation of the palladacycle complex **Ic**) followed by CO insertion and reductive elimination (*Scheme 2*, path c).



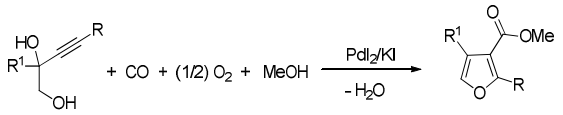
Scheme 2

Products deriving from cyclization–alkoxycarbonylation are instead formed through the general mechanism shown in *Scheme 3*, involving *exo* (*path a*) or *endo* (*path b*) intramolecular nucleophilic attack by YH to the triple bond coordinated to Pd(II) followed by CO insertion and nucleophilic displacement by NuH. The *exo*-intramolecular nucleophilic attack has been observed more frequently with respect to the *endo* one.[20]

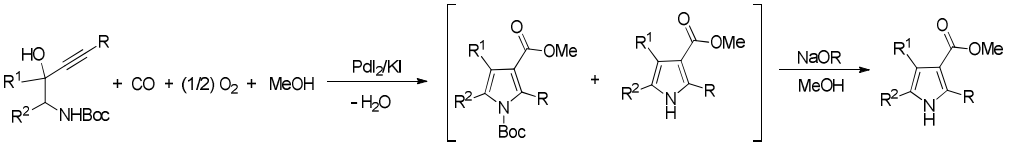


Scheme 3

With particular substrates, cyclization-alkoxycarbonylation process is accompanied by dehydration, triggered by molecule aromatization such as in the case of 3-yne-1,3-diols converted into furan-3-carboxylates. [21] (*Eq. 13*) Similarly, PdI_2/KI-catalysed oxidative heterocyclodehydration/alkoxycarbonylation of *N*-Boc-1-amino-3-yn-2-ols, followed by base-promoted deprotection, afford the *N*-unsubstituted pyrrole-3-carboxylates. *N*-deprotection may occur spontaneously under the reaction conditions.[22] (*Eq. 14*)

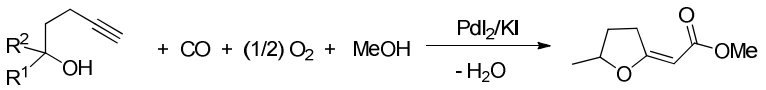


(13)

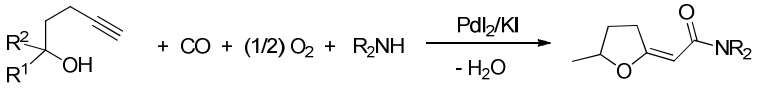


(14)

On the other hand, 4-yn-1-ols are readily converted into tetrahydrofuran derivatives through 5-*exo-dig* cyclization (*Scheme 3*, path a) followed by alkoxy or amino-carbonylation.[23] This kind of process is not possible for the 3-yn-1-ols and the 1-amino-3-yn-2-ols, seen before, for stereoelectronic reasons; the *endo* cyclization mode (*Scheme 3*, path b), although in principle stereoelectronically allowed, was not observed. [24] (*Eq. 15* and *Eq. 16*)

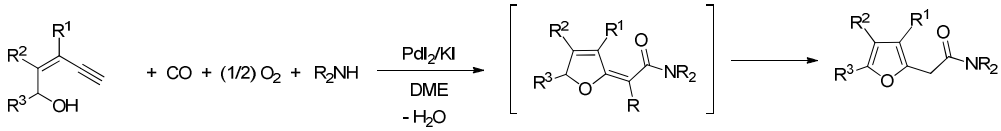


(15)



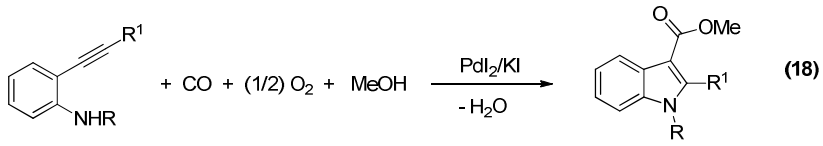
(16)

The oxidative aminocarbonylation/conjugate addition mechanism, followed by aromatization, is operative in the case of the PdI_2/KI-catalysed formation of furan-2-ylacetamides from (*Z*)-2-en-4-yn-1-ols and secondary amines.[25] (*Eq. 17*)



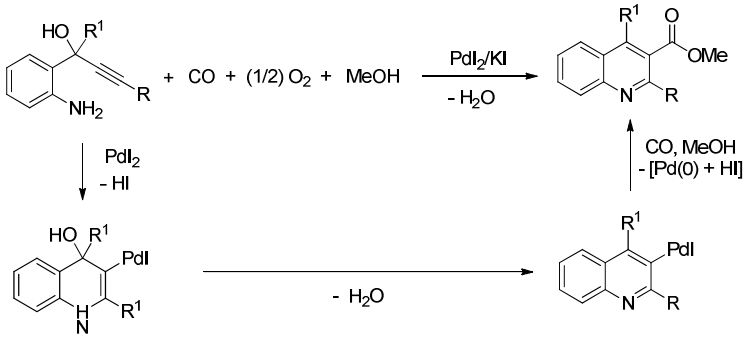
(17)

Under oxidative alkoxycarbonylation conditions, 2-alkynyl anilines with an internal triple bond and a secondary amino group lead to indole-3-carboxylates.[26] (*Eq. 18*) The presence of a secondary amino group and of an internal triple bond in the starting material was essential for the selectivity of the process. In fact, 2-ethynylanilines containing a terminal triple bond and a primary or a secondary amino group are known to lead to dihydroindol-2-one derivatives, whereas 2-alkynylanilines with an internal triple bond and a primary amino group afforded acyclic carbamates[27] through the intermediate formation of isocyanates.[28]



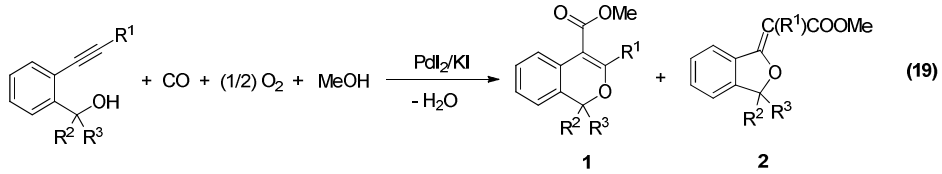
(18)

In the case of 1-(2-aminoaryl)-2-yn-1-ols, intramolecular nucleophilic attack to the triple bond coordinated with palladium is followed by dehydration/aromatization/alkoxycarbonylation so as to obtain quinoline-3-carboxylates.[29] (*Scheme 4*)



Scheme 4

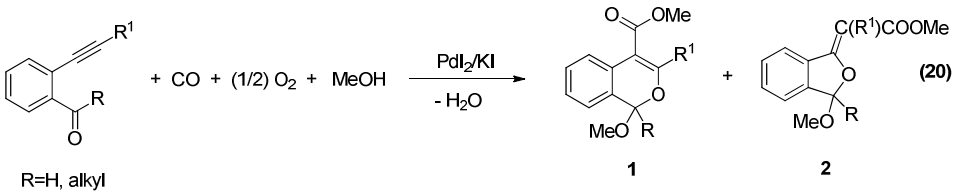
In contrast with the reaction of 4-yn-1-ols, both *6-endo-dig* and *5-exo-dig* cyclization modes were observed in the PdI_2/KI-catalyzed oxidative carbonylation of 2-(1-alkynylbenzyl)alcohols. The preferential formation of the 1*H*-isochromene **1** or the 1,3-dihydroisobenzofuran derivative **2** turned out to be dependent on the substitution pattern of the substrate. (*Eq. 19*) In particular, 1*H*-isochromenes were obtained as the main reaction products when the triple bond was substituted with an alkyl group and with a primary alcoholic group, while the isobenzofurans were preferentially formed with a tertiary alcoholic group and when the triple bond was terminal or conjugated with a phenyl group.[30]



(19)

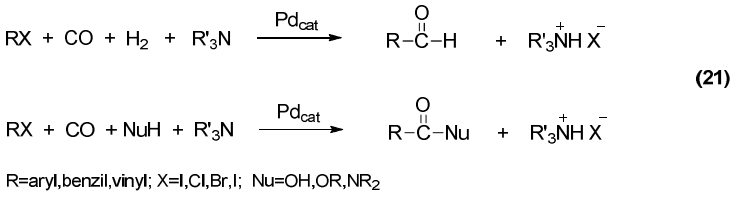
A suitably placed carbonyl oxygen can also act as intramolecular nucleophile in PdI_2-catalyzed oxidative cyclization–alkoxycarbonylation reactions. The nucleophilicity of simple aldehydic or ketonic groups is not sufficient to give a direct attack to a coordinated triple bond; however, in the presence of an alcohol as external nucleophile, the formation of a tetrahedral intermediate

takes place, in which the oxygen atom becomes nucleophilic. This possibility has been verified by reacting 2-(1-alkynyl)benzaldehydes or 2-(1-alkynyl)phenylketones in ROH-CH_3CN mixtures under oxidative conditions. Formation of isochromenes **1** was favored starting from aldehydes, while ketones mainly afforded dihydroisobenzofurans **2**. [30] (*Eq. 20*)



1.2.3 Palladium catalyzed carbonylation reactions of halides

Palladium catalyzed carbonylation reaction of aryl, benzyl and vinyl halides is an example of substitutive carbonylation to the formation of carbonylated aldehydes, esters and amides carried out in the presence of catalytic amount of Pd(0) or Pd(0) precursor. The attractiveness of this chemistry for forming carbonyl derivatives has led many researchers over the intervening years to attempt to increase the scope of the reaction beyond the originally described for bromide, iodide, and triflate substrates, with conditions suited to large-scale application (particularly low pressure). The reactions generally require to be performed of a tertiary amine required to neutralize HX obtained during the process.[31] (*Eq. 21*)



Reaction carried out in the presence of water or an alcohol or an amine as nucleophile lead to the formation of the corresponding hydroxycarbonylation, alkoxycarbonylation and aminocarbonylation procucts. In line with the C-X bond energy, the rate of the oxidative addition of the organic halide to an electronically unsaturated metal complex decreases in the order: C-I > C-OTf ≥ C-Br >> C-Cl >>C-F.[32] Carbonylation activity of aryl halides is only slightly affected by electronic effects from additional substituents (affecting primarily the initial oxidative addition but also having an effect on the carbonyl insertion step) but steric hindrance can have a profound influence on reaction rate. The first palladium-catalyzed

alkoxycarbonylation of aryl-X was firstly developed by Heck and co-workers: the aryl and vinyl iodides and bromides were treated with carbon monoxide (1 bar) in n-butanol at 100 °C to synthesize carboxylic acid n-butyl esters. In general, good yields were obtained in the presence of 1.5 mol% of either $[PdX_2(PPh_3)_2]$ or the respective halo(aryl)bis(triphenylphosphane) palladium(II) complex in the presence of a slight excess of tri-*n*-butylamine as the base. On the other hand carrying out the reaction with primary or secondary amines under 1 bar CO pressure at 60–100 °C in the presence of 1.5 mol% $[PdX_2(PPh_3)_2]$, fuctionalized amides was obtained in good yeald.[33] Since that pioneering report, gradual improvements in terms of solvents, bases, and catalyst systems, particularly ligands, have been made, which have significantly broadened the scope of the method.

1.3 Heterogeneous Catalysis

In heterogeneous catalysis, catalyst and reactants are in different phase; usually, the catalyst is a solid and reactants are fluids (liquids or gases). About 90% of all industrial processes involve heterogeneous catalysts because of the possibility to separate the catalyst from the product stream so as to carry out continuous chemical processes. In fact, even if homogeneous catalysts are usually more active and selective than their heterogeneous counterparts - it is sufficient to think that in homogeneous catalyst the catalytic sites are accessible and every single metal atom is a potential active site - many homogeneous catalytic systems have not been commercialized due to difficulties in catalyst separation, recovery, and recycling.[34] A heterogeneous catalytic reaction involves the initial *diffusion of the reactants* to the catalyst followed by *adsorption of reactants* on to the solid surface where the reaction can occur; being that the contact surface is greater, catalysts consisting of very small particles appear to be more active. As soon as the reaction occurs , there is the desorption - decomposition of the adsorbed product-surface complex - of products into the fluid phase. In this way the active site is available for a new set of molecules to attach to and react. The catalytic process is run inside a reactor typically operated with continuous flow under steady-state conditions. The rate is determined, apart from the nature of the catalytically active surface, by external parameters like temperature, partial pressures and flow rate.[35] Additionally, heterogeneous catalysts are typically more tolerant of extreme operating conditions than their homogeneous analogues. In 1908, the German chemist Fritz Haber succeeded in synthesizing ammonia starting from N_2 and H_2 at high pressures over an osmium catalyst. This discovery was picked up by Carl Bosch and

Alwin Mittasch at BASF, who tested over 2500 different materials until they found an iron-based compound which was active enough and cheap enough to serve as a commercial catalyst. The Haber–Bosch ammonia synthesis has become one of the most important chemical processes worldwide, earning Haber the 1918 Nobel Prize in chemistry. In the last two decades, with the advancement of green chemistry, heterogeneous catalysis has moved into the fine-chemicals and pharmaceuticals industry also. Solid catalysts are also used in clean energy applications such as fuel cells, solar energy conversion, and energy storage cycles.[36]

1.3.1 Preparation of heterogeneous catalysts

Heterogeneous catalyst can be prepared according to two possible techniques: the first one, obtaining bulk catalysts, starts with the precipitation of a catalyst precursor, which is then filtered, dried, and shaped. Calcination steps may be included after drying or after shaping. The second one involves a carrier material, which can be impregnated with salt solutions or coated with powders. Drying and calcination give the final supported catalyst. Small changes in drying temperatures, aging times, solvent compositions, or stirring rates can affect the catalyst performance. Moreover the final catalytic properties can depend on the purity and impurity of the starting materials.[37] Bulk catalysts can be prepared by precipitation - the most common - and by the fusion of mixtures of oxidic or metallic precursors. Precipitation is the process in which a phase-separated solid is formed from homogeneous solution, after super-saturation. The main advantage of precipitation is the possibility of creating very pure materials. On the other hand the fusion processes are rarely applied as they require extensive special equipment which is generally unavailable to research groups, and difficult to use in industry. Bulk catalysts are made of active material (metals or oxide or both). Impregnated catalysts are commonly used in the case of precious metals or unstable compounds. Here, the active metal precursor is deposited on a porous bulk support. This support can be an oxide (e.g., silica, titanium, alumina or ceria), an activated carbon, or even an organic or hybrid polymer resin. Examples of impregnated catalysts include the Pd/C hydrogenation catalysts, the $Pt/Sn/Al_2O_3$ dehydrogenation catalysts and the automotive three-way catalysts. In particular in wet impregnation, the porous support is immersed in a solution of the catalyst precursor. The precursor is either adsorbed spontaneously on the support, or precipitated there by changing the pH or by inducing another chemical reaction. The resulting catalyst is then filtered, dried, and calcined. The calcination process drying at high temperature (300–800 °C) removes all the

water from the catalyst, decomposes the nitrate/carbonate precursors, and forms metal-oxide links with the support. Depending on the temperature, calcination can also dehydrate surface hydroxyl groups. This is very important as it alters the catalyst surface hydrophobicity. Like drying, calcination should be carried out in a controlled manner, to avoid pore collapse.[38]

1.3.2 Catalyst Solid Supports

The catalyst support is the material, usually a solid with a high surface area, to which the catalyst is anchored. The reactivity of heterogeneous catalysts occurs at the surface atoms, so great effort is made to maximize the surface area of a catalyst by distributing it over the support. The support may be inert or participate in the catalytic reactions. Typical supports include various kinds of activated carbon[39], zeolite[40], metal oxides such as silica[41] or Fe_3O_4[42], and polymers[43]. In particular available activated carbons are prepared from carbon containing source materials such as coal (anthracite or brown coal), lignite, wood, nut shell, petroleum and sometimes synthetic high polymers. There are many types of carbon materials with different origins, thermal resistance, morphology, porosity and in different configuration such as nanonubes, nanoparticles, foams, powders and pellets. Commercial heterogeneous catalysts usually contain small amounts of promoters or modifiers, which are added intentionally during the catalyst synthesis. Adding these compounds improves the catalyst activity, selectivity, stability, and/or accessibility. The activity and selectivity of heterogeneous catalysts may change during the course of reaction. Usually activity decreases due to either chemical or physical reasons, or a combination both factors. The active sites of a catalyst may become inactive by the adsorption of impurities in the feed stream. In the case of temporary poisoning, adsorption of the poison is relatively weak and reversible and removal of the poison from the fluid phase results in restoration of the original catalytic activity. If adsorption of the poison is strong and not readily reversed, the poisoning is called permanent. Thermal degradation is a physical process leading to catalyst deactivation Chemical transformations, reactions in which the support is directly involved can also take place. Mechanical deactivation is important in giving the catalyst resistance against crushing. In a fluidized-bed reactor, attrition will always occur and the fines formed will be carried away with the product flow. Leaching of the active metal by dissolution into the surrounding liquid reaction mixture is often a concern. In most cases, leaching is the result of solvolysis of metal–oxygen bonds through which the catalyst is

attached to the support. This not only causes loss of catalyst activity, but also results in contamination of the product.[38]

[1] For recent reviews, *see*: (a) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825–6839. (b) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem. Int. Ed.* **2011**, 50, 10788–10799. (c) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, 40, 4986–5009. (d) Omae, I. *Coord. Chem. Rev.* **2011**, 255, 139–160. (e) Grigg, R.; Mutton, S.P. *Tetrahedron* **2010**, 66, 5515–5548. (f) Liu, J.; Chen, J.; Sun, W.; Xia, C. *Chin. J. Catal.* **2010**, 31, 1–11. (g) Brennfürer, A.; Neumann, H.; Beller, M. *Angew. Chem.* **2009**, 121, 4176; *Angew. Chem. Int. Ed.* **2009**, 48, 4114–4133; *ChemCatChem* **2009**, 1, 28–41. (h) Barnard, C.F.J. *Organometallics* **2008**, 27, 5402–5422. (i) Veige, A.S. *Polyhedron* **2008**, 27, 3177–3189. (j) Wolfe, J.P. *Eur. J. Org. Chem.* **2007**, 571–582. (k) Church, T.L.; Getzler, J.D.; Byrne, C.M.; Coates, G.W. *Chem. Commun.* **2007**, 657–674. (l) Mihovilovic, M.D.; Stanetty, P. *Angew. Chem.* **2007**, 119, 3684; *Angew. Chem. Int. Ed.* **2007**, *46*, 3612–3615. (m) Vasapollo, G.; Mele, G.; *Curr. Org. Chem.* **2006**, 10, 1397–1421. (n) Wiese, K.D; Obst, D. *Top. Organomet. Chem.* **2006**, 18, 1–33. (o) Claver, C.; Diéguez, M.; Pàmies, O. *Top. Organomet. Chem.* **2006**, 18, 35–64. (p) Eilbracht, P.; Schmidt, A.M. *Top. Organomet. Chem.* **2006**, 18, 65–95. (q) Kalck, P.; Urrutigoïty, M.; Dechy-Cabaret, O. *Top. Organomet. Chem.* **2006**, 18, 97–123. (r) Cavinato, G; Toniolo, L.; Vavasori, A. *Top. Organomet. Chem.* **2006**, 18, 125–164. (s) Strübing, D.; Beller, M. *Top. Organomet. Chem.* **2006**, 18, 165–178. (t) Haynes, A. *Top. Organomet. Chem.* **2006**, 18, 179–205. (u) von Wangelin, A.J.; Neumann, H.; Beller, M. *Top. Organomet. Chem.* **2006**, 18, 207–221. (v) Makano, K.; Nozaki, K. *Top. Organomet. Chem.* **2006**, 18, 223–238. (w) Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, 18, 239–272. (x) Muzart, J. *Tetrahedron* **2005**, 61, 9423–9463. (y) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *Curr. Org. Chem.* **2004**, 8, 919–946. (z) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 14, 2468–2483.

[2] Arpe, H.J. *Industrial Organic Chemistry* 5th Edition, Wiley- VCH, Weinheim, **2010**.

[3] Reppe, W.; Magin, A.; Schuster, C.; Keller, R.; Kroper, H.; Klein, T.; Kerchow, F.W.; Blank, G.; Merchel, K.; Scheller, H.; Weschky, L.; Wolff, K.; Schwenckendiek, W.; Hecht, W.; Gassenmeier, E.; Simon, A. *Liebigs Ann Chem* **1953**, 582, 1.

[4] (a) Beller, M.; Wu, X.F. *Transition Metal Catalyzed Carbonylation Reactions* Springer-Verlagn Berlin Heidelberg, Germany, **2013**. (b) Beller, M. (Ed.) *Catalytic Carbonylation Reaction* Springer-Verlag Berlin Heidelberg, Germany, **2006**. (c) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *J. Organomet. Chem.* **2003**, 687, 219–228. (d) Colquhoun, M.; Thompson, D.J.; Twigg, M.W. *Carbonylation-Direct Synthesis of Carbonyl Compounds* Plenum Press, New York, **1991**. (e) Jacobsen, E.N.; Pfaltz, A.; Yamamoto, H. (Eds) *Comprehensive Asymmetric Catalysis* Springer-Verlagn Berlin Heidelberg, Germany, **1999**.

[5] Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825–6839.

[6] Schoenberg, A.; Bartoletti, I.; Heck, R.F. *J. Org. Chem.* **1974**, 39, 3318; *J. Am. Chem. Soc.* **1974**, 96, 7761.

[7] (a) Barnard, C.F.J. *Organometallics* **2008***,* 27, 21, 5403. (b) Heck, R.F. *Palladium Reagent in Organic Synthesis* Academic Press, New York, **1985**. (c) Tsuji, J. *Organic Synthesis with Palladium Compound* Springer-Verlag, Berlin, **1980**.

[8] Rothenberg, G. *Catalysis-Concepts and Green Applications* WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim **2008**.

[9] Reppe, W. *Liebigs Ann Chem* **1953**, p 582.

[10] (a) Cornils, B.; Herrman, W.A. (Eds) *Applied Homogeneous Catalysis with Organometallic Compounds*, Second Completely Revised and Enlarged Edition; Wiley, Weinheim, **2002**. (b) Weissermel, K.; Arpe, J.H. (Eds) *Industrial Organic Chemistry*, Third Completely Revised Edition.; Wiley, Weinheim, **1997**.

[11] Huh, K.T.; Orita, A.; Alper H. *J. Org. Chem*. **1993**, 58, 9656.

[12] (a) Gabriele, B; Salerno, G.; Costa, M.; Chiusoli, G.P. *Tetrahedron Lett.* **1999**, 40, 989. (b) Chiusoli, G.P.; Costa, M.; Cucchia, L.; Gabriele, B.; Salerno, G.; Veltri, L. *J. Mol. Catal. A-Chem.* **2003**, 133, 204–205.

[13] (a) Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, 21, 849. (b) Vasilesky, S.F.; Trofinov, B.A.; Mal'kina, A.G.; Brandsma, L. *Synth. Commun.* **1994***,* 24, 85.

[14] Lil, J.; Jiang, H.; Feng, A.; Jia, L. *J. Org. Chem.* **1999**, 64,5984.

[15] Okumoto, S.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 2, 217.

[16] (a) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 14, 2468–2483. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *J. Organomet. Chem.* **2003**, 687, 219–228. (c) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *J. Organomet. Chem.* **1995**, 503, 21.

[17] (a) Gabriele, B.; Salerno, G.; Di Pascali, F.; Costa, M.; Chiusoli, G.P. *J. Chem. Soc.- Perkin. Trans. 1* **1997**, 1, 147. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *J. Chem. Soc.; Chem. Commun.* **1994**, p 1429.

[18] (a) Kadnikov, D.V.; Larock, R.G. *J. Org. Chem.* **2003**, 68, 9423. (b) Kadnikov, D.V.; Larock, R.G. *J. Organomet. Chem*. **2003**, 687, 425. (c) Kadnikov, D.V.; Larock, R.G. *Organic. Lett.* **2000**, 2, 3643.

[19] Murray, T.F.; Samsel, E.G.; Varma, V.; Norton, J.R. *J. Am. Chem. Soc.* **1981**, 103, 7520.

[20] (a) Costa, M.; Della Cà, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, 69, 2469. (b) Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G.P. *Tetrahedron Lett.* **1995**, 36, 7495. (c) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, 56, 1099.

[21] Gabriele, B.; Veltri, L.; Mancuso, R.; Plastina, P.; Salerno, G.; Costa, M. *Tetrahedron Lett.* **2010**, 51, 1663–1665.

[22] Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Maggi, S.; Aresta, B.M. *J. Org. Chem.* **2012**, *77*, 4005–4016.

[23] Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G.P. *J Organomet Chem* 2000, 594, 409.

[24] Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736.

[25] Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R. *Synthesis* **2006**, 4247–4251.

[26] Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. *Eur.J. Org. Chem.* **2012**, 2549–2559.

[27] Gabriele, B; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613.

[28] Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741–4750.

[29] Gabriele, B.; Mancuso,R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971–4977.

[30] Bacchi, A.; Costa, M.; Della Cà, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G. *J. Org. Chem.* **2004**, 69, 2469.

[31] Barnard, C.F.J. *Organometallics* **2008**, 27, 21, 5403.

[32] M. Beller in *Applied Homogeneous Catalysis with Organometallic Compounds*, Vol. 1 (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**, pp. 148 – 159.

[33] Schoenberg, A.; Heck, R.F. *J. Org. Chem.* **1974**, 39, 3327 – 3331.

[34] Gadi Rothenberg *Catalysis: Concepts and Green Applications* **2008**, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

[35] Chorkendorff, I.; Niemantsverdriet, J.W. *Concepts of Modern Catalysis and Kinetics, 2nd Edition,* Wiley, Weinheim, **2007**.

[36] (a) Chuang,S.S.C. *Catalysis* **2005**, 18, 186. (b) Carrette, L.; Friedrich, K.A.Sheldon, R.A.; van Bekkum, H. *Fine Chemicals Through Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2001**.

[37] Anderson, J.R. ; M. Boudart, M. (Eds.) *Catalysis: Science and Technology* vol. 4 Springer-Verlag, Berlin, **1983**.

[38] Deutschmann,O.; Knozinger, H.; Kochloelf, K.; Turek, T. *Heterogeneous Catalysis and Solid Catalysts* Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany **2009**.

[39] (a) Lian, Z.; Friis, FS.D; Skrydstrup, T. *Chem. Comm.* **2015**, 51, 10, 1870-1873; (b) Liu, J.; Chen, J.; Chungu Xia, C. *J. Catal.* **2008**, 253, 1, 50-56.

[40] (a) Cai, M.; Peng, J.; Hao, W; Ding, G. *Green Chem.* **2011**, 13, 1, 190-196. (b) Zhao, H.; Zheng, G.; Sheng, S.; Cai, M. *Catal. Comm.* **2009**, 11, 3, 158-161. (c) Cai, M.; Zheng, G.; Ding, G. *Green Chem.* **2009**, 11, 10, 1687-1693.

[41] (a) Natour, S.; Abu-Reziq, R. *ChemCatChem* **2015**, 7, 14, 2230-2240. (b) Niu, J.R.; Xing Huo, X.; Zhang, F.W.; Wang, H.B.; Zhao, P.; Hu, W.Q.; Ma, J.; Li, R. *ChemCatChem* **2013**, 5, 1, 349-354. (c) Cai, M.Z.; Song, C.S.; Huang, X. *J. Chem. Soc., Perkin Trans.* 1, **1997**, 2273-2274.

[42] Prasada, A.S.; Satyanarayana, B. *J. Mol. Catal. A* **2013**, 370, 205-209.

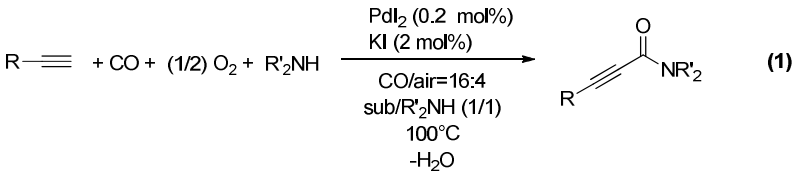
[43] (a) Ullah, E.; McNulty, J.; Sliwinski, M.; Robertson, A. *Tetrahedron Lett.* **2012**, 53, 3990-3993. (b) Qureshi, Z.S.; Deshmukh, K.M.; Tambade, P.J.; Bhanage, B.M.; *Synthesis* **2011**, 2, 243-250. (c) Wang, Y.; Liu, J.; Xia, C. *Tetrahedron Lett.* **2011**, 52, 14, 1587-1591.

Chapter 2

2.1 Divergent Palladium Iodide Catalyzed Multicomponent Carbonylative Approaches to Functionalized Isoindolinone and Isobenzofuranimine Derivatives

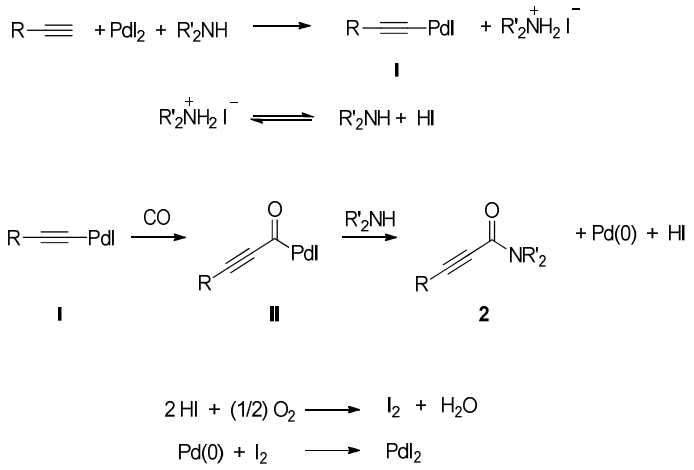
2.1.1 Synthesis of Carbonylated Isoindolinone Derivatives by PdI2-Catalyzed Aminocarbonylation−N-Heterocyclization of 2-Ethynylbenzamides

As known in the literature, the oxidative aminocarbonylation reaction of 1-alkynes leads to 2-yne-amide derivatives; the reaction is carried out with a secondary amine in ratio 1:1 with alkyne under 20 atmosphere of a mixture of carbon monoxide and oxygen (CO/air, 4:1)[1] in the presence of 0.2 mol% PdI_2 with 2 mol% of KI at a temperature of 100°C[2]. (*Eq. 1*)



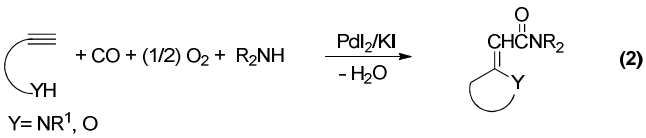
(1)

The catalytic process leading to 2-yne-amides occurs via formation of an alkynylpalladium species **I** as the key intermediate. Subsequent carbon monoxide insertion in the carbon-palladium bond followed by nucleophilic displacement on the acylpalladium intermediate **II** by the amine affords the product **2** and Pd(0). The latter is reoxidized according to a mechanism involving the oxygen present in the reaction, so that the catalytically active species PdI_2 is regenerated. (*Scheme 1*)



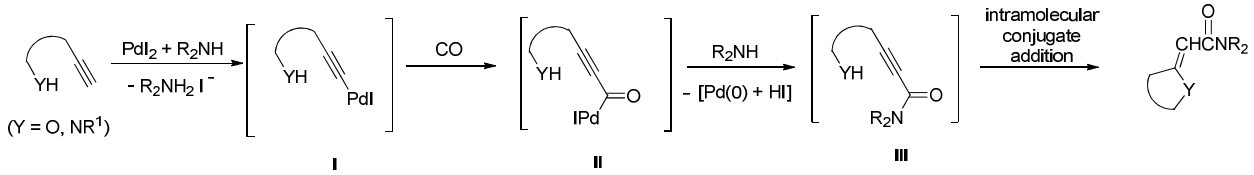
Scheme 1

Considering the study reported above we thought to verify the reactivity of acetylenic substrates bearing a suitably placed nucleophilic group under oxidative amino-carbonylation condition for the direct synthesis of carbonylated heterocycles.[3] (*Eq. 2*)



(2)

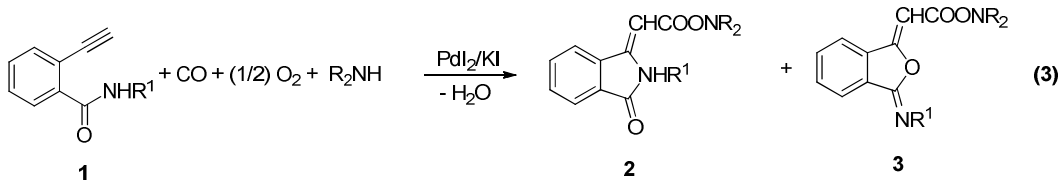
As shown in *Scheme 2* (anionic iodide ligands are omitted for clarity) formation of an alkynylpalladium intermediate **I** takes place by the reaction between acetylenic substrate, PdI_2, and the base, followed by CO insertion to give an alkynoylpalladium species **II**. Nucleophilic displacement by the amine then leads to the 2-ynamide intermediate **III** and Pd(0). The latter is reoxidized by the action of I_2 (formed in its turn by oxidation of HI, ensuing from the carbonylation process, and O_2).[4] As soon as the yne-amide **III** was formed, the nucleophilic group may give an intramolecular conjugate addition reaction that leads to the formation of the corresponding carbonylated heterocycle.



$Pd(0) + 2\,HI + (1/2)\,O_2 \longrightarrow PdI_2 + H_2O$

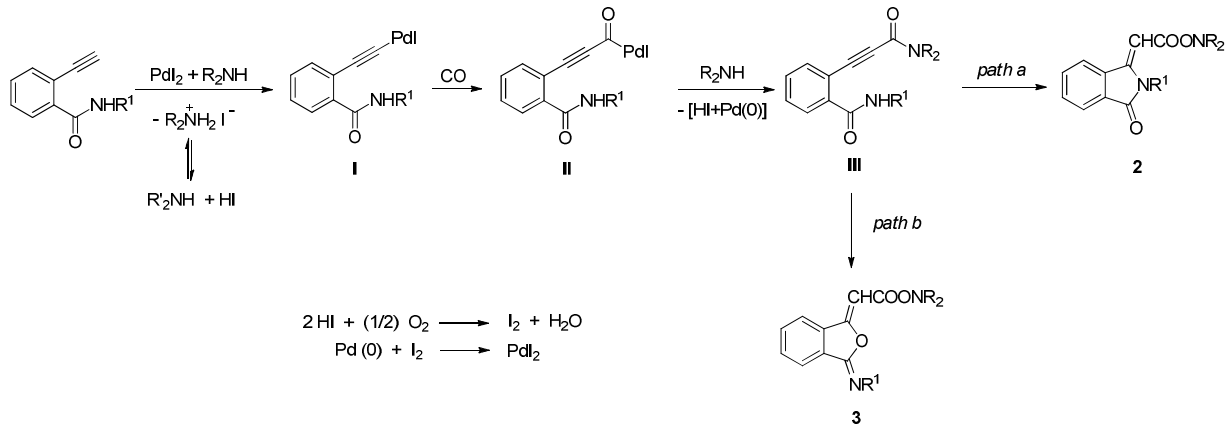
Scheme 2

In particular, in this thesis we tested the reactivity of 2-ethynylbenzamides in order to obtain isoindolinone derivatives **2** or isobenzofuran-yliden-imine derivatives **3** or both. (*Eq. 3*)



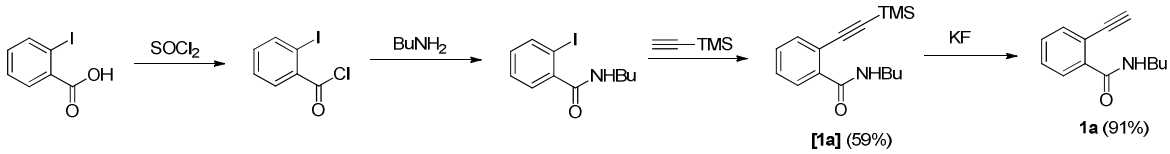
(3)

According to the reaction mechanism shown in *Scheme 2*, the formation of both products **2** and **3** correspond to the *5-exo-dig* intramolecular nucleophilic attack of the amide nitrogen (*path a*) or amide oxygen (*path b*) of intermediate **III** to the carbon-carbon triple bond. (*Scheme 3*)



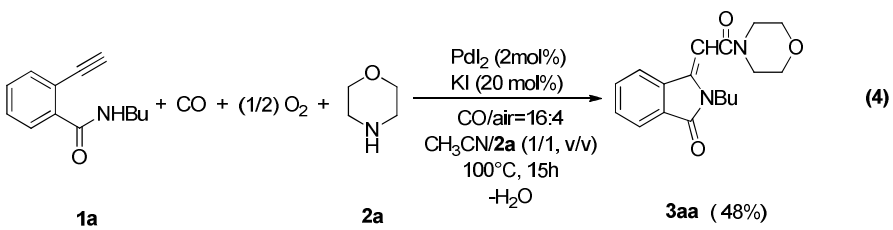
Scheme 3

The first substrate tested under PdI_2-catalyzed oxidative carbonylation conditions was *N*-butyl-2-ethynylbenzamide **1a** (R^1 = Bu), readily available by ethynylation of *N*-butyl-2-iodobenzamide. *N*-butyl-2-iodobenzamide, obtained in its turn starting from the 2-iodo-benzoic acid by two reaction step: synthesis of the acyl chloride followed by substitution with a primary amine to obtain the corresponding benzamide.[5] (*Scheme 4*)



Scheme 4

Substrate **1a** was initially allowed to react with CO, O_2, and morpholine (**2a**) at 100 °C for 15 h in a 1:1 (v/v) mixture of MeCN−morpholine as the solvent under a 4:1 mixture of CO−air (20 atm), in the presence of catalytic amounts of PdI_2 (2 mol %) in conjunction with KI (KI/PdI_2 molar ratio = 10). Under these conditions **1a** was exclusively converted into a ca. 2:1 *Z*/*E* mixture of 2-butyl-3-(2-morpholino-2- oxoethylidene)isoindolin-1-one **3aa** (*Scheme 3,* path a) which was isolated in 48% yield. (*Eq. 4*)



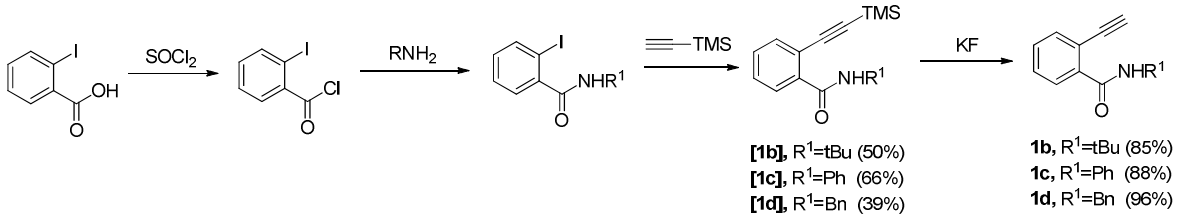
(4)

A brief optimization study was then carried out in which the gas total pressure, substrate concentration, temperature, the amount of KI and morpholine, and the nature of the solvent were changed. The results, shown in Table 1, allowed the identification of the optimal conditions for this process, which corresponded to 100 °C under 40 atm of a 4:1 mixture of CO−air, in a 2:1 mixture of MeCN−morpholine as the solvent (substrate concentration = 0.05 mmol per mL of solvent). Under these conditions, isoindolinone **3aa** was obtained in 81% yield after 5 h (Z/E = 2.0, *Table 1*, entry 12).

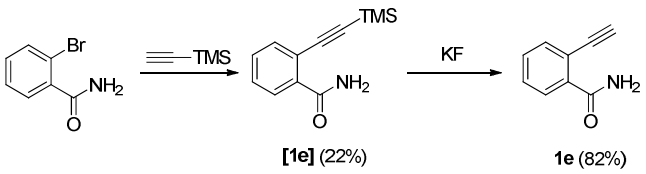
Table 1. *Optimization of reaction parameters*

entry	PdI_2/KI/2a	[sub] (mmol/ml)	P_{CO} (atm)	P_{air} (atm)	T (°C)	t (h)	CH_3CN/2a	Conv (%)	Yield 3aa (%)
1	1/10/50	0.05	16	4	100	15	1/1	100	48
2	1/10/50	0.05	32	8	100	15	1/1	100	70
3	1/10/50	0.05	32	8	80	15	1/1	100	61
4	1/5/50	0.05	32	8	100	15	1/1	100	59
5	1/10/50	0.1	32	8	100	15	1/1	100	58
7	1/10/50	0.05	32	8	100	15	Diox/**2a** 1:1	100	54
8	1/10/50	0.05	32	8	100	15	DME/**2a** 1:1	100	37
9	1/10/50	0.05	32	8	100	15	2/1	100	80
10	1/10/50	0.05	32	8	100	15	3/1	100	76
11	1/10/50	0.05	32	8	100	8	2/1	100	83
12	1/10/50	0.05	32	8	100	5	2/1	100	81

In order to generalize the process, *N*-substituted-2-ethynylbenzamides **2b-2d** were synthesized following the synthetic strategy previously described.[5] (*Scheme 5*) 2-Ethynylbenzamide **1e** instead was directly prepared from 2-bromobenzamide.[6] (*Scheme 6*)



Scheme 5



Scheme 6

The reactivity of substrates **1b**-**e**, bearing different substituents on nitrogen, was then tested with morpholine as the base and nucleophile (*Table 2*, entries 2−5). As can be seen from these data, the reaction also worked nicely with a benzyl (R^1 = Bn, *Table 2*, entry 2) and a phenyl (R^1 = Ph, *Table 1*, entry 3) substituent on nitrogen, with results similar to those obtained with R^1 = Bu (*Table 2*, entry 1). In both cases, the *Z* isomer was obtained as the major stereoisomer or sole diastereoisomer; the diastereoselectivity was higher with R^1 = Ph (**3ca-*Z***, only *Z*, *Table 1*, entry 3) with respect to R^1 = Bn (**3ba**, *Z*/*E* = 2.2, *Table 2*, entry 2). Quite predictably, the reaction was slower when the nitrogen was substituted with a bulky group, such as in substrate **1d** (R^1 = *t*-Bu, *Table 1*, entry 4); in any case, an excellent yield of the corresponding carbonylated isoindolinone **3da-*E*** was still obtained (93%). Moreover, in this case, complete diastereoselectivity toward the *E* isomer was observed, probably due to the necessity to minimize the steric repulsion between the bulky substituent and the morpholine ring. The structure of **3da-*E*** was confirmed by X-ray diffraction analysis, as shown in *Figure 1*. In the ^{1}H NMR spectrum of **3da-*E***, the olefinic proton absorbed at 6.1 ppm, so a chemical shift around 6 ppm could be considered diagnostic for an *E* configuration around the exocyclic double bond of diastereoisomers **3aa-*E*** and **3ba-*E***, while the olefinic proton for diastereoisomers **3aa-*Z***, **3ba-*Z***, and **3ca-*Z*** absorbed in the range 5.6−5.8 ppm. On the other hand, complete diastereoselectivity toward the isomer *Z* was observed when R^1 = H (**3ea-*Z***, *Table 2*, entry 5), due to the stabilization by intramolecular hydrogen bonding between the NH group and the carbonyl of the exocyclic amido group, as confirmed by the X-ray crystallographic analysis for **3ea-*Z***. (*Figure 2*)

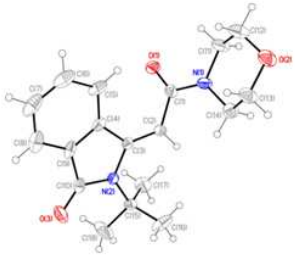


Figure 1

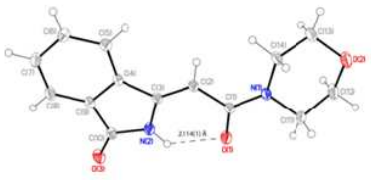
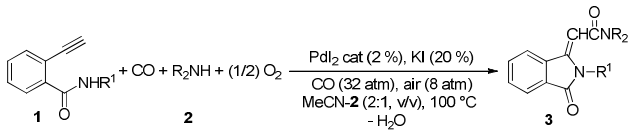
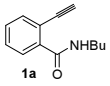
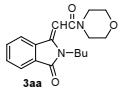
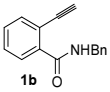
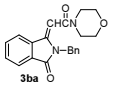
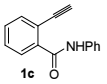
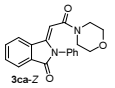
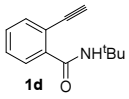
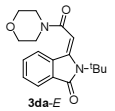
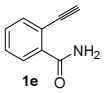
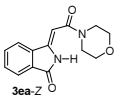
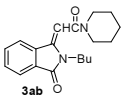
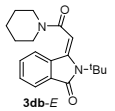
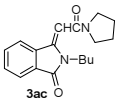
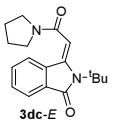
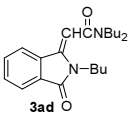


Figure 2

The nature of the secondary amine was also changed, with substrates **1a** (R^1 = Bu) and **1d** (R^1 = tert-butyl). As can be seen from the results reported in *Table 2*, entries 6−10, high to excellent yields of the corresponding isoindolinones (76−96%) were also observed working with other secondary nucleophilic cyclic or acyclic amines such as piperidine **2b** (*Table 2*, entries 6 and 7), pyrrolidine **2c** (*Table 2*, entries 8 and 9), or dibutylamine **2d** (*Table 2*, entry 10). With substrate **1d** (R^1 = *tert*-butyl), again complete *E* diastereoselectivity was observed in the final products **3db-*E*** and **3dc-*E*** (*Table 2*, entries 7 and 9). Finally hindered amines, such as diisopropylamine or amines with low basicity, like *N*-methylaniline, are unreactive. Clearly, the formation of alkynylpalladium complex **I** (and therefore of **II** and **III**, *Scheme 3*) is possible because the starting substrate **1a-e** bears a terminal triple bond. Accordingly, no reaction occurred with 2-alkynylbenzamides bearing an internal triple bond.

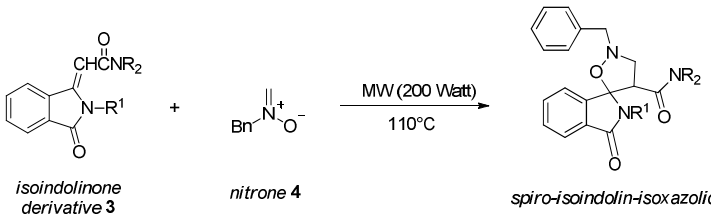
Table 2. *Scope*



entry	**1**	R^1	R_2NH	time (h)	**3**	yield of **3**[b] (%)
1	 **1a**	Bu	 **2a**	5	 **3aa**	81[c]
2	 **1b**	Bn	**2a**	5	 **3ba**	83[d]
3	 **1c**	Ph	**2a**	3	 **3ca**-*Z*	86[e]
4	 **1d**	*t*-Bu	**2a**	8	 **3da**-*E*	93[f]
5	 **1e**	H	**2a**	5	 **3ea**-*Z*	65[g]
6	**1a**	Bu	 **2b**	5	 **3ab**	90[h]
7	**1d**	*t*-Bu	**2b**	5	 **3db**-*E*	76[i]
8	**1a**	Bu	 **2c**	5	 **3ac**	86[j]
9	**1d**	*t*-Bu	**2c**	5	 **3dc**-*E*	82[i]
10	**1a**	Bu	Bu_2NH **2d**	5	 **3ad**	96[k]

[a] Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] *Z*/*E* ratio = 2.0 (determined by ^{1}H NMR). [d] *Z*/*E* ratio = 2.2 (determined by ^{1}H NMR). [e] The reaction was selective toward the formation of the *Z* isomer. [f] The reaction was selective toward the formation of the *E* isomer. The structure of **3da**-*E* was confirmed by X-ray diffraction analysis. [g] The reaction was selective toward the formation of the *Z* isomer. The structure of **3ea**-*Z* was confirmed by X-ray diffraction analysis. [h] *Z*/*E* ratio = 1.0 (determined by ^{1}H NMR). [i] The reaction was selective toward the formation of the E isomer. [j] *Z*/*E* ratio = 1.8 (determined by ^{1}H NMR). [k] *Z*/*E* ratio = 1.0 (determined by isolation of the diastereoisomers after column chromatography).

Isoindolinone derivatives **3aa**, **3ba**, **3ca-*Z***, **3da-*E***, **3ab**, **3ac** and **3db-*E*** were used as starting material to obtain the corresponding spiro-isoindolin isoxazolidines **5**. (*Eq. 5*)



(5)

Molecular docking studies showed that spiro-isoindolin isoxazolidines **5** are able to interact with the protein MDM2 in three points: the pocket of Leu26 (p53) contains the core cyclic amide, the pocket of the Trp23 (p53) contains the isoindolinic portion, while the pocket of Phe19 (p53) contains the N-benzyl portion of the isoxazolidinic ring. A further interaction stabilizing the complex is supplied by the hydrogen bond between Gly58 and the carbonyl of the isoindolinic core (*Figure 3*).

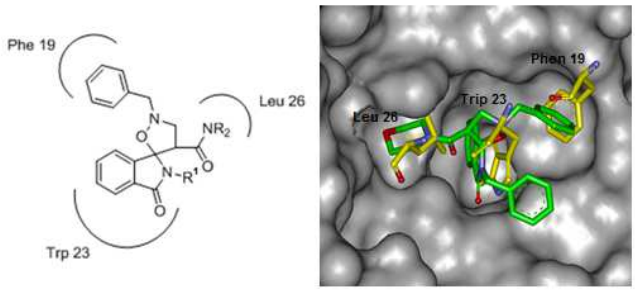


Figure 3

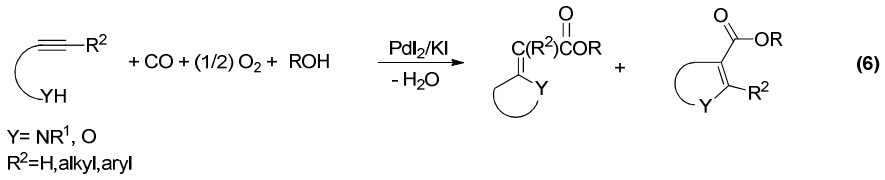
Thus, spiro-isoindolin isoxazolidines **5** work as inhibitors of the p53-MDM2 interaction: p53 is responsible of damage repairing as a result of insults to DNA and oncogenic activation but when MDM2 binds to p53 this kind of interaction induces its degradation; molecules able to act as inhibitors of p53-MDM2 interaction are therefore potential anticancer drugs. Biological test carried on compound **5** showed that these compounds have antiproliferative activity on cancer cell lines of neuroblastoma, colorectal adenocarcinoma and hepatocarcinoma in the µM range; in *Table 3* are reported data referring to IC50 of some rapresentative compounds.

Table 3. *EC50 (μM) of spiro-isoindolin isoxazolidines* ***5***

	SH-SY5Y *neuroblastoma*	**HT-29** *colorectal adenocarcinoma*	**HepG2** *hepatocarcinoma*
5aa (R^1=Bu; R^2=morpholine)	37	32	30
5ba (R^1=Bn; R^2=morpholine)	42	49	45
5da (R^1=*t*Bu; R^2=morpholine)	78	89	93
5ac (R^1=Bu; R^2=pyrrolydine)	41	51	43

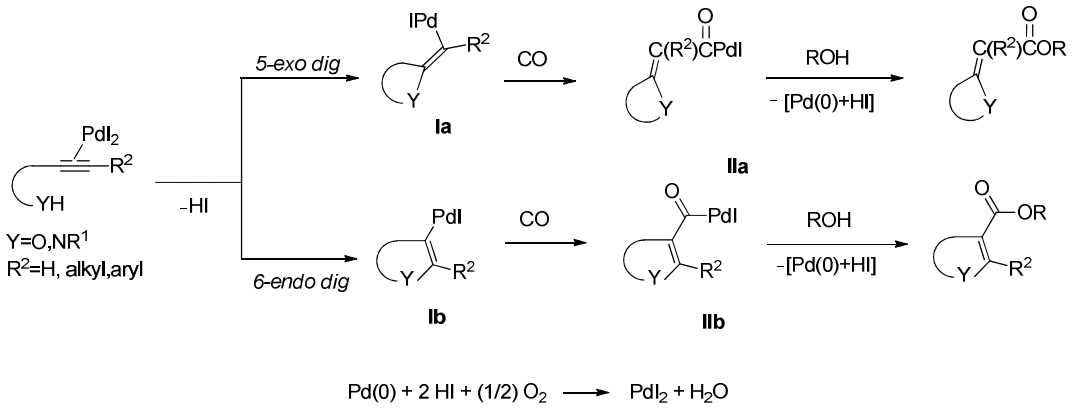
2.1.2 Synthesis of Carbonylated Isobenzofuranimine Derivatives by PdI_2-Catalyzed O-Heterocyclization–Alkoxycarbonylation of 2-Alkynylbenzamides

As known, substrates bearing an internal triple bond and a nucleophilic group in a suitable position, leads to the corresponding heterocyclization-carbonylation products if allowed to react under PdI_2-catalyzed oxidative alkoxycarbonylation conditions.[3,7,8] (*Eq. 6*)



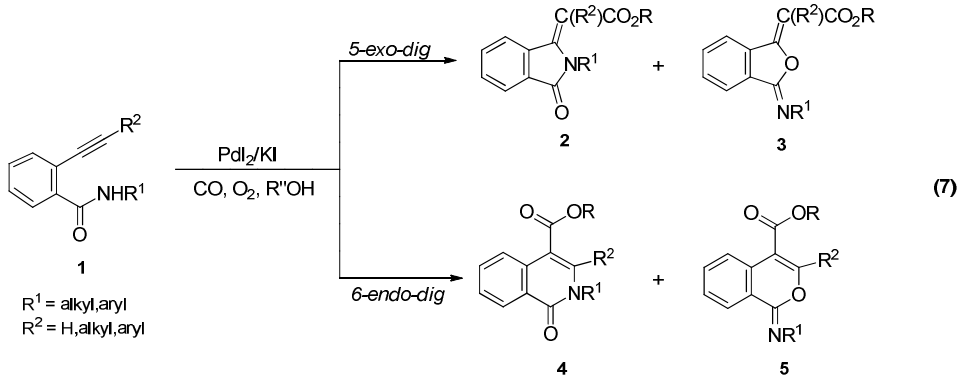
Y= NR^1, O
R^2=H,alkyl,aryl

A plausible reaction mechanism begin with the initial coordination of PdI_2 to the alkyne leading to electrophilic activation of the carbon-carbon triple bond; then intra-molecular nucleophilic attack (either *exo* or *endo*) by the nucleophilic group to the activated triple bond gives the vinylpalladium intermediate **Ia** and **Ib**. Subsequent carbon monoxide insertion in the carbon-palladium bond – with the formation of the acyl-Pd intermediate **IIa** and **IIb** - followed by nucleophilic displacement by ROH affords the product of alkoxycarbonylation and Pd(0). The latter is then reoxidized according to a mechanism involving the oxygen present in the reaction. (*Scheme 7*)

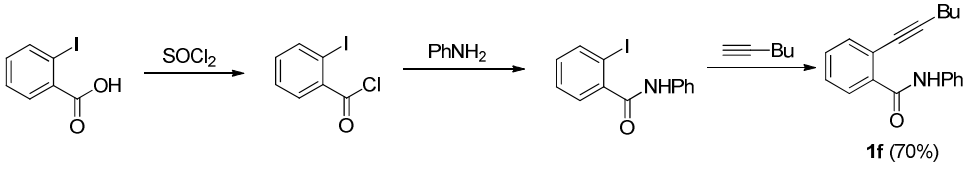


Scheme 7

According to this assumption, 2-alkynylbenzamides, under PdI_2-catalized oxidative carbonylation conditions, should react to give the isoindolinone **2** and the 3*H*-isobenzofuran-1-ylydenimine **3** (*5-exo dig attack*) and isoquinolinone **4** and isochromen-1-ylydenimine **5** (*6-endo dig attack*), as shown in *Eq. 7.*

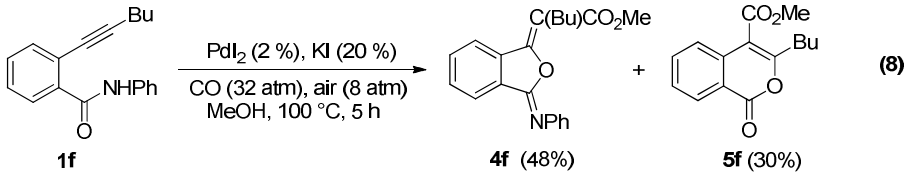


2-(Hex-1-ynyl)-N-phenylbenzamide **1a** is obtained starting from the 2-iodo-benzoic acid by three reaction step: firstly, synthesis of the acyl chloride; then substitution with a primary amine to obtain the corresponding benzamide which was allowed to react under Sonogashira coupling conditions to give the 2-alkynylbenzamide.[5] (*Scheme 8*)



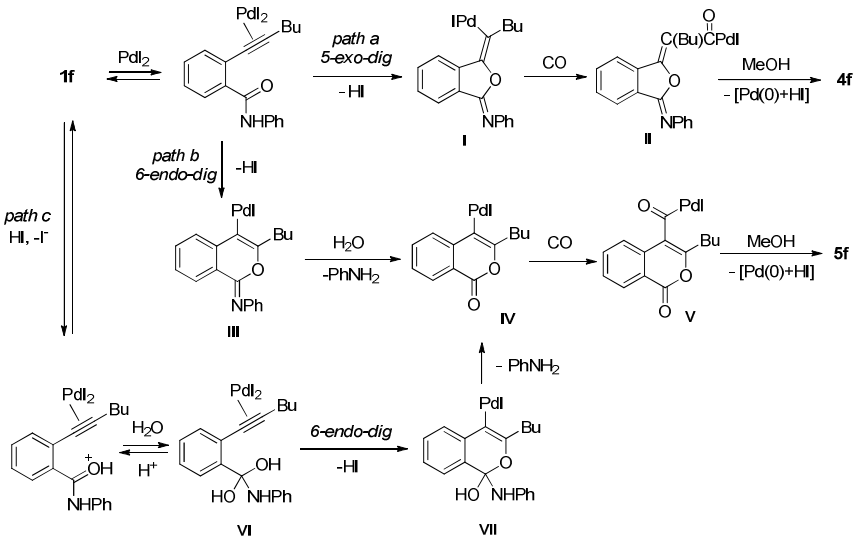
Scheme 8

2-(Hex-1-ynyl)-*N*-phenylbenzamide **1f** was allowed to react in MeOH as the solvent (M=0.02 mmol/mL) in the presence of 2 mol % PdI_2 and 20 mol % of KI, under 40 atm of a 4:1 mixture of CO–air at 100°C for 5 h. Under these reaction conditions, substrate **1f** underwent O-cyclization rather than N-cyclization, followed by alkoxycarbonylation, to give a mixture of methyl 2-[3-(phenylimino)isobenzofuran-1(3*H*)-ylidene]hexanoate **4f** (*Z*/*E* ca. 1.4) and methyl 3-butyl-1-oxo-1*H*-isochromene-4-carboxylate **5f.** (*Eq. 8*)



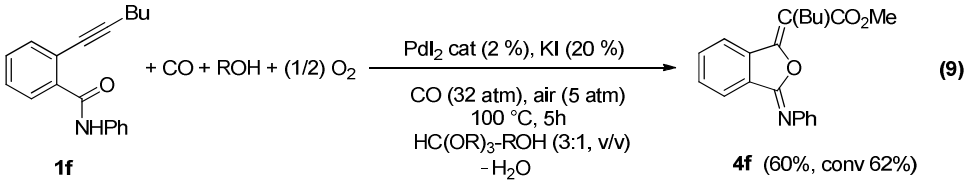
1f **4f** (48%) **5f** (30%)

Formation of **4f** clearly corresponded to the *5-exo-dig* nucleophilic attack of the amide oxygen to the coordinated triple bond to give the vinylpalladium complex **I** followed by alkoxycarbonylation (*Scheme 9*, *path a*. Partial isomerization of intermediate **I**[9] accounted for the formation of the E/Z mixture). On the other hand, the involvement of water with elimination of aniline is necessary to justify the formation of **5f**. It is conceivable that *6-endo-dig* nucleophilic attack of the amide oxygen to the coordinated triple bond gives the vinylpalladium complex **III**. Hydrolysis of the exocyclic imino group of **III** would then lead to the corresponding lactone-vinylpalladium intermediate **IV**, whose alkoxycarbonylation would eventually afford **5f** (*Scheme 9*, *path b*). However, the possibility of an HI promoted nucleophilic attack by water to the amidic carbonyl of **1f**, with formation of tetrahedral intermediate **VI**, cannot be ruled out. The latter would then undergo *6-endo-dig* O-cyclization to give complex VII, followed by elimination of aniline from the HO(C)NHPh moiety to afford the same lactone-vinylpalladium intermediate **IV** seen before (*Scheme 9*, *path c*).



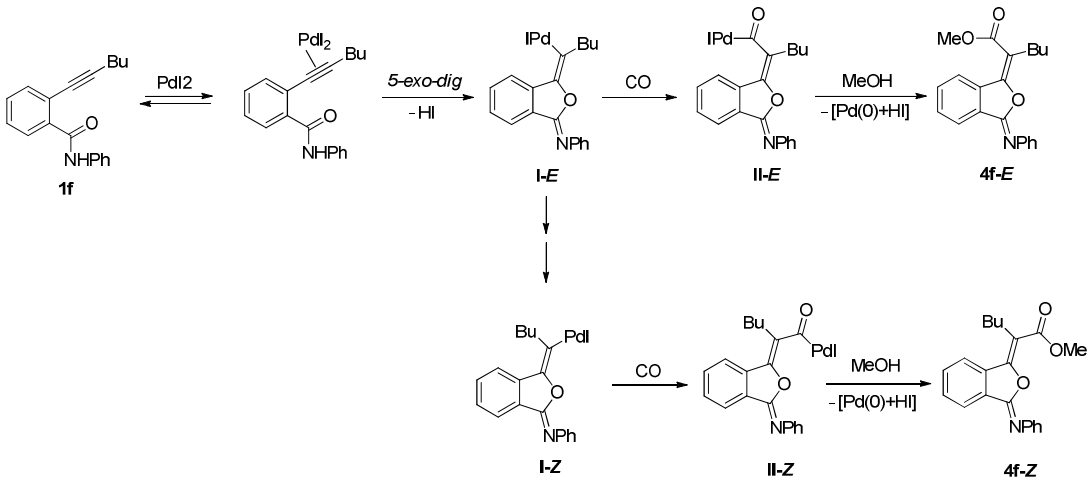
Scheme 9

In order to minimize the formation of byproduct **5f**, the next experiments were carried out in the presence of a dehydrating agent, such as trimethyl orthoformate. Indeed, when $HC(OMe)_3$ was used as a co-solvent together with MeOH (3:1 v/v), **2a** was selectively obtained in 60% yield, without any formation of **4f** . (*Eq. 9*)



(9)

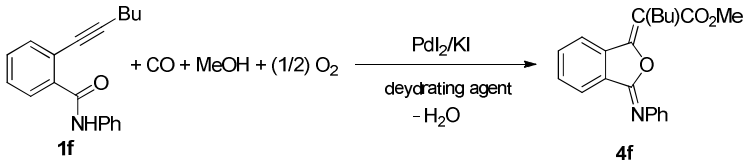
According to the mechanism described above, 5-*exo-dig* intramolecular nucleophilic attack of the amide oxygen to the activated carbon-carbon triple bond gives the vinylpalladium complex **I-*E***. Partial isomerization of intermediate **I-*E*** leads to the vinylpalladium complex **I-*Z*** . Then alkoxycarbonylation occurs. (*Scheme 10*).



Scheme 10

Starting from this encouraging initial result, we made a screening of the reaction parameters by changing time by time gas pressure, substrate concentration, catalyst amount, , solvent/dehydrating agent ratio, temperature and reaction time. We observed that either decreasing gas pressure or increasing substrate concentration the yield of desired product decreased because of the cycloisomerization of **1f** (*Table 4*, entries 2-3). We also verified how the amount of KI influences the catalyst activity (*Table 4*, entries 4-5) and the best result was obtained when the amount of KI was equal to 10 times the amount of PdI_2. Decreasing the temperature, we obtained the desired products in a lower yield (*Table 4*, entry 6). When the reaction was carried out with a dehydrating agent in a 2:1 ratio with MeOH, the yield was good as when dehydrating agent was used in ratio 3:1 (*Table 4*, entries 7-8); on the other hand, unsatisfactory results were obtained when the dehydrating agent amount was reduced or trimethyl orthoformate was substituted with trimethyl orthoacetate (*Table 4*, entries 9). Finally complete substrate conversion was achieved when the reaction time was increased to 8 h (*Table 4*, entries 10). Increasing the reaction time from 8 h to 15 h the yield remained unchanged, suggesting that product is rather stable at 100°C (*Table 4*, entry 11).

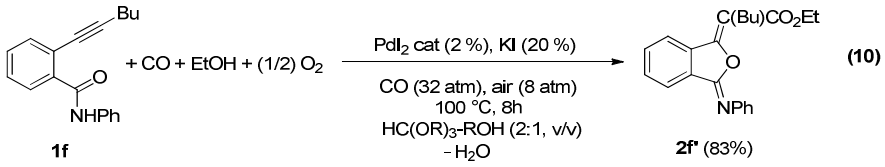
Table 4. *Optimization of reaction parameters*



entry	PdI_2/KI/1f	[sub]	MeOH/$HC(OMe)_3$	P_{CO}	P_{air}	T(°C)	t(h)	conv (%)	yield 4f (%)
1	1/10/50	0.02	1/3	32	8	100	5	62	60
2	1/10/50	0.02	1/3	16	4	100	5	77	34
3	1/10/50	0.05	1/3	32	8	100	5	90	44
4	1/5/50	0.02	1/3	32	8	100	5	79	50
5	1/20/50	0.02	1/3	32	8	100	5	92	23
6	1/10/50	0.02	1/3	32	8	80	5	38	37
7	1/10/50	0.02	1/2	32	8	100	5	64	58
8	1/10/50	0.02	1/1	32	8	100	5	79	16
9	1/10/50	0.02	1/2[a]	32	8	100	5	11	9
10	1/10/50	0.02	1/2	32	8	100	8	100	80
11	1/10/50	0.02	1/2	32	8	100	15	100	79

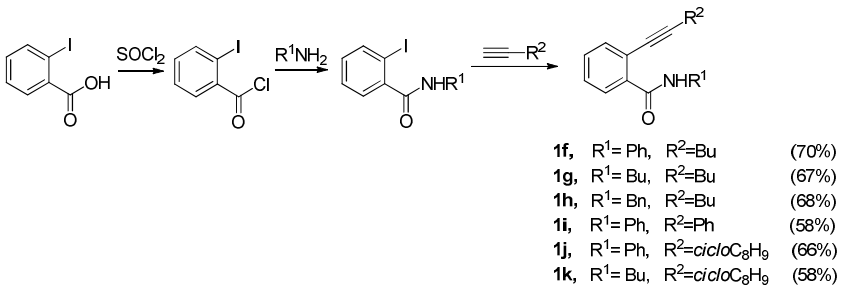
[a] MeOH/[$MeC(OMe)_3$]

The reaction with a higher alcohol, such as ethanol (R = Et), also afforded a high yield of the corresponding isobenzofuranimine derivative **3f'** (83% yield). (*Eq. 10*)



(10)

In order to verify if the process was general, different kind of starting materials were synthesized, as shown before. (*Scheme 11*)



1f, R^1= Ph, R^2=Bu (70%)
1g, R^1= Bu, R^2=Bu (67%)
1h, R^1= Bn, R^2=Bu (68%)
1i, R^1= Ph, R^2=Ph (58%)
1j, R^1= Ph, R^2=*cicloC*$_8$H$_9$ (66%)
1k, R^1= Bu, R^2=*cicloC*$_8$H$_9$ (58%)

Scheme 11

The protocol was thus extended to other 2-alkynylbenzamides bearing different substituents on nitrogen and on the triple bond. As shown in *Table 5*, the nitrogen could be successfully substituted with an alkyl or a benzyl group, while the triple bond could also bear a phenyl or a 1-cyclohexenyl group. The reaction also worked nicely with a terminal triple bond, as shown by entries 8−12. In this latter case, the process was consistently selective toward the formation of the *E* stereoisomer. The structure of representative products, in particular (*E*)-methyl 2-[3-(tert-butylimino)-isobenzofuran-1(3*H*)-ylidene]acetate **2d-*E*** and (*E*)-methyl 2-[3-(phenylimino)isobenzofuran-1(3*H*)-ylidene]-2-phenylacetate **2i-*E*** was confirmed by X-ray diffractometric analysis as shown in *Figures 4* and *5*. A chemical shift for the olefinic proton around 6.0 ppm was diagnostic of *E* stereochemistry for products **4a-*E***, **4a'-*E***, **4b-*E***, **4c-*E***, and **4d-*E***. On the other hand, for products **4f–k**, the chemical shift of aromatic proton at ca. 8.2−8.4 ppm was diagnostic for the *E* diastereoisomer, while the aromatic absorptions at ca. 8.5 ppm and 7.9−8.0 ppm were characteristic of the *Z* distereoisomer.

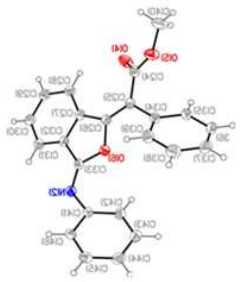


Figure 4

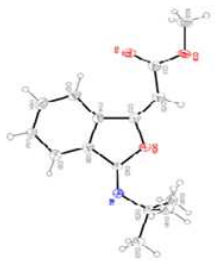
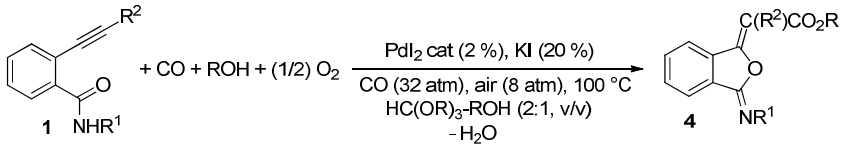
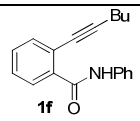
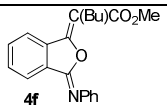
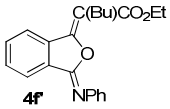
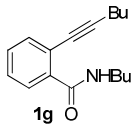
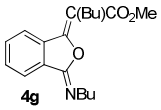
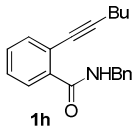
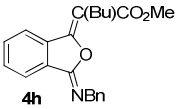
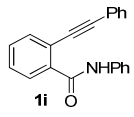
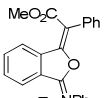
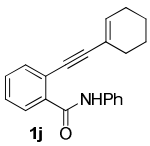
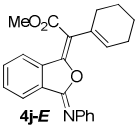
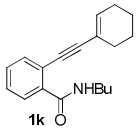
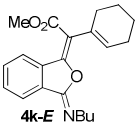
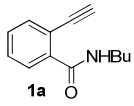
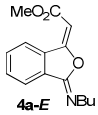
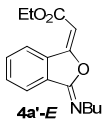
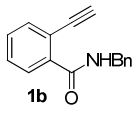
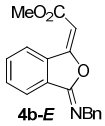
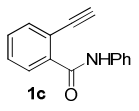
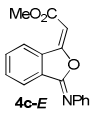
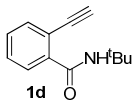
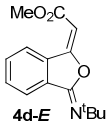


Figure 5

Table 5. *Scope*



entry	1	R^1	R^2	R	time (h)	4	yield of **2**[b] (%)
1	 **1f**	Ph	Bu	Me	8	 **4f**	80[c]
2	**1f**	Ph	Bu	Et	15	 **4f'**	83[d]
3	 **1g**	Bu	Bu	Me	5	 **4g**	75[e]
4	 **1h**	Bn	Bu	Me	15	 **4h**	45[f]
5	 **1i**	Ph	Ph	Me	15	 **4i-*E***	55[g]
6	 **1j**	Ph	1-cyclohexyl	Me	5	 **4j-*E***	78[h]
7	 **1k**	Bu	1-cyclohexyl	Me	5	 **4k-*E***	68[h]
8	 **1a**	Bu	H	Me	5	 **4a-*E***	70[h]
9	**1a**	Bu	H	Et	5	 **4a'-*E***	70[h]

10	 **1b**	Bn	H	Me	8	 **4b-*E***	60[h]
11	 **1c**	Ph	H	Me	5	 **4c-*E***	58[h]
12	 **1d**	*t*-Bu	H	Me	5	 **4d-*E***	70[i]

[a] Conversion of **1** was quantitative in all cases. [b] Isolated yield based on starting 1. [c] *Z*/*E* ratio = 1.4 (determined by ^{1}H NMR). [d] *Z*/*E* ratio ca. 1:1 (determined by ^{1}H NMR). [e] *E*/*Z* ratio = 6.2 (determined by ^{1}H NMR). [f] *E*/*Z* ratio = 4.9 (determined by ^{1}H NMR). [g] The reaction was selective toward the formation of the *E* isomer.. [h] The reaction was selective toward the formation of the *E* isomer. [i] The reaction was selective toward the formation of the *E* isomer.

Finally, the potential herbicidal activity of €-methyl 2-[3-(butylimino)isobenzofuran-1(3*H*)-ylidene]acetate **4a-*E*** and €-methyl 2- [3-(phenylimino)isobenzofuran-1(3H)-ylidene]-2-phenylacetate **2i-*E*** has been tested. Both compounds showed a strong phytotoxic effect on shoot and root systems of *Arabidopsis thaliana*, a weed which compete with crops for edaphic resources such as water and nutrients. The effects observed on the shoot were similar for both molecules, but while compound **2a-*E*** showed a stronger effect on root parameters, such as primary root length, root hair and density (*Figure 6*), compound **2i-*E*** caused important malformations in root morphology (*Figure 7*).

Figura 6

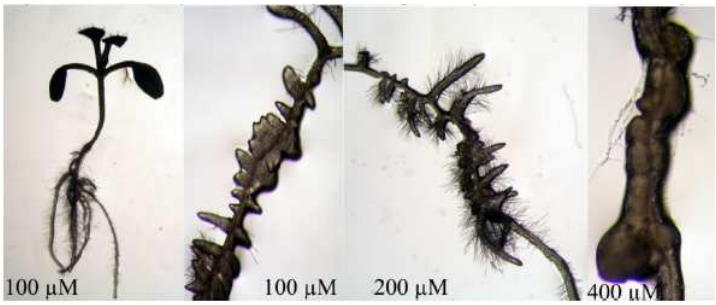


Figura 7

Even if the two molecules had different effects on root growth, a hormonal involvement has been suggested in both cases. Moreover, it is possible that the effects on the aerial part, similar for both molecules, are due to an indirect effect of the strong alterations on root morphology and anatomy. It is well known that the root system plays a crucial role on nutrient uptake, and an alteration of its function could be responsible for the limited nutrient supply and consequently for shoot form and function. All this results indicate that these isobenzofuran-1-imines are very promising synthetic herbicides[10].

2.2 General Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ or DMSO-d_6 solutions at 300 or 500 MHz and 75 or 126 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and hertz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC−MS apparatus at 70 eV ionization voltage. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70−230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

2.2.1 Preparation of N-Substituted 2-Alkynylbenzamides 1a−d,f−k

2-Alkynylbenzamides **1a−d**,**f−k** were prepared by coupling between the corresponding 2-iodobenzamide and the suitable terminal alkyne, followed (in the case of trimethylsilylacetylene) by deprotection, as described below. 2-Ethynylbenzamide **1e** was

prepared in a similar manner from 2- bromobenzamide according to a literature procedure.[11] All other materials were commercially available and were used without further purification.

First Step: **Preparation of 2-Iodobenzamides**

The method of Kundu and Khan[12] was employed. To a stirred solution of 2-iodobenzoyl chloride[13] (4.4 g, 16.5 mmol) in anhydrous benzene (43 mL) was slowly added, under nitrogen and dropwise, a solution of RNH_2 (33.3 mmol; R = Bu, 2.44 g; R = Bn, 3.57 g; R = Ph, 3.10 g; R = t-Bu, 2.44 g) in anhydrous benzene (15 mL). The resulting mixture was taken up with Et_2O (100 mL) and transferred in a separatory funnel. Aqueous HCl (1 M, 70 mL) was added, and the organic layer was separated and washed again with 1 M HCl (2 × 70 mL), satd Na_2CO_3 (3 × 70 mL), and water (3 × 70 mL). After drying over Na_2SO_4, the solvent was evaporated, and the crude 2-iodobenzamide thus obtained used as such for the next step.

Second Step: **Sonogashira Coupling To Give *N*-Substituted 2-[(2-Trimethylsilyl)ethynyl)]benzamides and 2-Alkynylbenzamides 1f–k**

The method of Kundu and Khan[12] was employed. A mixture of the crude 2-iodobenzamide (obtained as described above, formally corresponding to 16.5 mmol), $(Ph_3P)_2PdCl_2$ (405 mg, 0.58 mmol), CuI (251 mg, 1.32 mmol), and Et_3N (6.7 g, 66 mmol) in anhydrous DMF (82 mL) was stirred under nitrogen for 1 h. The 1-alkyne (19.8 mmol; trimethylsilylacetylene, 1.95 g; 1-hexyne, 1.63 g; phenylacetylene, 2.02 g; 1-ethynylcyclohex-1-ene, 2.10 g) was added under nitrogen, and the resulting mixture allowed to stir at 80–85 °C for 15 h. After cooling, CH_2Cl_2 was added (100 mL) followed by water (70 mL). The phases were separated, and the organic layer was washed with water (2 × 70 mL). After drying over Na_2SO_4, the product was purified by column chromatography on silica gel using as eluent 9:1 hexane–AcOEt (*N*-phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide, *N*-benzyl- 2-[2-(trimethylsilyl)ethynyl]benzamide, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**), or 8:2 hexane–AcOEt (*N*-butyl-2-[2-(trimethylsilyl)ethynyl]- benzamide, *N*-tert-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide).

Deprotection Step To Give *N*-Substituted 2-Ethynylbenzamides 1a–d

To a solution of 2-[2-(trimethylsilyl)ethynyl]benzamide obtained as described above (5.14 mmol; *N*-butyl-2-[2- (trimethylsilyl)ethynyl]benzamide, 1.4 g; *N*-tert-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide, 1.4 g; *N*-phenyl-2-[2- (trimethylsilyl)ethynyl]benzamide, 1.5 g; *N*-benzyl-2-[2- (trimethylsilyl)ethynyl]benzamide, 1.6 g) in MeOH (25 mL) was added KF (1.06

g, 18.2 mmol), and the resulting mixture was allowed to stir at room temperature for 2 h. The solvent was evaporated, and the residue was taken up with Et_2O (40 mL) and washed with water (40 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL), and the collected organic phases were dried over $MgSO_4$. After filtration, the solvent was evaporated to give the *N*-substituted 2- ethynylbenzamide, which was sufficiently pure for the carbonylation reactions.

2.2.2 General Procedure for the PdI_2-Catalyzed Aminocarbonylation−N-Heterocyclization of 2-Ethynylbenzamides 1a−e To Give Carbonylated Isoindolinone Derivatives 3

A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39 × 10−2 mmol), KI (23.0 mg, 1.39 × 10−1 mmol), and a solution of **1** [**1a** (141 mg), **1b** (165 mg), **1c** (155 mg), **1d** (141 mg), **1e** (102 mg); 0.70 mmol] in a 2:1 mixture MeCN−amine (MeCN: 9.4 mL; amine 2: 4.6 mL). The autoclave was sealed, and while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 1), the autoclave was cooled, degassed, and opened. When necessary, the mixture was filtered (to remove the solid oxamide byproduct deriving from double carbonylation of **2**) and the solid washed with cold Et_2O. The solvent was evaporated, and the products were purified by column chromatography on silica gel to give pure carbonylated isoindolinones **3** (eluent: chloroform for **3aa**; 7:3 hexane−AcOEt for **3ca-*Z*** and **3da-*E***; 8:2 hexane−AcOEt for **3ea-*Z***; 9:1 hexane−AcOEt for **3db-*E***) or neutral alumina (eluent: 8:2 hexane−AcOEt for **3ba**; 7:3 hexane−AcOEt for **3ab** and **3ad**; 9:1 hexane−AcOEt for **3ac**; 99:1 hexane−AcOEt for **3dc-*E***). In the case of **3aa**, **3ba**, **3ab**, and **3ac** an inseparable mixture of the *Z* and *E* diastereoisomers was obtained. In the case of **3ad**, it was possible to separate the *Z* and *E* isomers (order of elution: *E*, *Z*).

2.2.3 General Procedure for the Synthesis of 3-[(Alkoxycarbonyl)methylene]-isobenzofuran-1(3H)imines 4 by PdI_2-Catalyzed O-Heterocyclization−Alkoxycarbonylation of 2-Alkynylbenzamides 1a−d and 1f−k

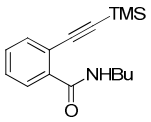
A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39 × 10−2 mmol), KI (23.0 mg, 1.39 × 10−1 mmol), and a solution of **1** [**1a** (141 mg), **1b** (165 mg), **1c** (155 mg), **1d** (141 mg), **1f** (194 mg), **1g** (180 mg), **1h** (204 mg), **1i** (208 mg), **1j** (211 mg), **1k** (197

mg); 0.70 mmol] in a ROH/$HC(OR)_3$ mixture [R = Me, Et; ROH: 11.6 mL; $HC(OR)_3$: 23.1 mL]. The autoclave was sealed, and while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for the required time (see Table 5), the autoclave was cooled, degassed, and opened. The solvent was evaporated, and the products were purified by column chromatography on neutral alumina to give pure **3** [(alkoxycarbonyl)- methylene]isobenzofuran-1(3*H*)imines **4** (eluent: 95:5 hexane− AcOEt for **4a-*E***, **4c-*E***, **4d-*E***, **4f**, **4f'**, **4g**, **4h**, **4i-*E***, **4j-*E***, and **4k-*E***; 9:1 hexane−AcOEt for **4a'-*E*** and **4b-*E***).

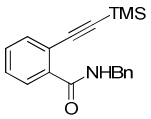
2.2.4 Formation of a Mixture of Methyl 2-[3-(Phenylimino)-isobenzofuran-1(3*H*)-ylidene]hexanoate 4f and Methyl 3-Butyl-1-oxo-1H-isochromene-4-carboxylate 5f by PdI_2-Catalyzed Heterocyclization−Alkoxycarbonylation of 2-(Hex-1-ynyl)-*N*-phenylbenzamide 1f (*Eq. 8*)

A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.6 mg, 1.0 × 10−2 mmol), KI (16.8 mg, 0.1 mmol), and a solution of **1f** (140 mg, 0.5 mmol) in MeOH (25 mL). The autoclave was sealed, and while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100 °C for 5 h, the autoclave was cooled, degassed, and opened. The solvent was evaporated, and the products were separated by column chromatography on neutral alumina (eluent: hexane−AcOEt from 99:1 to 95:5) to give methyl 3-butyl-1-oxo-1*H*-isochromene-4-carboxylate **5f** and methyl 2-[3-(phenylimino)isobenzofuran-1(3*H*)-ylidene]hexanoate **4f** (*Z*/*E* ca. 1.4, by ^{1}H NMR) in that order.

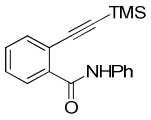
2.3 Characterization Data



N-Butyl-2-[2-(trimethylsilyl)ethynyl]benzamide: [14] yield 2.66 g, starting from crude *N*-butyl-2-iodobenzamide and trimethylsilylacetylene (59%); yellow oil; IR (film) ν = 3391 (w, br), 3304 (m, br), 2959 (m), 2157 (m), 1648 (m), 1536 (m), 1475 (w), 1304 (m), 1250 (m), 872 (m), 844 (s), 758 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.12−8.08 (m, 1 H), 7.68 (s, br, 1 H), 7.53 (dd, J = 7.3, 1.2, 1 H), 7.47−7.36 (m, 2 H), 3.53−3.45 (m, 2 H), 1.63 (quintuplet, J = 7.3, 2 H), 1.44 (sextuplet, J = 7.3, 2 H), 0.97 (t, J = 7.3, 3 H), 0.29 (s, 9 H); ^{13}C NMR (126 MHz, CDCl3) δ = 166.0, 135.7, 134.2, 130.5, 130.4, 129.3, 119.4, 103.9, 101.7, 40.1, 31.9, 20.6, 14.0, 0.00; GC−MS m/z = 273 (4) [M^+], 272 (5), 258 (22), 244 (7), 230 (15), 217 (31), 202 (73), 201 (80), 187 (100), 172 (7), 161 (13), 145 (17), 143 (26), 128 (12), 115 (8), 93 (23), 75 (22). Anal. Calcd for $C_{16}H_{23}NOSi$ (273.45): C, 70.28; H, 8.48; N, 5.12; Si, 10.27. Found: C, 70.32; H, 8.45; N, 5.14; Si, 10.31.

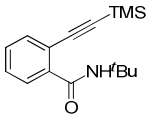


N-Benzyl-2-[2-(trimethylsilyl]ethynyl]benzamide: [15] yield 2.98 g, starting from crude *N*-benzyl-2-iodobenzamide and trimethylsilylacetylene (59%); yellow solid; mp 80−82 °C; IR (KBr) ν = 3383 (m), 3299 (w), 2154 (m), 1652 (s), 1533 (m), 1296 (m), 1250 (m), 866 (s), 844 (s), cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 8.23−8.10 (m, 2 H, 1 H), 7.60−7.49 (m, 1 H), 7.48−7.23 (m, 7 H), 4.67 (d, J = 5.5, 2 H), 0.11 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 165.7, 138.0, 134.8, 134.1, 130.6, 130.4, 129.2, 128.7, 127.8, 127.5, 119.4, 103.6, 102.1, 44.1, −0.5; GC−MS m/z = 307 (32) [M^+], 306 (47), 292 (19), 290 (22), 276 (5), 234 (20), 216 (22), 201 (27), 187 (91), 159 (14), 143 (17), 129 (11), 106 (11), 91 (100), 75 (27), 73 (42). Anal. Calcd for $C_{19}H_{21}NOSi$ (307.46): C, 74.22; H, 6.88; N, 4.56; Si, 9.13. Found: C, 74.19; H, 6.85; N, 4.59; Si, 9.12.

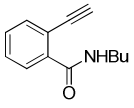


N-Phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide: yield 3.20 g, starting from crude 2-iodo-*N*-phenylbenzamide and trimethylsilylacetylene (66%); yellow solid; mp 97−98 °C (lit.[12] mp 95−96 °C, lit.[16] mp 96−97 °C); IR (KBr) ν = 3303 (m, br), 2959 (w), 2157 (m), 1660 (s), 1601 (m), 1541 (s), 1500 (m), 1447 (m), 1323 (m), 1250 (m), 868 (s), 844 (s), 756 (m) cm^{-1}; ^1H NMR (500 MHz, CDCl3) δ = 9.29 (s, br, 1 H), 8.13−8.09 (m, 1 H), 7.68 (d, J = 7.9, 2 H), 7.60−7.55 (m, 1 H), 7.48−7.40 (m, 2 H), 7.37 (t, J = 7.9, 2 H), 7.18−7.12 (t, J = 7.3, 1 H), 0.23 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.1, 138.0, 136.0, 134.0, 130.8,

130.3, 129.3, 129.0, 124.5, 120.3, 119.5, 103.1, 102.8, −0.18; GC−MS *m*/*z* = 293 (11) [M^+], 278 (5), 219 (6), 201 (100), 161 (7), 145 (12), 143 (9), 117 (5). Anal. Calcd for $C_{18}H_{19}NOSi$ (293.44): C, 73.68; H, 6.53; N, 4.77; Si, 9.57. Found: C, 73.62; H, 6.50; N, 4.78; Si, 9.62.

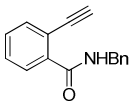


N-tert-Butyl-2-[2-(trimethylsilyl)ethynyl]benzamide: yield 2.25 g, starting from crude *N-tert*-butyl-2-iodobenzamide (50%) and trimethylsilylacetylene; yellow solid mp 58−59 °C; IR (KBr) *v* = 3293 (m, br), 2962 (m), 2161 (m), 1643 (s), 1598 (w), 1539 (s), 1478 (w), 1447 (w), 1362 (w), 1324 (m), 1249 (m), 1222 (m), 842 (s), 753 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.3, 1 H), 7.50 (d, *J* = 7.3, 1 H), 7.43−7.31 (m, 2 H), 7.22 (s, br, 1 H), 1.49 (s, 9 H), 0.28 (s, 9 H); ^{13}C NMR (126 MHz, CDCl3) δ = 165.5, 137.1, 134.3, 130.0, 129.7, 129.1, 119.3, 103.6, 101.3, 52.1, 28.9, 0.0; GC−MS *m*/*z* = 273 (3) [M^+], 258 (4), 217 (67), 202 (100), 184 (24), 161 (5), 145 (12), 143 (24), 121 (15), 75 (20). Anal. Calcd for $C_{16}H_{23}NOSi$ (273.45): C, 70.28; H, 8.48; N, 5.12; Si, 10.27. Found: C, 70.30; H, 8.44; N, 5.16; Si, 10.24.



1a

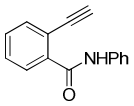
N-Butyl-2-ethynylbenzamide (**1a**): yield 0.941 g, starting from 1.40 g of *N*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide (91%); yellow solid; mp 53−54 °C (lit.[11] mp 58−60 °C); IR (KBr) *v* = 3296 (s, br), 3253 (s, br), 2950 (m), 2869 (m), 2106 (vw), 1655 (s), 1547 (s), 1468 (m), 1351 (m), 1258 (m), 1151 (m), 1099 (w), 942 (w), 856 (w), 761 (m), 694 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.97− 7.90 (m, 1 H), 7.57−7.52 (m, 1 H), 7.47−7.35 (m, 2 H), 6.88 (s, br, 1 H), 3.48 (s, 1 H), 3.47 (q, *J* = 6.6, 2 H), 1.68−1.55 (m, 2 H), 1.51− 1.36 (m, 2 H), 0.95 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.2, 137.1, 134.0, 130.2, 129.7, 129.3, 118.4, 83.3, 82.3, 39.9, 31.4, 20.3, 13.7; GC−MS *m*/*z* = 201 (absent) [M^+], 200 (2), 186 (7), 172 (9), 159 (26), 158 (26), 146 (12), 145 (60), 130 (21), 129 (100), 102 (11), 101 (45), 75 (18). Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.61; H, 7.54; N, 6.97.



1b

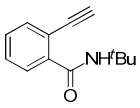
N-Benzyl-2-ethynylbenzamide (**1b**): yield 1.16 g, starting from 1.60 g of *N*-benzyl-2-[2-(trimethylsilyl]ethynyl]benzamide (96%); colorless solid; mp 87−88 °C; IR (KBr) *v* = 3286 (s, br), 3062 (w), 2112 (vw), 1643 (s), 1543 (m), 1428 (w), 1310 (m), 1239 (w), 764 (m), 701 (m), 669 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.98−7.91 (m, 1 H), 7.55−7.20 (m, 9 H), 4.65 (d, *J* = 5.6, 2 H), 3.32 (s, 1 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ = 166.2, 137.9, 136.6, 134.0, 130.4, 129.7, 129.3, 128.6, 127.9, 127.5, 118.6, 83.6, 82.1, 44.3 ; GC–MS *m*/*z* = 235 (61) [M^+], 234 (79), 218 (67), 216 (27), 189 (30), 130 (25), 129 (69), 102 (54), 101 (100), 91 (72), 77 (24), 75 (47), 65 (24), 51 (33). Anal. Calcd for $C_{16}H_{13}NO$ (235.28): C, 81.68; H, 5.57; N, 5.95. Found: C, 81.65; H, 5.56; N, 5.98.



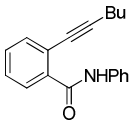
1c

2-Ethynyl-N-phenylbenzamide (**1c**): yield 1.00 g, starting from 1.50 g of *N*-phenyl-2-[2-(trimethylsilyl)ethynyl]benzamide (88%); yellow solid; mp 94–97 °C (lit.[16] mp 95–98 °C); IR (KBr) ν = 3282 (s, br), 3130 (w), 2107 (vw), 1647 (s), 1596 (m), 1538 (m), 1491 (w), 1446 (m), 1326 (m), 1256 (w), 754 (m), 675 (m), 633 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 9.00 (s, br, 1 H), 8.07–8.02 (m, 1 H), 7.67 (d, *J* = 7.9, 2 H), 7.63–7.58 (m, 1 H), 7.51–7.43 (m, 2 H), 7.37 (t, *J* = 7.9, 2 H), 7.19–7.13 (m, 1 H), 3.59 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 164.2, 138.0, 136.9, 134.2, 130.8, 130.1, 129.6, 129.1, 124.6, 120.1, 118.4, 84.3, 82.0; GC–MS *m*/*z* = 221 (99) [M^+], 220 (100), 193 (16), 178 (5), 165 (34), 152 (5), 130 (4), 102 (6), 95 (10), 77 (18), 51 (15). Anal. Calcd for $C_{15}H_{11}NO$ (221.25): C, 81.43; H, 5.01; N, 6.33. Found: C, 81.40; H, 5.02; N, 6.31.



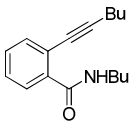
1d

N-tert-Butyl-2-ethynylbenzamide (**1d**): yield 0.88 g, starting from 1.40 g of *N-tert*-butyl-2-[2-(trimethylsilyl)ethynyl]benzamide (85%); yellow solid; mp 62.5–63.5 °C; IR (KBr) *v* = 3260 (s, br), 3069 (m), 2966 (m), 2106 (vw), 1634 (s), 1550 (s), 1448 (m), 1391 (w), 1364 (m), 1227 (s), 953 (w), 877 (m), 754 (s), 654 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 7.95–7.89 (m, 1 H), 7.56–7.50 (m, 1 H), 7.46–7.33 (s, 2 H), 7.03 (s, br, 1 H), 3.49 (s, 1 H), 1.47 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.4, 138.1, 133.9, 130.0, 129.4, 129.3, 118.3, 83.4, 82.3, 52.1, 28.7; GC–MS *m*/*z* = 201 (2) [M^+], 186 (10), 158 (2), 145 (95), 129 (100), 117 (5), 101 (45), 75 (19). Anal. Calcd for $C_{13}H_{15}NO$ (201.26): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.61; H, 7.54; N, 6.95.



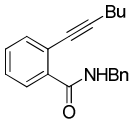
1f

2-(Hex-1-ynyl)-N-phenylbenzamide (**1f**): yield 3.20 g, starting from crude 2-iodo-*N*-phenylbenzamide and 1-hexyne (70%); yellow solid; mp 56−57 °C; IR (KBr) *v* = 3467 (m, br), 3315 (s), 2959 (w), 2927 (m), 2858 (w), 2225 (vw), 1664 (s), 1597 (m), 1524 (m), 1436 (m), 1322 (m), 892 (w), 756 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.40 (s, br, 1 H), 8.13−8.00 (m, 1 H), 7.66 (d, *J* = 7.9, 1 H), 7.53−7.43 (m, 1 H), 7.43−7.27 (m, 5 H), 7.12 (t, *J* = 7.3, 1 H), 2.49 (t, *J* = 7.0, 2 H), 1.64−1.50 (m, 2 H), 1.50−1.34 (m, 2 H), 0.87 (t, *J* = 7.0, 3 H); 13C NMR (75 MHz, $CDCl_3$) δ = 164.5, 138.1, 135.6, 133.7, 130.7, 130.1, 129.0, 128.3, 124.4, 120.3, 120.1, 98.4, 79.2, 30.6, 22.1, 19.4, 13.5; GC−MS *m*/*z* = 277 (100) [M+], 262 (4), 248 (38), 235 (86), 185 (89), 167 (11), 143 (39), 128 (18), 115 (51). Anal. Calcd for $C_{19}H_{19}NO$ (277.36): C, 82.28; H, 6.90; N, 5.05. Found: C, 82.30; H, 6.88; N, 5.07.



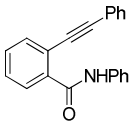
1g

N-Butyl-2-(hex-1-ynyl)benzamide (**1g**): yield 2.84 g, starting from crude *N*-butyl-2-iodo-benzamide and 1-hexyne (67%); yellow solid; mp 52−54 °C (lit.[17] mp 57−60 °C); IR (KBr) *v* = 3278 (m, br), 2953 (m), 2935 (m), 2861 (w), 2225 (vw), 1649 (s), 1548 (m), 1469 (w), 1435 (m), 1313 (m), 763 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.14−8.04 (m, 1 H), 7.63 (s, br, 1 H), 7.54−7.46 (m, 1 H), 7.45−7.36 (m, 2 H), 3.52 (q, *J* = 6.7, 2 H), 2.51 (t, *J* = 6.7, 2 H), 1.78−1.60 (m, 4 H), 1.59−1.45 (m, 4 H), 1.00 (t, *J* = 7.3, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.3, 135.4, 133.7, 130.2, 130.0, 128.1, 120.2, 97.2, 79.6, 39.8, 31.7, 30.6, 22.1, 20.3, 19.4, 13.8, 13.6; GC−MS *m*/*z* = 257 (99) [M^+], 242 (10), 228 (77), 215 (100), 200 (18), 185 (33), 172 (54), 158 (52), 143 (25), 128 (21), 115 (51), 103 (8), 77 (8). Anal. Calcd for $C_{17}H_{23}NO$ (257.37): C, 79.33; H, 9.01; N, 5.44. Found: C, 79.30; H, 9.02; N, 5.41.



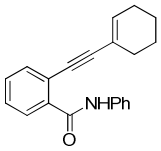
1h

N-Benzyl-2-(hex-1-ynyl)benzamide (**1h**):[15] yield 3.27 g, starting from crude *N*-benzyl-2-iodobenzamide and 1-hexyne (68%); yellow solid; mp 40−41 °C; IR (KBr) *v* = 3378 (m, br), 3311 (m, br), 2956 (m), 2935 (m), 2871 (w), 2227 (vw), 1651 (s), 1595 (w), 1531 (s), 1455 (w), 1298 (m), 1154 (w), 757 (m), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.16−8.08 (m, 1 H), 8.04 (s, br, 1 H), 7.48− 7.22 (m, 8 H), 4.66 (d, *J* = 5.4, 2 H), 2.14 (t, *J* = 6.8, 2 H), 1.45−1.23 (m, 4 H), 0.86 (t, *J* = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.0, 138.1, 134.7, 133.6, 130.5, 130.2, 128.7, 128.1, 128.0, 127.5, 120.3, 97.8, 79.5, 44.3, 30.3, 22.1, 19.1, 13.5; GC−MS *m*/*z* = 291 (9) [M^+], 262 (5), 249 (42), 231 (8), 200 (92), 182 (9), 172 (11), 158 (65), 143 (11), 132 (18), 115 (38), 91 (100). Anal. Calcd for $C_{20}H_{21}NO$ (291.39): C, 82.44; H, 7.26; N, 4.81. Found: C, 82.47; H, 7.23; N, 4.84.



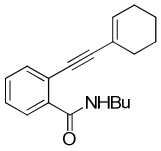
1i

N-Phenyl-2-(2-phenylethynyl)benzamide (**1i**): yield 2.83 g, starting from crude *N*-phenyl-2-iodobenzamide and phenylacetylene (58%); white solid; mp 153−154 °C (lit.[18] mp 151−153 °C); IR (KBr) *v* = 3277 (s), 3056 (w), 2217 (vw), 1654 (s), 1594 (m), 1524 (s), 1440 (m), 1323 (m), 921 (w), 889 (w), 759 (s), 687 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.20 (s, br, 1 H), 8.20−8.12 (m, 1 H), 7.72− 7.60 (m, 3 H), 7.54−7.46 (m, 4 H), 7.44−7.30 (m, 5 H), 7.20−7.10 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.4, 138.1, 136.1, 133.5, 131.7, 130.8, 130.3, 129.5, 129.3, 129.1, 128.6, 124.5, 122.0, 120.1, 119.7, 96.6, 87.3; GC−MS *m/z* = 297 (26) [M^+], 269 (9), 268 (11), 205 (100), 177 (21), 176 (45), 151 (17). Anal. Calcd for $C_{21}H_{15}NO$ (297.35): C, 84.82; H, 5.08; N, 4.71. Found: C, 84.80; H, 5.05; N, 4.70.



1j

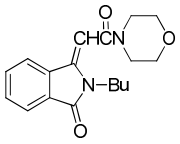
2-(2-Cyclohexenylethynyl)-N-phenylbenzamide (**1j**): yield 3.28 g, starting from crude 2-iodo-*N*-phenylbenzamide and 1-ethynylcyclohex-1-ene (66%); yellow solid; mp 97−98 °C (lit.[19] mp 99−100 °C); IR (KBr) v = 3450 (m, br), 3299 (m), 2929 (s), 2858 (m), 2200 (vw), 1667 (vs), 1601 (w), 1539 (m), 1496 (m), 1440 (m), 1386 (m), 1323 (m), 1255 (m), 1094 (m), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.33 (s, br, 1 H), 8.17−8.09 (m, 1 H), 7.69 (d, *J* = 7.7, 2 H), 7.55−7.48 (m, 1 H), 7.46−7.32 (m, 4 H), 7.19−7.10 (m, 1 H), 6.31−6.22 (m, 1 H), 2.27−2.07 (m, 4 H), 1.72−1.52 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 164.3, 138.1, 137.5, 135.4, 133.5, 130.8, 130.4, 129.0, 128.6, 124.4, 119.9, 98.9, 84.9, 29.0, 25.9, 22.2, 21.4; GC−MS *m/z* = 301 (54) [M^+], 272 (5), 209 (100), 194 (8), 178 (9), 165 (34), 152 (17), 143 (12), 139 (7), 115 (10). Anal. Calcd for $C_{21}H_{19}NO$ (301.38): C, 83.69; H, 6.35; N, 4.65. Found: C, 83.70; H, 6.36; N, 4.62.



1k

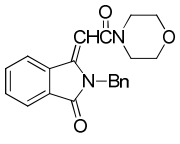
N-Butyl-2-(2-cyclohexenylethynyl)benzamide (**1k**): yield 2.69 g, starting from crude *N*-butyl-2-iodo-benzamide and 1-ethynylcyclohex-1-ene (58%); yellow solid; mp 89−90 °C; IR (KBr) *v* = 3446 (m, br), 3286 (m), 2928 (m), 2858 (w), 2205 (vw), 1636 (s), 1566 (m), 1434 (m), 1311 (m), 1143 (w), 765 (m), 711 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.09−8.02 (m, 1 H), 7.47 (s, br, 1 H), 7.50−7.43 (m, 1 H), 7.41−7.33 (m, 2 H), 6.30−6.15 (m, 1 H), 3.53−3.44 (m, 2 H), 2.28−2.12 (m, 4 H), 1.78−1.54 (m, 6 H),

1.53−1.38 (m, 2 H), 0.95 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, CDCl3) δ = 166.2, 136.7, 135.3, 133.4, 130.2, 130.1, 128.3, 120.2, 120.0, 97.6, 85.3, 39.9, 31.7, 29.0, 25.9, 22.2, 21.4, 20.3, 13.8; GC−MS *m*/*z* = 281 (98) [M^+], 264 (15), 252 (22), 238 (46), 225 (54), 224 (50), 209 (86), 197 (86), 181 (49), 165 (100), 152 (56), 139 (22), 130 (29), 115 (33), 102 (15), 97 (12), 77 (20). Anal. Calcd for $C_{19}H_{23}NO$ (281.39): C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.26; N, 4.97.



3aa

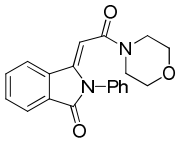
2-Butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3aa**): yield 178.4 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (81%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 2.0, determined by 1H NMR); pale yellow oil; IR (film) *v* = 2960 (m), 2928 (m), 1712 (s), 1684 (vs), 1435 (m), 1400 (w), 1231 (m), 1115 (m), 1040 (w), 769 (m), 699 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* = 8.12−8.01 [*Z* (m, 1 H)], 7.88−7.76 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.70−7.46 [*Z* (m, 2 H) + *E* (m, 3 H)], 6.01 [*E* (s, 1 H)], 5.81 [*Z* (s, 1 H)], 4.02 [*E* (t, *J* = 7.5, 2 H)], 3.88−3.55 [*Z* (m, 10 H) + *E* (m, 8 H)], 1.73−1.58 [*Z* (m, 2 H)], 1.58−1.23 [*E* (m, 4 H) + *Z* (m, 2 H)], 1.01−0.88 [*Z* (m, 3 H) + *E* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* = 168.1, 166.7, 165.3, 164.8, 142.2, 139.9, 137.2, 134.0, 132.5, 132.2, 130.4, 130.14, 130.07, 128.4, 124.7, 123.4, 123.1, 119.5, 99.5, 96.4, 66.8, 66.7, 66.6, 47.2, 47.1, 42.1, 41.9, 40.7, 39.2, 30.7, 30.3, 20.2, 20.0, 13.9, 13.8; GC−MS *m*/*z* = 314 (12) [M^+], 271 (5), 228 (100), 210 (11), 200 (48), 186 (11), 172 (32), 159 (12), 158 (12), 146 (6), 130 (34), 114 (4), 102 (8), 89 (7). Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.80; H, 7.04; N, 8.89.



3ba

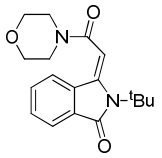
2-Benzyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3ba**): yield 202.7 mg, starting from 165.0 mg of *N*-benzyl-2- ethynylbenzamide (83%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 2.2, determined by ^{1}H NMR); colorless solid; mp 95−96 °C; IR (KBr) *v* = 3441 (m, br), 2964 (w), 2922 (m), 2856 (w), 1714 (s), 1647 (s), 1433 (m), 1272 (w), 1233 (w), 1115 (m), 968 (w), 696 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* = 8.19−8.11 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.97−7.88 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.70−7.51 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.38−7.18 [*Z* (m, 4 H) + *E* (m, 4 H)], 7.09−7.00 [*Z* (m, 1 H) + *E* (m, 1 H)], 5.94 [*E* (s, 1 H)], 5.63 [*Z* (s, 1 H)], 5.35 [*E* (s, 2 H)], 5.04 [*Z* (s, 2 H)], 3.79−3.53 [*Z* (m, 6 H) + *E* (m, 6 H)], 3.53−3.32 [*Z* (m, 2 H) + *E* (m, 2 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* = 168.3, 166.9, 164.8, 164.3, 160.9, 141.6, 139.7, 137.32, 137.28, 136.4, 134.0, 132.8, 132.5, 130.6, 130.3, 129.8, 128.9, 128.6, 128.5, 127.7, 127.6, 127.2, 126.9, 126.7, 126.4, 125.2, 123.9, 123.5, 119.6, 66.7, 66.6, 66.2, 65.9, 47.2, 46.7, 43.8, 43.3; GC−MS *m*/*z* = 348 (17)

[M^+], 262 (100), 234 (35), 172 (3), 91 (98), 65 (10). Anal. Calcd for $C_{21}H_{20}N_2O_3$ (348.40): C, 72.40; H, 5.79; N, 8.04. Found: C, 72.38; H, 5.81; N, 8.07.



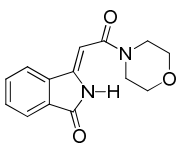
3ca-*Z*

(Z)-3-(2-Morpholino-2-oxoethylidene)-2-phenylisoindolin-1-one (**3ca**-*Z*): yield 201.6 mg, starting from 155.0 mg of 2-ethynyl-*N*-phenylbenzamide (86%); yellow solid; mp 133−134 °C; IR (KBr) *v* = 3010 (w), 2969 (m), 2923 (m), 2856 (w), 1716 (s), 1652 (m), 1500 (w), 1472 (w), 1392 (m), 1237 (m), 1117 (m), 1043 (m), 979 (w), 753 (s), 699 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.24−8.18 (m, 1 H), 7.98−7.92 (m, 1 H), 7.70−7.41 (m, 5 H), 7.39−7.32 (m, 2 H), 5.64 (s, 1 H), 3.81−3.69 (m, 4 H), 3.64−3.56 (m, 2 H), 3.47−3.38 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4, 165.2, 144.2, 134.0, 133.9, 133.0, 130.9, 129.8, 128.9, 128.7, 125.1, 123.7, 101.4, 66.8, 47.0, 42.1; GC−MS *m*/*z* = 334 (7) [M^+], 248 (100), 221 (11), 202 (3), 191 (7), 165 (23), 101 (3), 89 (3), 77 (10). Anal. Calcd for $C_{20}H_{18}N_2O_3$ (334.37): C, 71.84; H, 5.43; N, 8.38. Found: C, 71.86; H, 5.43; N, 8.36.



3da-*E*

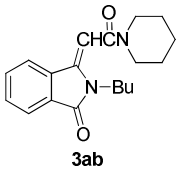
(E)-2-tert-Butyl-3-(2-morpholino-2-oxoethylidene)isoindolin-1-one (**3da**-*E*): yield 205.0 mg, starting from 141.0 mg of *N-tert*-butyl-2-ethynylbenzamide (93%); colorless solid; mp 145−146 °C; IR (KBr) *v* = 2979 (w), 2954 (w), 2855 (w), 1708 (s), 1637 (vs), 1433 (m), 1374 (w), 1301 (w), 1232 (m), 1115 (m), 1020 (w), 772 (m), 699 (w) cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ = 7.79−7.71 (m, 2 H), 7.56−7.43 (m, 2 H), 6.14 (s, 1 H), 3.86−3.52 (m, 8 H), 1.78 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.1, 160.9, 141.0, 134.4, 132.3, 130.0, 128.1, 122.99, 122.97, 104.5, 67.3, 66.5, 57.8, 42.1, 40.7, 30.3; GC−MS *m*/*z* = 314 (6) [M^+], 258 (3), 228 (2), 200 (10), 172 (100), 145 (13), 130 (28), 114 (8), 102 (6), 86 (22). Anal. Calcd for $C_{18}H_{22}N_2O_3$ (314.38): C, 68.77; H, 7.05; N, 8.91. Found: C, 68.80; H, 7.03; N, 8.90.



3ea-*Z*

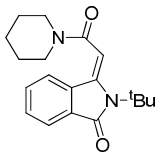
(Z)-3-(2-Morpholino-2-oxoethylidene)isoindolin-1-one (**3ea**-*Z*): yield 117.7 mg, starting from 102.0 mg of 2-ethynylbenzamide (65%); colorless solid; mp 186−187 °C; IR (KBr) *v* = 3412 (s, br), 1711 (s), 1647 (s), 1583 (w), 1399 (m), 1238 (m), 1120 (m), 758 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 10.34 (s, br, 1 H),

7.90−7.83 (s, 1 H), 7.73−7.65 (m, 1 H), 7.64−7.54 (m, 2 H), 6.06 (s, 1 H), 3.83−3.55 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.2, 166.0, 146.7, 137.0, 132.5, 131.2, 131.0, 129.7, 124.0, 120.5, 89.0, 66.9, 46.9, 45.8; GC−MS *m*/*z* = 258 (22) [M^+], 172 (100), 145 (16), 130 (45), 102 (15), 89 (28), 86 (41). Anal. Calcd for $C_{14}H_{14}N_2O_3$ (258.27): C, 65.11; H, 5.46; N, 10.85. Found: C, 65.10; H, 5.45; N, 10.87.



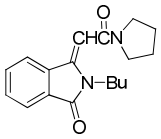
3ab

2-Butyl-3-[2-oxo-2-(piperidin-1-yl)ethylidene]isoindolin-1-one (**3ab**): yield 197.1 mg, starting from 141.0 mg of N-butyl-2-ethynylbenzamide (90%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.0, determined by ^{1}H NMR); pale yellow oil; IR (film) *v* = 2934 (m), 2956 (m), 1713 (s), 1652 (vs), 1470 (m), 1252 (m), 1023 (m), 953 (w), 770 (m), 698 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.03−7.96 [*Z* (m, 1 H)], 7.86−7.77 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.69−7.62 [*E* (m, 1 H)], 7.61−7.46 [*Z* (m, 2 H) + *E* (m, 2 H)], 6.04 [*E* (s, 1 H)], 5.83 [*Z* (s, 1 H)], 3.99 [*E* (t, *J* = 7.6, 2 H)], 3.83−3.49 [*Z* (m, 6 H) + *E* (m, 4 H)], 1.75−1.24 [*E* (m, 10 H) + *Z* (m, 10 H)], 0.96 [*Z* or *E* (t, *J* = 7.3, 3 H)], 0.92 [*Z* or *E* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 166.8, 165.0, 164.5, 140.9, 138.7, 137.4, 134.3, 132.3, 132.0, 130.1, 129.9, 124.5, 123.3, 123.1, 119.4, 111.7, 109.4, 101.0, 97.9, 48.0, 47.9, 42.8, 42.5, 40.7, 39.2, 30.7, 30.4, 26.7, 26.4, 25.8, 25.5, 24.58, 24.53, 20.2, 20.1, 13.82, 13.78; GC−MS *m*/*z* = 312 (35) [M^+], 283 (3), 269 (13), 239 (8), 228 (100), 210 (17), 201 (59), 200 (69), 186 (30), 172 (56), 159 (67), 146 (13), 130 (69), 112 (11), 102 (18), 84 (72). Anal. Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05; H, 7.74; N, 8.97. Found: C, 73.07; H, 7.71; N, 8.94.



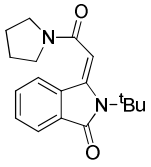
3db-*E*

(E)-2-tert-Butyl-3-[2-oxo-2-(piperidin-1-yl)ethylidene]isoindolin-1-one (**3db**-*E*): yield 166.2 mg, starting from 141.0 mg of *N-tert*-butyl-2-ethynylbenzamide (76%); colorless solid; mp 135−136 °C; IR (KBr) *v* = 3446 (m, br), 2987 (m), 2938 (m), 2857 (w), 2257 (m), 1713 (m), 1634 (s), 1443 (m), 1373 (m), 1232 (m), 1110 (m), 1023 (m), 756 (m), 696 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.80− 7.70 (m, 2 H), 7.55−7.40 (m, 2 H), 6.19 (s, 1 H), 3.85−3.70 (m, 2 H), 3.57−3.42 (m, 2 H), 1.78 (s, 9 H), 1.74−1.60 (m, 4 H), 1.60−1.40 (m, 2 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 165.6, 139.9, 134.6, 132.1, 130.6, 129.6, 123.1, 122.8, 106.0, 57.7, 48.0, 42.6, 30.4, 26.7, 25.5, 24.6; GC−MS *m*/*z* = 312 (17) [M^+], 256 (10), 255 (10), 200 (55), 172 (100), 145 (22), 130 (30), 112 (11), 84 (80). Anal.Calcd for $C_{19}H_{24}N_2O_2$ (312.41): C, 73.05; H, 7.74; N, 8.97. Found: C, 73.04; H, 7.72; N, 8.99.



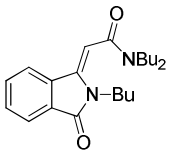
3ac

2-Butyl-3-[2-oxo-2-(pyrrolidin-1-yl)ethylidene]isoindolin-1-one (**3ac**): yield 180.0 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (86%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.8, determined by ^{1}H NMR); yellow oil; IR (film) *v* = 2952 (m), 2915 (w), 2871 (m), 1712 (s), 1652 (s), 1616 (s), 1432 (m), 1398 (m), 1346 (m), 1190 (w), 1092 (w), 943 (w), 768 (m), 696 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.61−8.53 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.89−7.78 [*Z* (m, 1 H) + *E* (m, 1 H)], 7.64−7.48 [*Z* (m, 2 H) + *E* (m, 2 H)], 6.01 [*E* (s, 1 H)], 5.83 [*Z* (s, 1 H)], 4.15−4.01 [*E* (m, 2 H)], 3.81−3.71 [*Z* (m, 2 H)], 3.60−3.35 [*Z* (m, 4 H) + *E* (m, 4 H)], 2.10−1.62 [*Z* (m, 4 H) + *E* (m, 4 H)], 1.50−1.11 [*Z* (m, 4 H) + *E* (m, 4 H)], 1.10−0.80 [*Z* (m, 3 H) + *E* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 167.1, 164.5, 164.4, 142.8, 138.9, 137.6, 134.2, 132.6, 132.1, 130.4, 130.1, 130.0, 128.6, 126.2, 123.4, 122.9, 119.4, 101.2, 98.3, 47.8, 47.6, 46.0, 45.8, 40.9, 39.2, 30.1, 29.7, 26.2, 26.1, 24.6, 24.5, 20.2, 20.0, 13.9, 13.8.; GC−MS *m*/*z* = 298 (23) [M^{+}], 255 (24), 228 (100), 200 (50), 186 (10), 172 (33), 158 (12), 130 (32), 102 (11), 70 (16), 55 (11). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.49; H, 7.42; N, 9.38 .



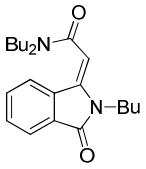
3dc-*E*

(E)-2-tert-Butyl-3-[2-oxo-2-(pyrrolidin-1-yl)ethylidene]isoindolin- 1-one (**3dc**-*E*): yield 171.6 mg, starting from 141.0 mg of *N-tert*-butyl-2-ethynylbenzamide (82%); yellow oil; IR (film) *v* = 2970 (w), 2875 (w), 1709 (s), 1631 (s), 1614 (s), 1434 (m), 1367 (m), 1298 (w), 1266 (w), 1112 (w), 1023 (w), 1006 (w), 797 (m), 693 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.05−7.91 (m, 1 H), 7.81−7.65 (m, 1 H), 7.60−7.45 (m, 2 H), 6.23 (s, 1 H), 3.70−3.52 (m, 2 H), 3.51−3.40 (m, 2 H), 2.05−1.85 (m, 4 H), 1.79 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.3, 163.2, 141.0, 132.3, 129.8, 128.9, 125.8, 123.6, 122.7, 106.5, 47.6, 45.8, 30.4, 28.7, 26.1, 24.5; GC−MS *m*/*z* = 298 (17) [M^{+}], 242 (7), 200 (46), 172 (100), 145 (14), 130 (27), 98 (12), 89 (10), 70 (51). Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.48; H, 7.44; N, 9.37.



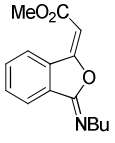
3ad-*Z*

(Z)-N,N-Dibutyl-2-(2-butyl-3-oxoisoindolin-1-ylidene)acetamide (**3ad**-*Z*): yield 120.0 mg, starting from 141.0 mg of N-butyl-2- ethynylbenzamide (48%); yellow oil; IR (film) *v* = 2958 (m), 2931 (s), 2873 (m), 1714 (m), 1634 (s), 1532 (m), 1467 (m), 1091 (w) cm^{-1} ; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.21−8.15 (m, 1 H), 7.85− 7.78 (m, 1 H), 7.61−7.46 (m, 2 H), 5.86 (s, 1 H), 3.61−3.05 (m, 6 H), 1.73−1.12 (m, 12 H), 1.05−0.62 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.0, 157.8, 141.7, 138.7, 132.4, 130.2, 129.9, 125.3, 123.0, 101.1, 47.2, 40.6, 39.3, 32.6, 30.9, 20.3, 20.2, 20.1, 13.9, 13.85, 13.76; GC−MS *m*/*z* = 356 (20) [M^+], 327 (5), 313 (5), 299 (3), 228 (100), 210 (11), 201 (49), 186 (20), 172 (37), 159 (44), 146 (10), 130 (42), 102 (9). Anal. Calcd for $C_{22}H_{32}N_2O_2$ (356.50): C, 74.12; H, 9.05; N, 7.86. Found: C, 74.11; H, 9.07; N, 7.85.



3ad-*E*

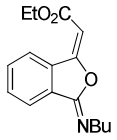
(E)-N,N-Dibutyl-2-(2-butyl-3-oxoisoindolin-1-ylidene)acetamide (**3ad**-*E*): yield 119.7 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (48%); yellow oil; IR (film) *v* = 2958 (m), 2931 (m), 2873 (m), 1716 (m), 1628 (s), 1533 (m), 1467 (m), 1376 (w), 1295 (w), 1219 (w), 1095 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.81−7.75 (m, 1 H), 7.72−7.40 (m, 3 H), 6.04 (s, 1 H), 3.52−3.01 (m, 6 H), 2.72−1.15 (m, 12 H), 1.10−0.52 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 165.6, 157.8, 139.0, 137.7, 132.1, 129.9, 125.5, 123.4, 119.3, 97.8, 47.1, 40.6, 32.6, 30.9, 20.4, 20.3, 13.88. 13.83; GC− MS *m*/*z* = 356 (19) [M^+], 327 (5), 313 (5), 228 (100), 210 (11), 201 (51), 186 (21), 172 (37), 159 (44), 146 (10), 130 (42), 102 (8). Anal. Calcd for $C_{22}H_{32}N_2O_2$ (356.50): C, 74.12; H, 9.05; N, 7.86. Found: C, 74.10; H, 9.06; N, 7.83.



4a-*E*

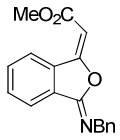
(E)-Methyl-2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]acetate (**4a**-*E*): yield 127.3 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (70%); colorless solid; mp 106−107 °C; IR (KBr) *v* = 2957 (m), 2932 (m), 2873 (w), 1687 (m), 1646 (s), 1582 (s), 1459 (m), 1402 (m), 1316 (w), 1221 (m), 1142 (m), 768 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.09−9.00 (m, 1 H), 7.92−7.84 (m, 1 H), 7.68−7.56 (m, 2 H), 5.94 (s, 1 H), 3.80 (s, 3 H), 3.66 (t, *J* = 7.2, 2 H), 1.78−1.61 (m, 2 H), 1.52−1.37 (m, 2 H), 0.97 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.0, 161.8, 152.8, 133.7, 132.6, 132.1, 132.0, 127.7, 122.6, 96.6, 51.5, 47.9,

32.9, 20.6, 13.9; GC–MS *m*/*z* = 259 (35) [M^+], 228 (13), 200 (100), 186 (29), 184 (26), 172 (29), 159 (44), 158 (83), 130 (41), 102 (16), 89 (18). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.50; H, 6.58; N, 5.39.



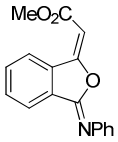
4a'-*E*

(E)-Ethyl-2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]acetate (**4a'**-*E*): yield 134.2 mg, starting from 141.0 mg of *N*-butyl-2-ethynylbenzamide (70%); yellow solid; mp 57–58 °C; IR (KBr) *v* = 2959 (w), 2929 (w), 1714 (m), 1640 (s), 1475 (w), 1398 (w), 1378 (w), 1249 (m), 1208 (m), 1144 (m), 1102 (m), 1051 (m), 851 (w), 781 (w), 669 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.09–9.01 (m, 1 H), 7.92–7.85 (m, 1 H), 7.67–7.55 (m, 2 H), 5.95 (s, 1 H), 4.27 (q, *J* = 7.1, 2 H), 3.66 (t, *J* = 7.1, 2 H), 1.75–1.62 (m, 2 H), 1.51–1.37 (m, 2 H), 1.35 (t, *J* = 7.1, 3 H), 0.96 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 161.6, 152.8, 133.8, 132.6, 132.04, 131.96, 127.7, 122.6, 97.2, 60.3, 47.9, 32.9, 20.6, 14.4, 13.9; GC–MS *m*/*z* = 273 (12) [M^+], 244 (11), 230 (19), 200 (89), 186 (44), 172 (100), 159 (65), 145 (20), 130 (76), 102 (21), 89 (11). Anal. Calcd for $C_{16}H_{19}NO_3$ (273.33): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.33; H, 7.02; N, 5.11.



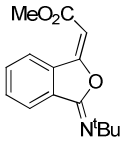
4b-*E*

(E)-Methyl 2-[3-(benzylimino)isobenzofuran-1(3H)-ylidene]-acetate (**4b**-*E*): yield 123.4 mg, starting from 165.0 mg of *N*-benzyl-2-ethynylbenzamide (60%); yellow solid mp 53–54 °C; IR (KBr) *v* = 2927 (m), 2854 (w), 1710 (s), 1648 (s), 1470 (m), 1385 (w), 1261 (m), 1208 (m), 1146 (m), 1109 (w), 1053 (m), 979 (m), 861 (m), 775 (m), 735 (m), 705 (m), 669 (m), 626 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 9.08–9.00 (m, 1 H), 7.97–7.89 (m, 1 H), 7.67– 7.54 (m, 2 H), 7.49–7.22 (m, 5 H), 5.99 (s, 1 H), 4.87 (s, 2 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, CDCl3) δ = 166.8, 161.7, 153.6, 139.6, 133.8, 132.23, 132.16, 128.5, 127.9, 127.7, 126.9, 122.9, 97.2, 51.9, 51.5; GC–MS *m*/*z* = 293 (22) [M^+], 262 (4), 234 (19), 232 (26), 130 (6), 102 (5), 91 (100), 65 (13). Anal. Calcd for $C_{18}H_{15}NO_3$ (293.32): C, 73.71; H, 5.15; N, 4.78. Found: C, 73.70; H, 5.12; N, 4.80.



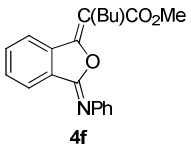
4c-*E*

(E)-Methyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]-acetate (**4c**-*E*): yield 113.6 mg, starting from 155.0 mg of 2-ethynyl-*N*-phenylbenzamide (58%); yellow solid; mp 97−98 °C; IR (KBr) *v* = 2939 (m), 1705 (s), 1647 (m), 1491 (w), 1379 (m), 1193 (w), 1138 (m), 847 (m), 762 (m), 692 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.10−9.03 (m, 1 H), 8.07−8.01 (m, 1 H), 7.73−7.62 (m, 2 H), 7.45−7.32 (m, 4 H), 7.24−7.16 (m, 1 H), 5.99 (s, 1 H), 3.80 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.6, 161.7, 151.8, 144.9, 133.4, 132.9, 132.6, 132.2, 128.7, 127.6, 125.2, 123.9, 123.3, 98.1, 51.5; GC− MS *m*/*z* = 279 (56) [M^+], 248 (37), 236 (8), 220 (100), 191 (8), 165 (29), 96 (5), 77 (13). Anal. Calcd for $C_{17}H_{13}NO_3$ (279.29): C, 73.11; H, 4.69; N, 5.02. Found: C, 73.10; H, 4.69; N, 5.05.



4d-*E*

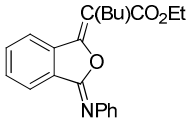
(E)-Methyl 2-[3-(tert-butylimino)isobenzofuran-1(3H)-ylidene]-acetate (**4d**-*E*): yield 127.2 mg, starting from 141.0 mg of *N*-*tert*-butyl-2-ethynylbenzamide (70%); yellow solid; mp 68−69; IR (KBr) *v* = 2967 (m), 2870 (w), 1711 (s), 1644 (s), 1474 (m), 1364 (w), 1261 (m), 1206 (m), 1146 (s), 1046 (s), 976 (m), 860 (w), 778 (m), 678 (m) cm^{-1}; ^{1}H NMR (300 MHz, CDCl3) δ = 9.08−8.97 (m, 1 H), 7.91−7.81 (m, 1 H), 7.67−7.53 (m, 2 H), 5.94 (s, 1 H), 3.80 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.0, 162.1, 149.4, 133.9, 132.9, 132.0, 131.8, 127.5, 123.0, 96.3, 55.1, 51.4, 30.5; GC−MS *m*/*z* = 259 (9) [M^+], 244 (35), 203 (23), 172 (100), 145 (37), 130 (35), 106 (11), 101 (10), 57 (35). Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.45; H, 6.60; N, 5.43.



4f

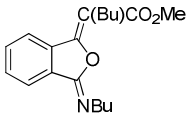
Methyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]-hexanoate (**4f**): yield 188.2 mg, starting from 194.0 mg of 2-(hex-1-ynyl)-*N*-phenylbenzamide (80%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.4, determined by ^{1}H NMR); yellow oil; IR (film) *v* = 2955 (m), 2926 (s), 2857 (m), 1715 (s), 1660 (s), 1624 (m), 1593 (m), 1530 (w), 1489 (m), 1455 (m), 1347 (w), 1314 (w), 1262 (m), 1212 (s), 1119 (w), 1064 (m), 1041 (m), 762 (m), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56−8.48 [*Z* (m, 1 H)], 8.38 [*E* (d, *J* = 7.9, 1 H)], 8.07−8.01 [*Z* (m, 1 H)], 7.64−7.48 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.43−7.30 [*Z* (m, 4 H), + *E* (m, 4 H)], 7.21−7.08 [*Z* (m, 1 H) + *E* (m, 2 H)], 3.92 [*E* (s, 3 H)], 3.88 [*Z* (s, 3 H)], 2.60 [*Z* (t, *J* = 7.9, 2 H)], 2.51 [*E* (t, *J* = 7.3, 2 H)],

1.60−1.46 [*Z* (m, 2 H) + *E* (m, 2 H)], 1.45−1.24 [*Z* (m, 2 H) + *E* (m, 2 H)], 0.90 [*Z* (t, *J* = 7.3, 3 H)], 0.85 [*E* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.1, 166.8, 159.4, 155.5, 152.4, 148.6, 146.1, 145.2, 134.0, 132.5, 132.4, 131.0, 130.9, 128.71, 128.65, 128.1, 127.6, 126.2, 125.1, 124.2, 123.8, 123.7, 123.4, 122.5, 113.6, 109.1, 52.2, 52.0, 31.8, 31.4, 29.3, 28.8, 22.7, 22.1, 13.8, 13.7; GC−MS *m*/*z* = 335 (100) [M^+], 320 (5), 304 (9), 293 (12), 278 (31), 261 (12), 233 (20), 208 (28), 190 (11), 165 (6), 114 (4), 77 (19). Anal. Calcd for $C_{21}H_{21}NO_3$ (335.40): C, 75.20; H, 6.31; N, 4.18. Found: C, 75.19; H, 6.33; N, 4.20.



4f'

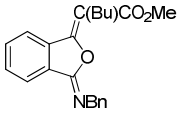
Ethyl 2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]-hexanoate (**4f'**): yield 203.2 mg, starting from 194.0 mg of 2-(hex-1-ynyl)-*N*-phenylbenzamide (83%) (mixture of diastereoisomers *Z*/*E*, *Z*/*E* ratio ca. 1.0, determined by ^{1}H NMR); yellow oil. IR (film) *v* = 2958 (m), 2925 (m), 1710 (s), 1664 (s), 1592 (s), 1489 (w), 1313 (w), 1262 (w), 1210 (m), 1064 (s), 764 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.57−8.50 [*Z* (m, 1 H)], 8.37 [*E* (d, *J* = 8.0, 1 H)], 8.06−8.00 [*Z* (m, 1 H)], 7.65−7.50 [*Z* (m, 2 H) + *E* (m, 2 H)], 7.47−7.30 [*Z* (m, 4 H), + *E* (m, 4 H)], 7.23−7.16 [*Z* (m, 1 H) + *E* (m, 2 H)], 4.40 [*Z* or *E* (q, *J* = 7.1, 2 H)], 4.35 [*E* or *Z* (q, *J* = 7.1, 2 H)], 2.66−2.56 [*Z* or *E* (m, 2 H)], 2.51 [*E* or *Z* (d, *J* = 7.3, 2 H)], 1.62−1.47 [*Z* (m, 2 H) + *E* (m, 2 H)], 1.45−1.22 [*Z* (m, 5 H) + *E* (m, 5 H)] 0.90 [*Z* or *E* (t, *J* = 7.3, 3 H)], 0.88 [*E* or *Z* (t, *J* = 7.3, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.7, 166.4, 159.0, 155.2, 152.4, 148.5, 146.3, 145.3, 134.1, 132.45, 132.35, 130.8, 128.7, 128.6, 128.0, 127.5, 126.1, 125.1, 124.2, 123.7, 123.6, 123.4, 122.5, 113.9, 109.3, 61.4, 60.9, 31.8, 31.3, 29.4, 28.7, 22.6, 22.1, 14.3, 13.8, 13.7; GC−MS *m*/*z* = 349 (100) [M^+], 320 (9), 292 (18), 264 (25), 248 (10), 234 (23), 220 (13), 208 (16), 190 (12), 165 (15), 89 (13), 77 (30). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.64; H, 6.66; N, 3.99 .



4g

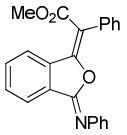
Methyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]-hexanoate (**4g**): yield 165.9 mg, starting from 180.0 mg of *N*-butyl-2-(hex-1- ynyl)benzamide (75%) (mixture of diastereoisomers *E*/*Z*, *E*/*Z* ratio ca. 6.2, determined by ^{1}H NMR); colorless solid; mp 57−58 °C; IR (KBr) *v* = 2956 (m), 2929 (m), 2863 (m), 1723 (s), 1671 (s), 1629 (m), 1456 (m), 1429 (m), 1348 (m), 1312 (m), 1261 (w), 1207 (m), 1105 (m), 1059 (s), 768 (m), 667 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.51−8.45 [*Z* (m, 1 H)], 8.19−8.13 [*E* (m, 1 H)], 7.90−7.84 [*Z* (m, 1 H)], 7.60−7.26 [*E* (m, 3 H), + *Z* (m, 2 H)], 3.92 [*E* (s, 3 H)], 3.87 [*Z* (s, 3 H)], 3.71−3.62 [*Z* (t, *J* = 7.3, 2 H)], 3.50 [*E* (t, *J* = 7.1, 2 H)], 2.71−2.61 [*Z* (m, 2 H)], 2.60 [*E* (t, *J* = 7.5, 2 H)], 1.77− 1.33 [*E* (m, 8 H) + *Z* (m, 8 H)], 1.01−0.91 [*E* (m, 6 H) + *Z* (m, 6 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.2, 159.6, 148.5, 132.2,

131.7, 131.5, 130.7, 130.2, 129.6, 128.9, 127.7, 126.7, 126.1, 125.0, 123.5, 123.3, 122.7, 111.9, 108.3, 52.0, 46.0, 32.9, 32.2, 29.5, 22.3, 20.8, 14.0, 13.9, 13.8; GC–MS *m*/*z* = 315 (19) [M^+], 286 (33), 284 (19), 272 (84), 259 (80), 226 (100), 217 (31), 214 (24), 198 (33), 185 (72), 184 (66), 170 (50), 158 (14), 143 (24), 130 (83), 115 (26), 102 (20), 85 (11). Anal. Calcd for $C_{19}H_{25}NO_3$ (315.41): C, 72.35; H, 7.99; N, 4.44. Found: C, 72.33; H, 8.00; N, 4.45.



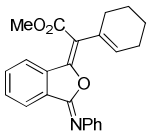
4h

Methyl 2-[3-(benzylimino)isobenzofuran-1(3H)-ylidene]-hexanoate (**4h**): yield 110.2 mg, starting from 204.0 mg of *N*-benzyl-2-(hex-1-ynyl)benzamide (45%) (mixture of diastereoisomers *E*/*Z*, *E*/*Z* ratio ca. 4.9, determined by ^{1}H NMR) yellow oil; IR (film) *v* = 2956 (s), 2931 (m), 2871 (m), 1723 (s), 1666 (s), 1486 (m), 1435 (m), 1345 (m), 1309 (m), 1259 (m), 1206 (m), 1106 (m), 1049 (m), 734 (m), 698 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.46 [Z (d, *J* = 7.8, 1 H)], 8.30 [E (d, *J* = 7.7, 1 H)], 7.91 [*Z* (d, *J* = 7.3, 1 H)], 7.61–7.20 [*E* (m, 8 H), + *Z* (m, 7 H)], 4.87 [*Z* (s, 2 H)], 4.73 [*E* (s, 2 H)], 3.92 [*E* (s, 3 H)], 3.88 [*Z* (s, 3 H)], 2.69 [*Z* (t, *J* = 7.6, 2 H)], 2.61 [*E* (t, *J* = 7.6, 2 H)], 1.73–1.31 [*E* (m, 4 H) + *Z* (m, 4 H)], 1.00– 0.87 [*E* (m, 3 H) + *Z* (m, 3 H)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.1, 159.4, 149.5, 140.7, 134.7, 134.4, 131.94, 131.86, 130.7, 130.2, 129.6, 128.5, 128.3, 127.9, 127.6, 126.9, 126.8, 126.5, 126.0, 125.0, 123.6, 122.9, 112.5, 108.7, 102.8, 52.1, 51.9, 50.8, 50.0, 32.2, 31.2, 29.5, 28.5, 22.6, 22.3, 13.9, 13.8; GC–MS ***Z***: *m*/*z* = 349 (6) [M+] 318 (3), 293 (27), 261 (52), 232 (6), 130 (7), 91 (100); ***E***: *m*/*z* = 349 (5), 318 (4), 293 (32), 261 (55), 207 (11), 193 (5), 130 (9), 117 (11), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_3$ (349.42): C, 75.62; H, 6.63; N, 4.01. Found: C, 75.61; H, 6.65; N, 4.02.



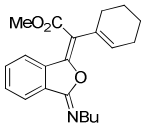
4i-*E*

(E)-Methyl 2-phenyl-2-[3-(phenylimino)isobenzofuran-1(3H)- ylidene]acetate (**4i**-E): yield 136.8 mg, starting from 208.0 mg of *N*-phenyl-2-(2-phenylethynyl)benzamide (55%); yellow solid; mp 56–57°C; IR (KBr) *v* = 3019 (w), 1712 (s), 1691(s), 1613 (m), 1590 (m), 1489 (w), 1300 (w), 1268 (w), 1216 (m), 1053 (s), 1006 (m), 757 (s), 692 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 7.1, 1 H), 8.07–8.02 (m, 1 H), 7.68–7.57 (m, 2 H), 7.50–7.43 (m, 2 H), 7.43–7.28 (m, 5 H), 7.26–7.19 (m, 2 H), 7.15–7.07 (m, 1 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 153.3, 151.8, 144.5, 134.1, 134.0, 132.4, 132.2, 131.2, 129.5, 128.6, 128.2, 127.9, 125.5, 125.2, 124.9, 123.7, 112.7, 52.5; GC–MS *m*/*z* = 355 (36) [M^+], 324 (16), 296 (100), 295 (46), 267 (21), 246 (5), 219 (5), 190 (7), 165 (7), 77 (16). Anal. Calcd for $C_{23}H_{17}NO_3$ (355.39): C, 77.73; H, 4.82; N, 3.94. Found: C, 77.71; H, 4.85; N, 3.90.



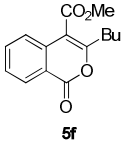
4j-*E*

(E)-Methyl 2-cyclohexenyl-2-[3-(phenylimino)isobenzofuran-1(3H)-ylidene]acetate (**4j**-*E*): yield 196.4 mg, starting from 211.0 mg of 2-(2-cyclohexenylethynyl)-*N*-phenylbenzamide (78%); yellow solid; mp 189−190 °C; IR (KBr) *v* = 2930 (s), 2958 (w), 1724 (s), 1660 (s), 1592 (m), 1489 (m), 1434 (m), 1347 (m), 1312 (m), 1221 (m), 1090 (m), 1057 (m), 771 (m), 694 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.42−8.33 (m, 1 H), 7.60−7.51 (m, 1 H), 7.48− 7.29 (m, 4 H), 7.21−7.06 (m, 3 H), 6.10 (s, br, 1 H), 3.84 (s, 3 H), 2.19−2.03 (m, 4 H), 1.72−1.53 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 156.2, 148.4, 146.2, 132.5, 131.8, 131.3, 128.6, 128.3, 127.6, 124.6, 123.7, 123.4, 122.7, 108.3, 52.3, 25.63, 25.59, 22.2, 21.5; GC−MS *m*/*z* = 359 (100) [M^+], 344 (10), 316 (14), 300 (10), 272 (8), 208 (7), 190 (10), 179 (9), 165 (8), 114 (3), 77 (24). Anal. Calcd for $C_{23}H_{21}NO_3$ (359.42): C, 76.86; H, 5.89; N, 3.90. Found: C, 76.86; H, 5.91; N, 3.92.



4k-*E*

(E)-Methyl 2-[3-(butylimino)isobenzofuran-1(3H)-ylidene]-2-cyclohexenylacetate (**4k**-*E*): yield 161.8 mg, starting from 197.0 mg of *N*-butyl-2-(2-cyclohexenylethynyl)benzamide (68%); colorless oil; IR (film) *v* = 2933 (m), 2863 (w), 1723 (s), 1668 (s), 1435 (w), 1338 (m), 1307 (w), 1220 (m), 1089 (m), 1051 (w), 756 (s) (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.4, 1 H), 7.50−7.24 (m, 3 H), 6.21−6.13 (m, 1 H), 3.82 (s, 3 H), 3.52−3.43 (m, 2 H), 2.38−2.28 (m, 2 H), 2.23−2.12 (m, 2 H), 1.79−1.60 (m, 6 H), 1.53−1.38 (m, 2 H), 0.96 (t, *J* = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.8, 156.5, 148.3, 132.4, 131.7, 131.5, 127.8, 126.6, 125.0, 123.1, 122.6, 107.7, 52.0, 45.9, 32.8, 25.7, 25.6, 22.3, 21.6, 20.7, 13.9; GC−MS *m*/*z* = 339 (17) [M^+], 322 (25), 310 (25), 296 (89), 280 (100), 264 (18), 258 (31), 226 (66), 170 (29), 142 (9) 114 (14), 109 (78), 81 (39). Anal. Calcd for $C_{21}H_{25}NO_3$ (339.43): C, 74.31; H, 7.42; N, 4.13. Found: C, 74.30; H, 7.41; N, 4.11.



5f

Methyl 3-Butyl-1-oxo-1H isochromene-4-carboxylate (**5f**): pale yellow oil; IR (film) *v* = 2958 (m), 2938 (m), 1728 (vs), 1631 (m), 1488 (w), 1457 (m), 1355 (m), 1319 (m), 1258 (m), 1215 (m), 1058 (m), 1024 (w), 758 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 8.29 (d, *J* = 7.9, 1 H), 7.79−7.63 (m, 2 H), 7.56−7.45 (m, 1 H), 3.97 (s, 3 H), 2.69 (t, *J* = 7.6, 2 H), 1.83−1.63 (m, 2 H), 1.50−1.32 (m, 2 H), 0.95 (t, *J* = 6.7, 3 H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ = 166.4, 161.3, 161.0, 135.0, 134.7, 129.7, 128.2, 124.2, 119.6, 110.0, 52.4, 32.5, 29.8, 22.4, 13.7; GC–MS *m*/*z* = 260 (99) [M^+], 229 (48), 218 (9), 203 (100), 199 (36), 190 (37), 186 (78), 176 (71), 161 (7), 148 (53), 133 (33), 115 (10), 104 (26), 88 (28), 57 (39). Anal. Calcd for $C_{15}H_{16}O_4$ (260.29): C, 69.22; H, 6.20. Found: C, 69.23; H, 6.23.

[1] These conditions (16 atm of CO together with 6 total atm of air, considering that the autoclave was loaded under 1 atm of air) corresponded to 73.0% of CO in air and were outside the explosion limits for CO in air (ca. 16−70% at 18−20 °C at atmospheric pressure, 14.8−71.4% at 100 °C and atmospheric pressure. At higher total pressure, the range of flammability decreases; for example, at 20 atm and 20 °C the limits are ca. 19 and 60%). *See*: Bartish, C. M.; Drissel,G. M. In Kirk−Othmer *Encyclopedia of Chemical Technology, 3rd ed.*; Grayson, M., Eckroth, D., Bushey, G. J., Campbell, L., Klingsberg, A., Van Nes, L., Eds.; *Wiley-Interscience*: New York, **1978**; Vol 4; p 7750.

[2] B. Gabriele, G. Salerno, L. Veltri , M. Costa. *J. Organomet. Chem.* **2001***,* 622, 84–88.

[3] For recent reviews on the synthesis of carbonylated heterocycles by carbonylation of acyclic substrates, see: (a) Wu, X.-F.; Neumann, H.; Beller, *M. Chem. Rev.* **2013**, 113, 1−35. (b) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, 6, 229−241. (c) Gabriele, B.; Mancuso, R.; Salerno, G. Eur. *J. Org. Chem.* **2012**, 6825−6839. (d) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem.*, Int. Ed**. 2011**, 50, 10788−10799. (e) Liu, J.; Chen, J.; Sun, W.; Xia, C. Chin. *J. Catal.* **2010**, 31, 1−11. (f) Brennfuehrer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, 1, 28−41. (g) Brennfuehrer, A.; Neumann, H.; Beller, M. *Angew. Chem.*, Int. Ed. **2009**, 48, 4114−4133. (h) Barnard, C. F. *J. Organometallics* **2008**, 27, 5402−5422. (i) Sapollo, G.; Mele, G. *Curr. Org. Chem.* **2006**, 10, 1397−1421. (j) Gabriele, B.; Salerno, G.; Costa, M. Top*. Organomet. Chem.* **2006**, 18, 239−272.

[4] Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83−87.

[5] *For cloruration* reaction *see*: Schultz, A.G.; Guzzo,P.R.; Nowak, D.M. *JOC* **1995**, 60,24, 8044-8050. *For amidation and Sonogashira coupling reaction see*: Kundu, N.G.; Khan,M.W. *Tetrahedron* **2000**, 56,27, 4777-4792. *For trimethylsilyl group deprotection*: Isono,N., Lautens,M. *Org. Lett.* **2009**, 11(6), 1329-1331.

[6] Varela-Fernandez, A.; Varela, J. A.; Saà, C. *Adv. Synth. Catal.* **2011**, 353, 1933−1937.

[7] (a) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319-3322. (b) Plastina, P.; Gabriele, B.; Salerno, G. *Synthesis* **2007**, 3083-3087. (c) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895-7898. (d) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R. *Synthesis* **2006**, 4247-4251. (e) Gabriele, B.; Plastina, P.; Salerno, G.; Costa, M. *Synlett* **2005**, 935-938; (f) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, 346, 351−358. (g) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, 622, 84−88.

[8] Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83-87.

[9] (a) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607-4613. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **1999**, 3305-3313. (c) Ji, J.; Wang, Z.; Lu, X.

Organometallics **1996**, *15*, 2821-2828. (d) Gibbs, R. A.; Krishnan, U.; Dolence, J. M.; Poulter, C. D. J. Org. Chem. 1995, 60, 7821-7829. (e) de Vaal, P.; Dedieu, A. *J. Organomet. Chem.* **1994**, *478*, 121-129. (f) Dyker, G.; Kellner, A. *Tetrahedron Lett.* **1994**, *35*, 7633-7636.

[10] F. Araniti, R. Mancuso, I. Ziccarelli, F. Sunseri 1, M. R. Abenavoli and B. Gabriele *Molecules* **2014**, *19*, 8261-827.

[11] Varela-Fernandez, A.; Varela, J. A.; Saà, C. *Adv. Synth. Catal.* **2011**, 353, 1933−1937.

[12] Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, 56, 4777−4792.

[13] Schultz, A. G.; Guzzo, P. R.; Nowak, D. N. *J. Org. Chem.* **1995**, 60, 8044−8050.

[14] Bubar, A.; Estey, P.; Lawson, M.; Eisler, S. *J. Org. Chem.* **2012**, 77, 1572−1578.

[15] Arcadi, A.; Bianchi, G.; Marinelli, F.; Rossi, L.; Chiarini, M. *Adv. Synth. Catal.* **2010**, 352, 136−142.

[16] Larock, R. C.; Mehta, S.; Waldo, J. P. *J. Org. Chem.* **2009**, 74, 1141−1147.

[17] Kawamukai, S. *Synthesis* **1999**, 1145−1148.

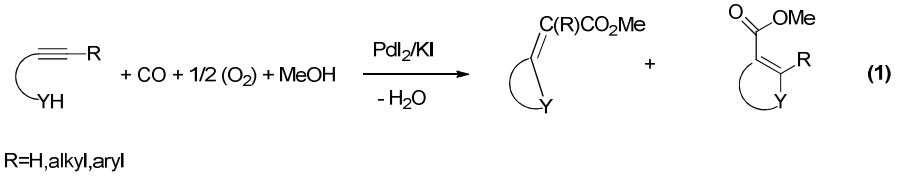
[18] (a) Yao, B.; Jaccoud, C.; Wang, Q.; Zhu, J. *Chem.- Eur. J.* **2012**, 18, 5864−5868. (b) Manita, J.; Masafumi, U.; Okiko, M. *Org. Lett.* **2011**, 13, 518−521.

[19] Mehta, S.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2012**, 77, 10938−10944.

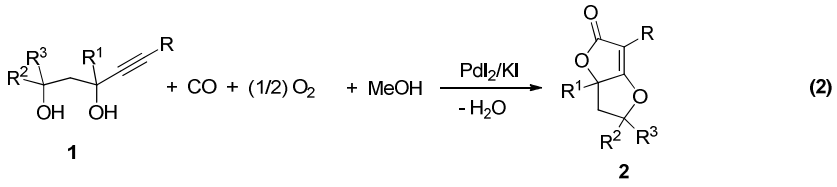
Chapter 3

3.1 New Synthesis of Furo-furanone Derivatives by PdI_2-Catalyzed Oxidative Carbonylation

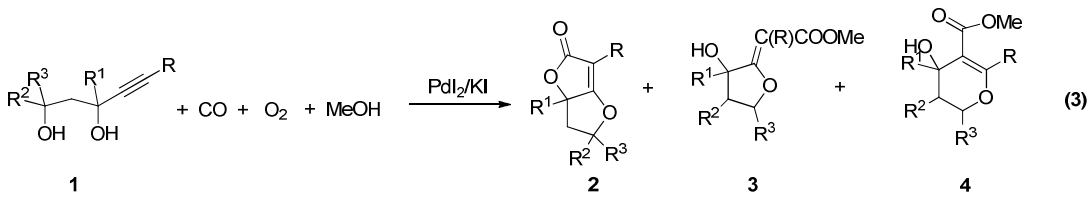
As shown above for the synthesis of isoindolinones and isobenzofuranimines, the oxidative carbonylation of alkynes bearing a nucleophilic group in a suitable position may lead to the formation of carbonylated heterocycles[1]; in particular, when the reaction is carried out in alcoholic solvent, such as MeOH or EtOH, the reaction lead to the corresponding alkoxycarbonylation products[2]. (*Eq. 1*)



Aim of this work is to test the reactivity of 4-yn-1,3-diols, substrates bearing themselves nucleophilic groups in a suitable position to give a "double" intramolecular nucleophilic attack so as to synthesize bicyclic molecules. (*Eq. 2*)

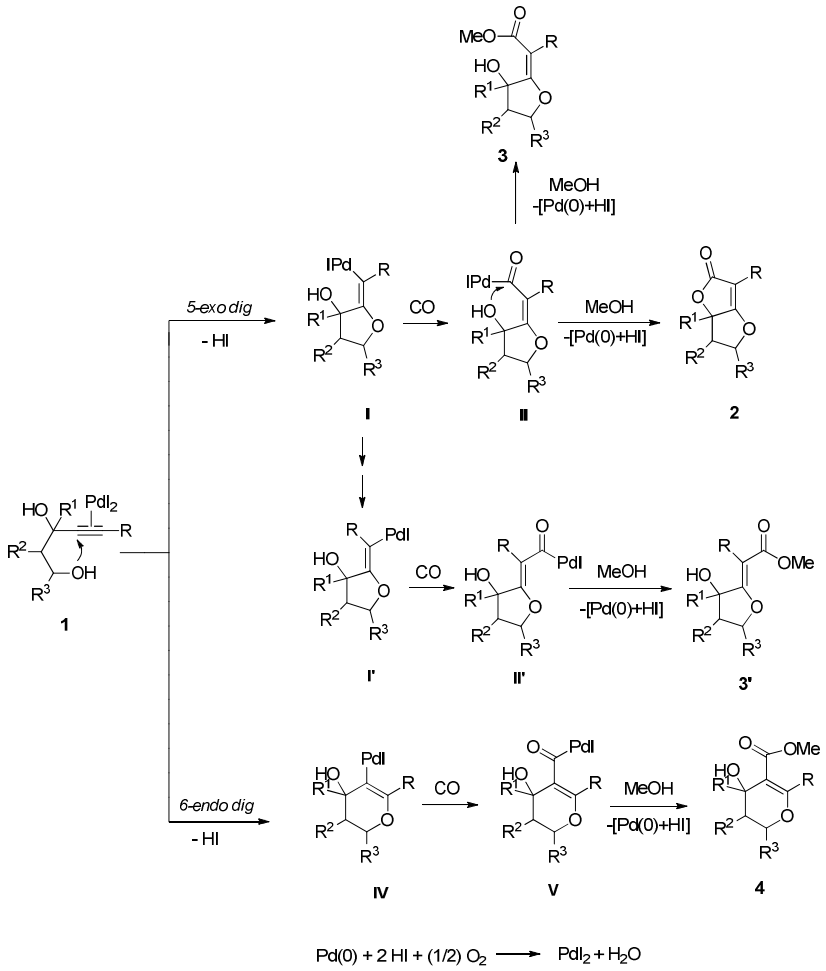


By carrying out the reaction in methanol we expected to obtain a mixture of products : the desired furo-furanone derivative **2** and also the "classical" alkoxycarbonylation products **3** and **4** (*Eq. 3*)



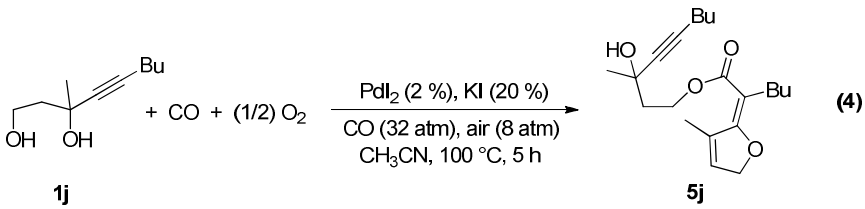
Following the coordination of PdI_2 , oxygen of C1-hydroxyl group can give intramolecular nucleophilic attack on the activated carbon-carbon triple bond so as to obtain vinylpalladium intermediate **I** (from *5-exo-dig* attack) and vinylpalladium intermediate **IV (** from *6-endo-dig* attack); then the insertion of carbon monoxide leads respectively to acylpalladium

intermediates **II** and **V**. While the acylpalladium intermediate **V** can only undergo nucleophilic displacement by MeOH, the acylpalladium intermediate **II** could undergo nucleophilic displacement by C3-hydroxyl group (to give the desired product **2**) or by MeOH (to give product **3**); partial isomerization of vinylpalladium intermediate **I** leads to product **3'**. (*Scheme 1)*



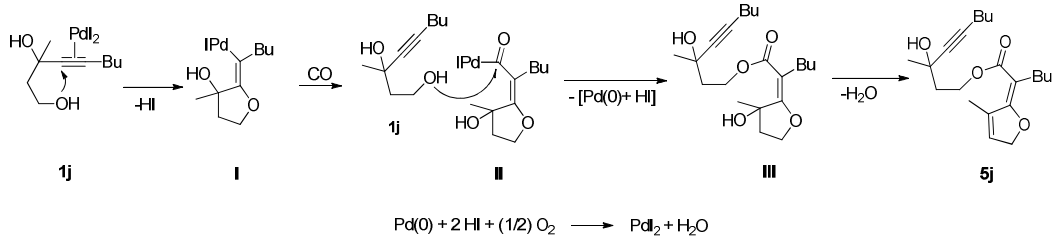
Scheme 12

In order to make the process selective to furo-furanone derivatives **2** we decided to carry out the reaction in CH_3CN instead of MeOH: surprisingly under oxidative carbonylation condition 3-methylnon-4-yne-1,3-diol **1j** led to **the** dehydration-alkoxycarbonylation product **5j**. (*Eq. 4*)



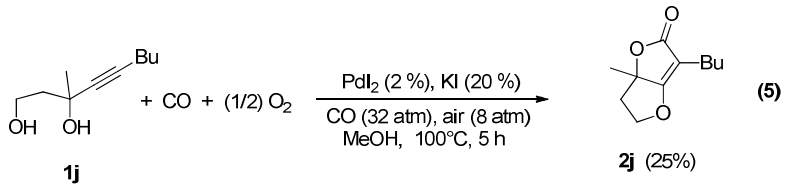
1j **5j** **(4)**

As shown in *Scheme 2*, after carbon monoxide insertion on the vinylpalladium intermediate **I**, the substrate itself gives nucleophilic attack to the acylpalladium intermediate **II** followed by dehydration**.**

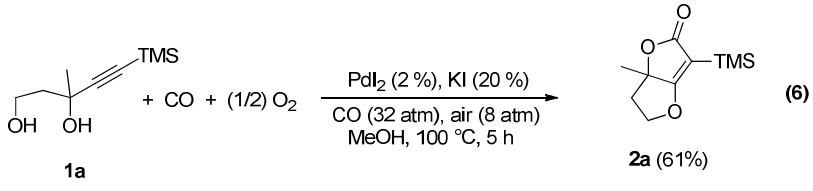


Scheme 13

The same reaction carried out in MeOH led to a very complicated mixture of products including the desired furofuranone derivative **2j** even though in modest yield (25%). (*Eq. 5*)

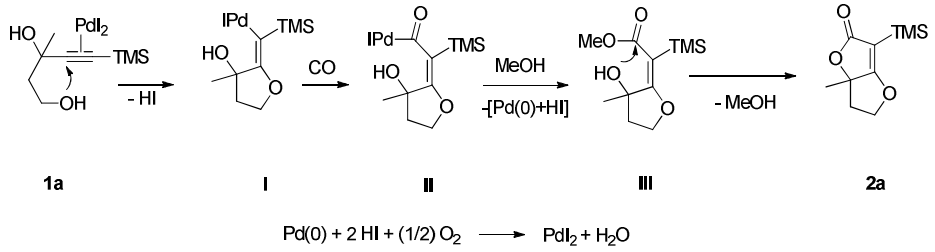


Starting from this result we verified the reactivity of an analogous substrate substituted on the carbon-carbon triple bond with the trimethylsilyl group. Substrate **1a** was allowed to react in the presence of PdI_2 (2 mol %) in conjunction with KI (20 mol %) in MeOH under a pressure of a mixture of CO (32 atm) and air (up to 40 atm). After 5 h at 80°C, the reaction was stopped, the autoclave cooled and degassed. The solvent was evaporated and the crude product purified by chromatographic column on neutral alumina (hexane/AcOEt, 99:1). GC-Massa, IR and NMR confirmed that the alkoxycarbonylation reaction of substrate **1a** leads to furo-furanone derivative **2a** with a good isolated yield of 61%. (*Eq. 6*)



This result suggests that MeOH plays a key role in the formation of the furo-furanone derivative as shown in *Scheme 3*. According to our hypothesis, MeOH firstly gives nucleophilic

displacement on the acylpalladium intermediate **II** followed by intramolecular nucleophilic attack by the C3-hydroxyl group.



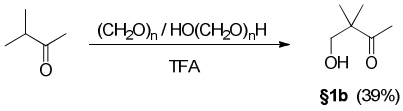
Scheme 14

We then carried out a screening of the reaction parameters by changing time by time gas pressure, substrate concentration, catalyst amount, temperature and reaction time. Decreasing temperature we obtained substrate conversion decreases (*Table1*, entry 2), so we decided to continue the screening at 80°C in order to understand how the other reaction parameters may influence the substrate conversion and the product yield. We observed that decreasing gas pressure the selectivity increases, while increasing gas pressure we obtained results comparable with the model reaction (*Table 1*, entries 3-4). Decreasing substrate concentration conversion worsens; on the other hand, increasing substrate concentration the selectivity improves although not significantly (*Table 1*, entries 5-6). We also verified how the amount of KI influences the catalyst activity (*Table 1*, entries 7-8) and the best result was obtained when the amount of KI is equal to 5 times the amount of PdI_2. Finally, the oxidative carbonylation of **1a** under optimized reaction condition led to furo-furanone derivative **2a** after 3 h with good isolated yield (61%). (*Table 1*, entry 10)

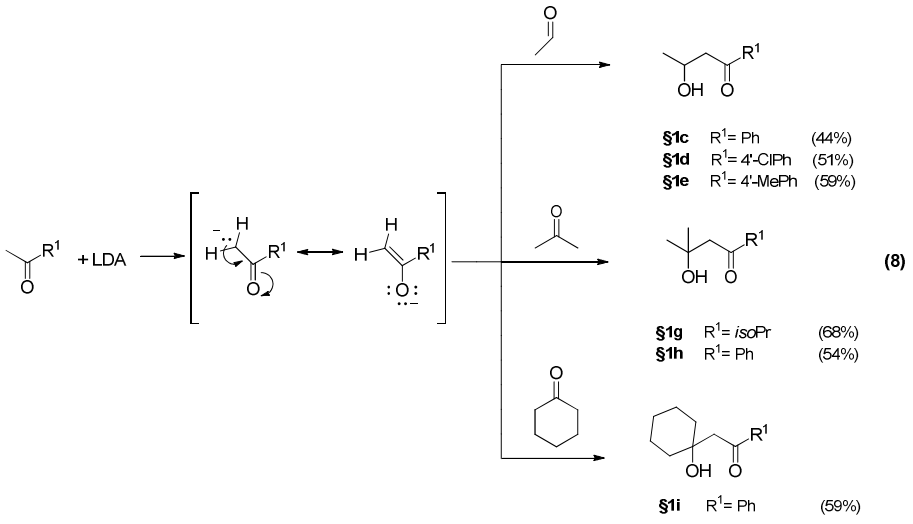
Table 1. *Optimization of reaction parameters*

Entry	PdI_2/KI/1a	[sub]	P_{CO}	P_{air}	T (°C)	t(h)	Conv (%)	Yield 2a (%)
1	1/10/50	0.05 M	32	8	100	5	100	61
2	1/10/50	0.05 M	32	8	80	5	82	49
3	1/10/50	0.05 M	16	4	80	5	72	58
4	1/10/50	0.05 M	48	12	80	5	85	48
5	1/10/50	0.02 M	32	8	80	5	50	30
6	1/10/50	0.1 M	32	8	80	5	79	52
7	1/5/50	0.05 M	32	8	80	5	87	61
8	1/20/50	0.05 M	32	8	80	5	74	33
9	1/5/50	0.05 M	16	4	100	5	100	61
10	1/5/50	0.05 M	16	4	100	3	100	68

All the substrates involved in the work have been synthesized starting from a β-hydroxy-ketone[3] obtained by reaction of 3-methyl-2-butanone with paraformaldehyde[4] (*Eq. 7*) or by aldolic condensation between the corresponding ketone and acetaldehyde or acetone using lithiumdiisopropylamide (LDA)[5] (*Eq. 8*). β-hydroxy-ketones then were allowed to react with a Grignard reagent in order to obtain 5-(trimethylsilyl)pent-4-yne-1,3-diols **1a-1i** and 5-(alkynyl)pent-4-yne-1,3-diols **1j-m.**[6] (*Eq. 9a and 9b*)



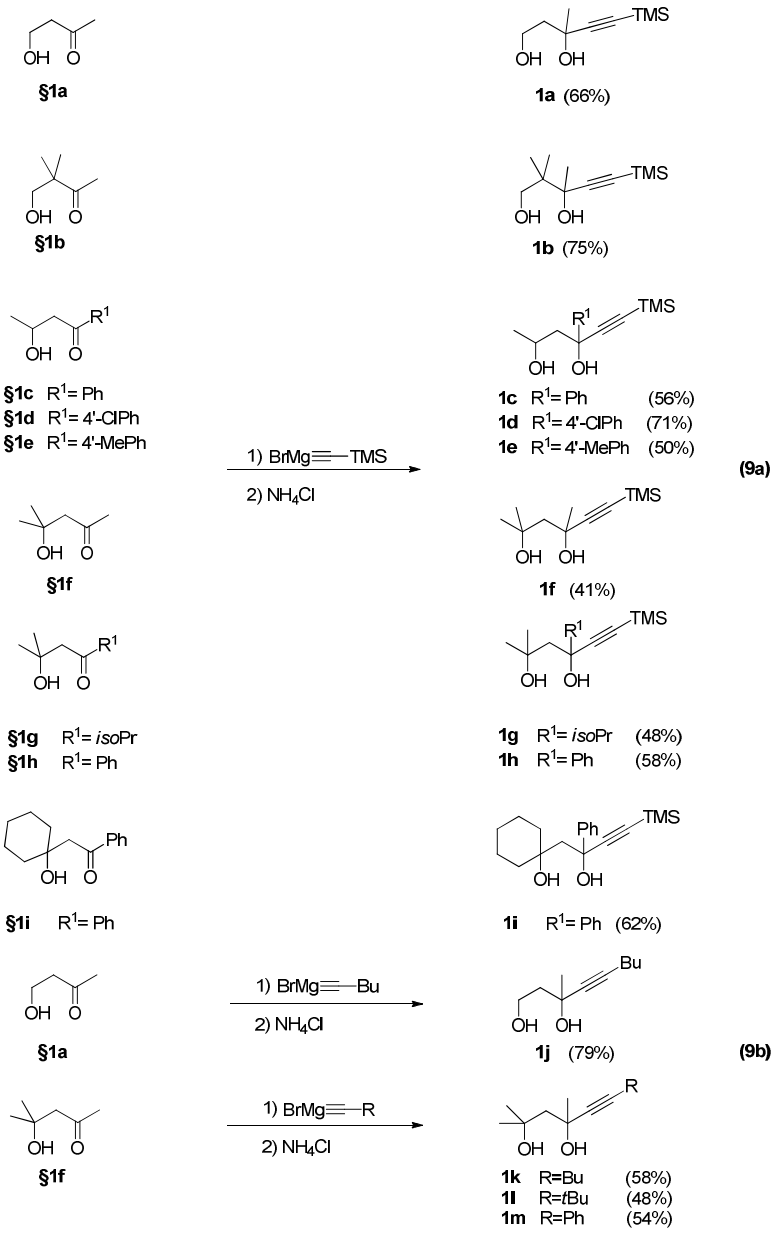
§1b (39%) **(7)**



§1c R^1= Ph (44%)
§1d R^1= 4'-ClPh (51%)
§1e R^1= 4'-MePh (59%)

§1g R^1= *iso*Pr (68%)
§1h R^1= Ph (54%)

§1i R^1= Ph (59%) **(8)**



In order to generalize the process, substrates **1b-1i** were allowed to react under optimized reaction conditions: even if the obtained yields were good, improved yields could be obtained when the reaction is carried out under a pressure of 40 atm of a mixture of carbon monoxide and air (*Table 2*); the structure of **2f** was confirmed by X-ray diffraction analysis, as shown in *Figure 1*.

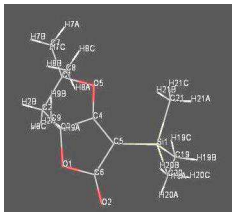
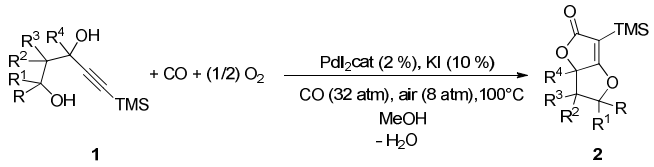
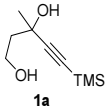
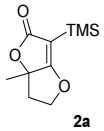
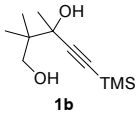
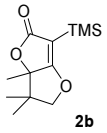
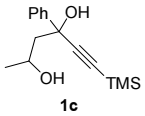
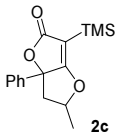
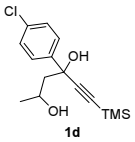
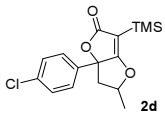
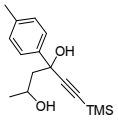
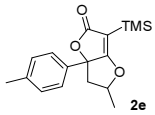
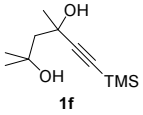
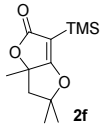
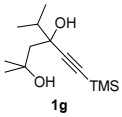
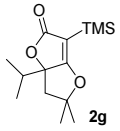
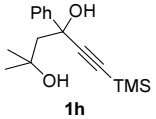
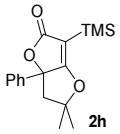
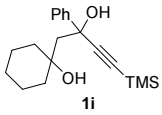
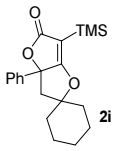


Figure 1

Table 2. *Scope*



Entry	**1**	R	R^1	R^2	R^3	R^4	t(h)	**2**	Yield of **2** (%)
1	 **1a**	H	H	H	H	Me	3	 **2a**	68
2	 **1b**	H	H	Me	Me	Me	3	 **2b**	82
3	 **1c**	Me	H	H	H	Ph	15	 **2c**	55
4	 **1d**	Me	H	H	H	4'-ClC_6H_4	15	 **2d**	49
5	 **1e**	Me	H	H	H	4'-MeC_6H_4	5	 **2e**	66
6	 **1f**	Me	Me	H	H	Me	3	 **2f**	86
7	 **1g**	Me	Me	H	H	*iso*Pr	3	 **2g**	88
8	 **1h**	Me	Me	H	H	Ph	3	 **2h**	82
9	 **1i**	-$(CH_2)_5$-		H	H	Ph	3	 **2i**	64

In particular substrates **1c-e,** bearing a secondary alcoholic group on C1, are obtained as mixture of two diastereoisomers named- for clarity- **1c-A**, **1d-A**, **1e-A** and **1c-B**, **1d-B**, **1e-B**. *Tables 3-5* shows data related to the reactions carried out with the two diastereoisomers together and separately. In all cases, when we allowed to react substrates as mixture of diastereoisomers, the yield of the corresponding furo-furanone derivatives was lower with respect to that obtained starting from pure diastereoisomers **1c-B**, **1d-B** and **1e-B**. The structure of **2d-B** (**2*S*-4*S***) was confirmed by X-ray diffraction analysis, as shown in *Figure 2*.

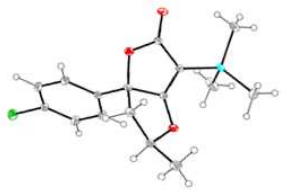
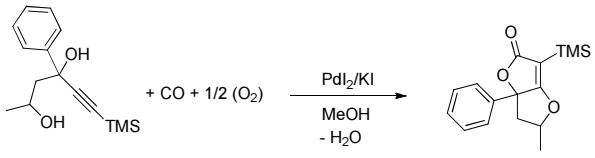


Figura 2

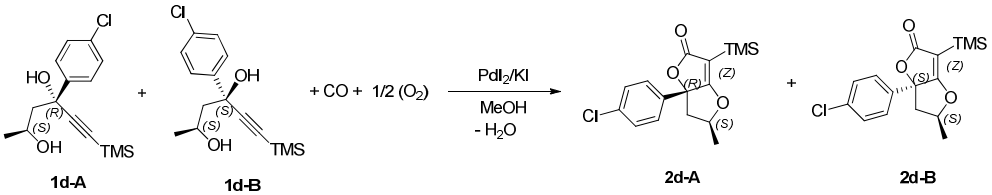
Table 3. *PdI_2-catalyzed oxidative carbonylation of 4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol* ***1c***



1c **2c**

entry	sub	PdI_2/KI/sub	[sub]	P_{CO}	P_{air}	T (°C)	t(h)	Conv (%)	Yield 2c (%)
1	**1c-A + 1d-B**	1/5/50	0.05 M	32	8	100	15	100	55
2	**1c-A**	1/5/50	0.05 M	32	8	100	8	91	52
3	**1c-B**	1/5/50	0.05 M	32	8	100	3	100	61

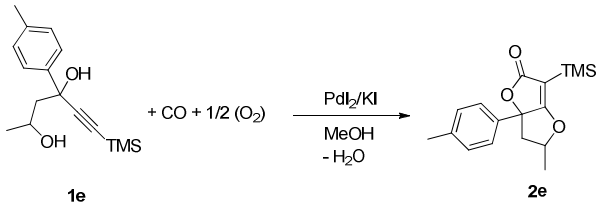
Table 4. *PdI_2-catalyzed oxidative carbonylation of 4-(4-chlorophenyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol* ***1d***



1d-A **1d-B** **2d-A** **2d-B**

entry	sub	PdI_2/KI/sub	[sub]	P_{CO}	P_{air}	T (°C)	t(h)	Conv (%)	Yield 2d (%)
1	**1d-A + 1d-B**	1/5/50	0.05 M	32	8	100	15	100	49
2	**1d-A (2*S*,4*R*)**	1/5/50	0.05 M	32	8	100	15	100	68
3	**1d-B (2*S*,4*S*)**	1/5/50	0.05 M	32	8	100	8	100	52

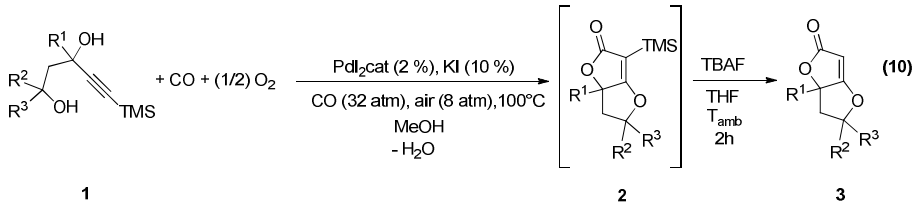
Table 5. *PdI_2-catalyzed oxidative carbonylation of 4-(p-tolyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol* ***1e***



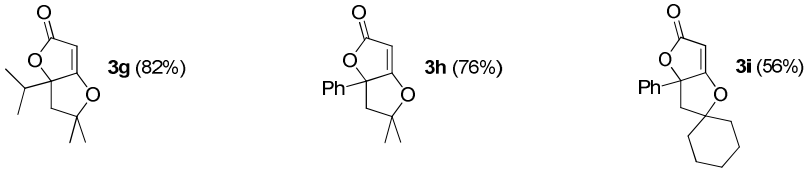
1e 2e

entry	sub	PdI_2/KI/sub	[sub]	P_{CO}	P_{air}	T (°C)	t(h)	Conv (%)	Yield 2e (%)
1	**1e-A + 1e-B**	1/5/50	0.05 M	32	8	100	5	100	66
2	**1e-A**	1/5/50	0.05 M	32	8	100	5	100	40
3	**1e-B**	1/5/50	0.05 M	32	8	100	3	100	80

Crude 3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)-ones **2g-l** could also be deprotected using TBAF *n*H_2O.



1 2 3



Finally, in order to extend the scope, the reactivity of substrates **1j-m** was tested. Also in the case of substrates **1k**, **1l** and **1m**, as well as for substrate **1j**, the results were unsatisfactory. The structure of **2m** was confirmed by X-ray diffraction analysis, as shown in *Figure 3*.

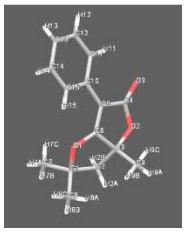
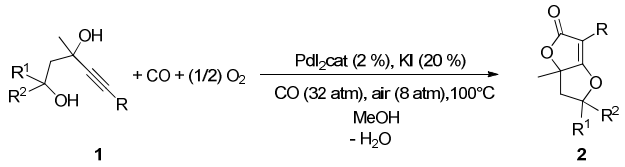
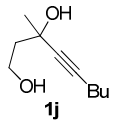
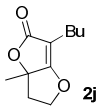
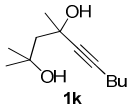
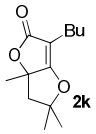
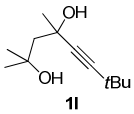
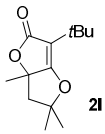
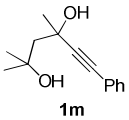
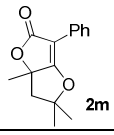


Figure 3

Table 6. ***Scope***



1 **2**

Entry	**1**	R	R^1	R^2	t(h)	**2**	Yield of **2** (%)
1	 **1j**	H	H	H	5	 **2j**	25
2	 **1k**	H	H	Me	15	 **2k**	41
3	 **1l**	Me	H	H	15	 **2l**	39
4	 **1m**	Me	H	H	15	 **2m**	27

3.2 Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solution at 300 or 500 MHz and 75 or 126 MHz respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in *Hz*, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} or on neutral alumina and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

3.2.1 General Procedure for the Preparation of pent-4-yne-1,3-diols 1a-1m

5-(trimethylsilyl)pent-4-yne-1,3-diols **1a-1i** were prepared by alkynylation of the appropriate β-hydroxy ketone using an excess of ((trimethylsilyl)ethynyl)magnesium bromide, as described below. All other materials, including β-hydroxy ketones **§1a** and **§1f,** were commercially available and were used without further purification.

1st Step: Preparation of β-hydroxy ketones §1b-e,g-i

β-hydroxy ketone **§1b** was prepared starting from 3-methyl-2-butanone by addition of paraformaldehyde.[7a] β-hydroxy ketones **§1c-e,g-i** were instead prepared from methyl ketones by aldol condensation with acetaldehyde or acetone according to a literature procedure.[7a-e] Aldols **§1b,**[7a] **§1c,**[7b] **§1d,**[7c] **§1e,**[7d] **§1g,**[7a,7e] **§1h**[7e] are known compounds. Data for aldols **§1i** are given in the *Characterization Data* Section.

Preparation of 4-hydroxy-3,3-dimethylbutan-2-one §1b. To a solution of 3-methyl-2-butanone (8.61 g, 100.0 mmol) in TFA (7.7 mL) were added paraformaldehyde (3 g, 100.0 mmol). The mixture was heated to 90 °C for 10 hours. The mixture was cooled to room temperature. Then, 180 mL of aqueous $NaHCO_3$ were carefully added in the reaction, until the solution turns yellow. The aqueous layer was extracted with 120 mL di CH_2Cl_2 and then with 2 × 60 mL of dichloromethane. The organic phase was dried over Na_2SO_4, filtered and concentrated. Purification over silica gel using as eluent 8:2 hexane-AcOEt provided 4.53 g of 4-hydroxy-3,3-dimethylbutan-2-one ***§1b*** as a colorless oil (Yield, 39%).

Preparation of β-*hydroxy ketones* ***§1c-e,g-i****.* To a stirred solution of diisopropylamine (5.57 g , 55 mmol) in anhydrous diethyl ether (150 mL) cooled to 0°C was slowly added, under nitrogen and dropwise, a solution of *n*-BuLi in hexane 1.6 M (34.4 mL, 55 mmoL). The resulting solution was stirred for 30 min at 0 °C prior to cooling to 78°C. The appropriate methyl ketone (50 mmol; R= Ph, 6.01 g; R= 4'ClPh, 7.73 g; R= 4'MePh, 6.71 g ; R= *iso*Pr, 4,31 g) was then slowly added to this solution. The resulting solution was stirred for 1 h at 78°C prior to slow addition of dry aldehyde or ketone (60 mmoL; acetaldehyde, 2.64 g; acetone, 3.49 g; cyclohexanone, 5.89 g). Stirring was continued for 3 h at 78 °C before the reaction was quenched with saturated aqueous ammonium chloride solution (50 mL). The reaction mixture was allowed to reach

room temperature. The layers were separated and the aqueous layer was extracted twice with diethyl ether (50 mL) . The combined organic layers were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using as eluent 9:1 hexane-Acetone for **§1c;** 8:2 hexane-Acetone for **§1d;** 9:1 hexane-diethyl ether for **§1e;** 7:3 hexane-AcOEt for **§1g;** 8:2 pentane-diethyl ether for **§1h;** 9:1 hexane-AcOEt for **§1i**.

2nd Step: Preparation of pent-4-yne-1,3-diols 1a-1m .[8] To a suspension of Mg turnings (1.74 g, 71.4 mmol) in anhydrous THF (14.8 mL), maintained under nitrogen and under reflux, was added pure ethyl bromide (1.3 mL, 17,5 mmoL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise in THF solution (3.9 mL, 52.5 mmoL of EtBr in 42.9 mL of THF; total amount of EtBr added 7.63 g, 70.0 mmol). The mixture was then refluxed for an additional 20 min. After cooling, the resulting solution of EtMgBr was transferred under nitrogen into a dropping funnel and added dropwise under nitrogen to a solution of 1-alkynes (70 mmol: trimethylsilylacetylene, 6.88 g; 1-hexyne, 5.75 g; *tert*-butylacetylene, 5.75 g; phenylacetylene, 7.15 g) in anhydrous THF (21 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was warmed to room temperature and then maintained at 40 °C for 2 h. While warm, to the solution of ((trimethylsilyl)ethynyl)magnesium bromide or alkynyl magnesium bromide thus obtained was then added dropwise under nitrogen to a solution of β-hydroxy ketone (28 mmol: **§1a,** 2.47 g; **§1b,** 3.25 g; **§1c,** 4.6 g; **§1d,** 5.56 g; **§1e,** 4.99 g; **§1f,** 3.25 g; **§1g,** 4.04 g; **§1h**, 4.99 g; **§1i,** 6.11 g) in anhydrous THF (34 mL). The resulting mixture was stirred at 40 °C for an additional 2 h. After the mixture was cooled to room temperature, saturated NH_4Cl (80 mL) and AcOEt (30 mL) were sequentially added. Phases were separated, and the aqueous phase was extracted with AcOEt (3 × 80 mL). The collected organic layers were washed with brine and dried over Na_2SO_4. After filtration and evaporation of the solvent, the product was purified by column chromatography on silica gel using as eluent 7:3 hexane-AcOEt for **1a, 1g and 1h**; 8:2 hexane-AcOEt for **1b, 1c, 1d** and **1j**; 9:1 hexane-AcOEt for **1k, 1l** and **1m**; 95:5 hexane-AcOEt for **1e**, **1f** and **1i.**

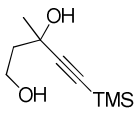
3.2.2 General Procedure for the Synthesis of 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)-ones 2 by PdI_2-Catalyzed-Heterocyclization-Carbonylation of pent-4-yne-1,3-diols *1a-m*.

A 250 mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (11,5 mg, 6.95×10^{-2} mmol) and a solution of **1** (0.7 mmol: **1a** (130,4 mg), **1b** (150.1 mg), **1c** (183.7 mg), **1d** (207.8 mg), **1e** (193.5 mg), **1f** (150.1 mg), **1g** (169.7 mg), **1h** (193.5 mg), **1i** (221.6 mg), **1j** (119.2 mg), **1k** (138.8 mg), **1l** (138.8 mg), **1m** (152.8 mg)] in MeOH (14 mL). The autoclave was sealed and, while the mixture was stirred, the autoclave was pressurized with CO (32 atm) and air (up to 40 atm). After being stirred at 100°C for the required time (3h for **1a**, **1b**, **1f**, **1g**, **1h** and **1i**; 5 h for **1e**; 15h for **1c**, **1d**, **1j**, **1k**, **1l** and **1m**) the autoclave was cooled, degassed and opened. The solvent was evaporated and the products were purified by column chromatography on neutral alumina using as eluent hexane to hexane/AcOEt 9:1.

3.2.3 General Procedure for the Desilylation of crude 3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)-ones *2g-i*

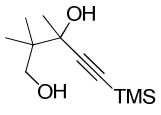
Substrates **1g-1h** (0.7 mmoL) were allowed to react under oxidative carbonylation conditions according to the procedure described in **3.2.2**. To the crude reaction mixture, dried under vacuum and then diluted again with THF (7 mL), was added was added TBAF nH_2O (201.3 mg, 0.77 mmoL). The resulting mixture was allowed to stir at room temperature for 2 h. The solvent was evaporated, and the residue taken up with Et_2O (40 mL) and washed with water (40 mL). The aqueous layer was extracted with Et_2O (3 × 40 mL), and the collected organic phases were dried over $NaSO_4$. After filtration, the solvent was evaporated and the products were purified by column chromatography on neutral alumina to give pure 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)-one derivatives **3g-i** (eluent: from hexane to hexane/AcOEt 9:1).

3.3 Characterization Data



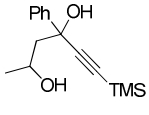
1a

*3-methyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (**1a**).* Yield: 3.44 g, starting from 2.47 g of 4-hydroxybutan-2-one (66%). White solid, mp 33.8-34.8 °C. IR (KBr): *v* = 3399 (s, br), 2963 (m), 2902 (w), 2168 (w), 1402 (m), 1286 (w), 1247 (m), 1125 (m), 930 (m), 842 (s), 759 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.20-4.09 (m, 1H, HOC*H*HCH$_2$C(OH)CH$_3$), 3.94-3.86 (m, 1H, HOCH*H*CH$_2$C(OH)CH$_3$), 3.69 (s br, 2H, 2O*H*), 2.00-1.91 (m, 1H, HOCH$_2$C*H*H(OH)CH$_3$), 1.85-1.78 (m, 1H, HOCH$_2$CH*H*(OH)CH$_3$), 1.52 (s, 3H, Me), 0.17 (s, 9H, Si(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.0, 88.1, 68.9, 60.5, 43.9, 30.7; GC-MS: *m/z* = 186 (absent) [M^+], 171 (4), 155 (1), 153 (7), 141 (100), 125 (14), 123 (34), 113 (1), 101 (13), 99 (12), 97 (5), 83 (7), 75 (18), 73 (15), 43 (6); anal. calcd for $C_9H_{18}O_2Si$ (186.33): C, 58.02; H, 9.74; Si,15.07; found: C, 58.06; H, 9.75; Si,15.09.



1b

*2,2,3-trimethyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (**1b**)*. Yield: 4.5 g, starting from 3.25 g of 4-hydroxy-3,3-dimethylbutan-2-one (75%). White solid, mp 45.3-46.3 °C. IR (KBr): *v* = 3335 (s, br), 2963 (s), 2898 (m), 2875 (w), 2167 (w), 1474 (m), 1393 (m), 1251 (s), 1192 (w), 1145 (m), 1111 (m), 1042 (m), 935 (m), 860 (s), 842 (s), 816 (m), 699 (w), 635 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.94 (d, J=10.8, 1H, HOC*H*HC(CH$_3$)$_2$), 3.72 (s br, 2H, 2O*H*), 3.49 (d, J=10.8,1H, HOCH*H*C(CH$_3$)$_2$), 1.44 (s, 3H, Me), 1.05 (s, 3H, (C*H*$_3$)C(CH$_3$), 0.98 (s, 3H, (C*H*$_3$)C(CH$_3$)), 0.17 (s, 9H, Si(CH$_3$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.9, 88.3, 75.0, 71.4, 40.8, 25.2, 21.8, 19.2; GC-MS: *m/z* = 214 (absent) [M^+], 183 (2), 182 (6), 181 (35), 151 (10), 143 (5), 142 (17), 141 (100), 127 (%), 125 (8), 101 (24), 99 (23), 97 (5), 83 (12), 75 (36), 73 (44), 56 (23); anal. calcd for $C_{11}H_{22}O_2Si$(214.38): C, 61.63; H, 10.34; Si, 13.10; found: C, 61.59; H, 10.35; Si, 13.13.

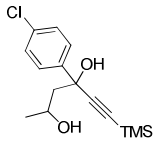


1c

*4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (**1c**).* Yield: 4.12 g, starting from 4.6 g of 3-hydroxy-1-phenylbutan-1-one (56%). White solid; anal. calcd for $C_{15}H_{22}O_2Si$ (262.42): C, 68.65; H, 8.45; Si, 10.70; found: C, 68.69; H, 8.46; Si, 10.67.

[*1c-A*] White solid, mp 63.9-64.9 °C. IR (KBr): *v* = 3226 (s, br), 2964 (s), 2908 (m), 2875 (w), 2168 (w), 1447(m), 1426 (m), 1313 (m), 1252 (s), 1134 (m), 1086 (m), 914 (w), 893 (m), 776 (s), 759 (s), 699 (s), 669 (s), 644 (w), 520 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67-7.60 (m, 2H, aromatic ring), 7.40-7.22 (m, 3H, aromatic ring), 4.61-4.45 (m, 1H, HOC*H*CH_3), 4.38 (s br, 1H, OH), 3.26 (s br, 1H, OH), 1.94 (dd dist, *J*=14.5, 10.0, 1H, CHC*H*HPh), 1.79 (dd dist, *J*=14.5, 1.9, 1H, CHCH*H*Ph), 1.20 (d, J=6.3, 3H, Me), 0.22 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 128.3, 127.8, 125.4, 108.1, 91.6, 74.1, 67.0, 53.2, 24.1; GC-MS: *m/z* = 262 (absent) [M^+], 247 (1), 244 (1), 229 (4), 217 (2), 205 (8), 204 (22), 203 (100), 187 (11), 185 (8), 161 (7), 159 (4), 135 (7), 128 (4), 125 (5), 105 (8), 77 (4), 73 (9), 45 (3);

[*1c-B*] Colorless oil. IR (film): *v* = 3323 (s, br), 2966 (s), 2918 (m), 2900 (w), 2167 (w), 1448 (m), 1423 (m), 1251 (s), 1139 (m), 1071 (m), 963 (w), 840 (s), 720 (s), 701 (s), 627 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.62-7.50 (m, 2H, aromatic ring), 7.39-7.20 (m, 3H, aromatic ring), 3.95-3.75 (m, 2H, OH + HOC*H*CH_3), 3.23 (s br, 1H, OH), 2.18 (dd dist, *J*=14.5, 9.6, 1H, CHC*H*HPh), 1.99 (dd dist, *J*=14.5, 1.4, 1H, CHCH*H*Ph), 1.11 (d, J=6.2, 3H, Me), 0.19 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = δ = 144.8, 128.5, 127.9, 125.6, 109.4, 91.1, 72.8, 65.3, 53.6, 24.0; GC-MS: *m/z* = 262 (absent) [M^+], 247 (1), 244 (1), 229 (5), 217 (2), 205 (8), 204 (21), 203 (100), 187 (10), 185 (7), 161 (7), 159 (4), 135 (8), 128 (4), 125 (5), 105 (10), 77 (5), 73 (10), 45 (4).



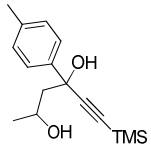
1d

*4-(4-chlorophenyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol (**1d**).* Yield: 5.9 g, starting from 5.56 g of 1-(4-chlorophenyl)-3-hydroxybutan-1-one (71%). White solid; anal. calcd for $C_{15}H_{21}ClO_2Si$ (296.87): C, 60.69; H, 7.13; Cl, 11.94; Si, 9.46; found: C, 60.75; H, 7.14; Cl, 11.92; Si, 9.43.

[*1d-A*] White solid, mp 79.8-80.8 °C. IR (KBr): *v* = 3203 (s, br), 2965 (s), 2912 (m), 2897 (w), 2167 (w), 1489(m), 1425 (m), 1400 (m), 1273 (m), 1252 (m), 1160 (m), 1132 (m), 1085 (m), 963 (m), 861 (s), 845 (s), 816 (m), 646 (w), 519 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60-7.51 (m, 2H, aromatic ring), 7.35-7.27 (m, 2H, aromatic ring), 4.38 (s br, 1H, OH), 4.62-4.85 (m, 1H, HOC*H*CH_3), 3.16 (s br, 1H, OH), 1.88 (dd dist, *J*=14.5, 9.6, 1H, CHC*H*HC_6H_4), 1.76 (dd dist, *J*=14.5, 1.9, 1H, CHCH*H*C_6H_4), 1.21 (d, J=6.3, 3H, Me), 0.22 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.9, 133.8, 128.5, 127.0, 107.4, 91.8, 73.6, 67.2 52.9, 24.2; GC-MS: *m/z* = 296 (absent) [M^+], 281 (1), 278 (1), 240 (7), 239 (39), 238 (20), 237 (100), 221 (22), 219 (30), 195 (8), 185 (1), 169 (9), 139 (12), 111 (4), 99 (5), 75 (10), 73 (15), 45 (5), 43 (5).

[*1d-B*] White solid, mp 75.2-76.2 °C. IR (KBr): *v* = 3211 (s, br), 2962 (s), 2911 (m), 2898 (w), 2166 (w), 1490 (s), 1404 (m), 1249 (s), 1186 (m), 1136 (s), 1008 (s), 958 (m), 895 (m), 846 (s), 816 (m), 763 (m), 726 (m), 570 (w), 499 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.91-7.47 (m, 2H, aromatic ring), 7.34-7.28 (m, 2H, aromatic ring), 3.98 (s br, 1H, OH), 3.92-3.80 (m, 1H, HOC*H*CH_3), 3.09 (s br, 1H, OH), 2.18 (dd dist,

J=14.5, 9.6, 1H, CHC*H*HC$_6$H$_4$), 1.97 (dd dist, *J*=14.5, 1.9, 1H, CHCH*H*C$_6$H$_4$), 1.11 (d, J=6.3, 3H, Me), 0.19 (s, 9H, Si(CH$_3$)$_3$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 143.5, 134.0, 128.7, 127.2, 108.8, 91.4, 72.5, 65.6, 53.4, 24.1; GC-MS: *m/z* = 296 (absent) [M$^+$], 281 (1), 278 (1), 240 (7), 239 (39), 238 (19), 237 (100), 221 (17), 219 (15), 195 (10), 185 (1), 169 (13), 139 (19), 111 (8), 99 (10), 75 (20), 73 (26), 45 (12), 44 (4), 43 (9).

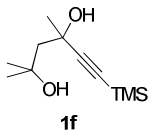


1e

*4-(p-tolyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol (**1e**).* Yield: 3.87 g, starting from 4.99 g of 3-hydroxy-1-(p-tolyl)butan-1-one (50%). White solid; anal. calcd for C$_{16}$H$_{24}$O$_2$Si (276.45): C, 69.52; H, 8.75; Si, 10.16; found: C, 69.56; H, 8.76; Si, 10.19.

[*1e-A*] White solid, mp 63.4-64.4 °C. IR (KBr): *v* = 3336 (m, br), 2965 (s), 2920 (m), 2167 (w), 1510 (m), 1422 (m), 1376 (m), 1311 (w), 1250 (s), 1180 (w), 1132 (m), 1086 (m), 962 (m), 844 (s), 760 (s), 701 (w), 617 (w), 512 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.57-7.42 (m, 2H, aromatic ring), 7.20-7.07 (m, 2H, aromatic ring), 4.60-4.45 (m, 2H, OH + HOC*H*CH$_3$), 3.73-3.30 (s br, 1H, OH), 2.34 (s, 3H, CH$_3$ on aromatic ring), 1.92 (dd dist, *J*= 14.5, 10.1, 1H, CHC*H*HC$_6$H$_4$), 1.78 (dd dist, *J*= 14.5, 1.8, 1H, CHCH*H*C$_6$H$_4$), 1.20 (d, J=6.3, 3H, Me), 0.22 (s, 9H, Si(CH$_3$)$_3$); NMR (75 MHz, CDCl$_3$): δ = 142.1, 137.3, 128.9, 125.1, 107.3, 91.0, 73.9, 66.9 52.4, 23.8, 21.0, -0.052; GC-MS: *m/z* = 276 (absent) [M$^+$], 281 (1), 243 (2), 231 (2), 219 (7), 218 (21), 217 (100), 201 (7), 175 (4), 149 (4), 119 (9), 97 (3), 75 (6), 73 (9).

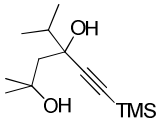
[*1e-B*] White solid, mp 84.5-85.5 °C. IR (KBr): *v* = 3335 (m, br), 2965 (s), 2921 (m), 2169 (w), 1510 (m), 1421 (m), 1376 (m), 1311 (w), 1250 (s), 1180 (w), 1140 (m), 1089 (m), 963 (m), 844 (s), 770 (m), 701 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.50-7.41 (m, 2H, aromatic ring), 7.22-7.13 (m, 2H, aromatic ring), 3.98-3.86 (m, 1H, HOC*H*CH$_3$), 3.47 (s br, 1H, OH), 3.10 (s br, 1H, OH), 2.36 (s, 3H, CH$_3$ on aromatic ring), 2.18 (dd dist, *J*= 14.5, 9.6, 1H, CHC*H*HC$_6$H$_4$), 1.98 (dd dist, *J*= 14.5, 1.7, 1H, CHCH*H*C$_6$H$_4$), 1.12 (d, *J*=6.3, 3H, Me), 0.19 (s, 9H, Si(CH$_3$)$_3$); NMR (75 MHz, CDCl$_3$): δ = 141.1, 137.4, 129.0, 125.2, 108.6, 90.3, 72.4, 64.9, 52.6, 23.6, 21.0, -0.21; GC-MS: *m/z* = 276 (absent) [M$^+$], 243 (2), 231 (1), 219 (9), 218 (23), 217 (100), 201 (8), 175 (5), 149 (6), 125 (8), 119 (12), 97 (5), 91 (8), 75 (8), 73 (12).



1f

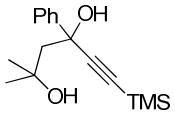
2,4-dimethyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (1f). Yield: 2.46 g, starting from 3,25 g of 4-hydroxy-4-methylpentan-2-one (41%). White solid, mp 69.1-70.1 °C. IR (KBr): *v* = 3335 (m, br), 2971 (s), 2936 (m), 2167 (w), 1408 (m), 1368 (m), 1251 (s), 1191 (s), 1097 (w), 1066 (w), 965 (m), 932 (w), 878 (s), 843 (s), 761 (m), 627 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.89 (s br, 2H, 2O*H*), 1.91 (s br, 2H, C*HH*),

1.54 (s, 3H, CH_3CCH_3), 1.51 (s, 3H, CH_3CCH_3), 1.29 (s, 3H, $C(OH)CH_3$), 0.16 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.4, 88.5, 72.4, 67.3, 52.4, 33.1, 32.6, 29.4, -0.25; GC-MS: *m/z* = 214 (1) [M^+], 199 (2), 181 (64), 143 (35), 142 (13), 141 (100), 138 (23), 125 (63), 123 (74), 101 (28), 99 (34), 97 (17), 83 (20), 77 (7), 75 (45), 73 (56); 59 (33), 56 (25), 55 (8), 45 (14), 43 (50); anal. calc for $C_{11}H_{22}O_2Si$ (214.38): C, 61.63; H, 10.34; Si, 13.10; found: C, 61.58; H, 10.36; Si, 13.13.



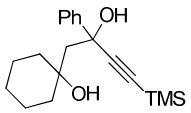
1g

*4-isopropyl-2-methyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (**1g**).* Yield: 3.26 g, starting from 4.04 g of 5-hydroxy-2,5-dimethylhexan-3-one (48%). White solid, mp 82.1-83.1 °C. IR (KBr): *v* = 3230 (s, br), 2973 (s), 2916 (m), 2875 (m), 2164 (w), 1471 (m), 1409 (s), 1367 (m), 1249 (s), 1195 (m), 1158 (m), 1062 (m), 1018 (m), 990 (w), 913 (w), 880 (s), 840 (s), 760 (s), 697 (w), 625 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.96-1.87 (m, 1H, C*H*H), 1.85-1.73 (m, 2H, CHH + $CH(CH_3)_2$), 1.54 (s, 3H, CH_3CCH_3), 1.30 (s, 3H, CH_3CCH_3), 1.03 (d, *J*=6.7, 3H, CH_3CHCH_3), 0.97 (d, J=6.7, 3H, CH_3CHCH_3), 0.16 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.2, 90.8, 73.9, 72.3, 48.6, 40.4, 32.6, 29.8, 17.6, 16.8, -0.21; GC-MS: *m/z* = 242 (absent) [M^+], 224 (1), 209 (7), 199 (4), 181 (19), 169 (15), 152 (9), 151 (52), 141 (54), 133 (10), 126 (13), 125 (100), 101 (7), 99 (9), 97 (20), 83 (21), 75 (28), 73 (81); 59 (34), 55 (8), 43 (44); anal. calc for $C_{13}H_{26}O_2Si$ (242.43): C, 64.41; H, 10.81; Si, 11.58; found: C, 64.45; H, 10.80; Si, 11.55.



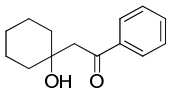
1h

*2-methyl-4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (**1h**).* Yield: 4.49 g, starting from 4.99 g of 3-hydroxy-3-methyl-1-phenylbutan-1-one (58%). White solid, mp 79.7-80.7 °C. IR (KBr): *v* = 3304 (m, br), 2968 (m), 2920 (m), 2169 (w), 1492 (m), 1448 (m), 1386 (m), 1250 (s), 1174 (s), 1049 (m), 950 (w), 875 (s), 844 (s), 785 (w), 760 (m), 744 (m), 689 (s), 645 (w), 603 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J=7.63, 2H, J=7.63, on aromatic ring), 7.34 8t, 2H, J= 7.63, on aromatic ring), 7.26 (t, J=7.63, 1H, on aromatic ring), 4.61 (s br, 1H, OH), 3.41 (s br, 1H, OH), 2.07 (q, J=15.0, 2H, C*H*H), 1.56 (s, 3H, CH_3CCH_3), 1.21 (s, 3H, CH_3CCH_3), 0.19 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.1, 128.2, 127.4, 125.2, 109.0, 91.5, 72.6, 72.5, 55.2, 32.2, 29.7, -0.31; GC-MS: *m/z* = 276 (absent) [M^+], 258 (1), 243 (25), 205 (9), 204 (18), 203 (100), 187 (14), 185 (30), 169 (3), 159 (14), 135 (12), 125 (9), 105 (21), 97 (6), 77 (14), 75 (17), 73 (31); 59 (11), 45 (8), 43 (20); anal. calc for $C_{16}H_{24}O_2Si$ (276.45): C, 69.52; H, 8.75; Si, 10.16; found: C, 69.56; H, 8.77; Si, 10.13.



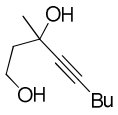
1i

*1-(2-hydroxy-2-phenyl-4-(trimethylsilyl)but-3-yn-1-yl)cyclohexan-1-ol (**1i**).* Yield: 5.5 g, starting from 6.11 g of 2-(1-hydroxycyclohexyl)-1-phenylethan-1-one (62%). White solid, mp = 38.9-39.9 °C. IR (KBr): *v* = 3244 (m, br), 2935 (s), 2860 (m), 2166 (m), 1449 (s), 1348 (m), 1250 (s), 1169 (m), 1075 (s), 950 (w), 1033 (w), 975 (s), 866 (s), 840 (s), 759 (s), 700 (m), 633 (w), 560 (w), 506 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J*=7.3, 2H, on aromatic ring), 7.56 (t, *J*=7.3, 1H, on aromatic group), 7.37 (t, *J*=7.5, 2H, on aromatic ring), 5.00 (s, 1H, OH), 3.14 (s, 1H, OH), 3.12 (s, 2H, C*HH*), 1.89-1.37 (m, 10H, on cyclohexane), 0.19 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ =137.4, 133.6, 128.1, 125.2, 109.1, 91.0, 73.8, 72.3, 47.6, 40.5, 37.7, 25.8, 21.9, -0.28; GC-MS: *m/z* = 316 (absent) [M^+], 298 (3), 283 (4), 255 (5), 205 (9), 204 (20), 203 (100), 200 (10), 185 (30), 159 (7), 135 (6), 105 (9), 81 (7), 77 (7), 75 (8), 73 (14); anal. calc for $C_{19}H_{28}O_2Si$ (316.52): C, 72.10; H, 8.92; Si, 8.87; found: C, 72.05; H, 8.91; Si, 8.85.



§1i

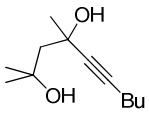
*2-(1-hydroxycyclohexyl)-1-phenylethan-1-one (**§1i**).* Yield: 6.44 g, starting from 6.01 g of acetophenone (59%). Colorless solid, mp = 74.5-75.5 °C. IR (KBr): *v* = 3515 (s), 3052 (w), 2937 (s), 2851 (m), 1674 (s), 1579 (w), 1447 (m), 1393 (m), 1309 (m), 1224 (w), 1176 (m), 982 (m), 840 (w), 751 (m), 737 (m), 680 (m), 570 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J*=7.3, 2H, on aromatic ring), 7.58 (t, *J*=7.3, 1H, on aromatic group), 7.47 (t, *J*=7.5, 2H, on aromatic ring), 4.04 (s, 1H, OH), 3.12 (s, 2H, C*HH*), 1.89-1.65 (m, 4H, on cyclohexane), 1.63-1.37 (m, 4H, on cyclohexane) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.0, 137.5, 133.6, 128.7, 128.1, 71.0, 47.7, 37.8, 25.8, 22.0; GC-MS: *m/z* = 218 (1) [M^+], 200 (7), 162 (18), 147 (5), 120 (27), 106 (8), 105 (100), 98 (5), 81 (5), 78 (10), 77 (30), 51 (7); anal. calcd for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found: C, 76.09; H, 8.32.



1j

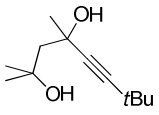
*3-methylnon-4-yne-1,3-diol (**1j**).* Yield: 3.77 g, starting from 2.47 g of 4-hydroxybutan-2-one (79%). Colorless oil. IR (film): *v* = 3361 (s, br), 2967 (s), 2931 (s), 2864 (m), 2235 (w), 1453 (m), 1427 (m), 1376 (m), 1269 (w), 1141 (m), 1090 (m), 1053 (m), 890 (m), 747 (w), 588 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ =4.19-4.06 (m, 1H, HOC*H*HCH_2), 3.88 (dt, *J*= 11.0, 4.5, 1H, HOCH*H*CH_2), 3.52 (s br, 2H, 2OH), 2.21 (t, *J*=6.9, 2 H, C*H*$_2CH_2CH_2CH_3$), 2.02-1.89 (m, 1H, $OHCH_2$C*H*H), 1.84-1.74 (m, 1H, $OHCH_2$CH*H*), 1.56-1.32 (m,

7H, Me + CH_2CH_2CH$_3$), 0.91 (t, *J*=7.1, 3H, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$): δ =84.5, 83.3, 68.8, 60.6, 44.0, 31.1, 30.8, 22.0, 18.3, 13.6; GC-MS: *m/z* = 170 (absent) [M$^+$] , 155 (3), 126 (9), 125 (100), 109 (11), 95 (5), 91 (7), 81 (8), 79 (12), 73 (13), 69 (11), 65 (4), 53 (7); anal. calcd for $C_{10}H_{18}O_2$ (170.25): C, 70.55; H, 10.66; found: C, 70.59; H, 10.65.



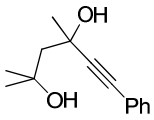
1k

*2,4-dimethyldec-5-yne-2,4-diol (**1k**).* Yield: 3.22 g, starting from 3,25 g of 4-hydroxy-4-methylpentan-2-one (58%). Yellow oil solid. IR (film): *v* = 3350 (s, br), 2982 (s), 2936 (s), 2875 (m), 2240 (w), 1473 (m), 1417 (m), 1386 (s), 1366 (s), 1330 (m), 1289 (m), 1187 (s), 1074 (m), 987 (w), 884 (w), 772 (w), 619 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.16 (s br, 1H, OH), 3.41 (s br, 1H, OH), 2.20 (t, *J*=7.0, 2 H, CH_2CH$_2$CH$_2$CH$_3$) 1.94-1.85 (m, 2H, C*HH*), 1.52 (s, 3H, CH$_3$CCH_3), 1.50 (s, 3H, CH_3CCH$_3$), 1.56-1.32 (m, 4H, CH_2CH_2CH$_3$), 1.29 (s, 3H, C(OH)CH_3), 0.90 (t, *J*=6.8, 3H, CH$_2$CH$_2$CH_3); ^{13}C NMR (75 MHz, CDCl$_3$): δ =85.0, 84.7, 72.2, 67.3, 52.8, 33.7, 32.4, 30.6, 29.7, 22.0, 18.4, 13.6; GC-MS: *m/z* = 198 (absent) [M$^+$], 183 (2), 165 (19), 151 (6), 142 (5), 138 (6), 126 (9), 125 (100), 109 (33), 99 (3), 93 (15), 81 (13), 79 (22), 69 (11), 59 (25), 57 (4); anal. calc for $C_{12}H_{22}O_2$ (198.30): C, 72.68; H, 11.18; found: C, 72.72; H, 11.15.



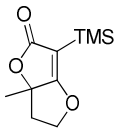
1l

*2,4,7,7-tetramethyloct-5-yne-2,4-diol (**1l**).* Yield: 2.67 g, starting from 3,25 g of 4-hydroxy-4-methylpentan-2-one (48%). White solid, mp 53.2-54.2 °C. IR (KBr): *v* = 3335 (m, br), 2971 (s), 2936 (m), 2868 (m), 2228 (w), 1457 (m), 1361 (m), 1266 (m), 1191 (s), 1066 (m), 983 (m), 945 (w), 893 (m), 851 (m), 768 (w), 516 (w) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$): δ =3.71 (s br, 1H, OH), 1.92-1.83 (m, 2H, C*HH*), 1.52 (s, 3H, CH$_3$CCH_3), 1.49 (s, 3H, CH_3CCH$_3$), 1.29 (s, 3H, C(OH)CH_3), 1.20 (s, 9H, C(CH_3)$_3$; ^{13}C NMR (75 MHz, CDCl$_3$): δ = 93.4, 83.9, 71.9, 67.3, 53.8, 33.8, 32.3, 31.0, 30.3, 27.5; GC-MS: *m/z* = 198 (absent) [M$^+$], 183 (1), 165 (17), 137 (5), 126 (4), 125 (100), 109 (24), 107 (39), 95 (6), 91 (15), 83 (6), 81 (14), 79 (11), 67 (6), 59 (22), 57 (9), 53 (8), 44 (15), 43 (43); anal. calc for $C_{12}H_{22}O_2$ (198.30): C, 72.68; H, 11.18; found: C, 72.64; H, 11.17.



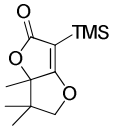
1m

*2,4-dimethyl-6-phenylhex-5-yne-2,4-diol (**1m**).* Yield: 3.30 g, starting from 3,25 g of 4-hydroxy-4-methylpentan-2-one (54%). White solid, mp 57.2-58.2 °C. IR (film): *v* = 3337 (s, br), 2975 (s), 2932 (m), 2235 (w), 1490 (m), 1443 (m), 1411 (m), 1368 (m), 1297 (w), 1260 (m), 1184 (s), 1068 (m), 983 (w), 897 (m), 873 (m), 820 (w), 757 (s), 691 (s), 567 (w), 533 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44-7.36 (m, 2H, on aromatic ring), 7.32-7.20 (m, 2H, on aromatic ring), 4.87 (s br, 1H, OH), 3.48 (s br, 1H, OH), 2.03-1.95 (m, 2H, C*HH*), 1.63 (s, 3H, CH_3CCH_3), 1.62 (s, 3H, CH_3CCH_3), 1.31 (s, 3H, C(OH)CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.5, 128.4, 128.3, 123.3, 94.2, 84.5, 72.3, 67.8, 53.3, 33.3, 32.7, 29.9; GC-MS: *m/z*= 218 (absent) [M^+], 200 (16), 185 (38), 162 (18), 146 (12), 145 (100), 141 (26), 129 (96), 119 (22), 115 (21), 102 (11), 91 (34), 77 (11), 59 (19), 57 (9); anal. calc for $C_{14}H_{18}O_2$ (218.29): C, 77.03; H, 8.31; found: C, 77.08; H, 8.32.



2a

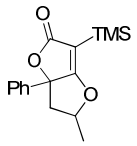
*6a-methyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2a**).* Yield: 101.1 mg, starting from 130.4 mg of 3-methyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (68%). White solid, mp=71.1-72.1 °C. IR (KBr): *v* = 2981 (w), 2961 (m), 2934 (w), 2900 (w), 1741 (s), 1636 (s), 1446 (w), 1390 (m), 1302 (m), 1279 (s), 1238 (s), 1181 (m), 1141 (w), 1096 (m), 977 (m), 845 (s), 780 (m), 701 (w), 685 (w), 601 (w), 557 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 4.84-4.74 (m, 1H, (O)C*H*H), 4.73-4.64 (m, 1H, (O)CH*H*), 2.27-2.18 (m, 2H, $CH_2CHHCCH_3$), 1.53 (s, 3H, Me), 0.22 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.2, 178.4, 95.3, 85.3, 36.3, 25.1, -0.02; GC-MS: *m/z* = 212 (7) [M^+], 198 (15), 197 (100), 141 (14), 124 (6), 123 (72), 97(3), 75 (76), 74 (7), 73 (65), 69 (7), 45 (18), 43 (24); anal. calcd for $C_{10}H_{16}O_3Si$ (212.32): C, 56.57; H, 7.60; Si, 13.23; found: C, 56.61; H, 7.59; Si, 13.20.



2b

*6,6,6a-trimethyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2b**).* Yield: 138.0 mg, starting from 150.1 mg of 2,2,3-trimethyl-5-(trimethylsilyl)pent-4-yne-1,3-diol (82%). White solid, mp = 69.6-70.6 °C. IR (KBr): *v* = 2980 (m), 2939 (m), 2902 (w), 1745 (s), 1638 (s), 1471 (w), 1377 (s), 1302 (m), 1241 (s), 1166 (w), 1124 (m), 1065 (m), 970 (w), 928 (m), 840 (s), 779 (m), 760 (w), 627 (w), 585 (w) cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ = 4.43 (d dist, *J*= 8.9, 1H, C*H*H), ,4.29 (d dist, *J*= 8.9, CH*H*), 1.45 (s, 3H, (O)CCH_3), 1.17 (s, 3H, CH_3CCH_3), 1.02 (s, 3H, CH_3CCH_3), 0.23 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.7, 177.3, 94.1, 89.0, 86.8, 42.3, 20.7, 20.6, 18.1, -1.64; GC-MS: *m/z* = 240 (18) [M^+], 226 (18), 225 (100), 207 (7), 185 (7), 151(24), 143 (6), 142 (6), 141 (97), 123 (5), 99 (8), 97 (5), 75 (54), 74 (9), 73 (98), 69 (7); anal. calcd for $C_{12}H_{20}O_3Si$ (240.37): C, 59.96; H, 8.39; Si, 11.68; found: C, 59.93; H, 8.41; Si, 11.71.

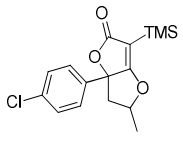


2c

*5-methyl-6a-phenyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2c**).* Yield: 111.0 mg, starting from 183.7 mg of 4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (55%). Colorless oil; anal. calcd for $C_{16}H_{20}O_3Si$ (288.42): C, 66.63; H, 6.99; Si, 9.74; found: C, 66.67; H, 7.01; Si, 9.77.

[*2c-A*] Colorless oil. IR (film): *v* = 2957 (m), 2900 (w), 1748 (s), 1637 (s), 1494 (w), 1449 (m), 1385 (m), 1358 (m), 1237 (s), 1193 (m), 1118 (m), 1144 (w), 1080 (w), 1019 (m), 924 (m), 845 (s), 770 (m), 700 (m), 625 (w), 575 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 4H, on aromatic ring), 4.90-4.73 (m, 1H, C*H*CH_3), 2.73 (ddd, *J*= 11.8, 4.0, 0.8, 1H, C*H*H), 2.10 (td, *J*=11.8, 0.8, 1H, CH*H*), 1.51 (dd, *J*=6.2, 0.8, 3H, Me), 0.28 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.0, 176.0, 138.7, 129.0, 125.9, 96.3, 88.1, 87.2, 44.0, 20.7, -0.15 ; GC-MS: *m/z* = 288 (26) [M^+], 273 (1), 229 (18), 220 (13), 215 (2), 200 (2), 155 (21), 141 (48), 105 (17), 77 (23), 73 (100), 45 (13), 44 (5).

[*2c-B*] White solid, mp = 86.6-87.6 °C. IR (KBr): *v* = 3025 (w), 2957 (m), 2904 (w), 1747 (s), 1637 (s), 1493 (w), 1450 (m), 1366 (m), 1247 (s), 1184 (s), 1141 (w), 1089 (m), 1017 (m), 911 (m), 845 (s), 776 (m), 712 (m), 638 (w), 536 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 4H, on aromatic ring), 5.30-5.15 (m, 1H, C*H*CH_3), 2.74-2.61 (m, 1H, C*H*H), 2.49-2.59 (m, 1H, CH*H*), 1.06 (d, *J*=6.9, 0.8, 3H, Me), 0.30 (s, 9H, Si$(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.5, 177.5, 142.5, 130.4, 127.9, 99.4, 89.9, 88.5, 40.7, 22.1, 0.00; GC-MS: *m/z* = 288 (20) [M^+], 273 (1), 229 (9), 220 (27), 219 (20), 214 (7), 200 (2), 178 (6), 155 (17), 141 (54), 105 (15), 77 (19), 73 (100), 45 (11).

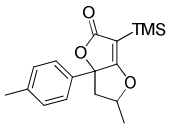


2d

*6a-(4-chlorophenyl)-5-methyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2d**).* Yield: 110.7 mg, starting from 207.8 mg of 4-(4-chlorophenyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol (49%). White solid; anal. calcd for $C_{16}H_{19}ClO_3Si$ (322.86): C, 59.52; H, 5.93; Cl, 10.98; Si, 8.70; found: C, 59.48; H, 5.94; Cl, 11.00; Si, 7.78.

[*2d-A*] White solid, mp= 84.1-85.1 °C; IR (KBr): *v* = 2957 (m), 2897 (w), 1748 (s), 1638 (s), 1493 (m), 1403 (w), 1357 (m), 1237 (s), 1189 (m), 1144 (w), 1098 (m), 1067 (w), 1014 (m), 921 (m), 845 (s), 772 (m), 697 (w), 628 (w), 526 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.25 (m, 4H, on aromatic ring), 4.88-4.74 (m, 1H, C*H*CH_3), 2.70 (dd, *J*=11.9, 4.0, 1H, C*H*H), 2.09 (dd, *J*=11.8, 10.6, 1H, CH*H*), 1.51 (d, *J*=6.2, 3H, Me), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 175.8, 137.3, 135.3, 129.3, 127.4, 96.5, 87.3, 43.8, 20.8, -1.43; GC-MS: *m/z* = 322 (26) [M^+], 264 (3), 263 (14), 249 (1), 229 (4), 214 (2), 211 (5), 167 (1), 153 (3), 152 (2), 141 (73), 139 (12), 111 (11), 76 (3), 75 (23), 73 (100), 58 (1), 45 (10), 43 (5).

[*2d-B*] White solid, mp = 83.8-84.8 °C. IR (KBr): *v* = 2957 (m), 2897 (w), 1747 (s), 1638 (s), 1493 (m), 1405 (w), 1366 (m), 1243 (s), 1180 (m), 1142 (w), 1097 (m), 1015 (m), 920 (m), 844 (s), 772 (m), 741 (m), 697 (w), 610 (w), 527 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43-7.17 (m, 4H, on aromatic ring), 5.31-5.13 (m, 1H, C*H*CH_3), 2.75-2.58 (m, 1H, C*H*H), 2.53-2.40 (m, 1H, CH*H*), 1.17-1.00 (m, 3H, Me), 0.29 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.6, 176.2, 139.2, 134.9, 129.1, 127.8, 97.7, 88.6, 86.4, 38.9, 20.7, -1.52; GC-MS: *m/z* = 322 (12) [M^+], 263 (4), 253 (5), 228 (9), 219 (11), 211 (3), 167 (1), 153 (3), 152 (2), 141 (69), 139 (11), 111 (8), 76 (2), 75 (17), 73 (100), 58 (1), 45 (10), 43 (5).



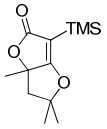
2e

*5-methyl-6a-(p-tolyl)-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2e**).* Yield: 139.7 mg, starting from 193,5 mg of 4-(p-tolyl)-6-(trimethylsilyl)hex-5-yne-2,4-diol (66%). Colorless oil; anal. calcd for $C_{17}H_{22}O_3Si$ (302.45): C, 67.51; H, 7.33; Si, 9.29; found: C, 67.55; H, 7.34; Si, 9.31.

[*2e-A*] Colorless oil. IR (film): *v* = 2958 (m), 2905 (w), 1747 (s), 1638 (s), 1513 (w), 1446 (w), 1358 (m), 1237 (s), 1193 (m), 1173 (m), 1144 (w), 1094 (w), 1017 (m), 925 (m), 845 (s), 791 (w), 768 (m), 734 (m), 697 (w), 634 (w), 554 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26-7.14 (m, 4H, on aromatic ring), 4.88-4.74 (m, 1H, C*H*CH_3), 2.73 (dd, *J*=11.8, 4.0, 1H, C*H*H), 2.34 (s, 3H, $CH_3C_6H_4$), 2.09 (dd dist, *J*=11.8, 4.0, 1H, CH*H*), 1.51 (d, *J*=6.3, 3H, Me), 0.28 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3, 176.5, 138.8, 135.2, 129.5, 125.7, 95.5, 87.9, 87.3, 43.6, 21.1, 20.6, -1.51; GC-MS: *m/z* = 302 (69) [M^+], 287 (5), 244 (5), 243 (21), 229 (5), 228 (21), 219 (32), 211 (8), 192 (9), 169 (15), 153 (6), 142 (8), 141 (51), 115 (6), 91 (23), 75 (16), 73 (100), 59 (5).

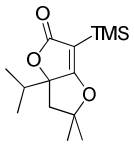
[*2e-B*] White solid, mp = 76.1-77.1 °C. IR (KBr): *v* = 3026 (w), 2957 (m), 2904 (w), 1744 (s), 1637 (s), 1513 (w), 1453 (w), 1365 (m), 1270 (m), 1248 (s), 1183 (s), 1141 (m), 1089 (m), 1058 (m), 1017 (m), 920 (m), 845 (s), 712 (m), 698 (m), 637 (w), 529 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = δ = 7.29-7.14 (m, 4H, on aromatic ring), 5.28-5.15 (m, 1H, C*H*CH_3), 2.60 (dd dist, *J*=12.2, 9.0, 1H, C*H*H), 2.53 (d dist, *J*=12.2, 1H, CH*H*), 2.35 (s, 3H, $CH_3C_6H_4$), 1.51 (d, *J*=7.0, 3H, Me), 0.29 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.3, 176.5, 138.8, 137.6, 129.5, 126.3, 97.3, 88.6, 87.0, 38.9, 21.2, 20.6, -1.48; GC-MS: *m/z* = 302 (90)

[M^+], 287 (6), 244 (5), 243 (23), 229 (5), 228 (21), 219 (100), 211 (9), 201 (11), 192 (8), 177 (12), 169 (18), 142 (10), 141 (60), 119 (48), 115 (9), 91 (27), 75 (15), 73 (91), 65 (11).



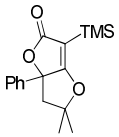
2f

*5,5,6a-trimethyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2f**).* Yield: 144.7 mg, starting from 150.1 mg of 2,4-dimethyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (86%). White solid, mp= 44.5-45.5 °C. IR (KBr): *v* = 2959 (m), 2900 (w), 1736 (s), 1638 (s), 1456 (m), 1381 (s), 1342 (s), 1268 (s), 1232 (s), 1123 (m), 1085 (m), 1006 (w), 961 (m), 917 (m), 848 (s), 778 (m), 699 (m), 622 (m), 532 (w) cm^{-1}; ^1H NMR (300 MHz, CDCl3): δ =2.14 (d dist, J=12.5, 1H, C*H*H), 2.01 (d dist, J=12.5, 1H, CH*H*), 1.63 (s, 3H, CH_3CCH_3), 1.62 (s, 3H, CH_3CCH_3), 1.47 (s, 3H, Me), 0.23 (s, 9H, $Si(CH_3)_3$) ; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 195.4, 176.7, 97.4, 95.4, 85.1, 45.2, 31.4, 27.9, 27.4, -1.51; GC-MS: *m/z* = 240 (12) [M^+], 225 (15), 207 (20), 185 (14), 169 (6), 157 (10), 141 (42), 123 (3), 99 (29), 83 (5), 75 (23), 74 (9), 73 (100), 55 (6), 45 (13), 43 (41); anal. calcd for $C_{12}H_{20}O_3Si$ (240.37): C, 59.96; H, 8.39; Si, 11.68; found: C, 60.00; H, 8.37; Si, 11.71.



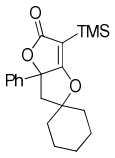
2g

*6a-isopropyl-5,5-dimethyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2g**).* Yield: 165.4 mg, starting from 169.7 mg of 4-isopropyl-2-methyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (88%). White solid, mp= 78.2-79.2 °C. IR (KBr): *v* = 2973 (m), 2946 (m), 2900 (w), 1735 (s), 1626 (s), 1458 (w), 1332 (m), 1284 (m), 1214 (m), 1173 (w), 1144 (m), 1112 (m), 1074 (w), 1020 (m), 919 (m), 846 (s), 708 (m), 632 (w), 567 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 2.31 (d, *J*=12.8, 1H, $CH(CH_3)_2$), 2.02-1.92 (m, 1H, C*H*H), 1.92-1.84 (m, 1H, CH*H*), 1.60 (s, 3H, CH_3CCH_3), 1.46 (s, 3H, CH_3CCH_3), 1.14 (d, *J*=6.8, 3H, CH_3CHCH_3), 0.84 (d, J=6.8, 3H, CH_3CHCH_3), 0.23 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 192.9, 177.2, 98.2, 96.7, 90.1, 42.5, 34.7, 31.5, 28.3, 17.0, 15.7, -1.45; GC-MS: *m/z* = 268 (2) [M^+], 253 (7), 226 (7), 225 (39), 195 (1), 169 (1), 157 (2), 143 (7), 141 (39), 135 (14), 127 (22), 123 (1), 109 (1), 99 (4), 83 (10), 79 (1), 75 (28), 74 (9), 73 (100), 71 (31), 55 (7), 45 (12), 43 (22), 41 (9); anal. calcd for $C_{14}H_{24}O_3Si$ (268.43): C, 62.64; H, 9.01; Si, 10.46; found: C, 62.59; H, 9.00; Si, 10.47.



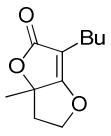
2h

*5,5-dimethyl-6a-phenyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2h**).* Yield: 173.6 mg, starting from 193.5 mg of 2-methyl-4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol (82%). White solid, mp = 77.4-78.4 °C. IR (KBr): *v* = 2956 (m), 2900 (w), 1741 (s), 1697 (s), 1495 (w), 1452 (m), 1390 (m), 1350 (s), 1268 (m), 1196 (m), 1128 (m), 1144 (m), 1055 (m), 987 (w), 937 (m), 847 (s), 755 (m), 704 (s), 629 (m), 580 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (s, 5H, on aromatic ring), 2.73 (d, *J*=12.4, 1H, C*H*H), 2.30 (d, *J*=12.4, 1H, CH*H*), 1.52 (s, 3H, CH_3CCH_3), 1.11 (s, 3H, CH_3CCH_3), 0.30 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =191.1, 176.0, 140.5, 128.9, 126.5, 98.2, 97.7, 88.5, 46.2, 31.1, 26.7, -1.38; GC-MS: *m/z* = 302 (18) [M^+], 247 (7), 234 (9), 228 (2), 225 (1), 201 (9), 178 (16), 161 (20), 153 (1), 152 (1), 142 (9), 141 (67), 105 (45), 99 (2), 83 (2), 77 (21), 75 (16), 74 (9), 73 (100), 45 (12), 44 (9), 43 (6); anal. calcd for $C_{17}H_{22}O_3Si$ (302.45): C, 67.51; H, 7.33; Si, 9.29; found: C, 67.55; H, 7.34; Si, 9.31.



2i

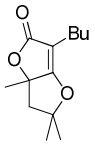
*3a'-phenyl-6'-(trimethylsilyl)-3',3a'-dihydro-5'H-spiro[cyclohexane-1,2'-furo[3,2-b]furan]-5'-one(**2i**).* Yield: 153.5 mg, starting from 221.6 mg of 1-(2-hydroxy-2-phenyl-4-(trimethylsilyl)but-3-yn-1-yl)cyclohexan-1-ol (64%). White solid, mp = 101.8-102.8 °C. IR (KBr): *v* = 2940 (m), 2861 (w), 1740 (s), 1635 (s), 1496 (w), 1449 (m), 1372 (w), 1249 (s), 1193 (m), 1128 (m), 1133 (w), 1003 (w), 929 (m), 840 (s), 756 (w), 701 (s), 630 (w), 568 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* = 7.35 (s, 5H, on aromatic ring), 2.78 (d, *J*=12.4, 1H, C*H*H), 2.16 (d, *J*=12.4, 1H, CH*H*), 1.90-1.40 (m, 10H, on cyclohexane), 0.31 (s, 9H, $Si(CH_3)_3$) ; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 192.1, 176.4, 140.4, 128.85, 128.8, 126.3, 100.1, 97.9, 87.8, 44.5, 39.9, 35.3, 24.7, 22.8, -1.42; GC-MS: *m/z* = 342 (17) [M^+], 249 (21), 248 (100), 247 (81), 232 (10), 231 (5), 219 (10), 202 (8), 201 (47), 142 (5), 141 (31), 105 (72), 77 (23), 75 (16), 74 (8), 73 (89), 55 (5); anal. calcd for $C_{20}H_{26}O_3Si$ (342.51): C, 70.14; H, 7.65; Si, 8.20; found: C, 70.10; H, 7.66; Si, 8.23.



2j

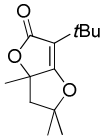
*3-butyl-6a-methyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2j**).* Yield: 34.3 mg, starting from 119.2 mg of 3-methylnon-4-yne-1,3-diol (25%). Colorless oil. IR (film): *v* = 2967 (m), 2941 (m), 2864 (w), 1754 (s), 1698 (s), 1463 (w), 1402 (m), 1279 (m), 1223 (m), 1135 (w), 1069 (m), 987 (m), 864 (w), 772 (w), 685 (w)

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 4.87-4.56 (m, 2H, (O)C*HH*), 2.32-2.02 (m, 4H, C*HH* + $CH_2CH_2CH_2CH_3$), 1.63-1.40 (m, 5H, Me + $CH_2CH_2CH_3$), 1.39-1.20 (m, 2H, $CH_2CH_2CH_3$), 0.91 (t, J=7.2, 3H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.9, 175.1, 98.7, 82.2, 77.8, 34.8, 29.6, 23.5, 22.4, 21.8, 13.8; GC-MS: *m/z* = 196 (4) [M^+], 181 (28), 165 (40), 153 (28), 152 (7), 139 (4), 125 (100), 123 (8), 109 (9), 108 (18), 95 (6), 79 (7), 69 (8), 57 (42); anal. calcd for $C_{11}H_{16}O_3$(196,24): C, 67.32; H, 8.22; found: C, 67.29; H, 8.24.



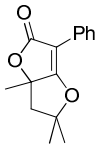
2k

*3-butyl-5,5,6a-trimethyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2k**).* Yield: 64.4 mg, starting from 138.8 mg of 2,4-dimethyldec-5-yne-2,4-diol (41%). Yellow oil. IR (film): *v* = 2959 (m), 2933 (m), 2873 (w), 1761 (s), 1695 (s), 1456 (m), 1384 (s), 1262 (m), 1182 (w), 1110 (s), 1031 (w), 936 (w), 838 (w), 773 (m), 694 (w), 532 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.22-2.08 (m, 3H, C*H*H+ $CH_2CH_2CH_2CH_3$), 2.02-1.94 (m, 1H, CH*H*), 1.62 (s, 6H, CH_3CCH_3), 1.53-1.42 (m, 5H, Me + $CH_2CH_2CH_3$), 1.37-1.28 (m, 2H, $CH_2CH_2CH_3$), 0.91(t, J=7.3, 3H, CH_2CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7, 153.6, 119.2, 97.4, 83.6, 45.5, 31.5, 29.7, 28.1, 27.2, 22.4, 21.7, 13.8; GC-MS: *m/z* = 224 (2) [M^+], 209 (6), 196 (16), 181 (5), 179 (4), 170 (7), 169 (72), 165 (7), 126 (19), 125 (100), 99 (7), 83 (6), 57 (24), 55 (11); anal. calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99; found: C, 69.65; H, 8.97.



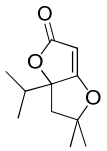
2l

*3-(tert-butyl)-5,5,6a-trimethyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2l**).* Yield: 61.2 mg, starting from 138.8 mg of 2,4,7,7-tetramethyloct-5-yne-2,4-diol**.** (39%). White solid, mp= 65.2-66.2 °C. IR (KBr): *v* = 2976 (m), 2870 (w), 1753 (s), 1680 (s), 1456 (m), 1351 (s), 1298 (m), 1261 (m), 1226 (w), 1091 (s), 991 (m), 843 (w), 777 (w), 676 (w), 648 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (d dist, *J*=12.5, 1H, C*H*H), 1.95 (d dist, *J*=12.5, 1H, CH*H*), 1.61 (s, 3H, CH_3CCH_3), 1.60 (s, 3H, CH_3CCH_3), 1.47 (s, 3H, Me), 1.25 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9, 173.5, 108.2, 96.8, 82.9, 45.2, 31.4, 30.7, 28.7, 28.0, 27.4; GC-MS: *m/z* = 224 (4) [M^+], 209 (10), 196 (3), 181 (1), 170 (3), 169 (25), 168 (14), 167 (1), 153 (52), 152 (1), 126 (2), 125 (30), 123 (2), 107 (1), 99 (5), 83 (10), 79 (1), 58 (4), 57 (100), 55 (7), 44 (3), 43 (44); anal. calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99; found: C, 69.58; H, 9.01.



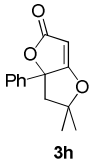
2m

*5,5,6a-trimethyl-3-phenyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**2m**).* Yield: 46.2 mg, starting from 152.7 mg of 2,4-dimethyl-6-phenylhex-5-yne-2,4-diol (27%). White solid, mp= 94.2-95.2 °C. IR (KBr): *v* = 2979 (m), 2929 (w), 1746 (s), 1667 (s), 1449 (m), 1388 (s), 1268 (m), 1185 (m), 1135 (m), 1090 (s), 1001 (w), 939 (s), 863 (w), 781 (m), 694 (s), 625 (w), 522 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98-7.89 (m, 2H, on aromatic ring), 7.44-7.33 (m, 2H, on aromatic ring), 7.31-7.21 (m, 2H, on aromatic ring), 12.5 (d, *J*=12.5, 1H, C*H*H), 2.10 (d, *J*=12.5, 1H, CH*H*), 1.74 (s, 3H, CH_3CCH$_3$), 1.60 (s, 3H, CH$_3$CCH_3), 1.47 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.0, 172.3, ,129.3, 128.4, 127.3, 126.8, 99.6, 99.2, 83.6, 45.4, 31.9, 28.1, 27.6; GC-MS: *m/z* = 244 (23) [M^+], 229 (1), 201 (2), 190 (4), 189 (31), 188 (62), 185 (14), 146 (11), 145 (100), 133 (4), 117 (11), 99 (1), 89 (27), 77 (3), 63 (6); anal. calcd for $C_{15}H_{16}O_3$ (244.29): C, 73.75; H, 6.60; found: C, 73.79; H, 6.62.



3g

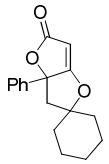
*6a-isopropyl-5,5-dimethyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**3g**).* Yield: 112.7 mg, starting from 169.7 mg of 4-isopropyl-2-methyl-6-(trimethylsilyl)hex-5-yne-2,4-diol **1g** (82%).White solid, mp= 64.9-65.9 °C. IR (KBr): *v* = 2974 (m), 2936 (m), 2874 (w), 1775 (s), 1653 (s), 1455 (w), 1350 (m), 1287 (m), 1214 (m), 1138 (m), 1009 (m), 887 (m), 808 (m), 782 (w), 742 (m), 597 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.06 (s, 1H, C=C*H*), 2.34 (d, *J*=12.8, 1H, CH(CH$_3$)$_2$), 2.13-1.90 (m, 2H, C*HH*), 1.62 (s, 3H, CH$_3$CCH_3), 1.51 (s, 3H, CH_3CCH$_3$), 1.16 (d, *J*=6.7, 3H, CH_3CHCH$_3$), 0.89 (d, J=6.7, 3H, CH$_3$CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.8, 174.6, 98.2, 90.7, 89.5, 42.7, 34.7, 31.6, 28.3, 17.0, 15.7; GC-MS: *m/z* = 196 (5) [M^+], 168 (6), 154 (10), 153 (100), 141 (10), 97 (4), 83 (60), 71 (40), 69 (53), 57 (4), 56 (8); anal. calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22; found: C, 67.28; H, 8.21.



3h

*5,5-dimethyl-6a-phenyl-6,6a-dihydrofuro[3,2-b]furan-2(5H)-one (**3h**).* Yield: 122.5 mg, starting from 193.5 mg of 2-methyl-4-phenyl-6-(trimethylsilyl)hex-5-yne-2,4-diol **1h** (76%). White solid, mp= 129.3-130.3 °C. IR (KBr): *v* = 2980 (m), 2928 (w), 1766 (s), 1651 (s), 1451 (m), 1352 (m), 1267 (m), 1193 (m),

1128 (m), 1055 (m), 937 (m), 878 (m), 806 (m), 725 (w), 703 (s), 629 (w) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45-7.29 (m, 5H, on aromatic ring), 5.20 (s, 1H, C=C*H*), 2.79 (d, *J*=12.4, 1H, CH*H*), 2.39 (d, *J*=12.4, 1H, CH*H*), 1.57 (s, 3H, CH_3CCH_3), 1.11 (s, 3H, CH_3CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =184.9, 173.6, 139.6, 129.2, 129.0, 126.4, 99.3, 89.0, 46.0, 31.1, 26.5; GC-MS: *m/z* = 230 (5) [M^+], 215 (30), 200 (7), 175 (13), 147 (6), 106 (8), 105 (100), 77 (27), 69 (11); anal. calcd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; found: C, 73.08; H, 6.14.



3i

*3a'-phenyl-3',3a'-dihydro-5'H-spiro[cyclohexane-1,2'-furo[3,2-b]furan]-5'-one (**3i**).* Yield: 106.0 mg, starting from 221.6 mg of 1-(2-hydroxy-2-phenyl-4-(trimethylsilyl)but-3-yn-1-yl)cyclohexan-1-ol (56%). White solid, m.p.= 125.7-126.7 °C. IR (KBr): *v* = 2937 (m), 2862 (w), 1771 (s), 1655 (s), 1498 (w), 1449 (m), 1361 (w), 1249 (m), 1182 (w), 1128 (w), 1012 (m), 881 (m), 805 (m), 767 (w), 706 (m), 666 (w), 568 (w) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* = 7.38 (s, 5H, on aromatic ring), 5.21 (s, 1H, C=C*H*), 2.85 (d, *J*=12.5, 1H, C*H*H), 2.25 (d, *J*=12.5, 1H, CH*H*), 1.96-1.64 (m, 5H, on cyclohexane), 1.61-1.39 (m, 5H, on cyclohexane),; ^{13}C NMR (75 MHz, $CDCl_3$): *δ* =184.9, 173.8, 139.9, 129.1, 128.9, 126.3, 101.8, 89.13, 89.1, 88.3, 44.5, 39.9, 35.1, 24.6, 22.9, 22.8; GC-MS: *m/z* = 270 (3) [M^+], 201 (15), 176 (100), 105 (84), 95 (23), 81 (11), 77 (30), 69 (10); anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71; found: C, 75.50; H, 6.72.

[1] For recent reviews on the synthesis of carbonylated heterocycles by carbonylation of acyclic substrates, see: (a) Wu, X.-F.; Neumann, H.; Beller, *M. Chem. Rev.* **2013**, 113, 1−35. (b) Wu, X.-F.; Neumann, H.; Beller, M. *ChemSusChem* **2013**, 6, 229−241. (c) Gabriele, B.; Mancuso, R.; Salerno, G. Eur. *J. Org. Chem.* **2012**, 6825−6839. (d) Liu, Q.; Zhang, H.; Lei, A. *Angew. Chem.*, Int. Ed**. 2011**, 50, 10788−10799. (e) Liu, J.; Chen, J.; Sun, W.; Xia, C. Chin. *J. Catal.* **2010**, 31, 1−11. (f) Brennfuehrer, A.; Neumann, H.; Beller, M. *ChemCatChem* **2009**, 1, 28−41. (g) Brennfuehrer, A.; Neumann, H.; Beller, M. *Angew. Chem.*, Int. Ed. **2009**, 48, 4114−4133. (h) Barnard, C. F. *J. Organometallics* **2008**, 27, 5402−5422. (i) Sapollo, G.; Mele, G. *Curr. Org. Chem.* **2006**, 10, 1397−1421. (j) Gabriele, B.; Salerno, G.; Costa, M. Top*. Organomet. Chem.* **2006**, 18, 239−272.

[2] See, for example: (a) Gabriele, B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G. *J. Org. Chem.* **2012**, 77, 8657−8668. (b) Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. Eur*. J. Org. Chem.* **2012**, 2549−2559. (c) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, 9, 3319−3322. (d) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, 346, 351−358. (e) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M. *J. Organomet. Chem.* **2001**, 622, 84−88. (f) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 83−87.

[3] **§1a** and **§1f** are commercially available.

[4] **§1b:** Markó, I.M.; Schevenels, F.T. *Belstein J. Org. Chem.* **2013**, *9, 1319-1325.*

[5] **§1c**: (a) Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers, R.A. *Org. Lett.* **2004**, 6, 16, 2685-2688. (b) Oare, D.A.; Henderson, M.A.; Sanner, M.A.; Heathcock, C.H *JOC* **1990**, 55, 1, 132-157 ; **§1d**: Ma, X.; Li, Z.; Liu, F.; Cao, S.; Rao, H. *Adv. Synth. Catal* **2014**, 356, 8, 1741-1746; **§1e**: Van Martin, A.; Murray, D.H.; Pratt, N.E.; Bo, Y.; Kim, Z.; Albizati, F. *J. Am. Chem. Soc.* **1990**, 112, 19, 6965-6978; **§1g:** (a) Markó, I.M.; Schevenels, F.T. *Belstein J. Org. Chem.* **2013**, 9, 1319-1325. (b) Schneider, C; Hansch, M.; Weide, T. *Chem. Eur. J.* **2005**, 11, 3010-3021.

[6] Gabriele,B.; Mancuso, R.; Maltese, V.; Veltri, L.; Salerno, G. *J. Org. Chem*, **2012**, 77, 8657-8668.

[7] (**a**) Markó, I.M.; Schevenels, F.T. *Belstein J. Org. Chem* **2013**, 9, 1319. (**b**) Chopade, P.R.; Davis, T.A.; Prasad, E.; Flowers, R.A. *Org. Lett. **2004***, 6, 16, 2685-2688; Oare, D.A.; Henderson, M.A.; Sanner, M.A.; Heathcock, C.H *JOC* **1990**, 55, 132. (**c**) Ma, X.; Li, Z.; Liu, F.; Cao, S.; Rao, H. *Adv. Synth. Catal* **2014**, 356, 8, 1741-1746. (**d**) Pratt, N.E.; Bo, Y.; Kim, Z.; Albizati, F. *J. Am. Chem. Soc.* **1990**, 112(19), 6965. (**e**) Schneider, C; Hansch, M.; Weide, T. *Chem. Eur. J.* **2005**, 11, 3010-3021.

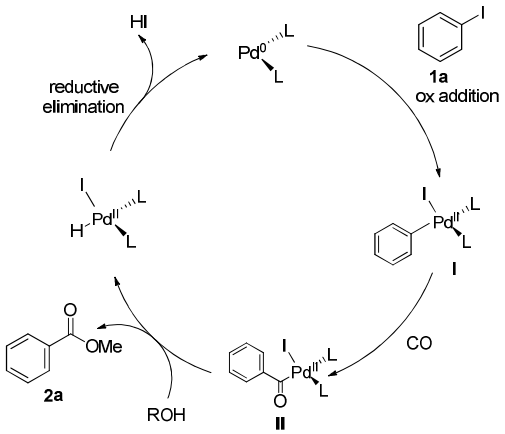
[8] *J. Org. Chem.* **2012**, 77, 8657-8668

Chapter 4

4.1 Palladium Supported on N-doped Carbon : A simple Heterogeneous Catalyst for Base-Free Alkoxycarbonylation of Aryl Iodides

Heterogeneous catalysis has a number of advantages, first of all the possibility of catalyst recovering and reusing. In fact, heterogeneous catalysts can be separated from the reaction mixture in very easy manner, such as by filtration or by centrifugation. The important economic benefits associated with the ability to recycle the catalysts- sometimes very expensive catalysts- drove sc0.ientific research to move in this direction.[1]

Heterogeneous catalysts based on different noble and no-noble metals are involved in several reactions. In this thesis, we have focused our attention on coupling reactions catalyzed by heterogeneous Pd catalys, in particular on the less common palladium-catalyzed carbonylative coupling reaction. According to the literature, the proposed mechanism for this reaction starts with the oxidative addition of ArI to Pd(0) to form the corresponding aryl-palladium complex **I**. This is followed by the coordination and insertion of CO, with formation of acylpalladium complex **II**. Finally, nucleophilic displacement by MeOH leads to the corresponding esters and H-Pd-I. With the help of base - generally Et_3N – Pd(0) is formed again and the next reaction cycle can start.[2] (*Scheme 1*)

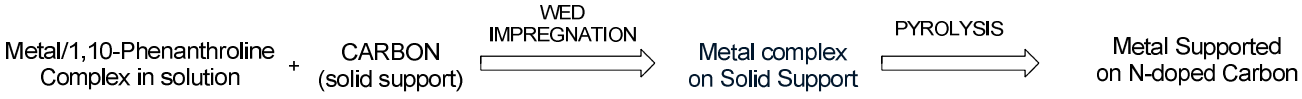


Scheme 15

In heterogeneous carbonylative coupling reactions, Pd is fixed to a solid support, such as activated carbon[3], zeolite[4], metal oxides, such as silica[5] or Fe_3O_4[6], and polymers[7]. Pd can also be fixed to a solid support as a complex with the ligands covalently bound to the support. In all

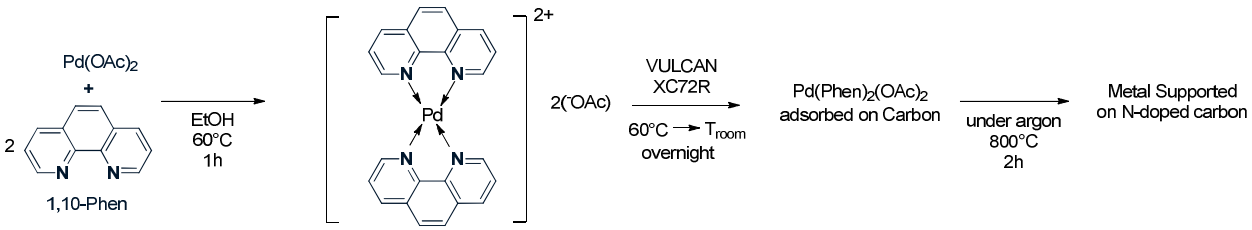
cases, it is possible to separate the heterogeneous catalyst after the reaction or to reuse it as long as it is not too deactivated or both.

In a preliminary catalyst screening, several kind of heterogeneous catalysts were prepared from the corresponding metal acetate and 1,10-phenantroline by adsorbing the metal complex on carbon, followed by pyrolysis under inert conditions (*Scheme 2*). In this way were prepared Fe_2O_x@NGr-C[8], Co_3O_4@NGr-C[9], CuO_x@NGr-C and Pd/PdO@NGr-C. All the prepared materials were tested in the carbonylative coupling reactions of iodobenzene, but only the last one showed activity.



Scheme 16

Palladium supported on N-doped carbon (Pd/PdO@NGr-C) was prepared using palladium acetate (as palladium precursor) and 1,10-phenanthroline as the nitrogen-rich ligand. The complex $[Pd\text{-}Phen]^{2+}$ was adsorbed on carbon and then underwent pyrolysis under vacuum at 800°C for 2 h. The amount of palladium in the thus prepared catalyst was determined by elemental analysis and it was measured as 5.63 wt%, meanwhile nitrogen and carbon content were 2.2 wt% nitrogen and 85.93 wt%, respectively.

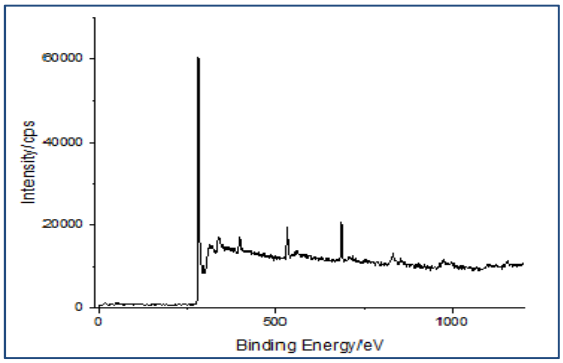


Scheme 17

4.1.1 Catalyst Characterization

In order to understand the real structure of the catalyst several characterization methods were carried out[10].

The nature of the palladium and nitrogen species on the surface of the catalyst was further analyzed by X-ray photoelectron spectroscopy (XPS, *Figure 1*). The Pd3d XPS data (*Figure 2*) reveal the presence of two Pd species. The first one has a binding energy of approximately 334.9 eV and is attributed to Pd(0) (19,7%) coordinated with phenanthroline. The second Pd species has a binding energy of approximately 337.3 eV and is attributed to Pd(II) in the form of palladium oxide (80.3%). Three distinct peaks are observed in the N1s spectra with an electron-binding energy of 398.2 eV , 399.5 eV and 400.5 eV (*Figure 3*). The lowest binding-energy peak can be attributed to pyridine-type nitrogen coordinated with Pd(0) (sp^2 hybridized, 41.4%). The electron-binding energy of 399.5 eV is characteristic of a pyrrole-type nitrogen (sp^3 hybridized, 24.8%) . The peak at 400.5 eV is typical of quaternary N (sp^2 hybridized, 24.6%). Apart from this three nitrogen types, N oxide of pyridinic N (small peak at 402.2 eV, 9.3%) was also observed probably because of the presence of air during pyrolysis step. The ratio between all palladium atoms and all nitrogen atoms in the near-surface region is 1:5.8. Deconvolution revealed that around 41% of all nitrogen atoms are bound to the metal ions, which means that 2.4 atoms are bound to one palladium atom. Also, the C1s spectra showed 3 peaks (*Figure 4*): the sharp peak at 283.8 eV corresponds to the sp^2 carbon with C=C, meanwhile the smaller peaks at 284.6 eV and 286.6 eV are assigned to C=N and C-N respectively. The peak observed at 289.1 eV is ascribed to the physisorbed oxygen on the carbon.



Peak name	Area/cps·eV	Ebin/eV	Sigma	Lambda	TF	Sens. Fact.	Norm. Area	Quant./at.%	
C1s Peak 1	7738.447830	283.81	1	20.3	0.836	16.971	455.9806628	46.14	88.96
C1s Peak 2	1018.328491	286.62	1	20.27	0.838	16.986	59.95104739	6.07	
C1s Peak 3	1138.321415	289.12	1	20.24	0.84	17.002	66.95220651	6.77	
C1s Peak 4	5031.719654	284.63	1	20.29	0.837	16.983	296.2797888	29.98	
N1s Peak 1	524.4429758	398.2	1.8	18.85	0.921	31.25	16.78217522	1.7	4.11
N1s Peak 2	314.9510609	399.5	1.8	18.83	0.922	31.25	10.07843394	1.02	
N1s Peak 3	313.3744520	400.53	1.8	18.82	0.923	31.268	10.02220967	1.01	
N1s Peak 4	117.8199834	402.21	1.8	18.8	0.925	31.302	3.763976214	0.38	
O1s Peak 1	2404.851157	532.03	2.93	17.09	1.046	52.377	45.91425925	4.65	5.88
O1s Peak 2	638.9659977	535.53	2.93	17.05	1.05	52.454	12.18145418	1.23	
Pd3d Doublet 1	373.3851655	334.87	16.04	19.66	0.872	274.98	1.357853116	0.14	0.71
Pd3d Doublet 2	1562.031254	337.32	16.04	19.63	0.874	275.19	5.676150668	0.57	
S2p Doublet 1	42.16584010	163.22	1.677	21.8	0.763	27.894	1.511645518	0.15	0.34
S2p Doublet 2	51.34256160	167.1	1.677	21.76	0.765	27.916	1.839180456	0.19	

Figure 1

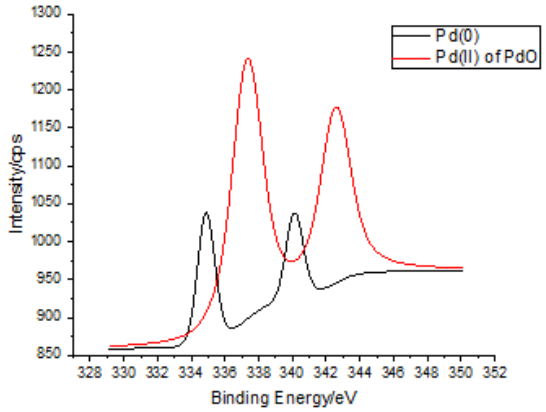


Figure 2

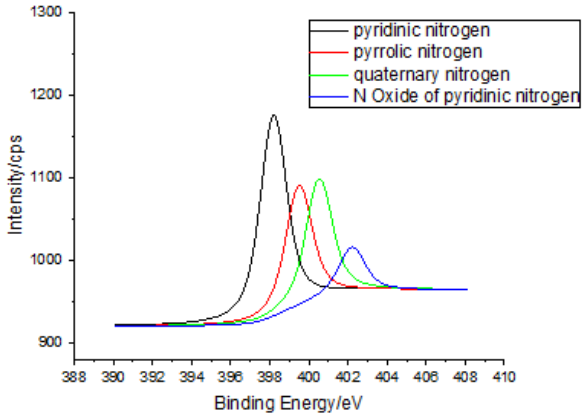


Figure 3

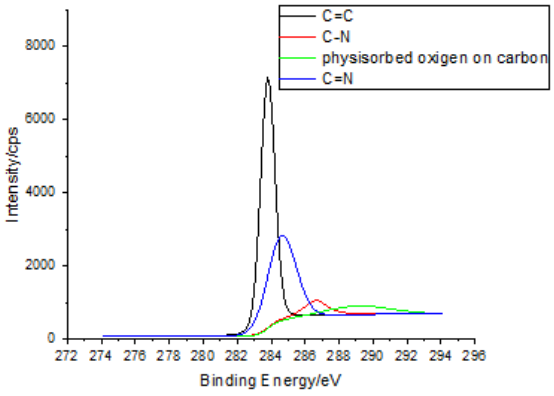


Figure 4

The X-ray diffraction (XRD) studies confirmed the presence of palladium dispersed into carbon powder (*Figure 5*). Compering XRD patterns of new material with the XRD patterns of Pd/C, it is possible to identify the characteristic broad peak of amorphous carbon support (around 2θ = 25°C) and also the three peaks belong to palladium (0) and located at 2θ = 40°, 46° and 68°. Instead the peaks located at 2θ = 31°, 44° and 55° belong to PdO.

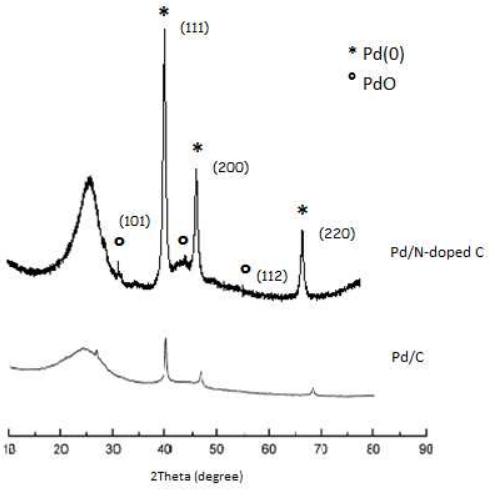


Figure 5

TEM confirmed the presence of well-defined and spherical-like Pd/PdO nanoparticles and agglomerates. N-doped graphene layers were formed through the carbonization of the nitrogen ligand, and these graphene layers - from two to six - surround the palladium/palladium oxide particles. (*Figure 6*)

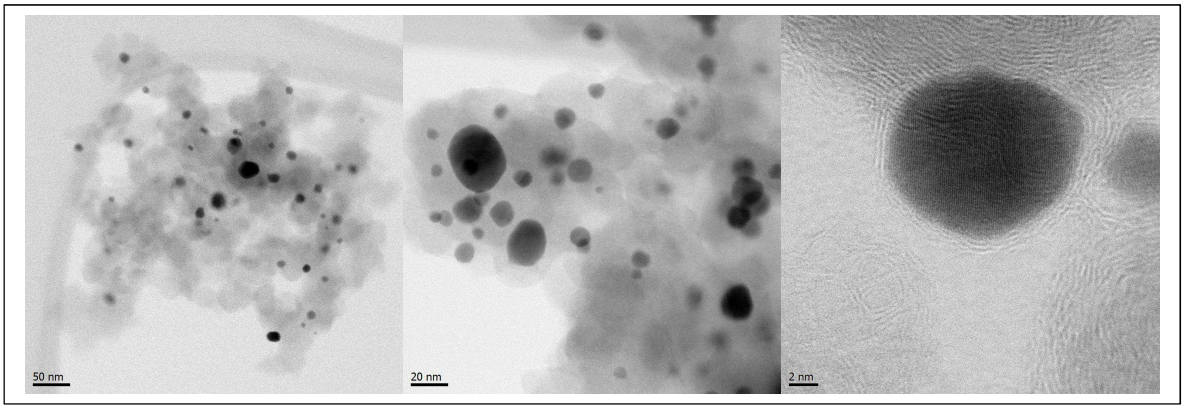
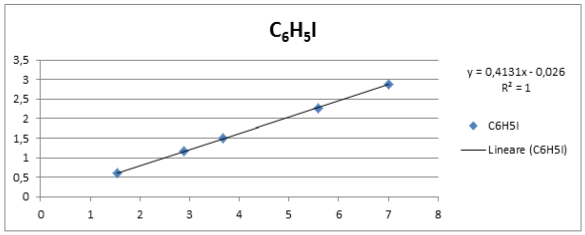


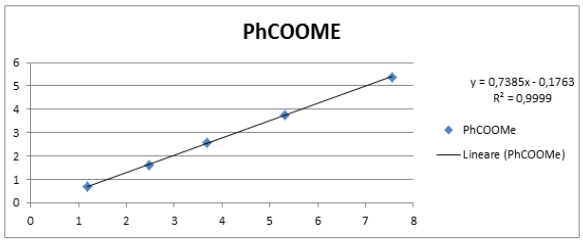
Figure 6

4.1.2 Results and Discussion

In order to examine the activity of the prepared catalyst for the alkoxycarbonylation of aryl halides, we initially tested Pd/PdO@NGr-C with iodo-benzene as the model substrate. The reaction was carried out in MeOH dry in the presence of catalytic amount of Pd/PdO@NGr-C (0.5 mol%, Pd=5.63 wt%) and hexadecane as internal standard under 20 bar CO pressure at 100-120°C for 19-24h. The reaction mixture was filtered through a silica plug and analyzed by GC and GC-MS. Below the calibration curves of calibration curves of iodo-benzene and methylbenzoate are shown (*Figure 7*)



A(C6H5I)	A(Standard)	A(C6H5I)/A(Stand)	m(C_6H_5)	m(Stand)	m(C_6H_5)/m(Stand)	k
152,23456	248,80013	0,611874921	14,9	9,6	1,552083333	0,394228137
294,58798	251,12346	1,173080285	27,8	9,6	2,895833333	0,405092472
561,19189	374,95221	1,496702446	40,8	11,1	3,675675676	0,407191107
572,53119	251,87892	2,273041309	58,6	10,5	5,580952381	0,407285559
784,52423	272,89325	2,874839264	81,4	11,6	7,017241379	0,409682254

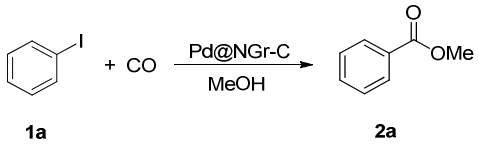


A(Prod)	A(Standard)	A(Prod)/A(Stand)	m(Prod)	m(Stand)	m(Prod)/m(Stand)	k
171,74954	242,23735	0,709013453	12,7	10,7	1,186915888	0,597357791
537,44403	330,07776	1,628234601	26,5	10,7	2,476635514	0,657438122
708,01147	276,83914	2,557483273	40,6	11	3,690909091	0,692914187
1142,1106	303,36554	3,764800049	61,1	11,5	5,313043478	0,708595754
1526,66736	283,28006	5,389251047	85,3	11,3	7,548672566	0,713933609

Figure 7

As shown in *Table 1*, the best results were obtained when the substrate **1a** was allowed to react with 0.5 mol% of catalyst at a temperature of 120 °C for 24 hours (*entry 7*). Interestingly, the same reaction, carried out in the presence of Et_3N as base, showed a lower selectivity (*entry 8*) probably because under this condition the deiodination reaction is promoted. On the other hand, when the reaction temperature was decreased to 100 °C, a high selectivity but a lower activity was observed (*entry 6*). Finally, reducing the catalyst amount the conversion and yield decreased (*entry 1-5*). A *"Hot filtration experiment"* showed that there is no palladium leaking, thus suggesting that the alkoxycarbonylation reaction proceeded by a "real" heterogeneous catalysis.

Table 2. *Model Reaction: Study of Reaction Conditions*[a]



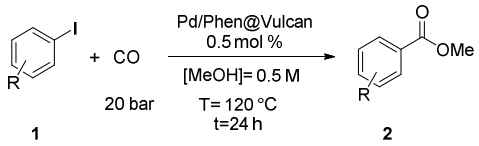
1a 2a

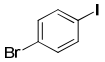
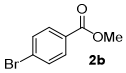
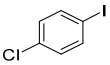
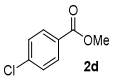
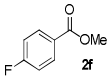
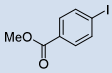
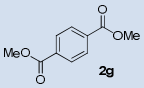
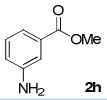
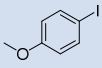
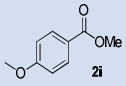
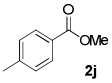
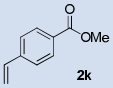
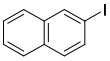
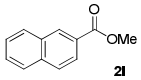
entry	Pd@NGr-C (mol %)	[MeOH]	T(°C)	T(h)	Conv (%)	Yield[b] (%)
1	0.01	0.25	100	19	64	53
2	0.1	0.25	100	19	79	71
3	0.1	1	100	19	59	57
4	0.1	0.5	100	19	78	78
5	0.1	0.5	120	19	74	55
6	0.5	0.5	120	19	86	84
7	0.5	0.5	120	24	90	79
8[c]	0.5	0.5	120	24	100	69

[a] Reaction conditions: 0.5 mmol iodobenzene, 20 bar CO. [b] The yields were obtained by GC using hexadecane as internal standard . [c] Et_3N (3 *equiv*).

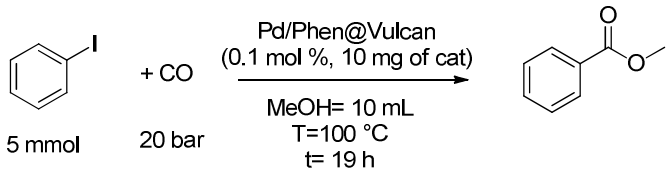
In order to generalize the use of the catalyst, the best reaction conditions found on the model substrate were applied to different aryl iodides to obtain the corresponding ester derivatives, as shown in *Table 2*. Among the different halogen substituted aryl iodides 4-bromo-iodobenzene gave the best result (*Table 2*, entries 2-6): as expected, when the electronegativity of the halide on the benzene ring decreases, the reactivity improvesd; at the same time, analogous substrates substituted in *meta* shown a lower reactivity because of the steric hindrance. The reaction worked also with the substrate substituted with a moderately deactivating carbo-methoxy group (*Table 2*, entry 7). Moreover, the reaction was extended to other aryl iodines having electron donating group such as amino, methoxy, methyl and vinyl group at para position to generate the corresponding esters in good to excellent yields (*Table 2*, entries 8-11). An excellent result was obtained with 2-iodonaphthalene. (*Table 2*, entries 12). All the products have been purified by chromatographic column on silica gel (hexane/ethyl acetate 9:1)

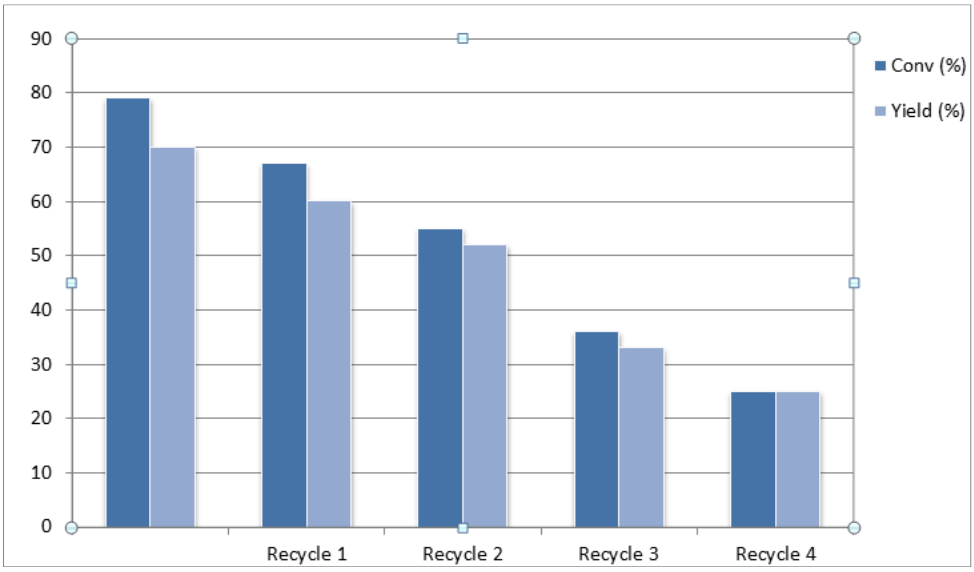
Table 2. *Substrate Scope*



entry	sub	Prod	Conv (%)	Yield (%)
1		 2a	98	59
2		 2b	98	84
3		 2c	99	74
4		 2d	100	82
5		 2e	99	74
6		 2f	98	52
7		 2g	96	55
8		 2h	98	70
9		 2i	99	84
10		 2j	98	57
11		 2k	100	53
12		 2l	99	90

To test the recyclability of the catalyst, the reaction was performed with iodo-benzene under the optimized reaction conditions. The catalyst was separated from the reaction mixture by centrifugation at 8000 RPM for 10 min: applying a gravitational force on a tube it is possible to gather the catalyst as a precipitate on the bottom of the tube. The supernatant solution was withdrawn with a Pasteur pipette and the catalyst washed with MeOH for two times. As shown in *Fig. 8* the catalyst could be reused for four times with a steady loss of catalytic activity probably because of the mechanical abrasion of the catalytic material during the reaction and the work-up procedure. Hence, we observed a decline of the conversion, but not of the selectivity which remained around 90% .





Finally, the ICP analysis on representative products **2a**, **2b**, **2g** and **2i** was performed in order to measure the amount of palladium in the products. The instrument reveals there is no trace of palladium in the products.[11] No metal contamination makes Pd/PdO@NGr-C a good catalyst for the synthesis of molecules of pharmaceutical interest where a high purity is required.

4.2 Experimental Section

The structure and morphology of the samples were characterized by transmission and scanning electron microscopy (TEM and SEM). TEM images were obtained using an aberration-corrected JEM-ARM200F (JEOL, Corrector: CEOS) operating at 200 kV. X-ray photoelectron spectroscopy (XPS) was performed using a VG ESCALAB220iXL (ThermoScientific) with monochromatic Al Kα (1486.6 eV) radiation. X-ray powder diffraction (XRD) pattern of the materials were recorded on a Stoe STADI P diffractometer, equipped with a linear Position Sensitive Detector (PSD) using Cu Kα radiation (λ = 1.5406 Å). The pyrolysis process was investigated through simultaneous thermal analysis (STA) experiments using an NETZSCH STA 449 F3 Jupiter®. A constant nitrogen flow rate was maintained over the sample throughout the process. The C/H/N/S-elemental analysis (EA) was performed by combustion of a 10 mg sample at 1000°C under O_2/He-flow using a Leco Microanalysator TruSpec. In addition, the metal content was determined by ICP-MS (Instrument Sensitivity= 0.5 ppm). ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solution at 300 MHz and 75 MHz, respectively. Chemical shifts (*δ*) and coupling constants (*J*) are given in *ppm* and in *Hz*, respectively. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70-230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

4.2.1 Preparation of Palladium Supported on N-doped Carbon

Palladium(II) acetate (Sigma-Aldrich >98%, 112.3 mg, 0.5 mmol) and 1,10-phenanthroline (Sigma-Aldrich, ≥99%, 180.2 mg, 1.0 mmol) (Pd:phenanthroline = 1:2 molar ratio) were stirred in ethanol (50 mL) for 1 h at 60 °C. Then, carbon powder (689.7 mg, VULCAN® XC72R) was added and the whole reaction mixture was leave to react at room temperature overnight. Ethanol was carefully removed under vacuo (40°C at 130 mBar). The solid sample obtained was dried at 25 °C for 4 hours, after which it was grinded to a fine powder. Then, the grinded powder was transferred into a ceramic crucible and placed in the oven. The oven was evacuated to ca. 5 mbar and then flushed with argon. The oven was heated to 800 °C at the rate of 25 °C per minute, and held at 800 °C for 2 hours under argon atmosphere. During the

whole process argon was constantly passed through the oven. Finally the pyrolyzed material is grinded again so as to obtain a fine powder. Elemental analysis of Pd-Phenanthroline/C (wt%): C = 85.93, H = 0.52, N = 2.2, Pd = 5.63.

4.2.2 General procedure for alkoxycarbonylation of aryl iodides

Into a reaction glass vial fitted with a magnetic stirring bar and a septum cap was added the palladium-catalyst (0.5 mol%, 5.63 wt% Pd-Phen/C, 9.5 mg) followed by the aryl iodide (1 mmol: **1a**, 204.0 mg; **1b**, 282.9 mg; **1c**, 282.9 mg; **1d**, 238.5 mg; **1e**, 238.5 mg; **1f**, 222.0 mg; **1g**, 262.0 mg; **1h**, 219.0 mg; **1i**, 234.0 mg; **1j**, 218.0 mg; **1k**, 230.1 mg; **1l**, 254.1 mg;), the internal standard (hexadecane, 0.2 equiv, 45.3 mg) and the solvent (MeOH dry, 2 mL). The reaction vial was then placed into a 300 mL steel Parr autoclave. The autoclave was flushed with carbon monoxide (5 bar for 5 times) and then it was pressurized to 20 bar carbon monoxide pressure and placed into an aluminium block preheated at 120 °C. After 24 h the reaction was completed and the autoclave was placed into an ice bath and cooled to room temperature. Finally, carbon monoxide gas was discharged and the samples were removed from the autoclave, diluted with ethyl acetate, filtered through a silica plug and analyzed by GC and GC-MS. All GC-yields are averages from at least 3 runs, the starting materials as well as products were calibrated from the commercially available materials. Isolated yields was determined by column chromatography on silica gel using as eluent only heptane to 9:1 heptane/AcOEt for **2b**, **2c** and **2j**; 95:5 heptane/AcOEt for **2a**, **2d**, **2e**, **2f**, **2g**, **2k** and **2l**; 9:1 heptane/AcOEt for **2i**; 9:1 heptane/AcOEt to 8:2 heptane/AcOEt for **2h**.

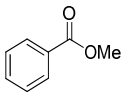
4.2.3 *Hot Filtration* Experiment

Iodobenzene (10 mmol, 2.04 g) diluted in MeOH (20mL) was stirred into a sovirel in the presence of catalytic amount of Pd/PdO@NGr-C (0.5 mol%, 5.63 wt% Pd-Phen/C, 95 mg) at 100°C for 1h. The reaction mixture was filtered under vacuum when it was already hot. The solution was put to react as described in **4.2.2** under a pressure of 20 bar of carbon monoxide at 120°C for 24 h. GC shown that iodo-benzene did not react.

4.2.4 Catalyst recycling experiment

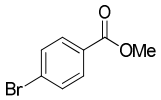
For the catalyst recycling experiments, the reactions were carried on a 5 mmol of iodo-benzene in the presence of 0.1 mol % of the catalyst (10 mg). All reactions were conducted in glass vials and set up according to procedures described in **4.2.2**. The catalyst was separated from the reaction mixture by centrifugation at 8000 RPM for 10 min. The supernatant solution was withdrawn with a Pasteur pipette, the catalyst washed with MeOH for two times and then dried under a high vacuum for 1 h before being resubmitted to the reaction conditions. All yields are averages from at least 2 runs.

4.3 Characterization Data



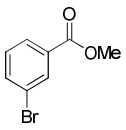
2a

*methyl benzoate (**2a**).* Yield: 80.3 mg, starting from 204.0 mg of iodobenzene (59%). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.08-8.04 (m, 2H, CH arom), 7.61-7.53 (m, 1H, CH arom), 7.49-7.41 (m, 2H, CH arom), 3.93 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.1 (CO), 132.9 (*p*-CH), 130.2 (C), 129.6 and 128.4 (CH), 52.1 (CH_3). GC-MS: *m/z* = 136 (39) [M^+], 105 (100), 77 (54), 59 (1), 51 (20).



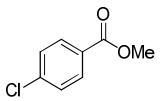
2b

*methyl 4-bromobenzoate (**2b**).* Yield: 180.6 mg, starting from 282.9 mg of 1-bromo-4-iodobenzene (84%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.92- 7.86 (m, 2H, CH arom), 7.60-7.54 (m, 2H, CH arom), 3.91 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4 (CO), 131.7 and 131.1 (CH), 129.1 and 128.1 (C), 52.3 (CH_3). GC-MS: *m/z* = 216 (36) [M^+], 215 (6), 214 (35), 185 (99), 184 (9), 183 (100), 157 (34), 155 (35), 76 (20), 50 (17).



2c

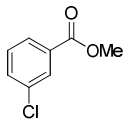
*methyl 3-bromobenzoate (**2c**).* Yield: 159.1 mg, starting from 282.9 mg of 1-bromo-3-iodobenzene (74%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.18 (t, *J*= 1.8, 1H, CH arom), 7.97 (dt, *J*= 7.8, 1.3**,** 1H, CH arom), 7.68 (ddd, *J*= 8.0, 2.1, 1.1, 1H, CH arom), 7.32 (t, *J*= 7.9, 1H, CH arom), 3.92 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.8 (CO), 135.9 and 132.7 (CH), 132.1 (C) , 130.0 and 128.2 (CH), 122.5 (C), 52.5 (CH_3). GC-MS: *m/z* = 216 (36) [M^+], 214 (35), 185 (99), 184 (9), 183 (100), 157 (34), 155 (35), 76 (20), 50 (17).



2d

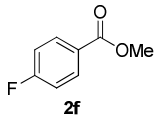
*methyl 4-chlorobenzoate (**2d**).* Yield: 139.9 mg, starting from 238.5 mg of 1-chloro-4-iodobenzene (82%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.00- 7.95 (m, 2H, CH arom), 7.44-7.38 (m, 2H, CH

arom), 3.91 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.4 (CO), 139.5 and 131.1 (CH), 128.9 and 128.7 (C), 52.4 (CH_3). GC-MS: *m/z* = 170 (32) [M^+], 141 (33), 139 (100), 113 (12), 111 (38), 75 (23).



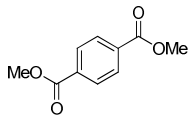
2e

*methyl 3-chlorobenzoate (**2e**).* Yield: 126.2 mg, starting from 238.5 mg of 1-chloro-3-iodobenzene (74%). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.04- 7.99 (m, 1H, CH arom), 7.92 (dt, *J*= 7.7, 1.4**,** 1H, CH arom), 7.52 (ddd, *J*= 8.0, 2.2, 1.1, 1H, CH arom), 7.42- 7.33 (m, 1H, CH arom), 3.92 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.0, 134.7 and 133.1, 132.0, 128.8 and 128.8, 52.5. GC-MS: *m/z* = 170 (37) [M^+], 141 (33), 139 (100), 113 (14), 111 (44), 75 (25).



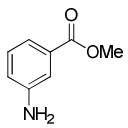
2f

*methyl 4-fluorobenzoate (**2f**).* Yield: 80.2 mg, starting from 222.0 mg of 1-fluoro-4-iodobenzene (52%). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.11- 7.99 (m, 2H, CH arom), 7.16-7.02 (m, 2H, CH arom), 3.91 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.6 (CF), 166.2 (CO), 164.2 (CF), 132.30 and 132.18 (CH), 126.56 and 126.52 (C), 115.78 and 115.49 (CH), 52.3 (CH_3). GC-MS: *m/z* = 154 (33) [M^+], 123 (100), 95 (44), 75 (17).



2g

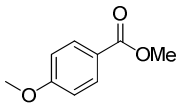
*dimethyl terephthalate (**2g**).* Yield: 106.8 mg, starting from 262.0 mg of methyl 4-iodobenzoate (55%). White solid.^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.09 (s, 4H, CH arom), 3.94 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.4 (CO), 134.0 (C), 129.7 (CH), 52.57 (CH_3). GC-MS: *m/z* = 194 (23) [M^+], 163 (100), 135 (19), 103 (11), 76 (9).



2h

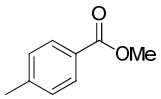
*methyl 3-aminobenzoate (**2h**).* Yield: 105.8 mg, starting from 219.2 mg of 3-iodoaniline (70%). Yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.42 (dt, *J*=7.7, 1.3, 1H, CH arom), 7.36 – 7.33 (m, 1H, CH arom), 7.20 (t, *J*=7.8, 1H, CH arom), 6.85 (ddd, *J*=8.0, 2.5, 1.0, 1H, CH arom), 3.88 (s, 3H, CH_3), 3.65 (d, *J*=7.6, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.40 (CO), 146.55 (CNH_2), 131.24 (C), 129.38 (CH), 119.84 (CH), 119.53

(CH), 115.90 (CH), 52.16 (CO_2CH_3). GC-MS: *m/z* = 151 (100) [M^+], 121 (8), 120 (9), 93 (19), 92 (70), 65 (32).



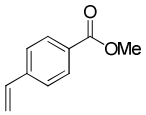
2i

*methyl 4-methoxybenzoate (**2i**).* Yield: 139.6 mg, starting from 234.0 mg of 1-iodo-4-methoxybenzene (84%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)**:** 7.99 (d, *J*=9.0, 2H, CH arom), 6.91 (d, *J*=8.9, 2H, CH arom), 3.88 (s, 3H, CO_2CH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.00 (CO), 163.45 ($COCH_3$), 131.71 (CH), 122.74 (C), 113.73 (CH), 55.54 (CO_2CH_3) , 51.99 (OCH_3). GC-MS: *m/z* = 166 (37) [M^+], 135 (100), 107 (9), 92 (13), 77 (15).



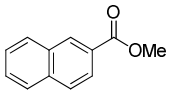
2j

*methyl 4-methylbenzoate (**2j**).* Yield: 85.6 mg, starting from 218.0 mg of 1-iodo-4-methylbenzene (57%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.93 (d, *J*=8.2, 2H, CH arom), 7.23 (d, *J*=8.0, 2H, CH arom), 3.90 (s, 3H, CO_2CH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 166.3 (CO), 143.7 (CCH_3), 129.7 and 129.2 (CH), 127.6 (C), 52.1 (CO_2CH_3), 21.8 (CH_3). GC-MS: *m/z* = 150 (35) [M^+], 120 (10), 119 (100), 91 (43), 65 (15).



2k

*methyl 4-vinylbenzoate (**2k**).* Yield: 86.0 mg, starting from 230.1 mg of 1-iodo-4-vinylbenzene (53%). White solid. ^{1}H NMR (300 MHz,$CDCl_3$) δ = 8.05 – 7.94 (m, 2H arom), 7.51 – 7.40 (m, 2H arom), 6.75 (dd, *J*=17.6, 10.9, 1H vinyl), 5.86 (dd, *J*=17.6, 0.8, 1H vinyl), 5.38 (dd, *J*=10.9, 0.7, 1H vinyl), 3.91 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.99 (CO), 142.05 ($CCHCH_2$), 136.15 ($CHCH_2$), 130.01 (CH), 129.41 (CH), 126.24 (CH), 116.60 ($CHCH_2$), 52.20 (CO_2CH_3). GC-MS: *m/z* = 162 (44) [M^+], 132 (10), 131 (100), 103 (34), 77 (26), 51 (9).



2l

*methyl 2-naphthoate (**2l**).* Yield: 167.6 mg, starting from 254.1 mg of 2-iodonaphthalene (90%). White solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.62 (s, 1H, CH arom), 8.07 (dd, *J*=8.6, 1.7, 1H, CH arom), 7.96

(d, *J*=8.1, 1H, CH arom), 7.88 (d, *J*=8.4, 2H, CH arom), 7.63 – 7.49 (m, 2H, CH arom), 3.99 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.4, 135.6, 132.6, 131.2, 129.5, 128.4, 128.3, 127.9, 127.5, 126.8, 125.4, 52.4. GC-MS: m/z = 186 (71) [M+], 156 (12), 155 (100), 127 (86), 126 (19), 77 (10).

[1] (a) Charles N. Satterfield. *Heterogeneous catalysis in industrial practice.* Krieger Pub Co.; 2° edition, **1996**. (b) *Heterogeneous Catalysis and Solid Catalysts*. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2009**.

[2] Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, 107, 133-173.

[3] (a) Lian, Z.; Friis, FS.D; Skrydstrup, T. *Chem. Comm.* **2015**, 51, 10, 1870- (b) Liu, J.; Chen, J.; Chungu Xia, C. *J. Catal.* **2008**, 253, 1, 50-56. (c) Abstracts of Papers, 235th ACS National Meeting, New Orleans, LA, United States, April 6-10, **2008**. (d) Davies ,I.W.; Matty ,L.; Hughes ,D.L.; Reider, R.J. *J. Am. Chem. Soc.*, **2001**, *123*, 41, 10139–10140.

[4] (a) Cai, M.; Peng, J.; Hao, W; Ding, G. *Green Chem.* **2011**, 13, 1, 190-196. (b) Zhao, H.; Zheng, G.; Sheng, S.; Cai, M. *Catal. Comm.* **2009**, 11, 3, 158-161. (c) Cai, M.; Zheng, G.; Ding, G. *Green Chem.* **2009**, 11, 10, 1687-1693.

[5] (a) Natour, S.; Abu-Reziq, R. *ChemCatChem* **2015**, 7, 14, 2230-2240. (b) Niu, J.R.; Xing Huo, X.; Zhang, F.W.; Wang, H.B.; Zhao, P.; Hu, W.Q.; Ma, J.; Li, R. *ChemCatChem* **2013**, 5, 1, 349-354. (c) Cai, M.Z.; Song, C.S.; Huang, X. *J. Chem. Soc., Perkin Trans.* 1, **1997**, 2273-2274.

[6] Prasada, A.S.; Satyanarayana, B. *J. Mol. Catal. A-Chem* **2013**, 370, 205-209.

[7] (a) Ullah, E.; McNulty, J.; Sliwinski, M.; Robertson, A. *Tetrahedron Lett.* **2012**, 53, 3990-3993. (b) Qureshi, Z.S.; Deshmukh, K.M.; Tambade, P.J.; Bhanage, B.M.; *Synthesis* **2011**, 2, 243-250. (c) Wang, Y.; Liu, J.; Xia, C. *Tetrahedron Lett.* **2011**, 52, 14, 1587-1591.

[8] Jagadeesh, R.V.; Stemmler, T.; Surkus, A.E.; Junge, H.; Junge, K; Beller, M. *Nature Protocols* **2015**, 10, 548–557.

[9] Felix A. Westerhaus, F.A.; Jagadeesh, R.V.;Wienhöfer, G.; Pohl, M.M.; Radnik, J.; Surkus, A.E.; Rabeah, J.; Junge, K.; Junge, H.; Nielsen, M.; Brückner, A.; Beller, M. *Nature Chemistry* **2013**, vol 5, 537-543.

[10] (a) Wang, H.; Maiyalagan, T.; Wang, X. *ACS Catal.* **2012**, 2, 781-794. (b) J. M. Thomas, W. J. Thomas. *Principles and Practice of Heterogeneous Catalysis.* Wiley-VCH; 1 edition (September **1996**).

[11] ICP Instrument Sensitivity= *0.5 ppm*

Aknowledgments

First of all, I would like to say thanks to my mentor at University of Calabria, *Prof.* Bartolo Gabriele, his expert knowledge has been an important support for me. My thanks will be never enough for the opportunity to spend my *PhD* in his group.

I would also like to express my gratitude to *Dr* Raffaella Mancuso, who followed me step by step during all the time of the work sharing her experience and helping me.

I would like to thanks Prof. Matthias Beller for the opportunity to join his group at *Leibniz Institute for Catalysis* in Rostock University. Thanks to all the people I met in *Likat,* in particular *Dr.* Helfried Neumann for his guidance and patience.

Finally thanks to all my colleagues in *Prof*. Gabriele group: it was great to work with you.

Publication on International Scientific Journals:

Araniti, F.; Mancuso, R.; Ziccarelli, I.; Abenavoli, M.R.; Sunseri, F.; Gabriele, B. "3-(Methoxycarbonylmethylene) isobenzofuran-1-imines as a new class of synthetic herbicides" *Molecules* **2014**, *19*, 8261-8275.

Mancuso, R.; Ziccarelli, I; Armentano, D.; Marino, N.; Giofrè, S. V.; Gabriele, B. "Divergent Palladium Iodide-Catalyzed Multicomponent Carbonylative Approaches to Functionalized Isoindolinone and Isobenzofuranimine Derivatives" *J. Org. Chem.* **2014** , 79 (8), 3506–3518

Gabriele, B.; Mancuso, R.; Ziccarelli, I; Salerno, G. "A new Approach to Isoindolinone derivatives by sequential palladium iodide-catalyzed oxidative Aminocarbonylation-Heterocyclization of 2-Ethynylbenzamides" *Tetrahedron Lett.* **2012**, 53, 6694–6696.

Conference Poster Presentation:

Ida Ziccarelli, Raffaella Mancuso, Donatella Armentano, Bartolo Gabriele
"A New Approach to Dihydrofuro[3,2-b]furan-2(5H)one Derivatives by Pd-Catalyzed Oxidative Carbonylation of 4-Yne-1,3-diols"
Ischia Advanced School of Oragnic Chemistry 2014
21-25 settembre **2014**, Albergo della Regina Isabella, Lacco Ameno, Ischia (Na); Abstract Book: P61

Ida Ziccarelli, Raffaella Mancuso, Donatella Armentano, Bartolo Gabriele
"A Novel Synthesis of Dihydrofuro[3,2-b]furan-2(5H)one Derivatives by Pd-Catalyzed Oxidative Carbonylationof 4-Yne-1,3-diols"
XXV Congresso Nazionale della Società Chimica Italiana
7-12 settembre **2014**, Arcavacata di Rende (Cosenza); Abstract Book: ORG-P96

Raffaella Mancuso, Fabrizio, Araniti, Ida Ziccarelli, Francesco Sunseri, Maria Rosa Abenavoli, Bartolo Gabriele.
"3-(Methoxycarbonylmethylene)-isobenzofuran-1-imines: a New Class of Synthetic Herbicides"
XXV Congresso Nazionale della Società Chimica Italiana
7-12 settembre **2014**, Arcavacata di Rende (Cosenza); Abstract Book: ORG-P39

Salvatore Giofrè, Raffaella Mancuso, Roberto Romeo, Ida Ziccarelli, Santa Cirmi, Bartolo Gabriele.

"*Spiro-Isoindolin Isossazoline: Potenziali agenti antitumorali*"

XXV Congresso Nazionale della Società Chimica Italiana

7-12 settembre **2014**, Arcavacata di Rende (Cosenza); Abstract Book: ORG-P31

Raffaella Mancuso, Ida Ziccarelli, Donatella Armentano, Bartolo Gabriele

" A Novel Syntheses of 3H-Isobenzofuran-1-ylideneamine Derivatives by Pd-Catalyzed Alkoxycarbonylation of 2-Alkynylbenzamide"

XXXV Convegno della Divisione di Chimica Organica- Società Chimica Italiana

9-13 settembre **2013**, Sassari (Italy), Abstract book P2

Raffaella Mancuso, Ida Ziccarelli, Donatella Armentano, Bartolo Gabriele

"A New Palladium-Catalyzed Carbonylation Approach to Isobenzofuran Derivatives"

9th International School of Organometallic Chemistry

30 Agosto-3 Settembre **2013**, Camerino (Italy), Abstract book P18

Raffaella Mancuso, Bartolo Gabriele, Ida Ziccarelli, Giuseppe Salerno

"*Sintesi di eterocicli azotati per carbonilazione ossidativa Pd-catalizzata di 2-alchinilbenzammidi*"

Convegno Congiunto delle Sezioni Calabria e Sicilia **2012**

6-7 dicembre **2012**, Rende (Cosenza). Abstract book P29

Raffaella Mancuso, Bartolo Gabriele, Ida Ziccarelli, Giuseppe Salerno

"*New Syntheses of Isoindolinone and Isoquinolinone Derivatives by Pd-Catalyzed Carbonylation of 2-ethynylbenzamides"*

XII Giornata Scientifica Borsisti CINMPIS

03 dicembre **2012**, Milano. Abstract book p9

Raffaella Mancuso, Bartolo Gabriele, Ida Ziccarelli, Giuseppe Salerno

"Palladium-Catalyzed Oxidative Carbonylation of 2-Alkynylbenzamides Leading to Nitrogen Heterocycles"

Ischia Advanced School Of Organic Chemistry

22-26 settembre **2012**, Ischia. Abstract book P55

Raffaella Mancuso, Bartolo Gabriele, Ida Ziccarelli, Giuseppe Salerno

"*New Syntheses of Isoindolinone and Isoquinolinone Derivatives by Pd-Catalyzed Carbonylation of 2-Alkynylbenzamides"*

XXXIV Congresso Nazionale della Divisione di Chimica Organica. Pavia (Italy)

10-14 settembre **2012**, Pavia. Abstract book O37 (O)