UNIVERSITÀ DEGLI STUDI DELLA TUSCIA DI VITERBO

DIPARTIMENTO PER L'INNOVAZIONE DEI SISTEMI BIOLOGICI, AGROALIMENTARI E FORESTALI (DIBAF).

CORSO DI DOTTORATO DI RICERCA IN
SCIENZE AMBIENTALI
XXV CICLO.

New Environmentally Friendly Procedures for the Synthesis of Biologically Active Compounds by C-C and C-Heteroatom Bond Formation

CHIM-06

Coordinatore: Prof. Maurizio Petruccioli

Tutor: Dott.ssa Roberta Bernini

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A Mamma, Papà,

Biagio, Nica,

Simone, Francesco e Carmine

Sommario

THESIS AIM

Over the last few years, industry focused its efforts on the development of new technologies for pollution prevention.[1] This approach is the way of modern business. It uses less energy, requires minimal product separations, generally involves less capital investment and there is no impact on the environment. In the last years, green chemistry has been recognized as a new approach to scientifically based environmental protection. Green chemistry "is the design of chemical products and processes which reduce or eliminate the use and the generation of hazardous substances in the design, manufacture and application of chemical products".[2] It utilizes a set of twelve principles[3] (Table 1) and in this context catalysis plays a fundamental role.[4] In the last decades, palladium-catalyzed reactions have become an important and extremely flexible tool for practicing organic chemists.[5,6] As palladium chemistry is generally tolerant of a wide range of functionalities, it is applicable to complex molecules. Thus, a large number of fine chemicals and biologically active ingredients have been prepared in fewer steps and with less wastes than classical methods. Even the design of heterocyclic synthesis has been deeply influenced and modified by the growing utilization of palladium catalysis,[7,8] as testified by the wide amount of studies on the palladium-catalyzed synthesis and functionalization of heterocycles.

In this context, the main research activity during this PhD course was directed to the development of green procedure for the synthesis of new class of derivatives, mainly through transition metal assisted processes. For example, well-known palladium-catalyzed cross-coupling protocol as the Myaura-Suzuki[9,10] and the Sonogashira-Cassar[11,12] alkynylation reaction was carefully optimized to obtaint functionalised dopamine derivatives.

At the same time, a quite general method for the synthesis of 2-amino ketones derivatives was reached through a novel palladium-catalyzed approach from arylpropargylic carbonates bearing neutral, electronrich, and electron-poor aromatic rings and cyclic secondary amines containing useful functional groups such as cyano, chloro, and bromo substituents.[13]

As part of the studies on the synthesis and functionalization of biologically active compounds, the construction of indole nucleus through a palladium catalyzed cascade

reaction of N-(2-bromophenyl)-2,2,2-trifluoro-N-(3-arylprop-2-ynyl)acetamide derivatives with arylboronic acids, has been investigated.

The development of efficient catalytic systems for the oxidative conversion of alcohols into ketones is an important goal to achieve both from an economic and environmental point of view. Classical methods are far from being environmentally benign. Generally, they do not respect the principles of *green chemistry* mainly because they use toxic chemicals, generate undesirable by-products and use stoichiometric reagents.[14-18] Recently, has been shown that supported and *quasi* homogeneous gold nanocatalysis could play a intersting role in chemical oxidation, particularly as to concern the practicability of achieve these reactions under *green conditions*.[19,20,21]

During this PhD course, a new kind of supported gold nanoparticles has been prepared, characterized and tested as new oxidant agent in alcohol to ketone oxidation reactions. The stabilizer agents used in nanoparticles generations were polysaccharides as alginate-gellan: this kind of polymers is non-toxic and biocompatible, and shows several physical-chemical properties that make it suitable for different applications. In addition, polysaccharides have economic benefits over synthetic polymers, since they derive from renewable sources.

Table 1 Principles of Green Chemistry

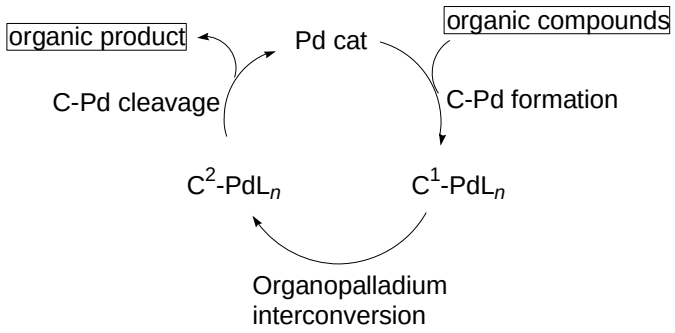
1.	It is better to prevent waste than to treat or clean up waste after it is formed
2.	Synthetic methods should be designed to maximize the incorporation of all materials used into the final product.
3.	Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4.	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5.	The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and, innocuous when used
6.	Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure
7.	A raw material of feedstock should be renewable rather than depleting wherever technically and economically practicable
8.	Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9.	Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10.	Chemical products should be designed to preserve efficacy of function while reducing toxicity.
11.	Analytical methodologies need to be developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12.	Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

1. Background of Palladium-Catalyzed Reactions

Over the last three-four decades palladium has definitely influenced and improved organic synthesis.[22] Being the 46^{th} atom in the periodic table, Pd is a second row transition metal of moderately large atomic size, larger than Ni but smaller than Pt. Its size influence significantly its chemical properties, such as the moderate stability of its compounds and their versatility and selectivity. Palladium typically exists in the 0 and +2 oxidation states (separated by a relatively narrow energy gap), rarely +1, +2, +4; thanks to these characteristics one-electron or radical processes are relatively rare whereas two electron oxidation and reduction is ready and reversible. Pd 's electronic configuration is [Kr]4d10 and tends to form d^{10} Pd(0) and d^{8} Pd(II) complexes of relatively low oxidation states, it is consequent that Pd is rather soft than the smaller Ni and the larger Pt. Coupled with the ready formation of coordinatively unsaturated species of 16 or even less electrons providing one or more empty coordination sites, Pd can indeed provide simultaneously at least one each of empty and filled nonbonding orbitals. Thus it can be understood why Pd can readily participate to concerted reactions with low activation energies. Some of the selectivity features, stereoselectivity is one of these, can be readily attributed this characteristic. The most significant consequence of its high propensity to run in concerted reactions, is the high affinity for nonpolar π-compounds, such as alkynes, alkenes and even arenes. Furthermore, it can also readily form σ bonds with nonbonding electron donors, such as amines, imines, nitriles, phosphines, phosphites, and various other N, P, S, O containing donors. Carbon monoxide and isonitriles are also representative examples of *C*-centered *n*-electron donors. Thank to this, Pd-mediated reactions are usually carried up in mild conditions. Palladium is relatively unreactive toward many functionalities, such as aldehydes, ketones, esters, amides, as well as nitro and ciano groups permitting to have often a wide generalization of the procedures. In the majority of Pd-catalysed reactions, some interconversions between Pd(0) and Pd(II) species must occur. As stated earlier the interconversion Pd(0) over Pd (II) is kinetically easily occurring in either direction under one set of reaction conditions so it is possible to have catalysis. Thus, this easy interconversion appears to be serving as a very favorable factor rather than a limitation. Finally, palladium appears to be relatively no-toxic, though very few substances can be definitely considered no-toxic at all.

1.1. Pd-Catalyzed reactions

Synthesis of organic compounds via organopalladium complexes in most cases involves generation of C-Pd bonds and their subsequent cleavage (Scheme 1).



Scheme 1

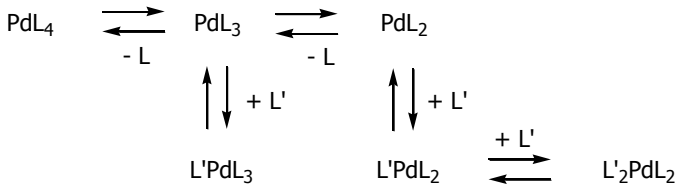
Pd catalysts and Pd-containing intermediates in a catalytic cycle itself must be regenerated in the reaction vessel under one set of reaction conditions without any additional external manipulations. This requires that the sum of Δ·FOS (i.e., change in formal oxidation state) for the whole catalytic cycle must be zero. This is but one of many "zero sum" principles governing various aspects of chemical processes.

There are different kinds of reagents and reactions that can reduce Pd(II) to Pd(0) species or provide the reverse oxidation. Pd(II) species added as precatalysts might be transformed into catalysts that appear in catalytic cycles themselves. A wide variety of reactions involving the reactants, ligands, and/or solvents present in a given reaction mixture can reduce Pd(II) species. Therefore, in some cases Pd(II) reduction can be achieved without adding externally reducing agents but by internal reduction. In fact it's known that reductive elimination, reductive decomplexation, and some processes involving nucleophilic attack on ligands can reduce Pd(II) species. Although the majority of Pd-catalyzed reactions are initiated by Pd(0) catalysts (which then undergo a series of Pd(0)-Pd(II) redox processes) there are many other Pd catalyzed reactions that are initiated by Pd(II) complexes. Most of the Pd(II) initiated reactions do involve reduction of Pd(II) species to Pd(0) species. In many of these reactions, the Pd(0) species must be externally oxidized to regenerate the original Pd(II) catalysts. For this purpose in addition to O_2, and CuCl, quinones (e.g., DDQ), peroxides (e.g., t-BuOOH) halogens, and halo-derivatives including organic halides have been used.

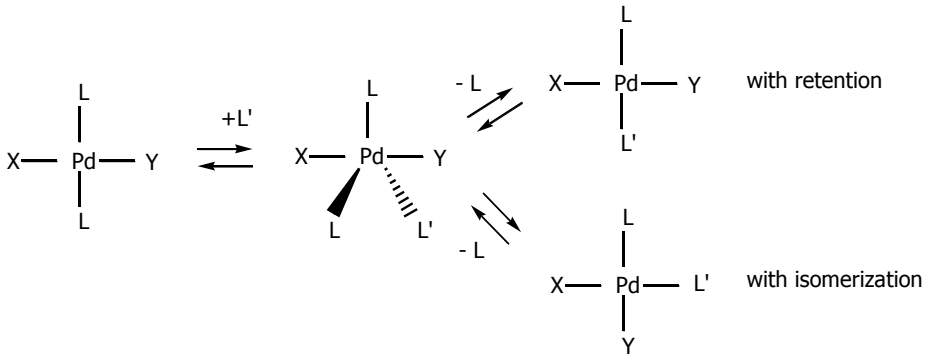
1.2. Organo-Palladium complexes

Pd(0) complexes tend to exists as coordinatively saturated 18-electron tetrahedral d^{10} complexes, but they can readily dissociate into coordinatively unsaturated 16 or less-electron d^{10} species. On the other hand, Pd(II) complexes tend to exist as coordinatively unsatured 16-electron square planar d^8 complexes. Although they are reluctant to form coordinatively saturated 18 electron five-coordinated d^8 complexes, such complexes are kinetically readily accessible, and they can serve as transient intermediates in ligand substitution. Pd(II) d^8 complexes may also undergo substitution by dissociative processes, which must involve 14 or less-electron species as transient intermediate. In all of these processes, the crucial requirement is the coordinative unsaturation or the presence of one or more valence-shell empty orbitals as Lewis acidic sites (Scheme 2).

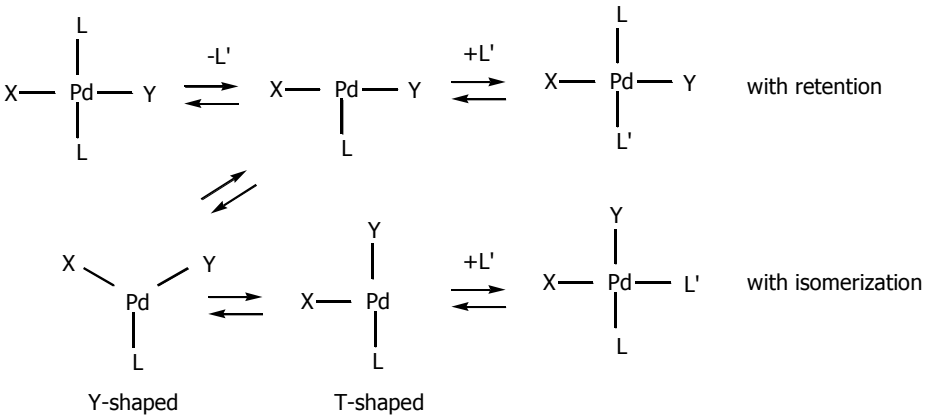
Dissociative ligand substitution reactions of 18-electron d10 Pd(0) complexes



Associative ligand substitution reactions of 16-electron d8 Pd(II) complexes



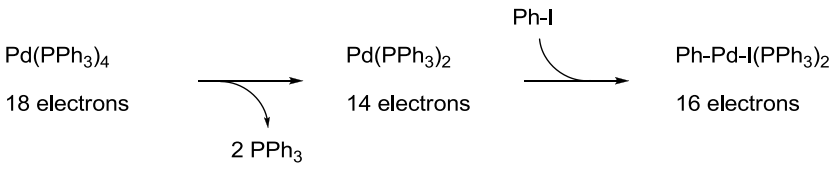
Dissociative ligand substitution reactions of 16-electron d8 Pd(II) complexes



Scheme 2

1.3. Ligands for Organo-Palladium complexes

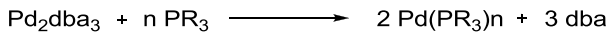
The nature of the ligand to be incorporated, especially its nucleophilicity or basicity, the electrophilicity or acidity of the leaving ligands and the nature and stereochemistry of the other ligands are factors that affect the rate and equilibrium of the ligand substitution. Two of the most commonly used palladium(0) complexes are the commercially available $Pd(PPh_3)_4$, unstable in air and light sensitive, and $Pd_2(dba)_3$ (dba = dibenzylideneacetone), whose storage and manipulation is quite easier than the former one. When $Pd(PPh_3)_4$ is used, the coordinatively unsaturated, catalytically active $Pd(PPh_3)_2$ (14 electrons species) is generated *via* a two-step equilibrium process involving the initial loss of a phosphine ligand to give $Pd(PPh_3)_3$ followed by the loss of a second phosphine ligand (Scheme 3).



Scheme 3

In the $Pd_2(dba)_3$ complex each palladium is coordinated to three olefinic double bonds. Being dba a weaker ligand than phosphine, $Pd_2(dba)_3$ represents a useful a source of Pd(0) to prepare palladium-phosphine complexes *in situ* by a ligand exchange reaction with a variety of monodentate and bidentate phosphines (Scheme 4).This quite easy

exchange is particularly useful when the reaction requires the use of Pd(0) complexes for instance containing chiral or electron-rich bulky phosphines.



Scheme 4

Palladium on charcoal, or other supported palladium metal catalysts, can also be used as a source of Pd(0). In these cases, reactions occur under heterogeneous conditions; the presence of phosphine ligands may involve soluble palladium complexes in a sort of a like $Pd(PR_3)_n$ catalyst system.[23] Palladium(0) species are frequently formed *in situ* through the reduction of palladium(II) species by several reagents such as alkenes, terminal alkynes, carbon monoxide, alcohols, amines, formiate anions, metal hydrides, butyl lithium as well as phosphines.[24]

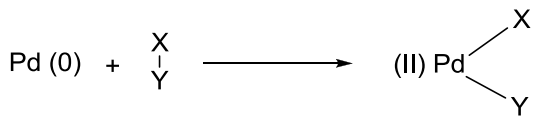
The most commonly used palladium(II) salts are commercially available $PdCl_2$ and $Pd(OAc)_2$, very often utilized as phosphines complexes such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2(PPh_3)_2$, tipically formed in situ combining $PdCl_2$ or $Pd(OAc)_2$ with PPh_3. Palladium(II) salts are fairly electrophilic species and tend to react with electron-rich compounds such as alkenes and alkynes, as well as arenes. Typical reaction of palladium(II) salts with alkenes or alkynes afford π-complexes. Palladium(0) complexes have usually nucleophilic character. Most of the catalytic processes based on their utilisation involve, in the initial step, their reaction with a variety of covalent polar and non polar single bonds such as H-H, N-H, O-H, C-H, C-O, as well as C-halogen; the latter is most employed. With arenes, palladium(II) salts such as $Pd(OAc)_2$, can produce palladation intermediates, basically through an electrophilic substitution reaction. These palladation intermediates can give rise to homocoupling reactions,[25] acetoxylation reactions,[26] or, in the presence of alkenes, vinylic substitution reactions. [27] In many Pd(II)-catalyzed reactions, Pd(II) species are reduced to Pd(0) species at the end of each cycle. Hence, the presence of oxidants such as Cu(II) salts and MnO_2 are required to make the reaction catalytic with respect to Pd(II).

1.4. General patterns of Pd and Pd complexes chemical processes

There are many different processes to generate palladium intermediates from Pd(0) and Pd(II). In this section some of most important patterns occurring in chemical processes involving palladium will be discussed, namely oxidative addition, insertion reaction, transmetallation, reductive elimination and electrophilic palladation.

1.4.1. Oxidative addition

The oxidative addition is the addition of an X-Y bond to Pd(0)[28] (Scheme 5) with cleavage of the covalent bond and formation of two new bonds. Since the two previously non bonding electrons of Pd are involved in bonding, the Pd increases its formal addition state by two units.[29]



X,Y = Atoms and groups containing H, C, heteroatoms and metals.

Scheme 5

The oxidative addition occurs with unsaturated complexes and leads to the formation of σ-organo-palladium complexes, containing an electrophilic palladium which, depending on reaction conditions, can undergo a variety of transformations. The substitution pattern of the arene plays an important role, since electron-withdrawing groups facilitate the oxidative addition, while electron-donating groups make difficult this process. Typically, oxidative addition is favoured by increasing the electron density on palladium, being the usual observed rate of oxidative addition with Csp^2-halogen bonds as follows: C-I > C-Br > C-CI > C-F (with aryl fluorides being almost inert). Vinyl triflates undergo facile oxidative addition while the reactivity of aryl triflates is more or less close to aryl bromides. Diazonium salts, aryl iodides, triflates and electron-deficient aryl-bromides do not generally requires ligands to go oxidative addition but are more disposed to undergo protonolysis and biaryl[30] formation during the reaction. Recently with the discovery of new electron rich ligands such us $P(t\text{-}Bu)_3$ or N-heterocyclic carbene ligands and Buchwald-type phosphines a some palladium-catalyzed reactions of

aryl chlorides and alkyl halides are emerging. The cost and ready avaibility of aryl chlorides make them the most attractive aryl donator albeit they are the most sluggish precursors. Thus, efficient catalysis requires high temperatures in combination with highly basic and air-sensitive phosphines as ligands to allow oxidative addition. Recently, the development of a procedure using air-stable tri-*t*-butyl phosphonium tetrafluoroborate[31] has simplified the implementation of the sluggish aryl chlorides, especially in Heck type reactions. In general, oxidative addition is favoured by σ-donor ligands coordinated to the palladium center. Hence, though there are examples of reactions carried out under "ligand-free" conditions, ligands (and other coordinating additives), are frequently required not only to generate soluble palladium catalysts, but to influence the course of a reaction as well. The ligands can bear one or two sites of coordination, being named respectively, mono- or bi-dentate. In the presence of mono-dentate ligands (Figure 1), the initially formed *cis*-complex subsequently isomerizes to the thermodynamically stable trans-complex. Typically with bidentate ligands (Figure 2) the isomerization is rather difficult being the *cis*-complex the usual intermediate, even if Buchwald et al.[32] has recently shown that Xantphos [9,9-dimethyl-4,6-bis(diphenylphosphino)xanthene],[33] a rigid bidentate ligand with a wide natural bite angle,[34] can be trans-chelating in palladium complexes.

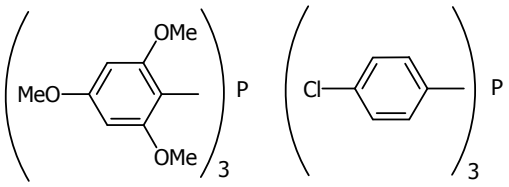
PPh_3

Most common ligand

$P(t\text{-}Bu)_3$; $P(cyclohexyl)_3$

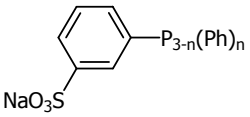
Phosphines that improve Oxidative Addition

ttmpp tcpp



Electron withdrawing and electron donating phosphines

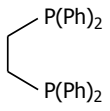
Sulphonic Phosphines



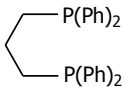
Water soluble phosphines

Figure 1

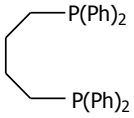
Bidentate phosphines



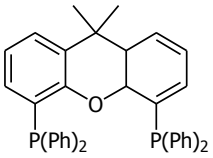
dppe



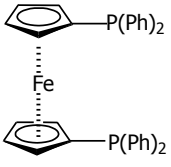
dppp



dppb



Xanthpos



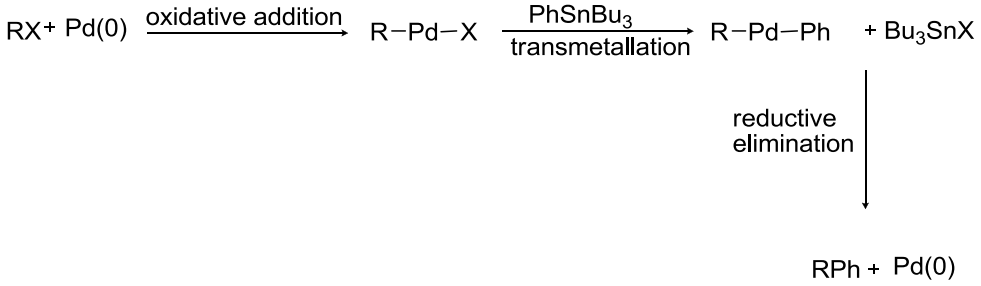
dppf

Figure 2

The use of additives such as halides[35], can also play a significant role in controlling the reaction outcome of Pd(0)-catalysed reactions. Beneficial effects of such additives have been demonstrated and described throughout a huge number of papers. For example, Jeffery[36] has showed that the Heck could be run under mild conditions in the presence of $Pd(OAc)_2$, carbonate or bicarbonate bases and Bu_4NCl as additive. Furthermore, the studies of Amatore and Jutand have shown that chloride anions can stabilize Pd(0) species providing more efficient catalytic cycles.[37] The nature of the halide anions is believed to influence the stability of five-coordinate palladium complexes[38] and the stability of dimeric palladium complexes in amination reaction.[39] The large ammonium cation plays also a significant role, since it can stabilize halide ligated zerovalent or divalent palladium-centered complexes. In some cases, a mixture of ammonium salts can be used both as additives and solvents. [40] Even if Bu_4NCl is generally superior to LiCI in this respect, there are some cases in which the presence of LiCl has been found to provide rather more beneficial effects on Pd(0)-catalyzed reactions. For example LiCl has been shown to play a key role in the Stille reaction,[41] or in preventing homocoupling reactions of aryl iodides. [42] Hence, one can't exactly know *a priori* the course of a reaction since the general behaviour of phosphine ligands and additives is not always clearly understood. Furthermore, it may also significantly vary not only from one type of reaction to another, but sometimes in the same reaction; for example, switching from electron-rich to electron-poor aryl halides.[43] This lack of general theories can be due to the involvement of several consecutive steps in the catalytic cycle. Consequently, a given species can exhibit opposing effects on different steps of a catalytic cycle and on the reactivity of each intermediate depending on reaction conditions. Thus, in some case the conditions for a given reaction can involve several different procedures specific for specific substrates.

1.4.2. Transmetallation and reductive elimination

Transmetallation reaction occur between σ-organo-palladium complexes and organometallic compounds with Li, Mg, Zn, Zr, B, Al, Sn, Si, Ge, Hg, Tl, Cu, Ni and more other. The physical driving force of transmetallation is the generation of less polar bonds. The transfer of the organic ligand to a more electronegative metal is always favoured from a thermodynamic standpoint. The process proceeds smoothly, typically at room temperature.(Scheme 6)

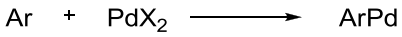


Scheme 6

As shown in the reductive elimination step involves the cleavage of C-Pd bonds, the formation of a new C-C bond, and the reduction of Pd(II) to Pd(0).

1.4.3. Electrophilic palladation

The reaction of Pd(II) species with unfunctionalised arenes can afford aryl metal intermediates (Scheme 7) [44]



Scheme 7

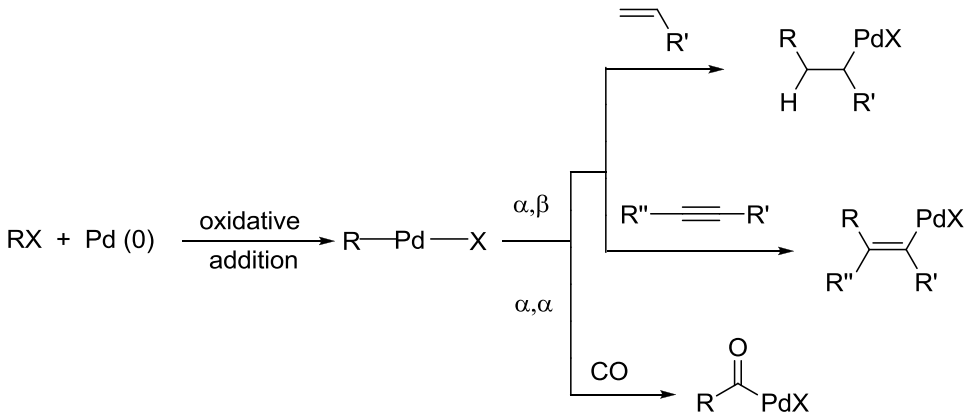
If a functionalised arene is subjected to such a transfornation, *ortho-meta-* or *para-*palladation is usually observed.[45] Nevertheless, this procedure seems attractive in terms of atom economy, since catalytic amounts of the transition metal are required when an effective palladium(0) reoxidation system is used and no organic salts are produced.

1.5. Reactivity of Organo-Palladium Complexes

As stated earlier synthesis of any organic compounds via organopalladium complexes involve the interconversion of organopalladium intermediates, *i.e.* the generation and cleavage of C-Pd bonds. Generally, palladium catalysis involves the intermediacy of σ- and π-complexes. Three types of π -complexes exist: η^2 type with alkenes and alkynes and η^3 with allyl compounds.

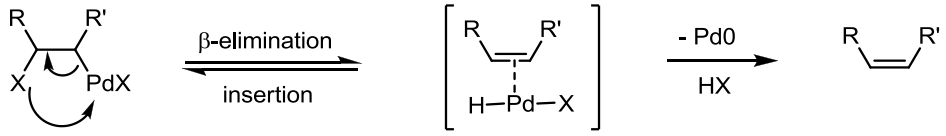
1.5.1. σ-Organo-Palladium complexes

Unsatured compounds react with σ-organopalladium complexes to undergo insertion reaction. Olefins and alkynes give rise to an α,β (or 1,2) type insertion and carbon monoxide, isonitriles, and carbenes to an α,α (or 1,1) type insertion (Scheme 8).



Scheme 8

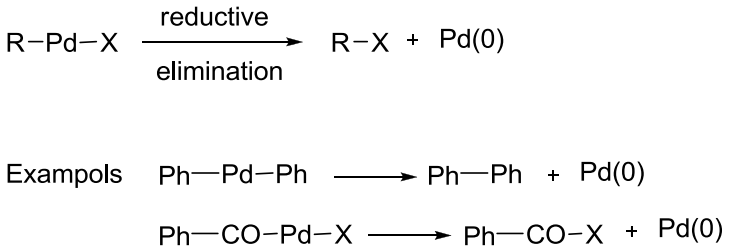
These insertion intermediates react according to a variety of reaction pathways. In the presence of β-hydrogens, a syn-β-elimination of HPdX species can occur with the formation of a vinylic substitution product (Scheme 9).[46]



Scheme 9

In the absence of β-hydrogens, a reductive elimination reaction can occur which affords a coupling derivative regenerating Pd(0) (

Scheme 10).



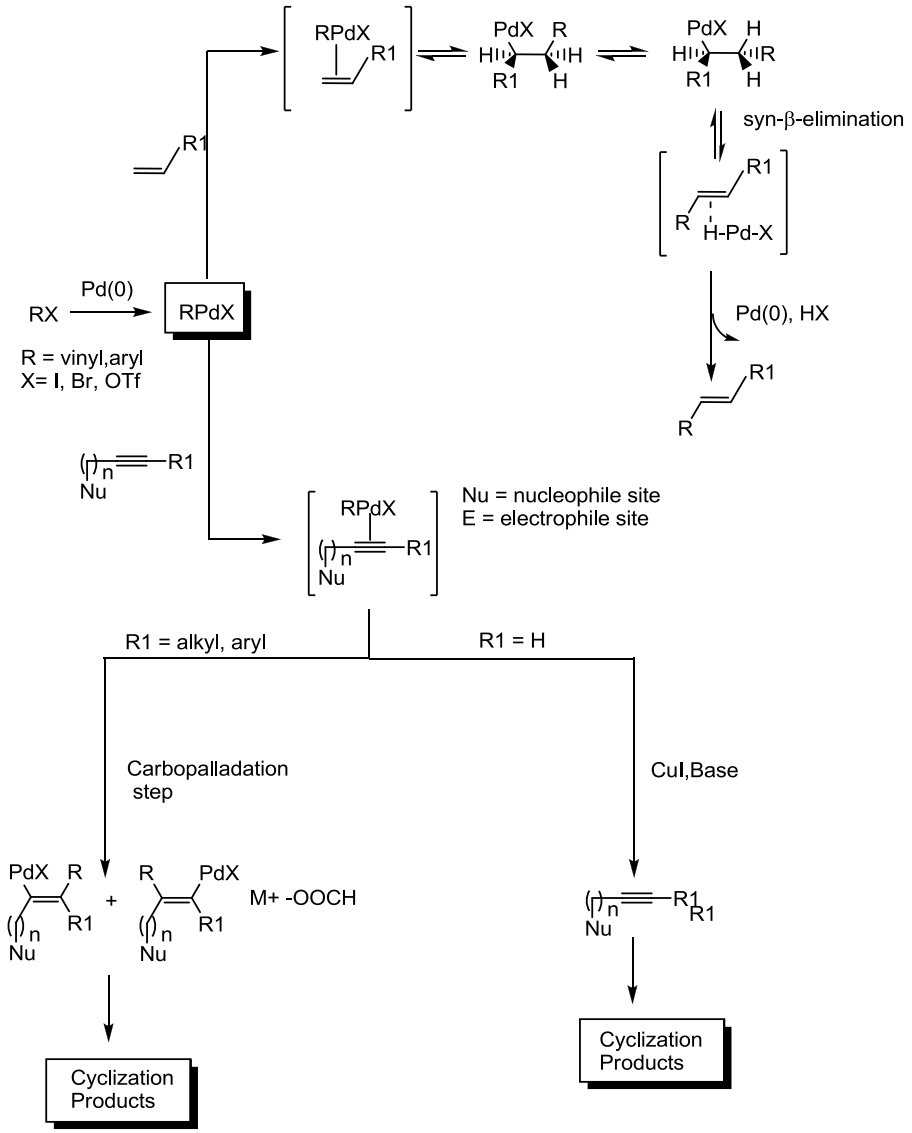
Scheme 10

1.5.2. η^2-Organo-Palladium complexes

When Pd(II) salts or σ-organo-palladium complexes coordinate unsatured carcbon-carbon bonds like alkenes, alkynes, dienes, π-palladium-complexes are generate.

Scheme 11

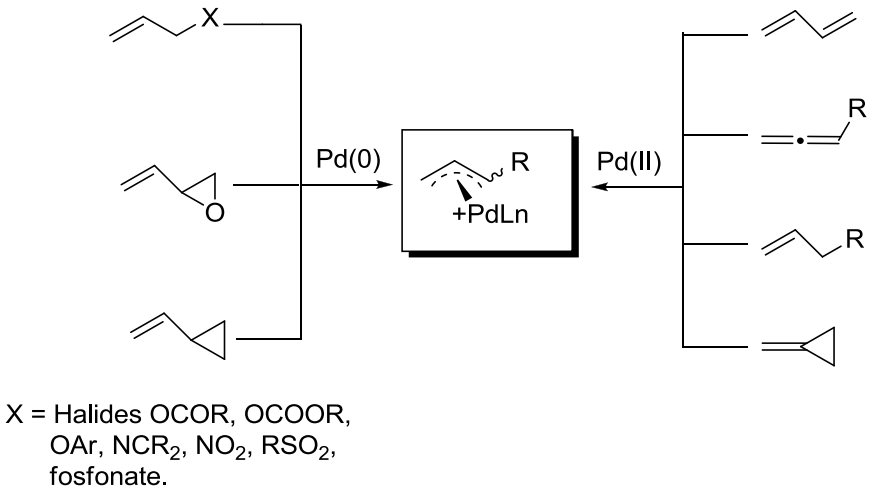
As shown in Scheme 11, both the acetylenic and the olefinic systems undergo a distortion of their structure because of the diminished order of bond due to the coordination. The effect can dramatically change depending on the type of substituents at the insature bond. Once formed, because of their decreased electron density at the carbon-carbon multiple bond, the complexes can undergo an intermolecular or intramolecular nucleophilic attack across the coordinated olefinic or acetylenic moiety. Intramolecular nucleophilic attack on π-palladium complexes by a heteroatom close to the carbon-carbon multiple bond is particularly useful and represent a powerful tool for an easy access to functionalized heterocycles. The reactivity of these complexes toward alkynes and alkenes is summarised in Scheme 12



Scheme 12

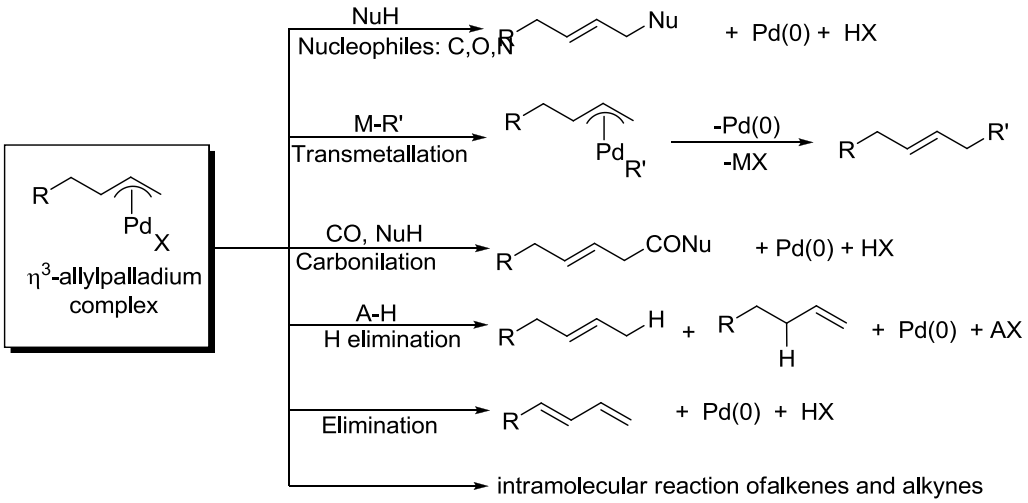
1.5.3. η^3-Organo-Palladium complexes

There are two different ways to generate the π-allyl palladium(II) complexes: by oxidative addition of allyl-derivatives such as acetate carbonate, nitro-compounds etc to Pd(0) or by reaction of different olefinic systems with Pd(II) salts in alkaline solution.(Scheme 13). [47]



Scheme 13

The reactivity of π-allyl palladium(II) complexes is showed in Scheme 14. When π-allyl palladium(II) complexes is generated using Pd(II) salts, the last have to be added in stoichiometric amount. In all the reaction of the following scheme Pd(0) is restored at the end of the catalytic cycle.



Scheme 14

1.6. Main Palladium-Catalyzed Reactions

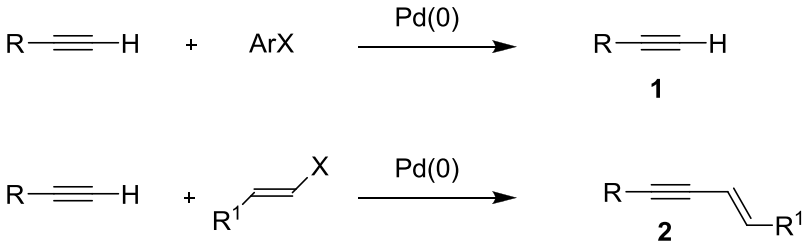
In this section, the main features of the palladium-catalyzed processes studied during my doctorate activity will be discussed.

1.6.1. Sonogashira Coupling

The carbon-carbon triple bond is a ubiquitous structural feature of organic molecules.[48] Alkynes are common motif in drugs, for example in enediyne antibiotics and in the

contraceptive pill. Furthermore, the unsaturated, highenergy structure makes alkynes an attractive functional group for further derivatization in many synthetic transformations.

Direct introduction of sp^2 carbon to alkynes by the reaction of Cu acetylides with aryl and alkenyl halides to form arylalkynes **1** andalkenylalkynes **2** is known as the Castro reaction.[49] Later it was found that coupling of terminal alkynes with halides proceeds more smoothly by using Pd catalysts (Scheme 15).



Scheme 15

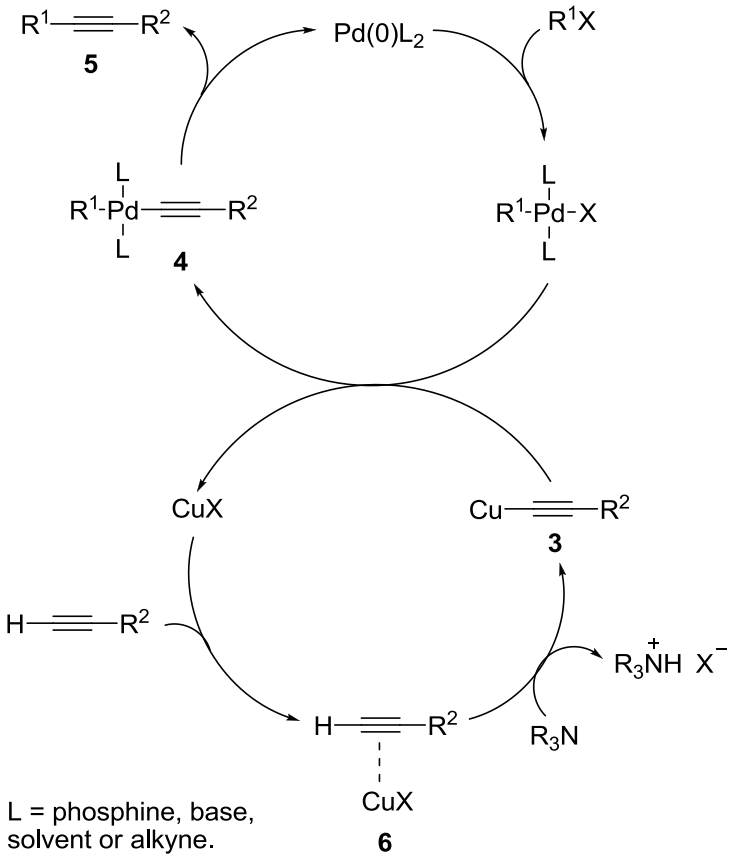
The two earlier studies on this topic were reported independently by Heck[50]and Cassar[51] in 1975. Heck's procedure was based on the known Mizoroki-Heck reaction for the palladium catalyzed arylation and alkenylation of alkenes, and consisted of performing the coupling employing a phosphanepalladium complex as a catalyst and triethylamine or piperidine as a base and solvent.

Cassar's procedure involved a phosphane-palladium catalyst in combination with sodium methoxide as a base and DMF as solvent. Both methods generally required high temperature (up to 100 °C). In the same year, Sonogashira and Hagihara found that the addition of CuI as a co-catalyst greatly accelerates the reaction rate, thus enabling performance of the alkynylation at room temperature. [52]

Therefore, the Sonogashira-Hagihara protocol, more often simply known as *Sonogashira coupling*, became the most popular procedure for alkynylation of aryl and alkenyl halides.

The copper co-catalyzed Sonogashira reaction is believed to take place through two independent catalytic cycles (Scheme 16), where a tertiary amine is represented as a base, with other amines or inorganic bases performing similarly. The generally accepted catalytic cycle for the palladium catalysis (Pd-cycle) is based on a usually fast oxidative addition of R^1X (R^1 = aryl, heteroaryl, vinyl; X = I, Br, Cl, OTf) to the real catalyst generated from the initial Pd complex. This is classically thought to be 14-electron $Pd(0)L_2$, formed by reduction of different Pd(II) complexes under the employed reaction

conditions, as it is known that n-electron donors, such as phosphines, amines and ethers, used as ligands and solvents, can reduce palladium(II) species. In the oxidative addition step, the characteristics of the R^1X substrate are crucial, with this step being facilitated if X = I or OTf and if the electronic density is reduced on C–X bond by the presence of electron-withdrawing groups. The next step in the Pd-cycle would connect with the cycle of the copper co-catalyst (the Cu-cycle). Thus, a usually rate-determining transmetallation from the copper acetylide **3** formed in the Cu-cycle would generate a $R^1Pd(–C{\equiv}CR^2)L_2$ species **4**, which gives the final coupled alkyne **5** after trans/cis isomerization and reductive elimination with regeneration of the catalyst. In the Cu-cycle, still poorly understood, the base is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming the copper acetylide **3** in the presence of the copper(I) salt. It should be pointed out that the generally employed amines are usually not basic enough to deprotonate the alkyne. Therefore, a π-alkyne–Cu complex **6** as shown in Scheme 16 could be involved in the cycle, [53] thus making the alkyne proton more acidic for easier abstraction. The copper acetylide **3** could also be involved in the formation of the initial $Pd(0)L_2$ catalytic species by reaction with the starting Pd(II) complexes, thus forming $Pd(–C{\equiv}CR^2)_2L_2$, which after reductive elimination would afford active $Pd(0)L_2$ and some amounts of diacetylene byproduct. Homocoupling is a serious competitive reaction, and low yields are obtained particularly when less reactive electron-rich aryl halides are used. It is well known that CuI catalyzes oxidative homocoupling of 1-alkynes in O_2 atmosphere (Glaser reaction). Also Pd(II) promotes the homocoupling. Therefore the reaction should be carried out with strict exclusion of O_2.

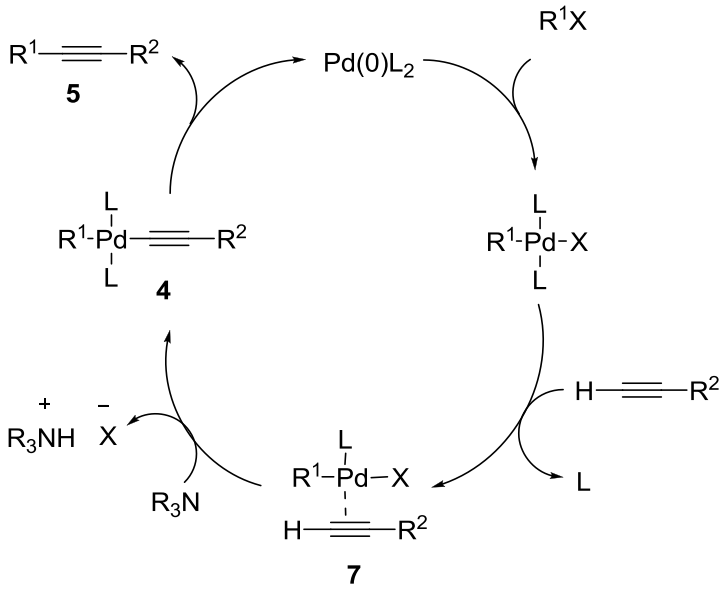


Scheme 16

The mechanism of the copper free Sonogashira coupling is also not-well known. The first step would be the oxidative addition of R^1X to the Pd(0) complex (Scheme 17).

However, the second step is under debate. Complexation of the alkyne to the *trans* R^1PdXL_2 complex is supposed to proceed first with displacement of one ligand to give the intermediate complex (η^2–$R^2C{\equiv}CH$)-R^1PdXL **7**. [54]

The ligated alkyne would be more easily deprotonated by the amine, forming the complex **4**, which gives the coupling product **5** by reductive elimination.



Scheme 17

Coupling catalyzed by Pd(0) and CuI proceeds via in situ generation of Cu acetylides **3**. Later acetylides of main group metals such as Mg, Zn, Sn, and B have been found to be good partners of the coupling. These are other preparative methods of arylalkynes 10 without CuI. Coupling of Zn acetylides is regarded as Negishi reaction, and that of Sn acetylides may be called Kosugi-Migita-Stille reaction. Since its introduction in 1975, numerous modifications to Sonogashira's original protocol have been reported, and improvements for many aspects of sp-sp^2 carbon-carbon bond formation under palladium catalysis have been achieved. [55]

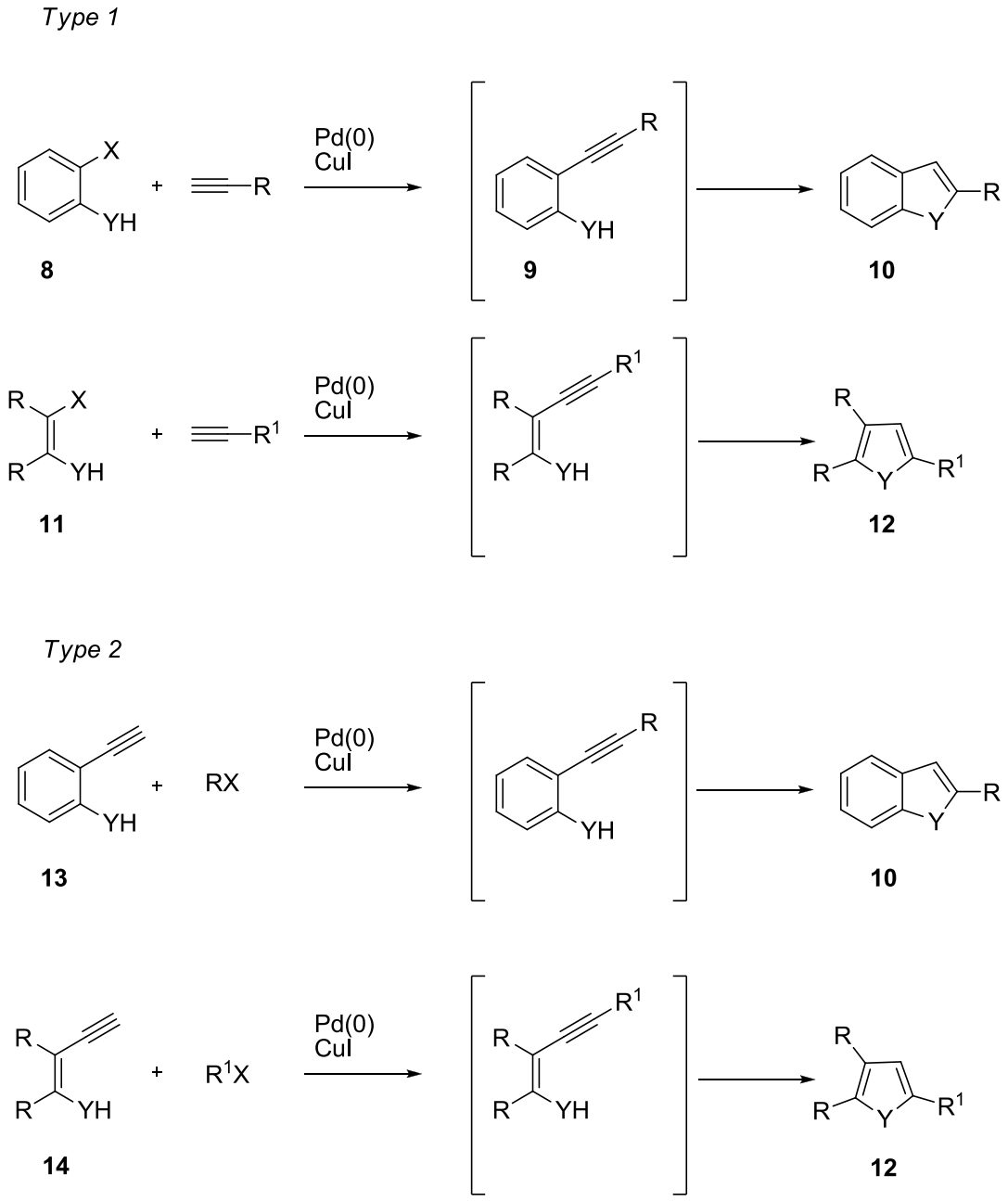
The traditionally used catalysts are triphenylphosphane-related complexes, $Pd(PPh_3)_4$, with the more stable and soluble $PdCl_2(PPh_3)_2$ being the most common, although catalysts with bidentate ligands such as $Pd(dppe)Cl_2$, $Pd(dppp)Cl_2$ or $Pd(dppf)Cl_2$ have also been employed. These conventional catalysts have also been used in some copper-free procedures. For example, in 1986, the coupling of enol triflates with terminal alkynes using $Pd(OAc)_2(PPh_3)_2$ was reported, [56] and in 1993, it was found the cyclic amines such as pyrrolidine and piperidine as base and solvent enhanced the reaction rate to promote the coupling of aryl or vinyl halides or triflates with 1-alkynes at room temperature using also the same palladium complex. [57]

Aryl iodides, bromides and triflates are reported to be good cross-coupling partners, while Pd catalysts with enhanced reactivity are required to perform cross-coupling reactions with electron-rich aryl bromides and aryl chlorides. Some success in this area has been achieved using bulky, electron-rich phosphane ligands such as P(*t*-Bu)$_3$. [58]

Increasing environmental awareness has led to a deep interest in the use of alterative solvents to traditional organics for metal catalysis. Among them, water is an especially attractive option because it is inexpensive, nontoxic, nonflammable, and environmentally sustainable. [59]

The conventional copper co-catalyzed Sonogashira coupling of iodoarenes has been achieved using $PdCl_2(PPh_3)_2$ and tributylamine in aqueous potassium carbonate at room, temperature. [60] In addition, aqueous organic solvents have been used for the Sonogashira reaction using isolated or in situ generated $Pd(PPh_3)_4$ in the presence of quaternary ammonium salts (Jeffery's conditions). [61]

Room temperature ionic liquids have also been considered in recent years as an alternative to volatile organic solvents for numerous catalytic transformations, [62] with advantages also derived from the frequent ionic liquid ability to contain the catalytic system, thus allowing its reuse after separation of the final products. Coupling of 1-alkynes with aryl halides having a nucleophilic group at an *ortho* position and subsequent cyclization offers useful synthetic methods of heterocycles. [63] Two main types are known. In ***type 1***, the halides **8** react with 1-alkynes to generate **9**, which undergo cyclization to afford 2-substituted heterocycles **10**. β-Substituted alkenyl halides **11** behave similarly to give 2-substituted heterocycles **12**. In ***type 2***, the ethynyl derivatives **13** and **14** react with aryl halides to generate disubstituted alkynes, which cyclize to afford **10** and **12**. These reactions are used extensively for the preparation of heterocycles such as benzo[b]furans, butenolides and indoles. In some cases, cyclization proceeds spontaneously in a *one-pot* reaction (Scheme 18).

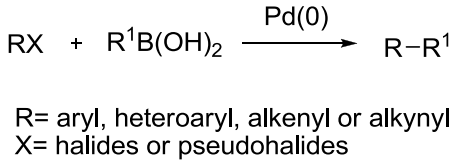


Scheme 18

The ability to effect bond formation between sp- and sp^2-hybridized carbon atoms continues to evolve, and new catalysts, substrates and conditions have all enhanced the effectiveness of these reactions. Somewhat surprising, however, is that a survey of the literature suggests that the most popular protocol in use today still consists of a mixture of an aryl iodide or bromide, a terminal alkyne, $PdCl_2(PPh_3)_2$, an amine and DMF: the same protocol as that introduced many years ago by Sonogashira and Hagihara.

1.6.2. Suzuki-Miyaura Coupling

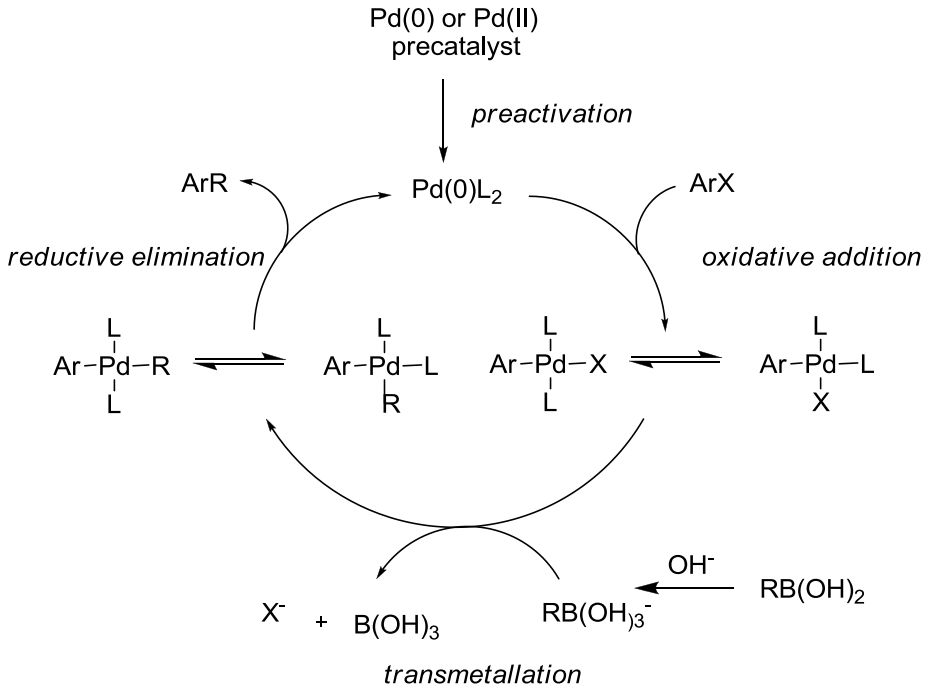
The palladium catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates provides a powerful and general methodology for the formation of carbon-carbon bonds (Scheme 19). [64]



Scheme 19

This reaction, which has been called *Suzuki-Miyaura* coupling, offers several advantages, such as the availability of the reagents, the minor effect of steric hindrance and the mild reaction conditions. Besides, it is largely unaffected by the presence of water, and tolerates a broad range of functional groups. Moreover, the inorganic by-products of the reaction are nontoxic and easily removed from the reaction mixture. Because of all these features, the Suzuki coupling has gained prominence in the recent years at an industrial level, mainly in the synthesis of pharmaceuticals and fine chemicals. In academic laboratories, it has been largely applied as the key step in total synthesis of natural [65] and non-natural products or in polymer synthesis. [66]

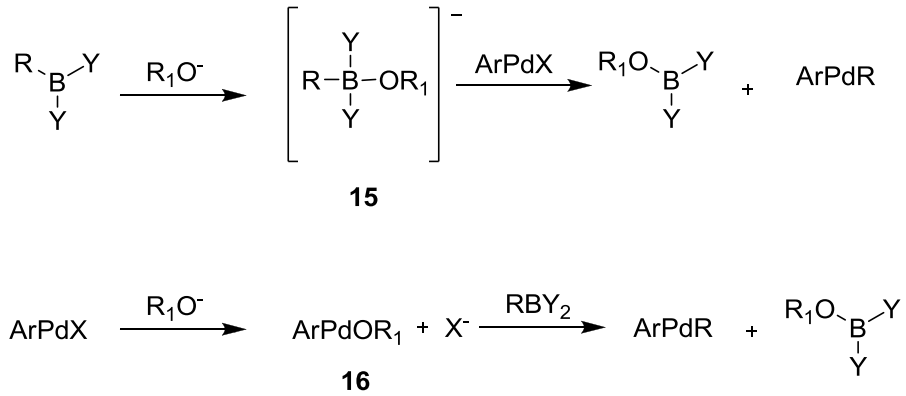
A general, likely catalytic cycle of Suzuki coupling proceeds through the oxidative addition of ArX to $Pd(0)L_2$, forming $ArPd(II)XL_2$ which undergoes *trans/cis* isomerization and transmetallation with $RB(OH)_3^-$. Through reductive elimination and concomitant regeneration of the active catalyst, $ArPd(II)RL_2$ gives rise to the desired coupled product Ar–R (Scheme 20).



Scheme 20

Various modifications, however, have been recently introduced involving catalysts, substrates, reaction media and conditions, in order to develop environmentally friendly and more efficient Suzuki cross-coupling reactions. [67]

A characteristic feature of organoboron reagents is the low nucleophilicity of the organic groups R on the boron atom, which makes their transmetallation more difficult than that of other organometallic reagents. The Suzuki reaction, in fact, proceeds in the presence of a base.[68] The role of the base is explained by activation of either Pd or boranes. The nucleophilicity of R is enhanced by quaternization of the boron atom with the base, generating the corresponding boronate complex **15**, which undergoes facile transmetallation. Alternatively, the formation of alkoxypalladium species $ArPdOR^1$ **16** from ArPdX facilitates the transmetallation with organoboranes (Scheme 21). No reaction takes place under neutral conditions.



Scheme 21

Aryl bromides and iodides, together with aryl triflates, are the most suitable substrates for the Suzuki-Miyaura reaction. Aryl triflates are, however, thermally labile, prone to hydrolysis and more expensive to prepare. Aryldiazonium tetrafluoroborates are attractive synthetic alternatives to the corresponding halides and triflates, since they can be prepared from the relatively inexpensive and readily available anilines and they do not need the presence of a base. In addition, they have been found to be more reactive than aryl halides or triflates in this reaction. [69]

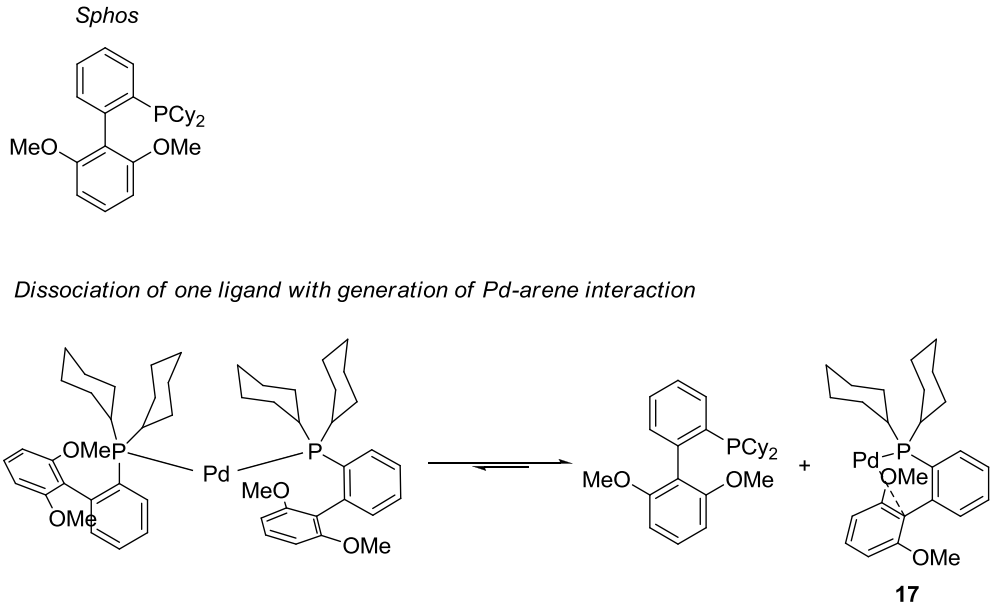
Aryl chlorides are, however, more attractive as starting materials because of their lower cost and the wider diversity of available compounds. They suffer, however, from a decreased reactivity that has been attributed to their reluctance towards oxidative addition to Pd(0), due to the strength of the C–Cl bond. Recently, several catalytic systems have been found to facilitate their use. [70]

Boronic acids, boronate esters and organoboranes have been utilized for many years as the primary boron source in Suzuki-Miyaura type reactions. Both boronic acids and esters are highly nucleophilic, exhibit a broad range of functional-group tolerance and are substantially less toxic than the heavymetal organometallic reagents. These organoboron reagents have, however, inherent limitations. A drawback associated with the use of boronic acids, for example, is the structural ambiguity, namely, the formation of the trimeric anhydride (boroxine),[71] associated with them, and consequently the uncertain stoichiometry. The purity of commercially available boronic acids is also of concern. Although purification via recrystallization, usually from water, affords a boronic acid of higher purity, removal of the water generally results in formation of mixtures of boronic acids and the corresponding boroxine. More recently, potassium organotrifluoroborates have been widely reported as a special class of organoboron reagents[72] because they are airand moisture-stable salts, readily accessible by a variety

of high-yielding methods (treatment of boronic acids with KHF_2, for example), and suitable for storage for extended periods of time. Besides, their post-reaction by-products are salts readily separated from the desired product and the BF_3K moiety is compatible with sensitive functional groups and is tolerant to several reaction conditions.

Phosphine-based palladium catalysts are generally used in the Suzuki reaction since they are stable on prolonged heating. In particular, triarylphoshines are excellent ligands to stabilize the palladium species. Trialkylphosphines, on the other hand, have been relatively neglected, probably as a result in large part of the fact that many of them are airsensitive and difficult to handle than triarylphosphines. There is, however, growing evidence that trialkylphosphines can furnish reactivity that is not generally accessible with triarylphosphines. In particular, P(*n*-Bu)$_3$[73] and P(*t*-Bu)$_3$[74] have proved to be useful in a number of important processes.

Unfortunately, they cannot readily be handled in air because of the ease with which they undergo oxidation. A simple but powerful strategy for handling these phosphines is to protect them as their conjugate acids. The phosphonium salt [(*t*-Bu)$_3$Ph]BF_4, stable to oxygen and to moisture, has been used together with $Pd_2(dba)_3$ and KF as a base, as a precatalyst in Suzuki cross-coupling.[75] The presence of a weak base is required to liberate the desired trialkylphosphine. The use of 2-(2',6'-dimethoxybiphenyl) dicyclo hexylphosphine (Sphos) allows Suzuki reactions to be performed at low catalyst levels, to prepare extremely hindered biaryls and to be carried out for reactions of aryl chlorides at room temperature. [76] One cause for the highly reactive nature of Sphos is the shift of the $L_2Pd(0)/LPd(0)$ equilibrium toward the monoligated complex **17**, due to the concurrent generation of a favorable Pd-arene interaction (Scheme 22).



Scheme 22

In Suzuki cross-coupling, it is generally believed that Lewis-base additives facilitates the process by binding to organoboron reagent, forming a more reactive four-coordinated "ate" complex that transfers the organic group to palladium. It has been suggested that treatment of arylboronic acids with excess fluoride might produce $ArBF_3^-$ and that this might be the species that undergoes transmetallation with Pd. [77] So, there is a large number of parameters in a Suzuki reaction (palladium source, ligand, additive, base, solvent, temperature, etc.) and there is, correspondingly, a wide number of protocols for accomplishing the transformation, the choice of which depends on the structure of the reactants. [78] Clearly, the development of a general protocol that could reliably effect cross-coupling, independent of the structure of the reactant, would be worthwhile.

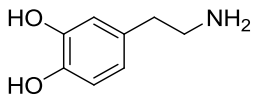
2. New palladium-catalyzed synthetic strategies

In this section will be discussed the features of the synthetic approaches to different classes of compounds studied during the PhD research activity that can be divided in two main actions:

a) synthetic modification of biologically active compounds through palladium-catalyzed reaction
b) study of new catalyzed routes to C–C or C–N bond formation towards the synthesis of interesting intermediates and heterocyclic derivatives

2.1. 5-Aryl- and 5-Alkynil-dopamine derivatives through palladium-catalyzed cross-coupling reactions.

Dopamine [2-(3,4-dihydroxyphenyl)ethylamine] **18** (Figure 3) is an endogenous catecholamine released by the sympathetic nervous system in response to different stimuli including physical activity, psychological stress, blood loss and many other normal or disease-related provocations. It plays an important role in the treatment of many clinical disorders, including hypertension, cardiovascular shock, arrhythmias, asthma, migraine headaches, and anaphylactic reactions. Dopamine is synthesized in human cells, but it is also present in other animals, including both vertebrates and invertebrates.

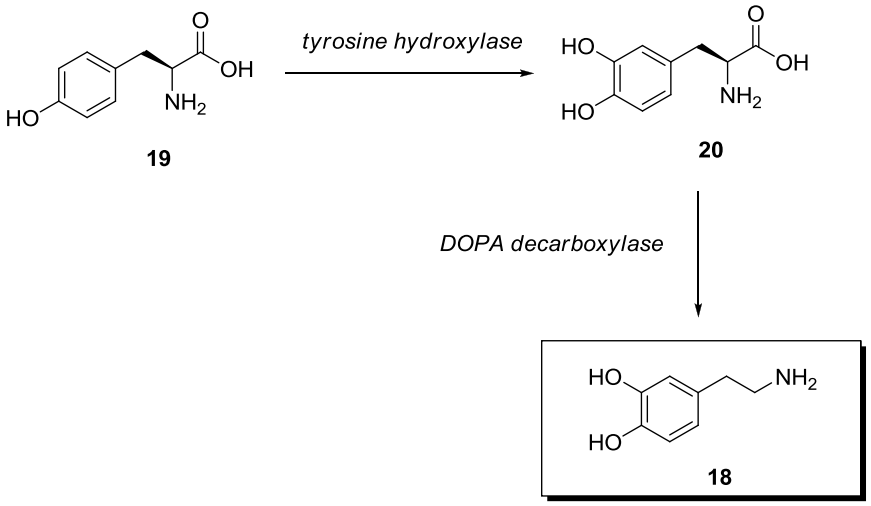


18

Figure 3

In the brain, dopamine operates as a neurotransmitter activating specific receptors, labeled as D_1, D_2, D_3, D_4 and D_5. Dopamine is produced in several areas of the brain, including the *substantia nigra*, and its primary action is to modulate the inhibitory activity of GABAergic neurons. Furthermore, dopamine acts as a neuro-hormone released by the hypothalamus. In this case, its main function is to inhibit the release of prolactin from the anterior lobe of the pituitary. Dopamine is a simple organic chemical belonging to the catecholamine family, and it is also a precursor in the biosynthesis of the neurotransmitters norepinephrine and epinephrine. The biosynthesis of dopamine

involves two steps (Scheme 23). In the first step, the amino acid L-Tyrosine **19** is hydroxylated into L-dihydroxyphenylalanine (L-DOPA) **20** by the enzyme tyrosine hydroxylase, then the enzyme DOPA decarboxylase converts L-DOPA into dopamine **18**, by a decarboxylation reaction.



Scheme 23

Furthermore, within some neurons, dopamine is further processed to norepinephrine and epinephrine. Upon its synthesis, dopamine is transported by the vesicular monoamine transporter 2(VMAT2) into synaptic vesicles. There, dopamine reamins stored until a potential presynaptic action occurs and forces synaptic vesicles to merge with the cell membrane, through a process known as exocytosis, resulting in the release of the neurotransmitter.

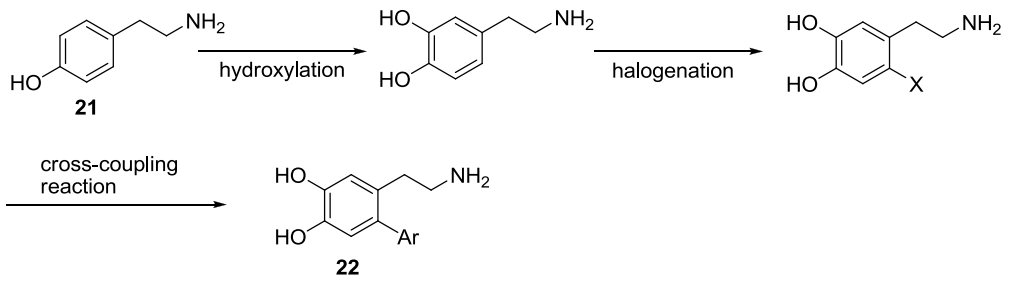
After dopamine has performed its synaptic duties, it can undergo degradation under two different patways. In the majority of the brain area dopamine is inactivated by re-uptake thanks to a specific transporter (DAT). The inactivate dopamine is subsequently transformed into 3,4-dihydroxyphenylacetic acid through enzymatic cleavage operated by monoamine oxidase (MAO-A and MAO-B). In the prefrontal cortex, however, there are few DAT proteins, and dopamine is inactivated through the re-uptake operated by the norepinephrine transporter (NET).

Dopamine has many functions in the brain, including important roles in behavior and cognition, voluntary movement and inhibition of prolactin production (involved in lactation and sexual gratification). It is also involved in regulation of spleep, dreaming, mood, attention, memory and learning processes.

Given its importance, much effort has been directed toward the preparation of dopamine derivatives. Surprisingly, despite the potential interest from a biological point of view of dopamine derivatives bearing substituents on the aromatic ring, no examples of selective functionalization in this position have been reported. On the other hand, such a functionalization might provide a convenient access to new classes of bioactive molecules.

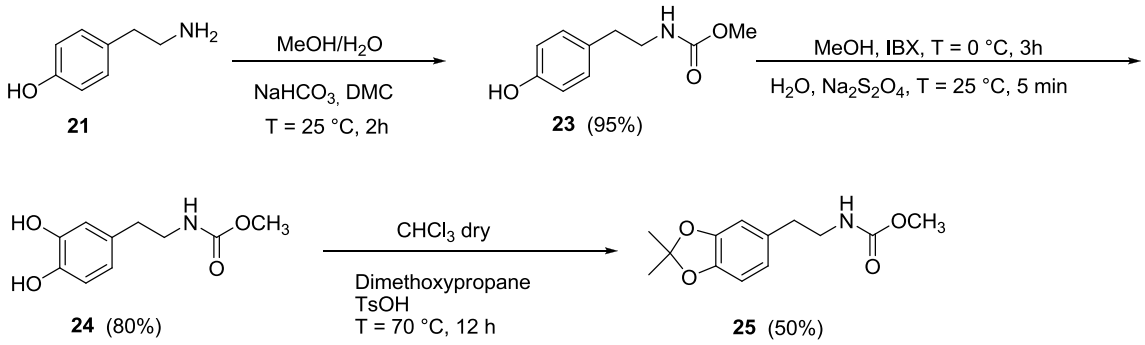
2.1.1. 5-Aryldopamine derivatives through Suzuki-Myaura Cross-Coupling Reaction.

The particular importance of dopamine has stimulated the research team to undertake a study aimed to obtain new aryl-dopamine derivatives, through the combined application of IBX/mediated hydroxylation reaction of commercially available 4-(2-aminoethyl)phenol **21**, and palladium-catalyzed chemistry. In particular, it was establish to synthesize the 5-aryl-dopamine derivatives **22**, according to the working hypothesis shown in Scheme 24. The scheme involves a regioselective halogenation reaction at 5 position of the dopamine derivative followed by its arylation with the Suzuki reaction.[9,10]



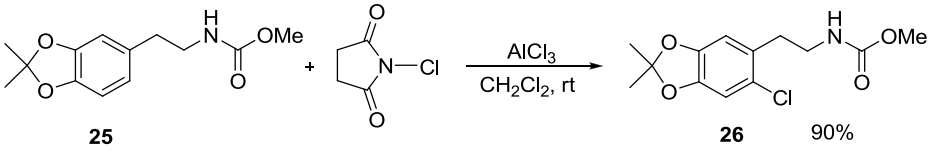
Scheme 24

Since the instability of the amine function under the reaction condition required for the oxidation step, it was necessary to transform dopamine **21** into its carbamate **23.** The protected derivative was then hydroxylated by IBX to *N*-methoxycarbonyldopamine **24**, successively treated with dimethoxypropane and *p*-toluenesulfonic acid (TsOH) to protect the catecholic function to acetonide **25**, as shown in Scheme 25



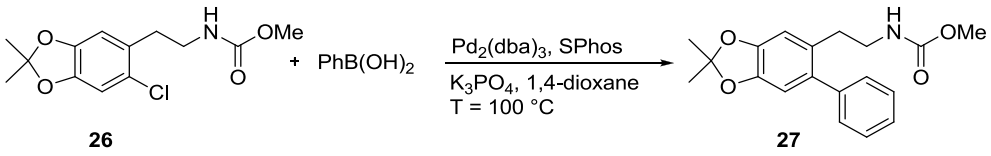
Scheme 25

The chlorination reaction was then carried out using *N*-chlorosuccinimide (NCS) as chlorinating agent with $AlCl_3$ as catalyst, as shown Scheme 26.



Scheme 26

The derivative **26** was then used in the cross-coupling reaction, using the catalytic system $Pd_2(dba)_3$/Sphos, as shown in the Scheme 27, in order to obtain the desired arylated product **27**.



Scheme 27

Unfortunately, the desired **27** derivative was not isolated and the main reaction product was **28**, obtained in 90% yield (Figure 4).

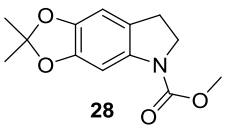
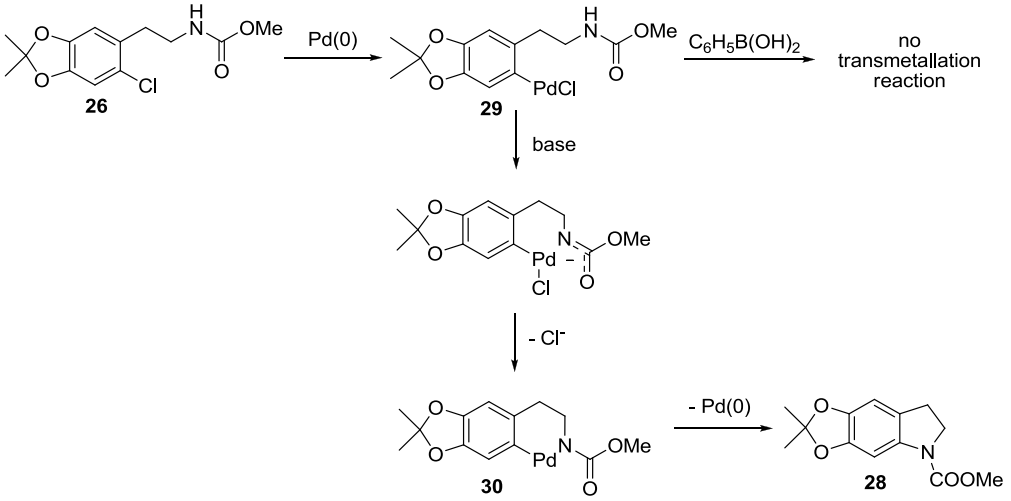


Figure 4

The dihydroxyindole product **28** is most probably formed through the intramolecular *N*-trapping of the σ-aryl-palladium chloride complex **29**, faster than its cross-coupling reaction with phenyl boric acid (Scheme 28).

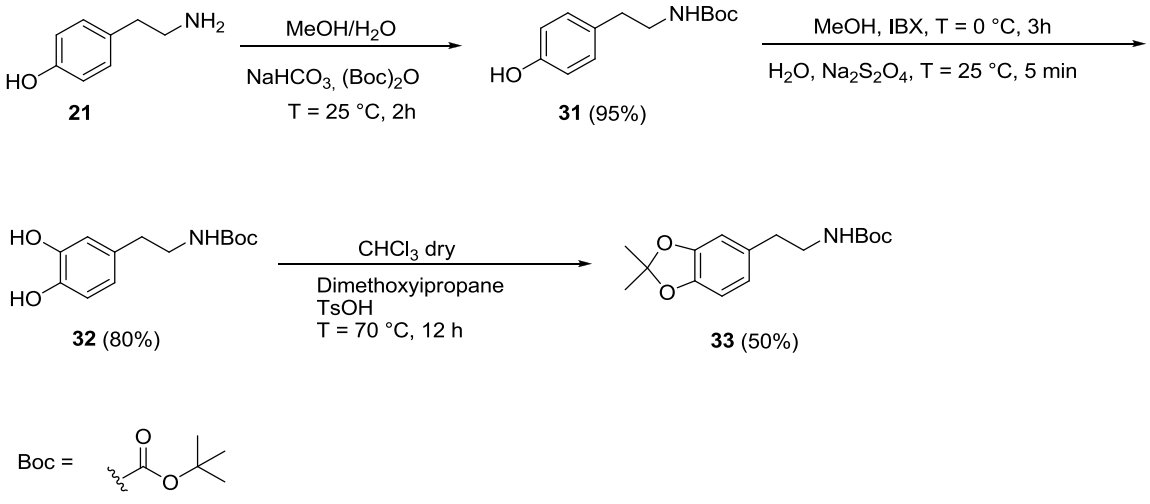


Scheme 28

More in details, the formation of derivative **28** can be explained as follows: **26** is transformed into the corresponding aryl-palladium chloride σ-complex **29** through its reaction with palladium(0) complex. Subsequently, **29** is attacked by the nitrogen atom, most probably deprotonated by the base present in the reaction medium: thus, it results in the formation of a 6-membered palladacycle **30** which, after reductive elimination of palladium(0), give the final dihydroindole derivative **28**.

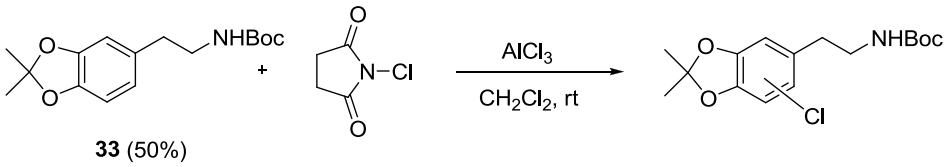
For this reason, it was necessary to carry out a structural change of the dopamine derivative (Scheme 29), consisting in the protection of the amine function as di-Boc derivative, in order to suppress the nitrogen nucleophility in basic medium. The new dopamine derivative was synthetized according to Schemes 29- 31.

The Boc-derivative **31** was hydroxylated using IBX as oxidant to give compound **32**, then the catecholic function was protect with the acetonide group to give **33**.



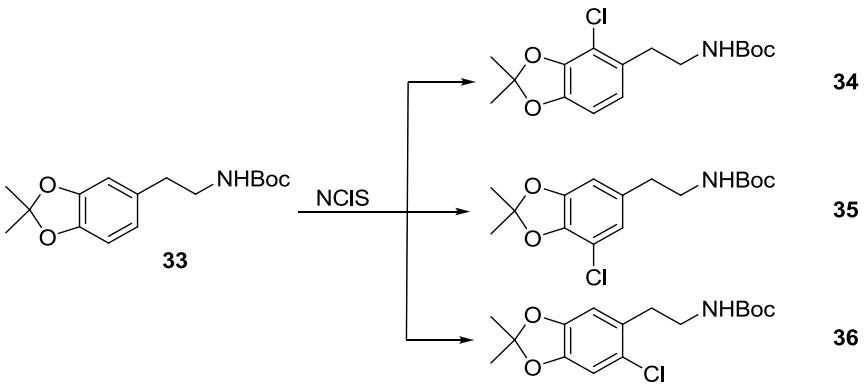
Scheme 29

The derivative **33** was then subjected to halogenation reaction, under the conditions reported in Scheme 30.



Scheme 30

The chlorination reaction of the derivative **33** can lead to the formation of three different chlorinated products, as illustrated in Scheme 31.



Scheme 31

However, due to the lack of literature data about the obtained product, it was necessary to perform a full NMR study to clarify the structure of the chlorinated derivative. The

^{1}H-NOESY spectra, shown in Figure 5, gave a robust proof of the selective halogenation at the 5 position.

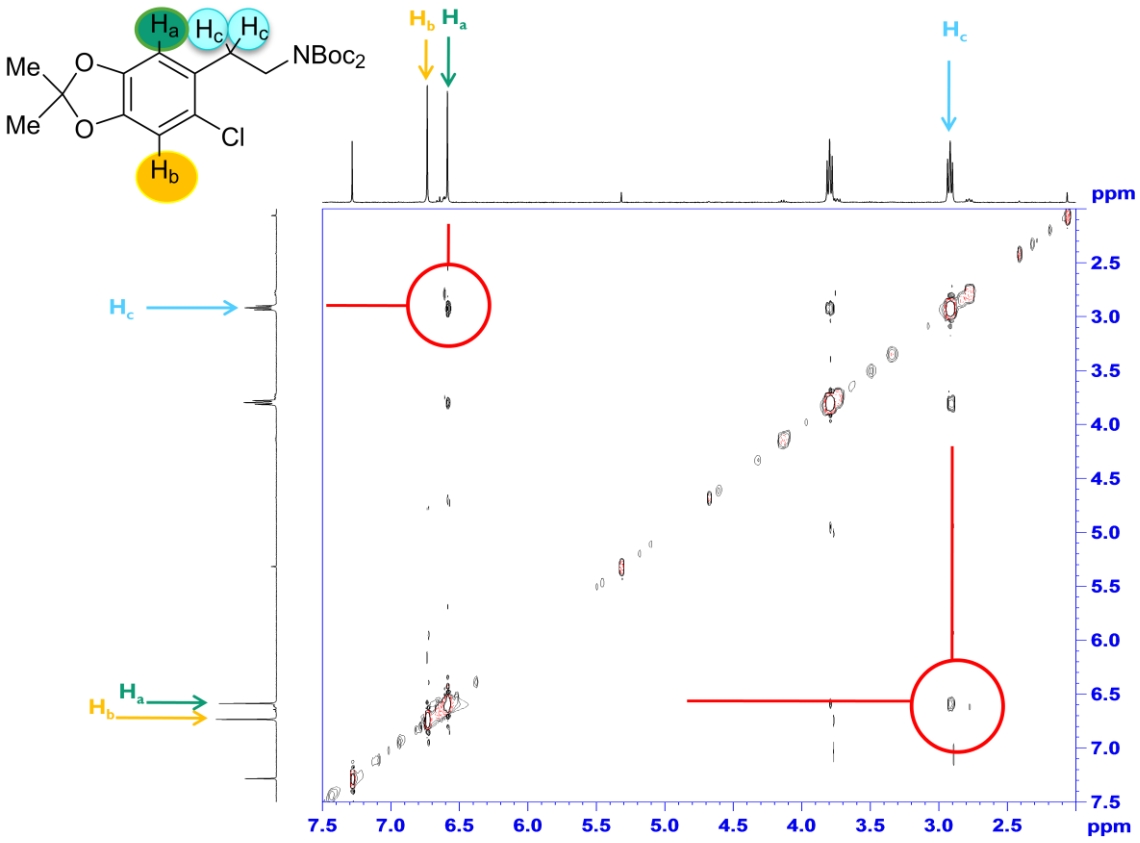
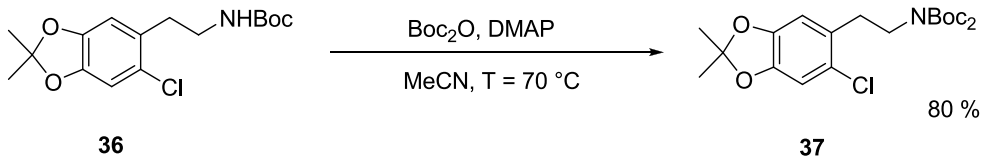


Figure 5

In fact, the analysis of the H-H map clearly shows a correlation peak with coordinates 6.60/3.80 ppm, which clearly indicates the spatial proximity between the proton H_a and the methylene group CH_{2C}. Instead, there is no comparable correlation peak between the proton H_b and the same methylene group. This consideration, combined to the fact that the two aromatic protons appear as singlets in the 1D spectrum (in the derivative **34** they would be coupled by a $J_{3H\text{-}H}$), indicates that the reaction of chlorination leads to the regioselctive formation of the derivative **36**.

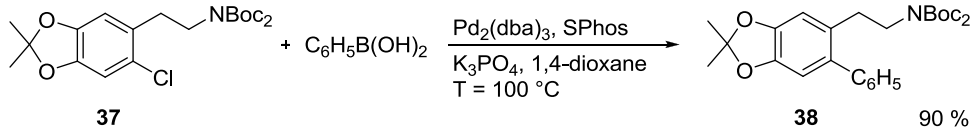
The 5-chloro-derivative **36** was finally treated with di-*t*-butyldicarbonate (Boc_2O) and *N*,*N*-dimethylaminopyridine (DMAP), in MeCN at T = 70 °C, to transform it into the di-Boc derivative **37** (Scheme 32).



36 **37**

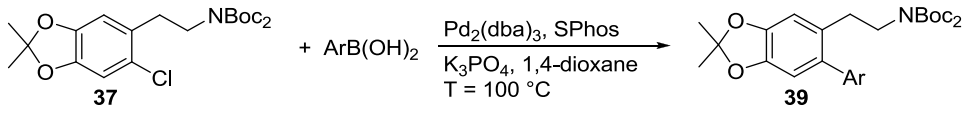
Scheme 32

Derivative **37** was then reacted with phenylboronic acid in the presence of the catalytic system $Pd_2(dba)_3$/SPhos, under the same reaction conditions used for the synthesis of the hydroxytyrosol derivatives[79] obtaining the cross-coupling derivative **38** with a 90% yield (Scheme 33).



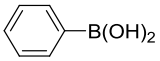
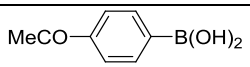
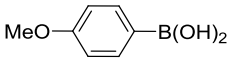
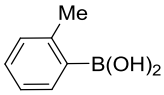
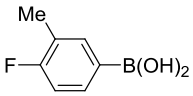
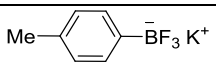
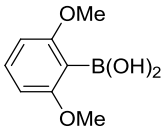
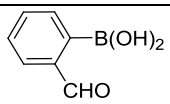
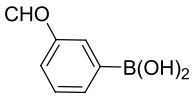
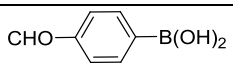
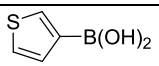
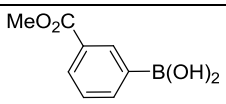
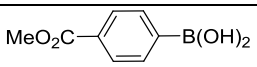
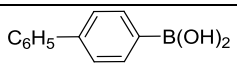
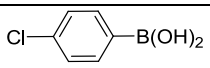
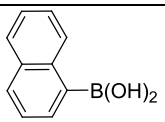
Scheme 33

The reaction was then extended to the use of a series of aryl-boronic acids (Scheme 34), obtaining the corresponding aryl derivatives in good to excellent yield, as reported in Table 2



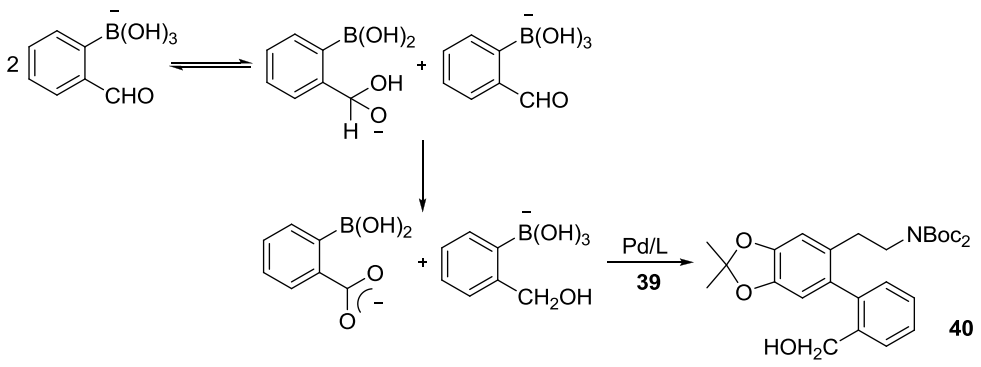
Scheme 34

Table 2 Reaction of boronic acids with 37: synthesis of 5-aryl derivatives of dopamine 39.[a]

Entry	$ArB(OH)_2$	t (h)	Yield 39 (%)
1		3	90
2		9	68
3		1	87
4		5	85
5		4.6	52
6		21	67
7		7	-
8		7	10
9		7	67
10		24	40
11			-
12		7	90
13		31	60
14		2.5	70
15		9.5	traces
16		4.5	60

[a] Reaction were carried out on a 0.22 mmol scale at 100 °C in 1,4-dioxane (1.6mL), under a nitrogen atmosphere, using 1 equiv. of **37**, 1.5 equiv. of arylboronic acid, 0.02 equiv. of $Pd_2(dba)_3$ and 0.04 equiv. of Sphos.

The analysis of the data shows that the aryl derivatives were generally obtained in good to high yields. Moreover, the reaction conditions are compatible with the use of boronic acids substituted with various organic functions, including some labile ones such as the ketonic (Table 2, *entry* 2), the formyl (Table 2, *entries* 8, 9 and 10) and the ester function (Table 2, *entries* 12 and 13). The formation of carbon-carbon bond is partly sensitive to steric effects: in fact, whereas in the case of *ortho*-substituted boronic acids (Table 2, *entry* 4) the cross-coupling derivative is obtained in high yield, the reaction does not proceed at all using the 2,6-dimethoxyboronic acid (Table 2, *entry* 7). Instead, the reaction product was obtained only in traces using the 4-chloro-phenyl boronic acid (Table 2, *entry* 15): in this case, the first choro-substituted cross-coupling product could react again with the boronic acid, giving a complex mixture of derivatives. Using the formyl-boronic acid *o*-, *m*-, and *p*-isomers (Table 2, *entries* 8, 9 and 10 respectively), the cross-coupling products were isolated only in the case of the *meta* and *para* isomers. Instead, using the *ortho* isomer, only the reduction derivative **40** was isolated: most probably, its formation derived from a Cannizzaro-type reaction of 2-formyl-phenyl-boronic acid, which was accelerated by the presence of the group in *ortho* position $[B(OH)_3]^-$ (Scheme 35).



Scheme 35

Due to the absence of spectroscopic data in literature of this kind of products, a complete NMR study was necessary to confirm the proposed structure: decisive to this scope was the ^{1}H-NOESY study on model derivative **41**, showed in Figure 6.

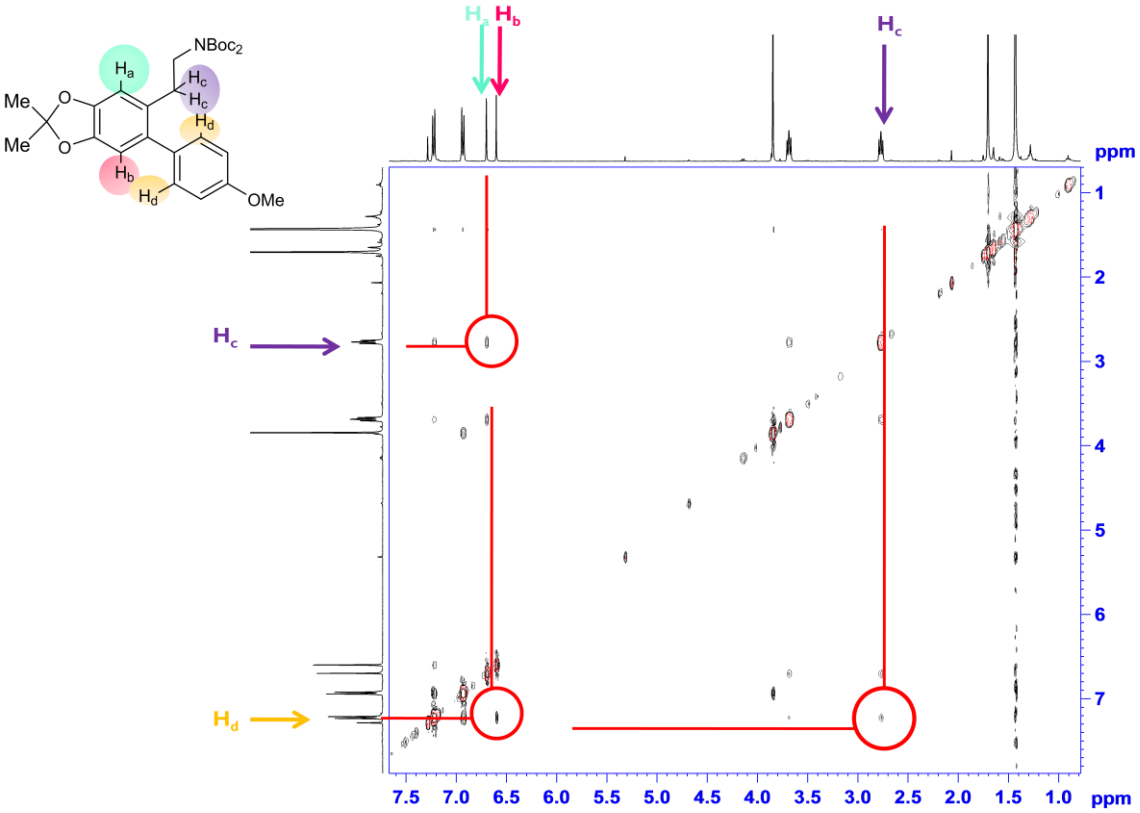


Figure 6

The map analysis shows the presence of several cross peaks that prove the structure proposed in figure 7: in particular, the couple of cross peaks at 7.22-6.60 ppm and 7.22-2.78 ppm indicates that the 4-MeO-C_6H_4 moiety is bonded at the 5 position, since the two equivalent H_d proton at 7.22 are be close simultaneously to the aromatic H_b proton and to the methylene group at 2.78 ppm. This information allows then to assign the ^1H NMR spectrum of the cross-coupling derivative **41** as shown in Figure 7.

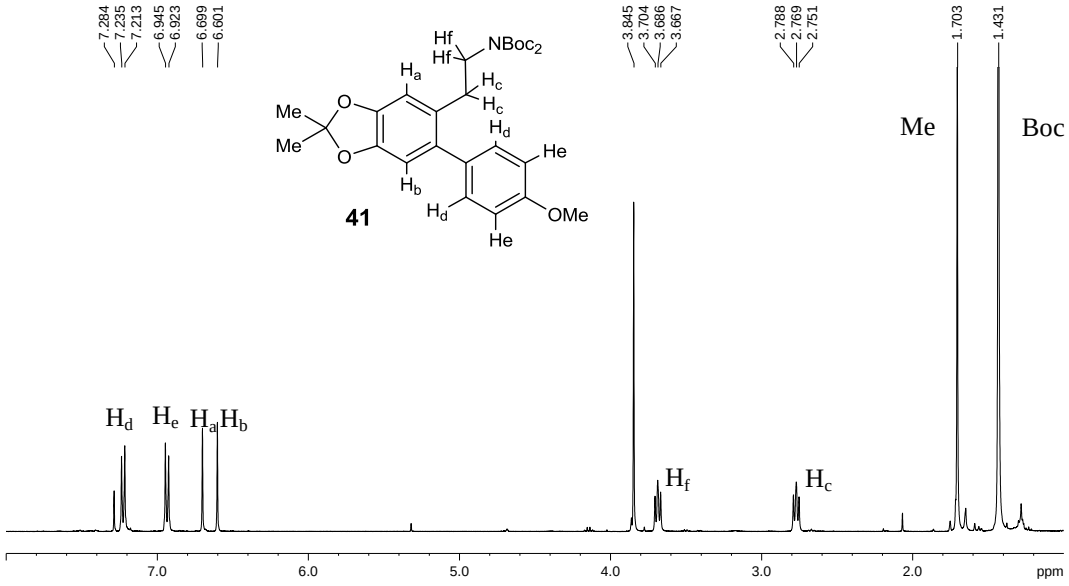


Figure 7

Finally, several experiments were carried out to optimize the conditions for the removal of the protective groups present in the products **39 (**Figure 8).

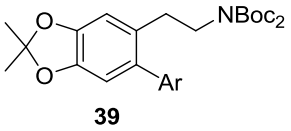
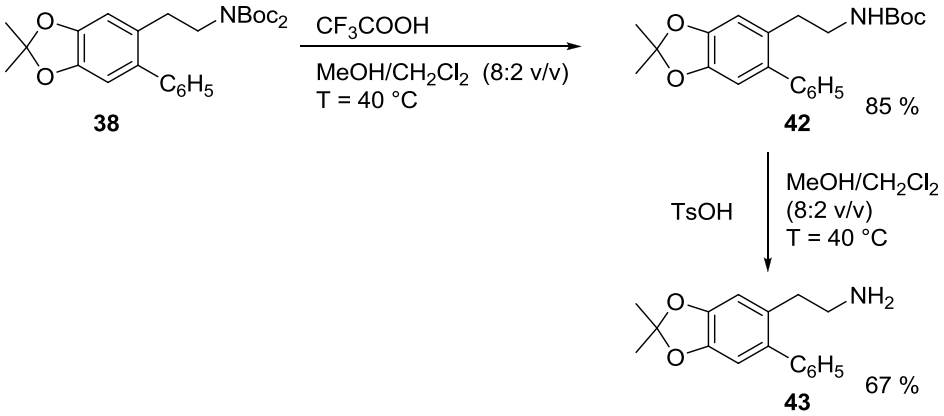
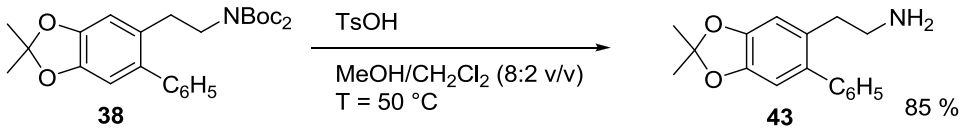


Figure 8

The carefully selection of the reaction conditions allowed to the selective removal in sequence of the two BOC group (shown in Scheme 36), or both (Scheme 37).

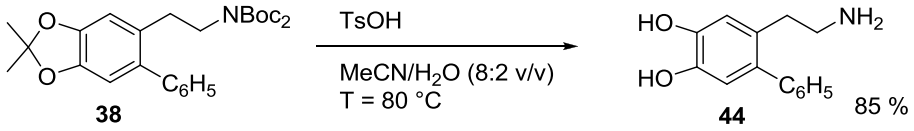


Scheme 36



Scheme 37

The complete removal of all protecting groups could be performed on the derivative **38** with TsOH in MeCN/H_2O as solvent mixture (8:2 v /v) at 80 °C (Scheme 38).

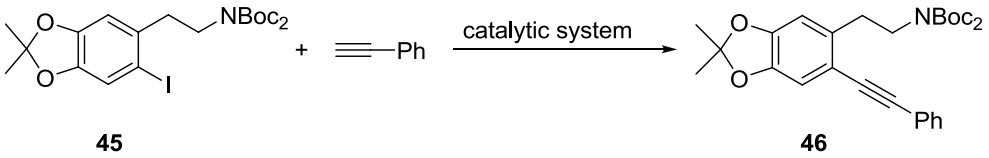


Scheme 38

In conclusion, a convenient, highly efficient method for the synthesis of novel analogues of dopamine has been developed. The cross-coupling reaction works effectively with a variety of neutral, electron-rich and electron-poor substituted aryl bororonic acids. Arylboronic acids bearing *ortho* substituents can also be used to prepare hindered cross-coupling products.

2.1.2. 5-Alkynylhydopamine derivatives through Sonogashira Cross-Coupling Reaction.

Conjugated alkynes, obtained through the Sonogashira coupling reaction of terminal acetylenes with aryl iodides, represent an important class of molecules that have found application in diverse areas ranging from natural product chemistry to materials science.[80] As extension of the main project aimed at the functionalization of naturally occurring bioactive molecules, the synthesis of 5-alkynyldopamines via Sonogashira cross-coupling reaction, starting from iododopamine with terminal alkynes, was selected as another interesting field to explore. This study starts testing the feasibility of the project under the standard Sonogashira conditions: however, mainly because the electron-releasing effect of the substituents in **45**, that hamper the oxidative addition of Pd(0) complexes, the desired 5-alkynyl derivative was isolated in an unsatisfactory 35% yield (Table 3, *entry* 1). To overcome this problem, a short screening was performed to found the best setup of the reaction (Table 3), using the model system shown in Scheme 39.



45 46

Scheme 39

When the reaction was carried out with Pd_2dba_3 and ligand as tricyclohexylphosphine (Table 3, *entry* 2), trifurylphosphine (Table 3, *entry* 3), or tris(2,4,6-trimethoxyphenyl)phosphine (Table 3, *entry* 4), the cross-coupling product was isolated in 48, 30 and 34% yields, respectively.

The use of $Pd_2(dba)_3$ and $[(t\text{-}Bu)_3Ph]BF_4$ in ratio 1:2 as precatalytic system, 1,4-dioxane as solvent, Cs_2CO_3 as base, in the presence of 1.0 equivalents of alkyne, allowed to the isolation of the coupling product **46** in 75% yield at 60 °C after 23 hours (Table 3, *entry 5*). Increasing the amount of alkyne led to a higher yield of **46** (Table 3, *entry 6*, 85% yield).

Table 3 Optimization studies for the Palladium catalyzed synthesis of 5-alkynyl dopamine derivatives[a]

Entry	Catalyst (%)	Ligand	Time(h)	Yield 46 (%)
1[c]	$PdCl_2(PPh_3)_2$ (2) CuI (4)		4	35
2	Pd_2dba_3 (2)	Tricyclohexylphosphine (8%)	20	48
3	Pd_2dba_3 (2)	Trifurylphosphine (8%)	19	30
4	Pd_2dba_3 (2)	Tris(2,4,6-trimethoxyphenyl)phosphine (8%)	48	34
5[b]	Pd_2dba_3 (2)	$[(t\text{-}Bu)_3Ph]BF_4$ (8%)	23	75
6	Pd_2dba_3 (2)	$[(t\text{-}Bu)_3Ph]BF_4$ (8%)	19	85

[a] All reactions were carried out using 1.0 eq. of compound **3**, 2.0 eq. of phenylacetylene, 1.1 eq. of Cs_2CO_3 as base, 1 mL of 1,4-dioxane as solvent at 60°C under a nitrogen atmosphere.
[b] Reaction carried out using 1.5 eq of phenylacetylene
[c] Reaction carried out using 0.5 mL of DMF and 1mL of *ipr*2NH as solvent without any base
[d] Reaction carried out using 1mL of DMF

On the basis of these results, the $Pd_2(dba)_3/[(t\text{-}Bu)_3Ph]BF_4$ catalytic system was selected to explore the synthetic scope of the reaction. The obtained preparative results were summarized inTable 4. Under the optimized reaction conditions, the synthetic procedure tolerated useful different functionalities, such as keto, cyano, nitro, methoxy methyl, and carbomethoxy substituents and could provide a ready access to 5-alkynyldopamine derivatives, all isolated in medium to good yields.

Table 4 Synthesis of 5-alkynil dopamine derivatives [a]

Entry	R	t (h)	Yield (%)
1	Ph-	19	85
2	C_6H_4-CH(OH)-	2.5	20
3	$(CH_3)_2$CH(OH)-	3	21
4	4-MeCO-C_6H_4-	17	63
5	4-NO_2-C_6H_4-	6.5	44
6	4-Me-C_6H_4-	24	80
7	4-MeO-C_6H_4-	0.5	55
8	$CH_3(CH_2)_3$C-	17	64
9	4-MeO_2C-C_6H_4-	8	50
10	2-NO_2-C_6H_4-	0.5	50
11	4-CN-C_6H_4-	0.5	80
12	3-CN-C_6H_4-	1.5	78

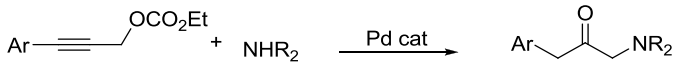
[a] Reaction conditions: 0.02 eq of Pd_2dba_3; 0.08 eq. of [(*t*-Bu)$_3$Ph]BF_4;1.5 eq. of terminal alkyne; 1.1 eq of Cs_2CO_3 as base; 1 mL of 1,4-dioxane as solvent at 60°C under a nitrogen atmosphere.

In conclusion, a new synthetic strategy for the preparation of analogues of dopamine, through the Sonogashira *cross coupling* reaction conditions, has been performed. The protocol is compatible with the utilization of terminal alkyl- and aryl-acetilenes with neutral, electron-rich and electron-poor substituents. Hindered alkynes can also be used.

2.3. Palladium-catalyzed synthesis of 2-amino ketones from propargylic carbonates and secondary amines [13]

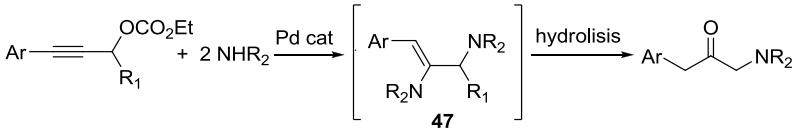
2-Amino-ketones are subunits of a variety of pharmaceutical and natural products with biological activities. Particularly they are substructure of mersingines A and B[81] and of a small family of linear peptides including the antitumor agent eponemycin.[82] Furthermore 2-amino-ketones are useful synthetic intermediates.[83] Despite their importance, direct synthesis of this class of compounds is rather limited. Current general synthetic approaches are based on the α-amination of ketones[84] and enolsilanes, [85] on the osmium-catalyzed ketamination of alkenes, [86] on the conversion of the carboxylic group of amino acids into a ketonic group[87] and on the formation of carbon-carbon bonds between carbonyl and amino-containing fragments. [88] Palladium catalysis has been rarely applied in this area. To the best of our knowledge, it has been used only in the preparation of 2-amino ketones from a α-sulfonamidoorganostannanes and benzoyl chlorides.[89]

In consideration of these data, a new palladium–catalyzed route to 2-amino-ketones from readily available propargylic carbonates and secondary amines that involves a formal anti-Markovnikov addition of water to the carbon-carbon triple bond and the substitution of the C $_{propargylic}$–N bond for the C $_{propargylic}$–O bond, has been developed (Scheme 40).



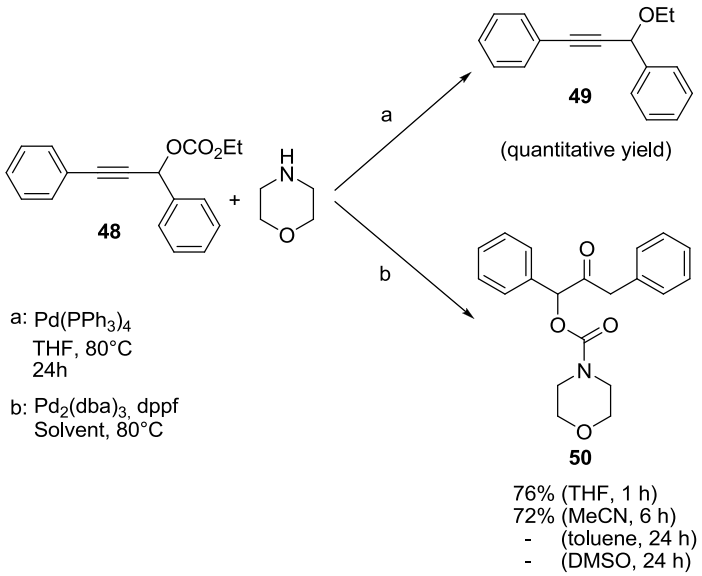
Scheme 40

On the basis of a previous study[90], showing that 2-aminomethyl indoles could be prepared from 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates and amines through a process involving sequential intramolecular/intermolecular C–N bond forming steps, it was hypothesized that a similar reaction, omitting the trifluoroacetamido group bound to the aromatic ring, might provide access to 2-amino-ketones via sequential intermolecular C–N bond forming steps, leading to enamine intermediates **47** and hydrolysis (Scheme 41).



Scheme 41

To evaluating the feasibility of reaction, the use of 1 equiv of **48** with 3 equiv of morpholine it was set out as model system.

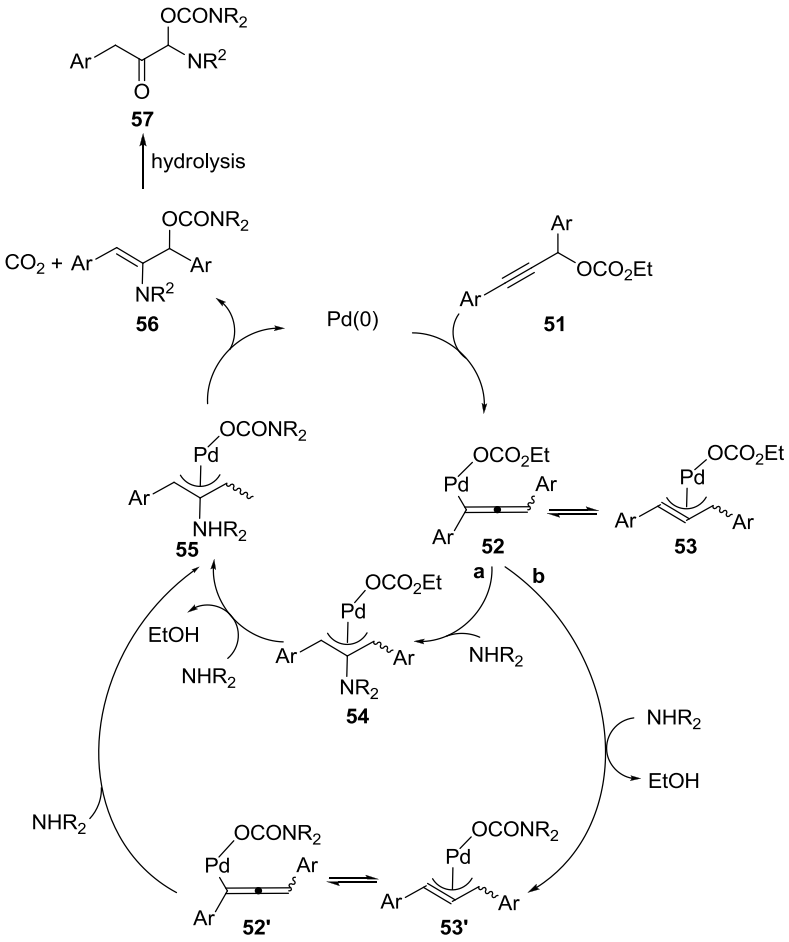


Scheme 42

First attemps met with failure: under the same conditions employed for the 2-aminomethyl indoles synthesis the ether **49** was formed in almost quantitative yield (Scheme 42a).

The reaction produced instead the ketocarbamate **50** in 76 % using the $Pd_2(dba)_3$/dppf combination in THF at 80°C (Scheme 42b). Using MeCN as solvent gave **50** in a slightly lower yield whereas only degradation products were formed in toluene and DMSO. For this reaction the following mechanism, has been proposed (Scheme 43). Palladium reacts with the phenylpropargylic carbonate **51** to give the σ allenyl-palladium complex **52** which would be in equilibrium with the propargylic palladium intermediate **53** . The nucleophilic attach of the morpholine at the central carbon of the complex followed by a protonatium step, give the allylic palladium complex **54** . This complex is attached by another molecule of morpholine to give the carbamate palladium complex **55**. Alternatively, morpholine can displace the ethoxy group of **52**/**53** to give

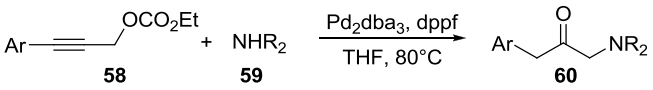
52'/**53'** that is converted in the carbamate complex **55** via nucleophilic attack of another molecule of morpholine at the central cabon of the allenylic/propargylic palladium complex and protonation. Subsequently, the intramolecular nucleophilic attack of the carbamate oxygen at one of the allylic carbons of **55** and the hydrolysis of the resultant enamine intermediate **56** generates the ketocabamate **57**. Experimental evidence for the intermediacy of **56** was obtained by NMR analysis of the crude reaction mixture before work up. Steric effects due to the substituents of **54** or **55** might occur for the preferential intramolecular nucleophilic attack of the less hindered carbamate fragment to one of the allylic termini with respect to the intermolecular nucleophilic attack of the more sterically demanding morpholine. Therefore, the reactivity of the unsubstituted propargylic carbonate **58** has been investigated. Pleasingly its reaction with morpholine in the presence of $Pd_2(dba)_3$/dppf in THF at 80 °C afforded the desired 2-aminoketones in 76% isolated yield after 3 h.



Scheme 43

As shown in Table 5, using these conditions, it was possible to explore the scope and the generality of the process: clean formation of 2-amino–ketones, was observed with a variety of propargilyc carbonates bearing neutral, electron-rich and electron poor aromatic rings and cyclic secondary amines containing useful functional groups.

Table 5 Palladium catalyzed synthesis of 2-amino-ketones from propargylic carbonates and secondary amines[a]



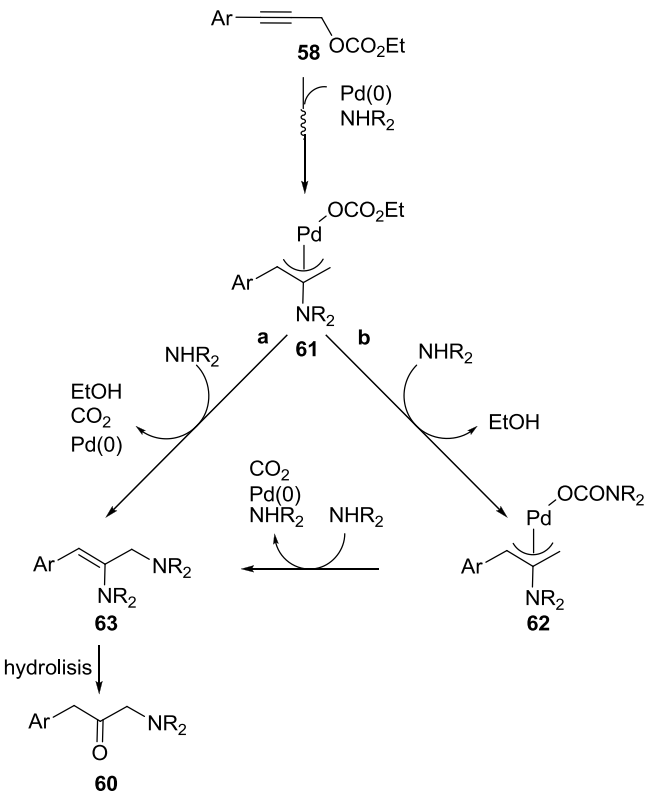
58 **59** **60**

Entry	Ar	Amine 69	t (h)	Yield 60 (%)
1	Ph	Morpholine	3	76
2	Ph	Piperidine	1.5	46
3	Ph	1-Ethylpiperazine	2	75
4	Ph	1-(4-fluorophenyl)piperazine	1	60
5	Ph	1-(4-bromobenzyl)piperazine	2	74
6	Ph	2-(piperazin-1-yl)benzonitrile	18	49
7	Ph	1-(4-methoxybenzyl)piperazine	55	92
8	Ph	Piperazine	0.5	57
9	4-$MeOC_6H_4$	Morpholine	4.5	57
10	4-$MeOC_6H_4$	1-(4-methylbenzyl)piperazine	2	66
11	4-$MeOC_6H_4$	1-(4-chlorolbenzyl)piperazine	4	73
12	4-$MeCOC_6H_4$	Morpholine	7	58
13	4-$EtO_2CC_6H_4$	Morpholine	3	88
14	4-$EtO_2CC_6H_4$	1-Ethylpiperazine	1	84
15	4-$EtO_2CC_6H_4$	1-(3,4-trichlorolbenzyl)piperazine	1.5	92
16	3-MeC_6H_4	Morpholine	1.5	65

[a]Reaction were carried out on a 0.35 mmol scale at 80°C in anhydrous THF (2mL), under a nitrogen atmosphere, using 1 equiv. of propargylic carbonates, 3 equiv. of amine, 0.025 equiv. of $Pd_2(dba)_3$ and 0.05 equiv. of dppf.

For the synthesis of the 2-aminoketones **60** the mechanism depicted in the following, Scheme 43 has been proposed.

After the initial reaction of Pd(0) with the aryl-propargylic carbonate **58** occurs an intamolecular nucleophilic attack of the nitrogen at the less substituted terminus of the π-allylic palladium complex **61** (Scheme 44a). The resultant enamine **53** generate the desired 2-aminoketone **60** after hydrolysis.



Scheme 44

Alternatively, (Scheme 44b) morpholine can displace the ethoxy group of **61** to give the carmamate palladium complex **62** that is converted in the enamine **63** after an intramolecular nucleophilic attack of the nitrogen at the less substituted allylic carbon.

In summary, a novel palladium-catalyzed approach to 2-amino ketones from arylpropargyl carbonates bearing neutral, electron-rich, and electron-poor aromatic rings and cyclic secondary amines containing useful functional groups such as cyno, chloro and bromo substituents, has been developed. The procedure is simple, uses readily available starting materials and may represent a useful tool for the synthesis of this class of compounds.

2.3 Palladium-catalyzed cascade reaction of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(3-arylprop-2-ynyl)acetamide derivatives with arylboronic acids.

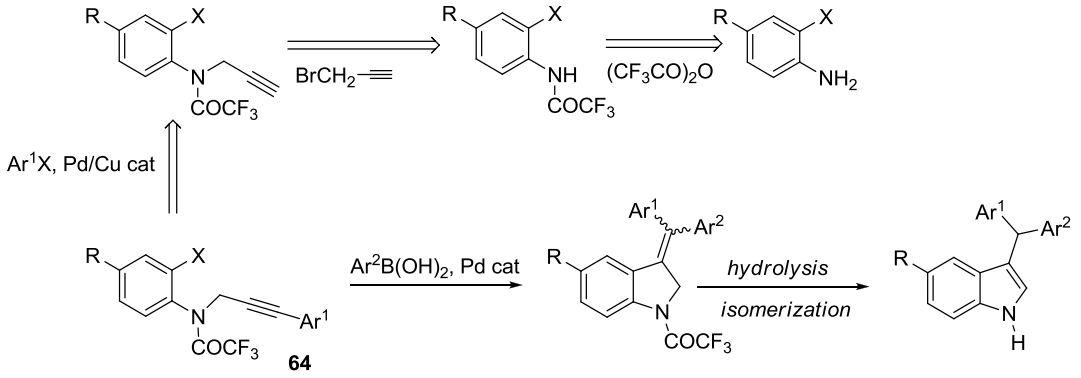
The substituted indole nucleus (indole is the acronym from ***ind****igo* - the natural dye - and ***ole****um* - used for the isolation) is a structural component of a vast number of biologically active natural and unnatural compounds.[91]

Synthetic methods for the synthesis and functionalization of indoles have been developed through many classical methods such as the Fischer indole synthesis, the Batcho-Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassman synthesis from *N*-haloanilines, the reductive cyclization of *o*-nitrobenzyl ketones, and the Madelung cyclization of *N*-acyl-*o*-toluidines.[92]

More recently, transition metal-based reactions, particularly palladium-catalyzed protocols have been widely employed providing increased functional group tolerance and improved yields as outlined by the number of studies developed in this area.

There are many approaches to the palladium-catalyzed synthesis of indole derivatives which could be categorized into two main categories: the *de novo* indole system construction from benzenoid precursors through cyclization reactions and the functionalization of preformed indole rings. Cyclization reactions usually involve the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold. This has been a very successful synthetic approach, as evidenced by the vast number of published material available. A considerable part of the studies dedicated to the development of new sequences in the bond-making process leading to the construction of the pyrrole ring is based on the utilization, as precursors, of compounds containing nitrogen nucleophiles and carbon-carbon triple bonds. Nitrogen nucleophiles and alkyne moieties can be part of the same molecule or belong to two different molecules. In consideration of the great importance of the indole chemistry, a further section of the PhD activity research was devoted to the planning, the optimization and the extension of a new palladium-catalyzed indole synthesis, based on a cross-coupling reaction between 2-halo-N-propargyl-trifluoroacetanylides **64** and boronic acids as shown in scheme 44, where are also summarized the retrosynthetic analysis of the **64** derivative. The generality, scope and limitations, as well as the product selectivity in this the cascade cyclocarbopalladation reaction followed by Suzuki-Miyaura coupling or cyclocarbopalladation/cross coupling/aromatization reactions of readily available of **64**

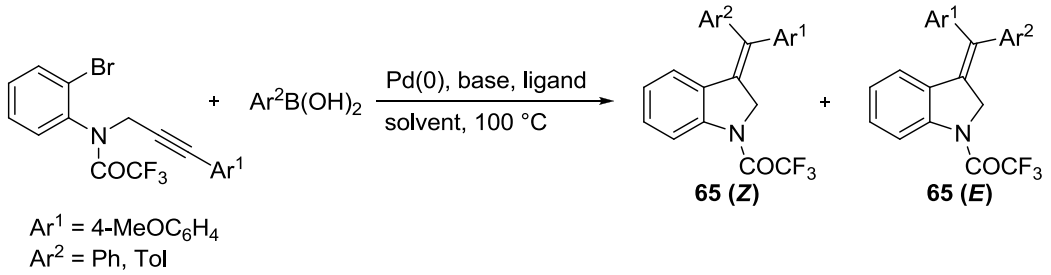
has not been previously investigated. Obviously, the applications of this key reaction can be relevant in the synthesis of new indole derivatives. Usually, different types of substitution patterns in these heterocycles provide new opportunities for drug discoveries and by a fine tuning of their physical properties for applications in material science.



Scheme 45

As shown in Scheme 45, compound **64** can be prepared through a two-step process from *o*-bromoaniline that has been protected as trifluoroacetamide, followed by alkynylation reaction with 3-bromoprop-1-yne. All the acetamide derivatives were prepared in moderate to high yields through a selective Sonogashira cross-coupling of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide with aryl iodides.

The reaction of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(3-(4-methoxyphenyl)prop-2-ynyl)acetamide with phenyl- and tolylboronic acid in presence of palladium as catalyst was selected as model system (Scheme 46).



Scheme 46

In order to optimize the reaction conditions, the influence of ligands, solvents and temperature was carefully investigated. Experimental results are summarized in Table 6**.**

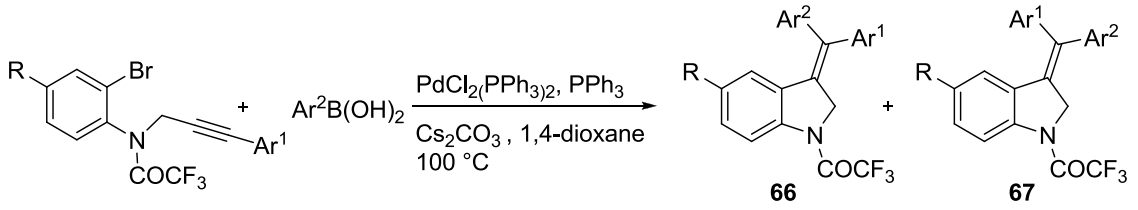
Table 6 Optimization studies for the Palladium-catalyzed cascade reaction of N-(2-bromophenyl)-2,2,2-trifluoro-N-(3-arylprop-2-ynyl)acetamide derivatives with arylboronic acids.[a]

Entry	Catalyst	Ligand	Solvent	Base	Ar	t(h)	Yield %	Z/E ratio
1	$Pd(PPh_3)_4$	-	CH_3CN	Cs_2CO_3	Ph	7	60	85/15
2	Pd_2dba_3	-	1,4-dioxane[b]	K_3PO_4	Ph	19	70	70/30
3	$PdCl_2(PPh_3)_2$	-	1,4-dioxane[b]	K_3PO_4	Ph	17	57	92/8
4	$Pd(PPh_3)_4$	-	1,4-dioxane[b]	K_3PO_4	Ph	18	70	90/10
5	Pd_2dba_3	ttmpp	1,4-dioxane	K_3PO_4	Ph	4.5		-
6	Pd_2dba_3	S-Phos	1,4-dioxane [b]	K_3PO_4	Ph	3.5	88	80/20
7[c]	Pd_2dba_3	Xantphos	1,4-dioxane[b]	K_3PO_4	Ph	24	70	80/20
8	Pd_2dba_3	S-Phos	1,4-dioxane[b]	K_3PO_4	Tol	3	82	80/20
9	Pd_2dba_3	S-Phos	1,4-dioxane[b]	K_3PO_4/KF	Tol	1	65	80/20
10[c]	Pd_2dba_3	S-Phos	1,4-dioxane[b]	K_3PO_4	Tol	2	60	80/20
11[d]	Pd_2dba_3	S-Phos	1,4-dioxane[b]	K_3PO_4	Tol	24	72	80/20
12	Pd_2dba_3	X-Phos	1,4-dioxane[b]	K_3PO_4	Tol	24	67	60/40
13	Pd_2dba_3	Xantphos	1,4-dioxane[b]	K_3PO_4	Tol	26	50	90/10
14	Pd_2dba_3	tfp	1,4-dioxane	K_3PO_4	Ph	30	62	90/10
15	Pd_2dba_3	$(4\text{-Cl-}C_6H_4)_3P$	1,4-dioxane	K_3PO_4	Ph	18	40	90/10
16	$PdCl_2(PPh_3)_2$	-	CH_3CN	Cs_2CO_3	Ph	23		-
17	$PdCl_2(PPh_3)_2$	PPh_3	1,4-dioxane	K_3PO_4	Ph	16	61	96/4
18	$PdCl_2(PPh_3)_2$	PPh_3 [e]	1,4-dioxane	K_3PO_4	Ph	30		96/4
19	$PdCl_2(PPh_3)_2$	PPh_3	1,4-dioxane	Cs_2CO_3	Ph	5	81	93/7
20	$PdCl_2(PPh_3)_2$	PPh_3	DMF	Cs_2CO_3	Ph	2	60	75/25
21	$PdCl_2(PPh_3)_2$	PPh_3	CH_3CN	Cs_2CO_3	Ph	21		-
22	$PdCl_2(PPh_3)_2$	PPh_3	Toluene	Cs_2CO_3	Ph	20		-
23	$PdCl_2(CH_3CN)_2$	ttmpp	1,4-dioxane	K_3PO_4	Ph	23	55	70/30
24	$PdCl_2[P(o\text{-Tol})_3]_2$	-	1,4-dioxane	K_3PO_4	Ph	24		-
25	$PdCl_2[P(cy)_3]_2$	-	1,4-dioxane[b]	K_3PO_4	Ph	29		-
26	$PdCl_2(ttmpp)_2$	-	1,4-dioxane	K_3PO_4	Ph	24		-
27	$PdCl_2[(4\text{-Cl-}C_6H_4)_3P]_2$	-	1,4-dioxane	K_3PO_4	Ph	19	40	90/10

[a]All reactions were carried out on 0.36 mmol scale of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(3-(4-methoxyphenyl)prop-2-ynyl)acetamide using 0.05 % of [Pd] and 0.1 % of ligand in 2.5 mL of solvent; [b]1.5 mL; [c]T=120 °C; [d]T=60 °C; [e]Ligand: 0.2 %; tfp = Tri(2-Furyl)phosphine; ttmpp= *tris*-(2,4,6-Trimethoxyphenyl)phosphin

The initial attempts showed the feasilibilty of the planned process: for example, the desired cross-copling product was obtained in very good yield with the standard palladium catalysts (Table 6**,** *entry* 1-3). However, the reaction outcome is poor from the stereoselective point of view: for example, the cross-coupling product was isolated as a 70/30 mixture of *Z* and *E* isomers using $Pd_2(dba)_3$ as catalyst (Table 6**,** *entry* 2). As discussed later (scheme 47), this isomerization most probably occurs because of the low reactivity of the σ-palladium intermediate **69** towards the boronic acid. A very broad screening about the role played by phosphine ligand was then carried out, revealing that the minimization of the isomerization process could be achived using the catalytic system $PdCl_2(PPh_3)2/PPh_3$ in 1,4-dioxane: under these conditions (Table 6**,** *entry* 19), the cross-coupling product **65** was isolated in 81% yield (*Z*/*E* ratio: 93/7).

The optimized conditions were then used for exploring the scope of the reaction, varying the nature of the Ar^1 and Ar^2 substituents respect to the model system (Scheme 47): the obtained preparative results are summarized in Table 7.



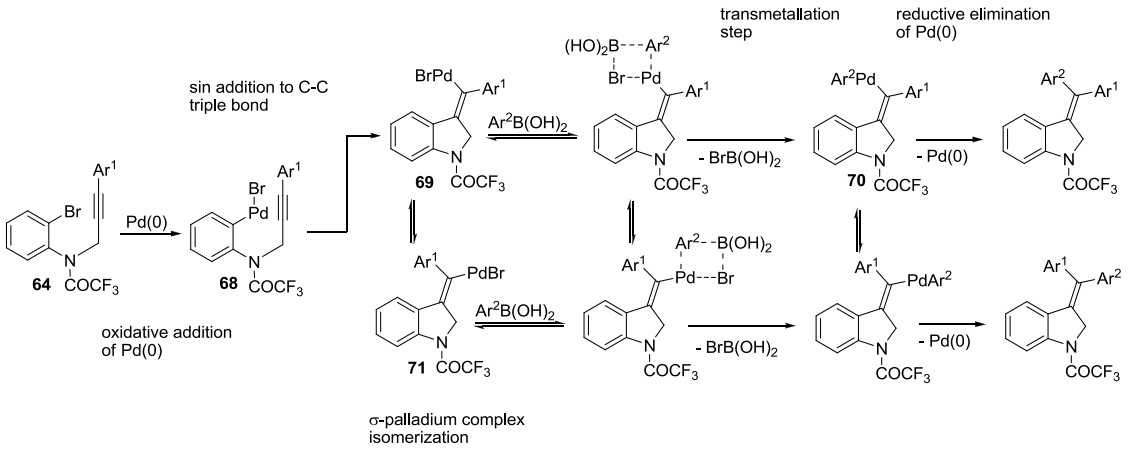
Scheme 47

Table 7 Palladium catalyzed synthesis of 1-(3-(diarylmethylene)indolin-1-yl)-2,2,-2-trifluoroethanone[a]

Entry	Ar^1	Ar^2	t (h)	Yield (%)	66/67ratio
1	4-MeO-C_6H_4	Ph	5	81	93/7
2	4-MeO-C_6H_4	4-MeO_2C-C_6H_4	2	82	93/7
3	4-MeO-C_6H_4	2-CHO-C_6H_4	0.5	64	93/7
4	4-MeO-C_6H_4	4-Me-C_6H_4	2	70	92/8
5	4-MeO-C_6H_4	4-F_3C-C_6H_4	1	68	87/13
6	4-MeO-C_6H_4	4-Cl-C_6H_4	1	70	90/10
7	4-MeO-C_6H_4	2-Me-C_6H_4	1	85	93/7
8	4-MeO-C_6H_4	4-MeO-C_6H_4	3	75	-
9	Ph	Ph	1.5	72	-
10	4-Me-C_6H_4	4-Me-C_6H_4	1	66	-
11	p-COCH3	p-COCH3	1	82	-
12	4-Cl-C_6H_4	4-Cl-C_6H_4	1.5	88	-
13	4-MeO_2C-C_6H_4	4-MeO_2C-C_6H_4	1	71	-

[a]Reactions were carried out on a 0.36 mmol scale at 100 °C in 1,4-dioxane (2,5mL), under a nitrogen atmosphere, using 1eq. of N-(2-bromophenyl)-2,2,2-trifluoro-N-(3-arylprop-2-ynyl)acetamide derivative, 1.5 eq. of arylboronic acid, 1,5 eq. of Cs_2CO_3 , 0.05 mmol % of $PdCl_2(PPh)_3$ and 0.10 mmol % of PPh_3.

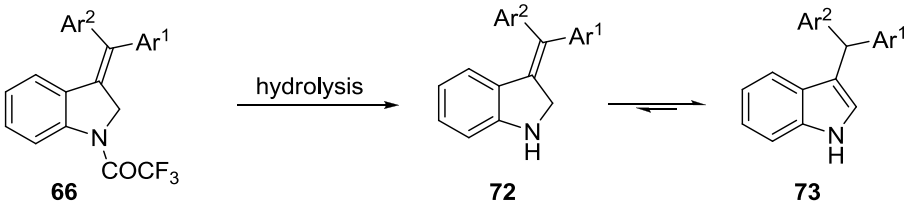
The proposed mechanism of the reaction is illustrated in Scheme 48.



Scheme 48

The 2-bromo-*N*-propargyl-trifluoroacetanylide **64** reacts with palladium catalyst to give the σ-palladium bromide intermediate **68** that, through a cyclization *exo-dig* step, forms the (*Z*)-σ-(3-arylmethylidene)indoline palladium bromide **69**. At this point, a fast transmetallation reaction of **69** with boronic acid, can give the σ-(3-diarylmethylidene)indoline palladium bromide **70** without loss of double bond configuration; finally, the reductive elimination of palladium(0) from **70** intermediate, release the final product. The isolation of variable amount of the (E) – isomer can derive by the competitive isomerization of (*Z*)-σ-(3-arylmethylidene)indoline palladium bromide **69** to its *E* isomer **71**: this process can be significant when the transmetallation step quickness slow down begin or as conseguence of steric effect of the used phosphine ligand that umper the positive interaction beteewn σ-palladium complex and boronic acid or when the electronic effect of the substituent present in the aryl moieties decreses the double bond order, assisting *Z* to *E* isomerization.

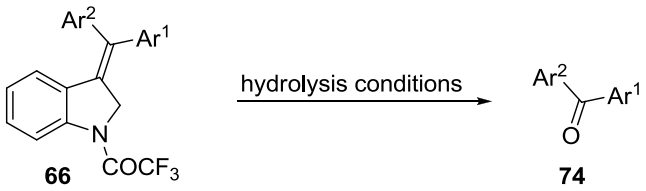
A series of attempts was also performed on indoline derivatives **66** for their conversion to 3-(diarylmetyl)indoles: this transformation formally requires a hydrolysis of the *N*-trifluoroacetamido group step followed by a basic (or acid) isomerization to indoles **73** (Scheme 49).



66 **72** **73**

Scheme 49

However, in all the cases studied the main product obtained was the acetophenone derivative **74**, most probably formed by the oxidation of the exocyclic double bond that results faster than the *N*-trifluoroacetamido group hydrolysis (Scheme 50).



66 **74**

Scheme 50

Due to the lack of spectroscopic data in literature of the 3-(diarylmethylidene)indoline derivative, a complete NMR study was necessary to assign main product double bond configuration: decisive to this goal was the ^{1}H-NOESY study on model derivative **66**, illustrated in Figure 9

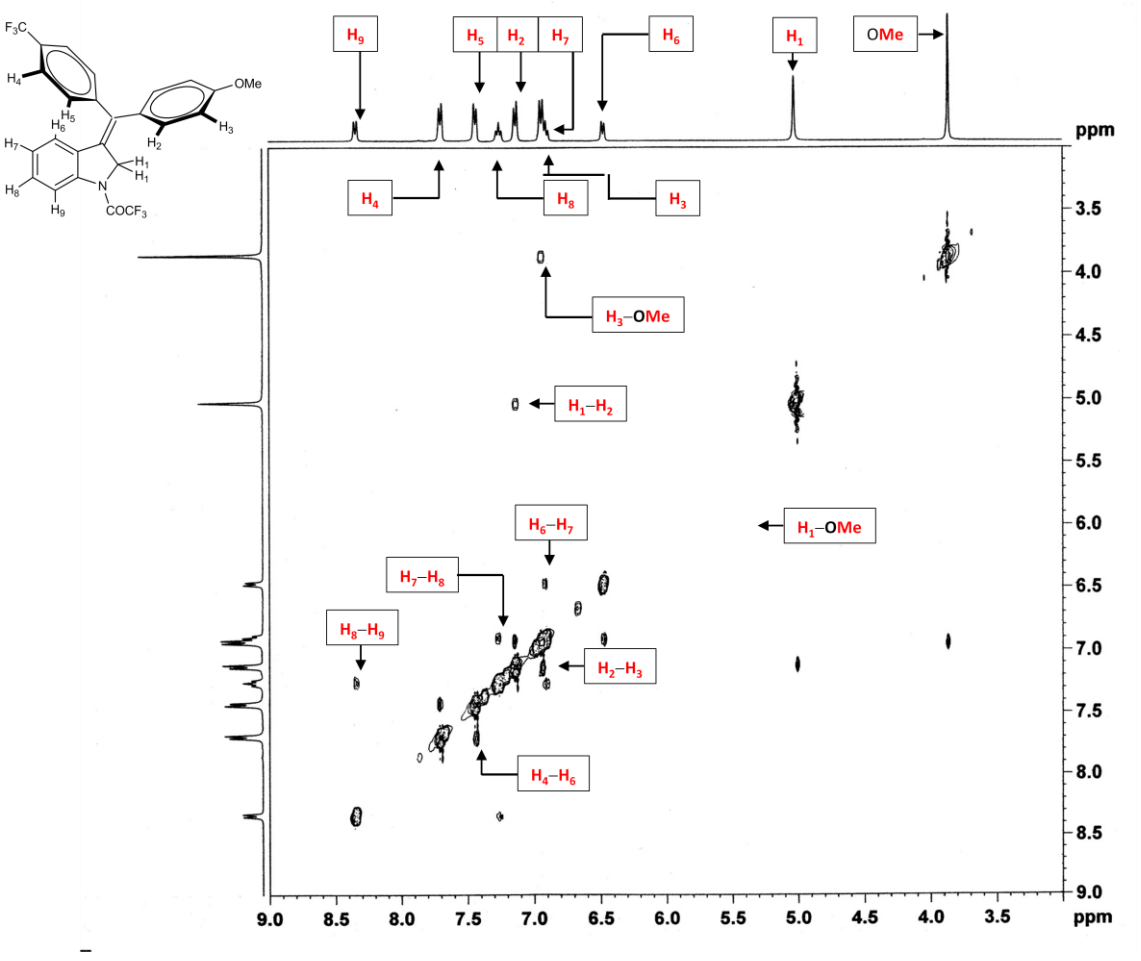


Figure 9

The 2D map shows the presence of several cross peaks that all together confirm the (*E*) configuration for the exocyclic double bond of **66**: for example, the correlation peack of coordinates 7.58-7.48 ppm relative to H_6 and H_5 protons (assigned by 1D experiments), confirms the position of the aromatic unit given by boronic acid (this evidence is also in agreement with the proposed mechanism illustrated before). The same conclusions are obtained from the 7.20-5.01 ppm cross peack, due to the correlation of H_1 and H_2 protons, that indicate the spatial proximity between the indoline protons H_1 and the aromatic proton of the 4-methoxyaryl moiety.

In conclusion, a convenient, highly stereoselective synthesis of novel 3-(1,1-diarylmethylidene)indoline derivatives has been developed. This class of compound has been prepared through a cascade cyclocarbopalladation reaction followed by Suzuki-Miyaura coupling or cyclocarbopalladation/cross coupling/aromatization reactions of 2-bromo-*N*-propargyl-trifluoroacetanylide **64.** The reaction works effectively with a variety of neutral, electron-rich and electron-poor substituted aryl bororonic acids.

3. Oxidation of alcohols to ketones by gold nanoparticles

3.1. Introduction.

The application of homogeneous or heterogeneous catalysis for the production of bulk chemicals is well established: many processes are known based on oxidation, hydroformylation, carbonylation, hydrocyanation, and metathesis. [93] In fine chemical production, however, the use of the catalysis is still fairly limited, although the number of transformations applied in production is somewhat higher.[94,95] In addition to the above reaction types, processes are known based on aromatic substitutions, such as Heck, Suzuki, Sonogashira, Kumada and Negishi couplings, isomerisations, racemisations and enantioselective catalysis such as hydrogenation and cyclopropanation. The fine chemical industry is highly diverse, comprising pharmaceuticals, agrochemicals, polymer additives, dyestuffs, food additives, flavours and fragrances, chemical intermediates, and many more. Particularly in the lower range of production size, there is a long tradition of simply scaling up from known stoichiometric laboratory procedures as this reduces the time necessary for development and usually leads to robust and reliable processes. The downside of this approach is that it generates rather large amounts of waste. Especially in high-value-added products, such as pharmaceuticals that are often produced by lengthy multi-step syntheses, this approach can lead to quite excessive waste/product ratios of ca. 25-100.[96] There are many advantages to the catalysis using in fine chemical production, which may be summarised as follows:

- Reduction of waste.
- High selectivity.
- Production of a desired single enantiomer through asymmetric catalysis.
- Shortcuts in lengthy total syntheses.
- C–C bond formation under mild conditions obviating the use of protective group.

In view of all these advantages, it seems surprising that the percentage of fine chemical production processes making use of catalysis is still below 10%. There are a number of reasons for this. Economics is often a decisive factor when there is a choice of production methods.[97] Obviously, many transition-metals are very expensive and the same holds true for ligands that have to be prepared by lengthy total syntheses. A key success factor, therefore, is the reaction rate, usually expressed as its turnover frequency

(TOF = moles of product/moles of catalyst × hour). Of same importance is the stability of the catalyst, expressed as its turnover number (TON = moles of product/moles of catalyst). A second factor is the scalability and robustness of the process. Many transition metal-catalysed reactions may work well on a laboratory scale, but, on scaling up, substrate and product inhibition may be an issue and sensitivity to impurities may become apparent. It is very important to keep the number of components of a reaction to a minimum, as extraction, crystallization, and distillation are the only economically viable means of purification. The presence of ligands can be a nuisance in this respect, particularly if they are used in amounts over 5 mol %. Reproducibility is also necessary, but by far the most important limiting factors are the reaction time and the reuse of the catalyst. In order to optimize this aspect, it is interesting to consider the nanoscience point of view. This discipline, in fact, have recently evolved as a major research direction of our modern society resulting from an ongoing effort to miniaturize at the nanoscale processes that currently use Microsystems. Towards this end, it is well admitted that bottom-up approach should now replace the classic top-down one, a strategic move that is common to several areas of nanoscience including optoelectronics, sensing, medicine and *catalysis*. In a recent "Focus" Article in Chemical Communication, Samorjai emphasized that catalysis is the central-field of nanoscience and nanotechnology.[98] In this context, the control of the size, composition, surface structure, the anchorage and the support of the nanoparticles is required for the development of successful nano-catalyst on laboratory and industrial-scale. He claimed, also, as ultimate goal the role of recoverable nano-catalysts in *Green chemistry*. [99]

Green catalysis aspects, infact, require that environmentally friendly (for instance phosphine-free) catalysts be designed for easy removal from the reaction media and recycling many times with very high efficiency. These conditions bring a new research impetus for catalyst development at the interface between homogeneous and heterogeneous catalysis, gathering the sophisticated fulfilment of all the constraints that were far from being fully taken into account by the pioneers and even the specialists in each catalytic discipline in the former decades. Yet the considerable knowledge gained from the past research in homogeneous, heterogeneous, supported and biphasic catalysis, including also studies in non-classical conditions (solvent-free, aqueous, use of ionic liquids, fluorine chemistry, micro-emulsions, micelles, surfactants, aereogels) should now help establish the desired optimized catalytic systems.

Transition metal NPs are clusters containing from a few tens to several thousand metal

atoms, stabilized by ligands, surfactants, polymers or dendrimers protecting their surfaces. Their sizes vary between the order of one nanometer to several tens or hundreds of nanometres, but the most active in catalysis are only one or a few nanometers in diameter, they contain a few tens to a few hundred atoms only. The nanoscale size of catalyst systems is shown schematically in Figure 10. Enzyme catalyst active sites, which are inorganic nanoclusters containing iron, carry out important oxidation and reduction chemistry.

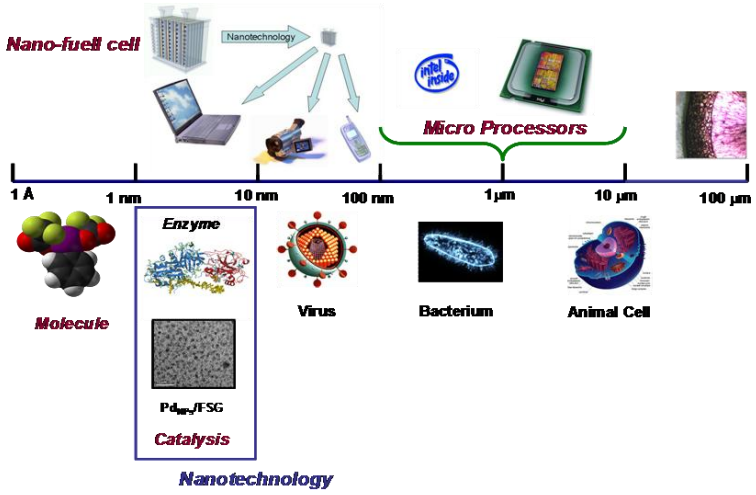


Figure 10

In view of the catalyst recycling, NPs catalysts are often immobilized or grafted onto inorganic or organic support.

3.2. The Transition-Metal Nanoparticle History

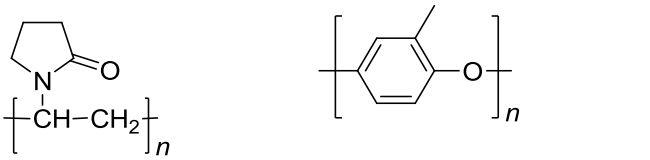
The use of NPs in catalysis apperared in the 19th century with photography (AgNPs) and the decomposition of hydrogen peroxide (PtNPs).[100] The real breakthrough came with *Haruta*'s seminal studies on oxide-supported Aunp-catalyzed CO oxidation by O_2 at low temperatures.[101] In the 1970s, *Bond* and *Sermon* [102] and *Hirai* et al.[103] disclosed Au*np*catalyzed olefin hydrogenation. In 1986 *Lewis* demonstrated the colloidal mechanism for the catalysis of olefin hydrosilylation by silanes using organometallic complexes of Co, Ni, Pd, or Pt including the Speier catalyst (alcoholic H2PtCl6).[104] These catalysts were formerly believed to follow the classic monometallic organometallic mechanism (oxidative addition of the Si-H bond of the

silane onto the transition-metal center and subsequent alkene insertion and reductive elimination).

In the mid-1990s, pioneering studies of Pd_{np} catalysis were reported by *Reetz* for Heck C-C coupling, such as the reaction between butyl acrylate and iodobenzene or aryl bromides and styrene.[105] In the first year of the 21st century have seem an growth in the number of publications in the Nano-catalysis field. Many scientists have contribute to improve the nano-catalyst activity and selectivity and to understand the catalytic mechanisms.[106] The modes of preparation of catalytically active NPs have been diversified and currently include impregnation,[107a] co-precipitation,[107b] deposition/precipitation,[107c] sol–gel,[107d] gasphase organometallic deposition,[107e] sonochemical,[107f] micro-emulsion, [107g] laser ablation,[108a] electrochemical,[108b] and cross-linking.[108c]

3.3. Stabilizers and Support agents of Transition-Metal Nanoparticles.

The stabilizers for transition-metal NPs can be divided into three categories: (i) those that provide electrostatic stabilization, such as cationic and anionic surfactants; (ii) those that provide steric stabilization, including compounds possessing a functional group endowed with a high affinity for metals such thiols, sulfides, amines, and phosphine; and (iii) those that simply entrap nanoparticles, such as polymer, cyclodextrines, and dendrimers. In all cases, protecting agents ought to interact in an attractive manner with the surface of the metal.[109]. In Figure 11 are show two major polymer families used as metal NP supports and stabilizer.



Poly(vinylpyrrolidone) poly(2,5-dimethylphenylene oxide)

Figure 11

Moreno-Mañas et al. have reported that some heavily fluorinated compounds and materials can stabilize transition-metal nanoparticles.[110] Thus, polymers such as Nafion and PTFE, as well as dendrimers fluorinated in the surface[111] have been reported as being stabilizing agents, probably by the inclusion of nanoparticulated metal into the interstices of the polymer or the no fluorinated core of the dendrimers.[112] Other heavily

fluorinated stabilizing agents are considered to act by classical stabilizing mechanisms. Thus, thiols C_nF_{2n+1}-CH_2CH_2-SH (n = 6, 8) and anions C_nF_{2n+1}-COO (n = 11-17) [113] owe their stabilizing ability to the SH group and to the carboxylate rather than to the Rf moiety. On the other hand, nanoparticles in the water core of a water-in-CO_2 emulsion have been stabilized by perfluorinated surfactants; however, stabilization seems to be caused by the hydrophilic polar part, whereas the perfluorinated moiety imparts solubility in CO_2.[114] heavily fluorinated compounds used in the preparation of Metal NPs are shown in Figure 12.

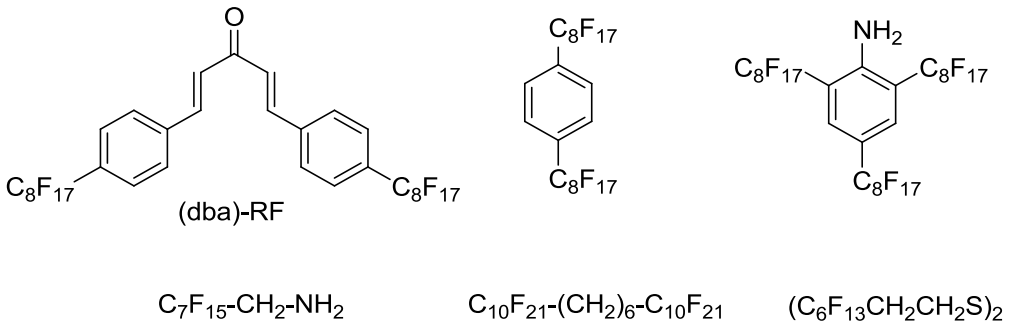
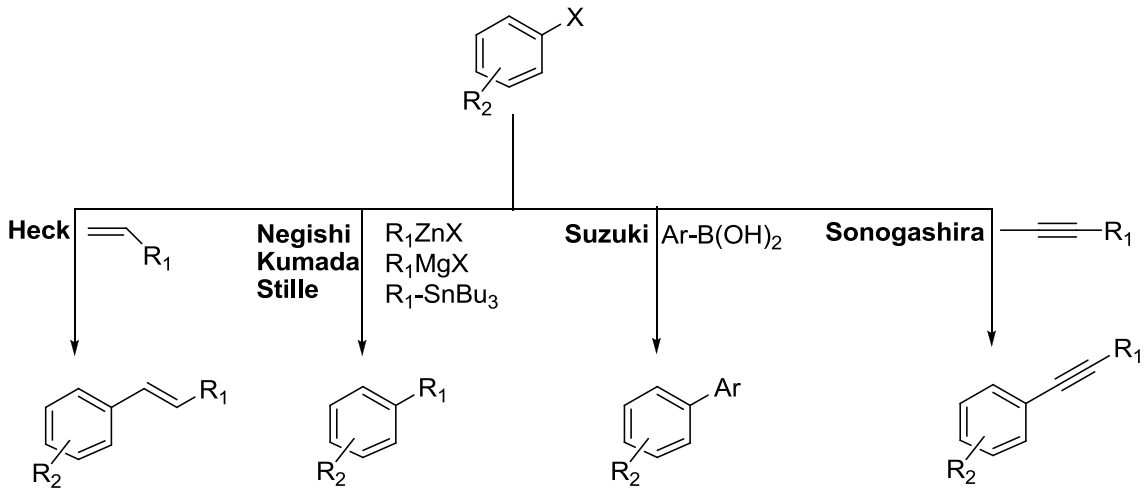


Figure 12

3.4 Application of Transition-Metal Nanoparticles in Organic Chemistry

The finding of catalytic formation of C–C and C–N bonds by Palladium catalyst has been a considerable breakthrough in synthetic organic chemistry.



Pd*nps* catalysed aromatic substitution reactions (X = halides or other suitable leaving group)

Scheme 51

Examples of Pd-catalyzed C–C coupling reactions include the Heck, Tsuji-Trost, Sonogashira, Suzuki, Stille, Negishi, Corriu-Kumada, and Ullmann reactions (Scheme 51). The Heck reaction and the Suzuki cross-coupling are among the most used processes in C–C bond forming processes. The Heck reaction does not involve organometallic reagents and boronic acids used in the Suzuki cross-coupling are essentially non-toxic, contrary to the organometallics used in other cross-coupling protocols. The Heck reaction has been widely studied using Pd_{np} catalysis whereas a few examples of the other C–C coupling reactions catalyzed by Pd_{np} have been described. The Heck reaction using Pd_{nps}, for instance, is a key reaction for the production of fine chemicals on a multi-ton scale per year such as the herbicide Prosulfuron^{TM}, the anti-inflammatory Naproxen^{TM} or the anti-asthma Singulair^{TM}. On the other hand, in terms of *Green Chemistry*, it is likely that procedures involving chemicals such as ionic liquids, micelles, surfactants and other additives in homogeneous solution will retain less attention than those interested in atom economy problems and applicable organic synthesis. Rh and Ru nanoparticles are mostly used as catalyst in hydrogenation reaction, particularly in olefin and alkyne hydrogenation.

Moreover, soluble transition metal nanoparticles are considered as a reference in monocyclic arene catalytic hydrogenation under mild conditions and several stabilized system have been describe.[115] Homogeneous and heterogeneous gold nanoparticles show interesting activity for a large number of reactions involving alkynes,[116a] alkenes,[116b] selective hydrogenations[116c] and oxidations[116d] among others.[116e] Selective oxidation of alcohols to carbonylic compounds is one of the most important transformations in organic chemistry. It is the final goal for solid catalysts to be able to perform this reaction with air at atmospheric pressure and low temperature, as well as to replace current stoichiometric alcohol oxidation by a general catalyst that is selective for any hydroxyl group. In response to this goal, various gold,[116f] palladium,[117] and gold/palladium[118] catalysts have given good results. Among these noble metals, gold, though less active than Pd or Au/Pd for some alcohols, is of more general use and exhibits higher selectivity than either Pd or Au/Pd. Owing to the interesting catalytic properties of Au for selective oxidation, A. Corma et al have carried out a detailed mechanistic study that addresses the influence of the gold nanoparticle size, nature of the support and influence of catalyst preparation procedure, to establish a detailed reaction mechanism that can help to design a new generation of more active gold catalysts for the aerobic oxidation of alcohols.

3.5 Gold Nanoparticles: a Good Opportunity for Sustainable and Green Chemistry.

There is a general concern in developing new chemistry that can be sustainable and benign for the environment.[119] Most of the current chemical industry is based on the use of oil and natural gas as feedstock and this situation has to change substantially in the near future. Also, sustainability has to be accompanied by the development of new processes that do not produce, or minimize up to an acceptable extent, any negative impact on the environment. For these reasons, a new scenario in chemistry has been set in which not only inefficient processes, but even the efficient ones, have to be replaced if they do not comply with certain principles that constitute the base of what has been called *Green Chemistry.* In Green Chemistry, two parameters, the *E-factor* (*E*) and the *Atom Efficiency* (*AE*), have been established to quantify the greenness of a transformation. The E-factor indicates the Kg of waste per Kg of products and AE-factor measures the percentage of the starting material that ends up in products.[120a-d] Both parameters are obviously interrelated. Considering a brief overview of organic reactions, it can be stated that are some reaction types that have a low E-factor and high AE. One example of this green general organic reaction type will be hydrogenations and also C-C couplings catalyzed by transition metals such as Suzuki, Heck, Sonogashira, Buchwald, etc. the vast majority of organic oxidations at the laboratory scale level or in the fine chemical industry also produce a large amount of wastes. Perusal of the current organic chemistry textbooks shows that all of the classical oxidation reactions, even though they give high product yields, are far from complying with the green chemistry principles, using hazardous or toxic chemicals, requiring volatile organic solvents and producing large amounts of toxic waste. Most of the current methods, in fact, for the oxidation in organic chemistry are not catalytic, but stoichiometric. It is mean that equivalent amounts of an oxidizing reagent, such as transition metal oxides or halo-oxo acids, are needed to promote the oxidation, leading to the stoichiometric formation of waste corresponding to the reduced form of the oxidizing reagent. Other non-metallic oxidants that have been used as oxidizing reagents are halogens, peroxy and hydro-peroxy compounds or even sulfoxides. The latter noxious reagents are transformed into equivalent amounts of sulphide in the selective Swern alcohol oxidation.[121a-c].

Table 8 List of some oxidizing reagents

Oxidizing reagent	Waste	O_2 %
$KMnO_4$	Mn^{2+}/MnO_2	-
K_2CrO_4	Cr^{3+}	-
CH_3COOH	CH_3CO_2H	26
t-BuOOH	*t*-BuOH	27
ClO^-	Cl^-	30
H_2O_2	H_2O	46
O_2	H_2O	50

Table 8 shows some typical oxidizing reagents, indicating the resulting by-product and the percentage of oxygen content. One of the principles of green chemistry is to substitute stoichiometric processes by catalytic processes. Application of these principles is particularly necessary in oxidations reactions, for which the ratio between kg of by-products per kg of product formed is notably high. By transforming a stoichiometric into catalytic process, is meant the use of unconventional, environmentally-friendly oxidizing reagents that do not readily react in a selective way with organic substrates unless suitable catalysts for the process are developed. One example of a catalytic oxidation is the *Meerwein-Ponndorf-Verley* that is carried out using Lewis acid catalysts. Following the rapid growth of gold nanotechnologies during the last decades the application of this metal in catalysis has become an important research area. However, only in recent years gold has been evaluated in fundamental reaction for organic synthesis such as oxidation and hydrogenation,[122] and the use of gold catalysts for industrial application in fine chemical intermediates has been explored by academic and industrial researchers.[123] Compared to other metals, one of the outstanding properties of gold in catalysis is represented by the high selectivity which allows discrimination within chemical group and geometrical positions, favoring high yield of the desired product. Considering other concomitant properties, such as *biocompatibility*, availability and easy recovery, gold appears as a promising green catalyst for sustainable processes using clean reagents, particularly O_2 and H_2, often in aqueous solution under mild conditions or in the absence of the solvent. In the book by Bond, Louis and Thompson there are five introductory chapters covering all aspects related to physical properties and characterization of gold nanoparticles as well as preparation of supported gold catalysts. The reader is referred to this reference book for

a coverage of these important aspects in gold catalysis. Another key precedent is the review from Hashmi and Hutchings on gold catalysis covering both homogeneous catalysis using gold salts and heterogeneous catalysis using supported gold nanoparticles.[124-126] Hutchings's Au/TiO_2 or Au/zeolite catalysts yielded at low conversion with benzyl alcohol a $TOF_{t=0.5\ h}$ of 200–500 h^{-1} at 100 °C and 2 atm O_2 under solvent-less conditions. Baiker's catalyst (Au on Cu–Mg–Al mixed oxides) gave at 90 °C and 1 atm O_2 in mesitylene a $TOF_{t=0.5\ h}$ of 316 h^{-1} with benzyl alcohol and a $TOF_{t=3\ h}$ of 11 h^{-1} with 1-octanol; much better results were obtained with 1-phenylethanol ($TOF_{t=1\ h}$ of 1294 h^{-1}). [127] Oxidation of 1-phenylethanol with Kobayashi's Au on polystyrene gave a $TOF_{t=1\ h}$ of 32 h^{-1} at room temperature and 1 atm O_2 in benzotrifluoride/water 1:1.[128] Oxidation of 4-hydroxybenzyl alcohol using Tsukuba's PVP-stabilized Au nanoclusters in water gave an actual $TOF_{t=1\ h}$ at 23 °C and 1 atm O_2 of 15 h^{-1} and an estimated $TOF_{t=1\ h}$ at 60 °C and 1.5 atm O_2 of 33 h^{-1}.[129] Finally, Corma's Au on nanocrystalline CeO_2 with benzylic alcohols exhibited a $TOF_{t=2\ h}$ of about 80 h^{-1} at 50 °C and 1 atm O_2 in water,[130] although in this case alcohol oxidation actually was carried out by the cerium(IV) centers in the support, with the Au metal merely acting to regenerate these centers with concomitant O_2 reduction.

3.5.1. Oxidation of alcohols to ketones by gold nanoparticles

In the fine chemical industry, as well as in traditional organic chemistry, many oxidations are being carried out using high valent inorganic oxidants. The application of these types of reagents often containing chromium or manganese inevitably leads to the generation of huge amounts of metal waste. In recent years several new procedures have been developed wherein a catalyst is used to facilitate oxidation of alcohols employing molecular oxygen as the stoichiometric oxidant.[131-137] In this emerging field of *green oxidation chemistry*, catalysts comprising gold nanoparticles have attained a very prominent role,[138] since they are often surprisingly active and on some occasions exhibit different chemoselectivity than platinum metal based catalysts. Thus, from a fundamental point of view, as well as from a technical one, gold catalysis is a topic of intense scientific interest; drawing attention from a very diverse group of researchers. So far, literature reports on selective oxidations using gold catalysts have focused primarily on oxidation of alcohols to aldehydes,[132] carboxylic acids[133] or esters, [139, 140] oxidation of aldehydes to esters,[141] epoxidations of olefins,[142–145] and activation of C–H bonds in alkanes.

3.5.2. New stabilizer agents for gold nanoparticles

Recently, in our lab has been studied the the oxidation of alcohols to ketones using Perfluoro-tagged gold nanoparticles.[146] With the aim to improve the process from the environmental point of view, during this PhD course new gold nanoparticles, prepared using polysaccharides as stabilizer agents, have been tested in catalysis: the use of non toxic and biocompatible materials instead of synthetic polymers allows to achieve several decisive results in green chemistry as, for example, the dispose of waste. In addition, since polysaccharides derive from renewable sources, their utilization has economic and eviromental benefits.

Alginate is a well known polysaccharide (Figure 13) widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper; it is also possible to obtain an alginic acid gel by lowering the environmental pH value. Alginate can be extracted from marine brown algae or it can be produced by bacteria. It exhibits a backbone of (1→4) linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues of widely varying composition and sequence. This polymer can be regarded as a true block copolymer composed of homopolymeric regions of M and G, called M- and G-blocks, respectively, interspersed with regions of alternating structure.[147]

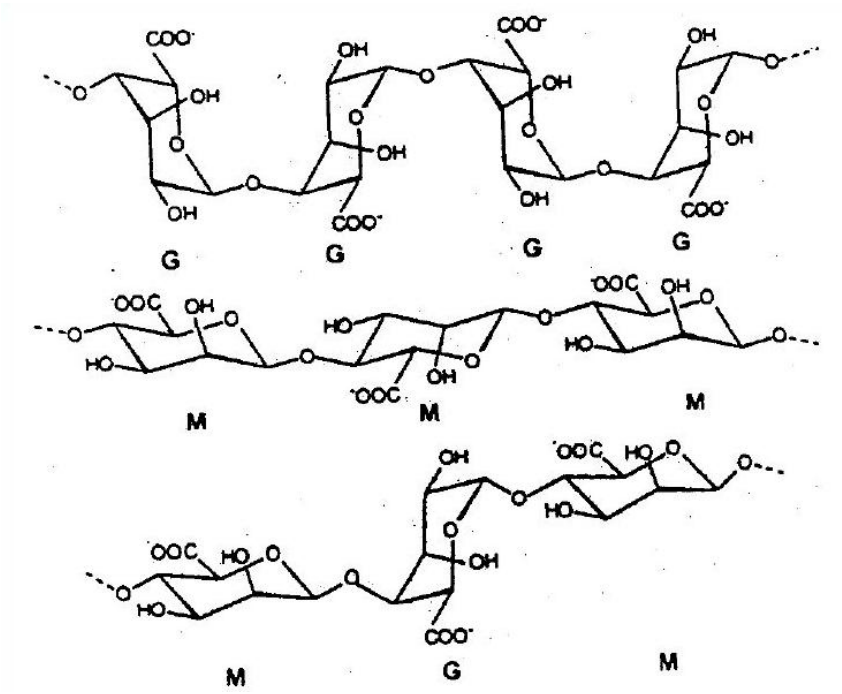


Figure 13

The physico-chemical properties of alginate have been found to be highly affected by the M/G ratio as well as by the structure of the alternating zones. The alginic acid can then be converted to a salt of which sodium alginate is the major form currently used. Alginates from different sources vary in their proportions of blocks. Hydration of alginic acid leads to the formation of a high-viscosity ‘‘acid gel’’ due to intermolecular binding. After gelation the water molecules are physically entrapped inside the alginate matrix, but are still free to migrate. This is of great importance in many applications (e.g., alginate gels for immobilization/encapsulation). The water-holding capacity of the gel is due to capillary forces. Heat-stable gels can develop at room temperature. Monovalent metal ions form soluble salts with alginate whereas divalent and multivalent cations (except Mg^{2+}) form gels or precipitates. The various cations show different affinity for alginate, and selective ion binding is the basis for the ability of alginate to form ionotropic hydrogels.[148] Alginates with a high content of guluronic acid blocks give gels of considerably higher strength compared to alginates rich in mannuronate, as the G residues exhibit a stronger affinity for divalent ions than the M residues (Figure 14). [149,150] Transmittancy, swelling, and viscoelasticity of alginate gel membranes are highly affected by the M/G ratio. [151,152] The calcium alginate gels are the most extensively studied. The ability of alginate to form two types of gel dependent on pH, i.e., an acid gel and an ionotropic gel, gives the polymer unique properties compared to neutral macromolecules. Alginic acid (or its sodium or calcium salt) is regarded as generally non-toxic and biocompatible.[153] These products are commercially available and over 200 different alginate grades, in addition to alginic acid and a number of corresponding salts, are manufactured. Alginates are widely used in the pharmaceutical, cosmetic, and food industry [154,155].

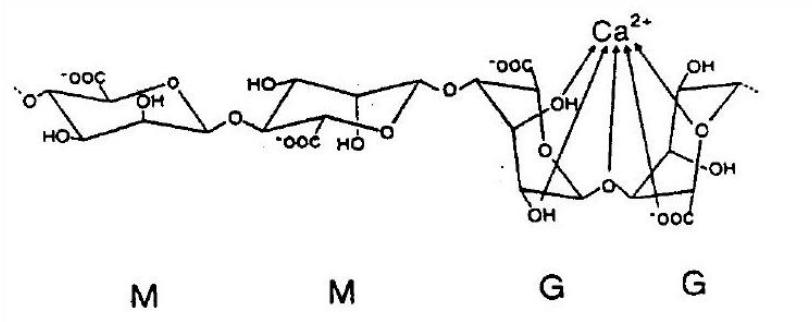


Figure 14

The term “dextran” was coined by Scheibler in 1874 when he determined that dextran was a carbohydrate, with a positive optical rotation, and with the empirical formula $(C_6H_{10}O_6)_n$. Dextrans can be defined as glucose homopolysaccharides that feature a substantial number of consecutive α-(1→6) linkages in their major chains, usually more than 50% of the total linkages. These α-D-glucans possess also side chains stemming from α-(1→2), α-(1→3), or α-(1→4) branch linkages (Figure 15).

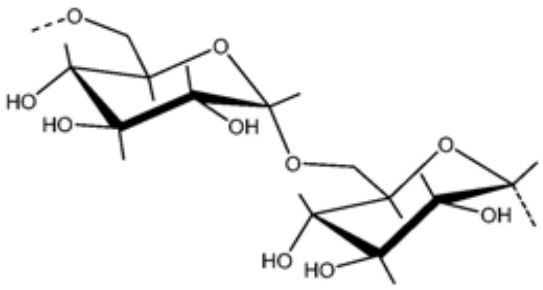


Figure 15

Dextran and its derivatives find various applications in the pharmaceutical field. [147] Dextran chemical hydrogels, containing methacrylate moieties in the side chain and obtained by means of irradiation of dextran derivatives, have been widely investigated because the photocross-linking reactions allows to avoid the usual disadvantages of the chemically cross-linked matrices.[156] Furthermore, glycidyl methacrylate dextrans (with different degree of substitution) were used for a radical polymerization in the presence of different radicalizing agents. [157,158] In the last few year, in situ polymerizable hydrogels are extensively investigated to implement new biomedical and pharmaceutical approaches,[159] because of their softness, high water content, and ease of manipulation, even if biocompatibility and bioelimination are important items that, in many cases, still need to be overcome.[160, 171] In this field, numerous polysaccharides can be very useful, as some of them possess hydrogel forming properties or can be easily derivatized to acquire such properties.[172] To modulate mechanical and delivery properties of hydrogels, a new feasible approach can be the development of interpenetrating polymer systems (IPN) or semi-interpenetrating polymer systems (semi-IPN). Hydrogels obtained by mixing two different polymeric systems can lead to new materials that can show completely different properties, with respect to the starting polymers, due to a synergistic effect. While much work has been performed on

synthetic IPNs, not many studies were carried out about the use of polysaccharides for such purposes. Casadei et al. recently obtained a novel polysaccharidic matrix based on calcium alginate (Ca(II)-Alg) hydrogeln and dextran methacrylate derivative (Dex-MA). The semi-interpenetrating polymer system (semi-IPN) obtained by a dispersion of Dex-MA chains into a Ca(II) hydrogel leads to a hydrogel with rheological properties quite different from those of Ca(II)-Alg; methacrylate derivatives of dextran chains dispersed into a Ca(II)-Alg hydrogel interact with the alginate hydrogel "egg-box" structure, thus remarkably modifying the gelling properties of alginate. [159]

Gellan gum is a bacterial exopolysaccharide commercially prepared by aerobic submerged fermentation of Sphingomonas elodea. Gellan gum is a linear tetrasaccharide built up by →4)-L-rhamnopyranosyl-(α-1→3)-D-glucopyranosyl-(β-1→4)-D-glucuronopyranosyl-(β1→4) D-glucopyranosyl-(β-1→ with O(2) L-glyceryl and O(6) acetyl substituents on the 3-linked glucose (Figure 16).

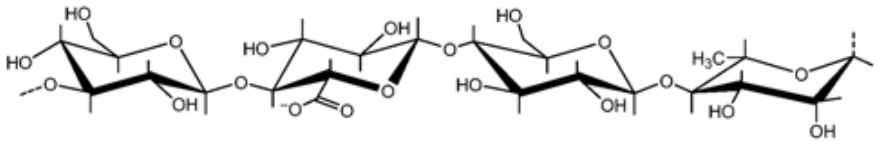


Figure 16

It consists of about 50,000 residues and it is normally de-esterified by alkali treatment before use. Gellan gum forms a 3-fold double helix from two left-handed chains with the acetate residues on the periphery, and glyceryl groups and hydrogen-bonds stabilizing the interchain associations. In the presence of counterions, this polymer is capable of forming gels that are particularly strong when formed with divalent cations. The degree of acylation also influences the strength of the resulting network. Indeed, when gellan is acylated it forms soft, elastic, transparent and flexible gels while de-acylation leads to hard, non-elastic and brittle gels. The gels are thermoreversible, with a melting temperature, Tm, at about 50 °C, depending on the concentration and presence of cations that, stabilizing the gel, increase the Tm value. Formation of gellan beads has also been recently experimented to evaluate the effect of various divalent cations on the encapsulation efficiency using a constant concentration of polymer and ionotropic medium.[173] It is well known that the gelling mechanism of gellan can be induced by cations and is temperature-dependent. In aqueous solution the gelation of gellan is accompanied by a two-step process which involves formation of double helices

from random coil chains (coil-tohelix transition) and an aggregation of pairs of double helices. The coil–helix transition is greatly affected by the electrostatic interaction with the cations present in the solution. Gellan forms gels in the presence of mono (Na^+ and K^+) and divalent (Ca^{2+} and $Mg^{2+)}$ cations but its affinity for the latter is much stronger than for the former

Preparation of alginate/gellan gum beads containing Au nanoparticles:

Gold nanoparticles stabilized by alginate/gellan beads were prepared dropping 10 ml of a 1% (w/v) solution of gellan gum and sodium alginate (1:1) into 100 ml of a $CaCl_2$ solution (0.24 M), at room temperature, using a syringe with a 0.7 mm diameter needle. Hydrogel beads were harden in the Ca (II) solution for 24 h, then filtered, washed with distilled water and soaked for 48 h in 50 ml of a $NaAuCl_4$ aqueous solution (5 mM) under magnetic stirring. After this time, the gel particles were recovered by filtration, washed with distilled water and added with 100 ml of a $NaBH_4$ (8 mM) for the reduction of Au(III) to Au metallic. The beads were then dried under supercritical CO_2 conditions (70°C and 200 mbar) and used without any further reduction or purification step. In Figure 17 were reported three SEM images that show the aspect of this new material at different magnification.

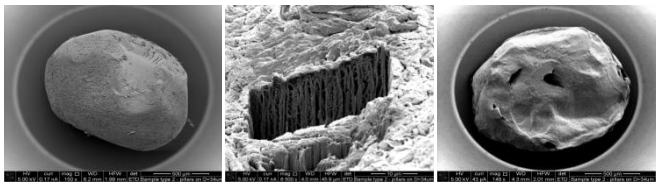
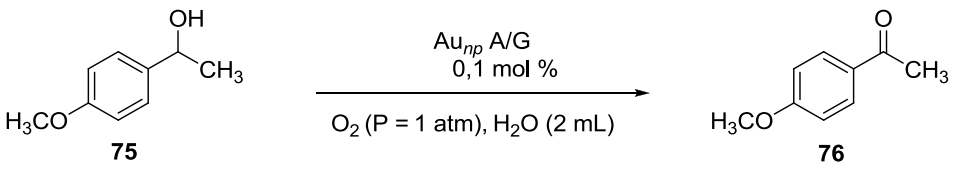


Figure 17

The oxidation of commercially available 1-(4-methoxy)phenyl ethanol **75** to the corresponding ketone **76** was used as model system. All the reaction was carried out in basic aqueous solution at 100 °C under O_2 atm 1.0 atm, with 0.1% of catalyst. The role played by the base on the outcome of the oxidation was carefully examined: the experimental results are showed in Table 9.



Scheme 52

Table 9 Oxidation of 1-(4-methoxy)phenyl ethanol catalyzed by gold nanoparticles of alginate gellan.[a]

Entry	Base	t (h)	Yield (%)[b]
1	K_2CO_3	24	90
2	K_2CO_3	24	76
3	K_2CO_3	24	87
4	K_2CO_3	24	96
5	K_2CO_3	24	84
6	K_2CO_3	24	81
7	K_2CO_3	-	50
8	$CaCO_3$	48	86
9	$CaCO_3$	48	82
10	$CaCO_3$	24	90
11	$CaCO_3$	40	86
12	$CaCO_3$-$CaCl_2$	48	84
13	$CaCO_3$-$Ca(OH)_2$	25	86
14	$Ca(OH)_2$	23	94
15	$Ca(OH)_2$	24	88
16	-	23	70
17	$Ca(OH)_2$	13	85
18	-	30	85
19	$CaCO_3$	24	-[c]
20	$CaCO_3$	24	-[d]

[a] Reactions conditions: 1.0 mmol 1-(4-methoxyphenyl)ethanol; 0.001 mmol Au nanoclusters; 2 mL H_2O; 100 °C.
[b] Yields refer to a single run.
[c] Reaction performed at T=70 °C
[d] Reaction carried out in presence of 0.0005 mmol of Au_{np}

The best results in terms of yield and reaction time were obtained using $Ca(OH)_2$ as base (Table 9, *entry 17*), even if in the presence of K_2CO_3 or $CaCO_3$ the oxidation proceeded in equally satisfactory yield (Table 9, *entries 1, 8, 12*). The recycle of the catalyst was carefully tested: in fact, several attempts were made changing the nature of the base, and the workup procedures but, in all the cases examined, the catalytic efficiency vanished. A likely explanation of these results may be that the electrostatic interactions that keep bonded the copolymer are weekened by the high ionic strength of the reaction medium and it results in the leaching of the metal nanoparticles. In order to overcome this problem, another type of gold nanoparticles was prepared using the dextran-gellan(methacrylate) copolymer (Dex-MA/gellan) as stabilizer. Dex-Ma/gellan is a more reticulated polymer that results from the methacrylate moiety polymerization that could be able to lower the metal leaching to the solution.

Preparation of DEX-MA/gellan gum beads containing Au nanoparticles:

Gold nanoparticles stabilized by Dex-MA/gellan beads were prepared dropping 10 ml of a 1% (w/v) solution of gellan gum and Dex-MA (1:1) into 100 ml of a $CaCl_2$ solution (0.24 M), at room temperature, using a syringe with a 0.7 mm diameter needle. Hydrogel beads were harden in the Ca (II) solution for 24 h, then 0.45 mmoles of APS and 0.25 mmoles of TEMED to promote Dex-MA polymerization. After the reaction, the beads are filtered, washed with distilled water, and then were soaked for 48 h in 50 mL of a $NaAuCl_4$ aqueous solution (5 mM) under magnetic stirring. After this time, the gel particles were recovered by filtration, washed with distilled water and then 100 ml of a $NaBH_4$ (8 mM) were added. The beads were then dried under supercritical CO_2 conditions (70°C and 200 bar) and used without any further reduction or purification step.

Three batch of nanoparticles were prepared and tested in the oxidation of 1-(4-methoxy)phenyl ethanol, as shown in Table 10. Best results were obtained using *t*-BuONa as base (Table 10, *entries* 1-4). The recycle experiments performed in the presence of *t*-BuONa (Table 10, *entries* 4, run 1 to 4) with batch 1 showed that the catalyst retains a good efficiency for three runs. However, the same experiment carried out with catalyst batch 1 and 2 showed a very poor reactivity and efficiency (Table 10, *entries* 5-6). These results revealed that at this stage of study the catalyst preparation is far to be optimized.

Table 10 Oxidation of 1-(4-methoxy)phenyl ethanol catalyzed by gold nanoparticles of dextran gellan methacrylate.[a]

Entry	base	t (h)	Yield (%) RUN 1	Yield (%) RUN 2	Yield (%) RUN 3	Yield (%) RUN 4
1[b]	-	25	(100)[c]			
2[b]	K_2CO_3	48	(100) [c]			
3[b]	$CaCO_3$	24	(100) [c]			
4[b]	$NaOBu^t$	23	83	70	72	50
5[d]	$NaOBu^t$	24	40	(100)[c]		
6[e]	$NaOBu^t$	24	(100)[c]			

[a] Reactions conditions: 1.0 mmol 1-(4-methoxyphenyl)ethanol; 0.001mmol Au_{nps}; 2 mL H_2O; 100 °C.
[b] *Batch 1* nanoparticles
[c] Recovered starting material; [d] *Batch 2* nanoparticles; [e] *Batch 3* nanoparticles.

In conclusion, new active gold nanoparticles stabilized by polysaccharides have been prepared and tested in the alcohols oxidation, obtaining good results in term of selectivity, yield and reaction time. However, other work is necessary to get gold nanoparticles able to be recycled several times whitout loss of catalytic activity.

4. Experimental section

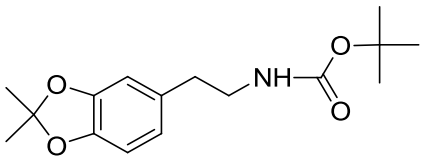
4.1. General information

Melting points were determined with a Büchi B-545 apparatus andare uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. When it was possible, starting materials were purified on axially compressed columns, packed with SiO2 25-40 μm, connected to a preparative pump for solvent delivery and to a refractive index detector, and eluting with *n*-hexane/EtOAc mixtures. ^{1}H NMR (400.13 MHz), ^{13}C NMR (100.6 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. Splitting patterns are designed as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or bs (broad singlet). Infrared (IR) spectra were recorded on a JASCO FT/IR-430 spectrophotometer. Mass spectra were determined with a QP2010 Gas Chromatograph Mass spectrometer (EI ion source) and a Thermo Finnigan LXQ spectrometer (ESI ion source).

4.2. Additional information and characterization data on the synthesized compounds.

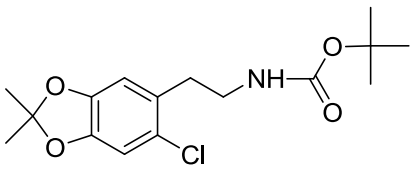
4.2.1. Additional information and characterization data of 5-aryl dopamine derivatives.

Typical procedure for the preparation of *tert*-butyl-2-(2,2-dimethylbenzo[d][1,3] dioxol-5-yl)ethylcarbammate: a flask equipped with a magnetic stirring bar was charged with *tert*-butyl-3,4-dihydroxyphenethylcarbamate (4 mmol, 1000 mg) and 2,2-dimethoxypropane (32 mmol, 3335 mg) dissolved in $CHCl_3$ (50 mL). The resultant solution was stirred at room temperature, under Nitrogen for 10 minutes before adding 4-methylbenzenesulfonic acid (0.80 mmol, 138.0 mg). The reaction mixture was stirred for 24 hours at 60°C. After this time, the reaction mixture was diluted with ethyl acetate and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 70/30 (v/v) *n*-hexane/AcOEt mixture to obtain 615 mg (50% yield) of *tert*-butyl-2-(2,2-dimethylbenzo[d][1,3] dioxol-5-yl)ethylcarbammate:



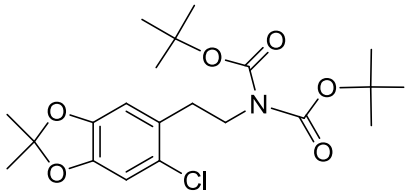
mp: 70.4-72.4 °C; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 6.68-6.60 (m, 3H), 4.58 (bs, 1H), 3.35-3.32 (m, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 1.68 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 155.9, 147.6, 146.0, 132.1, 121.0, 117.7, 108.9, 108.1, 79.2, 42.0, 36.0, 28.4, 25.9.

Typical procedure for the preparation of *tert*-butyl-2-(6-cloro-2,2-dimethylbenzo [d][1,3]dioxol-5-yl)ethylcarbammate: a flask equipped with a magnetic stirring bar was charged with *tert*-butyl-2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylcarbammate (2.91 mmol, 856 mg) and aluminium chloride (0.292 mmol, 40 mg) dissolved in CH_2Cl_2 (25 mL). The resultant solution was stirred at room temperature for 5 minutes before adding *N*-chlorosuccinimide (3.80 mmol, 507.0 mg). The reaction mixture was stirred for 4 hours at room temperature. After this time, the reaction mixture was diluted with CH_2Cl_2 and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture to obtain 780 mg (80% yield) of *tert*-butyl-2-(6-cloro-2,2-dimethylbenzo [d][1,3]dioxol-5-yl)ethylcarbammate:



mp: 85.3-87.4 °C; IR (KBr) 3372, 1689, 835 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 6.75 (s, 1H), 6.61 (s, 1H), 4.63 (bs, 1H), 3.36-3.34 (m, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 1.68 (s, 6H), 1.46 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 155.9, 146.8, 146.6, 128.9, 124.9, 119.0, 110.1, 109.6, 79.2, 40.5, 33.9, 28.4, 25.8.

Typical procedure for the preparation of *N,N*-di-*tert*-butil-dicarbonato-2-(6-cloro-2,2-dimethiybenzo[d][1,3]dioxol-5-yl)ethylamine: a Carousel Tube Reactor (Radley Discovery), equipped with a magnetic stirrer, was charged with *tert*-butyl-2-(6-cloro-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylcarbammate (1.93 mmol, 632 mg) and 4-dimethylaminopyridine (1.93 mmol, 235 mg) and anhydrous CH_3CN (15 mL). The resultant solution was stirred at room temperature under Nitrogen for 5 minutes before adding di-*tert*-butyldicarbonate (1.44 mmol, 315.0 mg). The reaction mixture was stirred for 1 hour at 80 °C before adding another amount of di-*tert*-butyldicarbonate (1.44 mmol, 315.0 mg). The reaction mixture was stirred for 5 hours at 80 °C. After this time, the reaction mixture was diluted with ethyl acetate and washed with HCl 2N, with and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture to obtain 760 mg (85% yield) of *N,N*-di-*tert*-butil-dicarbonato-2-(6-cloro-2,2-dimethiybenzo[d][1,3]dioxol-5-yl)ethylamine:

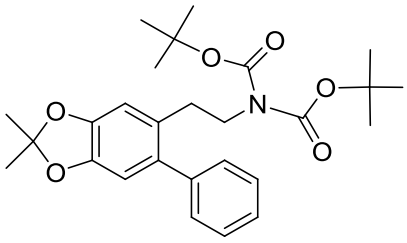


mp: 74,8-76.9 °C; IR (KBr) 1751, 1712 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 6.74 (s, 1H), 6.60 (s, 1H), 3.80 (t, *J* = 7.2 Hz, 2H), 2.92 (t, *J* = 7.2 Hz, 2H), 1.67 (s, 6H), 1.51 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.2, 146.8, 146.5, 128.8, 125.0, 118.9, 110.3, 109.5, 82.2, 46.1, 33.1, 28.0, 25.8.

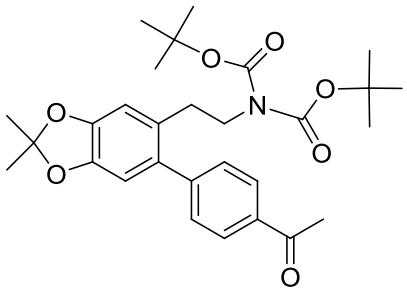
Typical procedure for the preparation of 5-aryl dopamine derivatives.

A Carousel Tube Reactor (Radley Discovery), equipped with a magnetic stirrer, was charged with $Pd_2(dba)_3$ (3.66 mg, 0.004 mmol), Sphos (3.28 mg, 0.008 mmol) and 1,4-dioxane (1.6 ml). After solubilization of the precatalyst system at room temperature under Nitrogen atmosphere, 5-chloro dopamine derivative **37** (85.58 mg, 0.2 mmol) was added to the mixture and, after 10 minutes, K_3PO_4 (127.2 mg, 0.6 mmol) and phenylboronic acid (76.5 mg, 0.47 mmol). The resulting mixture was stirred at 100 °C for 3 hours. After this time, the mixture was cooled, diluted with ethyl acetate, washed

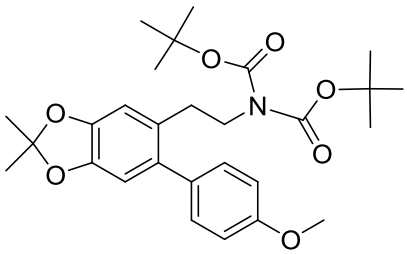
with a 0.1 N HCl solution and subsequently with a saturated NaCl solution. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, 30 g, n-hexane/AcOEt 80/20 v/v) to give 83.7 mg (90% yield) of following compound:



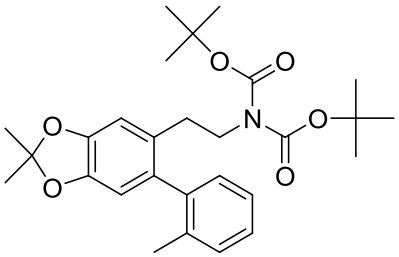
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-phenyl-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl) ethylamine**; mp: 98.4-100.5 °C; IR (KBr) 1745, 1695 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.40-7.30 (m, 5H), 6.73 (s, 1H), 6.62 (s, 1H), 3.70 (t, *J* = 7,6 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 1.71 (s, 6H), 1.43 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.3, 146.8, 145.7, 141.7, 135.1, 129.6, 129.0, 128.1, 126.7, 117.9, 110.0, 109.3, 82.0, 47.7, 32.1, 28.0, 25.9; Anal. Calcd. For: $C_{27}H_{35}NO_6$: C, 69.06; H, 7.51; N, 2.98; Found: C, 69.14; H, 7.52; N, 2.97.



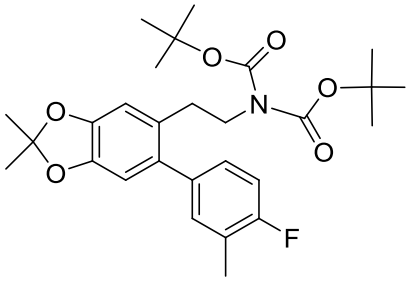
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(4-acethylphenyl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 122-124 °C; IR (KBr) 1752, 1716, 1675, 983, 869 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.72 (s, 1H), 6.58 (s, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.63 (s, 3H), 1.70 (s, 6H), 1.41 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 197.7, 152.3, 147.3, 146.8, 146.0, 135.5, 133.9, 129.9, 129.0, 128.3, 118.2, 109.6, 82.0, 47.5, 32.1, 28.0, 26.6, 25.9; Anal. Calcd. For: $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74; Found: C, 68.17; H, 7.30; N, 2.72.



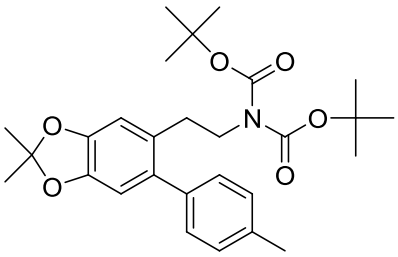
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(4-methoxyphenyl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 99.8-101.9 °C; IR (KBr) 1752, 1687, 981, 848 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8,4 Hz, 2H), 6.79 (s, 1H), 6.60 (s, 1H), 3.85 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 1.70 (s, 6H), 1.43 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 158.5, 152.3, 146.6, 145.7, 134.8, 134.1, 130.6, 129.1, 117.8, 113.6, 110.1, 109.3, 81.9, 55.2, 47.7, 32.2, 28.0, 25.9; Anal. Calcd. For: $C_{28}H_{37}NO_7$: C, 67.31; H, 7.46; N, 2.80; Found: C, 67.39; H, 7.44; N, 2.81.



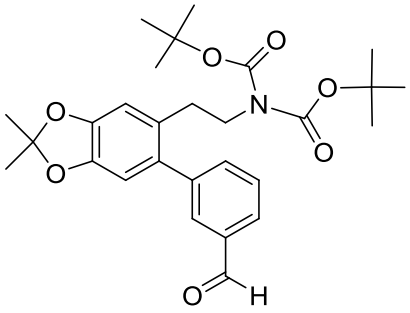
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-*o*-tolyl-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl) ethylamine;** mp: 79.5-81.6 °C; IR (KBr) 1735, 1698, cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.24-7.14 (m, 4H), 7.14 (s, 1H), 6.49 (s, 1H), 3.63 (t, *J* = 7.2 Hz, 2H), 2.63-2.60 (m, 1H), 2.51-2.48 (m, 1H), 2.09 (s, 3H), 1.71 (s, 3H), 1.41 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.2, 146.6, 145.6, 141.1, 136.3, 134.2, 130.1, 129.8, 129.2, 127.1, 125.6, 117.8, 109.5, 109.0, 81.9, 47.3, 32.1, 28.0, 25.9, 20.0. Anal. Calcd. For: $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90; Found: C, 69.62; H, 7.72; N, 2.91.



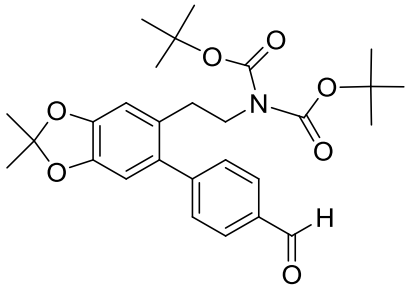
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(4-fluro-3-methylphenyl)-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)ethylamine;** mp: 109.1-111.2 °C; IR (KBr) 1743, 1698, cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.14-6.99 (m, 3H), 6.70 (s, 1H), 6.58 (s, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.70 (s, 6H), 1.43 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 160.5 (d, *J* = 24.5 Hz), 152.3, 146.8, 145.7, 137.3 (d, *J* = 4 Hz), 134.2, 132.6 (d, *J* = 5 Hz), 129.1, 128.3 (d, *J* = 7.8 Hz), 124.3 (d, *J* = 17.4 Hz), 117.9, 114.5 (d, *J* = 22.2 Hz), 110.0, 109.3, 82.0, 47.7, 32.1, 28.0, 25.9, 14.5 (d, *J* = 3.4 Hz); Anal. Calcd. For: $C_{28}H_{36}NO_6$: C, 67.05; H, 7.23; N, 2.79; Found: C, 67.14; H, 7.25; N, 2.80.



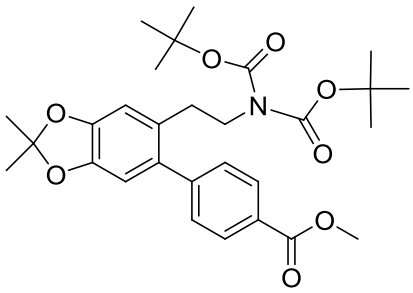
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(p-tolyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylamine;** mp: 84.6-86.7 °C; IR (KBr) 1739, 1697, 862 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.2 (s, 4H), 6.70 (s, 1H), 6.61 (s, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.39 (s, 3H), 1.71 (s, 6H), 1.43 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.3, 146.7, 145.7, 138.8, 136.2, 135.1, 129.4, 129.1, 128.8, 117.8, 110.0, 109.3, 81.9, 47.7, 32.2, 28.0, 25.9, 21.1; Anal. Calcd. For: $C_{28}H_{37}NO_6$: C, 69.54; H, 7.71; N, 2.90; Found: C, 69.62; H, 7.70; N, 2.92.



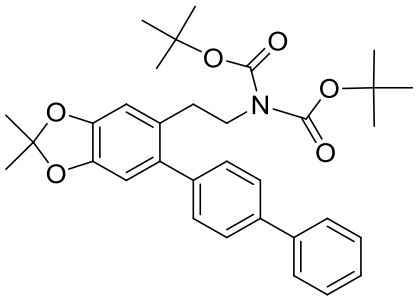
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(3-formylphenyl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 133.6-135.7 °C; IR (KBr) 1727, 1689, 862 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.10 (s, 1H), 7.88-7.84 (m, 2H), 7.61-7.57 (m, 2H), 6.74 (s, 1H), 6.62 (s, 1H), 3.70 (t, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 1.72 (s, 6H), 1.42 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 191.9, 152.3, 148.2, 147.4, 146.0, 134.9, 133.7, 130.4, 129.6, 129.1, 118.3, 109.7, 109.5, 82.1, 47.5, 32.1, 28.0, 25.9; Anal. Calcd. For: $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.81; Found: C, 67.67; H, 7.10; N, 2.82.



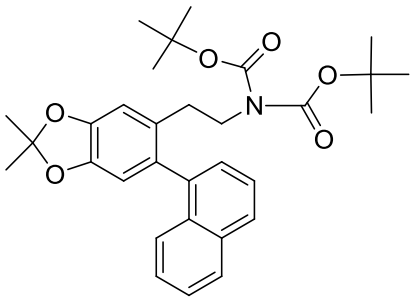
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(4-formylphenyl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 121-123 °C; IR (KBr) 1739, 1702, 862 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 10.06 (s, 1H), 7.92 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 6.73 (s, 1H), 6.60 (s, 1H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.76 (t, *J* = 7.2 Hz, 2H), 1.71 (s, 6H), 1.41 (s, 18H), ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 191.9, 152.3, 148.2, 147.4, 146.0, 134.9, 133.7, 130.4, 129.6, 129.1, 118.3, 109.7, 109.5, 82.1, 47.5, 32.1, 28.0, 25.9; Anal. Calcd. For: $C_{28}H_{35}NO_7$: C, 67.59; H, 7.09; N, 2.81; Found: C, 67.65; H, 7.10; N, 2.82.



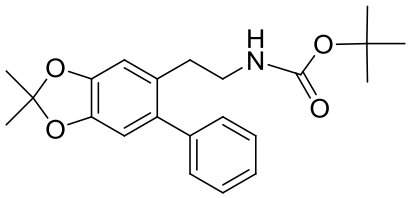
Methyl-4-[6-(2-(bis-(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3] dioxol-5-yl]benzoate; mp: 140.2-142.1 °C; IR (KBr) 1725, 1714, 1687, 858, 779 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.07 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 6.72 (s, 1H), 6.59 (s, 1H), 3.39 (s, 3H), 3.68 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 1.70 (s, 6H), 1.41 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 167.0, 152.3, 147.2, 146.6, 145.9, 134.0, 129.7, 129.5, 129.0, 128.5, 118.2, 109.61, 109.57, 82.1, 52.1, 47.5, 32.1, 28.0, 25.9; Anal. Calcd. For: $C_{29}H_{37}NO_8$: C C, 66.02; H, 7.07; N, 2.65; Found: C, 66.07; H, 7.05; N, 2.66.



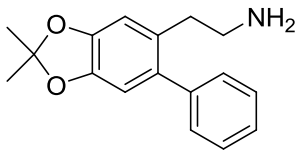
***N,N*-di-*tert*-butyl-dicarbonate-2-[6-(biphenyl-4-yl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 136.5-138.5 °C; IR (KBr) 1751, 1716, 1687, 840, 767 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.64-7.62 (m, 4H), 7.50-7.46 (m, 2H), 7.40-7.38 (m, 3H), 6.75 (s, 1H), 6.67 (s, 1H), 3.72 (t, *J* = 7.2 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 1.73 (s, 6H), 1.42 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.2, 146.9, 145.8, 140.9, 140.7, 139.5, 134.6, 130.0, 129.1, 128.8, 127.2, 127.0, 126.9, 118.0, 110.0, 109.4, 82.0, 47.7, 32.2, 28.0, 26.0; Anal. Calcd. For: $C_{33}H_{39}NO_6$: C, 72.64; H, 7.20; N, 2.57; Found: C, 72.72; H, 7.19; N, 2.58.



***N,N*-di-*tert*-butyl-dicarbonate-2-[6-(naphthalene-1-yl)-2,2-dimethylbenzo[*d*][1,3] dioxol-5-yl)ethylamine;** mp: 106-108 °C; IR (KBr) 1741, 1697, 840, 767 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.90-7.84 (m, 2H), 7.57-7,40 (m, 5H), 6,81 (s, 1H), 6,62 (s, 1H), 3,61-3,56 (m, 2H), 2,64-2,57 (m, 1H), 2,47-2,40 (m, 1H), 1,77 (s, 3H), 1,74 (s, 3H), 1,33 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152,2, 147,0, 145,7, 139,1, 133,6, 132,7, 132,6, 130,4, 128,1, 127,4, 126,2, 126,0, 125,7, 125,4, 117,9, 110,6, 109,2, 81,9, 47,6, 32,6, 27,9, 26,01, 26. Anal. Calcd. For: $C_{31}H_{37}NO_6$: C, 71.65; H, 7.18; N, 2.70; Found: C, 71.73; H, 7.19; N, 2.69.

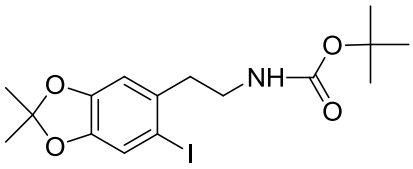


Tert-butyl-2-(6-phenyl-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethyilcarbammate; mp: 96-98 °C; IR (KBr) 1741, 1697, cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.42-7.26 (m, 5H), 6.70 (s, 1H), 6.62 (s, 1H), 4.39 (s, 1H), 3.17 (m, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.72 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 155.7, 146.9, 145.8, 141.7, 135.2, 129.0, 128.5, 127.4, 126.8, 125.7, 125.4, 118,0, 117.9, 110.1, 109.2, 81.9, 47.6, 32.6, 27.9, 26.01, 26.



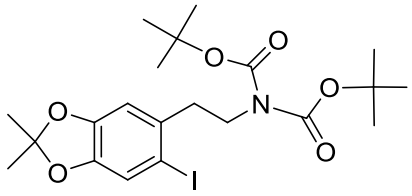
2-(2,2-dimethyl-6-phenylbenzo[d][1,3]dioxol-5-il)ethanamine; Wax; IR (KBr) 1741, 1697, cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.39-7.6 (m, 5H), 6.69 (s, 1H), 6.63 (s, 1H), 2.77-2.68 (m, 6H), 3.17 (m, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 1.72 (s, 6H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 146.8, 145.7, 141.7, 135.1, 129.4, 129.2, 128.2, 126.8, 118.0, 110.1, 109.2, 43.0, 36.0, 25.6.

Typical procedure for the preparation of *tert*-butyl-2-(6-iodo-2,2-dimethylbenzo [d][1,3]dioxol-5-yl)ethylcarbammate: a flask equipped with a magnetic stirring bar was charged with *tert*-butyl-2-(2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylcarbammate (2.91 mmol, 856 mg) and aluminium chloride (0.292 mmol, 40 mg) dissolved in CH_2Cl_2 (25 mL). The resultant solution was stirred at room temperature for 5 minutes before adding *N*-iodosuccinimide (3.80 mmol, 854 mg). The reaction mixture was stirred for 4 hours at room temperature. After this time, the reaction mixture was diluted with CH_2Cl_2 and washed with a satured $Na_2S_2O_3$ solution and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture to obtain 1054 mg (86% yield) of *tert*-butyl-2-(6-iodo-2,2-dimethylbenzo [d][1,3]dioxol-5-yl)ethylcarbammate:



^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.14 (s, 1H), 6.65 (s, 1H), 4.63 (bs, 1H), 3.33-3.31(m, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 1.66 (s, 6H), 1.45 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 155.9, 144.8, 144.1 135.0, 127.5, 122.9, 116.0, 88.2, 78.5, 39.0, 33.9, 28.4, 25.8.

Typical procedure for the preparation of *N,N*-di-*tert*-butil-dicarbonate-2-(6-iodo-2,2-dimethiybenzo[d][1,3]dioxol-5-yl)ethylamine: a Carousel Tube Reactor (Radley Discovery), equipped with a magnetic stirrer, was charged with *tert*-butyl-2-(6-iodo-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylcarbammate (1.93 mmol, 808 mg) and 4-dimethylaminopyridine (1.93 mmol, 235 mg) and anhydrous CH_3CN (15 mL). The resultant solution was stirred at room temperature under Nitrogen for 5 minutes before adding di-*tert*-butyldicarbonate (1.44 mmol, 315.0 mg). The reaction mixture was stirred for 1 hour at 80 °C before adding another amount of di-*tert*-butyldicarbonate (1.44 mmol, 315.0 mg). The reaction mixture was stirred for 5 hours at 80 °C. After this time, the reaction mixture was diluted with ethyl acetate and washed with HCl 2N, with and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 80/20 (v/v) *n*-hexane/AcOEt mixture to obtain 830 mg (86% yield) of *N,N*-di-*tert*-butil-dicarbonato-2-(6-iodo-2,2-dimethiybenzo[d][1,3]dioxol-5-yl)ethylamine:

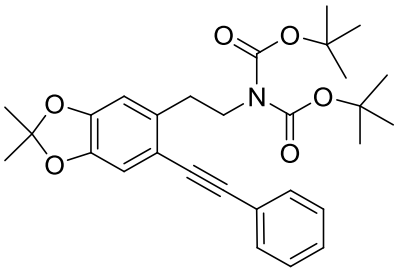


^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.14 (s, 1H), 6.65 (s, 1H), 3.79 (t, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H), 1.65 (s, 6H), 1.50 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.2, 148.3, 147.0, 134.4, 118.9, 118.2, 109.9, 87.3, 82.2, 46.2, 40.0, 28.1, 25.9.

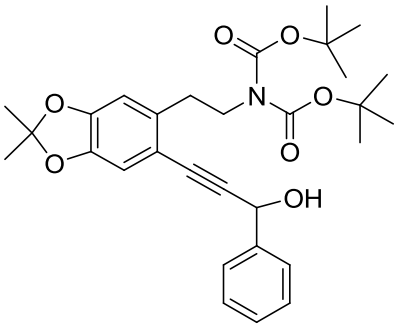
Typical procedure for the preparation of 5-alkynyl dopamine derivatives.

To a stirred solution of Pd_2dba_3 (3.7 mg, 0.004 mmol) and [(*t*-Bu)$_3$ Ph]BF_4 (4.3 mg, 0.015 mmol) in 1 ml of 1.4-dioxane, Cs_2CO_3 (69 mg, 0.212 mmol), 5-iododopamine derivative **45** (100 mg, 0.193 mmol), and phenylacetylene (39.4 mg, 0.386 mmol) were sequentially added at room temperature under Nitrogen atmosphere. The resulting mixture was stirred at 60 °C for 19 hours. After this time, the reaction mixture was diluted with Et_2O, washed with a saturated NaCl solution, dried over Na_2SO_4 and

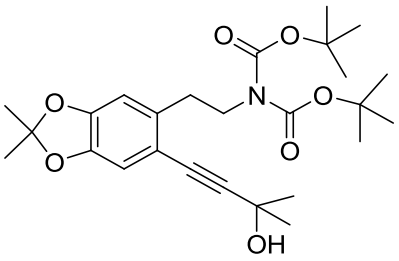
concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 [*n*-hexane/EtOAc 80/20 (v/v)] to afford 80.3 mg (85% yield) of following compound:



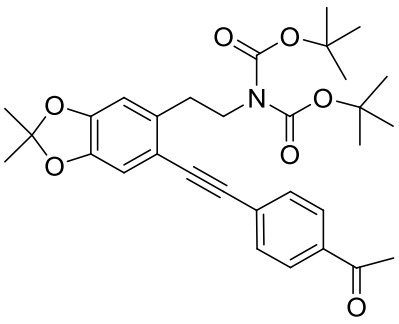
***N,N*-di-*tert*-butyl-dicarbonate-2-[(2,2-dimethyl-6(phenylethynyl)benzo[d][1,3] dioxol-5-yl)ethyl]ethylamine;** Orange wax; IR (KBr) 3409, 2972, 2209, 1596, 691 (cm^{-1}); ^{1}H NMR (CDCl3) 400 MHz δ 7.58 (d, *J* = 7.6 Hz 2H), 7.36 (m, 3H), 6.89 (s, 1H), 6.62 (s, 1H), 3.92 (t, *J* = 6.8 Hz, 2H), 3,10 (t, *J* = 6.8 2H), 1,68 (s, 6H), 1,47 (s, 18H); ^{13}C (100.6 MHz) (CDCL3) δ 152.4, 147.9, 145.9, 135.4, 131.5, 128.2, 127.9, 123.7, 118.5, 115.2, 111.4, 109.7, 91.4, 88.3, 82.0, 46.8, 34.0, 27.1, 25.8 Anal. Calcd. For: $C_{29}H_{35}NO_6$: C, 70.57; H, 7.15; N, 2.84; Found: C, 70.65; H, 7.14; N, 2.86.



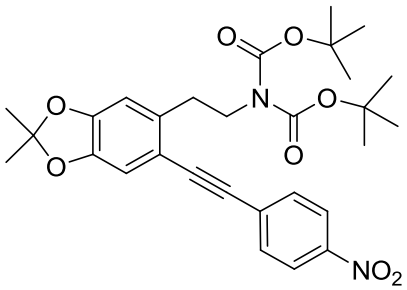
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(3-hydroxy-3-phenylprop-1-ynyl)2,2-dimethy lbenzo[d][1,3]dioxol-5-yl)ethylamine;** White solid; MP: 112-114 °C; IR (KBr) 3482, 1760, 1638, 1319, 1225, 886 cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 7.65 (d, *J* = 6.8 Hz, 2H), 7.39 (m,3H), 6.78 (s, 1H), 6.63 (s, 1H), 5.68 (brs, 1H), 4.53 (brs, 1H), 3.80 (t, *J* = 7.2 Hz, 3H), 3.00 (t, *J* = 7.2 Hz, 3H), 1.67 (brs, 6H), 1.52 (brs.18H); ^{13}C NMR (400MHz) (CDCl3) δ 152.9, 148.0, 145.9, 143, 135.2, 128.4, 127.8, 126.7, 118.5, 114.7, 111. 2, 109.7, 91.5, 84.5, 82.8, 64.8, 47.0, 34.3, 28.1, 25.8; Anal. Calcd. For: $C_{30}H_{37}NO_7$: C, 68.81; H, 7.12; N, 2.67; Found: C, 68.89; H, 7.13; N, 2.66.



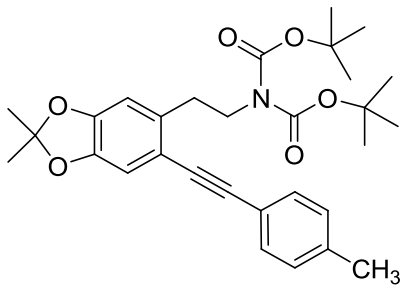
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(3-hydroxy-3-methylbut-1-ynyl)-2,2-dimethy lbenzo[d][1,3]dioxol-5-yl)ethylamine;** Beige solid; MP: 128-130 °C; IR (KBr) 3510, 2976, 2934, 1725, 1684, 1347, 1137, 860, 769 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 6.74 (s, 1H), 6.60 (s, 1H), 4.22 (brs, 1H), 3.76 (t, *J* = 8 Hz, 2H), 2.95 (t, *J* = 8 Hz), 1.66 (s, 1H), 1.62 (s, 6H), 1.54 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.9, 147.7, 145.9, 134.9, 118.4, 115.0, 111.1, 109.7, 96.5, 82.7, 80.0, 65.0, 46.1, 34.2, 31.3, 28.1, 25.8. Anal. Calcd. For: $C_{26}H_{37}NO_7$: C, 65.66; H, 7.84; N, 2.95; Found: C, 65.75; H, 7.83; N, 2.96.



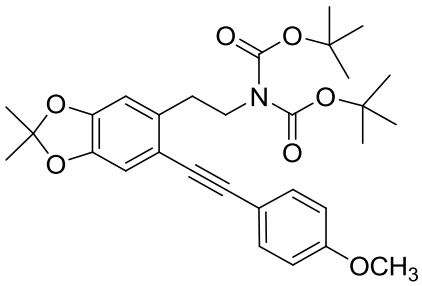
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-((4-acetylphenyl)ethynyl)-2,2-dimethylbenzo [d][1,3]dioxol-5-yl))ethylamine;** White solid; MP: 143-145 °C; IR (KBr) 3464, 2981, 2208, 1671, cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.93 (d, *J* = 8 Hz, 2H), 7.66 (d, *J* = 8 Hz, 2H), 6.89 (s, 1H), 6.64 (s, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 2.63 (s, 3H), 1.69 (s, 6H), 1.48 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.5, 148.4, 145.9, 135.9, 135.8, 131.6, 128.8, 128.2, 118.7, 114.5, 111.5, 109.8, 91.9, 82. 1, 46.8, 33.9, 28.0, 26.6, 25.9; Anal. Calcd. For: $C_{31}H_{37}NO_7$: C, 69.51; H, 6.96; N, 2.62; Found: C, 69.59; H, 6.97; N, 2.63.



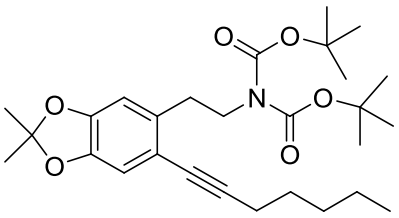
***N,N*-di-*tert*-butyl-dicarbonate-2-(2,2-dimethyl-6-((4-nitrophenyl)ethynyl)benzo [d][1,3]dioxol-5-yl)ethylamine;** Yellow solid; MP: 158-160°C; IR (KBr) 2984, 2210, 1686, 1343, 981 cm^{-1}; ^{1}H NMR (400MHz) ($CDCl_3$) δ 8.20 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 8 Hz, 2H), 6.88 (s, 1H), 6.66 (s, 1H), 3.85 (m, 2H), 3.08 (m, 2H), 1.69 (s, 6H), 1.49 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.6, 148.9, 146.6, 146.1, 136.3, 132.1, 130.9, 123.5, 118.9, 114.0, 111.5, 109.9, 94.0, 89.8, 82.2, 46.9, 34.0, 28.0, 25.9; Anal. Calcd. For: $C_{29}H_{34}N_2O_8$: C, 64.67; H, 6.36; N, 5.20; Found: C, 64.75; H, 6.35; N, 5.21.



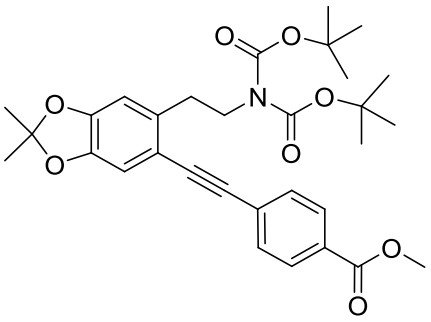
***N,N*-di-*tert*-butyl-dicarbonate-2-(2,2-dimethyl-6-(p-tolylethynyl)benzo[d][1,3] dioxol-5-yl)ethylamine;** Brown solid; MP: 108-110 °C; IR (KBr) 3465, 2979, 1730, 1638 cm^{-1}; ^{1}H NMR (400MHz) ($CDCl_3$) δ 7.45 (d, *J* = 8 Hz, 2H), 7.15 (d, *J* = 8 Hz, 2H), 6.88 (s, 1H), 6.60 (s, 1H), 3.91 (t, *J* = 6.8 Hz, 2H) 3.07 (t, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 1.67 (s, 6H), 1.47 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 152.3, 147.7, 145.8, 138.0, 131.4, 129.0, 120.6, 118.4, 115.4, 111.3, 109.7, 91.5, 87.5, 82.0, 46.7, 34.0, 28.0, 25.9, 21.5; Anal. Calcd. For: $C_{30}H_{37}NO_6$: C, 70.98; H, 7.35; N, 2.76; Found: C, 71.06; H, 7.34; N, 2.77.



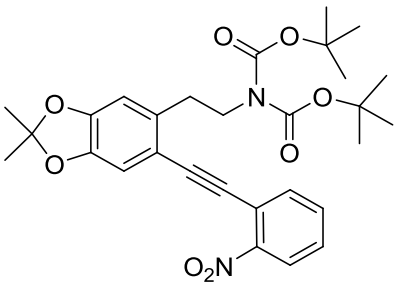
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-((4-methoxyphenyl)ethynyl)-2,2-dimethylbenzo [d][1,3]dioxol-5-yl)ethylamine;** Brown solid; MP: 91.3-93.4 °C; IR (KBr) 2980, 1727, 1604, 1230, 1134 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.50 (d, *J* = 8 Hz), 6.88-6.86 (m, 3H), 6.60 (s, 1H), 3.91 (t, *J* = 6.8 Hz, 2H), 3.84 (s, 3H), 3.07 (t, *J* = 6.8 Hz, 2H), 1.67 (s, 6H), 1.47 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 159.4, 152.4, 147.6, 145.9, 135.0, 133.0, 118.4, 116.0, 115.5, 113.9, 112.1, 111.3, 91.3, 86.8 , 82.0, 55.3, 46.8, 34.0, 28.0, 25.8; Anal. Calcd. For: $C_{30}H_{37}NO_7$: C, 68.81; H, 7.12; N, 2.67; Found: C, 68.89; H, 7.13; N, 2.68.



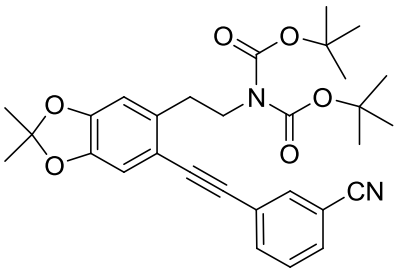
***N,N*-di-*tert*-butyl-dicarbonate-2-(6-(hept-1-ynyl)-2,2-dimethylbenzo[d][1,3]dioxol-5-yl)ethylamine;** Oil; IR (Neat) 2978, 2932, 1747, 1697, 859 cm^{-1}; ^{1}H NMR (400MHz) (CDCl3) δ 6.75 (s, 1H), 6.53 (s, 1H), 3.84 (t, *J* = 6.8 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 1.64-1.60 (m, 9H), 1.53-1.48 (m, 21H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 152.3, 147.1, 145.7, 134.7, 118.1, 116.1, 111.5, 109.5, 92.3, 81.9, 79.0, 46.6, 33.9, 31.2, 28.6, 28.0,, 25.8, 22.2, 19.1, 14.0; Anal. Calcd. For: $C_{28}H_{41}NO_6$: C, 68.97; H, 8.47; N, 2.87; Found: C, 69.06; H, 8.46; N, 2.88.



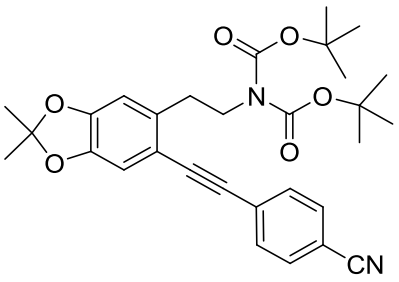
Methyl-4-((6-(2-(bis(tert-butoxycarbonyl)amino)ethyl)-2,2-dimethylbenzo[d][1,3] dioxol-5-yl)ethynyl)benzoate; White solid; MP: 119-120 °C; IR (KBr) 2977, 2215, 1710, 979 cm^{-1};^{1}H NMR (400MHz) ($CDCl_3$) δ 8.01 (d, *J* = 8.4Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 6.88 (s, 1H), 6.64 (s, 1H), 3.94 (s, 1H), 3.89 (t, *J* = 7.6 Hz, 2H) 3.09 (t, *J* = 7.6 Hz, 2H) 1.68 (s, 6H), 1.48 (s, 18H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 166.7, 152.4, 148.4, 135.8, 131.4, 129.4, 129.0, 128.6, 118.7, 114. 6, 111.5, 109.8, 91.5, 90.7, 82.1, 52.2, 46.8, 34.0, 28.0, 25.9; Anal. Calcd. For: $C_{31}H_{37}NO_8$: C, 67.50; H, 6.76; N, 2.54; Found: C, 67.59; H, 6.77; N, 2.55.



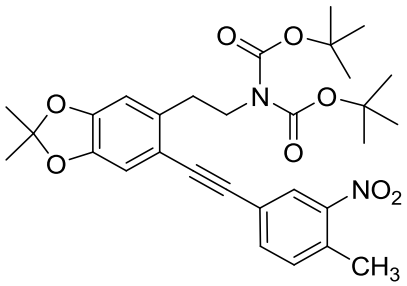
N,N-di-tert-butyl-dicarbonate-2-(2,2-dimethyl-6-((2-nitrophenyl)ethynyl)benzo [d][1,3]dioxol-5-yl)ethylamine; Orange solid; MP: 102.1-103.2 °C; IR (KBr) 2985, 2209, 1686 cm^{-1}; ^{1}H NMR (400MHz) ($CDCl_3$) δ 8.09 (d, *J* = 8 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.58 (t, *J* = 8 Hz, 1H), 7.44 (t, *J* = 8 Hz, 1H), 6.95 (s, 1H), 6.60 (s, 1H) 3.94 (t, *J* = 6.8 Hz, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 1.67 (s, 6H), 1.45 (s, 18H); ^{13}C NMR 100.6 MHz) (CDCl3) δ 152.4, 148.9, 148.8, 146.0, 136.8, 134.8, 132.7, 128.0, 124.7, 119.4, 118.8, 114.9. 110.0, 96.6, 87.1, 82.0, 46.8, 33.9, 27.9, 25.9; Anal. Calcd. For: $C_{29}H_{34}N_2O_8$: C, 64.67; H, 6.36; N, 5.20; Found: C, 64.76; H, 6.37; N, 5.22.



***N,N*-di-*tert*-butyl-dicarbonate-2-(2,2-dimethyl-6-((3-cianophenyl)ethynyl)benzo [d][1,3]dioxol-5-yl)ethylamine;** White solid; MP: 125-127 °C; IR (KBr) 2981, 2227, 2208,1131 cm^{-1}; ^{1}H NMR (400MHz) (CDCl3) δ 7.98 (s, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.45 (t, *J* = 8 Hz, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 3.86 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 1.69 (s, 6H) 1.51 (s, 18H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 152.6, 148.5, 146.0, 135.9, 135.6, 134.9, 130.9, 129.0, 125.4, 118.8, 118.2, 114.2, 112.7, 111.4, 109.9, 90.7, 89.0, 82.2, 47.0, 34.0, 28.1, 25.9; Anal. Calcd. For: $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40; Found: C, 69.57; H, 6.60; N, 5.41.



***N,N*-di-*tert*-butyl-dicarbonate-2-(2,2-dimethyl-6-((4-cianophenyl)ethynyl)benzo [d][1,3] dioxol-5-yl)ethylamine;** Pale yellow solid; MP: 187-189 °C; IR (KBr) 2982, 2212, 1725, 1601 cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 7.70-7.61 (m, 4H), 6.88 (s, 1H), 6.65 (s, 1H), 3.87 (t, *J* = 7.6 Hz, 2H) 3.07 (t, *J* = 7.6 Hz), 1.69 (s, 6H), 1.49 (s, 18H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 152.5, 148.7, 146.0, 136.1, 132.0, 131.9, 128.8, 118.8, 118.7, 114.1, 111.4, 110.8, 109.9, 92.9, 89.9, 82.2, 46.9, 34.0, 28.0, 25.9; Anal. Calcd. For: $C_{30}H_{34}N_2O_6$: C, 69.48; H, 6.61; N, 5.40; Found: C, 69.57; H, 6.62; N, 5.42.



***N,N*-di-*tert*-butyl-dicarbonate-2-(2,2-dimethyl-6-((4-methyl-3-nitrophenyl)ethynyl) benzo[d][1,3]dioxol-5-yl)ethylamine;** White solid; MP: 115-117 °C; IR (KBr) 3449, 2983, 1730, 1136 cm^{-1}; ^{1}H NMR (400MHz) (CDCl3) δ 8.20 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 6.87 (s, 1H) 6.64, (s, 1H), 3.87 (t, *J* = 8 Hz, 2H) 3.06 (t, *J* = 8 Hz, 2H), 2.62 (s, 3H), 1.69 (s, 6H), 1.49 (s, 18H); ^{13}C NMR (100.6MHz) (CDCl3) δ 152.5, 149.2, 148.4, 146.0, 135.8, 135.6, 132.8, 132.6, 127.2, 123.0, 118.7, 114.3, 111.4, 109.8, 90.1, 88.9, 82.2, 46.8, 34.0, 28.0, 25.9, 20; Anal. Calcd. For: $C_{30}H_{34}N_2O_6$: C, 65.20; H, 6.57; N, 5.07; Found: C, 65.29; H, 6.56; N, 5.08.

4.2.2. Additional information and characterization data on 2-amino ketones.

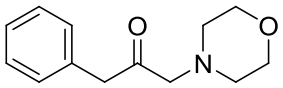
General information: Ethyl propargyl carbonates were prepared via Sonogashira cross-coupling of aryl iodides with propargyl alcohols. The isolated cross-coupling products were treated with ethyl chlorocarbonate to give the propargylic esters in 70-98% overall yield.

Typical procedure for the preparation of 3-*m*-tolylprop-2-yn-1-ol: a flask equipped with a magnetic stirring bar was charged with $PdCl_2(PPh_3)_2$ (0.017 mmol, 12.0 mg) and CuI (0.017 mmol, 3.2 mg) dissolved in diisopropylamine (1.8 mL) and *N*,*N*-dimethylformamide (0.9 mL). The resultant solution was stirred under Nitrogen at room temperature for 10 minutes before adding 3-iodotoluene (1.7 mmol, 372.8 mg) in *N*-ethyl-*N*-diisopropylamine (1.2 mL) and 2-propyn-1-ol (2.05 mmol, 115.0 mg). The reaction mixture was stirred for 3 hours at room temperature. After this time, the reaction mixture was diluited with Et_2O and washed with HCl 2N, with a saturated NH_4Cl solution and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a 73/27 (v/v) n-hexane/AcOEt mixture to obtain 211.0 mg (85% yield) of 3-*m*-tolylprop-2-yn-1-ol.

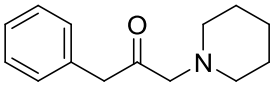
Typical procedure for the preparation of ethyl 3-*m*-tolylprop-2-ynyl carbonate: a flask equipped with a magnetic stirring bar was charged with 3-*m*-tolylprop-2-yn-1-ol (1.46 mmol, 218.8 mg) dissolved in CH_2Cl_2 (3 mL) and 4-(*N*,*N*-dimethylamino)pyridine (2.19 mmol, 267.6 mg). The resultant solution was stirred at -30°C for 10 minutes before adding ethyl chloroformate (1.75 mmol, 189.0 mg). The reaction mixture was stirred for 30 minutes at -30°C and then for an hour at 0°C. After this time, the reaction mixture was diluted with Et_2O and washed with HCl 2N and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 312mg (98% yield) of 3-*m*-tolylprop-2-ynyl carbonate.

^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.30-7.27 (m, 2 H), 7.24-7.20 (m, 1 H), 7.17-7.15 (m, 1 H), 4.97 (s, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 2.34 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 154.7, 138.0, 132.5, 129.8, 129.0, 128.2, 121.9, 87.3, 82.1, 64.5, 56.1, 21.2, 14.3;

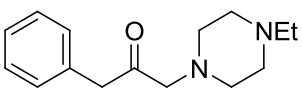
Typical procedure for the preparation of 1-amino-3-arylpropan-2-ones: a Carousel Tube Reaction (Radley Discovery) was charged with Pd_2dba_3 (8.0 mg, 0.087 mmol), dppf (9.7 mg, 0.0175 mmol) and anhydrous THF (1 mL). The solution was stirred under Nitrogen at room temperature for 10 minutes before adding ethyl 3-phenylprop-2-ynyl carbonate (71.4 mg, 0.350 mmol) dissolved in anhydrous THF (1 mL) and morpholine (91.45mg, 1.05 mmol). The reaction mixture was warmed at 80°C and stirred for 3 hours. After cooling, the volatile materials were evaporated at reduced pressure and the residue was purified by chromatography on neutral aluminum oxide (Brockmann 1) to afford 58.2 mg (76% yield) of the following compound:



1-morpholino-3-phenylpropan-2-one: Oil; IR (Neat) 3060, 3028, 2960, 2922, 2856, 1714, 1452, 1385 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.36-7.24 (m, 5 H), 3.76-3.74 (m, 6 H), 3.23 (s, 2 H), 2.47-2.46 (m, 4 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.8, 134.0, 129.4, 128.8, 127.1, 67.0, 66.8, 53.7, 47.8; Anal. Calcd. For: $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; Found: C, 71.13; H, 7.83.

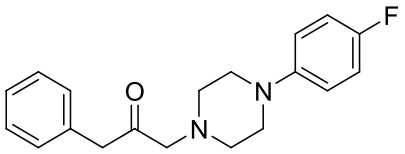


1-phenyl-3-(piperidin-1-yl)propan-2-one: oil; IR (Neat) 3060, 3028, 2935, 2854, 2804, 1714, 1597, 1574, 1454, 1385 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.35-7.32 (m, 2 H), 7.28-7.25 (m, 3 H), 3.78 (s, 2 H), 3.17 (s, 2 H), 2.40-2.39 (m, 4 H), 1.66-1.61 (m, 4 H), 1.46-1.45 (m, 2 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 207.0, 134.3, 129.4, 128.6, 126.9, 67.7, 54.7, 47.5, 25.8, 23.8; Anal. Calcd. For: $C_{14}H_{19}NO$: C, 77.38; H, 8.81; Found: C, 77.44; H, 8.78.

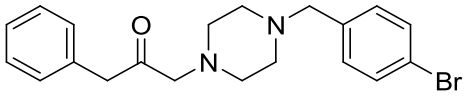


1-(4-ethylpiperazin-1-yl)-3-phenylpropan-2-one: oil; IR (Neat) 3060, 3028, 2970, 2933, 2812, 1720, 1454, 1385 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.32-7.21 (m, 5 H),

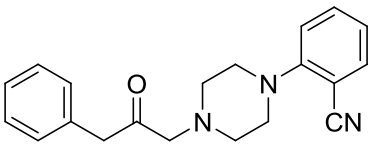
3.73 (s, 2 H), 3.20 (s, 2 H), 2.50 (m, 8 H), 2.42 (q, J = 7.2 Hz, 2 H), 1.07 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$): δ 206.2, 134.1, 129.4, 128.7, 127.0, 66.8, 53.4, 52.6, 52.3, 47.7, 12.0; Anal. Calcd. For: $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; Found: C, 73.35; H, 9.02.



1-(4-(4-fluorophenyl)piperazin-1-yl)-3-phenylpropan-2-one: Oil; IR (Neat) 3060, 3030, 2931, 2821, 1722, 1510, 1454, 1385, 1232 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.37-7.26 (m, 5 H), 7.00-6.96 (m, 2 H), 6.90-6.87 (m, 2 H), 3.79 (s, 2 H), 3.30 (s, 2 H), 3.18-3.16 (m, 4 H), 2.65-2.63 (m, 4 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.9, 157.2 (d, J_{CF} = 237.4 Hz), 147.9 (d, J_{CF} = 2.1 Hz), 134.0, 129.4, 128.7, 127.1, 117.9 (d, J_{CF} = 7.6 Hz), 115.5 (d, J_{CF} = 21.9 Hz), 66.6, 53.3, 50.0, 47.8; ^{19}F NMR {H} (376.5 MHz) ($CDCl_3$): δ -124.3; Anal. Calcd. For: $C_{19}H_{21}FN_2O$: C, 73.05; H, 6.78; Found: C, 73.06; H, 6.77.

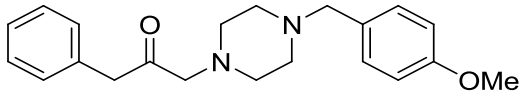


1-(4-(4-bromobenzyl)piperazin-1-yl)-3-phenylpropan-2-one: oil; IR (Neat) 3060, 3028, 2935, 2812, 1720, 1487, 1454, 1011 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 2 H), 7.34-7.31 (m, 2 H), 7.28-7.19 (m, 5 H), 3.75 (s, 2 H), 3.46 (s, 2 H), 3.22 (s, 2 H), 2.49 (bs, 8 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.2, 137.3, 134.1, 131.4, 130.8, 129.5, 128.7, 127.1, 120.9, 66.8, 62.2, 53.4, 52.9, 47.7; Anal. Calcd. for $C_{20}H_{23}BrN_2O$: C, 62.02; H, 5.99; Found: C, 62.15; H, 6.01.

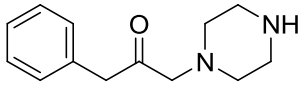


2-(4-(2-oxo-3-phenylpropyl)piperazin-1-yl)benzonitrile: oil; IR (Neat) 3062, 3030, 2916, 2825, 2220, 1716, 1595, 1489, 1448, 1383, 1230 cm^{-1}; ^{1}H NMR (400 MHz)

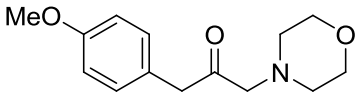
($CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.36-7.25 (m, 5 H), 7.03-7.00 (m, 2 H), 3.77 (s, 2 H), 3.33 (s, 2 H), 3.28-3.26 (m, 4 H), 2.70-2.67 (m, 4 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.6, 155.6, 134.3, 133.9, 133.8, 129.4, 128.8, 127.1, 121.9, 118.7, 118.4, 106.1, 66.5, 53.3, 51.3, 47.8; Anal. Calcd. For: $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; Found: C, 75.26; H, 6.64.



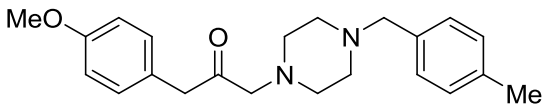
1-(4-(4-methoxybenzyl)piperazin-1-yl)-3-phenylpropan-2-one: oil; IR (Neat) 3060, 3030, 2933, 2810, 1720, 1612, 1512, 1454, 1246 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.35-7.23 (m, 7 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 3.81 (s, 3 H), 3.75 (s, 2 H), 3.47 (s, 2 H), 3.21 (s, 2 H), 2.50 (bs, 8 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.3, 158.8, 134.2, 130.4, 130.1, 129.5, 128.7, 127.0, 113.6, 66.8, 62.4, 55.3, 53.4, 52.8, 47.7; Anal. Calcd. For: $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; Found: C, 74.42; H, 7.71.



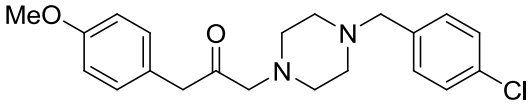
1-phenyl-3-(piperazin-1-yl)propan-2-one: Oil; IR (Neat) 3060, 3028, 2815, 1716, 1496, 1455, 1270, 1008, 732, 701 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.33-7.22(m, 5 H), 3.75 (s, 2 H), 3.17 (s, 2 H), 2.90 (bs, 4 H), 2.41 (bs, 4 H), 2.04 (bs, 1 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.3, 134.1, 129.4, 128.6, 127.0, 67.3, 54.5, 47.6, 45.8; Anal. Calcd. for C, 71.53; H, 8.31; Found: C, 71.43; H, 8.30.



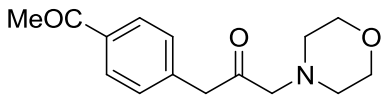
1-(4-methoxyphenyl)-3-morpholinopropan-2-one: oil; IR (Neat) 2918, 2852, 1722, 1610, 1512, 1454, 1248, 1117 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 3.80 (s, 3 H), 3.75-3.73 (m, 4 H), 3.68 (s, 2 H), 3.21 (s, 2 H), 2.47-2.45 (m, 4 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.1, 158.7, 130.4, 125.9, 114.2, 66.80, 66.77, 55.2, 53.6, 46.9; Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; Found: C, 67.57; H, 7.70.



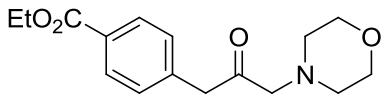
1-(4-methoxyphenyl)-3-(4-(4-methylbenzyl)piperazin-1-yl)propan-2-one: Wax; IR (KBr) 2933, 2810, 1716, 1510, 1246 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.21 (d, *J* = 7.7 Hz, 2 H), 7.17-7.13 (m, 4 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 3.81 (s, 3 H), 3.68 (s, 2 H), 3.51 (s, 2 H), 3.20 (s, 2 H), 2.52-2.50 (m, 8 H), 2.35 (s, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.6, 158.7, 136.7, 134.7, 130.4, 129.3, 128.9, 126.2, 114.2, 66.6, 62.7, 55.3, 53.3, 52.8, 46.8, 21.1; Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; Found: C, 74.81; H, 7.99.



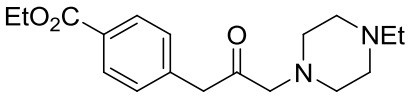
1-(4-(4-chlorobenzyl)piperazin-1-yl)-3-(4-methoxyphenyl) propan-2-one: oil; IR (Neat) 2935, 2812, 1720, 1610, 1512, 1456, 1248 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.30-7.25 (m, 4 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.68 (s, 2 H), 3.49 (s, 2 H), 3.21 (s, 2 H), 2.50 (bs, 8 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 206.5, 158.7, 136.7, 132.8, 130.4, 128.4, 126.1, 114.2, 66.6, 62.2, 55.3, 53.3, 52.9, 46.8; Anal. Calcd. for $C_{21}H_{25}ClN_2O_2$: C, 67.64; H, 6.76; Found: C, 67.73; H, 6.77.



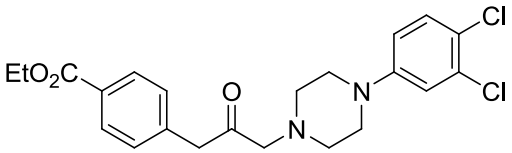
1-(4-acetylphenyl)-3-morpholinopropan-2-one: oil; IR (Neat) 2922, 2856, 1724, 1680, 1606, 1452, 1385, 1269, 1115 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.83 (s, 2 H), 3.73-3.71 (m, 4 H), 3.21 (s, 2 H), 2.58 (s, 3 H), 2.47-2.44 (m, 4 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 204.9, 197.5, 139.3, 136.0, 129.7, 128.7, 67.4, 66.7, 53.7, 47.3, 26.5; Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; Found: C, 68.85; H, 7.33.



ethyl 4-(3-morpholino-2-oxopropyl)benzoate: oil; IR (Neat) 2978, 2925, 2856, 1712, 1610, 1448, 1385, 1275 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 3.80 (s, 2 H), 3.72-3.70 (m, 4 H), 3.19 (s, 2 H), 2.45-2.42 (m, 4 H), 1.37 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.0, 166.3, 139.0, 129.9, 129.5, 129.4, 67.3, 66.8, 61.0, 53.7, 47.5, 14.3; Anal. Calcd. for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; Found: C, 65.59; H, 7.30.

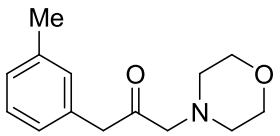


ethyl 4-(3-(4-ethylpiperazin-1-yl)-2-oxopropyl)benzoate: oil; IR (Neat) 2974, 2931, 2816, 1716, 1452, 1385, 1277, 1105 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 3.83 (s, 2 H), 3.22 (s, 2 H), 2.54 (bs, 8 H), 2.46 (q, *J* = 7.2 Hz, 2 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.11 (t,*J* = 7.1 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.5, 166.3, 139.2, 129.8, 129.5, 129.3, 67.1, 60.9, 53.4, 52.5, 52.2, 47.3, 14.3, 11.9; Anal. Calcd. for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; Found: C, 67.81; H, 8.21.



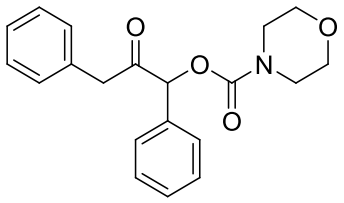
ethyl 4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxopropyl)benzoate: oil; IR (Neat) 2979, 2933, 2827, 1714, 1593, 1483, 1452, 1385, 1277 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.9 Hz, 1 H), 6.93 (d, *J* = 2.7 Hz, 1 H), 6.71 (dd, J^1 = 8.9 Hz, J^2 = 2.7 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.84 (s, 2 H), 3.28 (s, 2 H), 3.21-3.19 (m, 4 H), 2.62-2.59 (m, 4 H), 1.40 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.0, 166.3, 150.5, 139.0, 132.8,

130.5, 129.9, 129.5, 122.3, 117.3, 115.4, 66.8, 61.0, 53.0, 48.5, 47.5, 14.4; Anal. Calcd. for $C_{22}H_{24}Cl_2N_2O_3$: C, 60.70; H, 5.56; Found: C, 60.81; H, 5.57.



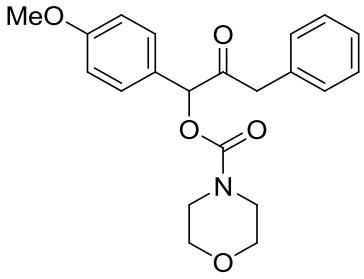
1-morpholino-3-m-tolylpropan-2-one: oil; IR (Neat) 2958, 2920, 2854, 2812, 1720, 1606, 1452, 1385, 1117 cm^{-1}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.22 (t, *J* = 7.5 Hz, 1 H), 7.10-7.03 (m, 3 H), 3.75-3.73 (m, 4 H), 3.71 (s, 2 H), 3.22 (s, 2 H), 2.47-2.45 (m, 4 H), 2.35 (s, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 205.9, 138.4, 133.9, 130.2, 128.7, 127.9, 126.4, 66.9, 66.8, 53.7, 47.8, 21.4; Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; Found: C, 72.19; H, 8.24.

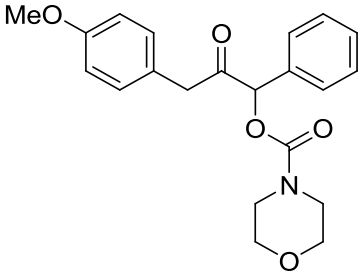
Typical procedure for the preparation of 2-oxo-1,3-diphenylpropylamino-4-carboxylates : a Carousel Tube Reaction (Radley Discovery) was charged with Pd_2dba_3 (7.8 mg, 0.0085 mmol), dppf (9.4 mg, 0.0170 mmol) and anhydrous THF (1 ml). The resultant solution was stirred under Nitrogen at room temperature for 10 minutes before adding 1,3-diphenylprop-2-ynyl ethyl carbonate (95.0 mg, 0.34 mmol) dissolved in THF (1 ml) and morpholine (88.7 mg, 1.02 mmol). The rection mixture was warmed at 80°C and stirred for 1 hours. After cooling, the volatile materials were evaporated at reduced pressure and the residue was purified by chromatography on silica gel eluting with a 70/30 (v/v) n-hexane/AcOEt mixture to afford 76.7 mg (77% yield) of the following compound:



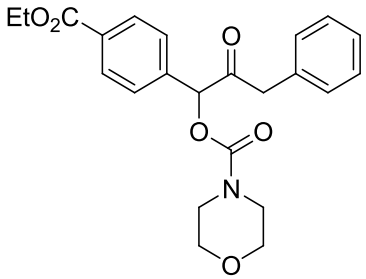
2-oxo-1,3-diphenylpropyl morpholine-4-carboxylate: mp: 132-134 °C; IR (KBr) 3066, 2974, 2904, 2860, 1732, 1714, 1431, 1234, 1117 cm^{-11}; ^1H NMR (400 MHz) ($CDCl_3$) δ 7.41-7.23 (m, 8 H) 7.05-7.03 (m, 2 H), 6.09 (s, 1 H), 3.75-3.53 (m, 10 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 202.2, 154.3, 133.3, 133.0, 129.7, 129.4, 129.1,

128.5, 128.4, 127.1, 81.0, 66.5, 45.7, 44.6, 44.1; Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; Found: C, 70.89; H, 6.26.

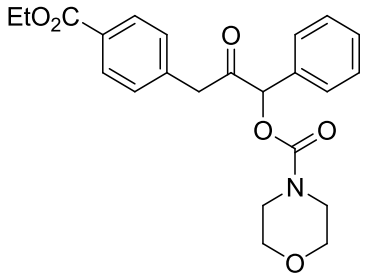




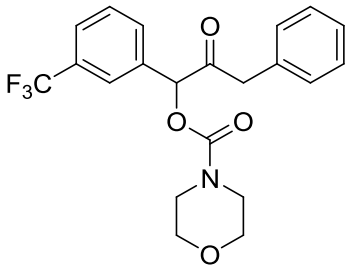
1-(4-methoxyphenyl)-2-oxo-3-phenylpropyl morpholine-4-carboxylate and 3-(4-methoxyphenyl)-2-oxo-1-phenylpropyl morpholine-4-carboxylate: Mixture; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.41-7.39 (m, 2 H), 7.30-7.21 (m, 3 H), 7.06-7.04 (m, 1 H), 6.96-6.92 (m, 2 H), 6.81 (m, 1 H), 6.08 (s, 0.25 H, PhC<u>H</u>OCO, 7b'), 6.04 (s, 0.75 H, *p*-CH_3OPhC<u>H</u>OCO, 7b), 3.83 (s, 2.25 H, *p*-C<u>H</u>$_3$OPhCHOCO, 7b), 3.77 (s, 0.75 H, *p*-C<u>H</u>$_3$OPhCH_2, 7b'), 3.73-3.43 (m, 10 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ (some chemical shifts are isochronous) 202.6 (*p*-MeOPhCH_2<u>C</u>O, 7b'), 202.4 (PhCH_2<u>C</u>O, 7b), 160.4, 158.7, 154.5, 154.4, 133.3, 133.1, 130.7, 129.9, 129.7, 129.4, 129.0, 128.5, 128.4, 127.0, 125.1, 125.0, 114.5, 114.0, 80.9 (Ph<u>C</u>HOCO, 7b'), 80.5 (*p*-MeOPh<u>C</u>HOCO, 7b), 66.5, 55.4, 55.2, 45.7, 44.8, 44.6, 44.0.



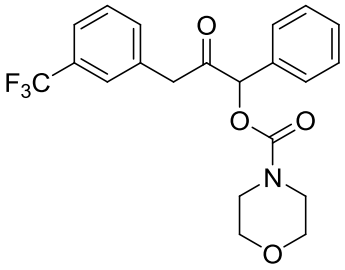
1-(4-(ethoxycarbonyl)phenyl)-2-oxo-3-phenylpropyl morpholine-4-carboxylate: oil; IR (Neat) 2924, 2858, 1712, 1612, 1456, 1433, 1277, 1238, 1111 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.28-7.26 (m, 3 H), 7.05-7.03 (m, 2 H), 6.12 (s, 1 H), 4.42 (q, *J* = 7.0 Hz, 2 H), 3.76 (s, 2 H), 3.71-3.47 (m, 8 H), 1.43 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 201.8, 166.0, 154.1, 138.0, 132.6, 131.4, 130.2, 129.6, 128.6, 128.1, 127.2, 80.4, 66.4 (bs), 61.3, 45.9, 44.6, 44.1, 14.3; Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; Found: C, 67.20; H, 6.14.



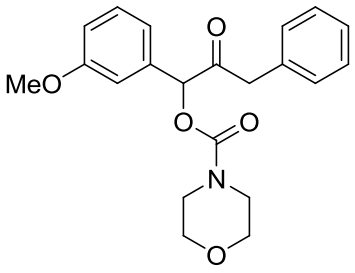
3-(4-(ethoxycarbonyl)phenyl)-2-oxo-1-phenylpropyl morpholine-4-carboxylate: oil; IR (Neat) 2978, 2925, 2858, 1712, 1612, 1429, 1277, 1238, 1107 cm^{-1}; ^{1}H NMR (400 MHz) (DMSO-d_6) (350 K) δ 7.84 (d, *J* = 7.6 Hz, 2 H), 7.47-7.42 (m, 5 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 6.14 (s, 1 H), 4.33 (q, *J* = 6.8 Hz, 2 H), 4.00 (d, *J* = 16.4 Hz, 1 H), 3.88 (d, *J* = 16.4 Hz, 1 H), 3.63-3.61 (m, 4 H), 3.48-3.47 (m, 4 H), 1.34 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz) (DMSO-d_6) (350 K) δ 202.4, 166.1, 154.2, 139.7, 134.3, 130.3, 129.4, 129.35, 129.28, 129.1, 128.2, 81.2, 66.3, 61.0, 44.8, 44.6, 14.5; Anal. Calcd. for $C_{23}H_{25}NO_6$: C, 67.14; H, 6.12; Found: C, 67.20; H, 6.16.

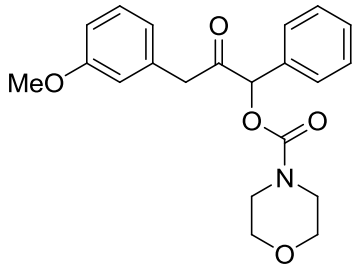


2-oxo-3-phenyl-1-(3-(trifluoromethyl)phenyl)propyl morpholine-4-carboxylate: oil; IR (Neat) 2924, 2858, 1712, 1433, 1331, 1238, 1124 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.66-7.64 (m, 1 H), 7.54-7.49 (m, 3 H), 7.28-7.23 (m, 3H), 7.05-7.04 (m, 2 H), 6.12 (s, 1 H), 3.78 (s, 2 H), 3.72-3.53 (m, 8 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ (323 K) δ 201.9, 154.0, 134.6, 132.5, 131.5, 131.4 (q, J = 32.6 Hz), 129.6, 129.5, 128.6, 127.3, 126.1 (q, J = 3.6 Hz), 125.0 (q, J = 3.8 Hz), 123.7 (q, *J* = 271.5 Hz), 80.0, 66.5, 46.3, 44.6, 44.1; ^{19}F NMR {H} (376.5 MHz) ($CDCl_3$) δ -62.7; Anal. Calcd. for $C_{21}H_{20}F_3NO_4$: C, 61.91; H, 4.95; Found: C, 61.82; H, 4.93.



2-oxo-1-phenyl-3-(3-(trifluoromethyl)phenyl)propylmorpholine-4-carboxylate: mp: 97-99 °C; IR (KBr) 2862, 1728, 1705, 1433, 1336, 1117 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 1 H), 7.44-7.37 (m, 6 H), 7.24 (d, *J* = 7.9 Hz, 1 H), 7.21 (s, 1 H), 6.07 (s, 1 H), 3.81-3.48 (m, 10 H); ^{13}C NMR (100.6 MHz) (DMSO-d6) (350 K) δ 202.6, 154.2, 135.8, 134.2, 134.1, 129.7, 129.5, 129.4, 129.3, 128.3, 126.5 (q, *J* = 4.0 Hz), 124.7 (q, *J* = 271.4 Hz), 123.7 (q, *J* = 3.8 Hz), 81.3, 66.3, 44.6, 44.4;; ^{19}F NMR {H} (376.5 MHz) ($CDCl_3$) δ -62.6; Anal. Calcd. for $C_{21}H_{20}F_3NO_4$: C, 61.91; H, 4.95; Found: C, 61.82; H, 4.93.



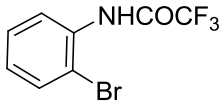


1-(3-methoxyphenyl)-2-oxo-3-phenylpropyl morpholine-4-carboxylate and 3-(3-methoxyphenyl)-2-oxo-1-phenylpropyl morpholine-4-carboxylate: Mixture; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.40-7.16 (m, 5 H), 7.06-7.05 (m, 1 H), 6.99-6.97 (m, 1 H), 6.88 (s, 0.43 H), 6.79-6.77 (m, 0.56 H), 6.64-6.62 (m, 0.56 H), 6.56 (s, 0.57 H), 6.08 (s, 0.57 H, PhC<u>H</u>OCO, 7e'), 6.06 (s, 0.43 H, *m*-MeOPhC<u>H</u>OCO, 7e), 3.80 (s, 1.3 H, *m*-C<u>H</u>$_3$OPhCHOCO,7e), 3.74-3.51 (m, 11.7 H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) (some chemical shifts are isochronous) δ 202.13 (*m*-MeOPhCH_2<u>C</u>O,7e'), 202.11 (PhCH_2<u>C</u>O,7e), 160.01, 159.64, 154.33, 154.30, 134.7, 134.4, 133.3, 133.1, 130.1, 129.7, 129.5, 129.4, 129.1, 128.5, 128.4, 127.1, 122.0, 120.7, 115.09, 114.95, 113.8,

112.8, 81.0 (PhCHOCO,7e'), 80.9 (*m*-MeOPhCHOCO,7e), 66.5, 55.3, 55.1, 45.7, 45.6, 44.6, 44.1.

4.2.3. Additional information and characterization data on indole derivatives.

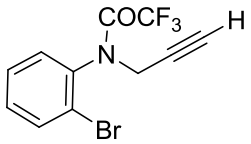
Typical procedure for the preparation of N-(2-bromophenyl)-2,2,2-trifluoroacetamide: a flask equipped with a magnetic stirring bar was charged with 2-bromoaniline (11.20 mmol, 1930 mg) dissolved in anhydrous THF (12 mL) The resultant solution was stirred at 0°C for 10 minutes before adding 2,2,2-trifluoroacetic anhydride (22.4 mmol, 4704 mg) in anhydrous THF (12 mL). The reaction mixture was stirred for 30 minutes at 0°C and then for 30 minutes at room temperature. After this time, the reaction mixture was diluited with Et_2O and washed with a saturated $NaHCO_3$ solution and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 95/5 (v/v) *n*-hexane/AcOEt mixture to obtain 2853 mg (95% yield) of *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide:



^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.48 (s, 1H), 8.32 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.63 (dd, J_1 = 8 Hz, J_2 = 1.2 Hz, 1H), 7.41 (m, 1H)), 7.14 (m, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 154.6 (q, J_{CF} = 37.3 Hz), 133.2, 132.6, 128.7, 127.2, 112.1, 116 (q, J_{CF} = 287.8 Hz), 114.1. ^{19}F NMR (CDCl3) δ -62.5.

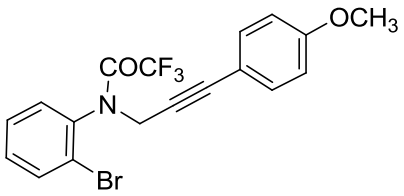
Typical procedure for the preparation of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide: a flask equipped with a magnetic stirring bar was charged with *N*-(2-bromophenyl)-2,2,2-trifluoroacetamide (18.60 mmol, 4978 mg), K_2CO_3 (27.90 mmol, 3860 mg) and dissolved in *N*,*N*-dimethylformamide (17 mL). The resultant solution was stirred at room temperature for 10 minutes before adding 1-bromobut-2-yne (27.90 mmol, 3.10mL), in *N*,*N*-dimethylformamide (17 mL). The reaction mixture was stirred for 4 hours at 40°C. After this time, the reaction mixture was diluted with Et_2O and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by

chromatography on silica gel, eluting with a 90/10 (v/v) *n*-hexane/AcOEt mixture to obtain 4709 mg (83% yield) of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide:



^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.69 (d, *J* = 8Hz, 1H), 7.46-7.32 (m, 3H), 5.09 (d, *J* = 17.6 Hz, 1H), 3.95 (d, *J* = 17.6 Hz, 1H), 2.30 (s, 1H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 156.4 (q, J_{CF} = 37 Hz), 136.6, 133.6, 131.8, 131.3, 128.1, 123.4, 116 (q, J_{CF} = 287.8 Hz), 76.4, 74.2, 39.1.

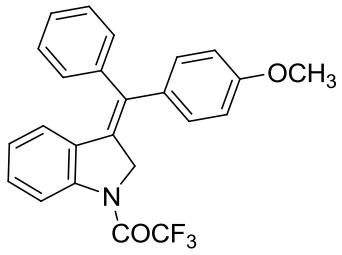
Typical procedure for the preparation of *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(3-(aryl)prop-2-ynyl)acetamide: a flask equipped with a magnetic stirring bar was charged with $PdCl_2(PPh_3)_2$ (0.118 mmol, 82.8 mg) and CuI (0.236 mmol, 45.8 mg) dissolved in *N*,*N*-dimethylformamide (1 mL), triethylamine (9 mL) and diisopropylamine (4 mL). The resultant solution was stirred under Nitrogen at room temperature for 10 minutes before adding 3-iodoanisole (7.681 mmol, 2012 mg) in *N*,*N*-dimethylformamide (3 mL) and *N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(prop-2-ynyl)acetamide (5.908 mmol, 1808 mg). The reaction mixture was stirred for 5 hours at room temperature. After this time, the reaction mixture was diluted with Et_2O and washed with HCl 2N, with a saturated NH_4Cl solution and with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with a 90/10 (v/v) *n*-hexane/AcOEt mixture to obtain 1710mg (70% yield) of following desired compound:



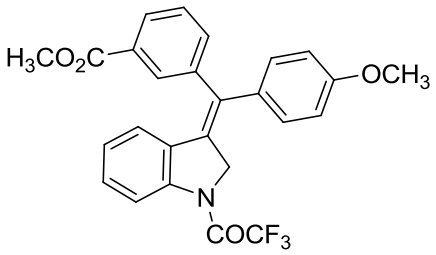
***N*-(2-bromophenyl)-2,2,2-trifluoro-*N*-(3-(4-methoxyphenyl)prop-2-ynyl)acetamide:** ^{1}H NMR (400 MHz) ($CDCl_3$) δ 7.73 (d, *J* = 8Hz, 1H), 7.49 (d, *J* = 8Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.36 (t, *J* = 8 Hz, 1H), 7.30, (d, *J* = 9 Hz, 1H), 6.83(d, *J* = 9 Hz, 1H), 5.30 (d,

J = 17.6 Hz, 1H), 4.27 (d, *J* = 17.6 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 160.0, 156.2 (q, J_{CF} = 37 Hz), 137.0, 133.5, 133.2, 132.0, 131.1, 128.0, 123.8, 116 (q, J_{CF} = 287.8 Hz), 114.2, 114, 86.1, 80.2 55.2, 40.0; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ-62.7.

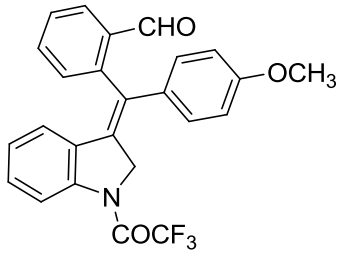
Typical procedure for the preparation of (Z)-2,2,2-trifluoro-1-(3-((4-methoxyphenyl)(phenyl)methylene)indolin-1-yl)ethanone: a Carousel Tube Reaction (Radley Discovery) was charged with $PdCl_2(PPh_3)_2$ (13 mg, 0.018 mmol), PPh_3 (9.5 mg, 0.0364 mmol) and 1.4-dioxane (1 mL). The solution was stirred under Nitrogen at room temperature for 10 minutes before adding N-(2-bromophenyl)-2,2,2-trifluoro-N-(3-(4-methoxyphenyl)prop-2-ynyl)acetamide (150 mg, 0.364 mmol) dissolved 1.4-dioxane(1.5 mL), Cs_2CO_3 (178mg, 0.546 mmol) and phenylboronic acid (67mg, 0.546 mmol). The reaction mixture was warmed at 100 °C and stirred for 5 hours. After this time, the mixture was cooled, added with diethyl ether, washed with a saturated NaCl solution. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2, 30 g, n-hexane/AcOEt 90/10 v/v) to afford 120 mg (81% yield) of the following compound:



Beige solid; mp 130-132°C; IR (KBr) 3400, 1700, 1638, 1251, 1213, 1176 cm^{-1}; ^{1}H NMR (400 MHz) ($CDCl_3$) δ 8.35 (d, *J* = 8 Hz, 1H), 7.42-7.16 (m, 9H), 6.96 (d, *J* = 8 Hz, 1H), 6.92 (t, *J* = 8 Hz, 2H), 6.46, (d, J = 8 Hz, 1H), 5.04 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 159.1, 153.5 (q, J_{CF} = 37 Hz), 144.2, 141.1, 135.9, 134.0, 130.2, 129.5, 129.3, 129.2, 129.1, 128.2, 128.0, 125.3, 124.4, 117.9, 116 (q, J_{CF} = 287.8 Hz), 114.1, 55.3, 53.7 (q, J_{CF} = 4 Hz); ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.63; MS m/z (relative intensity): 409 (M^+ 100 %); Anal. Calcd. For $C_{24}H_{18}F_3NO_2$: C, 70.41; H, 4.43; Found C, 70.49; H, 4.42.

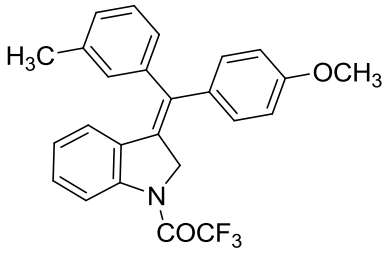


(E)-methyl-3-((4-methoxyphenyl)(1-(2,2,2-trifluoroacetyl)indolin-3-ylidene)methyl)benzoate;
Pale yellow solid; mp 175-177 °C; IR (KBr) 2959, 1720, 1691, 1605, 1434, 1250, cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.24 (t, *J* = 8.4 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.86 (t, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.03 (s, 2H), 3.97 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 166.8, 159.3, 153.5(q, J_{CF} = 37 Hz), 145.9, 144.4, 134.6, 133.3, 130.4, 129.7, 129.6, 129.5, 129.5, 129.1, 125.4, 124.3, 118.0, 116.3 (q, J_{CF} = 288 Hz), 55.3, 53.73 (q, J_{CF} = 4 Hz), 52.2; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.64; MS m/z (relative intensity): 463(M^+ 100 %); Anal. Calcd. For $C_{26}H_{22}F_3NO_4$: C, 66.81; H, 4.31; N, 3.00; Found C, 66.89; H, 4.30; N, 3.01.

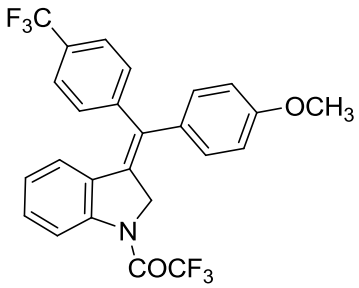


(E)-2-((4-methoxyphenyl)(1-(2,2,2-trifluoroacetyl)indolin-3-ylidene)methyl)benzaldehyde;
Pale yellow solid; mp 146-148 °C; IR (KBr) 3374, 2841, 1693, 1510, 1252, 1029 cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 10.17 (s, 1H), 8.33 (d, *J* = 8 Hz, 1H), 8.08 (d, *J* = 8 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.21 (m, 3H), 6.93 (d, *J* = 7.6 Hz, 2H **)**, 6.82 (t, *J* = 7.6 Hz, 1H), 6.07 (d, *J* = 7.2 Hz, 1H), 5.24 (d, *J* = 15.6 Hz,1H), 5.12 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100.6 MHz) ($CDCl_3$) δ 159.3, 153.4 (q, J_{CF} = 37.7 Hz), 144.3, 144.15, 135.1, 134.0, 133.0, 131.0, 130.9, 130.6, 130.2, 129.7, 129.6, 129.4, 129.1, 128.8, 125.6, 124.0, 118.1, 116.1 (q, J_{CF} = 286 Hz), 114.3, 55.3, 53.5; ^{19}F NMR {H} (376.5 MHz) ($CDCl_3$) δ -72.61; MS m/z

(relative intensity): 437 (M^+ 100%); Anal. Calcd. For $C_{25}H_{20}F_3NO_3$: C, 68.65; H, 4.15; N, 3.20; Found C, 68.74; H, 4.16; N, 3.19.

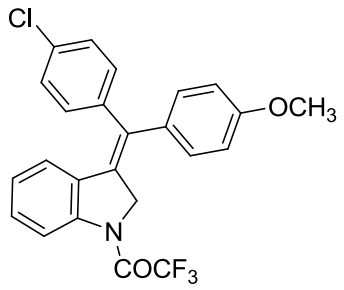


(E)-2,2,2-trifluoro-1-(3-((4-methoxyphenyl)(m-tolyl)methylene)indolin-1-yl)ethanone; Orange solid; mp 131-133°C; IR (KBr) 3460, 1697, 1637, 1465, 1250 cm^{-1}; ^1H NMR (400 MHz) (CDCl3) δ 8.32 (d, *J* = 8 Hz, 1H), 7.25 (m, 7H), 6.93-6.91 (m, 3H) 6.55 (d, *J* = 8 Hz, 1H), 5.02 (s, 2H), 3.86 (s, 3H), 2.44 (s, 3H) ^{13}C NMR (100.6 MHz) (CDCl3) δ 159.1, 153.4 (q, J_{CF} = 37.4 Hz) 144.2, 138.1, 137.7, 135.9, 134.2, 130.5, 130.4, 129.8, 129.5, 129.4, 129.1, 128.9, 128.1, 127.9, 125.3, 124.4, 118, 115.8 (q, J_{CF} = 288 Hz), 114.3, 55.3, 53.75 (q, J_{CF} = 4Hz) 21.3; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.4; MS m/z (relative intensity): 423 (M^+ 100%); Anal. Calcd. For $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31; Found C, 70.99; H, 4.75; N, 3.30.

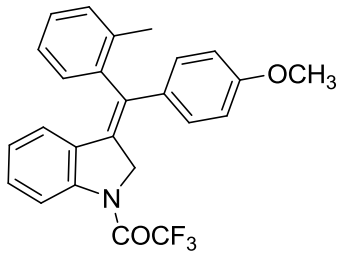


(Z)-2,2,2-trifluoro-1-(3-((4-methoxyphenyl)(4-(trifluoromethyl) phenyl)methylene) indolin-1-yl)ethanone; Brown solid; mp 188-190°C; IR (KBr) 3443, 1702, 1637, 1324, 1276, 1251 cm^{-1}; ^1H NMR (400 MHz) (CDCl3) δ 8.34 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.26 (t, J = 8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 8 Hz, 1H), 6.47 (d, *J* = 8 Hz, 1H), 5.03 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 159.3, 153.5 (q, J_{CF} = 37.7 Hz), 144.8, 144.4, 134.1, 133.2, 130.5, 130.2, 129.9, 129.6 (q, J_{CF} = 3.4 Hz), 129.5 (q, J_{CF} = 28 5 Hz), 129.3, 128.6, 126.1 (q, J_{CF} = 3.4 Hz), 125.5, 124.1 (q, J_{CF} = 271 Hz), 118.2, 115.7 (q, J_{CF} = 286 Hz), 114.2, 55.3, 53.7 (q, J_{CF} = 4Hz); ^{19}F NMR {H} (376.5 MHz)

(CDCl3) δ-62.42, δ -72.62; MS m/z (relative intensity): 477 (M^+ 100%); Anal. Calcd. For $C_{25}H_{17}F_6NO_2$ C, 62.90; H, 3.59; N, 2.93; Found C, 62.99; H, 3.58; N, 2.94.

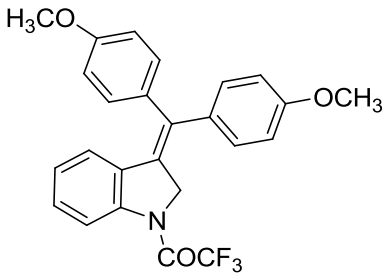


(E)-1-(3-((4-chlorophenyl)(4-methoxyphenyl)methylene)indolin-1-yl)-2,2,2-trifluoroethanone; Brown solid; mp 182-184°C; IR(neat) 3430, 1702, 1636, 1460, 1210 cm^{-1}; ^1H NMR (400 MHz) (CDCl3) δ 8.33 (d, *J* = 8 Hz, 1H), 7.41 (d, *J* = 8 Hz, 2H), 7.24-7.22 (m, 3H), 7.13 (d, *J* = 8Hz, 2H), 6.94-6.92 (m, 3H), 6.57 (d, *J* = 8 Hz, 1H), 5.01 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 159.2, 153.5 (q, J_{CF} = 36.8 Hz), 144.3, 139.5, 134.4, 133.9, 133.5, 130.9, 130.5, 129.8, 129.6, 129.4, 128.8, 118.1, 116.3 (q, J_{CF} = 287 Hz), 114.2, 55. 3, 53.7 (q, J_{CF} = 3.8 Hz); ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.5**;** MS m/z (relative intensity): 433 (M^+ 100%); Anal. Calcd. For $C_{24}H_{19}ClF_3NO_2$: C, 64.95; H, 3.86; N, 3.16; Found C, 65.04; H, 3.87; N, 3.15.

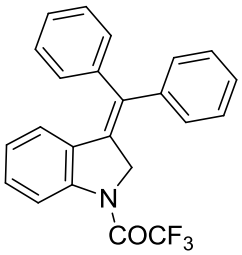


(E)-2,2,2-trifluoro-1-(3-((4-methoxyphenyl)(o-tolyl)methylene)indolin-1-yl)ethanone; Yellow solid; mp: 148-150°C IR (neat) 3370, 2931, 1693, 1509, 1248 cm^{-1} ; ^1H NMR (400 MHz) (CDCl3) δ 8.36 (d, *J* = 8 Hz, 1H), 7.38-7.21 (m, 7H), 6.95 (d, *J* = 8 Hz, 1H), 6.87 (t, *J* = 8 Hz, 2H), 6.20 (d, *J* = 8 Hz, 1H), 5.26 (d, *J* = 15.6 Hz, 1H), 5.11 (d, *J* = 15.6 Hz, 1H), 3.87 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 159.1, 153.2 (q, J_{CF} = 37 Hz), 143.9, 140.3, 136.3, 134.8, 132.9, 131.0, 130.6, 130.2, 129.3, 129.0, 128.2, 126.9, 125.7, 125.4, 124.0, 117.8, 115.8 (q, J_{CF} = 288 Hz), 114.2, 114.0, 55.3, 53.3 (q, J_{CF}= 3.8 Hz), 19.5; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.7**;** MS m/z

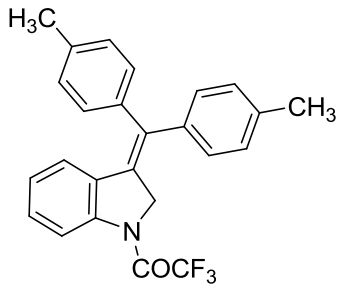
(relative intensity): 423 (M^+ 100%); Anal. Calcd. For $C_{25}H_{20}F_3NO_2$: C, 70.91; H, 4.76; N, 3.31; Found C, 70.99; H, 4.75; N, 3.32.



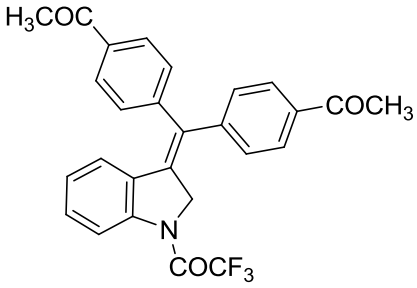
1-(3-(bis(4-methoxyphenyl)methylene)indolin-1-yl)-2,2,2-trifluoroethanone; Brown solid; mp 174.3-176.4°C; IR (KBr) 2961, 1692, 1466, 1208 cm^{-1}; ^1H NMR (400 MHz) (CDCl3) δ 8.31 (d, *J* = 8.4 Hz, 1H), 7.24-7.15 (m, 5H), 6.97-6.88 (m, 5H), 6.60 (d, *J* = 8.4 Hz, 1H) 5.02 (s, 2H), 3.87 (s, 6H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 159.3, 159.1, 153.4 (q, J_{CF} = 37.6Hz), 144.2, 135.6, 134.3, 133.3, 130.6, 130.5, 129.6, 128.9, 127.8, 125.3, 124.3, 117.9, 116.4 (q, J_{CF} = 288 Hz), 114.5, 114.0, 55.3, 53.8 (q, J_{CF} = 4Hz); ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.62; MS m/z (relative intensity): 439 (M^+ 100%); Anal. Calcd. For $C_{25}H_{20}F_3NO_3$ C, 68.33; H, 4.59; N, 3.19; Found C, 68.42; H, 4.60; N, 3.18.



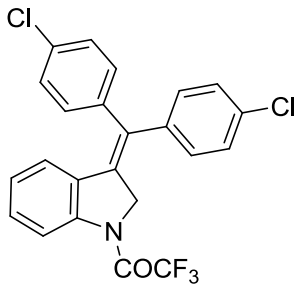
1-(3-(diphenylmethylene)indolin-1-yl)-2,2,2-trifluoroethanone; Yellow wax; IR (Neat) 3453, 1698, 1460, 1246, 1151 cm^{-1}; ^1H NMR (400 MHz) (CDCl3) δ 8.35 (d, *J* = 7.6 Hz, 1H), 7.44-7.25 (m, 11H), 6.90 (t, *J* = 7.6Hz, 1H), 6.53 (d, *J* = 7.6 Hz, 1H)), 5.02 (s, 2H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 153.5 (q, J_{CF} = 37.5 Hz), 144.5, 141.6, 140.9, 136.1, 129.9, 129.4, 129.2, 129.1, 128.8, 128.1, 128.0, 127.9, 125.4, 124.5, 123.8, 118.0, 116.3 (q, J_{CF} = 288 Hz), 53.5 (q, J_{CF} = 4Hz); ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.7; MS m/z (relative intensity): 379 (M^+ 100%); Anal. Calcd. For $C_{23}H_{16}F_3NO$: C, 72.82; H, 4.25; N, 3.69; Found: C, 72.91; H, 4.24; N, 3.70.



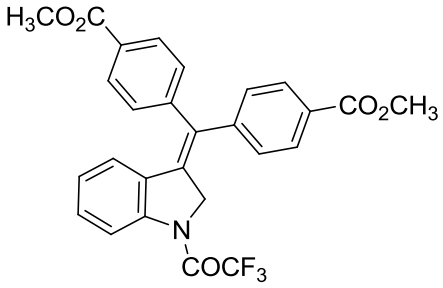
1-(3-(dip-tolylmethylene)indolin-1-yl)-2,2,2-trifluoroethanone; Orange solid; mp 179-181 °C IR (KBr) 3451, 1698, 1636, 1475, 1205 cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 8.33 (d, *J* = 8 Hz, 1H), 7.25-7.1 (m, 10H), 6.90 (t, *J* = 8Hz, 1H), 6.58 (d, *J* = 8 Hz, 1H), 5.02 (s, 2H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 153.4 (q, J_{CF} = 37.4 Hz), 144.3, 138.9, 138.0, 137.7, 137.6, 136.2, 130.3, 129.9, 129.4, 129.1, 128.3, 128.1, 125.3, 124.5, 117.9, 115.8 (q, J_{CF}= 286Hz), 53.6 (q, J_{CF} = 4Hz), 21.4, 21.3 ; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.62; MS m/z (relative intensity): 407 (M^{+} 100%); Anal. Calcd. For $C_{25}H_{20}F_3NO$: C, 73.70; H, 4.95; N, 3.44; Found: C, 73.79; H, 4.94; N, 3.45.



1,1'-(4,4'-((1-(2,2,2-trifluoroacetyl)indolin-3-ylidene)methylene)bis(4,1-phenylene))diethanone; Green solid; mp 196-198 °C; IR (KBr) 3473, 1682, 1437, 1246, cm^{-1}; ^{1}H NMR (400MHz) (CDCl3) δ 8.35 (d, *J* = 8.4Hz, 1H), 8.06-8.00 (m, 4H), 7.44-7.30 (m, 6H), 6.91 (t, *J* = 8.4 Hz), 6.55 (d, *J* = 8.4Hz, 1H), 5.00 (s, 2H), 2.68 (s, 3H), 2.64 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 197.5, 197.2, 153.4 (q, J_{CF} = 37.2Hz), 145.5, 145.1, 144.8, 136.8, 136.5, 133.4, 131.4, 130.4, 129.7, 129.4, 129.0, 128.8, 128,4, 125.5, 124.8, 118.2, 115.8 (q, J_{CF} = 286 Hz), 53.4 (q, J_{CF} = 4Hz), 26.7, 26.6; ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.5; MS m/z (relative intensity): 262 (M^{+} 100%); Anal. Calcd. For $C_{27}H_{20}F_3NO_3$: C, 69.97; H, 4.35; N, 3.02; Found: C, 70.06; H, 4.36; N, 3.01.



1-(3-(bis(4-chlorophenyl)methylene)indolin-1-yl)-2,2,2-trifluoroethanone; Gray solid; mp 152-154 °C; IR (KBr) 3365, 1691, 1488, 1342 cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3) δ 8.34 (d, *J* = 8.4 Hz, 1H), 7.44-7.38 (m, 4H), 7.30-7.15 (m, 5H), 6.94 (t, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.00 (s, 2H) ^{13}C NMR (100.6 MHz) (CDCl3) δ 153.4 (q, J_{CF} = 37.7 Hz), 144.6, 139.6, 138.8, 134.3, 134.0, 133.3, 130.8, 130.3, 130.0, 129.6, 129.5, 129.4, 129.2, 125.5, 124.4, 118.1, 116.3 (q, J_{CF} = 294 Hz) 53.48 (q, J_{CF} = 4 Hz); ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -71.8; MS m/z (relative intensity): 447 (M^+ 100%); Anal. Calcd. For $C_{23}H_{14}Cl_2F_3NO$: C, 61.63; H, 3.15; N, 3.12; Found: C, 61.72; H, 3.14; N, 3.13.



Dimethyl-4,4'-((1-(2,2,2-trifluoroacetyl)indolin-3-ylidene)methylene)dibenzoate; Yellow solid; mp 184-186 °C; IR (KBr) 2952, 1721, 1688, 1434, 1285, cm^{-1}; ^{1}H NMR (400 MHz) (CDCl3): δ 8.33 (d, *J* = 8 Hz, 1H), 8.12 (d, *J* = 8 Hz, 2H),8.07 (d, *J* = 8 Hz, 2H), 7.39 (d, *J* = 8 Hz, 2H), 7.31-7.26 (m, 3H), 6.90 (t, *J* = 8 Hz, 1H), 6.51 (d, *J* = 8 Hz, 1H), 4.98 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100.6 MHz) (CDCl3) δ 166.6, 166.4, 153.4 (q, J_{CF} = 38 Hz), 145.4, 144.9, 144.8, 133.6131.2, 130.6, 130.2, 130.0, 129.8, 129.5, 128.9, 128.2, 125.5, 124.5, 118.1, 115.8 (q, J_{CF} = 285 Hz), 53.4 (q, J_{CF} = 4 Hz), 52.3, 52.2 ^{19}F NMR {H} (376.5 MHz) (CDCl3) δ -72.6**;** MS m/z (relative intensity): 467 (M^+ 100%); Anal. Calcd. For $C_{27}H_{20}F_3NO_5$: C, 65.45; H, 4.07; N, 2.83; Found: C, 65.54; H, 4.06; N, 2.82.

4.2.4. Additional information on gold nanoparticles

Materials

Gellan gum (Gelzan^{TM}) from *Sphingomonas elodea*, a copolymer of glucose, glucuronic acid and rhamnose residues in a 2:1:1 ratio: [→3)– β –D–glucose–(1→4)– β –D–glucuronic acid–(1→4)– β –D– glucose–(1→4)– α –L–rhamnose–(1→] and alginate sodium salt from brown algae, a copolymer of (1→4) linked β-D-mannuronic acid and α-L-guluronic acid (mannuronic/guluronic ratio 1.56, Mw=2.4×105), were purchased from Sigma-Aldrich. Dextran (DEX) from *Leuconostoc ssp.* (Mw 40,000), 4-dimethylaminopyridine (DMAP), sodium borohydride, N,N,N',N'-tetramethylethylenediamine (TEMED) and anhydrous dimethylsulfoxide (DMSO) were purchased from Fluka (Switzerland). Glycidyl methacrylate (GMA), D_2O, ammonium persulfate (APS) were purchased from Sigma–Aldrich (England). Dialysis tubes (cut-off 12,000–14,000) were purchased from Medicell International (UK).

Synthesis of dextran methacrylate (DEX-MA)

Dextran methacrylate was synthesized as already reported (van Dijk-Wolthuis et al., 1997). Briefly, to a solution of dextran (Mw 40,000, DEX40, 5.0 g) in anhydrous DMSO (40 ml), DMAP (1.0 g) and GMA (1.50 g, 1 mol/3 mol of repetitive unit) were added. The solution was maintained under stirring at room temperature for 24 h. EtOH (200 ml) was added dropwise; the precipitated solid was recovered by filtration and dissolved in water (15 ml). The solution was neutralized with 0.1 M HCl and submitted to exhaustive dialysis against distilled water. After freeze-drying, the polymer was characterized by FT-IR, ^{13}C NMR and ^{1}H NMR. FT-IR spectra were recorded using KBr pellets with a PerkinElmer Paragon 1000 spectrophotometer in the range 4000–400 cm−1 (resolution of 1 cm^{-1}). ^{13}C NMR and ^{1}H NMR spectra were obtained in D_2O with a Bruker AC-400 instrument. The degree of derivatization (number of methacrylic groups for 100 glucopyranosyl residues, DD), calculated on the basis of the 1H NMR spectrum, was 20 ± 1.

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