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**XXV ciclo**

# Transition Metals Catalysis in C–C and C–Heteroatom Bonds Forming Reactions


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*“Non ho talenti particolari, sono solo appassionatamente curioso”*

*Albert Einstein*

# *Summary*

# Introduction

Transition metals catalysis represents an important and versatile tool for the organic synthesis. Indeed its use is associated with several advantages in terms of reaction selectivity, and "atom economy". In the last decade the growing utilization of transition metals catalysis has deeply influenced and modified the design of heterocyclic synthesis as testified by the wide amount of studies on the palladium-catalyzed cross-coupling reaction that in 2010 led Prof. Richard F. Heck (University of Delaware, USA), Prof. Ei-ichi Negishi (Purdue University, USA) and Prof. Akira Suzuki (Hokkaido University, Japan) to achieve the Nobel Prize for Chemistry.

In this context, during my doctorate activity, we investigated the construction of heterocyclic rings and the production of derivatives of heterocyclic compounds of biological interest through palladium, copper and gold catalyzed reactions.

As part of our studies on the palladium catalysis we developed several synthetic strategy for the construction of different classes of compounds such us functionalized 2,3-dihydrofurans, substituted 2,3-substituted quinolin-4-(1*H*)-ones, dibenzo[*a,c*]carbazoles, 2-amino ketones and aryl sulfones. Then, the economic attractiveness of copper-based methods and the growing interest in copper-catalyzed syntheses stimulated us to investigate some copper-catalyzed protocol. In this area we studied the oxidation reaction of the 1,2-diarylethanones and the cyclization reaction of the *N*-(2-bromoaryl)enaminones to obtain 2,4-diarylbenzo[*b*][1,4]oxazepines. Finally, using gold complexes we developed a new sinthetical approach to 2,4-diaryl-2,3-dihydro-1H-benzo[*b*][1,4]diazepines.

# 1. Palladium catalysis

## 1.1 Palladium catalysts

Among all the transition metals, palladium is the most useful in organic synthesis, because of his versatility in the C–C, C–heteroatoms bonds forming reaction. [1]

Palladium has ten electrons in the valence shell and exists mainly in two oxidation states: (0) and (+2), so it tends to form d 10 and d 8 complexes of relatively low oxidation states. 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 $\pi$-compounds, such as alkynes, alkenes and even arenes. Furthermore, it can also readily form $\sigma$ 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.

There are several features which make reactions involving Pd catalysts and reagents particularly useful and versatile among many transition metals used for organic synthesis. Most importantly, Pd catalysts offer an abundance of possibilities of carbon-carbon bond formation.

A further important aspect of the palladium catalysis is the tolerance to many functional groups such as carbonyl and hydroxy groups; for this reason Pd-catalyzed reactions can be carried out without protection of these functional groups.

Oxidation state has a considerable influence on the palladium complexes reactivity. The Pd(0) complexes of are good nucleophiles, good bases and are easily oxidized. Two of the most widely utilized are $Pd_2(dba)_3$ and $Pd(PPh_3)_4$. In the $Pd_2(dba)_3$ each palladium atom is coordinated by the double bonds of the three molecules of dba to form a 16 electrons complex (Figure 1).

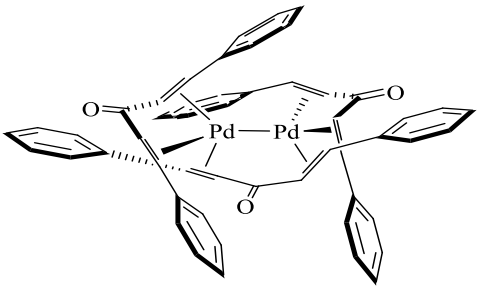



**Figure 1**

In the $Pd(PPh_3)_4$ palladium is coordinated by four molecule of triphenylphosfine and generates a 18 electron complex.

The Pd(II) salts display different characteristic: they are electrophiles species and could react with electron rich species such as arenes and alkenes. These compounds could be used as stoichiometric reagents or as catalysts. When used as catalysts, they rapresent Pd(0) forerunners. Alkenes, alkynes, carbon monoxide [2], metal hydrides organometallic compounds [3] and phosphines [4] could be the reducing agent for the Pd(II). Pd(II) salts commonly used are $PdCl_2$, $Pd(OAc)_2$ and the $PdCl_2(CH_3CN)_2$. Palladium activity could be modulated by using phosphines with specific steric and electronic characteristics.

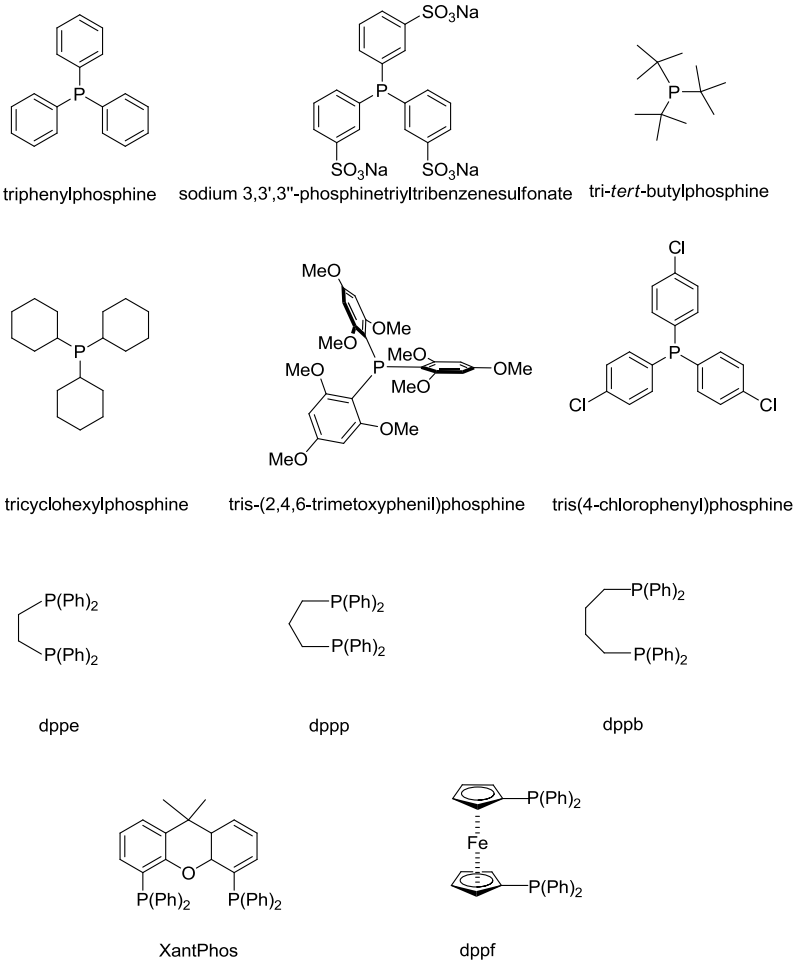



**Figure 2**

In this regard should remember the alkyl-phosphines and arylfosfine with electron-withdrawing groups, such as tris (4-chlorophenyl) phosphine, alkyl-phosphines and arylfosfine with electron-donating groups such as tris (2,4,6-trimethoxyphenyl) phosphine, the sulfonated phosphines which allow operate in the aqueous phase due to the high hydrophilicity, the bidentate

phosphines such as diphenylphosphinopropane, the dipheylphosphinobutane or diphenylphosphinoferrocene, which are particularly used in the carbonylation reactions (Figure 2).

## 1. 2 Main palladium-catalyzed reactions

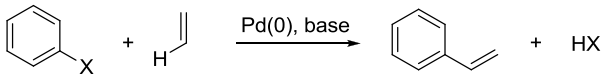
In this section, the main features of the palladium-catalyzed processes studied during my doctorate activity will be discussed.

### 1.2.1 Heck reaction

More than 40 years ago Mizoroki [5] and Heck [6] independently designed and executed the first Pd-catalyzed coupling reactions of aryl and alkenyl halide with alkenes. This process, known worldwide as the Heck reaction is attractive from a synthetic point of view because high chemoselectivity and mild conditions are associated with low toxicity and low costs of the reagents. [7]

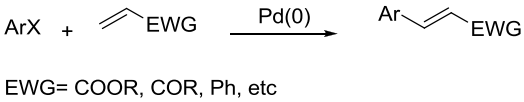
Howewer, the real drive to utilize this powerful C–C bond forming process, began only in the second half of the 1970s when several coupling reactions mechanistically related to the Heck reaction, as Sonogashira and Suzuki cross-coupling, were developed. Application of the Heck reaction range from the preparation of a large variety of hydrocarbons, novel polymers, and other unsaturated compounds, many of which are useful as UV screen, pharmaceuticals, etc. Although the potential of this Pd-catalyzed process has not yet been fully explored, it is appropriate to say, even at this stage, the carbometallation reactions are true "power tools" in contemporary organic synthesis.

The Heck reaction is a process in which the formation of a new C-C bond takes place, starting from an aryl/vinyl halide or triflate and an alkene, in presence of a base and of a catalytic amount of palladium, to give the vinylic substitution product (Scheme 1).

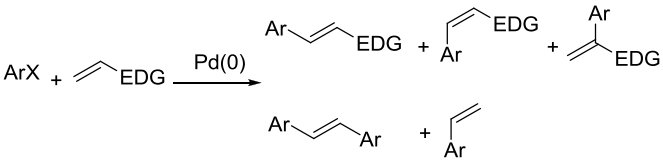



**Scheme 1**

The Pd-catalyzed reaction proceeded smoothly with terminal alkenes substituted with electron-withdrawing groups, but electronically neutral alkenes or electron-donating alkenes were less suitable as substrates. With the latter class of non-electron-poor alkenes, diarylated products, regioisomers, double bond isomers, mixtures of *cis*- and *trans*- isomers, products in which a heteroatom substituent bonded to the alkene had been eliminated, or sometimes even tar were encountered under the traditional conditions (Scheme 2 and 3).




**Scheme 2**



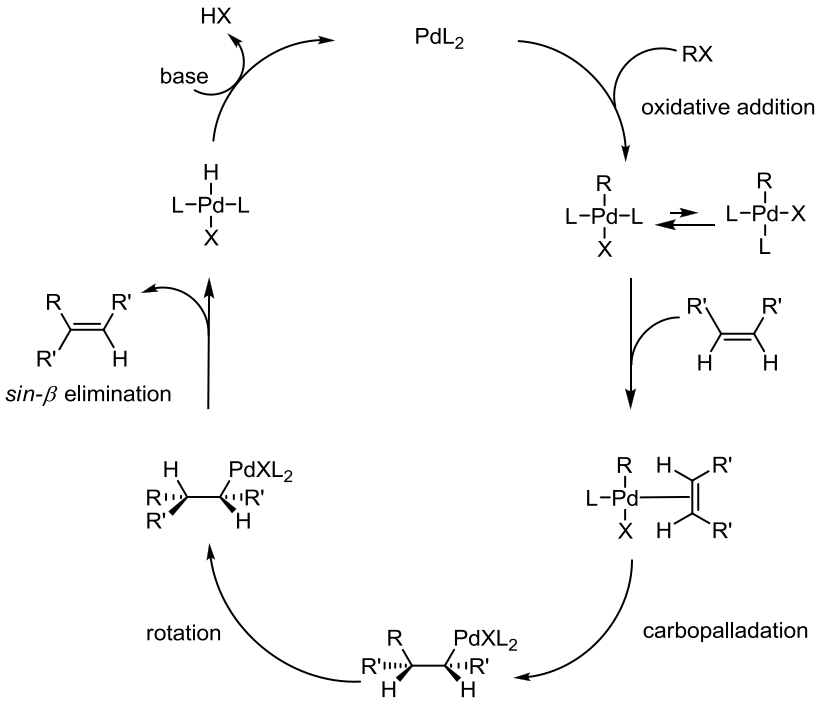

**Scheme 3**

In scheme 4 is reported the general mechanism of Heck reaction.

The catalytically active species is a 14-electron complex, $PdL_2$, [8] it is commonly generated in situ either from a Pd(0) complex or by reduction of relatively inexpensive Pd(II) acetate or chloride. [9] The first step of mechanism is oxidative addition of RX to the Pd(0) complex to generate a σ-alkenyl or σ-aryl-palladium(II) complex *cis*-$RPdXL_2$. Cis-$RPdXL_2$ isomerizes to most stable

*trans*-$RPdXL_2$ can undergo syn-insertion into the C–C double bond of the in-plane coordinated alkene, to yield to generate $\eta^2$–organo–palladium complex. Then there is a carbopalladation or a migratory step which produces new σ–C–Pd and σ–C–C bond.

The elimination of HPdX occur only after an internal rotation around the former double bond as it requires a β-hydrogen atom to be oriented synplanar with respect to the halopalladium residue so Heck reaction results stereoselective. After that alkene product and $L_2Pd(H)X$ are produced, and the presence of a base is necessary in order to transform the $L_2Pd(H)X$ into the starting $L_2Pd(0)$ complex and close the catalytic cycle.




**Scheme 4**

The most frequently used catalyst system for Heck-type coupling reactions consist of commercially available palladium compounds in the presence of various ligands. The first chance is often the air-stable and relatively inexpensive palladium acetate; however, several of other published variants can be preferable for certain applications. It is commonly assumed that the palladium(II) species is reduced *in situ* by the solvent, the alkene, the amine or the added ligand.

Typical bases used in the Heck reaction are tertiary amines ($Et_3N$, $iPr_2NEt$, etc.) or acetate or carbonate bases (AcONa, $K_2CO_3$, etc.). Except for aryl iodides, the presence of ligands is necessary in order to effect at a reasonable temperature. Ligands for Heck reaction could be monodentate [10] and bidentate phosphines [11] and 1,10-phenanthroline derivatives. [12]

Heck reaction is reported to be a high regioselective reaction [13] using procedures that favour the coordination-insertion process via dissociation of the ligand.

Regarding the solvent, initially, only dipolar aprotic solvents such as tertiary amines, acetonitrile, dimethyilformamide, N-methylpirrolidone, and dimethylsulfoxide, were used. However, as originally observed by Heck, the presence of water can generate certain coupling reactions. A further achievement was the discovery that Heck reactions are greatly accelerated in the presence of quaternary ammonium salts ("Jeffery" conditions: $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NX$, DMF). In these conditions iodoarenes and iodoalkenes can be coupled to alkenes at room temperature. The assistance of tetraalkylammoniun salts in the regeneration of the catalytically active Pd(0) species apparently plays the major role.

The nature of the leaving group greatly affects the reaction rate: aryl iodides react faster than bromides, and aryl chlorides are notoriously unreactive unless special catalysts or ligands and elevated temperatures are used to enhance the reaction rate. This has been taken to indicate that the oxidative addition of the haloarene to Pd(0) is the rate-determining step. This reaction can be catalyzed by palladium complexes with or without phosphine

ligands (phosphine assisted *vs* phosphine-free catalysis). A primary role of phosphine ligands is to support palladium in its zero oxidation state in the form of stable $PdL_4$ or $PdL_3$ species. The phosphine-assisted approach is the classical and well-established method which gives excellent results in a majority of cases, but, for economical and chemical reasons, research was addressed in seeking for anything else. Phosphine ligands are expensive, toxic, and unrecoverable. In large-scale applications on industrial and semi-industrial scale, the phosphines might be a more serious economical burden than even palladium itself, which can be recovered at any stage of production or from wastes. The chemical reason is lower reactivity of fully ligated complexes of palladium, the main result of which is the need for higher loads of catalyst to achieve appropriate rates of reaction and therefore further aggravation of procedure cost.

Both underligated and phosphine-free catalysis are opposite to the phosphine-assisted conservative methodology. It relies not on the intrinsic stability of properly ligated isolable complexes, but rather on making zerovalent palladium species run for life within the Heck catalytic cycle or die as inactive black sediments. Underligated Pd(0) species (the term underligated means that a given palladium complex bears less strongly bonded ligands than is required to form a stable complex) are intrinsically unstable to survive outside of the cycle but are likely to have higher reactivity; therefore, their stationary concentration in a catalytic system is much lower. Unlike phosphine-assisted systems which are based on thoughtful design and knowledge of intimate details of coordination chemistry, phosphine-free systems are not so predictable yet. The primary reduction of Pd(II) to Pd(0) is most likely accomplished by phosphine in the phosphine assisted catalytic cycles. The reduction is assisted by hard nucleophiles, of which the most common are hydroxide and alkoxide ions, water, and acetate ion, though in special cases even fluoride in the presence of water can play the role.

In phosphine-free systems, the primary reduction of Pd(II) can be effected by amines, if these are used as base, or olefin. It is

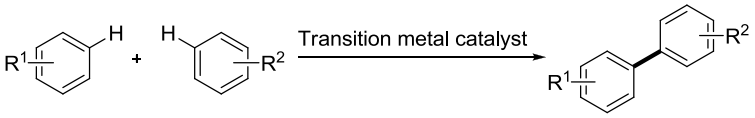
interesting to note that neither $Et_3N$ nor olefin have any detectable influence on the reduction rate in the presence of phosphine. Still, it is well-known that in the absence of phosphine, olefins are oxidized by Pd(II) via the first turn of a Waker-type catalytic cycle. This process may be a serious yield-decreasing factor in the reactions with high initial loads of palladium salts in phosphine-free systems if the olefin is taken in an equimolar amount with respect to the electrophilic substrate (that is the by-default case in the intramolecular Heck cyclizations).

## 1.2.2 C–H activation, direct arylation

In the past several decades, synthetic chemists started changing organic synthetic pathways to avoid unfriendly chemicals and developing new, straightforward methods for approaching final goals. In this context, transition metal-catalyzed C–H bond functionalization for the C–C bond formation has emerged as a promising area in organic synthesis. [14] In particular, reactions involving Pd-catalyzed activation of $sp^2$ or $sp^3$ C–H bonds of arenes or alkenes have been extensively investigated. [15] Successful application of the C–H activation strategy on readily available substrates have been also reported using various metals other than Pd catalyst. [16] [17]

While the coupling of an aryl halide or pseudohalide with an organometallic reagent is commonly referred to as a cross-coupling reaction, several terms such as C–H (bond) activation, C–H (bond) functionalization, cross-dehalogenative coupling, and catalytic direct arylation have been used to describe the corresponding coupling of an aryl halide or pseudohalide with a simple arene. Although the previous two terms are more prevalent in the literature, the term direct arylation is now the most used, and can be described as the direct coupling of a nonactivated aryl C–H bond with an activated arene. Although there exist a variety of routes for the construction of aryl-aryl bonds, arguably the most common method is through the use of transition-metalmediated reactions. Chemo- and regioselectivities can, in

principle, be achieved by tweaking the properties of the metal complex through choice of metal and by ligand design. Typically, these reactions involve either the coupling of an aryl halide or pseudohalide with an organometallic reagent, or the homocoupling of two aryl halides or two organometallic reagents.



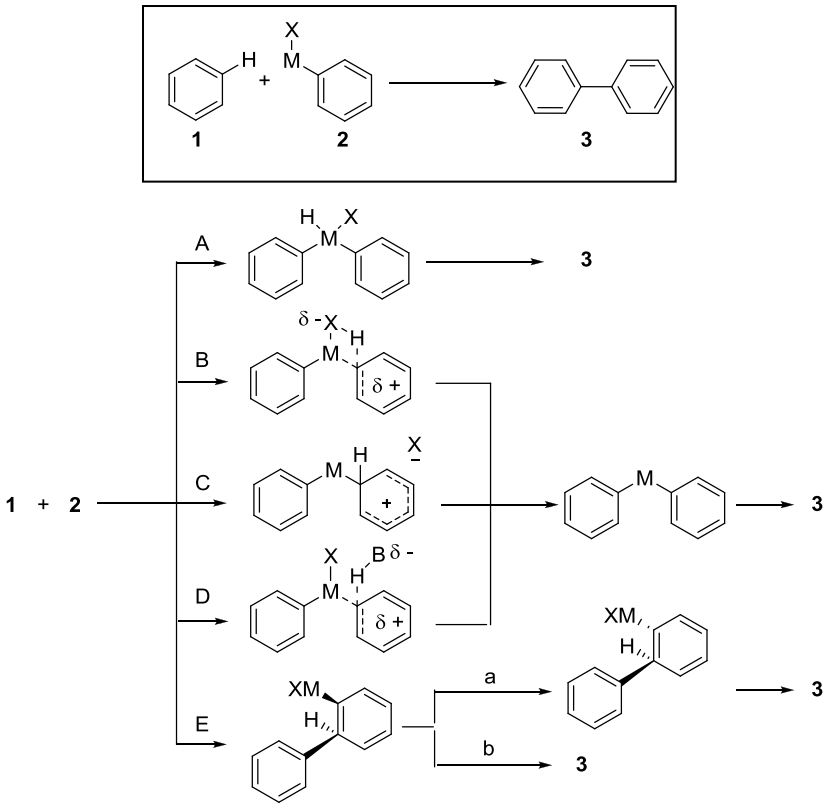

**Scheme 5**

The simplest approach would involve the coupling of two aryl C–H bonds to give the corresponding biaryl product (Scheme 5), although this process is unfavorable from a thermodynamic perspective due to the high bond strength of an aryl C–H bond (e.g., the homocoupling of benzene to give biphenyl and hydrogen is thermodynamically disfavored by 13.8 kJ/mol). Furthermore, while such an approach is alluring, the ubiquitous and diverse nature of C–H bonds in complex organic compounds makes a regioselective oxidative coupling of this type a formidable challenge.

One solution which addresses the thermodynamic issue as well as the need for stoichiometric activating agents on both coupling partners is to use a preactivated aryl substrate as one coupling partner and a simple unactivated aryl substrate as the other (Scheme 5). Although the advantages of this strategy for aryl-aryl coupling have made it a popular topic of research since the first reports over 20 years ago, the more subtle issue of C–H bond regioselectivity remains unsolved in some systems.

Although a variety of transition metals have been used for the formation of aryl-aryl bonds, second-row transition metals in low oxidation states (Rh, Ru, Pd) have emerged as the preferred catalysts in catalytic direct arylation reactions. In some cases, the high reactivity of the transition-metal complexes employed in direct arylation reactions has allowed for the use of extremely low

catalyst loadings (as low as 0.1 mol %), making them industrially attractive. The ligands used in direct arylation depend on the nature of the aryl halide being used. For more reactive aryl iodides, moderately electron-rich monodentate phosphines such as $P(Ph)_3$ are typically used. These same phosphines have also been successfully utilized for aryl bromides, although in some systems far superior yields have been obtained using palladium and more sterically bulky and electron-rich trialkylphosphine or Buchwald's biphenylphosphines. Recently, the use of aryl chlorides in a palladium-catalyzed direct arylation reaction has also been reported. However, as in other cross-coupling reactions, the low reactivity of the C–Cl bond to oxidative addition necessitated the use of electron-rich and sterically-hindered trialkylphosphines, Buchwald's biphenylphosphines, or *N*-heterocyclic carbene ligands to achieve synthetically useful yields of the direct arylation product. It should also be noted that ligand-free conditions (Jeffery's conditions) have also been successfully used in palladium-catalyzed direct arylation reactions for a variety of aryl halides. While base is generally required in direct arylation reactions, in most cases the exact role of the base remains unclear. Some recent evidence, however, suggests that in some systems the base may be intimately involved in the formation of the diarylpalladium(II) species (and not simply as a bystander whose role is to regenerate the active catalyst). Typically, inorganic bases such as $K_2CO_3$, $Cs_2CO_3$, KOAc, *t*-BuOK, and CsOPiv are used. In particular, cesium carbonate and cesium pivalate have proven to be very effective in many cases due to increased solubility in organic solvents. While polar, aprotic solvents such as DMF, DMA, MeCN, NMP, and DMSO are commonly used, nonpolar solvents such as toluene and xylene have also been employed successfully. In addition, temperatures >100 °C are typically used, and in most cases heating for several hours to days is necessary.




A.Oxidative addition B. σ-bond metathesis C. electrophilic substitution D. $SE^3$
E. Heck type

**Scheme 6**

Direct arylation reactions can take place in either an intermolecular or an intramolecular fashion. While intramolecular direct arylation reactions employ tethers to limit the degree of freedom in a system, thereby controlling the regioselectivity of the reaction, intermolecular direct arylation reactions present a more formidable task since the catalyst has a greater degree of freedom when reacting at the C-H bond. Two factors that influence the regioselectivity of the intermolecular direct arylation are the electronics of the arene being functionalized, for

example the reaction occurs *ortho* or *para* to the electrondonating group via an electrophilic aromatic substitution process, and more commonly the directing group. Typically, directing group-assisted reactions employ nitrogen- and oxygen-coordinating functional groups to direct the arylation, although in some cases external alkenes or alkynes in a cascade process have been used to create a "directing" alkyl- or alkenylmetal species in situ.

Mechanistically, the direct arylation of arenes is proposed to occur via oxidative addition of the transition metal into the aryl halide, followed by one of a number of possible key C-C bond-forming steps (Scheme 6):

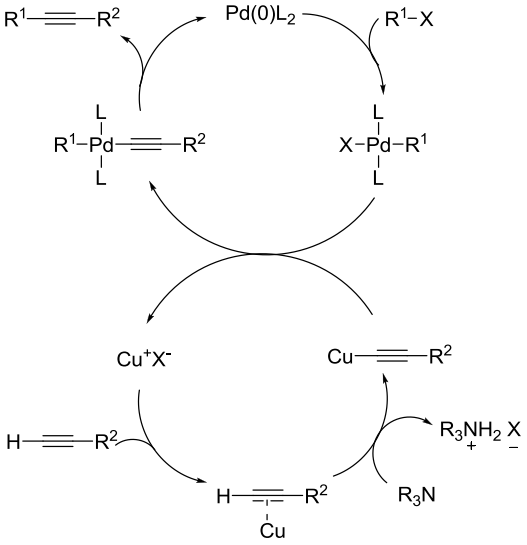
- a C–H bond oxidative addition
- a σ–bond metathesis
- electrophilic aromatic substitution at the metal ($SE_{Ar}$)
- a Heck-type (or carbometalation) process either through a formal anti β-hydride elimination or via isomerization followed by a *syn* β-hydride elimination
- a concerted $SE^3$ process

While the exact nature of this step has been investigated for some systems, it should be noted that the exact mechanism for any given example depends on the substrate, transition metal, solvent, base, and ligand used.

## 1.2.3 Sonogashira coupling

The Sonogashira-Hagihara reaction (more often simply known as Sonogashira coupling) is the most popular procedure for the alkynylation of aryl or alkenyl halides, originally reported in 1975. This protocol is based on the the addition of copper salts as cocatalysts thus accelerating the coupling reaction and enabling performance of the alkynylation at room temperature.

The copper-cocatalyzed Sonogashira reaction is believe to take place through two independent catalytic cycles as shown in scheme 7, where a tertiary amine is represented as base, with other amines or inorganic bases performing similarly. [18, 19, 20] The Pd-cycle is based on fast oxidative addition of $R^1$–X ($R^1$= aryl, hetaryl, vinyl; X= I, Br, Cl, OTf) to the catalyst. This is classically thought to be 14-electron $Pd(0)L_2$, formed by reduction of different Pd(II) complexes using ligands and solvents that can reduce Pd(II) species typically via σ-complexation-dehydropalladation-reductive elimination.




**Scheme 7**

In the oxidative addition step, the characteristics of the $R^1$–X substrate are crucial because this step results facilitated if X= I or OTf and if the electronic density is reduced on the 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 cocatalyst. Thus, a usually rate-determining transmetalation from the copper acetylide formed in the Cucycle would generate a $R^1$Pd-($CCR^2$)$L_2$ species, which gives the final coupled alkyne after *trans/cis* isomerisation and reductive elimination with regeneration of the catalyst. The second Cu-cycle is still poorly understood. The base (generally an amine) is supposed to abstract the acetylenic proton of the terminal alkyne, thus forming a copper acetylide 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 in order to generate the anionic nucleophile that should form the copper acetylide. Therefore, a π-alkyne-Cu complex could be involved in the cycle, thus making the alkyne proton more acidic for easier abstraction.

The copper acetylides 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-($CCR^2$)$_2L_2$, which after reductive elimination would afford active Pd(0)$L_2$ and some amounts of a diacetylene byproduct.

The two catalysts tipically used in this reaction are $PdCl_2(PPh_3)_2$ and CuI. In this case, the oxidation of triphenylphosphine to triphenylphosphine oxide leads to the formation of Pd(0) *in situ*. In contrast, CuI reacts with the terminal alkyne and produces a copper(I) acetylide, which acts as an activated species for the coupling reactions.

The reaction medium have to be basic to neutralize the hydrogen halide produced as the byproduct of this coupling reaction, so alkylamine compounds such as triethylamine and diethylamine are sometimes used as solvents, but also DMF, THF or ether can be used as solvent. In addition, deoxygenated conditions are formally needed for Sonogashira coupling

reactions because the palladium(0) complexes are unstable in the air, and oxygen promotes the formation of homocoupled acetylenes. Recently, development of air-stable organopalladium catalysts enable this reaction to be conducted in the ambient atmosphere.

As in the other Pd-catalyzed cross-coupling reactions, the reactivity order of the organic electrophiles, with respect to leaving groups, is on the same trends as mentioned in Heck preface:

$I \geq OTf \geq Br > Cl$. For the substituents the reactivity order is:

$EWG > H > EDG$.

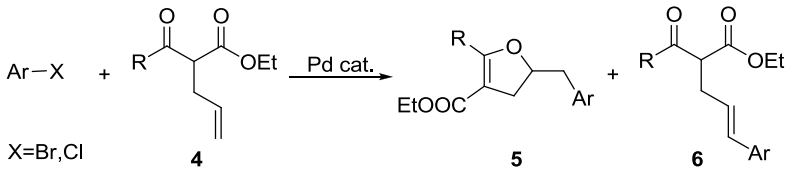
## 1.3 New palladium-catalyzed synthetic strategies

In this section the main features of our synthetic approaches to different classes of compounds will be discussed.

### 1.3.1 Functionalized 2,3-dihydrofurans via palladium-catalyzed oxyarylations of α-allyl-β-ketoesters [21]

The 2,3 dihydrofuran motif is displayed in a large number of bioactive natural products as well as pharmaceutically important unnatural compounds such us neo-clerodane diterpenoids [22] and aflatoxin B1. [23] In addition, 2,3 dihydrofuran derivatives are useful synthetic intermediates. [24] Some of the most convenient approaches to the construction of the 2,3-dihydrofuran system are based on the reaction of active methylene compounds [25] or ylides with suitable electophiles. [26] Palladium catalyzed approaches are also known. [27] Despite the number of methods developed, the search of more general and versatile synthetic approaches to this class of compounds continues to be an active area of research.

Recently, we have developed a synthesis of hexahydro-3*H*-pyrrolizin-3-ones through Pd-catalyzed carboamination. [28] Subsequently, Wolfe at al. have reported the same reactivity between aryl bromide and 4-(but-3-enyl)-substituted-oxazolidin-2-ones to give trans-2,5 disubstituted pirrolidines. [29] On the basis of our studies, we have investigated the palladium catalyzed oxyarylation of α-allyl-β-ketoesters to obtain a catalytic route for the synthesis of substituted 2,3-dihydrofurans as shown in scheme 8.

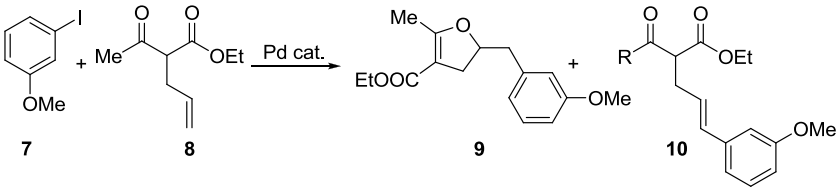



**Scheme 8:** Work hypothesis

Using the reaction of 3-bromanisole **7** with ethyl 2-acetylpent-4-enoate **8** as probe for evaluating the reaction condition, we starting our study by examining the influence of ligands, bases, and solvents in the presence of $Pd_2(dba)_3$ at 100°C in 0.08 M solutions. Low to moderate yields of **9** were obtained using XantPhos [30] and $Cs_2CO_3$ in 1,4-dioxane by increasing loading of catalyst from 0.01 to 0.025 equiv. (Table 1, entry 1-7). With dppf or dppb ligands no evidence of **9** was obtained and the Mizoroki-Heck derivative **10** was isolated as the main product (Table 1, entry 8-10).

Pleasingly, an increase of both the yield and the *oxypalladation/ Mizoroki-Heck reaction* selectivity were observed by switching to RuPhos (Table 1, entry 13). Higher yields and selectivity were observed using MeCN as solvent (Table 1, entry 14). Further optimization studies revealed that the best results could be obtained by using 0.025 equiv $Pd_2(dba)_3$, 0.05 equiv RuPhos, and 1.2 equiv $Cs_2CO_3$, in a more concentred 0.25 M MeCN solution at 100°C. Under these conditions **9** was isolated in 79 % yield in 2.5 h and no
Mizoroki-Heck product was observed (Table 1, entry 17).
Under the optimized conditions, we have obtained a variety of polyfunctionalized-2,3-dihydrofurans from electron-poor aryl halides.
However, using electron-rich aryl halides produced the desired dihydrofurans in low yield. In these cases, raising the ligand to palladium ratio from 1:1 to 2:1, led to the isolation of the corresponding dihydrofurans in good yield. Consequently, we decided to employ 0.05 equiv RuPhos with neutral or electron-poor aryl halides and 0.1 equiv RuPhos with electron-rich aryl halides.

**Table 1** Catalysts, Solvents, Bases in the reaction of 3-bromoanisole with ethyl 2-acetylpent-4-enoate




| Entry | Ligand or catalyst (equiv) | Solvent(ml) | Base | Time (h) | Yield 9 (%) | Yield 10 (%) |
|---|---|---|---|---|---|---|
| 1 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 5 | 20[a] | - |
| 2 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 5.5 | 27[a] | - |
| 3 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 3.5 | 25[b,c] | - |
| 4 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 5.5 | 27[b,d] | - |
| 5 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 8 | 24[b] | - |
| 6 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 3 | 31[e] | - |
| 7 | Xantphos | 1,4-dioxane | $Cs_2CO_3$ | 3 | 23[e,f] | - |
| 8 | Dppf | 1,4-dioxane | $Cs_2CO_3$ | 2.5 | -[e] | 60 |
| 9 | dppb | 1,4-dioxane | $Cs_2CO_3$ | 6 | -[e] | 65 |
| 10 | $Pd(PPh_3)_4$ | 1,4-dioxane | $Cs_2CO_3$ | 3 | - | 30 |
| 11 | Sphos 0.05 | 1,4-dioxane | $Cs_2CO_3$ | 22 | 52[e] | 28 |
| 12 | Sphos | 1,4-dioxane | $K_3PO_4$ | 24 | 32[e] | 28 |
| 13 | Ruphos 0.05 | 1,4-dioxane | $Cs_2CO_3$ | 2.5 | 65[e] | 13 |
| 14 | Ruphos 0.05 | MeCN | $Cs_2CO_3$ | 2.5 | 74[e] | - |
| 15 | Ruphos 0.05 | Toluene | $Cs_2CO_3$ | 1 | 44[e] | 25 |
| 16 | Ruphos 0.05 | DMF | $Cs_2CO_3$ | 1.5 | 55[e] | - |
| 17 | Ruphos 0.05 | MeCN | $Cs_2CO_3$ | 2.5 | 79[c,e] | - |
| 18 | Ruphos 0.05 | MeCN | $K_3PO_4$ | 1 | 60[c,e] | 8 |
| 19 | Ruphos 0.05 | MeCN | $K_2CO_3$ | 2 | 55[c,e] | - |
| 20 | Ruphos 0.05 | MeCN | $NaHCO_3$ | 9 | Traces[c,e] | - |

Reactions are carried out on a 0.05 mmol scale at 100°C in a 0.08 M solution under a nitrogen atmosphere using 1 equiv. of **7**, 1.2 equiv of **8**, 1.2 equiv of base and 0.01 equiv of $Pd_2(dba)_3$. [b] 0.015 equiv of $Pd_2(dba)_3$. [c] 0.25 M. [d] 0.05 M. [e] 0.025 equiv of $Pd_2(dba)_3$. [f] 1 equiv of **7** and 2 equiv. of **8**.

A possible explanation of these results could arise from the catalyst precipitation, most probably due to the slow rate of the oxidative addition usually observed with electron-rich aryl halides. An increased amount of ligand should allow for a better solubilization of the catalyst. Using these conditions we next explored the scope and generality of the process. In general, clean formation of 2,3 dihydrofurans was observed with a variety of neutral, electron-rich and electron-poor aryl bromides. The reaction tolerates several useful substituents including chloro, fluoro, ether, ketone, ester, cyano, and nitro groups. The ability to incorporate chloro substituent is particulary interesting since it can be used for further synthetic manipulations via transition metals catalyzed coupling reactions. *Ortho* substituents such as *o*-methyl and *o*-cyano groups are also well tolerated.

The method can be extended to aryl nonaflates and chlorides, although electron –poor aryl chlorides afford oxyarylation products in excellent yields whereas electron-rich aryl chlorides are less successful substrates.

Heterocyclic halides were briefly investigated and were found to give the corresponding 2,3-dihydrofurans in moderate to high yields. The influence of the substituent diversity of the α-allyl-β-ketoesters was also explored. We found that the oxyarylation reaction appear to be disfavored by substituents decreasing the nucleophilicity of the enolate of the β-ketoester both with electron-rich and electron poor aryl halydes.

Our preparative results are summarized in the table 2.

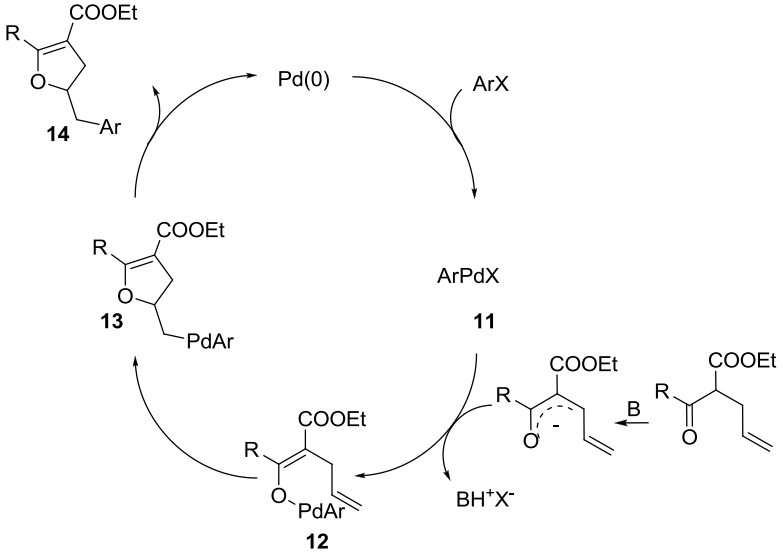
**Table 2**: Synthesis of functionalized 2,3-dihydrofurans from α-allyl-β-ketoesters

| Entry | Aryl halide | R | Time (h) | Yield |
|---|---|---|---|---|
| 1 | 3-$MeOC_6H_4Br$ | Me- | 2.5 | 79 |
| 2 | 4-$MeOC_6H_4Br$ | Me- | 4.5 | 64 |
| 3 | 3-$CF_3C_6H_4Br$ | Me- | 2.5 | 92 |
| 4 | 3-$MeC_6H_4Br$ | Me- | 5 | 79 |
| 5 | 4-$MeC_6H_4Br$ | Me- | 4.5 | 73 |
| 6 | 4-$CNC_6H_4Br$ | Me- | 1.5 | 86 |
| 7 | 4-$MeCOC_6H_4Br$ | Me- | 1 | 91 |
| 8 | 2-$CNC_6H_4Br$ | Me- | 2.5 | 92 |
| 9 | 3-$NO_2C_6H_4Br$ | Me- | 4.5 | 81 |
| 10 | 3-bromoquinoline | Me- | 5 | 75 |
| 11 | 4-$FC_6H_4Br$ | Me- | 2.5 | 70 |
| 12 | 4-$MeOC_6H_4Br$ | Me- | 7 | 44 |
| 13 | 3-$MeC_6H_4Br$ | Me- | 7 | 65 |
| 14 | 4-$MeC_6H_4Br$ | Me- | 24 | 54 |
| 15 | 4-$MeOC_6H_4Cl$ | Me- | 24 | 44 |
| 16 | 3-$CF_3C_6H_4Cl$ | Me- | 5.5 | 94 |
| 17 | 4-(Me)2C6H4Br | Me- | 5 | 33 |
| 18 | 2-bromopyridine | Me- | 5.5 | 51 |
| 19 | 3-chloropyridine | Me- | 24 | 37 |
| 20 | 4-$CNC_6H_4Br$ | Furyl- | 0.66 | 84 |
| 21 | 4-$MeC_6H_4Br$ | Furyl- | 2,5 | 74 |
| 22 | 4-$CNC_6H_4Br$ | *i*-Pr | 0.75 | 90 |
| 23 | 4-$MeC_6H_4Br$ | *i*-Pr | 2.5 | 83 |
| 24 | 4-$CNC_6H_4Br$ | Ph- | 2.5 | 84 |
| 25 | 4-$MeC_6H_4Br$ | Ph- | 17 | 31 |

Reactions were carried out on a 0.5 mmol scale, at 100°C in a 0.25 M solution of anhydrous acetonitrile, under a nitrogen atmosphere using 1 equiv of aryl halide, 1.2 equiv of **1**, 1.2 equiv of $Cs_2CO_3$, 0.025 equiv of $Pd_2dba_3$ 0.05 equiv of Ruphos. Reactions 2, 4, 5, 17, 21 with 0.1 equiv of Ruphos. Reaction 24 with 0.1 equiv of Ruphos at 100°C

Most probably the reaction proceeds according to a mechanism analogous to that described for related palladium-catalyzed reaction [31] (Scheme 9).

Palladium(0) reacts with the aryl halide through an oxidative addition to give the σ-complex **11** that could undergo an oxygen displacement with the *in situ* generated enolate to afford the adduct **12**. A subsequent intramolecular oxypalladation would provide the intermediate **13** from which the 2,3 dihydrofuran derivative **14** would form *via* reductive elimination .



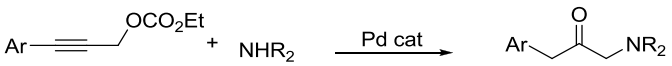

**Scheme 9** Proposed reaction mechanism

In summary, we have shown that palladium catalysis provides an efficient tool for the construction of polifunctionalized dihydrofurans from α-allyl-β-ketoesters and aryl halides. The reaction tolerates a variety of neutral, electron-rich and electron-poor aryl bromides. *Ortho* substituents are also tolerated. Similar yields are obtained employing aryl chlorides. Main advantages of our procedure include simplicity of operation and use of readily available, inexpensive and harmless starting materials.

## 1.3.2 Palladium-catalyzed synthesis of 2-amino ketones from propargylic carbonates and secondary amines [32]

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 [33] and of a small family of linear peptides including the antitumor agent eponemycin. [34] Furthermore 2-amino-ketones are useful synthetic intermediates. [35] 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 [36] and enolsilanes, [37] on the osmium-catalyzed ketamination of alkenes, [38] on the conversion of the carboxylic group of amino acids into a ketonic group [39] and on the formation of carbon-carbon bonds between carbonyl and amino-containing fragments. [40] 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. [41]

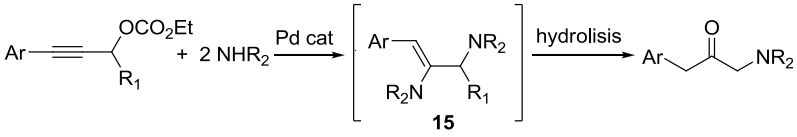
We have developed a new palladium–catalyzed route to 2-amino-ketones from readily available propargylic carbonates and secondary amines that involves a formal anti-Markovnikov addition of water to the carbon-carbon triple bond and the substitution of the $C_{propargylic}$–N bond for the $C_{propargylic}$–O bond (Scheme 10).




**Scheme 10** Palladium-catalyzed synthesis of 2-amino ketones from propargylic carbonates and secondary amines

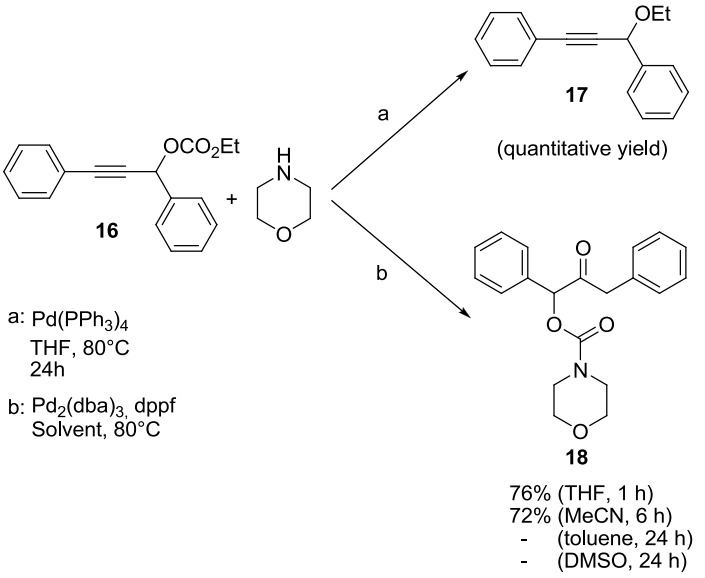
On the basis of our previous study showing that 2-aminomethyl indoles could be prepared from 3-(*o*-trifluoroacetamidophenyl)-1-propargylic carbonates and amines

through a process involving sequential intramolecular/intermolecular C–N bond forming steps, we 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 **15** and hydrolysis (Scheme 11).




**Scheme 11** Work hypothesis

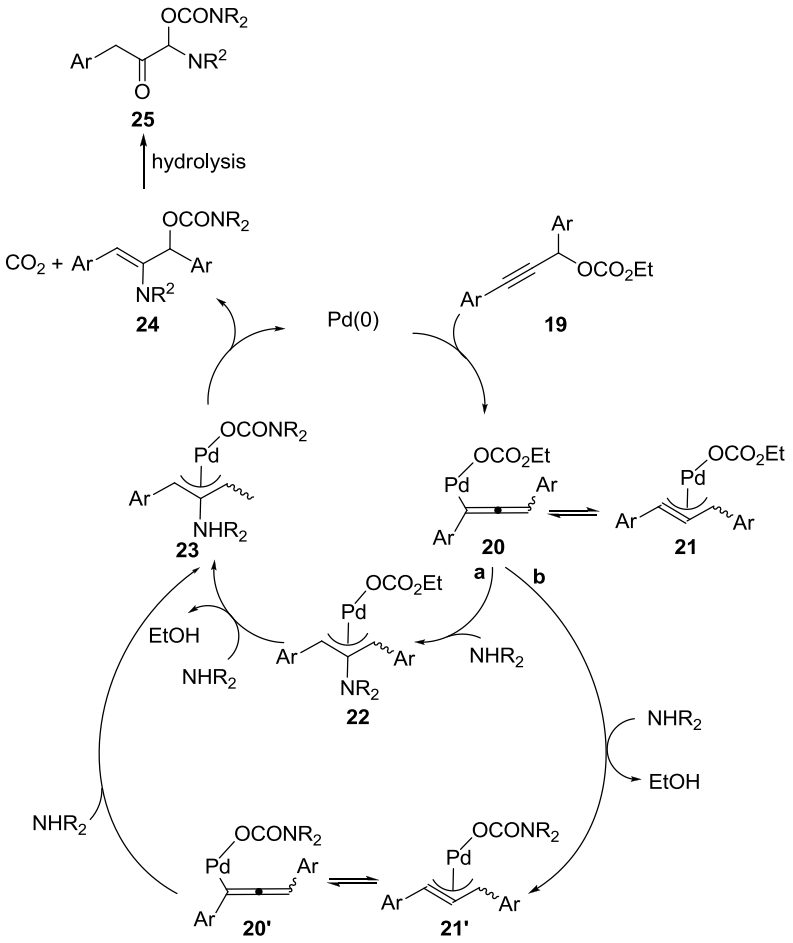
We set out to use the reaction of 1 equiv of **16** with 3 equiv of morpholine as model system to evaluating the feasibility of reaction.




**Scheme 12** Reaction of **16** with morpholine in the presence of $Pd(PPh_3)_4$ and $Pd_2(dba)_3$/dppf.

First attemps met with failure: under the same conditions employed for the 2-aminomethyl indoles synthesis the ether **17** was formed in almost quantitative yield (Scheme 12 a).

The reaction produced instead the ketocarbamate **18** in 76 % using the $Pd_2(dba)_3$/dppf combination in THF at 80°C (Scheme 12 b). Using MeCN as solvent gave **18** in a slightly lower yield whereas only degradation products were formed in toluene and DMSO. For this reaction we proposed the following mechanism (Scheme 13). Palladium reacts with the phenylpropargylic carbonate **19** to give the σ allenyl-palladium complex **20** which would be in equilibrium with the propargylic palladium intermediate **21**. The nucleophilic attach of the morpholine at the central carbon of the complex followed by a protonatium step, give the allylic palladium complex **22**. This complex is attached by another molecule of morpholine to give the carbamate palladium complex **23**. Alternatively, morpholine can displace the ethoxy group of **20**/**21** to give **20'**/**21'** that is converted in the carbamate complex **23** 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 **23** and the hydrolysis of the resultant enamine intermediate **24** generates the ketocabamate **25**. Experimental evidence for the intermediacy of **24** was obtained by NMR analysis of the crude reaction mixture before work up. Steric effects due to the substituents of **22** or **23** 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 we decided to investigated the reactivity of the unsubstituted propargylic carbonate **26**. 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.

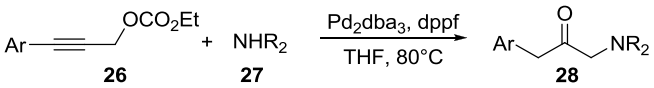



**Scheme 13** Proposed mechanism for the formation of the carbamate derivative **25**

Using these conditions we next explore the scope and the generality of the process; as shown in table 3 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 3** Palladium catalyzed synthesis of 2-amino-ketones from propargylic carbonates and secondary amines



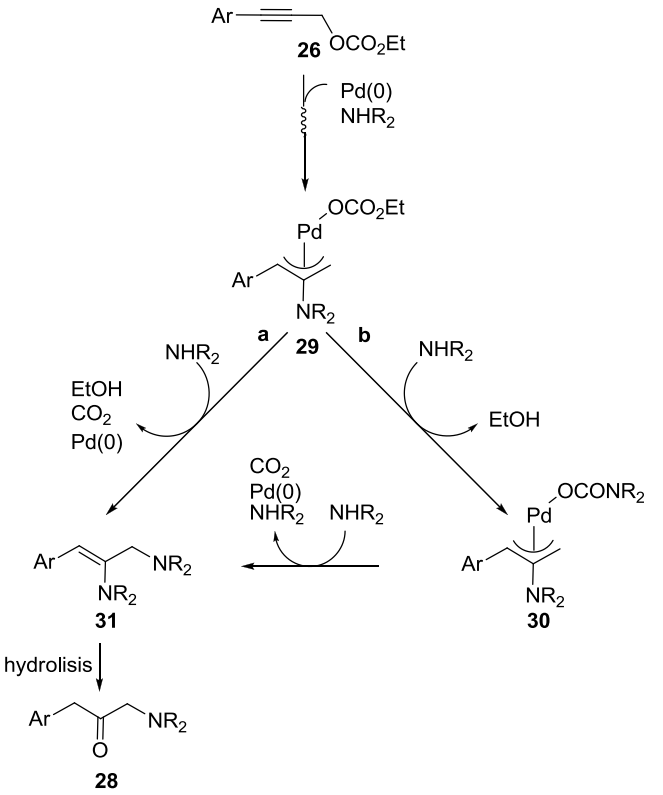

**26** **27** **28**

| Entry | Ar | Amine 27 | t (h) | Yield 28 (%) |
|---|---|---|---|---|
| 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 |

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 **28** we proposed the mechanism depicted in the following Scheme 13.

After the initial reaction of Pd(0) with the aryl-propargylic carbonate **26** occurs an intamolecular nucleophilic attack of the nitrogen at the less substituted terminus of the π-allylic palladium complex **29** (Scheme 14 a). The resultant enamine **31** generate the desired 2-aminoketone **28** after hydrolysis.



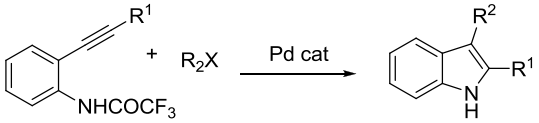

**Scheme 14** Proposed reaction mechanism for the formation of 2-aminoketone **28**

Alternatively, (Scheme 14 b) morpholine can displace the ethoxy group of **29** to give the carmamate palladium complex **30** that is converted in the enamine **31** after an intramolecular nucleophilic attack of the nitrogen at the less substituted allylic carbon.

In summary, we have developed 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. Our procedure is simple, uses readily available starting materials and may represent a useful tool for the synthesis of this class of compounds.

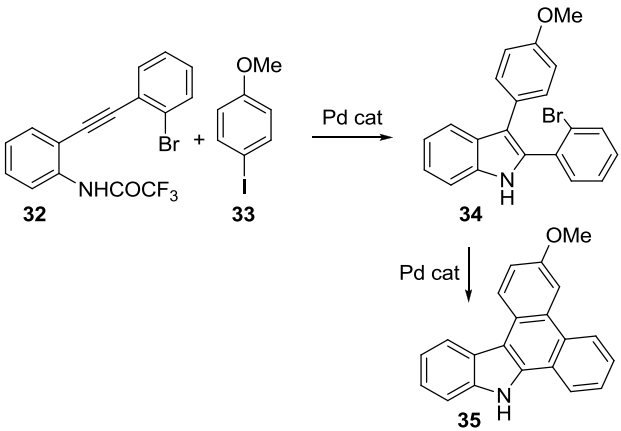
## 1.3.3 Dibenzo[*a,c*]carbazoles from *N*-(2-bromoaryl)-3-arylindoles via a palladium-catalyzed intramolecular C–H funtionalization/C–C bond formation process [42]

The palladium catalyzed reaction of alkynyltrifluoroacetanilides with organopalladium intermediates generated in situ from Pd (0) species and aryl and vinylic halides or triflates, alkyl halides, alkynyl halides and allylic esters has been proved to be a powerful and versatile tool for the construction of the substituted indole ring (Scheme 15). [43]




**Scheme 15** Palladium catalyzed synthesis of indoles from trifluoroacetanilides

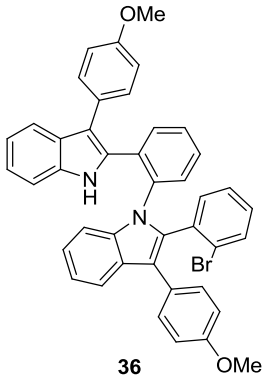
As part of our ongoing study, we hypothesized that in presence of appropriate functional groups this indole synthesis might be exploited to provide a new ready access to condensed carbazoles (Scheme 16).




**Scheme 16** Work hypothesis

The stimulus for this study has been provided by the growing importance of condensed (hetero)aromatic rings in organic material science [44] and by their biological avtivities. [45] In addition, combining our indole synthesis with a cyclization based on a C–H functionalization/C–C bond formation reaction appeared particularly attractive for us. Indeed, direct transition metal-catalyzed functionalization of (hetero)arenes via the activation of inert C–H bonds has attracted a great deal of attention in recent years.[46]

Initial attempts to cyclize [2-(2-Bromoaryl)ethynyl]trifluoroacetanilides **32** to the corresponding carbazole derivatives **35** were carried out using $Pd(OAc)_2$ as the source of Pd (0) species. We tested various ligands, bases, solvents and reaction temperature but formation of only traces of the desired carbazole was observed in several cases along with the N-arylation byproduct **36** (Figure 3).



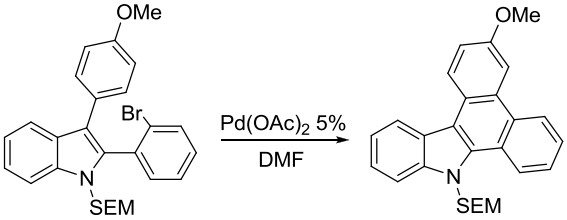

**36**

**Figure 3** *N*-arylation byproduct

To avoid the formation of N-arylation byproducts we decided to protect the indole NH group; several protecting groups was explored but best results were obtained with 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl). The SEM derivative was isolated in 95% yield upon treatment of 34 with SEM-Cl in the presence of NaH in DMF at room temperature for 1h. With an efficient procedure for the preparation of the starting indole in the hands, the cyclization of **37** into the corresponding carbazole was next investigated.

As shown in table 4, the best result both in term of yield and reaction time was observed using $P(Ph)_3$ and Cs(OAc) in DMF at 120°C (Table 4, entry 6). The protecting group could be readily removed by treating the *N*-SEM carbazole with a THF solution of *n*-$Bu_4NF$ at 60°C. Furthermore the cyclization/deprotection sequence could be performed omitting the isolation of the intermediate protected carbazole, by adding the reagents required for the deprotection step to a crude mixture following the cyclization of **37** had been concentred under reduced pressure. Under these conditions the corresponding free NH carbazole was isolated in 70% overall yield.

**Table 4** Cyclization of the SEM derivative **37**




**37** **38**

| Entry | Ligand (equiv) | Base | Time (h) | Temperature (°C) | Yield 38 (%) |
|---|---|---|---|---|---|
| 1 | Dppe (0.05) | $K_2CO_3$ | 7 | 100 | 25[a] |
| 2 | Dppe (0.01) | $K_2CO_3$ | 8 | 120 | 23[b] |
| 3 | Dppe (0.02) | $K_2CO_3$ | 23 | 120 | 37[c] |
| 4 | Dppe (0.01) | CsOAc | 7 | 120 | 40[d] |
| 5 | Dppe (0.02) | CsOAc | 1.5 | 120 | 89 |
| 6 | $P(Ph)_3$ (0.02) | CsOAc | 0.5 | 120 | 97 |

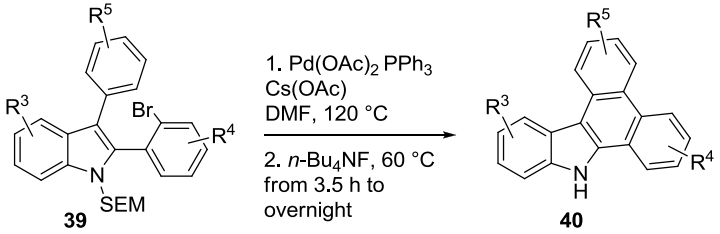
Reaction were carried out under a nitrogen atmosphere on a 0.25 mmol scale in 5 mL of DMF using 0.05 equiv. of $Pd(OAc)_2$, a phosphine ligand, and 2 eqiuv. of base.
[a] The starting material was recovered in 74% of yield; [b] the starting material was recovered in 49% of yield; [c] the starting material was recovered in 37% of yield; [d] the starting material was recovered in 25% of yield.

This protocol was then used when the process was extended to include other *N*-SEM indoles. Our preparative results are summarized in table 5. Several carbazole derivatives bearing a variety of functional groups have been prepared in good to excellent yield. With indoles bearing *meta* substituent on the aryl ring at the C 3 position, two regioisomeric carbazole derivatives can form and the nature of the substituents was found to play an important role in controlling the composition of the reaction mixture. In the presence of *m*-Me or *m*-OMe groups almost equimolecular amounts of the two regioisomers are formed (table

5, entries 13 and 14). With the more steric demanding *m*-$CF_3$ group the new C–C bond is formed regioselectively at the less crowded *ortho* position (Table 5, entry 3). With indoles derivatives bearing a metha cyano substituent the new C–C bond is formed preferentially at the more crowded *ortho* position (Table 5, entry 3). Such a behavior may be accounted for by the coordination of the cyano group to the palladium atom of the aryl-palladium complex formed *in situ* via oxidative addition. The resultant intermediate would exert a directing effect on the cyclization step.

As to the mechanism of the cyclization step, an intermolecular competition experiment using the compound **41** (Figure 4) and the corresponding indole containing a deuterium labeled 3-phenyl substituent **42** suggest that a hydrogen-abstraction step is not involved in the rate limiting step. No isotope effects was observed when this two compounds were subjected to cyclization conditions supporting the view that the reaction proceeds through an electrophilic aromatic substitution involving the intermediate **43**.

**Table 5** Cyclization of the SEM derivatives




| Entry | $R^3$ | $R^4$ | $R^5$ | Time (h) | Yield 40 (%) |
|---|---|---|---|---|---|
| **1** | H | H | 4-OMe | 0.5 | 70 |
| **2** | H | H | 4-CN | 7 | 92 |
| **3** | H | H | 3-$CF_3$ | 24 | 60 |
| **4** | H | H | 2-Me | 0.5 | 84 |
| **5** | H | H | 4-MeCO | 5 | 65 |
| **6** | H | H | 4-EtOCO | 24 | 65 |
| **7** | H | H | 4-$NO_2$ | 5 | 73 |
| **8** | H | H | 4-Cl | 24 | 80 |
| **9** | H | H | H | 9 | 62 |
| **10** | 5-CN | H | H | 1 | 75 |
| **11** | H | 4-Me | 4-MeO | 9 | 61 |
| **12** | H | 4-Me | 4-MeCO | 1 | 77 |
| **13** | H | H | 3-Me | 24 | 95[a] |
| **14** | H | H | 3-MeO | 24 | 60[b] |
| **15** | H | H | 3-CN | 24 | 55[c] |

Reactions were carried out under a nitrogen atmosphere on a 0.25 mmol scale in 5mL of DMF at 120 °C using 0.05 equiv of $Pd(OAc)_2$, 0.2 equiv of $P(Ph)_3$ and 2 equiv of CsOAc. [a] Yield refers to a mixture of two regioisomers which ratio is 50:50; [b] yield refers to a mixture of two regioisomers which ratio is 45 : 55; [c] yield refers to a mixture of two regioisomers which ratio is 75 : 25.

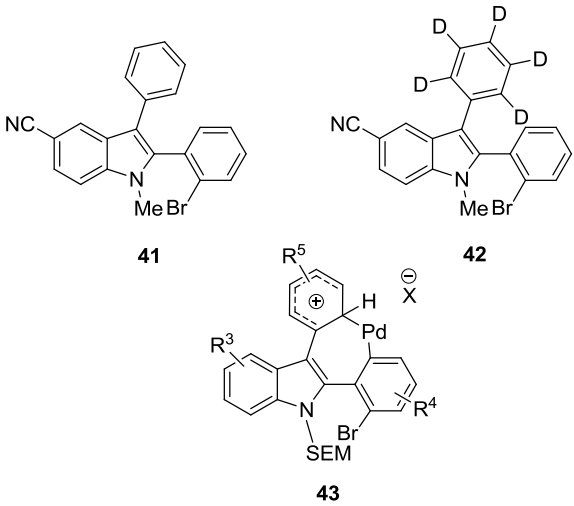
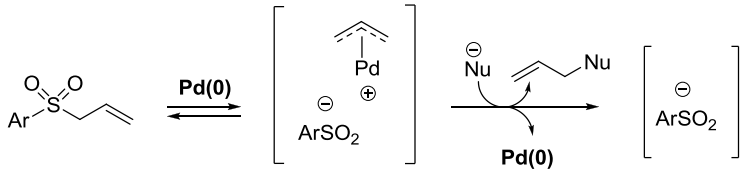



**Figure 4** Mechanicistic hypothesis

To summarize, this work describes a general protocol for the synthesis of dibenzo[a,c]carbazoles from 2-(2-bromoaryl)-3-arylindoles, readily available from 2-[(2-bromoaryl)ethynyl]trifluoroacetonilidies. The reaction tolerates a variety of useful substituents including chloro, nitro ether , cyano, keto, and ester groups. and proceeds through an intramolecular palladium-catalyzed C–H fuctionalization/C–C bond formation process that most probably involves an electrophilic aromatic substitution.

## 1.3.4 Palladium-catalyzed aromatic sulfonylation: a new catalytic domino process exploiting in situ generated sulfinate anions [47]

Aromatic sulfones are compounds of considerable interest embedding a number of positive features such as stability, crystallinity, chromophoric activity, [48] as well as antibactarical anti fungal and antitumor activities.[49] As reported under palladium catalysis, allyl sulfoxides can generate sulfonenate anions which can in turn be easily cross-coupled to afford aryl sulfoxides. [50, 51] On the basis of these our previous study we hypothesized the extension of palladium catalyzed allyl-to-aryl conversion domino process from sulfoxides to solfones according to the scheme 17.

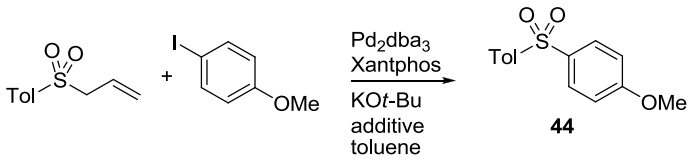



**Scheme 17** Work hypothesis

As shown, the desired sulfinate anion is generated via oxidative addition of an allylic sulfone onto a palladium complex. Subsequent nucleophilic interception of the thus formed $\eta^3$–allyl–palladium complex is then expected to trigger the sulfinate anion release, which may in turn be further reacted in a palladium-catalyzed arylation reaction.

We selected ad model system for our preliminary studies the palladium–catalyzed sulfonylation reaction of the allyl *p*-tolyl sulfone and 4-iodoanisole. Some of our results are summarized in table 6.

**Table 6** Optimization studies of the palladium-catalyzed aromatic sulfonylation



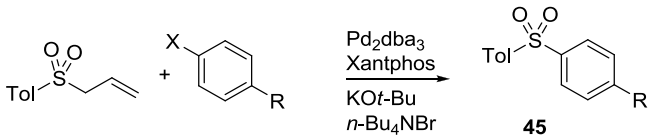

| Entry | Additive | Temperature (°C) | Yield 44 (%) |
|---|---|---|---|
| 1 | - | 80 | - |
| 2 | *n*-$Bu_4NCl$ | 80 | - |
| 3 | *n*-$Bu_4NBr$ | 80 | 65 |
| 4 | *n*-$Bu_4NHSO_4$ | 80 | 15 |
| 5 | *n*-$Bu_4NBr$ | reflux | 88 |

Reactions were carried out using 1.2 equiv. of 4-iodoanisole, 1 equiv. of allyl p-tolyl sulfone, 0.02 mol % of $Pd_2dba_3$, 0.05 mol % of XantPhos, 2 equiv. of KO*t*-Bu and 2.0 equiv. of additive (if used).

As shown, best results was obtained using 2eq of *n*-$Bu_4NBr$ in presence of 0.02 mol % of $Pd_2dba_3$, 0.05 mol % of Xantphos and 2 equiv. of KO*t*-Bu in toluene (Table 6, entry 5).

With the optimized conditions in the hands we investigate the reaction of the p-tolylsulfone with a variety of substituted aryl halides. Results of these studies are summarized in the next table 7.

**Table 7** Palladium-catalyzed aromatic sulfonylation of different aryl halides



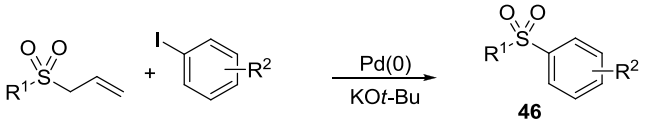

| Entry | X | R | Yield 45 (%) |
|---|---|---|---|
| 1 | I | -OMe | 88 |
| 2 | I | -Me | 66 |
| 3 | I | $-CF_3$ | 16 |
| 4 | I | $-NO_2$ | - |
| 5 | Br | -OMe | 48 |
| 6 | Br | -Me | 52 |
| 7 | Cl | -OMe | - |

Reactions were carried out in toluene at reflux for 16h

According to these results aryl-iodide and aryl-bromide could be successfully used as partners but aryl-chloride did not allow the desired coupling to take place (see entry 7).

The reaction was next studied using different substituted allyl sulfones as the sulfinate anion source and various aryl iodides (Table 8). Starting from allyl *p*-tolyl sulfone, the reaction with *m*-iodoanisole afforded sulfone in 55% yield (Table 8, entry 2) to compare with 88% yield previously obtainedwith *p*-iodoanosole (Table 8, entry 1). Under the same conditions *o*-iodoanisole did not allow the generation of the expected sulfone (Table 8, entry 4). This suggest that the present coupling is very sensitive to steric hindrance in the vicinity of the aryl halide reacting center.

**Table 8** Palladium-catalyzed aromatic sulfonylation of different allyl sulfones with aryl iodides




| Entry | $R^1$ | $R^2$ | Yield 46 (%) |
|---|---|---|---|
| 1 | 4-Me$C_6H_4$ | 4-MeO | 88 |
| 2 | 4-Me$C_6H_4$ | 3-MeO | 55 |
| 3 | 4-Me$C_6H_4$ | 2-MeO | - |
| 4 | 4-MeO$C_6H_4$ | 4-Me | 40 |
| 5 | 4-MeO$C_6H_4$ | 4-MeO | 37 |
| 6 | 4-$O_2NC_6H_4$ | 4-Me | 21 |
| 7 | 4-$O_2NC_6H_4$ | 4-MeO | - |
| 8 | 2-naphthyl | 4-Me | 60 |
| 9 | 2-naphthyl | 4-MeO | 61 |
| 10 | Bn | 4-MeO | - |

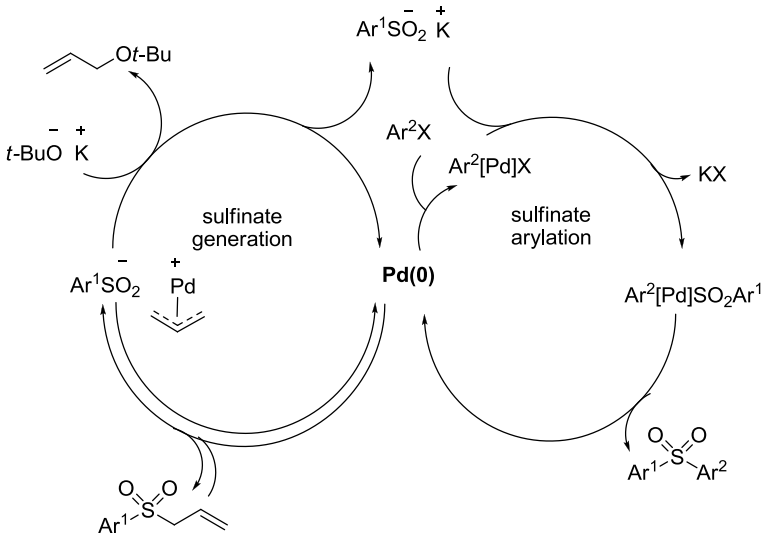
Reactions were carried out in toluene at reflux for 16h

A mechanistic proposal for the palladium-catalyzed sulfinate generation-arylation pseudo-domino [52] catalytic sequence is described in the following scheme 18. First, oxidative addition of the allylic sulfone to Pd(0) is expected to afford the corresponding $\eta^3$-allylpalladium(II) complex. Interception of the allyl moiety of the palladium complex by potassium *tert*-butoxide liberates the sulfinate anion as well as Pd(0), which are both set to enter the second catalytic cycle.

Halide-to-sulfinate ligand exchange on the s-arylpalladium(II) complex in turn to generated from the oxidative addition of the aryl iodide to Pd(0) gives, after reductive elimination, the corresponding aromatic sulfone.

Inspection of this mechanism reveals that such a pseudo-domino process can only be successful if the oxidative addition of the allyl sulfone to the Pd(0) complex is faster than the associated to the aryl halide.

The second catalytic cycle (sulfinate arylation), would probably stall at the irreversibly generated σ-arylpalladium(II) complex stage and no spare Pd(0) complex would be available to feed the first catalytic cycle (sulfinate generation). Such analysis is in accord with the fact yhat the electron-poor aryl halides, which are associated to a fast ossidative addition, did not afford satisfactory results (Table 7, entries 3 and 4).



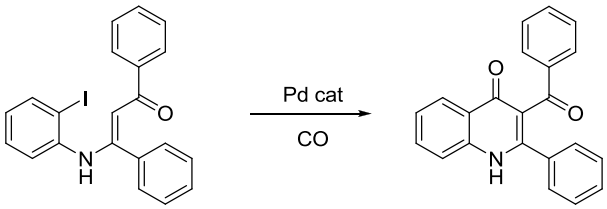

**Scheme 18** Proposed reaction mechanism

In conclusion, we have reported a pseudo-domino sequence involving the palladium-catalyzed generation of sulfinate anions followed by their arylation to afford aromatic sulfones. Study to elucidate the details of the reaction mechanism are presently under investigations.

## 1.3.5 2,3-substituted 4-(1*H*)-quinolones via intramolecular palladium-catalyzed carbonylative cross-coupling of *N*-(2-iodoaryl)enaminones

Palladium-catalyzed cross-coupling reactions have made an enormous impact on organic synthesis over the past few decades. Moreover the synthetic potential of these reactions has been considerably expanded be the development of carbonylative cross-coupling reactions in which carbon monoxide is inserted between the two coupling partners.[53]

As part of our studies on the chemistry of *N*-(2-iodoaryl)enaminones, we have recently hypothesized that a carbonylation reaction could give access to 2,3-substituted 4-(1*H*)-quinolones according to the scheme 19.



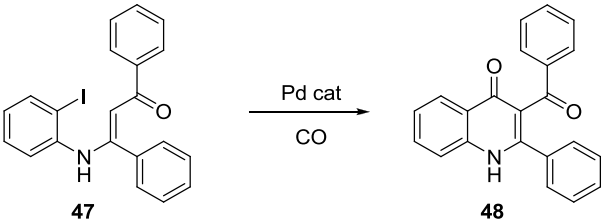

**Scheme 19** Work hypothesis

The stimulus for this study has been provided by the great pharmaceutical importance of the 4-(1-*H*)quinolone derivatives: they are found in many naturally occurring alkaloids [54] which exhibit broad biological activities. For example 4-(1-*H*)quinolone derivatives might posses potential as antimalarial agents [55] as anti- tuberculosis drug, [56] [57] and as antitumor agents. [58]

We set out to investigate the potential of the Pd-catalyzed carbonylative cross-coupling in the synthesis of 2,3-substituted quinolin-4-(1*H*)-ones using the reaction of the *N*-(2-iodoaryl)enaminones **47** in presence of palladium catalyst under an atmosphere of CO**.** To our delight, the quinolone derivative **48** was obtained in 54% yield using 0.05 equiv $Pd(PPh_3)_4$, 2 equiv

$Cs_2CO_3$ , at 100°C and 20 bar of carbon monoxide in 5 mL of MeCN (Table 9, entry 2). Nevertheless we decided to optimize this model reaction in term of catalyst, pressure and solvent. Our optimization studies are summarized in table 9.

**Table 9** Optimization of the reaction conditions



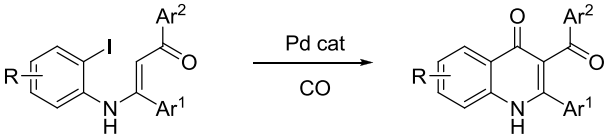

**47** **48**

| Entry | Catalyst | CO pressure (bar) | Solvent | Time (h) | 47 (%) | Yield 48 (%) |
|---|---|---|---|---|---|---|
| **1** | $Pd(PPh_3)_4$ | 10 | MeCN | 72 | 98 | - |
| **2** | $Pd(PPh_3)_4$ | 20 | MeCN | 38.5 | - | 53 |
| **3** | $Pd_2dba_3$/Xphos | 20 | MeCN | 72 | - | 68 |
| **4** | $Pd_2dba_3$/Xphos | 30 | MeCN | 48 | 4 | 44 |
| **5** | $Pd_2dba_3$/Sphos | 20 | MeCN | 48 | - | 56 |
| **6** | $Pd_2dba_3$/Sphos | 20 | MeCN | 72 | - | 64 |
| **7** | $Pd_2dba_3$/Xantphos | 20 | MeCN | 48 | - | 59 |
| **8** | $Pd_2dba_3$/dppf | 20 | MeCN | 72 | 35 | 36[a] |
| **9** | $Pd_2dba_3$/Xphos | 20 | THF | 68 | 50 | 41 |
| **10** | $Pd_2dba_3$/Xphos | 20 | DMF | 24 | - | 54[b] |
| **11** | $Pd_2dba_3$/Xphos | 20 | MeCN | 72 | 33 | 42[c] |

Reaction were carried on a 0.2 mmol scale by using 0.05 equiv of Pd, 0.05 equiv of ligand, 2 equiv of $Cs_2CO_3$ in 5 mL of solvent at 100°C.[a] We observed the formation of 2-(phenanthridin-6-(5-*H*)-ylidene)-1-phenylethanone in 9% yield.[b] We isolated the corresponding indole in 14 % yield.[c] Reaction was carried out by using $K_2CO_3$ as base.

As shown with $Pd(PPh_3)_4$, at lower CO pressure (10 bar), the formation of the 4-(1-*H*)quinolone nucleus is not observed and we recovered almost quantitatively the stating material (Table 9, entry 1). Best results was obtained using $Pd_2(dba)_3$ and Buchwald's ligands: the desired cyclic compound was isolated in 68% yield using $Pd_2(dba)_3$ /XPhos combination in MeCN at 20 bar CO and 100°C (Table 9, entry 3). Higer pressure of carbon monoxide led to the isolation of the desired cyclic compound in lower yield (Table 9, entry 4). Under the optimized condition we synthesized a variety of 2,3-substituted 4-(1*H*)-quinolones with moderate to good yields. Our results are reported in table 10.

**Table 10** Synthesis of 2,3-substituted 4-(1*H*)-quinolones

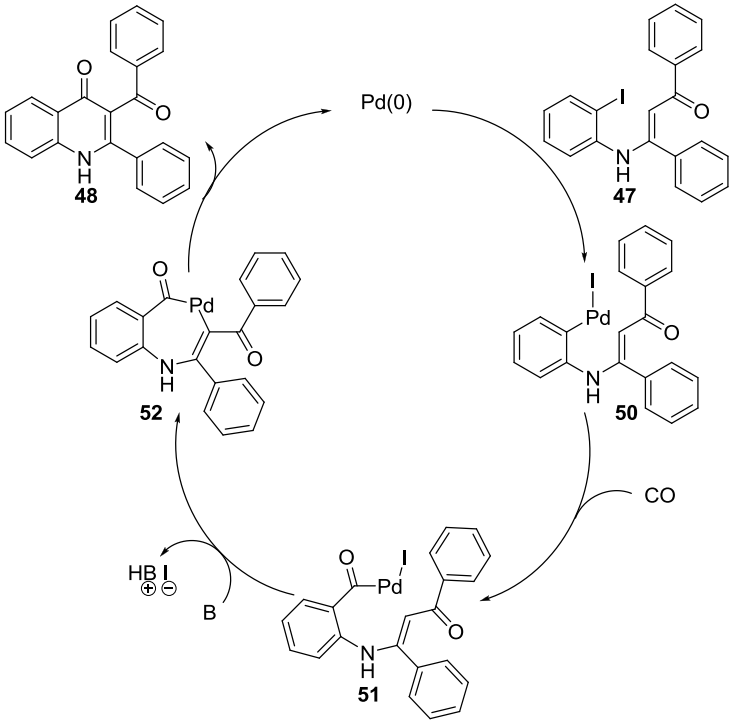



**49**

| Entry | R | $Ar^1$ | $Ar^2$ | Time (h) | Yield 49 (%) |
|---|---|---|---|---|---|
| 1 | H | H | 4-$CF_3$ | 72 | 65 |
| 2 | H | H | 4-F | 72 | 73 |
| 3 | H | H | 3-OMe | 72 | 82 |
| 4 | H | H | 3-Me | 72 | 51 |
| 5 | H | H | 4-Me | 72 | 33 |
| 6 | H | H | H | 72 | 68 |
| 7 | H | 4-COMe | H | 72 | 91 |
| 8 | H | 4-COOMe | H | 72 | 83 |
| 9 | H | 3-OMe | H | 72 | 45[a] |
| 10 | H | 4-OMe | H | 72 | 25 |
| 11 | H | 4-Cl | 4-COMe | 72 | 47 |
| 12 | 4-Br | H | H | 72 | 37 |
| 13 | 4-Br | H | $CF_3$ | 72 | 30 |

[a] 35 % of starting material recovered

A plausible pathway for this synthesis is outlined in scheme 20. First, palladium oxidatively insert into the C–I bond to generate the palladium complex **50** in which carbon monoxide inserts to give the complex **51**. After a deprotonation step results the seven-membered palladacycle **52** that via a reductive elimination affords the desired 2,3-substituted 4-(1*H*)-quinolone **48**.




**Scheme 20** Proposed mechanism

To sum up, we have developed an efficient palladium catalyzed intramolecular carbonylative cross-coupling reaction of readily available *N*-(2-iodoaryl)enaminones, yielding 2,3-diarylquinolones that represents a class of compounds of considerable interest in medicinal chemistry.

# 2. Copper catalysis

The enormous development of palladium-catalyzed methods in C–C and C–heteroatom bond forming reaction occurred during the past four decades results today in the common way of thinking according to which the cross coupling reactions are closely associated with the palladium catalysis. A certain effort is required to realize that the cross-coupling chemistry is actually much older and that the copper has been the ancestor of palladium in this domain. [59] Classical Ullmann chemistry along with closely related methods have been known for a full century and served well for C–N, C–S, C–O and some other bond formation reactions. C–C bond formation has been excellently serviced by organocuprate chemistry .

Howevar, the last years witness a steady increase of interest in copper assisted cross-coupling chemistry with dozens of new effective procedures emerging in all areas. A number of methods using various copper complexes and salts to carry out cross-coupling reactions leading to the formation of C–heteroatom (C–N, C–O, C–S, C–P, C–Se), C–C, and C–metal bonds have been proposed.

These methods aim at overcoming the deficiencies of conventional copper-assisted substitution methods (Ullmann chemistry) due to dramatic softening of reaction conditions extension of scope towards unactivated substrates and new types of nucleophiles, and increasing tolerance to sensitive functionality. On the other hand, the scope and selectivity of copper-assisted methods are often complimentary to the parallel palladium-catalyzed cross-coupling methods.

## 2.1 Comparison between copper and palladium catalysts

Copper salts and complexes are versatile reagents for cross-coupling reagents, with breadth of scope similar to that of palladium from C–C, C–heteroatom (N, P, O, S, Se) to C–H and C–metal.

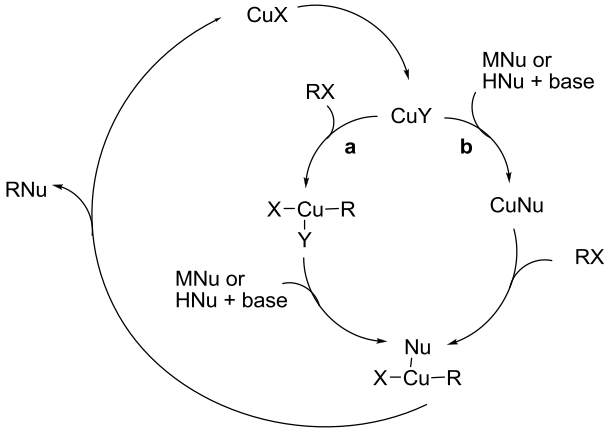
It presents an easy accessibility of four oxidation states from (0) to (+3), while palladium has at its disposal only two stable oxidation states (0) and (+2). There are indeed (+1), (+3) and (+4) oxidation states for palladium, but these are either extremely rare or play no unambiguously identifiable role in cross-coupling reactions. Most likely, the cross-coupling catalytic cycle with copper is serviced by (+1)/(+3) oxidation states. The accessibility of odd-electron states in copper, implying that it can take part in redox single-electron transfer processes, and thus an alternative free-radical mechanism should be taken into consideration. Copper is much cheaper than Palladium, (ca. by $10^5$ cheaper) and copper catalysts usually employ much cheaper ligands while palladium prefers expensive phosphines, copper satisfy itself with more trivial N or O ligands, many of which are common analytical or general purpose reagents. For this reason almost nobody bothers to optimize the amount of copper as soon as the required yield of target products is achieved, while in the case of palladium-driven reaction the cost of palladium makes the optimization of catalytic efficiency a vital task. On the other hand most copper catalyzed reactions are slow to require a day or so for completion, and the turnover frequencies are very low. In Pd chemistry very high TONs exceeding 104 and TOFs exceeding $10^3$ $h^{-1}$ are now quite usual. Thus, the actual cost of catalyst may not be so favorable for copper. To this we should add a strict preference of copper for expensive organic iodides as substrates, with bromides being much less useful, and only a few systems being devoted to organic chlorides, whereas palladium has achieved considerable success in recent years reactions with unactivated substrates. Copper assisted cross-coupling is not so

far applicable to sulfonate (triflate, tosylate, etc.) leaving groups, with the sole exception of copper-catalyzed reactions of Grignard reagents. This is a serious omission, as sulfonate esters allow one to introduce the large field of phenols and carbonyl compounds into cross-coupling; palladium catalysts serve excellently in such chemistry.

The copper assisted chemistry is environmentally unaware. One of the most evident trends in organic synthesis today is environmental awareness, definitely a must for any chemistry that aims at large scale applications. In copper assisted chemistry practically no efforts to develop green methods can be found. Meanwhile in Pd-catalyzed chemistry a lot of successful ideas on clean media, recyclable systems, highly effective catalysts, etc. have already been implemented gives poorer results than the heterogeneous copper salts

Copper assisted methods do not exactly follow their palladium counterparts – copper apparently has its own applications, where it is superior to palladium, e.g. in better tolerance to functional groups and double bonds, and more flexible chemoselectivity (cf. C–N, C–O cross-coupling, etc.). Copper-assisted methods allow to successfully extend cross-coupling methods to some classes of processes, which are still unfavorable targets for palladium catalysts, e.g. secondary alcohols in C–O coupling, $sp^3$–$sp^2$ and $sp^3$–$sp^3$ C–C coupling.

As to the catalytic cycle (Scheme 21), unlike Palladium-driven cross-coupling, in which an oxidative addition step is believed to precede the transmetallation, the ordering of oxidative addition and transmetallation steps in the copper cycle is unknown, so either of two possibilities can take place (pathways a or b).




**Scheme 21**

As shown, the catalytic specie Cu(I) is regenerated at the product forming reductive elimination step as a compound CuX, which may bear different ligands than the compound CuY which entered the catalytic cycle. Therefore, the regeneration, in this case, means the regeneration of oxidation state, and not exactly of the form used to initiate the cycle. This form may or may not be reactive, it may or may not undergo ligand exchange to form the active species that enters the second turn of the catalytic cycle. If this form is not reactive, the cycle is disrupted, and we cannot regard the reaction as catalytic, though the chemistry involved in a single turn is exactly the same as it would be if the reaction were catalytic, capable of two or more turns. In fact, this means that the factors effecting the deactivation of copper catalysts remain poorly understood.

## 1.3 New copper-catalyzed synthetic strategies

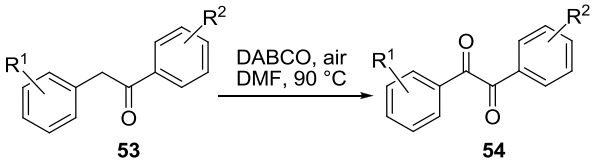
In this section the main features of our copper catalyzed synthetic approaches to several classes of compounds will be discussed.

### 1.3.1 Copper-catalyzed oxidation of deoxybenzoins to benzils under aerobic conditions.

As part of our continuing interest in the synthesis of heterocycles, [60] we lately turned our attention to the development of new approaches to heterocyclic derivatives starting from 1,2-diketones, a class of versatile synthetic intermediates. Indeed they are substructure of natural products [61] and a variety of biologically active heterocyclic compounds, such as imidazoles, triazines and quinoxaline, can be synthesized from benzil derivatives. [62]

Among the wide variety of methods described in literature for their preparation, [63] the recently reported conversion of readily available deoxybenzoins to benzils in the presence of DABCO and air [64] appeared to us particularly attractive and convenient as well as environmentally benign. However, when we attempted the conversion of the deoxibenzoin into the corresponding benzil under the described conditions, a reaction described to afford the benzil in 95% yield, the desired product was isolated only in 19% yield and the starting material was recovered in 74% yield (Table 11, entry 1). Similar disappointing results were obtained with different substituents (Table 11, entry 2-4).

**Table 11** Synthesis of benzils from deoxibenzoins in presence of DABCO




**53** **54**

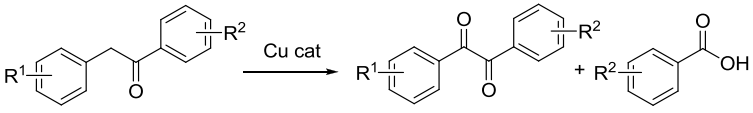
| Entry | $R^1$ | $R^2$ | Yield 54 (%) | Recovered 53 (%) |
|---|---|---|---|---|
| 1 | H | H | 19 | 74 |
| 2 | OMe | H | 20 | 80 |
| 3 | Cl | I | traces | 60 |
| 4 | H | CN | traces | 90 |

We then turned our attention to the other methods that allow for the synthesis of benzils via oxidation of deoxybenzoins. However, they are all based on the use of stoichiometric amounts or an excess of oxidants such as selenium dioxide, [63a] thallium nitrate, [63b] pyridinium chlorocromate, [63g, h] and potassium permanganate. [63i] Furthermore, methods based on thallium and chromium salts suffer from the drawback of using toxic reagents. Therefore, it appeared to us of interest to explore an alternative, more environmentally friendly approach. Particularly, given the known ability of copper to catalyze oxidation reactions, [65] we settled to investigate the feasibility of a copper-catalyzed oxidation process.

We started our study by examining the oxidation of deoxibenzoin with $Cu(OAc)_2$ and $P(Ph)_3$ in *o*-xylene under a balloon of oxygen. An initial screen showed that the oxidation byproduct could be isolated only in 15% yield at 80 °C, the main product being benzoic acid (50% yield) (Table 1, entry 1). The starting material was recovered in 35% yield. Pleasingly, increasing the reaction temperature to 100 °C led to the isolation of **54** in 95% yield (Table 1, entry 2). However, when these conditions were applied to 1-(4-methoxyphenyl)-2-

phenylethanone the reaction afforded the corresponding benzil derivative in 24% yield and *p*-anisic acid was isolated in 70% yield (Table 1, entry 3). Thus, we decided to optimize the reaction conditions for this substrate exploring the influence of temperature, copper salts, ligands, and solvents on the reaction outcome. Increasing the reaction temperature to 130 °C led to the isolation of the desired oxidation byproduct in 48% yield along with significant amounts of *p*-anisic acid (Table 1, entry 4). The use of other copper salts and ligands gave similar results (Table 1, entries 5-9). Similar results were also obtained in *m*-xylene (Table 1, entry 10) whereas the starting material was recovered in almost quantitative yield using 1,4-dioxane, acetonitrile, and toluene (Table 1, entries 11-13). An increase of the yield (57%) was observed in 1,2,4-trimethylbenzene substituting air for oxygen (Table 1, entry 14) and when the reaction was carried out under these last conditions decreasing the reaction temperature to 100 °C the desired oxidation byproduct could be isolated in a satisfactory 62% yield (Table 1, entry 15). We then came back to evaluate the behavior of deoxibenzoin under these conditions but the corresponding benzil was formed in a yield lower than that observed in *o*-xylene under oxygen. Thus, we decided to use both the oxidation protocols [$Cu(OAc)_2$, $PPh_3$, *o*-xylene, $O_2$, 100 °C and $Cu(OAc)_2$, $PPh_3$, 1,2,4-trimethylbenzene, air, 100 °C] when other substrates where investigated to explore the scope and generality of the reaction. Most probably, the best think is to evaluate the effectiveness of these protocols each time.

**Table 12** Optimization studies



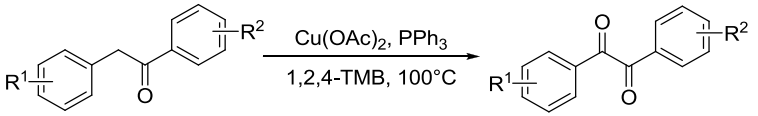

**53** **54** **55**

| Entry | Catalyst (%) | Solvent | T (°C) | t (h) | Yield 54(%) | Yield 55(%) |
|---|---|---|---|---|---|---|
| 1 [a, d] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | *o*, xylene | 80 | 24 | 15 | 50 |
| 2 [a] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | *o*, xylene | 100 | 4 | 95 | - |
| 3 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | *o*, xylene | 100 | 4 | 24 | 70 |
| 4 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | *o*, xylene | 130 | 0.75 | 48 | 19 |
| 5 [b] | $Cu(OTf)_2$ (20) | *o*, xylene | 130 | 3 | 44 | 31 |
| 6 [b] | CuI (15) $PPh_3$ (30) | *o*, xylene | 130 | 24 | 46 | 6 |
| 7 [b] | CuI (20) Proline (40) | *o*, xylene | 130 | 0.75 | 24 | 30 |
| 8 [b] | $CuCl_2$ (20) | *o*, xylene | 130 | 5.5 | 50 | 8 |
| 9 [b] | $Cu(OAc)_2$ (15) CHDA [e] (30) | *o*, xylene | 130 | 2.5 | 48 | - |
| 10 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | *m*, xylene | 130 | 0.75 | 49 | 19 |
| 11 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | 1,4-dioxane | 130 | 24 | - | - [f] |
| 12 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | MeCN | 130 | 4 | - | - [f] |
| 13 [b] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | toluene | 130 | 0.75 | - | - [f] |
| 14 [b, c] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | 1,2,4-TMB [g] | 130 | 0.75 | 57 | - |
| 15 [b, c] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | 1,2,4-TMB [g] | 100 | 0.75 | 62 | - |
| 16 [b, c] | $Cu(OAc)_2$ (15) $PPh_3$ (15) | 1,2,4-TMB [g] | 100 | 0.75 | 83 | - |

Reactions were carried out on a 0.4 mmol scale in 1,6 mL of solvent under an atmosphere of oxygen. [a] Reaction was carried out using deoxibenzoin as starting material. [b] Reaction was carried out using 1-(4-methoxyphenyl)-2-phenylethanone as starting material. [c] Reaction was carried out under air. [d] Starting material was recovered in 34% yield. [e] CHDA= cyclohehanediamine. [f] Starting material was recovered in 99% yield. [g] 1,2,4-TMB= 1,2,4-trimethylbenzene.

Our preparative results (Table 13) show that reaction affords benzils from deoxybenzoins in moderate to excellent yields and tolerates a variety of useful substituents including chloro, bromo, iodo, keto, ester, and cyano groups. Substituents in the ortho position of the benzylic fragment are are also tolerated (Table 2, entry 18).

**Table 13** Oxidation of 1,2 diarylethanones to benzil derivatives under the optimized conditions

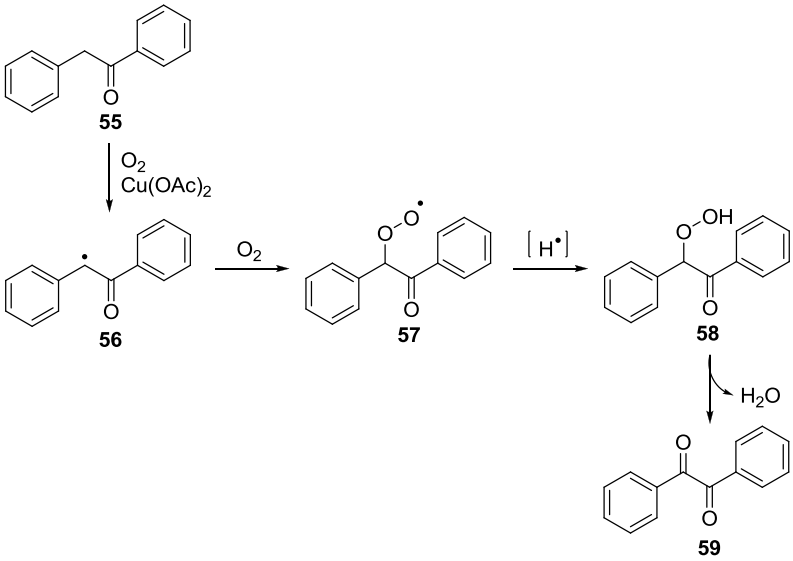



**53** **54**

| Entry | $R^1$ | $R^2$ | t (h) | Yield 54 (%) |
|---|---|---|---|---|
| 1 | H | H | 0.92 | 83 |
| 2 | H | *p*-OMe | 0.75 | 62 |
| 3 | *p*-OMe | H | 0.75 | 55 |
| 4 | H | *p*-Me | 7 | 70 |
| 5 | H | *o*-Me | 0.5 | 45 |
| 6 | H | *p*-COOMe | 1 | 72 |
| 7 | H | *p*-CN | 1 | 66 |
| 8 | H | *p*-COMe | 5 | 53 |
| 9 | *p*-Cl | H | 1.5 | 53 |
| 10 | *p*-Cl | *p*-I | 2.5 | 70 |
| 11 | H | *p*-I | 7 | 60 |
| 12 | H | *p*-Br | 2.5 | 75 |
| 13 | *p*-Cl | *p*-Br | 5 | 60 |
| 14 | *p*-Cl | *p*-OMe | 0.5 | 56 |
| 15 | *p*-OMe | *p*-OMe | 0.75 | 51 |
| 16 | *o*-Br | - | 7h | 62 |

Reaction were carried out on a 0.4 mmol scale, using 0.15 equiv. of $Cu(OAc)_2$, 0.3 equiv. of $PPh_3$ in 1.6 ml of solvent at 100°C under an atmosphere of air.

Although the detailed mechanism of this copper-catalyzed oxidation is unclear at the moment, it is likely that the reaction proceeds according to the following basic steps (Scheme 22): initial formation of the benzylic radical **56** from the starting deoxybenzoin **55** in the presence of the copper catalyst and oxygen; its subsequent reaction with oxygen to afford the peroxoradical **57**; conversion of **57** into the hydroperoxide **58** via capture of a hydrogen from the reaction medium; elimination of water [66] to give the benzil derivative **59**.

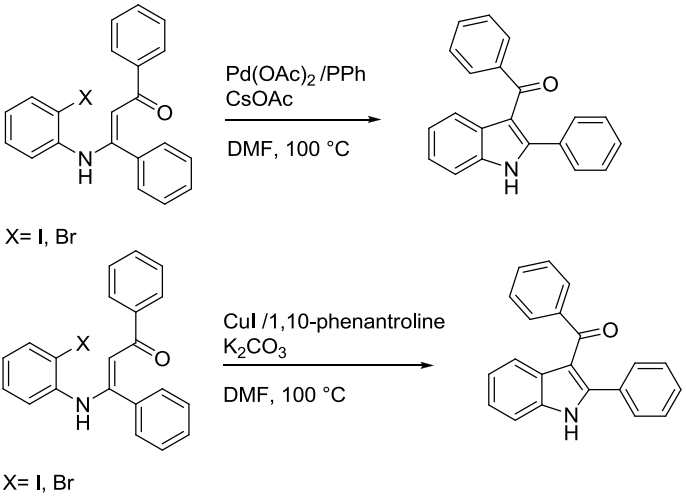



**Scheme 22** Proposed reaction mechanism

In summary, a simple and convenient copper-catalyzed oxidation of deoxybenzoins to benzils under neutral conditions using air as the oxidant has been developed; reaction allows to obtain benzil derivatives with the contemporary presence of chloro, bromo and iodo substituents: these products could be useful for increasing molecular complexity via a selective double functionalization.

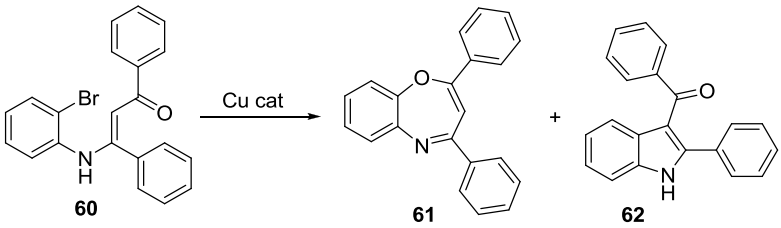
## 1.3.2 Copper catalyzed synthesis of 2,4-diarylbenzo[*b*][1,4]oxazepines from *N*-(2-bromoaryl)enaminones

For a long time our research group has studied the reactivity of the *N*-(2-haloaryl)enaminones. These studies have led to the development of new synthetic strategies for the 3-Acylindoles by exploiting both palladium and copper catalyst (Scheme 23). [67, 68]




**Scheme 23** Our previous studies

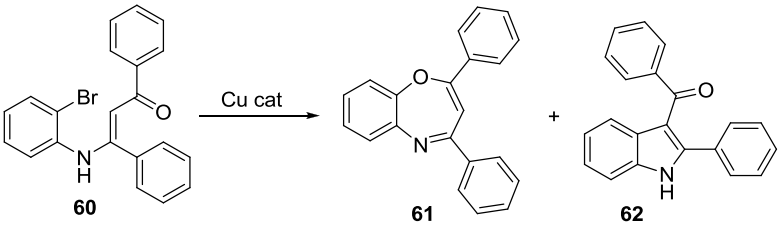
Particularly, studying the copper-catalyzed reaction and investigating the reactivity of the bromo-containing enaminones, we were surprised to find that the formation of the expected indole product was accompanied by the formation of a benzoxazepine derivative. We next hypothesized that changing the reaction conditions in a suitable way we could obtain the benzoxazepinic nucleus as the principal product (Scheme 24).




**Scheme 24** Our work hypothesis

We started our study by examining whether the enaminone **60** could be converted in the corresponding benzoxazepine derivative **61**, using a copper catalyst under an atmosphere of air. After an initial screen of bases ($Cs_2CO_3$, $K_2CO_3$, $Na_2CO_3$) and solvents (DMA, DMF, DMSO) we found that the cyclic compound **61** could be isolated in 40% of yield by using 0.05 equiv of CuI, 0.05 equiv of 1,10-phenantroline, 2 equiv of $K_2CO_3$ in DMA after 8h (Table 13, entry 1). Optimization studies were then performed varying the nature of ligands and the temperature (Table14). A satisfactory result was obtained using 0.05 equiv of CuI, 0.05 equiv of $P(Ph)_3$, 2 equiv of $K_2CO_3$ in DMA at 140°C: the desired product **61** was isolated in 56% yield while the indole derivative **62** was obtained in 22% yield (Table 14, entry 8).

**Table 14** Optimization of the reaction conditions

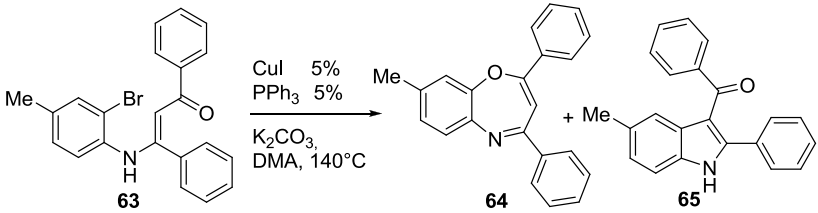



60 61 62

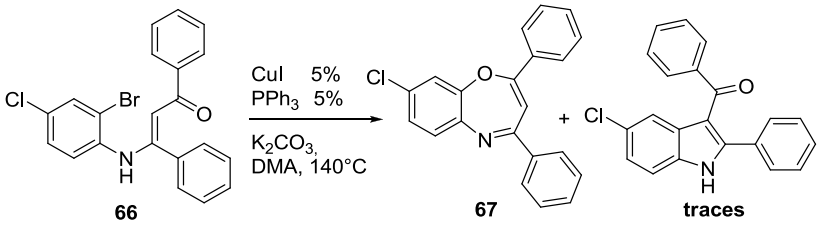
| Entry | Ligand (equiv) | Temperature °C | Time (h) | Yield 61(% | Yield 62(%) |
|---|---|---|---|---|---|
| 1 | 1,10-Phenantroline 5% | 140 | 8 | 40 | 11 |
| 2 | $PPh_3$ 5% | 140 | 6.5 | 54 | 27 |
| 3 | TMEDA 5% | 140 | 30 | 33 | 30 |
| 4 | (2,4,6-OMe-$C_6H_4$)$_3$P | 140 | 5 | 54 | 25 |
| 5 | Ru-Phos 5% | 140 | 5 | 55 | 24 |
| 6 | $PPh_3$ 10% | 140 | 6 | 47 | 30 |
| 7 | $PPh_3$ 5% | 150 | 3.5 | 54 | 2 |
| 8 | $PPh_3$ 5% | 140 | 3.5 | 56[a] | 22 |
| 9 | $PPh_3$ 5% | 120 | 24 | - | 18 |

Reactions were carried out with 0.05 equiv of CuI freshly purified by crystallization. [a] Reaction was carried out with 0.05 equiv of CuI as purchased without further purification.

To evaluate the scope and the generality of the process we set out to investigate the reaction of substituted *N*-(2-Bromoaryl)enaminones on the *N*-aryl fragment. Interestingly, we found that reaction of 3-(2-bromo-4-methylphenylamino)-1,3-diphenylprop-2-en-1-one **63** gave both the corresponding benzoxazepine **64** (40% yield) and the corresponding indole **65** (20% yield), while the 3-(2-bromo-4-chlorophenylamino)-1,3-diphenylprop-2-en-1-one **66** gave the benzoxazepine nucleus **67** in 84% of yield as the only product (Scheme 25, Scheme 26).



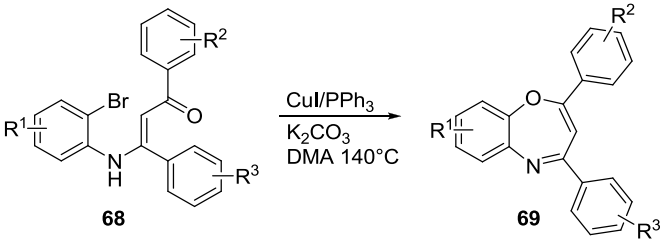

**Scheme 25** Reaction of 3-(2-bromo-4-methylphenylamino)-1,3-diphenylprop-2-en-1-one **63**




**Scheme 26** Reaction of 3-(2-bromo-4-chlorophenylamino)-1,3-diphenylprop-2-en-1-one **66**

Under the optimized conditions we synthesized a variety of 2,4-diarylbenzo[*b*][1,4]oxazepine from *N*-(2-bromoaryl)enaminones and our results are summarized in table 15.

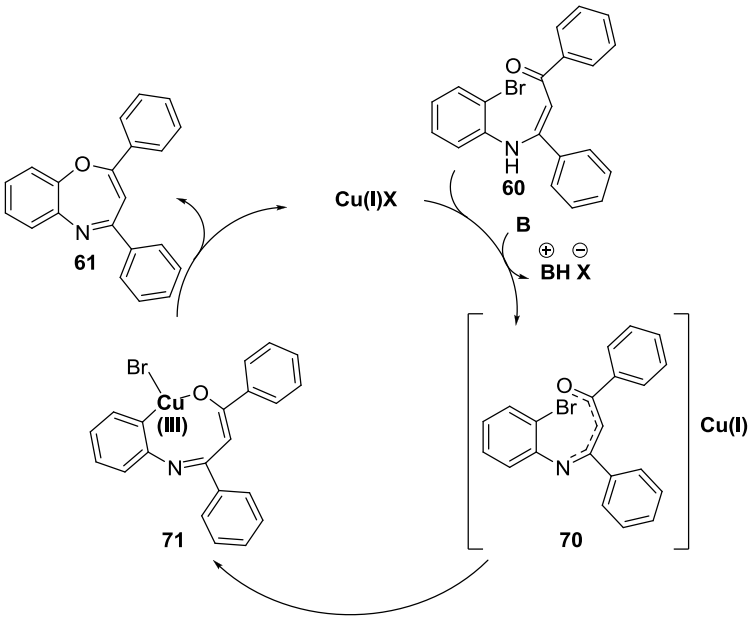
**Table 15** Copper catalyzed synthesis of 2,4-diarylbenzo[*b*][1,4]oxazepines




| Entry | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yield 69 (%) |
|---|---|---|---|---|---|
| 1 | H | H | H | 3.5 | 56 |
| 2 | Me | H | H | 8 | 40 |
| 3 | Cl | H | H | 1 | 84 |
| 4 | Cl | 4-Cl | H | 6 | 78 |
| 5 | Cl | 3-OMe | H | 1 | 82 |
| 6 | Cl | 4-Me | H | 0.75 | 83 |
| 7 | Cl | H | 4-COOMe | 0.5 | 71 |
| 8 | Cl | H | 3-OMe | 0.75 | 90 |
| 9 | F | H | H | 0.5 | 86 |
| 10 | F | H | 4-COOMe | 0.5 | 61 |

Reactions were carried out on a 0.20 mmol scale under an atmosphere of air in 1.5 mL of DMA.

A plausible pathway for this synthesis, outlined in scheme 27, begins with the initial coordination of -(2-Bromoaryl)enaminone with copper. The resulting complex **70** undergoes an oxidative addition of the C–X bond to copper to afford the Cu(III) intermediate **71**. Subsequent reductive elimination releases the product **61** with concomitant regeneration of the catalyst.




**Scheme 27** Proposed reaction mechanism

In conclusion, we have shown that *N*-(2-iodoaryl)enaminones can be converted selectively into the corresponding 2,4-diarylbenzo[*b*][1,4]oxazepine in the presence of catalytic amounts of CuI.

# 3. Gold catalysis

Despite the extensive use of gold and gold salts in heterogeneous catalysis since the 1960s, the golden era of homogeneous gold catalysis has begun at the end of the 20th century, evident by the dramatically increased number of publications in this field (Figure 5 and 6). [69]

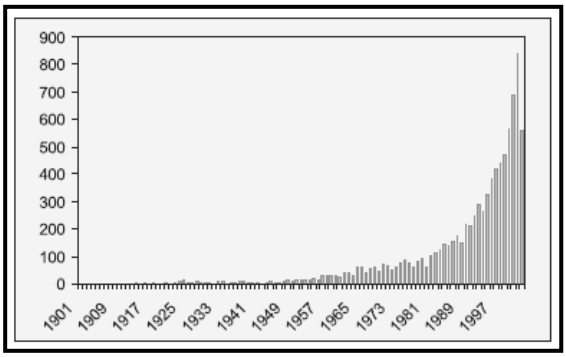



**Figure 5** Overall publications number by year in gold-catalysis

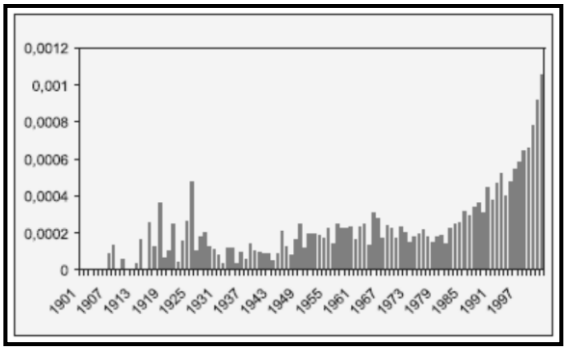



**Figure 6** Pubblications rate on gold catalysis mediated on the total number of scientific papers on organometallic catalysis.

Nowadays homogeneous gold catalysis is an emerging area of transition-metal catalysis with tremendous potential for organic synthesis. [70]

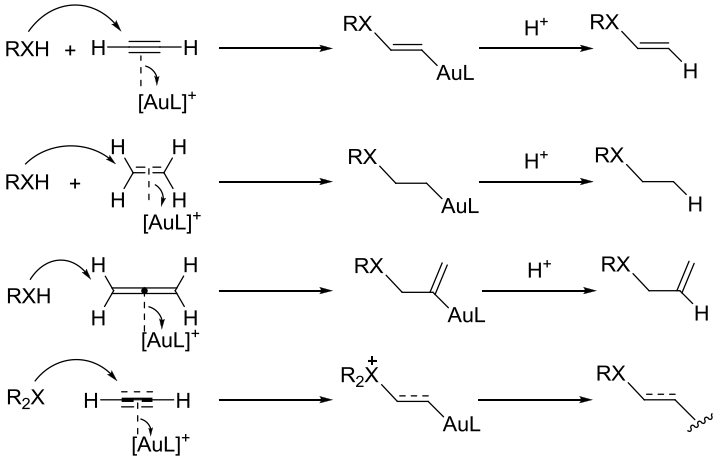
Both gold(I) and gold (III) salts are soft carbophilic Lewis acids and can activate C–C double and triple bonds for an inter- or intramolecular attack of a nucleophile to form new C–C or C–heteroatom bonds. Among various substrates amenable to activation, alkynes play a dominant role. Many of the investigations into the catalytic reactivity of Au exploit the propensity of both Au(III) and cationic Au(I) complexes to activate alkynes towards nucleophilic addition. Research in this area has been extensively reviewed. [71]

Gold-catalyzed reactions have displayed several unique features. Specifically, with an electron configuration of $[Xe]4f^{14}5d^{10}6s^{1}$ for the gold atom, gold catalysts mainly exist in (+1) and (+3) oxidation states. The high oxidation potential of Au(I) to Au(III) allows most Au(I)-catalyzed reactions to proceed without precautions to exclude air. In addition, gold catalysts are exceptionally alkynophilic, but not as oxophilic as most Lewis acids. Thus oxygen, water, and alcohols are often well-tolerated, in sharp contrast to most air- and moisture-sensitive Lewis acid or transition metal-catalyzed transformations. Besides convenient procedures without the concern of air and moisture, gold-catalyzed reactions often provide efficientaccess to structures of immense diversity and/or complexity from much simpler starting materials. Furthermore, distinct from classical carbocations, the non-classical carbocation or carbenoid feature of intermediates involved in gold-catalyzed transformations often leads to well-controlled product selectivity. Lastly, carbon gold bonds are labile toward proto-deauration, but not susceptible to b-hydride elimination, which frequently occurs in other transition metal-catalyzed reactions, thereby increasing the product selectivity. These reactions are all based upon a common platform, namely, the activation of alkynes, allenes, and sometimes alkenes by the gold species.

The gold-catalyzed transformations are convenient, and often accomplished under remarkably mild conditions. In addition to high level control of chemo-, regio-, and diastereoselectivity of many reactions, highly enantioselective gold catalysis has also emerged. Finally, the broad substrate scope and diverse product scaffolds of these reactions will undoubtly increase their impact on medicinal chemistry and natural product synthesis.

## 3.1 Heteroatom addition to unsaturated C–C bonds [72]

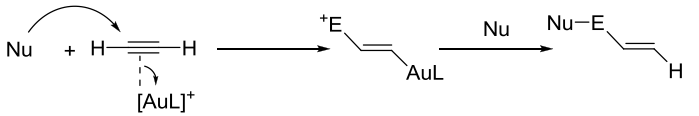
Gold-activated alkynes and allenes, and occasionally alkenes are good electrophiles for both $sp^2$- and $sp^3$-hybridized heteroatom nucleophiles. If a heteroatom X is $sp^3$-hybridized and HXR serves as a nucleophile, the proposed mechanism involves a *trans* heteroatom auration in most cases and the ensuing protodeauration (Scheme 28).




**Scheme 28**

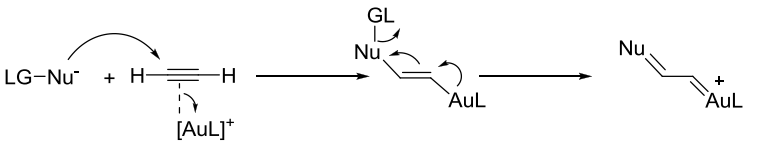
Typically an intramolecular C–X bond formation followed by protodeauration leads to an X-containing heterocycle. In the cases

where $R_2X$ (X=O, S) is used as a nucleophile, the resulting X cation often leads to a subsequent rearrangement reaction. When X is $sp^2$ hybridized, particularly in the cases of ketones, aldehydes, and imines, upon the addition of X to gold-activated unsaturated C–C bonds, the resulting X cation, as an electrophile, could thereby trigger the addition of another nucleophile (Scheme 29).




**Scheme 29**

Of particular interest is the third reaction mode in which the nucleophile also bears a leaving group thus setting the stage to generate a gold carbenoid (Scheme 30), a versatile intermediate for further transformations.




**Scheme 30**

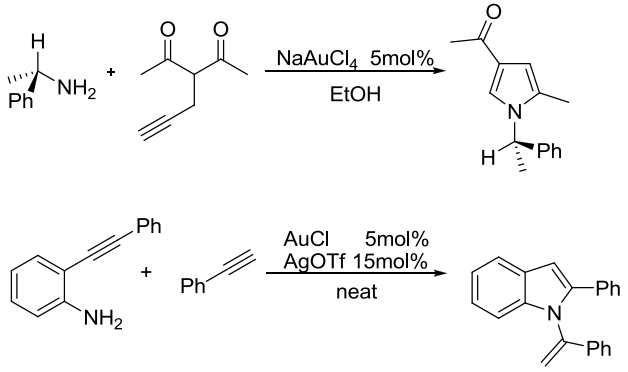
The regioselectivity of these reactions is often excellent, and high enantioselectivity has been accomplished in cyclization reactions of alcohols and amine derivatives with allenes. Reactions are generally conducted under very mild conditions, with excellent efficiency and functional group compatibility.

The gold-catalyzed 5-endo-dig, 5-exo-dig or 6-exo-dig cyclization reactions of heteroatom nucleophiles onto alkynes followed by protodeauration provide straightforward and efficient approaches to various five- and six-membered heterocycles. The nucleophiles can be the oxygen atom of alcohols, [73]carboxylic acids, [74] carbonates, [75] carbamates, [76] and amides [77], and the

nitrogen atom of amines, [78] carbamates, [79] trichloroacetimidates, [80] and anilines. [81]

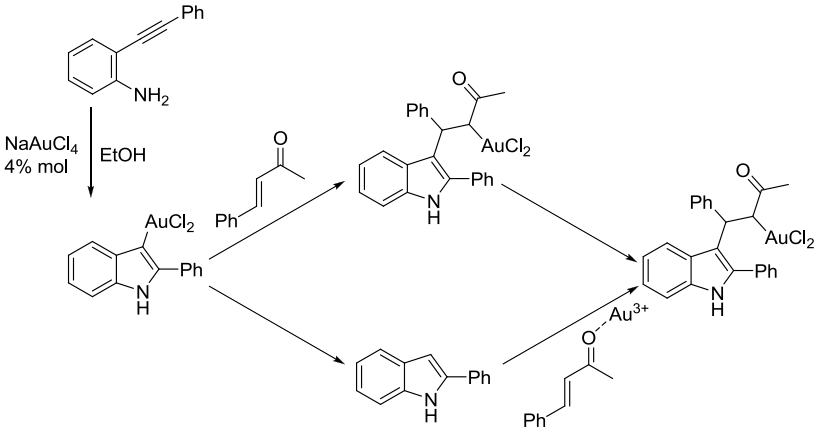
We focused our attention on Gold-catalyzed sequential or tandem reactions involving the addition of nitrogen nucleophiles to alkynes to obtain biologically interesting heterocycles.

In this context a remarkable processes is the reaction of enamines resulting from the hydroamination of amine [82] or aniline, [83] that readily cyclize onto alkynes to form pyrroles or indoles (Scheme 31).




**Scheme 31**

Another important gold-catalyzed process is the cyclization of 2-alkynylaniline to obtain C-3-functionalized indole (Scheme 32). [84] Reaction provides the formation of an indolyl-gold specie, which then adds to α,β-unsaturated ketone, or undergoes a gold-catalyzed FriedeleCrafts-type process .


Ph
NH2
NaAuCl4
4% mol
EtOH
AuCl2
Ph
N
H
O
Ph
AuCl2
Ph
N
H
Ph
O
Ph
AuCl2
Ph
N
H
Ph
Au3+
O
Ph

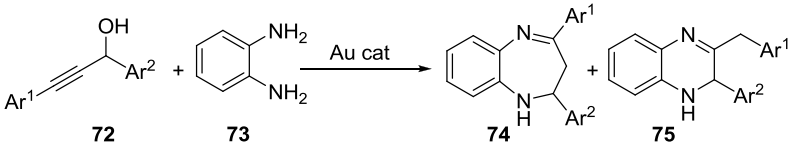
**Scheme 32**

## 3.2 New gold-catalyzed synthetic strategies

In this section the main features of our gold-catalyzed synthetic approache to 2,4-diaryl-2,3-dihydro-1h-benzo[*b*][1,4]diazepines will be discussed.

### 3.2.1 Synthesis of 2,4-diaryl-2,3-dihydro-*1H*-benzo[*b*][1,4]diazepines by gold(I) catalyzed reaction of 1,2-phenylenediamine and propargylic alcohols

The direct Au(III)-catalyzed substitution of propalgylic alcohols in the presence of various nucleophiles is a reaction described in 2005 by Georgy *et al*. This work showed that gold could acts as a Lewis acid to promote a SN reaction through the formation of a stabilized propagylic carbocation intermediate. [85] On the basis of this literature data we hypothesized that the 1,3-diaryl-propargylic alchols could react with a double nucleophile such as the *o*-phenylendiamine to give the six-membered **74** or seven-membred heterocyclic compound **75** (Scheme 33).

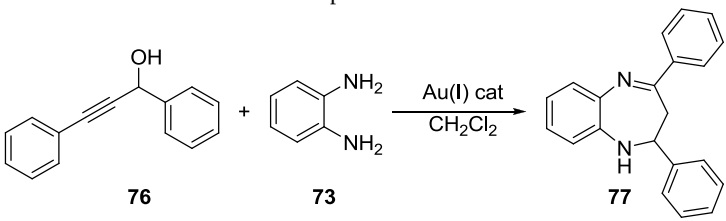



**Scheme 33** Work hypothesis

We set out to evaluate the feasibility of reaction by using the 1,3-diphenylprop-2-yn-1-ol with the *o*-phenylendiamine in presence of a gold catalyst**.** Unfortunately our first attempts with Au(III) catalysts did not give the expected result and we decide to try a new Au(I)-catalyst: (Acetonitrile)-[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate. To our delight the use of 1.1 equiv. of *o*-phenylendiamine **73**, 0.02 equiv of catalyst

in 2 mL of $CH_2Cl_2$ at 60°C led to the desired product **74** in 72% of yield (Table 16, entry 3). Formation of the six-membered cyclic compound **75** was not observed. Results of our preliminary studies are reported in table 16.

**Table 16** Optimization studies




**76** **73** **77**

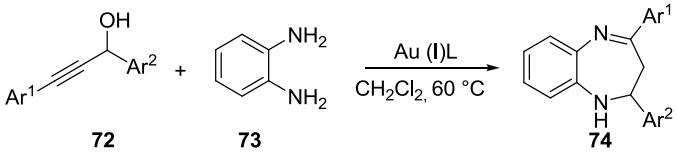
| Entry | Temperature °C | Time (h) | Recovered 76 (%) | Yield 77 (%) |
|---|---|---|---|---|
| 1 | 25 | 48 | 62 | 30 |
| 2 | 80 | 96 | 29 | 34 |
| 3 | 60 | 24 | 4 | 72 |

Reactions were carried out on a 0.5 mmol scale using 0.02 equiv. of catalyst in 2 mL of $CH_2Cl_2$ under an atmosphere of air

Having optimized the reaction conditions we focused our attention on the determination of the scope of this methodology. To this end we synthesized various 1,3-diaryl-propargylic alcohols with electron-rich and electron deficient groups on the two aromatic rings and we observed that the 1,3-diaryl-propargylic alchols with electron-deficient groups on the aromatic ring of the benzylic moiety required highest amount of catalyst for their full conversion in the corresponding benzodiazepine. Indeed, using 0.02 equiv of catalyst, after 48 h we obtained the desired cyclic compound in 31% of yield recovering wide amount of starting material (41%) (Table 17, entry 1). Otherwise by using 0.03 equiv. of catalyst, after 24 h, we obtained the 1,5-benzodiazepine in 68% of yield and just 4% of the propargylic alchol was recovered (Table 17, entry 2). With electron-rich groups on the aromatic ring linked to the C–C triple bond, by

increasing the catalyst rate from 0.02 to 0.03 equiv. we obtained worst results (Table 17, entry 4).

**Table 17** Optimization studies



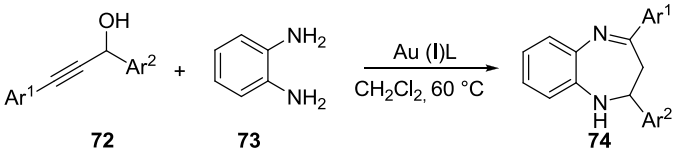

**72** **73** **74**

| Entry | $Ar^1$ | $Ar^2$ | Catalyst (eqiuv) | Time (h) | Recovered 72 | Yield 74 |
|---|---|---|---|---|---|---|
| 1 | 4-CN | H | 0.02 | 48 | 41 | 36 |
| 2 | 4-CN | H | 0.03 | 24 | 4 | 68 |
| 3 | H | 4OMe | 0.02 | 20 | 16 | 36 |
| 4 | H | 4-OMe | 0.03 | 20 | - | 12 |

Reactions were carried out on a 0.5 mmol scale in 2 mL of $CH_2Cl_2$ under an atmosphere of air at 60 °C.

In agreement with these experimental evidences we synthetized a variety of 2,4-diaryl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines with good to moderate yields using a catalyst loading ranging from 0.02 to 0.03 equiv. Some of our preparative results are reported in the following table 18.

**Table 18** Synthesis of 2,4-diaryl-2,3-dihydro-1h-benzo[*b*][1,4]diazepines by gold(I) catalyzed reaction of 1,2-phenylenediamine and propargylic alcohols

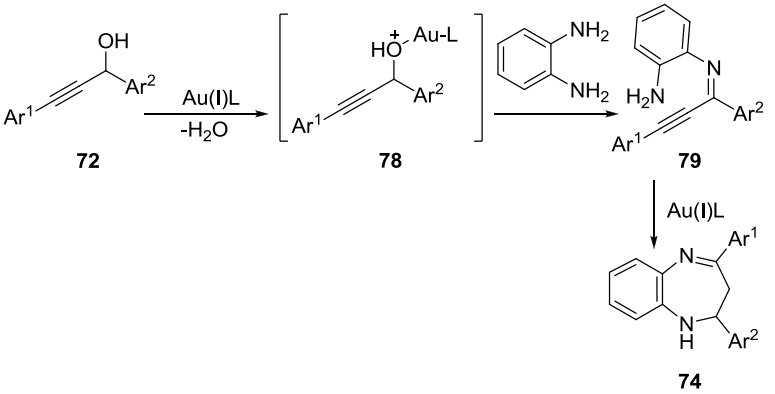



**72** **73** **74**

| Entry | $Ar^1$ | $Ar^2$ | Time (h) | Yield 74 (%) |
|---|---|---|---|---|
| 1 | H | H | 24 | 72 |
| 2 | 4-OMe | H | 16 | 62 |
| 3 | H | 4-OMe | 20 | 36 |
| 4 | 4-Me | H | 30 | 57 |
| 5 | H | 4-Me | 20 | 63 |
| 6[a] | 4-CN | H | 24 | 68 |
| 7 | H | 4-CN | 24 | 56 |
| 8 | 3-OMe | H | 24 | 66 |
| 9 | H | 3-OMe | 7 | 67 |
| 10[a] | 4-Br | H | 24 | 67 |
| 11 | H | 4-Br | 24 | 65 |
| 12 | H | 3-Br | 20 | 60 |
| 13[a] | 4-COOEt | H | 9 | 63 |
| 14[a] | 4-Cl | H | 10 | 70 |
| 15 | 4-OMe | 4-OMe | 24 | 46 |
| 16[a] | 4-COOEt | 4-OMe | 20 | 36 |

Reaction were carried out on a 0.5 mmol scale using 0.02 equiv of catalyst 1.2 equiv of *o*-phenylendiamine in $CH_2Cl_2$ at 60°C under an atmosphere of air.
[a] Reactions were carried out using 0.03 equiv of catalyst.

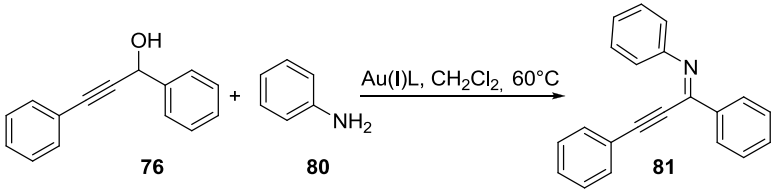
A probable reaction mechanism is outlined in the following scheme 34. The catalyst Au(I) interacting with the propargylic alchol promote a nucleophilic substitution $SN_2$ type to generate the intermediate **79**. Once again this compound could interacts with Au(I) to give the desired heterocyclic compound **74**.




72 78 79 74

**Scheme 34** Proposed reaction mechanism

The formation of the enamine intermediate **79** has been highlighted carrying out a reaction with the 1,2-diphenylpropargilalchol **76** and the aniline **80** in the presence of the Au(I) catalyst. Under these conditions we observed the formation of the enamine **81** as the principal products (Scheme 35).




76 80 81

**Scheme 35** Reaction of 1,2-diphenylpropargilalchol with the aniline

In summary this work describes a new synthetic route to 2,4-diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines. Our procedure

is simple, uses readily available starting materials and may represent a useful tool for the synthesis of this class of compounds.

# 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 $SiO_2$ 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).

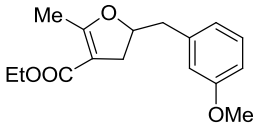
## 4.2 Additional information and characterization data on the synthesized compounds

### 4.2.1 Additional information and characterization data on functionalized 2,3-dihydrofurans

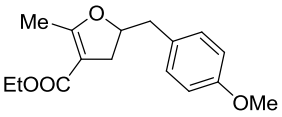
**General Information**: All the aryl halides, catalysts, bases, and solvents used are commercially available and were used as purchased, without further purification. The α–allyl–β–chetoesters were prepared according to literature.[86]

**General procedure for the synthesis of functionalized 2,3-dihydrofurans:** An oven-dried Schlenk tube equipped with a

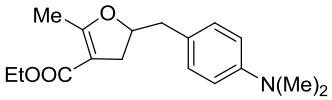
magnetic stirring bar was charged under argon with $Pd_2(dba)_3$ (11.4 mg, 0.0125 mmol), Ruphos (11.7 mg, 0.025 mmol) and anhydrous acetonitrile (1.0 ml). The resultant solution was stirred under $N_2$ at room temperature for 10 minutes before adding cesium carbonate (195.5 mg, 0.6 mmol), the aryl halide (93.0 mg, 0.5 mmol), the 2-allyl-β-ketoester dissolved in anhydrous acetonitrile (1.0 mL). The reaction mixture was warmed at 100°C and stirred until starting material ending. After cooling, the reaction mixture was diluted with AcOEt and washed twice with $H_2O$, and with a saturated NaCl solution. The organic layer was dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired product.



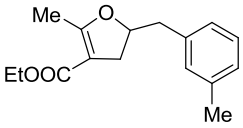

**ethyl 5-(3-methoxybenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** pale yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.26-7.22 (m, 1 H), 6.84-6.79 (m, 3 H), 4.90-4.82 (m, 1 H), 4.17 (q, $J$ = 7.2 Hz, 2 H), 3.81 (s, 3 H), 3.05 (dd, $J_1$ = 14 Hz, $J_2$ = 6.8 Hz, 1 H), 2.94 (dd, $J_1$ = 13.6 Hz, $J_2$ = 6.4 Hz, 1 H), 2.80 (m, 1H), 2.68-2.62 (m, 1 H), 2.21 (s, 3 H), 1.28 (t, $J$= 7.2 Hz); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.5, 166.2, 159.7, 138.6, 129.4, 121.7, 115.2, 111.8, 101.7, 82.5, 59.4, 55.1, 42.0, 34.8, 14.5, 14.1; IR (neat, $cm^{-1}$) 2935, 2836, 1695, 1646, 1513, 1384, 1247, 1228,1081, 1035, 975 $cm^{-1}$; MS m/z (relative intensity) 109 (9.8%), 155 (15.1%), 276 ($M^+$ 22.5%), 83 (24.1%), 122 (100%); Anal. Calcd. For $C_{16}H_{20}O_4$; C, 69.54; H, 7.30; Found C, 69.65; H, 7.32.



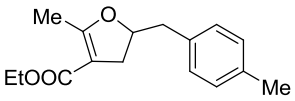

**ethyl 5-(4-methoxybenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** pale yellow liquid;$^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.17-7.15 (m, 2 H), 6.88-6.86 (m, 2 H), 4.86-4.78 (m, 1 H), 4.20-4.15 (m, 2 H), 3.81 (s, 3 H), 3.00 (dd, $J_1$ = 14 Hz, $J_2$ = 6.8 Hz, 1 H), 2.95-2.91 (m, 1 H), 2.89-2.79 (m,1 H), 2.66-2.60 (m, 1 H), 2.20 (s, 3 H), 1.28 (t, $J$ = 7.2 Hz); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.6, 166.3, 158.4, 130.3, 129.0, 113.9, 101.6, 82.8, 59.4, 55.2, 41.1, 34.7, 14.5, 14.2;IR (neat, $cm^{-1}$) 2935, 2836,1695, 1646, 1612, 1583, 1513, 1442, 1384, 1247, 1228, 1081, 1035, 975, 873, 763;
MS m/z (relative intensity) 147 (4.6%), 231 (8.1%), 65 (8.5%), 109 (9.8%), 155 (15.1%), 134 (16.2%), 91 (19.8%), 55 (22.4%), 276 ($M^+$ 22.5%), 83 (24.1%), 122 (100%);Anal. Calcd. For $C_{16}H_{20}O_4$; C, 69.54; H, 7.30; Found C, 69.64; H, 7.32.



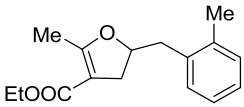

**ethyl 5-(4-(dimethylamino)benzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** Yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.12 (d, $J$ = 8.8 Hz, 2 H), 6.73 (d, $J$ = 8.8 Hz, 2 H), 4.86-4.78 (m, 1 H), 4.21-4.15 (m, 2 H), 3.02-2.88 (m, 8 H), 2.78 (dd, $J_1$ = 14,0 Hz, $J_2$ = 6.8 Hz, 1 H), 2.68-2.62 (m, 1 H), 2.22 (s, 3 H), 1.29 (t, $J$ = 7.2 Hz 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.7, 166.4, 149.4, 130.0, 125.0, 112.9, 101.6, 83.2, 59.4, 41.0, 40.8, 34.7, 14.5, 14.2; IR (neat, $cm^{-1}$) 2923, 1695, 1644, 1521, 1444, 1384, 1226, 1081, 973, 763;
MS m/z (relative intensity) 65 (2.4%), 55 (4.5%), 91 (7.3%), 289 ($M^+$ 9.2%),118 (12.9%),134 (100%); Anal. Calcd. For $C_{17}H_{23}NO_3$ C,70.56; H, 8.01; N, 4.84; Found C,70.65; H, 8.00; N, 4.85.



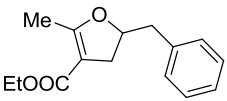

**ethyl 2-methyl-5-(3-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.25-7.21 (m, 1 H), 7.09-7.04 (m, 3 H), 4.91-4.83 (m, 1 H), 4.22-4.16 (m, 2 H), 3.08-3.03 (m, 1 H), 2.97-2.91 (m, 1 H) 2.91-2.83 (m, 1 H), 2.82-2.63 (m, 1 H), 2.43 (s, 3 H), 2.22 (t, *J* = 1.6 Hz, 3 H), 1.32-1.28 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.6, 166.3, 138.0, 136.9, 130.1, 128.4, 127.4, 126.3, 101.7, 82.7, 59.4, 42.0, 34.8, 21.4, 14.5, 14.2; IR (neat, $cm^{-1}$) 2925, 1697, 1648, 1444, 1384, 1226, 1081, 975; MS m/z (relative intensity) 260 ($M^+$ 13.5%), 127 (20.5 %), 91 (34.9%), 155 (37.7%), 83 (29.9%), 106 (100%); Anal. Calcd. For $C_{16}H_{20}O_3$ C, 73.82; H 7.74; Found C, 73.75; H, 7.75.




**ethyl 2-methyl-5-(4-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.14-7.12 (m, 4 H), 4.89-4.81 (m, 1 H), 4.22-4.16 (m, 2 H), 3.07-3.02 (m, 1 H), 2.97-2.90 (m, 1 H), 2.87-2.62 (m,1 H), 2.36 (s, 3 H), 2.22 (t, *J* = 1.6 Hz, 3 H), 1.31-1.28 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.6, 166.3, 136.1, 133.9, 129.2, 129.1, 101.6, 82.8, 59.4, 41.6, 34.8, 21.0, 14.5, 14.2; IR (neat, $cm^{-1}$) 2925, 1697, 1648, 1446, 1384, 1226, 1081, 975 $cm^{-1}$; MS m/z (relative intensity) 127 (24.4%), 260 ($M^+$ 25.9%), 91 (32.9%), 155 (35.0%), 83 (38.7%), 106 (100%); Anal. Calcd. For $C_{16}H_{20}O_3$ C, 73.82; H 7.74; Found C, 73.70; H, 7.75.

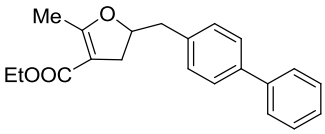



**ethyl 2-methyl-5-(2-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.22-7.17 (m, 4 H), 4.93-4.86 (m, 1 H), 4.20 (q, $J$ = 7.2 Hz, 2 H), 3.11 (dd, $J_1$ = 14 Hz, $J_2$ = 7.2 Hz, 1 H), 3.01-2.95 (m, 1 H), 2.86 (dd, $J_1$ = 14.4 Hz, $J_2$ = 6.4 Hz, 1 H), 2.71-2.60 (m, 1 H), 2.36 (s, 3 H), 2.22 (s, 3 H), 1.31 (t, $J$ = 7.2, 3 H);
$^{13}$C NMR(100.6 MHz) ($CDCl_3$) 167.6, 166.3, 136.5, 135.5, 130.4, 129.8, 126.8, 126.0, 101.7, 82.0, 59.4, 39.2, 35.1, 19.7, 14.5, 14.2.;
IR (neat, $cm^{-1}$) 2977, 1697, 1648, 1461, 1384, 1326, 1261, 1226, 1081, 975, 873, 763, 744; MS m/z (relative intensity) 171 (5.1%), 143 (6.9%), 65 (12.3%), 215 (15.2%), 117 (22.8%), 260 ($M^+$ 31.2%), 127 (49.1%), 91 (55.5%), 55 (59.0%), 155 (66.2%), 83 (87.6%), 106 (100%); Anal. Calcd. For $C_{16}H_{20}O_3$ C, 73.82; H, 7.74; Found C, 73.90; H, 7.72.

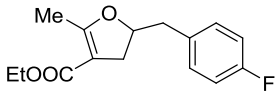



**ethyl 5-benzyl-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.35-7.24 (m, 5 H), 4.91-4.83 (m, 1 H), 4.24-4.16 (m, 2 H), 3.08 (dd, $J_1$ = 14 Hz, $J_2$ = 6.8 Hz, 1 H), 2.97-2.86 (m, 2 H), 2.66 (dd, $J_1$ = 14.8 Hz, $J_2$ = 7.2 Hz, 1 H), 2.22 (s, 3 H), 1,13 (t, $J$ = 6.8 Hz ); $^{13}$C NMR(100.6 MHz) ($CDCl_3$) δ 167.6, 166.3, 137.0, 129.4, 128.5, 126.7, 101.7, 82.6, 59.4, 42.0, 34.8, 14.5, 14.2; IR (neat, $cm^{-1}$) 2931, 1695, 1644, 1454, 1384, 1228, 1083, 873, 752, 700; MS m/z (relative intensity) 93 (10.3%), 97 (14.6%), 115 (15.2%), 201 (15.3%), 104 (22.4%), 246 ($M^+$ 26.0%), 65 (33.6%), 127 (46.9%), 55 (58.1%), 155 (67.6%), 83 (78.6%), 91 (100%);

Anal. Calcd. For $C_{15}H_{18}O_3$ C, 73.15; H, 7.37; Found C, 73.32; H, 7.30.

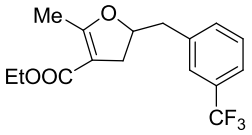



**ethyl 5-(biphenyl-4-ylmethyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow solid; Mp: 47-50°C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.59 (dd, $J_1$ = 15.8 Hz, $J_2$ = 7.2 Hz, 4 H), 7.46 (t, $J$ = 7.2 Hz, 2 H), 7.35 (dd, $J_1$ = 18.8 Hz, $J_2$ = 7.2 Hz, 3 H), 4.95-4.87 (m, 1 H), 4.25-4.16 (m, 2 H), 3.12 (dd, $J_1$ = 14.0 Hz, $J_2$ = 6.8 Hz, 1 H), 3.02-2.90 (m, 2 H), 2.72-2.59 (m, 1 H), 2.23 (s, 3 H), 1.30 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR(100.6 MHz) ($CDCl_3$) 167.6, 166.3, 140.9, 139.6, 136.2, 129.8, 128.8, 127.2, 127.0, 117.5, 101.7, 82.6, 59.5, 41.7, 34.9, 14.5, 14.2; IR (KBr, $cm^{-1}$) 3029, 2989, 2925, 2876, 1695, 1648, 1484, 1448, 1384, 1367, 1321, 1261, 1228, 1143, 1079, 975, 819, 761, 698; MS m/z (relative intensity) 63 (5.4%), 91 (12.1%), 109 (12.2%), 191 (13.5%), 253 (13.5%), 322 ($M^+$ 21.7%), 281 (25.2%), 152 (26.0%), 127 (27.8%), 55 (41.7%), 83 (51.4%), 167 (52.9%), 207 (66.1%), 168 (100%); Anal. Calcd. For $C_{21}H_{22}O_3$ C, 78.23; H, 6.88; Found C, 78.32; H, 6.86.

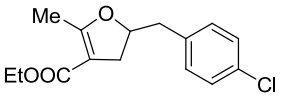



**ethyl 5-(4-fluorobenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** white solid; Mp: 52-54 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.21-7.18 (m, 2 H), 7.03-6.99 (m, 2 H), 4.86-4.78 (m, 1 H), 4.20-4.14 (m, 2 H), 3.04-2.83 (m, 3 H), 2.65-2.59 (m, 1 H), 2.19 (t, $J$ = 1.6 Hz, 3 H), 1.28 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.5, 166.2, 161.8, (d, $J$ = 245 Hz), 132.7 (d, $J$ = 3 Hz), 130.8 (d, $J$ = 8 Hz), 115.2, (d, $J$ = 21 Hz), 101.7, 82.4, 59.5, 41.1, 34.7, 14.5, 14.1; $^{19}$F (376.5 MHz)

($CDCl_3$) δ -105.94 (s); IR (KBr, $cm^{-1}$) 2923, 1693, 1654, 1508, 1380, 1324, 1261, 1218, 1147, 1091, 979, 759; MS m/z (relative intensity) 219 (13.7%), 122(17.8%), 97 (18.6%), 264 ($M^+$ 31.2%), 127 (37.4%), 155 (48.0%), 55 (51.7%), 83 (85.0%), 109 (100%); Anal. Calcd. For $C_{15}H_{17}FO_3$ C, 68.17; H, 6.48; Found C, 68.25; H, 6.46.

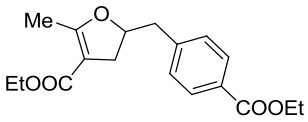



**ethyl 2-methyl-5-(3-(trifluoromethyl)benzyl)-4,5-dihydrofuran-3-carboxylate:** pale yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.50-7.42 (m, 4 H), 4.90-4.82 (m, 1 H), 4.16 (q, J = 6.8 Hz, 2 H), 3.06 (dd, $J_1$ = 14 Hz, $J_2$ = 7.2 Hz, 1 H), 3.01-2.92 (m, 2 H), 2.65-2.60 (m, 1 H), 2.18 (s, 3 H) 1.27 (t, J = 6.8 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.3, 165.9, 138.0, 132.8, 130.7 (q, *J* = 32 Hz), 128.8, 126.0 (q, *J* = 4 Hz), 124.1 (q, *J* = 272 Hz), 123.5 (q, *J* = 4 Hz), 101.7, 81.8, 59.4, 41.7, 34.8, 14.4, 14.0; $^{19}$F NMR (376.5 MHz) ($CDCl_3$) δ -62.59 (s); IR (neat, $cm^{-1}$) 3397, 2358, 1695, 1650, 1450, 1384, 1330, 1124, 1076, 703; MS m/z (relative intensity) 97 (20.9%), 269 (22.7%), 314 ($M^+$ 32.8%), 109 (48.0%), 127 (54.4%), 55 (61.1%), 155 (96.6%), 83 (100%); Anal. Calcd. For $C_{16}H_{17}F_3O_3$; C, 61.14; H, 5.45; Found C, 61.21; H, 5.43.

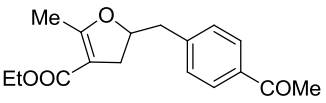



**ethyl 5-(4-chlorobenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.29 (d, J = 4.4 Hz, 2 H), 7.20 (d, J = 8 Hz, 2 H), 4.86-4.78 (m, 1 H), 4.22-4.14 (m, 2 H), 3.03-2.83 (m, 3 H), 2.61 (dd, $J_1$ = 13.4 Hz, $J_2$ = 6.8, 1 H), 2.19 (s, 3 H), 1.28 (t, J = 6.8 Hz); $^{13}$C NMR(100.6

MHz) ($CDCl_3$) δ 167.4, 166.1, 135.5, 132.5, 130.7, 128.6, 101.7, 82.2, 59.4, 41.3, 34.8, 14.4, 14.1); IR (neat, $cm^{-1}$) 2981, 2360, 2341, 1695, 1644, 1492, 1444, 1384, 1263, 1228, 1085, 873, 763, 669; MS m/z (relative intensity) 63 (7.3%), 235 (16.3%), 109 (19.3%) ,91 (24.1%), 280 ( $M^+$ 29.9%), 125 (52.8%), 55 (57.4%), 127 (74.3%), 155 (93.1%), 83 (100%); Anal. Calcd. For $C_{15}H_{17}ClO_3$ C, 64.17; H, 6.10; Found C, 64.19; H, 6.09.

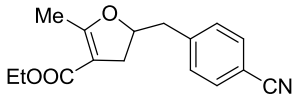



**ethyl 5-(4-(ethoxycarbonyl)benzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, $J$ = 8 Hz 2 H), 7.29 (d, $J$ = 8 Hz, 2 H), 4.89-4.82 (m, 1 H), 4.37 (q, $J$ = 6.8 Hz, 2 H) 4.15 (q, $J$ = 6.4 Hz, 2 H), 3.07 (dd, $J_1$ = 14 Hz, $J_2$ = 7.2 Hz, 1 H) 2.97-2.90 (m, 2 H), 2.64-2.59 (m, 1 H), 2.17 (s, 3 H), 1.39 (t, $J$ = 7.2 Hz, 3 H), 1.26 (t, $J$ = 7.2 Hz, 3 H);
$^{13}C$ NMR(100.6 MHz) ($CDCl_3$) δ 167.4, 166.4, 166.1, 142.3, 129.7, 129.3, 129.0, 101.7, 82.0, 60.8, 59.4, 41.9, 34.8, 14.4, 14.3, 14.1;
IR (neat, $cm^{-1}$) 2981, 1714, 1648, 1612, 1446, 1384, 1369, 1276, 1228, 1178, 1105, 1022, 979, 873, 761; MS m/z (relative intensity) 65 (7.1%), 281 (7.6%), 227 (7.6%), 118 (16.2%), 207 (16.9%), 318 ($M^+$ 18.4%), 109 (18.5%), 273 (19.7%), 55 (43.2%), 91 (51.5%), 83 (56.4%), 155 (57.9%), 136 (65.1%), 164 (100%); Anal. Calcd. For $C_{18}H_{22}O_5$ C, 67.91; H, 6.97; Found C, 67.99; H, 6.95.

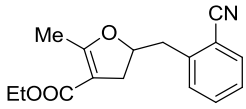



**ethyl 5-(4-acetylbenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow wax; Mp: 51-53 °C; $^1H$ NMR (400 MHz)

($CDCl_3$) δ 7.89 (d, *J* = 8 Hz, 2 H), 7.31 (d, *J* = 8 Hz, 2 H), 4.88-4.81 (m, 1 H), 4.13 (q, *J* = 7,2 Hz, 2 H), 3.06 (dd, $J_1$ = 14 Hz, $J_2$ = 7.2 Hz, 1 H), 2.96-2.87 (m, 2 H), 2.63-2.57 (m, 4 H), 2.15 (s, 3 H), 1.24(t, *J* = 7.0 Hz, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 197.7, 167.3, 166.0, 142.7, 135.7, 129.6, 128.5, 101.7, 81.9, 59.4, 41.9, 34.8, 26.5, 14.4, 14.1; IR (KBr, $cm^{-1}$) 2958, 2902, 2867, 1697, 1679, 1648, 1604, 1267, 1224, 1145, 1087, 962, 761 $cm^{-1}$; MS m/z (relative intensity) 115 (5.4%), 243 (8.1%), 105 (11.1%), 288 ($M^+$ 11.2%), 155 (13.3%), 90 (14.7%), 55 (27.0%), 83 (28.1%), 134 (100 %);
Anal. Calcd. For $C_{17}H_{20}O_4$ C, 70.81; H 6.99; Found C, 70.72; H, 7.01.

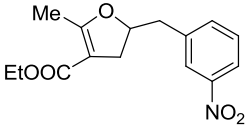



**ethyl 5-(4-cyanobenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** Yellow solid; Mp: 115-117 °C; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.61(d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 4.89-4.81(m, 1 H),4.16 (q, *J* = 7.2 Hz, 2 H), 3.10-2.93 (m, 3 H), 2.64-2.58 (m, 1 H) 2.17 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3 H);
$^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.2, 165.9, 142.7, 132.2, 130.1, 118.8, 110.7, 101.8, 81.5, 59.5, 42.0, 34.9, 14.4, 14.1;
IR (KBr, $cm^{-1}$) 3855, 2227, 1697, 1654, 1457, 1384, 1228, 1149, 1085, 977; MS m/z (relative intensity) 271 ($M^+$ 7.0%),109 (10.3%), 116 (14.1%), 55 (14.4%), 127 (20.5%), 83 (21.5%), 40 (22.9%), 155 (27.7%), 44 (100%); Anal. Calcd. For $C_{16}H_{17}NO_3$ C, 70.83; H, 6.32; N,5.16; Found C, 70.91; H, 6.30; N,5.15.

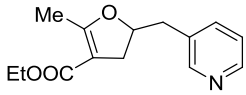



**ethyl 5-(2-cyanobenzyl)-2-methyl-4,5-dihydrofuran-3-carboxylate:** yellow solid; Mp: 61-65°C; $^1H$ NMR (400 MHz)

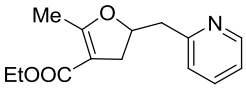
($CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 1 H), 7.588 (t, *J* = 1.2 Hz, 1 H), 7.416-7.354 (m, 2 H), 4.946-4.870 (m, 1 H), 4.184 (q, *J* = 7.2 Hz, 2 H), 3.248 (dd, $J_1$ = 14 Hz, $J_2$ = 8.4 Hz, 1 H), 3.124-3.029 (m, 2 H), 2.717-2.660 (m, 1 H), 2.205(t, *J* = 1.2 Hz, 3 H), 1.294 (t, *J* = 7.2 Hz, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.2, 166.0, 141.1, 132.9, 132.8, 130.5, 127.3, 118.0, 113.3, 101.8, 81.3, 59.5, 40.6, 35.1, 14.4, 14.1; IR (KBr, $cm^{-1}$) 2989, 2954, 2225, 2689, 2648, 1263, 1224, 1128, 1089, 979, 761; MS m/z (relative intensity) 271 ($M^+$ 21.6%), 226 (22.4%), 89 (42.8%), 109 (48.5%), 55 (60.5%), 116 (67.1%), 83 (81.6%), 127 (88.0%), 155 (100%); Anal. Calcd. For $C_{16}H_{17}NO_3$ C, 70.83; H, 6.32; N, 5.16; Found C, 70.85; H, 6.31 ; N, 5.17.



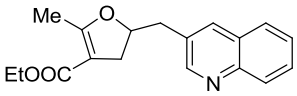

**ethyl 2-methyl-5-(3-nitrobenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow solid; Mp: 58-60 °C, yield: 81%; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.14-8.12 (m, 2 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.52-7.48 (m, 1 H), 4.93-4.46 (m, 1 H), 4.17 (q, *J* = 6.8 Hz, 2 H), 3.12 (dd, $J_1$ = 14,2 Hz, $J_2$ = 7.6 Hz, 1 H), 3.05-2.99 (m, 2 H), 2.67-2.61 (m, 1 H), 2.19 (t, *J* = 1.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.2, 166.0, 148.3, 139.1, 135.6, 129.3, 124.2, 121.8, 101.8, 81.5, 59.5, 41.5, 34.9, 14.4, 14.0; IR (KBr, $cm^{-1}$) 2925, 1698, 1654, 1429, 1382, 1351, 1230, 1089, 690; MS m/z (relative intensity) 63 (9.5%), 115 (11.9%), 246 (16.7%), 291 ($M^+$ 20.8%), 90 (29.4%), 109 (35.7%), 55 (57.2%), 127 (60.8%), 83 (79.2%), 155 (100%); Anal. Calcd. For $C_{15}H_{17}NO_5$ C, 61.85; H, 5.88; N, 4.81; Found C, 61.93; H, 5.86; N, 4.80.



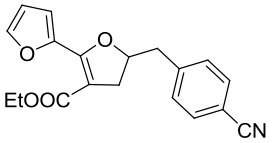

**ethyl 2-methyl-5-(pyridin-3-ylmethyl)-4,5-dihydrofuran-3-carboxylate:** , Brown liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.48 (br s, 2 H), 7.54 (d, $J$ = 7.7 Hz, 1 H), 7.24 (dd, $J_1$ = 7.7 Hz, $J_2$ = 4.9 Hz, 1 H); 4.85-4.77 (m, 1 H), 4.12 (q, $J$ = 6.8 Hz, 2 H), 3.00-2.84 (m, 3 H), 2.62-2.56 (m, 1 H), 2.14 (s, 3 H), 1.24 (t, $J$ = 6.8 Hz, 3 H);
$^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.5, 166.2, 157.4, 149.4, 136.3, 123.9, 121.7, 101.7, 81.4, 59.4, 44.3, 34.9, 14.4, 14.1; IR (neat, $cm^{-1}$) 2925, 1695, 1648, 1425, 1384,1326, 1263, 1226, 1083, 1027, 979, 763, 715, 759; MS m/z (relative intensity) 109 (10,1%), 202 (12.0%), 130 (12.0%), 83 (17.3%), 93 (100%), 247 ($M^+$ 18.4%);
Anal. Calcd. For $C_{14}H_{17}NO_3$ C, 68.0; H, 6.44; N, 6.93; Found C, 68.8; H, 6.45; N, 6.92.




**ethyl 2-methyl-5-(pyridin-2-ylmethyl)-4,5-dihydrofuran-3-carboxylate:** Brown liquid, yield: 74%;
$^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.535 (t, $J$ = 0.8 Hz, 1 H), 7.625-7.582 (m, 1 H), 7.189-7.127 (m, 2 H), 5.132- 5.055 (m, 1 H), 4.141 (q, $J$ = 6.8 Hz, 2 H), 3,188 (dd, $J_1$ = 14 Hz, $J_2$ = 7.6 Hz, 1 H), 3.60-2.950 (m, 2 H), 2.692-2.634 (m, 1 H), 2.159(t, $J$ = 1.6 Hz, 3 H), 1.251 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.5, 166.2, 157.4, 149.4, 136.3, 123.9, 121.7, 101.7, 81.4, 59.4, 44.3, 34.9, 14.4, 14.1; IR (neat, $cm^{-1}$) 2927, 1957, 1695, 1644, 1589, 1436, 1384, 1228, 1081, 975, 761 $cm^{-1}$; MS m/z (relative intensity) 247 ($M^+$ 0.1%), 202 ( 2.6%), 65 (3.4%), 130 (7.2%), 93 (100%);
Anal. Calcd. For $C_{14}H_{17}NO_3$ C, 68.00; H 6.93**;** Found C, 68.15; H, 6.91.

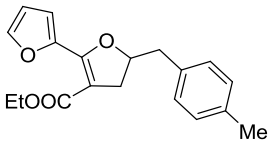



**ethyl 2-methyl-5-(quinolin-3-ylmethyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.79 (d, *J* = 2.0 Hz, 1 H), 8.08(d, *J* = 8.8 Hz, 1 H), 7.97 (s, 1 H), 7.76 (d, *J* = 8.4Hz, 1 H), 7.68-7.64 (m, 1 H), 7.51 (t, *J* = 7.6 Hz, 1 H), 4.94-4.87 (m, 1 H), 4.13 (q, *J* = 7.2Hz, 2 H), 3.15 (dd, $J_1$ = 14,4 Hz, $J_2$ = 7.2 Hz, 1 H), 3.07-2.95 (m, 2 H), 2.69-2.63 (m, 1 H), 2.17 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H) ); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.3, 166.0, 152.1, 147.1, 135.7, 129.9, 129.2, 129.1, 127.9, 127.4, 126.7, 101.8, 81.8, 59.5, 39.2, 34.9, 14.4, 14.1; IR (neat, $cm^{-1}$) 2927, 1695, 1650, 1494, 1444, 1382, 1326, 1261, 1224, 1083, 977, 755;
MS m/z (relative intensity) 252 (6.0%), 155 (6.3%), 207 (6.8%), 127 (8.9%), 180 (11.2%), 297 ($M^+$ 15.0%), 83 (17.5%), 55 (18.5%), 115 (23.2%) 143 (100%); Anal. Calcd. For $C_{18}H_{19}NO_3$ C, 72.71; H, 6.44; N, 4.71; Found C, 72.65; H, 6.45; N, 4.70.

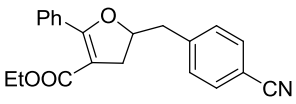



**ethyl 5-(4-cyanobenzyl)-2-(furan-2-yl)-4,5-dihydrofuran-3-carboxylate:** pale yellow solid, mp: 59-62 °C, yield 84%; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.43 (s, 1 H), 7.61 (d, *J* = 8.0 Hz, 2 H), 7.41-7.35 (m, 3 H), 6.91(s, 1 H), 4.95-4.87 (m, 1 H), 4.20 (q, *J* = 7.2 Hz, 2 H), 3.20-3.11 (m, 2 H), 2.99 (dd, $J_1$ = 14.0 Hz, $J_2$ = 5.2 Hz, 1 H), 2.79 (dd, $J_1$ = 15.2 Hz, $J_2$ = 7.2 Hz, 1 H), 1.31-1.26 (m, 3 H);
$^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.2, 157.7, 146.8, 142.8, 142.5, 132.2, 130.2, 118.8, 116.3, 110.7, 110.0, 101.1, 80.9, 59.8, 42.0, 36.4, 14.5; IR (KBr, $cm^{-1}$) 3160, 2979, 2931, 2227, 1695,

1633,1504, 1446, 1369, 1332, 1249, 1157, 1103, 1074, 908, 873, 817, 763, 601;
MS m/z (relative intensity) 63 (10.0%), 278 (10.8%), 105 (22.1%), 135 (23.0%), 73 (29.2%), 323 ($M^+$ 44.6%), 116 (47.0%), 207 (49.1%), 161(69.4%), 95 (100%); Anal. Calcd. For $C_{19}H_{17}NO_3$ C,74,25; H, 5.58; N, 4.56; Found C, 74,34; H, 5.56; N, 4.55.

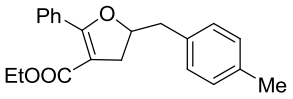



**ethyl 2-(furan-2-yl)-5-(4-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.49 (d, $J$ = 0.8 Hz, 1 H), 7.45-7.44 (m, 1 H), 7.17 (s, 4 H), 7.02 (dd $J_1$ = 2.0 Hz, $J_2$ = 0.7 Hz, 1 H), 4.96-4.88 (m, 1 H), 4.30-4.18(m, 2 H), 3.16-3.10 (m , 2 H), 2.92-2.81 (m, 2 H), 2.38 (s, 3 H), 1.33 (t, $J$ = 7.2 Hz 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.5, 158.1, 146.8, 142.3, 136.2, 134.0, 129.3, 129.2, 116.6, 110.2, 101.1, 82.1, 59.7, 41.6, 36.3, 21.1, 14.5; IR (neat, $cm^{-1}$) 3160, 2979, 2360, 1698, 1629, 1504, 1446, 1367, 1332, 1247, 1157, 1103, 1074,873, 806, 763, 599;
MS m/z (relative intensity) 134 (19.8%), 51 (22.7%), 117 (23.1%), 207 (38.2%), 77 (48.2%), 312 ($M^+$ 51.5%), 95 (87.0%), 105 (100%);
Anal. Calcd. For $C_{19}H_{20}O_3$ C, 77.0; H, 6.80; Found C, 76.8; H, 6.81.

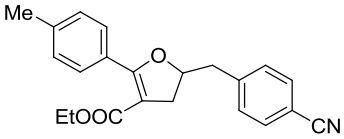



**ethyl 5-(4-cyanobenzyl)-2-phenyl-4,5-dihydrofuran-3-carboxylate:** brown solid; Mp:108-110 °C; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.754-7.733 (m, 2 H), 7.632 (d, $J$ = 8.0 Hz, 2 H),

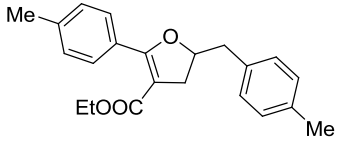
7.457-7.281 (m, 5 H), 5.040-4.964 (m, 1 H), 4.144 (q, $J$ = 6.8 Hz, 2 H), 3.277-3.179 (m, 2 H), 3.062 (dd, $J_1$ = 14.2 Hz, $J_2$ = 5.6 Hz, 1 H), 2.874 (dd, $J_1$ = 15,2 Hz, $J_2$ = 7.6 Hz, 1 H), 1.216 (t, $J$ = 7.2 Hz, 3 H);
$^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.1, 164.3, 142.7, 132.3, 130.4, 130.2, 129.8, 129.2, 127.7, 118.8, 110.7, 102.2, 81.1, 59.9, 42.0, 36.8, 14.2; IR (KBr, $cm^{-1}$) 2925, 2225, 1702, 1637, 1598, 1247, 1091, 1025, 755, 698; MS m/z (relative intensity) 63 (11.2%), 127 (17.3%),253 (17.7%), 51 (23.4%), 281 (23.6%), 145 (28.4%), 217 (35.7%), 333 ($M^+$ 35.9%), 89 (36.5%), 207 (58.0%), 116 (74.2%), 77 (82.9%), 171 (85.1%), 105 (100%); Anal. Calcd. For $C_{21}H_{19}NO_3$ C, 75.66; H, 5.74; N, 4.20; Found C, 75.56; H, 5.73; N, 4.22.




**ethyl 5-(4-methylbenzyl)-2-phenyl-4,5-dihydrofuran-3-carboxylate:** orange liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.822-7.802 (m, 2 H), 7.444-7.388 (m, 3 H), 7.213-7.160 (m, 4 H), 5.036-4.959 (m, 1 H), 4.215-4.135 (m, 2 H), 3.215-3.153 (m, 2 H), 2.895-2.886 (m, 2 H), 2.376 (s, 3 H), 1.251-1.192 (m, 3 H);
$^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.4, 164.7, 136.2, 133.9, 130.2, 129.4, 129.3,129.2, 128.7, 127.6, 102.2, 82.3, 59.7, 41.4, 36.5, 21.1, 14.3;
IR (neat, $cm^{-1}$) 2979, 2925, 1737, 1687, 1625, 1598, 1446, 1384, 1243, 1085, 873, 757, 692; MS m/z (relative intensity) 308 ($M^+$ 0.6%), 188 (2.3%), 322 (3.4%), 65 (9.4%), 128 (11.1%), 51 (15.1%), 144 (16.7%), 91 (31.6%), 171 (36.6%), 115 (55.0%), 77 (67.5%), 105 (100%); Anal. Calcd. For $C_{21}H_{22}O_3$ C, 78.23; H, 6.88; Found C, 78.16; H, 6.86.

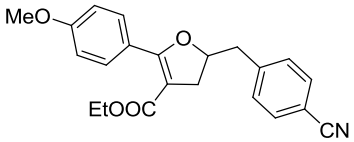



**ethyl 5-(4-cyanobenzyl)-2-p-tolyl-4,5-dihydrofuran-3-carboxylate:** yellow solid; Mp: 84 - 90 °C; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 5.13-4.94 (m, 1 H), 4.15 (q, *J* = 7.2 Hz, 2 H), 3.26-3.16 (m, 2 H), 3.05 (dd, $J_1$ = 14.0 Hz, $J_2$ = 5.2 Hz, 1 H), 2.86 (dd, $J_1$ = 15,2 Hz, $J_2$ = 7.6 Hz, 1 H), 2.40 (s, 3 H),1.24 (t, *J* = 6.8 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.2, 164.5, 142.8, 140.8, 132.3, 130.2, 129.2, 128.4, 126.9, 118.9, 110.7, 101.6, 80.9, 59.8, 42.0, 36.8, 21.5, 14.3; IR (KBr, $cm^{-1}$) 2927, 2225, 1697, 1621, 1509, 1243, 1083, 829, 755; MS m/z (relative intensity) 103 (12.6%), 281 (14.6%), 347 (26.9%), 158 (30.3%), 297 (34.5%), 65 (33.1%), 73 (48.3%), 129 (46.0%), 185 (51.6%), 91 (87.4%), 116 (100%); Anal. Calcd. For $C_{22}H_{21}NO_3$, 76.06; H, 6.09; N, 4.03; Found C, 76.21; H, 6.07; N, 4.04.

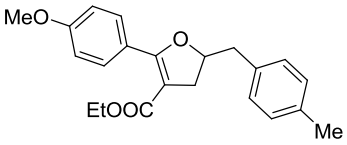



**ethyl 5-(4-methylbenzyl)-2-p-tolyl-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.7450 (d, *J* = 8 Hz, 2 H), 7.235-7.178 (m, 6 H), 5.014-4.937 (m,1 H), 4.199-4.146 (m, 2 H), 3.203-3.142 (m, 2 H), 2.974-2.876 (m, 2 H), 2.416 (s, 3 H) 2.377 (s, 3 H), 1.271-1.201 (m, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.5, 164.9, 140.5, 136.1, 134.0, 129.4, 129.3, 129.2, 128.8, 128.3, 117.3, 101.5, 82.1, 59.6, 36.6, 21.7, 21.5, 14.3;

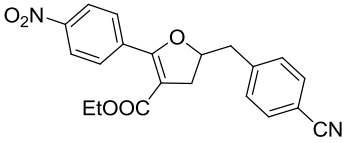
IR (KBr, $cm^{-1}$) 2979, 1737, 1683,1608, 1511, 1446, 1384, 1243, 1184,1081,821,761; MS m/z (relative intensity) 291 (9.0%), 141 (11.1%), 207 (14.4%), 65 (30.7%), 336 ($M^+$ 32.9%), 77 (34.6%), 158 (35.7%), 230 (47.6%), 129 (52.9%), 185 (62.9%), 105 (83.2%), 119 (86.6%), 91 (100%); Anal. Calcd. For $C_{22}H_{24}O_3$ C, 78.54; H, 7.19; Found C, 78.44; H, 7.18.




**ethyl 5-(4-cyanobenzyl)-2-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.80 (d, $J$ = 8.8 Hz, 2 H), 7.62 (d, $J$ = 8 Hz, 2 H) 7.39 (d, $J$ = 8 Hz, 2 H), 6.91 (d, $J$ = 8.8 Hz, 2 H), 4.99-4.91 (m, 1 H), 4.16 (q, $J$ = 6.8 Hz, 2 H), 3.85 (s, 3 H), 3.25-3.16 (m, 2 H), 3.04 (dd, $J_1$ = 14.4 Hz, $J_2$ = 5.6 Hz, 2 H) 2.85 (dd, $J_1$ = 14.8 Hz, $J_2$ = 7.6 Hz, 2 H), 1.25 (t, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 165.3, 164.2, 161.3, 142.9, 132.3, 131.1, 130.2, 122.0, 118.8, 113.0, 110.7, 100.8, 80.7, 59.7, 55.3, 42.0, 36.9, 14.3; IR (Neat, $cm^{-1}$) 2933, 2227, 1695, 1606, 1509, 1461, 1384, 1247, 1178, 1079, 1027, 873, 838, 763; MS m/z (relative intensity) 267 (10.1%), 118 (10.6%), 63 (11.4%), 191 (17.1%), 103 (19.6%), 253 (22.1%), 89 (22.3%),147 (23.5%), 246 (24.4%), 363 ($M^+$ 24.8%), 174 (25.4%), 116 (29.7%), 281 (38.2%), 73 (88.3%), 135 (88.3%), 207 (100%); Anal. Calcd. For $C_{22}H_{21}NO_3$ C, 72.71; H, 5.82;N, 3.85; Found C, 72.83; H, 5.83, N, 3.86.

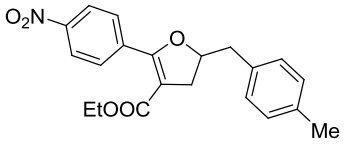



**ethyl 2-(4-methoxyphenyl)-5-(4-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow solid; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 2 H), 7.21-7.16 (m, 4 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 4.99-4.91 (m, 1 H), 4.18 (q, *J* = 6.8 Hz, 2 H), 3.87 (s, 3 H), 3.17 (dd, $J_1$ = 14 Hz, $J_2$ = 8.8 Hz, 2 H), 2.96-2.86 (m, 2 H), 2.38 (s, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H);
$^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 165.7, 164.6, 161.2, 136.1, 134.0,131.1, 129.3, 129.2, 122.5, 113.0, 100.7, 81.9, 59.6, 55.3, 41.5, 36.7, 21.1, 14.4; IR (KBr, $cm^{-1}$) 2933, 2227, 1695, 1606, 1509, 1461, 1384, 1303, 1247, 1178, 1079, 1027, 873, 763; MS m/z (relative intensity) 267 (10.1%), 218 (10.6%), 63 (11.4%), 191 (17.1%), 103 (19.6%), 253 (22.1%), 89 (22.3%), 147 (23.5%), 246 (24.4%), 363 ($M^+$ 24.8%) 174 (25.4%), 116 (29.7%), 281 (38.2%), 73 (88.3%), 135 (88.3%), 207 (100%); Anal. Calcd. For $C_{22}H_{24}O_4$ C, 74.98; H, 6.86; Found C, 75.06; H, 6.85.

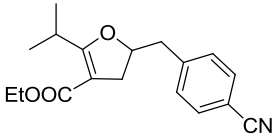



**ethyl 5-(4-cyanobenzyl)-2-(4-nitrophenyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid, yield: 23%; $^{1}$H NMR (400 MHz) ($CDCl_3$) δ 8.253 (d, *J* = 9.2 Hz, 2 H), 7.962 (d, *J* = 8.8 Hz, 2 H), 7.657 (d, *J* = 8.4 Hz, 2 H), 7.399 (d, *J* = 8.4 Hz, 2 H), 5.106-5.029 (m, 1 H), 4.198-4.135 (m, 2 H), 3.321-3.203 (m, 2 H), 3.099 (dd, $J_1$ = 14.4 Hz, $J_2$ = 5.6 Hz, 1 H), 2.922 (dd, $J_1$ = 15.6 Hz, $J_2$ = 8 Hz, 1 H), 1.246 (t, *J* = 7.2 Hz, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 164.5, 161.4, 148.6, 142.2, 135.8, 132.4, 130.3, 130.1, 123.6, 122.8, 111.0, 105.2, 81.6, 60.3, 41.9, 36.9, 14.2; IR (Neat, $cm^{-1}$)

2925, 2227, 1695, 1592, 1519, 1454, 1384, 1346, 1245, 1085, 873, 754; MS m/z (relative intensity) 63 (17.3%), 55 (33.0%), 378 ($M^+$ 41.5%), 155 (100%); Anal. Calcd. For $C_{21}H_{18}N_2O_5$ C, 66.66; H, 4.79; N, 7.40; Found C, 66.75; H, 4.80; N, 7.38.

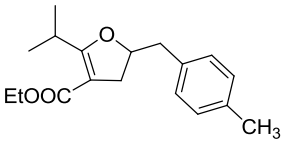



**ethyl 5-(4-methylbenzyl)-2-(4-nitrophenyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.24 (dd, $J_1$= 5.6 Hz, $J_2$=2 Hz, 2 H), 8.00-7.98 (m, 2 H), 7.17 (m, 4H), 5.08-5.00 (m, 1 H), 4.16 (q, $J$= 7.2 Hz, 2 H), 3.24-3.13 (m, 2 H), 3.00-2.90 (m, 2 H), 2.37 (s, 3 H), 1.24 (t, $J$= 7.2 Hz, 3 $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 164.2, 161.3, 142.9, 132.3, 131.1, 130.2, 122.0, 118.8, 113.0, 110.7, 100.7, 80.7, 59.7, 42.0, 36.9, 21.7, 14.4;
IR (Neat, $cm^{-1}$) 2925, 1695, 1592,1519, 1461, 1374, 1301, 1247, 1079, 1085, 873, 763; MS m/z (relative intensity), 55 (13.4%), 63 (15.4%) 105 (21.7%), 367 ($M^+$ 33.5%), 155 (100%); Anal. Calcd. For $C_{21}H_{21}NO_5$ C, 68.65; H, 5.76 N, 3.81; Found C, 68.70; H, 5.75 N, 3.83

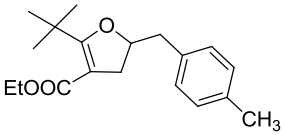



**ethyl 5-(4-cyanobenzyl)-2-isopropyl-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.60 (d, $J$ = 8.0 Hz, 2 H), 7.34 (d, $J$ = 8.4 Hz, 2 H), 4.85-4.77 (m, 1 H), 4.15 (q, $J$ = 6.8 Hz, 2 H), 3.60 (ept, $J$ = 6.8 Hz, 1 H), 3.06-2.89 (m, 3 H), 2.58 (dd, $J_1$ = 14.4 Hz, $J_2$ = 7.2 Hz, 1 H), 1.26 (t, $J$ = 7.2 Hz, 3 H), 1.10 (d, $J$ = 6.8 Hz, 3H), 1.08 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) 174.9, 165.8, 142.8, 132.2, 130.3, 118.8, 110.6, 99.4, 81.3, 59.4, 42.0, 34.9, 26.7, 19.6, 19.5, 14.4;

IR (neat, $cm^{-1}$) 2973, 2873, 2229, 1695, 1633, 1469, 1371, 1342, 1236, 1116, 1045, 815, 765, 557; MS m/z (relative intensity) 141 (23.2%), 254 (24.9%), 111 (25.2%), 69 (28.3%), 55 (37.0%), 299 ($M^+$ 44.2%), 137 (44.9%), 155 (65.9%), 116 (77.3%), 183 (100%); Anal. Calcd. For $C_{18}H_{21}NO_3$,C, 72.22; H, 7.07; N, 4.68; Found C, 72.35; H, 7.05, N, 4.65.




**ethyl 2-isopropyl-5-(4-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** brown liquid; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.14 (s, 4 H), 4.85-4.78 (m, 1 H), 4.21-4.15 (m, 2 H), 3.65 (ept, $J$ = 6.9 Hz, 1 H), 3.09 (dd, $J_1$ = 14 *Hz*, $J_2$ = 6.4 Hz, 1 H), 2.92 (dd, $J_1$ = 14.4 Hz, $J_2$ = 10 Hz, 1 H), 2.81 (dd, $J_1$ = 14 Hz, $J_2$ = 6.4 Hz, 1 H), 2.63 (dd, $J_1$ = 14.8 Hz, $J_2$ = 7.2 Hz, 1 H), 2.36 (s, 3 H), 1.29 (t, $J$ = 7.2 Hz, 4 H), 1.17 (d, $J$ = 6.9 Hz, 3H), 1.14 (d, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 175.4, 166.2, 136.1, 134.0, 129.4, 129.1, 99.2, 82.5, 59.3, 41.5, 34.7, 26.8, 21.0, 19.7, 19.6, 14.4; IR (neat, $cm^{-1}$) 2923, 1959, 1633, 1450, 1384, 1047, 873, 713, 406; MS m/z (relative intensity) 243 (10.5%), 141 (12.4%), 69 (17.6%), 55 (18.6%), 155 (20.0%), 113 (21.7%), 79 (30.6%), 288 ($M^+$ 30.6%), 153 (30.7%), 91 (35.3%), 105 (69.7%), 106 (100%); Anal. Calcd. For $C_{18}H_{24}O_3$ C, 74.97; H, 8.39; Found C, 74.86; H, 8.37.




**ethyl 2-tert-butyl-5-(4-methylbenzyl)-4,5-dihydrofuran-3-carboxylate:** yellow liquid; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.16 (s, 4 H), 4.77-4.69 (m,1 H), 4.18-4.12 (m, 2 H), 3.03-2.95 (m, 2

H), 2.79 (dd, $J_1$ = 14 *Hz*, $J_2$ = 6.4 Hz, 1 H), 2.69 (dd, $J_1$ = 14.4 *Hz*, $J_2$ = 7.2 Hz, 1 H), 2.35 (s, 3 H), 1.31 (m, 12 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.6, 162.8, 136.2, 133.2, 129.2, 129.1, 101.6, 82.8, 59.4, 41.6, 34.7, 32.8, 21.0, 14.2; IR (neat, $cm^{-1}$) 2923, 1959, 1633, 1450, 1397,1370, 1047, 873, 713, 406; MS m/z (relative intensity) 105 (11.3%), 302 ($M^+$ 27.3%), 63 (55.1%), 155 (100%); Anal. Calcd. For $C_{19}H_{26}O_3$ C, 75.46; H, 8.67; Found C, 75.66; H, 8.65

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

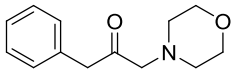
**General information**: Ethyl propargyl carbonates were prepared via Sonogashira cross-coupling of aryl iodides with propargyl alcohols. The isolated cross-coupling products were treated with ethyl chlorocarbonate to give the propargylic esters in 70-98% overall yield.

**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.

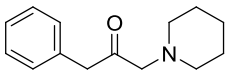
**Typical procedure for the preparation of ethyl 3-*m*-tolylprop-2-ynyl carbonate:** A flask equipped with a magnetic stirring bar was charged with 3-*m*-tolylprop-2-yn-1-ol (1.46 mmol, 218.8 mg) dissolved in $CH_2Cl_2$ (3 mL) and 4-(*N*,*N*-dimethylamino)pyridine (2.19 mmol, 267.6 mg). The resultant 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;

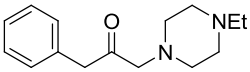
**Typical procedure for the preparation of 1-amino-3-arylpropan-2-ones:** A Carousel Tube Reaction (Radley Discovery) was charged with $Pd_2dba_3$ (8.0 mg, 0.087 mmol), dppf (9.7 mg, 0.0175 mmol) and anhydrous THF (1 mL). The solution was stirred under Nitrogen at room temperature for 10 minutes before 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:



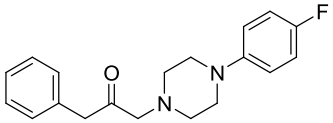

**1-morpholino-3-phenylpropan-2-one**: Oil; IR (neat): 3060, 3028, 2960, 2922, 2856, 1714, 1452, 1385 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$): δ 7.36-7.24 (m, 5 H), 3.76-3.74 (m, 6 H), 3.23 (s, 2 H), 2.47-2.46 (m, 4 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$): δ 205.8, 134.0, 129.4, 128.8, 127.1, 67.0, 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.



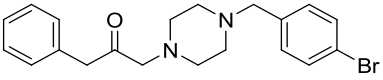
**1-phenyl-3-(piperidin-1-yl)propan-2-one**: oil; IR (Neat): 3060, 3028, 2935, 2854, 2804, 1714, 1597, 1574, 1454, 1385 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$): δ 7.35-7.32 (m, 2 H), 7.28-7.25 (m, 3 H), 3.78 (s, 2 H), 3.17 (s, 2 H), 2.40-2.39 (m, 4 H), 1.66-1.61 (m, 4 H), 1.46-1.45 (m, 2 H); $^{13}C$ 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.



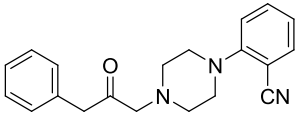

**1-(4-ethylpiperazin-1-yl)-3-phenylpropan-2-one:** oil; IR (Neat) 3060, 3028, 2970, 2933, 2812, 1720, 1454, 1385 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$):δ 7.32-7.21 (m, 5 H), 3.73 (s, 2 H), 3.20 (s, 2 H), 2.50 (m, 8 H), 2.42 (q, $J$ = 7.2 Hz, 2 H), 1.07 (t, $J$ = 7.2 Hz, 3 H); $^{13}C$ NMR (100.6 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.



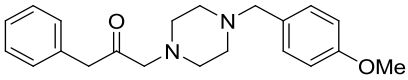

**1-(4-(4-fluorophenyl)piperazin-1-yl)-3-phenylpropan-2-one:** Oil; IR (Neat) 3060, 3030, 2931, 2821, 1722, 1510, 1454, 1385, 1232 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$): δ 7.37-7.26 (m, 5 H), 7.00-6.96 (m, 2 H), 6.90-6.87 (m, 2 H), 3.79 (s, 2 H), 3.30 (s, 2 H), 3.18-3.16 (m, 4 H), 2.65-2.63 (m, 4 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.

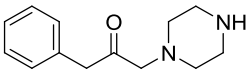



**2-(4-(2-oxo-3-phenylpropyl)piperazin-1-yl)benzonitrile:** oil; IR (Neat) 3062, 3030, 2916, 2825, 2220, 1716, 1595, 1489, 1448, 1383, 1230 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$): δ 7.56 (d, *J* = 7.9 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.36-7.25 (m, 5 H), 7.03-7.00 (m, 2 H), 3.77 (s, 2 H), 3.33 (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.

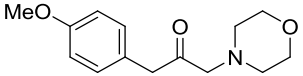



**1-(4-(4-methoxybenzyl)piperazin-1-yl)-3-phenylpropan-2-one:** oil; IR (Neat) 3060, 3030, 2933, 2810, 1720, 1612, 1512, 1454, 1246 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.35-7.23 (m, 7 H), 6.87 (d, *J* = 8.3 Hz, 2 H), 3.81 (s, 3 H), 3.75 (s, 2 H), 3.47 (s, 2

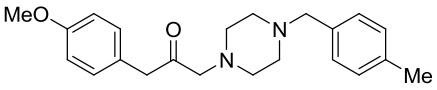
H), 3.21 (s, 2 H), 2.50 (bs, 8 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 206.3, 158.8, 134.2, 130.4, 130.1, 129.5, 128.7, 127.0, 113.6, 66.8, 62.4, 55.3, 53.4, 52.8, 47.7; Anal. Calcd. For: $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; Found: C, 74.42; H, 7.71.




**1-phenyl-3-(piperazin-1-yl)propan-2-one:** Oil; IR (Neat) 3060, 3028, 2815, 1716, 1496, 1455, 1270, 1008, 732, 701 $cm^{-1}$; $^1$H 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.

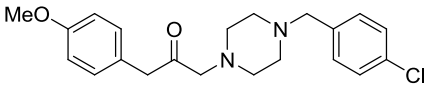



**1-(4-methoxyphenyl)-3-morpholinopropan-2-one:** oil; IR (Neat) 2918, 2852, 1722, 1610, 1512, 1454, 1248, 1117 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 3.80 (s, 3 H), 3.75-3.73 (m, 4 H), 3.68 (s, 2 H), 3.21 (s, 2 H), 2.47-2.45 (m, 4 H); $^{13}$C 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.

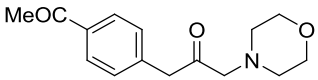



**1-(4-methoxyphenyl)-3-(4-(4-methylbenzyl)piperazin-1-yl)propan-2-one:** Wax; IR (KBr) 2933, 2810, 1716, 1510, 1246 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.21 (d, *J* = 7.7 Hz, 2 H), 7.17-7.13 (m, 4 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 3.81 (s, 3 H), 3.68

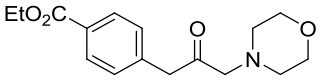
(s, 2 H), 3.51 (s, 2 H), 3.20 (s, 2 H), 2.52-2.50 (m, 8 H), 2.35 (s, 3 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 206.6, 158.7, 136.7, 134.7, 130.4, 129.3, 128.9, 126.2, 114.2, 66.6, 62.7, 55.3, 53.3, 52.8, 46.8, 21.1; Anal. Calcd. for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; Found: C, 74.81; H, 7.99.



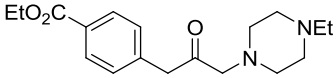

**1-(4-(4-chlorobenzyl)piperazin-1-yl)-3-(4-methoxyphenyl) propan-2-one:** oil; IR (Neat) 2935, 2812, 1720, 1610, 1512, 1456, 1248 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.30-7.25 (m, 4 H), 7.15 (d, *J* = 8.3 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.68 (s, 2 H), 3.49 (s, 2 H), 3.21 (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.



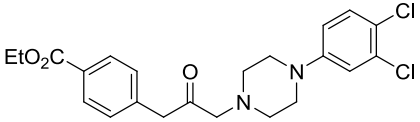

**1-(4-acetylphenyl)-3-morpholinopropan-2-one:** oil; IR (Neat) 2922, 2856, 1724, 1680, 1606, 1452, 1385, 1269, 1115 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 3.83 (s, 2 H), 3.73-3.71 (m, 4 H), 3.21 (s, 2 H), 2.58 (s, 3 H), 2.47-2.44 (m, 4 H); $^{13}$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 $cm^{-1}$; $^1H$ 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.

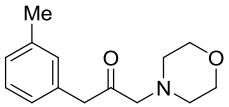


**ethyl 4-(3-(4-ethylpiperazin-1-yl)-2-oxopropyl)benzoate:** oil; IR (Neat) 2974, 2931, 2816, 1716, 1452, 1385, 1277, 1105 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2 H), 7.27 (d, *J* = 8.1 Hz, 2 H), 4.33 (q, *J* = 7.1 Hz, 2 H), 3.83 (s, 2 H), 3.22 (s, 2 H), 2.54 (bs, 8 H), 2.46 (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.



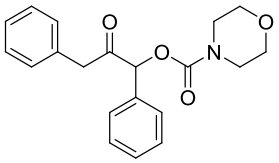
**ethyl 4-(3-(4-(3,4-dichlorophenyl)piperazin-1-yl)-2-oxopropyl)benzoate:** oil; IR (Neat) 2979, 2933, 2827, 1714, 1593, 1483, 1452, 1385, 1277 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.9 Hz, 1 H), 6.93 (d, *J* = 2.7 Hz, 1 H), 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.

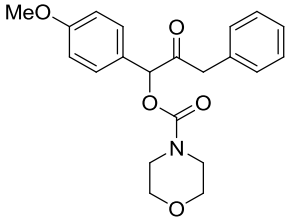


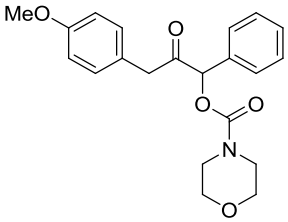

**1-morpholino-3-m-tolylpropan-2-one**: oil; IR (Neat) 2958, 2920, 2854, 2812, 1720, 1606, 1452, 1385, 1117 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.22 (t, $J$ = 7.5 Hz, 1 H), 7.10-7.03 (m, 3 H), 3.75-3.73 (m, 4 H), 3.71 (s, 2 H), 3.22 (s, 2 H), 2.47-2.45 (m, 4 H), 2.35 (s, 3 H); $^{13}$C NMR (100.6 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:

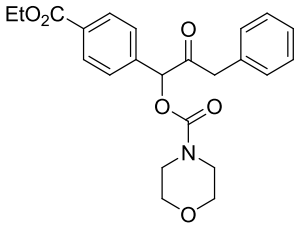


**2-oxo-1,3-diphenylpropyl morpholine-4-carboxylate**: mp: 132-134 °C; IR (KBr) 3066, 2974, 2904, 2860, 1732, 1714, 1431, 1234, 1117 $cm^{-11}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.41-7.23 (m, 8 H) 7.05-7.03 (m, 2 H), 6.09 (s, 1 H), 3.75-3.53 (m, 10 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 202.2, 154.3,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

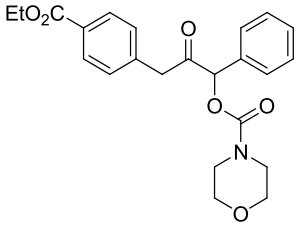




**1-(4-methoxyphenyl)-2-oxo-3-phenylpropyl morpholine-4-carboxylate** and **3-(4-methoxyphenyl)-2-oxo-1-phenylpropyl morpholine-4-carboxylate:** Mixture; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.41-7.39 (m, 2 H), 7.30-7.21 (m, 3 H), 7.06-7.04 (m, 1 H), 6.96-6.92 (m, 2 H), 6.81 (m, 1 H), 6.08 (s, 0.25 H, PhC<u>H</u>OCO, 7b'), 6.04 (s, 0.75 H, *p*-$CH_3$OPhC<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>$_3$OPhC$H_2$, 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*-MeOPhC$H_2$<u>C</u>O, 7b'), 202.4 (PhC$H_2$<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.

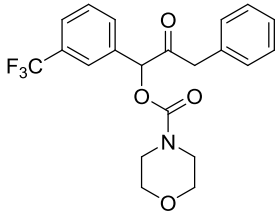


**1-(4-(ethoxycarbonyl)phenyl)-2-oxo-3-phenylpropyl morpholine-4-carboxylate:** oil; IR (Neat) 2924, 2858, 1712, 1612, 1456, 1433, 1277, 1238, 1111 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.07 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.28-7.26 (m, 3 H), 7.05-7.03 (m, 2 H), 6.12 (s, 1 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.

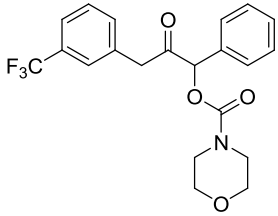


**3-(4-(ethoxycarbonyl)phenyl)-2-oxo-1-phenylpropyl morpholine-4-carboxylate:** oil; IR (Neat) 2978, 2925, 2858, 1712, 1612, 1429, 1277, 1238, 1107 $cm^{-1}$; $^1H$ NMR (400 MHz) (DMSO-$d_6$) (350 K) δ 7.84 (d, *J* = 7.6 Hz, 2 H), 7.47-7.42 (m, 5 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 6.14 (s, 1 H), 4.33 (q, *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.

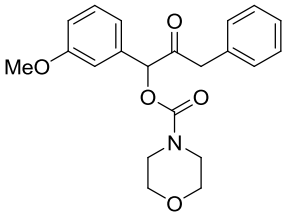


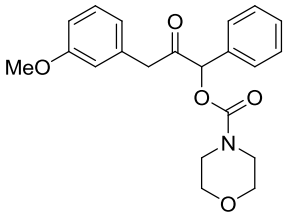
**2-oxo-3-phenyl-1-(3-(trifluoromethyl)phenyl)propyl morpholine-4-carboxylate:** oil; IR (Neat) 2924, 2858, 1712, 1433, 1331, 1238, 1124 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.66-7.64 (m, 1 H), 7.54-7.49 (m, 3 H), 7.28-7.23 (m, 3H), 7.05-7.04 (m, 2 H), 6.12 (s, 1 H), 3.78 (s, 2 H), 3.72-3.53 (m, 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)propyl morpholine-4-carboxylate: mp**: 97-99 °C; IR (KBr) 2862, 1728, 1705, 1433, 1336, 1117 $cm^{-1}$; $^1H$ 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 (Ph<u>C</u>HOCO,7e'), 80.9 (*m*-MeOPh<u>C</u>HOCO,7e), 66.5, 55.3, 55.1, 45.7, 45.6, 44.6, 44.1.

## 4.2.3 Additional information and characterization data on dibenzo[*a,c*]carbazoles

**General information**: The appropriate 2-alkynyltrifluoroacetanilides were prepared, usually in high yields, from 2-iodoaniline via a two-step process involving a Sonogashira cross-coupling with terminal alkynes followed by a trifluoracetylation step. [87]

**Typical procedure for the preparation of 2-(2-bromophenyl)-3-(4-methoxyphenyl)-1*H*-indole:** In a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar, *N*-(2-((2-bromophenyl)ethynyl)phenyl)-2,2,2-trifluoroacetamide (368.1 mg, 1.0 mmol), 4-iodoanisole (468.0 mg, 2.0 mmol) and $Pd(PPh_3)_4$ ( 57.8 mg, 0.05 mmol) were dissolved in 5 mL of anhydrous MeCN. Then,$Cs_2CO_3$ (651.6 mg, 2.0 mmol) was added and the mixture was stirred for 40 min at 80°C. After this time the reaction mixture was cooled to room temperature, diluted with EtOAc, and washed with brine. The organic layer was separated, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, *n*-hexane/EtOAc 85/15 v/v) to afford 302.6 mg (80% yield) of desired product.
$^1$H NMR (400.13 MHz, $CDCl_3$): δ 8.34 (bs, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.71 (d, *J* = 6.4 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.34-6.92 (m, 7 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 3.84 (s, 3 H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 135.7, 134.1, 133.5, 133.3, 132.6, 130.7, 129.8, 127.4, 127.3, 127.2, 123.9, 122.8, 120.3, 119.9, 116.4, 113.9, 111.0, 108.2, 55.2.

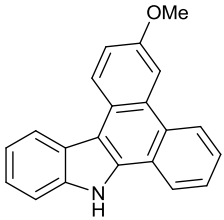
**Typical procedure for the preparation of 2-(2-bromophenyl)3-(4-methoxyphenyl)-1-(2-((trimethylsilyl)-methoxy)ethyl)-1*H*-indole:** to a solution of pre-activated NaH (60 % in mineral oil, 99.9 mg, 2.5 mmol; anhydrous DMF, 6 mL)2-(2-bromophenyl)3-(4-methoxyphenyl)-1*H*-indole (472.6

mg, 1.25 mmol), dissolved in 6 mL of anhydrous DMF, was added dropwise under argon at 0°C.
After stirring for 30 min at room temperature, the solution was cooled down in a ice bath,SEM-Cl (330 μL, 1.88 mmol) was added and the mixture was stirredat room temperature until completition. Then, the reaction mixture was diluted with $Et_2O$ and washed with brine. The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure, to give 603 mg (95% yield) of desired product.
$^1$H NMR (400.13 MHz, DMSO $d_6$): δ 7.79 (d, $J$ = 8.0 Hz, 1 H), 7.66-7.61 (m, 2 H), 7.47-7.39 (m, 3 H), 7.31-7.30 (m, 1 H), 7.29-7.14 (m, 3 H), 6.87 (d, $J$ = 8.8 Hz, 2 H), 5.54 (d, $J$ = 11.1 Hz, 1 H), 5.10 (d, $J$ = 11.1 Hz, 1 H), 3.72 (s, 3 H), 3.28 (m, 2 H), 0.70-0.65 (m, 2 H), -0.14 (s. 9 H); $^{13}$C NMR (100.6 MHz, $CdCl_3$): δ 158.0, 136.8, 135.2, 134.2, 133.5, 132.8, 130.2, 127.6, 127.2, 127.0, 126.4, 122.8, 120.7, 119.9, 116.8, 113.8, 110.6, 73.3, 65.7, 55.1, 17.8, -1.48.

**Typical procedure for the preparation of 3-methoxy-9-((2-(trimethylsilyl)ethoxy)methyl)-9*H*-dibenzo[a,c]carbazole:**
in a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $PPh_3$ (10.5 mg, 0.04 mmol) were dissolved under argon in 2 mL of anhydrous DMF. Then, 2-(2-bromophenyl)-3-(4-methoxyphenyl)-1-(2-((trimethylsilyl)methoxy) ethyl)-1*H*-indole (101.7 mg, 0.2 mmol), CsOAc (77 mg, 0.4 mmol) and 2 mL of solvent were added and the mixture was stirred for 30 min at 120°C under argon. After cooling, the reaction mixture was diluted with $Et_2O$, washed with $NaHCO_3$, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography using neutral $Al_2O_3$Brockmann activity II (Fluka) as stationary phase, eluting with *n*-hexane/ethyl acetate 95/5 to give 83.3 mg (97% yield) of desired product.
$^1$H NMR (400.13 MHz, $CDCl_3$): δ 8.80 (d, $J$ = 9.2 Hz, 1 H), 8.79-8.73 (m, 2 H), 8.58 (d, $J$ = 8.0 Hz, 1 H), 8.20 (d, $J$ = 2.4 Hz, 1 H), 7.70-7.65 (m, 3 H), 7.56-7.48 (m, 1 H), 7.48-7.40 (m, 2 H), 5.96

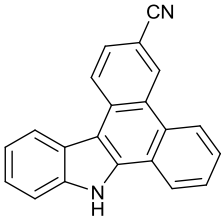
(s, 2 H), 4.08 (s, 3 H), 3.93 (t, *J* = 8.0 Hz, 1 H), 1.10 (t, *J* = 8.4 Hz, 1 H), 0.03 (s, 9 H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): δ 156.5, 141.4, 133.9, 130.3, 128.9, 126.8, 125.6, 125.1, 124.2, 124.1, 124.0, 123.98, 123.77, 123.76, 121.9, 120.9, 116.5, 114.6, 109.7, 105.8, 74.7, 66.0, 55.5, 18.1, -1.3

**Typical procedure for the preparation of 3-methoxy-9H-dibenzo[a,c]carbazole:** in a 50 mL Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and $PPh_3$ (10.5 mg, 0.04 mmol)were dissolved under argon in 2 mL of anhydrous DMF. Then, 2-(2-bromophenyl)-3-(4-methoxyphenyl)-1-(2-((trimethylsilyl)methoxy) ethyl)-1*H*-indole (101.7 mg, 0.2 mmol), CsOAc (77 mg, 0.4 mmol) and 2 mL of solvent were added and themixture was stirred for 30 min at 120°C under argon. After cooling,the reaction mixture was diluted with $Et_2O$, washed with $NaHCO_3$, dried over $Na_2SO_4$, and concentrated under reduced pressure.To the solution of the crude in anhydrous THF (2 mL) containing 2-(2-bromophenyl)-3-(4-methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indole, 2 mL of TBAF (THF solution, 1M, 10 eq.) were added and the mixture was stirred at 60°C until completion. The reaction mixture was cooled, diluted with EtOAc, washed with $NaHCO_3$;the organic layer was separated, dried over $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography using neutral $Al_2O_3$Brockmann activity II (Fluka) as stationary phase, eluting with *n*-hexane/ethyl acetate 95/5 to give 42 mg (70% yield) of desired product.

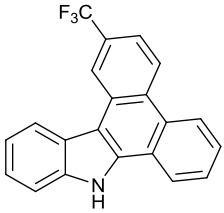



**3-methoxy-9H-dibenzo[a,c]carbazole:** white solid; mp: 195-198 °C. IR (KBr): 3425, 2923, 1531, 1461, 1257, 1043, 808, 738 (cm$^{-}$

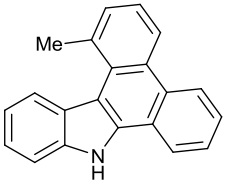
[1]).[1]H NMR (400.13 MHz, $CDCl_3$): δ 8.78 (bs, 1 H), 8.73-8.69 (m, 2 H), 8.50 (d, *J* = 7.8 Hz, 1 H), 8.19 (s, 1 H), 8.09-8.03 (m, 1 H), 7.71-7.60 (m, 3 H), 7.49-7.38 (m, 3 H), 4.07 (s, 3 H); [13]C NMR (100.6 MHz, DMSO): δ 156.4, 139.0, 133.4, 129.3, 128.2, 127.5, 126.5, 125.3, 124.8, 124.3, 124.0, 123.9, 123.5, 122.7, 121.7, 120.3, 117.3, 112.2, 111.9, 106.8, 55.9. ESI MS: 298 ($M^{+1}$, 100).Analcalcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.71; H, 5.07; N, 4.74.



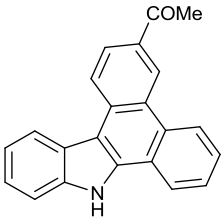

**9*H*-dibenzo[*a,c*]carbazole-3-carbonitrile:** white solid; mp: 334-337 °C. IR (KBr): 3311, 2223, 1531, 1448 ($cm^{-1}$).[1]H NMR (400.13 MHz, DMSO $d_6$): δ 12.69 (bs, 1 H), 9.41 (s, 1 H), 9.04 (d, *J* = 8.2 Hz, 1 H), 8.89 (d, *J* = 8.4 Hz, 1 H), 8.63 (d, *J* = 8.0 Hz, 1 H), 8.56 (d, *J* = 7.9 Hz, 1 H), 8.05 (d, *J* = 8.0 Hz, 1 H), 7.89-7.82 (m, 1 H), 7.81-7.73 (m, 2 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H); [13]C NMR (100.6 MHz, DMSO $d_6$): δ 139.1, 136.5, 132.7, 129.9, 129.74, 129.71, 128.9, 128.5, 127.7, 126.5, 124.9, 124.7, 123.8, 123.3, 122.9, 121.8, 121.2, 120.4, 112.6, 111.1, 105.8. ESI MS: 293 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{12}N_2$: C, 86.28; H, 4.14; N, 9.58. Found: C, 86.20; H, 4.13; N, 9.60.



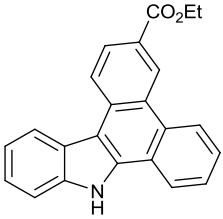

**2-(trifluoromethyl)-9*H*-dibenzo[*a,c*]carbazole**: yellow solid; mp: 203-207 °C. . IR (KBr): 3418, 1531, 1446, 1111 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.62 (bs, 1 H), 9.13 (d, $J$ = 8.8 Hz, 1 H), 9.01- 8.95 (m, 2 H), 8.66 (d, $J$ = 8.0 Hz, 1 H), 8.49 (d, $J$ = 8.0 Hz, 1 H), 7.92-7.74 (m, 4 H), 7.51-7.39 (m, 2 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): 139.0, 135.5, 129.6, 129.2, 128.9, 128.8, 128.0 (q, $J$ = 31.0 Hz), 127.5, 125.6, 125.2, 124.6, 124.1 (q, $J$ = 278.0 Hz), 123.8, 123.6, 122.9, 121.4, 121.1, 120.1(q, $J$ = 4.0 Hz),119.5 (q, $J$ = 4.0 Hz),118.8, 112.6,111. $^{19}F$ (376.5 MHz, DMSO $d_6$) δ -60.3.ESI MS: 336 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{12}F_3N$: C, 75.22; H, 3.61; N, 4.18. Found: C, 75.29; H, 3.60; N, 4.15.




**1-methyl-9*H*-dibenzo[*a,c*]carbazole**: yellow solid; mp: 173-176 °C. IR (KBr): 3440, 2923, 1436, 736 ($cm^{-1}$)**.** $^{1}H$ NMR (400.13 MHz, $CDCl_3$): δ 8.87 (bs, 1 H), 8.74 (d, $J$ = 8.0 Hz, 1 H), 8.64 (d, $J$ = 8.0 Hz, 1 H), 8.30 (d, $J$ = 8.2 Hz, 1 H), 8.00 (d, $J$ = 7.6 Hz, 1 H), 7.69-7.53 (m, 5 H), 7.45-7.30 (m, 2 H), 3.13 (s, 3 H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ 138.3, 135.1, 133.2, 130.6, 130.2, 129.4, 128.4, 126.7, 126.5, 125.6, 124.8, 124.1, 123.7, 123.4, 122.3, 120.9, 120.5, 119.5, 113.0, 111.1, 24.8. ESI MS: 282 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{15}N$: C, 89.65; H, 5.37; N, 4.98. Found: C,89.71; H, 5.35; N, 5.00.

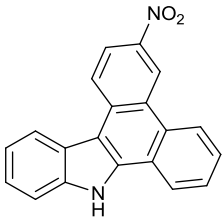



**1-(9*H*-dibenzo[*a,c*]carbazole-3-yl)ethanone**: yellow solid; mp: 208-211 °C. IR (KBr): 3248, 2923, 1646, 1608, 1531, 1460,1330, 738 ($cm^{-1}$).$^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.63 (bs, 1 H), 9.47 (s, 1 H), 9.09 (d, $J$ = 8.0 Hz, 1 H), 8.90 (d, $J$ = 8.6 Hz, 1 H), 8.67-8.59 (m, 2 H), 8.30 (dd, $J_1$= 8.6 Hz, $J_2$= 1.2 Hz 1 H), 7.88-7.78 (m, 2 H), 7.76 (d, $J$ = 8.0 Hz, 1 H), 7.48 (t, $J$ = 7.6 Hz, 1 H), 7.38 (t, $J$ = 7.6 Hz, 1 H), 2.84 (s, 3 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 198.2, 139.1, 136.3, 133.2, 132.2, 129.9, 128.1, 127.5, 126.8, 125.9, 125.6, 124.7, 124.6, 124.0, 123.9, 123.2, 122.9, 121.9, 121.0, 112.5, 111.5, 27.3. ESI MS: 310 ($M^{+1}$, 100).Anal calcd for $C_{22}H_{15}NO$: C, 85.41; H, 4.89; N, 4.53. Found: C, 85.37; H, 4.90; N, 4.50.

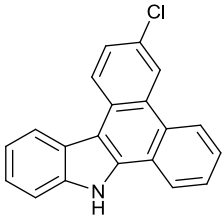



**ethyl 9*H*-dibenzo[*a,c*]carbazole-3-carboxylate**: yellow solid; mp: 200-204 °C. IR (KBr): 3421, 2918, 1521, 1459, 1360, 738 ($cm^{-1}$).$^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.62 (bs, 1 H), 9.44 (s, 1 H), 8.95-8.88 (m, 2 H), 8.64 (d, $J$ = 7.5 Hz, 1 H), 8.60 (d, $J$ = 8.1 Hz, 1 H), 8.30 (d, $J$ = 8.5 Hz, 1 H), 7.89-7.73 (m, 3 H), 7.50-7.45 (m, 1 H), 7.38 (t, $J$ = 7.4 Hz, 1 H), 4.45 (q, $J$ = 7.0 Hz, 2 H), 1.44 (t, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 166.6, 139.1, 136.2, 133.2, 129.6, 128.1, 127.8, 127.6, 126.0,

125.7, 124.9, 124.6, 124.3, 124.1, 123.9, 123.2, 122.9, 121.9, 121.0, 112.5, 111.4, 61.2, 14.8. ESI MS: 340 ($M^{+1}$, 100).Anal calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found:C, 81.50; H, 5.04; N, 4.12.

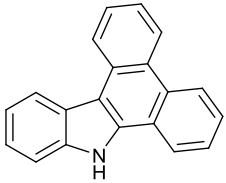



**3-nitro-9*H*-dibenzo[*a,c*]carbazole**: orange solid; mp: 292-295 °C. IR (KBr): 3350, 1606, 1498, 1321, 735 ($cm^{-1}$). $^1$H NMR (400.13 MHz, DMSO $d_6$): δ 12.81 (bs, 1 H), 9.54 (d, $J$ = 2.2 Hz, 1 H), 8.90 (d, $J$ = 8.2 Hz, 1 H), 8.82 (d, $J$ = 8.8 Hz, 1 H), 8.57 (d, $J$ = 7.8 Hz, 1 H), 8.50 (d, $J$ = 8.1 Hz, 1 H), 8.41 (dd, $J_1$= 9.0 Hz, $J_2$= 2.1 Hz, 1 H), 7.87-7.71 (m, 3 H), 7.48 (t, $J$ = 7.6 Hz, 1 H), 7.37 (t, $J$ = 7.5 Hz, 1 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 143.1, 139.1, 137.1, 134.2, 129.4, 128.7, 127.9, 125.9, 124.9, 124.7, 124.6, 123.7, 123.3, 123.0, 121.8, 121.7, 121.4, 120.2, 112.7, 111.2. ESI MS: 313 ($M^{+1}$, 100).Anal calcd for $C_{20}H_{12}N_2O_2$: C, 76.91; H, 3.87; N, 8.97. Found: C, 76.83; H, 3.88; N, 8.99.

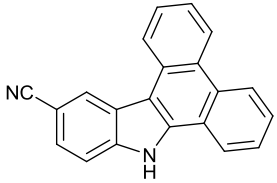



**3-chloro-9*H*-dibenzo[*a,c*]carbazole**: yellow solid; mp: 240-243 °C. IR (KBr): 3338, 2918, 1685, 1608, 1240 ($cm^{-1}$).$^1$H NMR (400.13 MHz, DMSO $d_6$): δ 12.49 (bs, 1 H), 8.98-8.90 (m, 2 H), 8.82 (d, $J$ = 8.8 Hz, 1 H), 8.62 (d, $J$ = 7.9 Hz, 1 H), 8.54 (d, $J$ = 7.9 Hz, 1 H), 7.86-7.70 (m, 4 H), 7.46 (t, $J$ = 7.2 Hz, 1 H), 7.35 (t,

*J* = 7.6 Hz, 1 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 139.0, 134.8, 133.1, 128.8, 128.7, 128.5, 128.2, 128.0, 127.2, 125.7, 124.9, 124.3, 123.9, 123.8, 123.4, 122.8, 121.7, 120.7, 112.4, 111.3. ESI MS: 302 ($M^{+1}$, 100).Anal calcd for $C_{20}H_{12}ClN$: C, 79.60; H, 4.01; N, 4.64. Found: C, 79.66; H, 3.99; N, 4.65.

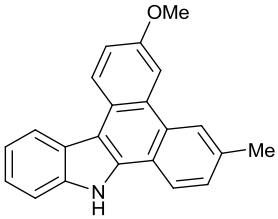



**9*H*-dibenzo[*a,c*]carbazole**: white solid; mp: 185-188 °C. $^1$H NMR (400.13 MHz, DMSO $d_6$): δ 12.51 (bs, 1 H) 8.94-8.86 (m, 3 H), 8.65 (d, *J* = 8.0 Hz, 1 H), 8.57 (d, *J* = 7.6 Hz, 1 H), 7.83-7.65 (m, 4 H), 7.59 (t, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 1 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ139.0, 134.7, 130.1, 129.8, 128.0, 127.4, 126.9, 126.7, 125.2, 124.4, 124.1, 124.0, 123.84, 123.82, 123.1, 122.8, 121.8, 120.5, 112.3, 111.7. ESI MS: 268 ($M^{+1}$, 100).Anal calcd for $C_{20}H_{13}N$: C, 89.86; H, 4.90; N, 5.24. Found: C, 89.80; H, 4.93; N, 5.20

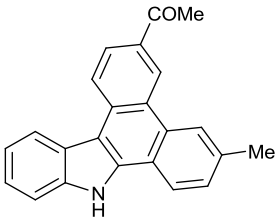



**9*H*-dibenzo[*a,c*]carbazole-12-carbonitrile**: white solid; mp: 305-308 °C.IR (KBr): 3336, 2360, 2223, 1531, 1448, 757 ($cm^{-1}$).$^1$H NMR (400.13 MHz, DMSO $d_6$): δ 12.95 (bs, 1 H), 9.12 (s, 1 H), 8.94-8.85 (m, 3 H), 8.59 (d, *J* = 7.6 Hz, 1 H), 7.87-7.72 (m, 5 H), 7.62 (t, *J* = 7.6 Hz, 1 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 140.8, 136.2, 130.3, 129.1, 128.3, 127.73, 127.70, 127.1, 127.0, 126.9, 124.8, 124.5, 124.4, 124.3, 123.9, 122.9, 122.6, 121.1, 113.3, 111.7, 102.6. ESI MS: 293 ($M^{+1}$, 100).Anal calcd for

$C_{21}H_{12}N_2$; C, 86.28; H, 4.14; N, 9.58. Found: C, 86.19; H, 4.15; N, 9.60.

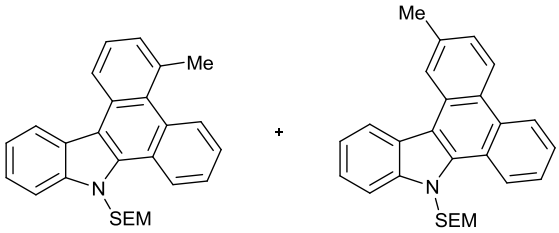



**3-methoxy-6-methyl-9*H*-dibenzo[*a,c*]carbazole**: yellow solid; mp. 283-287 °C.IR (KBr): 3426, 1529, 1450, 1249, 1176, 1089, 738$^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.76 (bs, 1 H), 8.83 (s, 1 H), 8.80 (s, 1 H), 8.72 (d, $J$ = 8.8 Hz, 1 H), 8.60 (d, $J$ = 8.0 Hz, 1 H), 8.32 (s, 1 H), 7.97 (d, $J$ = 8.0 Hz, 1 H), 7.57 (d, $J$ = 8.4 Hz, 1 H), 7.49 (t, $J$ = 7.6 Hz, 1 H), 7.46-7.34 (m, 2 H), 4.04 (s, 3 H), 2.64 (s, 3 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 156.8, 141.2, 135.9, 133.5, 130.4, 128.9, 128.6, 125.4, 124.54, 124.49, 124.3, 123.7, 123.3, 121.81, 121.80, 121.4, 117.5, 113.3, 110.9, 106.4, 55.9, 21.8. ESI MS: 312 ($M^{+1}$, 100).Anal calcd for $C_{22}H_{17}NO$; C, 84.86; H, 5.50; N, 4.50. Found: C, 84.78; H, 5.49; N, 4.52.

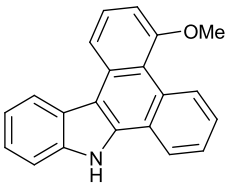



**1-(6-methyl-9*H*-dibenzo[*a,c*]carbazol-3-yl)ethanone**: white solid, mp: 313-318 °C. $^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.63 (bs, 1 H), 9.39 (s, 1 H), 8.90-8.85 (m, 2 H), 8.72 (d, $J$ = 8.4 Hz, 1 H), 8.64 (d, $J$ = 8.0 Hz, 1 H), 8.25 (d, $J$ = 8.0 Hz, 1 H), 8.01 (d, $J$ = 8.0 Hz, 1 H), 7.61 (d, $J$ = 8.8 Hz, 1 H), 7.55 (t, $J$ = 7.2 Hz, 1 H), 7.44 (t, $J$ = 7.2 Hz, 1 H), 2.83 (s, 3 H), 2.66 (s, 3 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 198.2, 141.2, 136.9, 136.2,

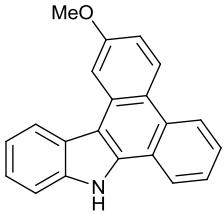
132.7, 132.5, 131.0, 129.4, 126.7, 126.3, 125.2, 124.9, 124.6, 124.3, 124.0, 123.3, 122.0, 121.9, 121.1, 112.9, 111.1, 27.3, 21.9. ESI MS: 324 ($M^{+1}$, 100).Anal calcd for $C_{23}H_{17}NO$; C, 85.42; H, 5.30; N, 4.33. Found: C, 85.35; H, 5.29; N, 4.32.



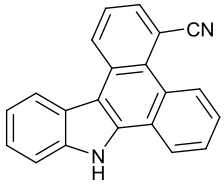

**4-methyl-9-((2-(trimethylsilyl)ethoxy)methyl)-9*H*-dibenzo [*a,c*]carbazole** and **2-methyl-9-((2-(trimethylsilyl)ethoxy)methyl)-9*H*-dibenzo[*a,c*]carbazole:** mixture**;** IR (neat): 3396, 2950, 1465, 1076, 835, 734 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$) (unselected signals): δ 8.92-8.63 (m, 4.4 H), 8.03-7.95 (m, 1.0 H), 7.70-7.60 (m, 2.7 H), 7.57-7.38 (m, 3.3 H), 6.11 (s, 0.9 H), 6.06 (s, 0.9 H), 3.86 (q, $J$ = 8.0 Hz, 2 H), 3.09 (s, 1.4 H), 2.67 (s, 1.4 H), 1.10-0.92 (m, 2 H), -0.06 (s, 4.5 H), -0.09 (s, 4.5 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$) (unselected signals): δ 141.6, 141.3, 137.7, 135.7, 134.69, 134.66, 131.4, 130.8, 129.5, 129.3, 129.0, 127.6, 127.3, 126.9, 126.8, 126.7, 126.4, 125.3, 125.1, 124.8, 124.5, 124.3, 124.2, 124.1, 123.6, 123.5, 123.4, 122.8, 122.3, 122.1, 121.9, 121.7, 121.6, 114.3, 113.7, 111.2, 111.0, 74.7, 74.5, 65.85, 65.81, 27.3, 21.9, 17.95, 17.93, -0.88. Anal calcd for $C_{27}H_{29}NOSi$: C, 78.79; H, 7.10; N, 3.40. Found: C, 78.68; H, 7.13; N, 3.42.



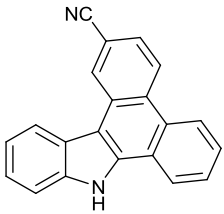
**4-methoxy-9*H*-dibenzo[*a*,*c*]carbazole**: white solid, mp: 200-203 °C. IR (KBr): 3409, 2254, 1484, 1252, 1025, 873 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.69 (bs, 1 H), 9.85 (d, $J$ = 7.6 Hz, 1 H), 8.93-8.87 (m, 1 H), 8.65 (d, $J$ = 8.0 Hz, 1 H), 8.58 (d, $J$ = 7.6 Hz, 1 H), 8.01 (d, $J$ = 8.4 Hz, 1 H), 7.79-7.60 (m, 3 H), 7.54 (t, $J$ = 7.2 Hz, 1 H), 7.43 (t, $J$ = 7.2 Hz, 1 H), 4.15 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 159.1, 141.7, 135.2, 131.6, 130.6, 129.4, 128.6, 126.6, 126.3, 124.9, 124.0, 123.5, 123.4, 122.2, 121.8, 117.2, 116.7, 114.0, 111.8, 107.8, 56.4. ESI MS: 298 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.75; H, 5.10; N, 4.69.




**2-methoxy-9*H*-dibenzo[*a*,*c*]carbazole**: yellow solid, mp: 210-213 °C. IR (KBr): 3423, 1467, 1247, 1027, 825, 730 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.48 (bs, 1 H), 8.89-8.82 (m, 3 H), 8.61 (d, $J$ = 7.6 Hz, 1 H), 8.21 (d, $J$ = 2.4 Hz, 1 H), 8.04 (d, $J$ = 8.0 Hz, 1 H), 7.75-7.65 (m, 2 H), 7.55 (t, $J$ = 7.2 Hz, 1 H), 7.45 (t, $J$ = 7.2 Hz, 1 H), 7.30-7.25 (m, 1 H), 4.08 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 159.4, 141.3, 135.1, 130.9, 130.7, 126.9, 126.3, 126.1, 124.8, 124.5, 123.9, 123.3, 122.0, 121.9, 121.8, 121.3, 114.2, 113.6, 111.0, 105.3, 55.8. ESI MS: 298 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71. Found: C, 84.74; H, 5.06; N, 4.69.



**9*H*-dibenzo[*a*,*c*]carbazole-4-carbonitrile**: IR (KBr): 3423, 2227, 1523, 1467, 1438, 1070 ($cm^{-1}$).$^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.73 (bs, 1 H), 9.65 (d, *J* = 8.0 Hz, 1 H), 9.20 (d, *J* = 8.0 Hz, 1 H), 8.88 (d, *J* = 8.0 Hz, 1 H), 8.63 (d, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 7.2 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.92-7.77 (m, 4 H), 7.72 (d, *J* = 8.0 Hz, 1 H). ESI MS: 293 ($M^{+1}$, 100).




**9*H*-dibenzo[*a*,*c*]carbazole-4-carbonitrile**: white solid, mp: 299-302 °C. IR (KBr): 3421, 2228, 1467, 1438, 1068, 837, 734 ($cm^{-1}$).$^{1}$H NMR (400.13 MHz, DMSO $d_6$): δ 12.99 (bs, 1 H), 9.26 (s, 1 H), 9.10 (d, *J* = 8.8 Hz, 1 H), 9.07 (d, *J* = 8.0 Hz, 1 H), 8.89 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.89-7.80 (m, 1 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.46 (d, *J* = 7.2 Hz, 1 H); $^{13}$C NMR (100.6 MHz, DMSO $d_6$): δ 141.3, 135.2, 130, 129.6, 129.1, 128.9, 128.3, 127.4, 126.5, 125.7, 125.44, 125.37, 124.8, 124.1, 122.7, 122.3, 122.1, 119.8, 113.0, 11.2, 110.6. ESI MS: 293 ($M^{+1}$, 100).Anal calcd for $C_{21}H_{12}N_2$: C, 86.28; H, 4.14; N, 9.58. Found: C, 86.22; H, 4.13; N, 9.56.

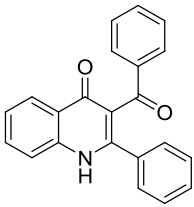
## 4.2.4 Additional information and characterization data on 2,3-substituted 4-(1*H*)-quinolones

**General information**: α,β-Ynones were prepared via Sonogashira cross-coupling of terminal alkynes with aroyl chlorides; the *N*-(2-Iodoaryl)enaminones were obtained by the conjugate addition of 2-iodoanilines with the α,β-ynones.

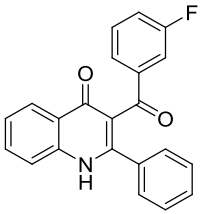
**Typical procedure for the preparation of 1,3-diphenylprop-2-yn-1-one:** Benzoyl chloride (168.7 mg, 1.2 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and $Et_3N$ (167 µl, 1.2 mmol) in anhydrous THF (4 mL) were stirred for 10 min under argon atmosphere at room temperature. CuI (7.6 mg, 0.04 mmol) was added and the reaction mixture was stirred for other 10 min before adding ethynylbenzene (102.2 mg, 1.0 mmol). After 2 h at room temperature, the reaction mixture was worked-up with ethyl acetate and washed with 2 N HCl and a saturated $NH_4Cl$ solution. The organic phase was separated, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford the desired 1,3-diphenylprop-2-yn-1-one.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 7.3 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.57-7.43 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 137.1, 134.2, 133.1, 130.8, 129.6, 128.8, 128.7, 120.3, 93.1, 87.0.

**General procedure for the preparation of N-(2-iodoaryl)enaminones**: An oven-dried Schlenk tube was charged with the appropriate α,β-enone (1.5 mmol), the substituted *o*-iodoaniline (1 mmol) and anhydrous MeOH (1 mL). The tube was sealed and stirred at 120 °C. The reaction mixture was cooled to room temperature, the solvent was evaporated and the residue was purified by silica gel, eluting with hexane/ethyl acetate mixtures.

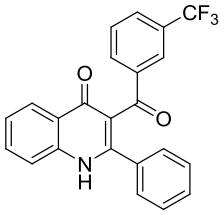
**Typical procedure for the preparation of 3-benzoyl-2-phenylquinolin-4(*1H*)-one:** A metal pressure reactor was charged with $Pd_2(dba)_3$ (0.05 mmol, 4.6 mg), XPhos (0.01 mmol, 4.8 mg), $Cs_2CO_3$ (0.4 mmol, 130 mg), 3-(2-iodophenylamino)-1,3-diphenylprop-2-en-1-one (0.2 mmol, 85.1 mg) and MeCN (5 mL). The reactor was sealed and stirred at 100 °C under a CO pressure of 20 bar for 48 h. 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 44.2 mg (68% yield) of the following compound.



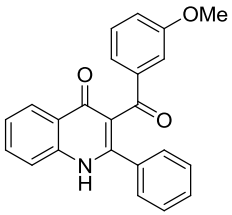

**3-benzoyl-2-phenylquinolin-4(*1H*)-one:** pale yellow solid; mp: 280-282°C. IR (KBr): 3060, 1731, 1668, 1508 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.15 (bs, 1H), 8.11(d, $J$ = 8.0 Hz, 1 H), 7.80-7.73 (m, 4 H), 7.56 (t, $J$ = 7.6 Hz, 1 H), 7.49-7.40 (m, 8 H);$^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 196.17, 175.5, 149.9, 140.4, 138.4, 134.1, 133.4, 132.9, 130.4, 129.4, 129.1, 129.0, 128.9, 125.3, 125.2, 124.4, 120.7, 119.3; Anal calcd for $C_{22}H_{15}NO_2$: C, 81.21; H, 4.65; N, 4.30; Found: C, 81.25; H, 4.64; N, 4.31;



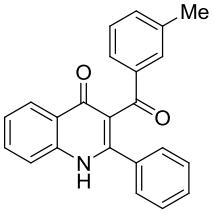

**3-(3-fluorobenzoyl)-2-phenylquinolin-4(*1H*)-one:** withe solid; mp: 260-263°C. IR (KBr): 3062, 1681, 1506 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.19 (bs, 1 H), 8.11(d, *J* = 8.0 Hz, 1 H), 7.77 (bs, 2 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.56-7.42 (m, 9H);$^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.1, 175.6, 162.0, 150.6, 140.9 (d, *J*= 5.7 Hz), 140.3, 133.0, 132.6 (q, *J*= 283 Hz), 131.3, 130.5, 129.1, 129.0, 125.7 (d, *J*= 3.5 Hz), 125.3 (d, *J*= 2.7 Hz), 124.5, 120.4, 120.2, 119.4, 115.4 (d, *J*= 21.8 Hz); $^{19}F$ (376.5 MHz, DMSO $d_6$) δ -112.8; Anal calcd for $C_{22}H_{14}FNO_2$: C, 76.96; H, 4.11; N, 4.08; Found: C, 76.99; H, 4.10; N, 4.09.



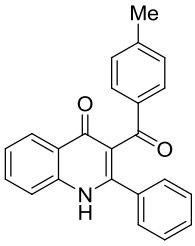

**2-phenyl-3-(3-(trifluoromethyl)benzoyl)quinolin-4(1*H*)-one:** withe solid; mp: 238-240 °C; IR (KBr): 3502, 1683, 1670, 1508 $cm^{-1}$ $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.28 (bs, 1 H), 8.12-8.11(m, 2 H), 8.02 (bs, 1 H), 7.94 (d, *J* = 7.2 Hz, 1 H), 7.78 (bs, 2 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.47-7.45 (m, 6 H);$^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.0, 175.6, 151.3, 140.3, 139.3, 134.0, 133.6, 133.1, 140.9 (d, *J*= 5.7 Hz), 140.3, 133.0, 130.54, 130.49, 130.0, 129.7, 129.6, 125.4 (q, *J*= 9.3 Hz), 125.1 (q, *J*= 4.2 Hz), 124.3 (q, *J*= 272 Hz), 119.6 (q, *J*= 29.5 Hz), Anal calcd for $C_{23}H_{14}F_3NO_2$: C, 70.23; H, 3.59; N, 3.56; Found: C, 70.25; H, 3.58; N, 3.55;



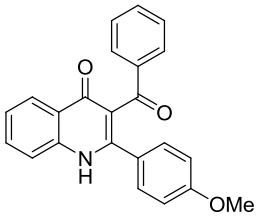

**3-(3-methoxybenzoyl)-2-phenylquinolin-4(*1H*)-one:** yellow solid; mp: 248-250 °C; IR (KBr): 3060, 1675, 1571, 1504 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.21 (bs, 1H), 8.10 (d, $J$ = 8.0 Hz, 1 H), 7.78-7.75 (m, 2 H), 7.50-7.32 (m, 8 H), 7.27 ( s, 1 H), 7.15-7.32 (m, 1 H), 3.76 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.9, 175.5, 159.8, 149.9, 140.4, 139.9, 134.1, 132.9, 130.5, 130.2, 129.1, 128.9, 125.3, 125.2, 124.4, 122.4, 120.7, 119.4, 113.5, 55.7; Anal calcd for $C_{23}H_{17}NO_3$: : C, 77.73; H, 4.82; N, 3.94; Found: : C, 77.77; H, 4.81; N, 3.95.



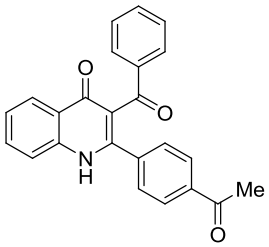

**3-(3-methylbenzoyl)-2-phenylquinolin-4(*1H*)-one:** yellow solid; mp: 257-259 °C; IR (KBr): 3062, 1666, 1571, 1508 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.13 (bs, 1H), 8.11 (d, $J$ = 8.0 Hz, 1 H), 7.79-7.73 (m, 2 H), 7.59 (d, $J$ = 10.0 Hz, 2 H), 7.49-7.29 (m, 8 H), 2.31 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$) (some chemical shifts are isochronous): δ 196.2, 175.5, 149.8, 140.3, 138.5, 138.3, 134.14, 134.10, 132.8, 130.4, 129.6, 129.1, 128.9, 126.8, 125.3, 125.2, 124.4, 120.9, 119.3, 21.3; Anal calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13; Found: C, 81.37; H, 5.06; N, 4.12.



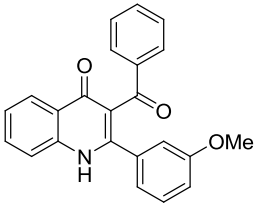

**3-(4-methylbenzoyl)-2-phenylquinolin-4(1*H*)-one:** brown solid; mp 329-331 °C; IR (KBr): 3444, 3062, 1664, 1571, 1500 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.12 (bs, 1H), 8.10 (d, $J$ = 8.0 Hz, 1 H), 7.78-7.75 (m, 2 H), 7.68 (d, $J$ = 8.0 Hz, 2 H), 7.48-7.40 (m, 6 H), 7.23 (d, $J$ = 8.0 Hz, 2 H), 2.34 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.7, 175.5, 149.6, 143.8, 140.4, 136.0, 134.2, 132.8, 130.4, 129.60, 129.57, 129.1, 128.9, 125.3, 125.2, 124.3, 120.9, 119.3, 21.6; Anal calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13; Found: C, 81.36; H, 5.04; N, 4.12.



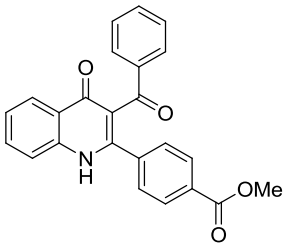

**3-benzoyl-2-(4-methoxyphenyl)quinolin-4(1*H*)-one**: yellow solid; mp: 250-253 °C; IR (KBr): 3430, 1627, 1509 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.03 (bs, 1H), 8.08 (d, $J$ = 7.6 Hz, 1 H), 7.80-7.74 (m, 4 H), 7.56 (t, $J$ = 7.2 Hz, 1 H), 7.45-7.40 (m, 5 H), 6.98 (d, $J$ = 8.4 Hz, 2 H), 3.75 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 196.4, 175.5, 161.0, 149.6, 140.4, 138.4, 133.4, 132.8, 130.7, 129.4, 129.0, 126.2, 125.3, 125.1, 124.3, 120.4, 119.3,114.4, 55.8; Anal calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94; Found: C, 77.69; H, 4.81; N, 3.95.



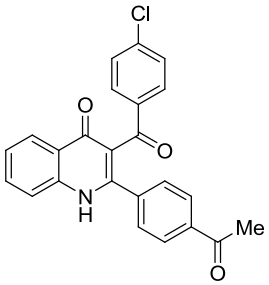

**2-(4-acetylphenyl)-3-benzoylquinolin-4(1*H*)-one:** brown solid; mp: 250-252 °C; IR (KBr): 3451, 3068, 1685, 1550, 1513 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.29 (bs, 1H), 8.11 (d, $J$ = 8.0 Hz, 1 H), 8.00-7.95 (m, 2 H), 7.82-7.77 (m, 3 H),7.64-7.56 (m, 2 H) 7.52-7.43 (m, 3 H), 2.58 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 197.9, 196.0, 175.8, 149.2, 140.3, 138.4, 138.3, 138.1, 133.5, 133.0, 129.6, 129.4, 129.1, 128.6, 125.4, 124.6, 120.9, 119.4, 27.3; Anal calcd for $C_{24}H_{17}NO_3$: C, 78.46; H, 4.66; N, 3.81; Found: C, 78.50; H, 4.65; N, 3.80.




**3-benzoyl-2-(3-methoxyphenyl)quinolin-4(1*H*)-one:** yellow solid: mp: 242.244 °C; IR (KBr): 3405, 2958, 1654, 1623, 1550, 1509 ($cm^{-1}$). $^1H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.14 (bs, 1H), 8.10 (d, $J$ = 7.6 Hz, 1 H), 7.82-7.73 (m, 4 H), 7.57 (t, $J$ = 7.6 Hz, 1 H), 7.46-7.40 (m, 3 H), 7.33 (t, $J$ = 8.4 Hz, 1 H), 7.03-7.00 (m, 3H), 3.65 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 196.1, 175.5, 159.3, 149.5, 140.3, 138.4, 134.3, 133.4, 132.9, 130.2, 129.4, 129.0, 125.3, 125.2, 124.4, 121.3, 120.7, 119.3, 116.1, 114.8 55.6; Anal calcd for $C_{23}H_{17}NO_3$: C, 77.73; H, 4.82; N, 3.94; Found: C, 77.70; H, 4.81; N, 3.93.

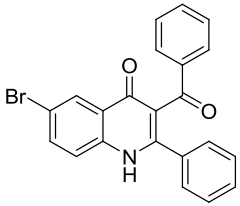



**methyl 4-(3-benzoyl-4-oxo-1,4-dihydroquinolin-2-yl)benzoate:** brown wax; ; IR (KBr): 3444, 1727, 1629, 1508 ($cm^{-1}$); $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.26 (bs, 1H), 8.13 (d, $J$ = 7.6 Hz, 1 H), 8.08 (d, $J$ = 6.8 Hz, 1 H) 7.98-7.90 (m, 2 H), 7.79 (t, $J$ = 6.8 Hz, 3 H), 6.63 (d, $J$ = 7.6 Hz, 2 H), 7.56-7.43 (m, 4H), 3.85 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.9, 175.2,166.0, 149.0, 140.3, 138.5, 138.4, 133.5, 133.0, 131.3, 129.7, 129.6, 129.4, 129.2, 129.0, 125.4, 124.6, 121.0, 119.4, 52.8; Anal calcd for $C_{24}H_{17}NO_4$: C, 75.19; H, 4.47; N, 3.65; Found: C, 75.21; H, 4.46; N, 3.64.

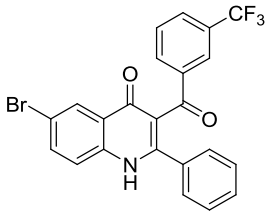



**2-(4-acetylphenyl)-3-(4-chlorobenzoyl)quinolin-4(1*H*)-one:** yellow solid; mp: 294-296 °C; 3444, 1687, 1509 ($cm^{-1}$). $^{1}H$ NMR (400.13 MHz, DMSO $d_6$): δ 12.32 (bs, 1H), 8.13-8.09 (m, 1 H), 8.02-7.93 (m, 3 H) 7.86-7.76 (m, 4 H), 7.64-7.42 (m, 6 H), 2.59 (s, 3 H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 197.9, 195.0, 175.5, 149.7, 140.3, 138.4, 138.2, 137.2, 133.7, 133.1, 131.3, 129.6, 129.2, 128.6, 125.3, 124.7, 120.4, 119.4, 114.7, 27.3; Anal

calcd for $C_{24}H_{16}CLNO_3$: C, 71.73; H, 4.01; N, 3.49; Found: C, 71.69; H, 4.02; N, 3.50.




**3-benzoyl-6-bromo-2-phenylquinolin-4(1H)-one:** yellow solid; mp: 265-267 °C; IR (KBr): 3256, 1670, 1567, 1494 ($cm^{-1}$); $^1H$ NMR (400.13 MHz, DMSO $d_6$): ): δ 12.30 (bs, 1H), 8.19 (s, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.79 (d, *J* = 7.6 Hz, 2 H) 7.73 (d, *J* = 8.8 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48-7.42 (m, 8H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$): δ 195.7, 174.2,150.3, 139.3, 138.2, 135.6, 133.8, 133.6, 130.6, 129.4, 129.10, 129.06, 129.00, 127.5, 126.7, 121.9, 121.1, 117.1; Anal calcd for $C_{22}H_{14}BrNO_2$: C, 65.36; H, 3.49; N, 3.46; Found: C, 65.37; H, 3.48; N, 3.45;




**6-bromo-2-phenyl-3-(3-(trifluoromethyl)benzoyl)quinolin-4(1H)-one:** brown solid; mp: 248-250 °C; IR (KBr): 3250, 3087, 1675, 1571, 1508 1494 ($cm^{-1}$); $^1H$ NMR (400.13 MHz, DMSO $d_6$): ): δ 12.42 (bs, 1H), 8.19 (bs, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 8.02 (bs, 1 H), 7.94 (d, *J* = 8.8 Hz, 2 H) 7.74 (d, *J* = 8.8 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.46 -7.45 (m, 5H); $^{13}C$ NMR (100.6 MHz, DMSO $d_6$) (some chemical shifts are isochronous): δ 194.6, 174.3, 151.6, 139.3, 139.1, 135.8, 133.7 (q, *J*= 10.9 Hz), 130.6 (q, , *J*= 17.9 Hz), 129.9 (q,, *J*= 32.2 Hz), 129.8 (q,, *J*= 3.7 Hz), 129.1,

129.0, 127.5, 126.9, 125.2 (q, *J*= 3.5 Hz), 124.3 (q, *J*= 272.5 Hz), 122.0, 120.0, 117.4; $^{19}F$ (376.5 MHz, DMSO $d_6$) δ -61.4; Anal calcd for $C_{23}H_{13}BrF_3NO_2$: C, 58.50; H, 2.77; N, 2.97; Found C, 58.48; H, 2.78; N, 2.98.

## 4.2.5 Additional information and characterization data on benzil derivatives

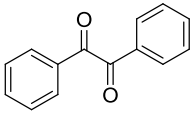
**General information**: The 1,2-diarylethanones were prepared through the Friedel-Kraft reaction or through a palladium catalyzed cross-coupling depending on the desired subtituent.

**Typical procedure for the preparation of 2-(4-chlorophenyl)-1-phenylethanone:** A flask equipped with a magnetic stirring bar was charged with 2-(4-chlorophenyl)acetyl chloride (283.5 mg, 219 μl, 1.5 mmol) dissolved in $CH_2Cl_2$ (1 mL). The solution was stirred under nitrogen at 0°C before adding $AlCl_3$ (219 mg, 1.65mmol) and benzene dissolved $CH_2Cl_2$ (1 mL). Reaction mixture was stirred at room temperature for 0.5 h and after this time was added $H_2O$ (10 mL) dropwise. The resultant mixture was diluited 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 flash chromatography on silica gel, eluiting with n-hexane/AcOEt mixture to obtain 2-(4-chlorophenyl)-1-phenylethanone (256 mg, 88% yield).

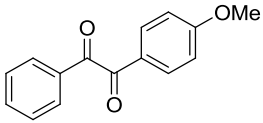
**Typical procedure for the preparation of 4-(2-phenylacetyl)benzonitrile**: A Carousel Tube Reaction (Radley Discovery) was charged with $Pd(OAc)_2$ (7 mg, 0.03 mmol), XPhos (29 mg, 0.06 mmol) and toluene (2 mL). The solution was stirred under Nitogen at room temperature for 10 minutes before adding NaOtBu (720 mg, 7.5mmol), 4-acetylbenzonitrile (522 mg, 3.6 mmol) and bromobenzene (471 mg, 3 mmol) dissolved in toluene (2 ml). The reaction mixture was warmed at 90°C and stirred for 5 hours. After cooling, the mixture was diluited with

$Et_2O$ and washed with $H_2O$ 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, eluiting with n-hexane/AcOEt mixture to obtain 471 mg of 4-(2-phenylacetyl)benzonitrile (71% yield).

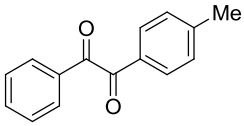
**Typical procedure for the preparation of 1,2-diarylethandiones:** a Carousel Tube Reaction (Radley Discovery) was charged with $Cu(OAc)_2$ (12 mg, 0.06 mmol), $P(Ph)_3$ (31 mg, 0.12 mmol) and 1,2,4-trimethylbenzene (1 mL). The solution was stirred under air at room temperature for 10 minutes before adding 1,2-diphenylethanone (78.5 mg, 0.4 mmol) dissolved in 1,2,4-trimethylbenzene (0.6 mL). The reaction mixture was warmed at 100°C and stirred for 0.83 hours. After cooling, the mixture was diluited with $Et_2O$ and washed with a satured solution of $NH_4Cl$ 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, eluiting with *n*-hexane/AcOEt mixture to obtain 71.4 mg (83% yield) of the following compound:



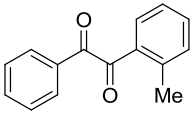

**Benzil:** Pale yellow solid; Mp: 91-93 °C; IR (KBr): 2921, 2856, 1658, 1594, 1450, 1384, 1211, 1101, 875 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.00 (d, *J*= 7.2 Hz, 4 H), 7.69 (t, *J*=7.2 Hz, 2H) 7.54 (t, *J*=7.6 Hz, 4H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 194.6, 134.9, 133.0, 129.9, 129.1; MS m/z (relative intensity): 210 ( $M^+$ 0.2%), 64 (10.1%), 105 (11.6%), 51 (14.8%), 92 (15.6%), 77 (43.1%), 135 (100%) Anal. Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79; Found: C, 79.88; H, 4.77.




**1-(4-Methoxyphenyl)-2-phenylethane-1,2-dione:** Yellow oil; IR (neat): 2933, 2842, 1779, 1675, 1596, 1265, 1216, 1166, 1024, 875 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.98 (t, *J*= 8.8 Hz, 4H), 7.66 (t, *J*= 7.6 Hz, 1H) 7.52 (t, *J*= 7.6 Hz, 2H), 7.00 (d, *J*= 8.8 Hz, 2H), 3.90 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 194.9, 193.2, 165.0, 134.7, 133.2, 132.4, 129.9, 129.0, 126.1, 114.4, 55.6; MS m/z (relative intensity): 240 ($M^+$ 0.7%), 64 (10.2%), 105 (12.0%), 92 (15.0%), 51 (15.7%), 77 (44.4%), 135 (100%); Anal. Calcd. for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; Found: C, 74.89; H, 5.04.

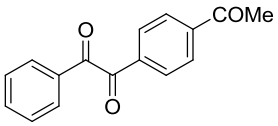



**1-Phenyl-2-p-tolylethane-1,2-dione:** Yellow oil; IR (neat): 2923, 2854, 1604, 1450, 1384, 1214, 1174, 875 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, *J*= 7.2 Hz, 2H), 7.9 (d, *J*= 8.4 Hz, 2H), 7.68 (t, *J*= 7.2 Hz, 1H), 7.53 (t, *J*= 8.0 Hz, 2H) 7.33 (d, *J*= 8.0 Hz, 2H), 2.46 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 194.8, 194.3, 146.2, 134.8, 133.1, 130.6, 130.0, 129.9, 129.7, 129.0, 21.9; MS m/z (relative intensity) : 224 ($M^+$ 1.5%), 51 (22.7%), 65 (24.3%), 105 (25.1%), 77 (34.8%), 91 (37.0%), 119 (100%); Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39; Found: C, 80.42; H, 5.40.

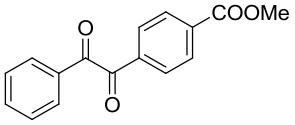



**1-phenyl-2-o-tolylethane-1,2-dione**: Pale yellow solid; Mp: 53-55 IR (KBr): 3064, 2969, 2929, 1994, 1820, 1679, 1596, 1452, 1205, 1166, 881 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 8.0 (d, *J*=

7.6 Hz, 2H), 7.69-7.51 (m, 3H), 7.38-7.29 (m, 4H) 2.73 (s, 3H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 196.7, 194.8, 141.3, 134.7, 133.7, 133.2, 130.0, 132.6, 129.9, 129.0, 128.5, 126.0, 21.9; MS m/z (relative intensity) : 224 ($M^+$ 1.4%), 51 (21.5%), 65 (23.3%), 105 (25.2%), 77 (35.2%), 91 (37.3%), 119 (100%); Anal. Calcd. for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39; Found: C, 80.39; H, 5.38.

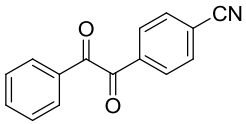



**1-(4-acetylphenyl)-2-phenylethane-1,2-dione:** Pale yellow solid; Mp: 78-80 °C; IR (KBr): 2923, 2852, 1677, 1436, 1213, 885 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.09-8.01 (m, 4H), 7.99 (d, *J*= 1.2 Hz, 2H), 7.69 (t, 7.6 Hz, 1H), 7.54 (t, 7.6 Hz, 2H), 2.65 (s, 3H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 197.1, 193.7, 193.6, 141.3, 136.0, 135.1, 132.7, 130.1, 129.9, 129.1, 128.7, 26.9; MS m/z (relative intensity): 252 ($M^+$ 2.51%), 91 (10.7 %), 147 (24.5%), 77 (44.8%), 105 (100%); Anal. Calcd. For $C_{16}H_{12}O_3$: C, 76.18; H, 4.79; Found: C, 76.22; H, 4.78.

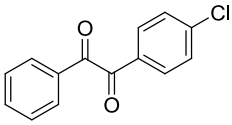



**Methyl 4-(2-oxo-2-phenylacetyl)benzoate:** Pale yellow solid; Mp: 65-67 °C; IR (KBr): 2954, 2927, 2848,1720, 1671, 1436, 1286, 1209, 1105, 885 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.18 (d, *J*= 8.4 Hz, 2H), 8.06 (d, *J*= 8.0 Hz, 2H), 8.00 (d, *J*= 7.6 Hz, 2H), 7.70 (t, *J*= 7.6 Hz, 1H) 7.54 (t, *J*= 7.6 Hz, 2H), 3.97 (s, 3H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 193.7, 193.6, 165.8, 136.1, 135.3, 135.1, 132.8, 130.1, 130.0, 129.8, 126.3, 52.6; MS m/z (relative intensity): 135 (9.1%), 51 (22.1%), 163 (24.7%), 77

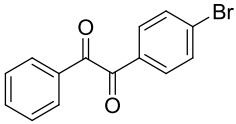
(51.3%), 105 (100%); Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51; Found: C, 71.54; H, 4.50.



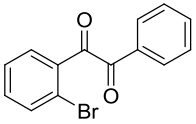

**4-(2-Oxo-2-phenylacetyl)benzonitrile:** Pale yellow solid; Mp: 110-112 °C; IR (KBr): 3112, 3073, 3046, 2225, 1683, 1660, 1594, 1172, 881 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.12 (d, *J*= 8.8 Hz, 2H), 8.00 (dd, $J_1$= 8.4 Hz, $J_2$= 0.8 Hz, 2H), 7.84 (d, *J*= 8.4 Hz, 2H), 7.73 (t, *J*= 7.6 Hz, 1H), 7.57 (t, *J*= 8.0 Hz, 2H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.0, 192.4, 135.9, 135.4, 132.8, 132.5, 130.2, 130.0, 129.2, 117.9, 117.6;MS m/z (relative intensity): 163 (6.3%), 235 ($M^+$ 7.2%), 102 (26.6%), 51 (42.9%), 77 (62.2%), 105 (100%); Anal. Calcd. for $C_{15}H_9NO_2$: C, 76.59; H, 3.86; N, 5.95; Found: C, 76.65; H, 3.84; N, 5.97.



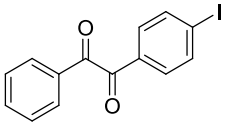

**1-(4-chlorophenyl)-2-phenylethane-1,2-dione**: Pale yellow solid; Mp: 70-72 °C; IR (KBr): 2931, 1666, 1585, 1450, 1402, 1209, 1174, 1095, 875 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.00 (m, 4H), 7.67-7.49 (m, 5H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.9, 193.0, 141.6, 135.1, 132.8, 131.4, 131.2, 129.9, 129.4, 129.1;MS m/z (relative intensity): 245 ($M^+$ 0.6%), 141 (10.5%), 139 (29.8%), 51 (35.8%), 77 (56.8%), 105 (100%); Anal. Calcd. for $C_{14}H_9ClO_2$: C, 68.72; H, 3.71; Found: C, 68.69; H, 3.72



**1-(4-bromophenyl)-2-phenylethane-1,2-dione:** Yellow solid; IR (neat): 3087, 2967, 2927, 1668, 1579, 1450, 1398, 1209, 1174, 1070, 873 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, *J*= 7.2 Hz, 2H) 7.86 (d, *J*= 8.4 Hz, 2H) 7.71-7.67 (m,3H), 7.54 t, *J*= 7.6 Hz, 2H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.9, 193.3, 135.1, 132.8, 132.5, 131.7, 131.3, 130.5, 130.0, 129.1; MS m/z (relative intensity): 289 ($M^+$ 2.0%), 183 (9.0%), 155 (11.9%), 51 (32.8%), 77 (55.5%), 105 (100%); Anal. Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Found: C, 58.20; H, 3.13

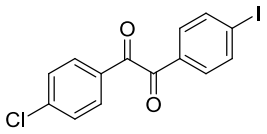



**1-(2-bromophenyl)-2-phenylethane-1,2-dione:** Yellow oil; IR (KBr): 2923, 1677, 1585, 1450, 1253, 1027 860 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.09 (d, *J*= 0.8 Hz, 2H), 7.85-7.83 (m, 1H), 7.71-7.62(m, 2H), 7.58-7.44 (m, 4H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 194.2, 191.5, 136.0, 134.5, 134.4, 133.8, 132.7, 132.6, 130.4, 128.9, 127.8, 121.8; MS m/z (relative intensity): 289 ($M^+$ 2.0%), 183 (11.2%), 155 (12.9%), 51 (32.9%), 77 (54.5%), 105 (100%); Anal. Calcd. for $C_{14}H_9BrO_2$: C, 58.16; H, 3.14; Found: C, 58.21; H, 3.13.

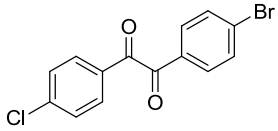



**1-(4-Iodophenyl)-2-phenylethane-1,2-dione:** Yellow solid; Mp: 89-90 °C; IR (KBr): 3060, 2927, 2861, 1670, 1579, 1394, 1211, 1174, 879 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.98 (d, *J*= 7.6 Hz, 2H), 7.91 (d, *J*= 8.4 Hz, 2H), 7.71-7.68 (m, 3H) 7.54 (t, *J*= 7.6 Hz, 2H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.9, 193.7, 138.4, 135.1, 132.8, 132.3, 131.0, 130.0, 129.1, 103.7; MS m/z (relative intensity): 336 ($M^+$ 0.5%), 203 (6.5%), 231 (19.1%), 51

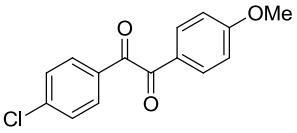
(32.7%), 50 (33.7%), 77 (56.7%), 105 (100%); Anal. Calcd. for $C_{14}H_9IO_2$: C, 50.03; H, 2.70; Found: C, 50.10; H, 2.71.



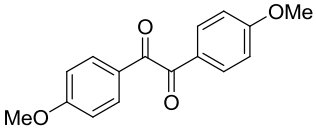

**1-(4-Chlorophenyl)-2-(4-iodophenyl)ethane-1,2-dione:** Yellow solid; Mp: 208-210 °C; IR (KBr): 3087, 2954, 2913, 1662, 1579, 1394, 1209, 1172, 1091, 881 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.94-7.91 (m, 4H), 7.19 (d, *J*= 8.4 Hz, 2H), 7.52 (d, *J*= 8.4 Hz, 2H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.0, 192.3, 141.4, 138.5, 132.1, 131.3, 131.1, 131.0, 129.5, 103.9; MS m/z (relative intensity): 370 ($M^+$ 6.0%), 203 (18.3%), 51 (18.7%), 141 (35.3%), 111 (58.1%), 50 (71.5%) 231 (85.1%) 76 (85.6%), 139 (100%); Anal. Calcd. for $C_{14}H_8ClIO_2$: C, 45.38; H, 2.18; Found: C, 45.42; H, 2.16.




**1-(4-bromophenyl)-2-(4-chlorophenyl)ethane-1,2-dione:** Yellow solid; Mp: 203-205 °C; IR (KBr):2923, 1664, 1587, 1209, 1172, 835 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.94 (d, *J*= 8.4 Hz, 2H), 7.86 (d, *J*= 8.4 Hz, 2H), 7.69 (d, *J*= 8.4 Hz, 2H), 7.52 (d, *J*= 8.4 Hz, 2H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 192.6, 192.3, 141.8, 132.5, 131.5, 131.3, 131.1, 130.7, 129.5; MS m/z (relative intensity): 237 (11.4%), 51 (18.2%), 155 (30.1%), 141 (41.7%), 185 (46.5%), 111 (50.2%), 50 (58.9%), 75 (92.5%), 139 (100%); Anal. Calcd. for $C_{14}H_8BrClO_2$: C, 51.97; H, 2.49; Found: C, 52.01; H, 2.51.




**1-(4-chlorophenyl)-2-(4-methoxyphenyl)ethane-1,2-dione:** Pale yellow solid; Mp: 127-128 °C; IR (KBr): 3093, 3002, 2937, 2838, 1670, 1654, 1598, 1267, 1214, 1168, 1027, 881 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.96-7.92 (m, 4H), 7.49 (d, *J*= 8.4 Hz, 2H), 6.99 ((d, *J*= 8.8 Hz, 2H), 3.90 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.4, 192.4, 165.1, 141.4, 132.4, 131.6, 131.2, 129.4, 125.9, 114.4, 55.7; MS m/z (relative intensity): 274 (M+ 1.5%), 139 (18.2%) 77 (20.2%) 141 (52.2%), 135 (100%) Anal. Calcd. for $C_{15}H_{11}ClO_3$: C, 65.58; H, 4.04; Found: C, 65.66; H, 4.02.




**1,2-bis(4-methoxyphenyl)ethane-1,2-dione** Yellow solid; Mp: 130-131 °C; IR (KBr): 3025, 2925, 2850, 1654, 1598, 1571, 1263, 1160, 1016, 879 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.99 (d, *J*= 8.8 Hz, 4H), 7.00 (d, *J*= 8.8 Hz, 4H), 3.91 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 193.5, 164.9, 132.4, 126.3, 114.3, 55.6; MS m/z (relative intensity): 270 ($M^+$ 2.2%), 77 (17.9%), 207 (49.4%), 44 (85.1%), 135 (100%); Anal. Calcd. for Formula: $C_{16}H_{14}O_4$: C, 71.10; H, 5.22; Found: : C, 71.21; H, 5.23.

## 4.2.6 Additional information and characterization data on 2,4-diarylbenzo[*b*][1,4]oxazepines

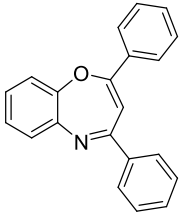
**General information**: α,β-Ynones were prepared via Sonogashira cross-coupling of terminal alkynes with aroyl chlorides; the *N*-(2-Bromoaryl)enaminones were obtained by the conjugate addition of 2-bromoanilines with the α,β-ynones.

**Typical procedure for the preparation of 1,3-diphenylprop-2-yn-1-one:** Benzoyl chloride (168.7 mg, 1.2 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) and $Et_3N$ (167 µl, 1.2 mmol) in anhydrous THF (4 mL) were stirred for 10 min under argon atmosphere at room temperature. CuI (7.6 mg, 0.04 mmol) was added and the reaction mixture was stirred for other 10 min before adding ethynylbenzene (102.2 mg, 1.0 mmol). After 2 h at room temperature, the reaction mixture was worked-up with ethyl acetate and washed with 2 N HCl and a saturated $NH_4Cl$ solution. The organic phase was separated, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.
$^1$H NMR (400 MHz, $CDCl_3$) δ: 8.26 (d, *J* = 7.3 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.57-7.43 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 178.1, 137.1, 134.2, 133.1, 130.8, 129.6, 128.8, 128.7, 120.3, 93.1, 87.0.

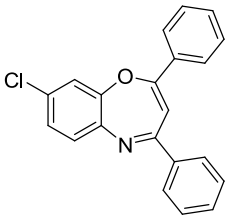
**General procedure for the preparation of N-(2-iodoaryl)enaminones**: An oven-dried Schlenk tube was charged with the appropriate α,β-enone (1.5 mmol), the substituted *o*-iodoaniline (1 mmol) and anhydrous MeOH (1 mL). The tube was sealed and stirred at 120 °C. The reaction mixture was cooled to room temperature, the solvent was evaporated and the residue was purified by silica gel, eluting with hexane/ethyl acetate mixtures.

**Typical procedure for the preparation of 2,4-diphenylbenzo[*b*][1,4]oxazepine:** An oven-dried Schlenk tube

was charged with CuI (0.008 mmol, 1.5 mg ), $P(Ph)_3$ (0.008 mmol, 2 mg) and DMA (1 mL). The tube was stirred for 10 minutes before adding $K_2CO_3$ (0.3 mmol, 41.4 mg) and 3-(2-bromophenylamino)-1,3-diphenylprop-2-en-1-one (0.15 mmol, 56.7 mg) dissolved in DMA (1 mL). The resulting mixture was stirred at 140°C for 6.5 h. After this time the reaction mixture was worked-up with $Et_2O$ and washed with $H_2O$ and with a saturated $NH_4Cl$ solution. The organic phase was separated, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel.

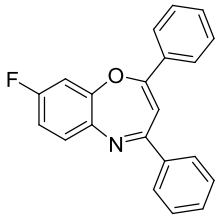



**2,4-diphenylbenzo[*b*][1,4]oxazepine**: Yellow solid; Mp: 66-68 °C; IR (KBr): 1737, 1629, 757 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.07-8.04 (m, 2H), 7.96-7.93(m, 2H), 7.51-7.48 (m, 7H), 7.27-7.23 (m, 2H), 7.14-7.12 (m, 1H), 6.68 (s, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 164.1, 163.3, 151.1, 142.1, 139.7, 133.4, 130.5, 130.4, 128.8, 128.6, 128.5, 128.1, 127.6, 126.2, 125.8, 120.8, 106.2 Anal. Calcd. for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71; Found: C, 84.87; H, 5.07; N, 4.72.

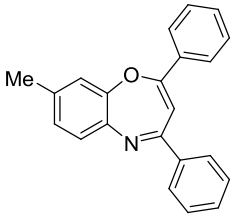



**8-chloro-2,4-diphenylbenzo[*b*][1,4]oxazepine**: Yellow solid; Mp: 124-126 °C; IR (KBr): 1633, 1008, 761 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.04-8.03 (m, 2H), 7.91-7.90 (m, 2 H), 7.52-7-

51 (m, 6H),7.41 (d, *J*= 8 Hz, 1 H) 7.24 (d, *J*= 8 Hz, 1 H), 7.13 (s,1 H), 6.67 (s, 1 H). $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 164.2, 162.9, 151.0, 140.9, 139.4, 133.03, 132.98, 130.7, 130.6, 129.3, 128.9, 128.5, 127.5, 126.2, 126.0, 121.2, 106.3; Anal. Calcd. for $C_{21}H_{14}ClNO$: C, 76.02; H, 4.25; N, 4.22; Found: C, 76.10; H, 4.24; N, 4.21;

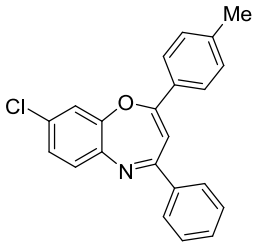



**8-fluoro-2,4-diphenylbenzo[*b*][1,4]oxazepine**: Yellow solid; Mp: 101-103 °C; IR (KBr): 1633, 1484, 1010, 742 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.04-8.02 (m, 2H), 7.91-7.90 (m, 2H), 7.51-7.44 (m,7 H), 7.02-6.97 (m,1 H), 6.89-6.83 (m, 1 H), 6.67-6.63 (m, 1 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 163.5, 163.4, 162.4, 162.3 (d, *J*= 248 Hz), 151.1 (d, *J*= 10,9 Hz), 139.5, 138.6, 133.1, 130.6 (d, *J*= 4 Hz), 129.4 (d, *J*= 9.6 Hz), 128.9, 128.5, 127.5, 126.1, 112.8 (d, *J*= 22.2 Hz), 108.4 (d, *J*= 23.7 Hz), 106.3; $^{19}$F NMR (376.5 MHz) ($CDCl_3$) δ – 113.6; Anal. Calcd. for $C_{21}H_{14}FNO$; C, 79.98; H, 4.47; N, 4.44; Found: C, 80.08; H, 4.46; N, 4.44.

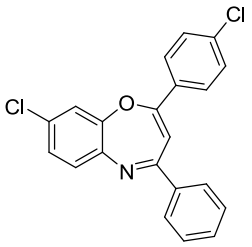



**8-methyl-2,4-diphenylbenzo[*b*][1,4]oxazepine**: Yellow solid; Mp: 93-95 °C; IR (KBr): 1737, 1629, 757 cm$^{-1}$ $^1$H NMR (400

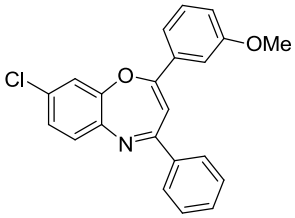
MHz) ($CDCl_3$) δ 8.04 - 8.02 (m, 2H), 7.95 - 7.93 (m, 2H), 7.50-7.48 (m, 6 H), 7.37 (d, *J*= 8 Hz, 1H), 7.06 (d, *J*= 7.2 Hz, 1H), 6.93 (s, 1H), 6.64 (s, 1H), 2.37 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 163.3, 162.8, 150.6, 139.9, 139.6, 138.7, 133.6, 130.31, 130.26, 128.9, 128.8, 128.4, 127.4, 126.5, 126.2, 121.2, 106.2, 20.9; Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; Found: C, 84.90; H, 5.51; N, 4.49.



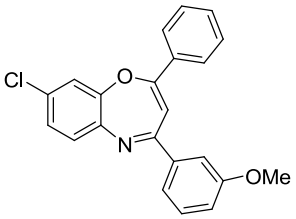

8-**chloro-4-phenyl-2-p-tolylbenzo[*b*][1,4]oxazepine**: Yellow solid; Mp: 134-136 °C; IR (KBr): 1737, 1631, 1473, 1006, 763 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.02 (d, *J*= 4.8Hz, 2H), 7.80 (d, *J*= 8 Hz, 2H), 7.51 (m, 4H), 7.40 (d, *J*= 8.4 Hz, 1H), 7.30 (d, *J*= 8Hz, 2H), 7.23 (d, *J*= 8.4 Hz, 1H), 7.12 (s, 1H), 6.62 (s, 1 H), 2.45 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 164.3, 163.1, 151.0, 141.1, 140.9, 139.6, 132.9, 130.7, 130.2, 129.6, 129.2, 128.5, 127.5, 126.2, 125.9, 121.2, 105.5, 21.5; Anal. Calcd. for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05; Found: C, 76.48; H, 4.67; N, 4.04.



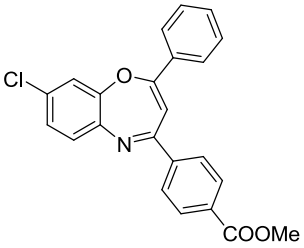

**8-chloro-2-(4-chlorophenyl)-4-phenylbenzo[*b*][1,4]oxazepine:** Yellow solid; Mp: 140-142 °C; IR (KBr): 1631, 1475, 1008, 763 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 8.00 (d, *J*= 6 Hz, 2H), 7.81 (d, *J*= 8.4 Hz, 2H), 7.57-7.39 (m, 6 H), 7.23 (d, *J*= 8.4 Hz, 1H), 7.08 (s,1 H), 6.62 (s, 1 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 163.9, 161.6, 150.7, 140.7, 139.2, 136.7, 133.1, 131.5, 130.8, 129.4, 129.2, 128.5, 127.5, 127.4, 126.1, 121.1, 106.6; Anal. Calcd. for $C_{21}H_{13}Cl_2NO$: C, 68.87; H, 3.58; N, 3.82; Found**:** C, 68.90; H, 3.59; N, 3.83.



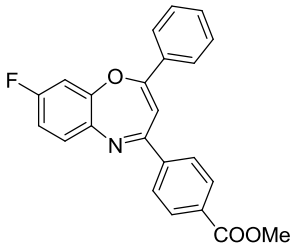

**8-chloro-2-(3-methoxyphenyl)-4-phenylbenzo[b][1,4]oxazepine:** Yellow solid; Mp: 96-98 °C; IR (KBr): 1737, 1635, 1473, 767 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 8.02 (d, *J*= 5.6 Hz, 2H), 7.51-7.39 (m, 7 H), 7.23 (dd, $J_1$= 8.4 Hz, $J_2$= 1.2 Hz 1 H), 7.12 (s, 1 H), 7.04 (d, *J*= 8 Hz, 1H), 6.65 (s, 1 H), 3.91 (s, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 164.1, 162.5, 159.9, 150.9, 140.8, 139.4, 134.4, 133.0, 130.7, 130.0, 129.3, 128.5, 127.5, 126.0, 121.2, 118.6, 116.0, 111.9, 106.6, 55.5; Anal. Calcd. for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87; Found: C, 73.08; H, 4.45; N, 3.88.




**8-chloro-4-(3-methoxyphenyl)-2-phenylbenzo[*b*][1,4]oxazepine:** Yellow wax; IR (KBr): 1737, 1635, 1473, 767 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.90-7.87 (m, 2 H), 7.63-7.29 (m, 7 H), 7.24 (dd, $J_1$= 5.2 Hz, $J_2$= 1.2 Hz 1 H), 7.22 (d, *J*= 2 Hz, 1H), 7.13-7.05 (m,1 H), 6.65 (s, 1 H), 3.92 (s, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ: 163.9, 162.8, 159.8, 151.0, 140.9, 140.8, 133.0, 130.6, 129.5, 129.3, 128.9, 126.2, 126.0, 121.2, 120.2, 116.8, 112.5, 106.4, 55.4; Anal. Calcd. for $C_{22}H_{16}ClNO_2$ C, 73.03; H, 4.46; N, 3.87; Found: C, 73.10; H, 4.45; N, 3.88.




**methyl 4-(8-chloro-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)benzoate:** Yellow solid; Mp: 180-182 °C; IR (KBr): 1725, 1635, 1295, 1008, 761 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.15(d, *J*= 6.4 Hz, 2H), 8.08(d, *J*= 6.4 Hz, 2H), 7.90-7.89 (m, 2 H), 7.51 (bs, 3H), 7.41 (dd, $J_1$= 8.2 Hz, $J_2$= 1.6 Hz 1 H), 7.28-7.23 (m, 1 H), 7.12 (s, 1H), 6.65 (s, 1 H), 6.64 (s, 1 H), 3.98 (s, 3H);$^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ166.6, 163.3, 163.1, 150,7, 143.3, 140.6, 133.6, 132.7, 131.8, 130.8, 129.7, 129.4, 128.9, 127.5, 126.2, 126.1, 121.3, 105.9, 52.3; Anal. Calcd. for $C_{23}H_{16}ClNO_3$.C, 70.86; H, 4.14; N, 3.59; Found C, 70.90; H, 4.13; N, 3.60;




**methyl 4-(8-fluoro-2-phenylbenzo[*b*][1,4]oxazepin-4-yl)benzoate:** Yellow solid; Mp: 155-157 °C; IR (KBr): 1727, 1637, 1295, 1010, 771 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 8.14 (d, *J*= 8 Hz, 2H), 8.07 (d, *J*= 8 Hz, 2H), 7.89 (m, 2H), 7.50-7.43 (m, 4 H), 6.99 (t, *J*= 7.6 Hz, 1H), 6.85 (d, *J*= 8.4 Hz, 1H), 6.63 (s, 1 H), 3.97 (s, 3 H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 166..7, 162.8, 160.8 (d, *J*= 292.7 Hz), 150.9 (d, *J*= 10.9 Hz), 143.4, 138.3, 132.9, 131.7, 130.7, 129.7 129.6 (d, *J*= 10.6 Hz), 128.9, 127.4, 126.2, 112.9 (d, *J*= 21.9 Hz), 108.5 (d, *J*= 24.3 Hz), 105.9, 52.3; $^{19}F$ NMR (376.5 MHz) ($CDCl_3$) δ – 112.7;
Anal. Calcd. for $C_{23}H_{16}FNO_3$: C, 73.99; H, 4.32; N, 3.75; Found C, 73.93; H, 4.31; N, 3.76.

## 4.2.6 Additional information and characterization data on 2,4-diaryl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepines

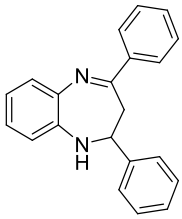
**General information**: The 1,3 diarylpropargilic alcohols were prepared, usually in high yields, using two main synthetic strategies: a) Sonogashira cross-coupling of 1-arylprop-2-yn-1-ols and substituted aryl-iodides; b) Nucleophilic addition of a terminal alkyne to an aldeyde.

**Typical procedure for the preparation of 3-(4-bromophenyl)-1-phenylprop-2-yn-1-ol:** in a Carousel Tube Reactor (Radely Discovery Technology) containing a magnetic stirring bar $PdCl_2(PPh_3)_2$ (30.8 mg, 0.044 mmol) and CuI (8.4 mg, 0.044 mmol) were dissolved under nitrogen in 2.3 mL of anhydrous DMF and 2mL of *N*-diisopropylamine. The resultant solution was stirred under Nitrogen at room temperature for 10 minutes before adding 1-bromo-4-iodobenzene (1245 mg, 4.4 mmol) and 1-phenylprop-2-yn-1-ol (700 mg, 657 μl, 5.3 mmol) dissolved in *N*-diisopropylamine (1.5 ml). 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, to obtain 1136 mg (90 % yield) of 3-(4-bromophenyl)-1-phenylprop-2-yn-1-ol.
$^1$H NMR (400 MHz) ($CDCl_3$) δ 7.62 (d, *J*= 7.2 Hz, 2 H), 7.45-7.33 (m, 7 H), 5.69 (s, 1 H), 2.62(bs, 1 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 140.4, 133.2, 131.6, 128.7, 128.5, 126.7, 122.9, 121.4, 90.0, 85.6, 65.1.

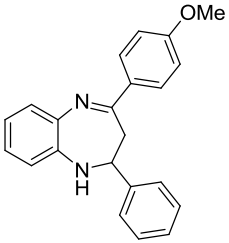
**Typical procedure for the preparation of 4-(1-hydroxy-3-phenylprop-2-ynyl)benzonitrile:** to a solution of ethynylbenzene (1838 mg, 1.98 ml, 18 mmol) in anhydrous THF (10 mL) were added dropwise, at -78 °C, 9 ml of a 2 M BuLi solution. The

resultant solution was stirred for 1 hour before adding dropwise 4-formylbenzonitrile (1838 mg, 14 mmol) dissolved in 10 mL of anhydrous THF. Reaction was stirred at room temperature until starting material ending. Then, reaction mixture was cooled at 0°C and 10 mL of a satured $NH_4Cl$ solution were added dropwise. Resulting mixture was worked-up with ethyl acetate and washed with $H_2O$ and a saturated $NH_4Cl$ solution. The organic phase was separated, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to afford 3262 mg ( 80% yield) of 4-(1-hydroxy-3-phenylprop-2-ynyl)benzonitrile.
$^1$H NMR (400 MHz) ($CDCl_3$) δ 7.75 (d, *J*= 8.0 Hz, 2 H), 7.71 (d, *J*= 8.4 Hz, 2 H) 7.48 (dd, $J_1$= 7.6 Hz, $J_2$= 1.2 Hz, 2H), 7.40-7.33 (m, 3 H), 5.77 (d, *J*= 5.2 Hz 1 H), 2.65 (d, *J*= 5.6 Hz 1 H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 145.6, 132.5, 131.8, 129.0, 128.4, 127.3, 121.8, 112.1, 87.55, 87.51, 64.2..

**Typical procedure for the preparation of 2,4-diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** a Carousel Tube Reactor (Radely Discovery Technology) equipped with a magnetic stirring bar was charged with (Acetonitrile)-[(2-biphenyl)-di-*tert*-butylphosphine]gold(I) hexafluoroantimonate. (7.7 mg, 0.01 mmol), 1,3-diphenylprop-2-yn-1-ol (104 mg, 0.5 mmol), and $CH_2Cl_2$ (2 mL). The resultant solution was stirred for 10 minutes before adding the 1,2-phenylenediamine (65 mg, 0.6 mmol). Reaction mixture was warmed at 60°C and stirred for 24 hours. After this time, the mixture was diluited with AcOEt and washed with $H_2O$, 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, to obtain 107 mg (72% yield) of 2,4-diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine.

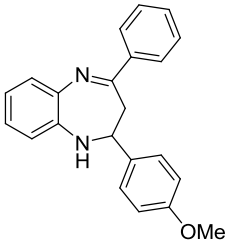



**2,4-diphenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** Brown solid; Mp: 110-112 °C; IR (KBr): 3335, 3054, 1608, 1475, 1448, 1114, 865, 765 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.91-7.89 (m, 2H), 7.53-7.33 (m, 9H), 7.14-7.07 (m, 2H), 6.85 (dd, $J_1$= 7.6 Hz, $J_2$= 1.6 Hz, 1H), 5.22 (dd, $J_1$= 8.8 Hz, $J_2$= 3.6 Hz, 1H), 3.82 (s, 1H), 3.28 (dd, $J_1$= 13.6 Hz, $J_2$= 3.6 Hz, 1H), 3.10 (dd, $J_1$= 13.6 Hz, $J_2$= 8.8 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.1, 145.0, 139.2, 138.4, 130.2, 129.1, 128.9, 128.4, 128.1, 127.0, 126.5, 126.0, 121.3, 120.6, 70.5, 37.8; Anal. Calcd. for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39; Found: C, 84.42; H, 6.07; N, 9.40.

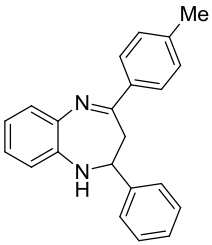



**4-(4-methoxyphenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** Yellow solid; Mp: 131-133 °C; IR (KBr): 3347, 3050, 2996, 2933, 2859, 1599, 1511, 1475, 1253, 1174, 838, 750 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.85 (d, $J$= 8 Hz, 2H), 7.48-7.33 (m, 7H), 7.08 (t, $J$= 3.2 Hz, 2H), 6.92 (d, $J$= 8 Hz, 2H), 6.84 (d, $J$= 7.2 Hz, 1H), 5.20 (dd, $J_1$= 8.4 Hz, $J_2$= 2.8 Hz, 1H), 3.87 (s, 3H), 3.76 (s,1H), 3.23 (dd, $J_1$= 13.6 Hz, $J_2$= 3.2 Hz, 1H), 3.04 (dd, $J_1$= 13.2 Hz, $J_2$= 8.8 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 166.7, 161.4, 145.0, 139.7, 138.2, 131.7, 128.9, 128.73, 128.66, 128.0, 126.1, 126.0, 121.4, 120.7, 113.7, 70.7,

55.4, 37.4; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.55; H, 6.12; N, 8.52.

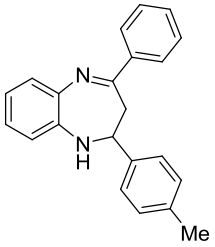



**2-(4-methoxyphenyl)-4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** Yellow solid; Mp: 114-116 °C; IR (KBr): 3347, 3060, 2994, 2836, 1901, 1606, 1508, 1473, 1240, 1176, 1031, 813, 769 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.89 (dd, $J_1$= 7.6 Hz, $J_2$= 1.6 Hz, 2H), 7.44-7.35 (m, 6H), 7.11-7.04 (m, 2H), 6.90 (d, $J$= 8.8 Hz, 2H), 6.82 (dd, $J_1$= 7.6 Hz, $J_2$= 1.6 Hz, 1H), 5.16 (dd, $J_1$= 9.2 Hz, $J_2$= 3.6 Hz, 1H), 3.83 (s, 3H), 3.79(bs, 1H), 3.25 (dd, $J_1$= 13.2 Hz, $J_2$= 3.6 Hz, 1H), 3.05 (dd, $J_1$= 13.6 Hz, $J_2$= 9.2 Hz, 1H); **$^{13}$C NMR** (100.6 MHz) ($CDCl_3$) δ 167.2, 159.4, 139.1, 139.0, 138.2, 137.3, 130.1, 129.0, 128.4, 127.1, 127.0, 126.4, 121.2, 120.6, 114.2, 69.9, 55.4, 38.0; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.57; H, 6.12; N, 8.54.

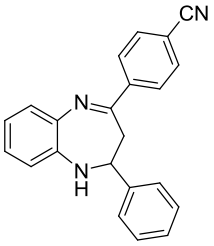



**2-phenyl-4-p-tolyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** Yellow solid; Mp: 117-119 °C; IR (KBr): 3351, 3048, 2915, 2857, 1901, 1677, 1602, 1475, 1450, 1292, 1182, 1039, 819, 750

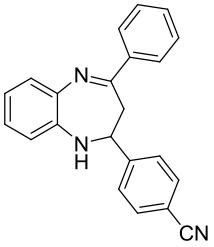
$cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.80 (d, *J*= 8.0 Hz, 2H), 7.47 (m, 6H), 7.24 (d, *J*= 8.0 Hz, 2H), 7.13-7.06 (m, 2H), 6.85 (dd, $J_1$= 7.2 Hz, $J_2$= 1.6 Hz, 1H), 5.21 (dd, $J_1$= 9.2 Hz, $J_2$= 4 Hz, 1H), 3.79 (bs, 1H), 3.26 (dd, $J_1$= 13.2 Hz, $J_2$= 3.6 Hz, 1H), 3.06 (dd, $J_1$= 13.2 Hz, $J_2$= 9.2 Hz, 1H), 2.43 (s, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.2, 145.1, 140.5, 139.4, 138.3, 136.4, 129.2, 128.9, 128.8, 128.0, 127.1, 126.3, 126.0, 121.4, 120.7, 70.7, 37.6, 21.4; Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.48; H, 6.44; N, 8.96.




**4-phenyl-2-p-tolyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:**
Yellow solid; Mp: 88-90 °C; IR (KBr): 3332, 3029, 2854, 1606, 1471, 1446, 1348, 1228, 1112, 1014, 871, 759 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.95-7.93 (m, 2H), 7.49-7.43 (m, 4H),7.36-7.31(m, 2H), 7.22 (d, *J*= 7.6 Hz, 2H), 7.14-7.07 (m, 2H), 6.84 (dd, $J_1$= 8.0 Hz, $J_2$= 1.6 Hz, 1H), 5.16 (dd, $J_1$= 9.2 Hz, $J_2$= 3.6 Hz, 1H), 3.80 (bs, 1H), 3.28 (dd, $J_1$= 13.6 Hz, $J_2$= 3.6 Hz, 1H), 3.08 (dd, $J_1$= 13.2 Hz, $J_2$=9.2 Hz, 1H), 2.41 (s, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.1, 142.1, 139.2, 139.1, 138.4, 137.8, 130.2, 129.6, 129.1, 128.4, 127.1, 126.5, 125.9, 121.2, 120.6, 70.2, 38.0, 21.2; Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97 Found C, 84.67; H, 6.46; N, 8.98.

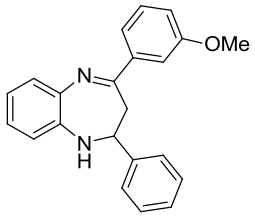



**4-(2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-4-yl) benzonitrile:** Orange wax; IR (KBr): 3359, 3060, 2923, 2227, 1689, 1608, 1471, 1328, 1261, 836, 754 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.86 (d, *J*= 8 Hz, 2H), 7.62 (d, *J*= 7.6 Hz, 2H), 7.44-7.30 (m, 6H), 7.14-7.03 (m, 2H), 6.85 (d, *J*= 7.6 Hz, 1H), 5.23-5.21 (m, 1H), 3.93 (bs, 1H), 3.24 (dd, $J_1$= 14 Hz, $J_2$= 3.2 Hz, 1H), 6.19 (dd, $J_1$= 13.6 Hz, $J_2$= 4 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 164.8, 144.3, 143.2, 138.8, 138.1, 132.0, 129.8, 128.9, 128.2, 127.4, 126.0, 121.3, 120.5, 118.7, 113.1, 70.0, 38.1; Anal. Calcd. for $C_{22}H_{17}N_3$: C, 81.71; H, 5.30; N, 12.99; Found: C, 81.61; H, 5.31; N, 12.97;

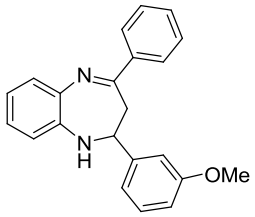



**4-(4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-2-yl) benzonitrile:** Orange solid; Mp: 143-145 °C; IR (KBr): 3374, 3056, 2964, 2888, 2221, 1612, 1471, 1329, 1101, 836, 759 $cm^{-1}$; $^{1}H$ NMR (400 MHz) ($CDCl_3$) δ 7.85 (d, *J*= 8 Hz, 2H), 7.61 (d, *J*= 8 Hz, 2H), 7.62-7.31 (m, 6H), 7.14-7.03 (m, 2H), 6.84 (d, *J*= 7.6 Hz, 2H), 5.22 (bs, 1H), 3.96 (bs, 1H), 3.23 (dd, $J_1$= 14 Hz, $J_2$= 3.2 Hz, 1H), 3.09 (dd, $J_1$= 13.6 Hz, $J_2$= 7.6 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 164.8, 144.4, 143.2, 138.8, 138,0, 132.0, 130.0,

128.9, 128.2, 127.4, 126.0, 121.2, 120.5, 118.7, 113.1, 70.0, 38.1; Anal. Calcd. for $C_{22}H_{17}N_3$**:** C, 81.71; H, 5.30; N, 12.99; Found: C, 81.62; H, 5.29; N, 13.00.

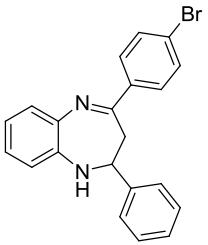



**4-(3-methoxyphenyl)-2-phenyl-2,3-dihydro-1*H*-benzo [*b*][1,4]diazepine:** Pale yellow solid; Mp: 144-146 °C; IR (KBr): 3386, 3056, 2933, 1592, 1500, 1274, 1155, 871, 750 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.50-7.31 (m, 9H), 7.12-7.05 (m, 2H), 7.00 (d, *J*= 6.4 Hz, 1H), 6.85 (d, *J*= 7.6 Hz, 1H), 5.21 (dd, $J_1$= 8.8 Hz, $J_2$= 3.2 Hz, 1H), 3.86 (s, 3H), 3.81 (bs, 1H), 3.25 (dd, $J_1$= 13.2 Hz, $J_2$= 3.6 Hz, 1H), 3.07 (dd, $J_1$= 13.6 Hz, $J_2$= 8.8 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 166.9, 159.7, 144.9, 140.6, 139.1, 138.3, 129.3, 129.0, 128.9, 128.0, 126.5, 126.0, 121.3, 120.6, 119.6, 116.6, 111.7, 70.6, 55.4, 37.9; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.50; H, 6.15; N, 8.55.

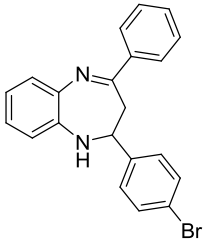



**2-(3-methoxyphenyl)-4-phenyl-2,3-dihydro-1*H*-benzo[*b*] [1,4]diazepine:** Pale yellow solid; Mp: 125-127 °C; IR (KBr): 3386, 3056, 2933, 1614, 1596, 1484, 1330, 1251, 1145, 871, 748 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.90 (d, *J*= 6.4 Hz, 2H), 7.45-7.40 (m, 4H), 7.31-7.28 (m, 1H), 7.13-7.02 (m, 4H), 6.88-

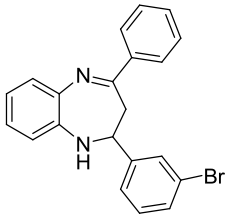
6.87 (m, 2H), 5.19 (dd, $J_1$= 8.8 Hz, $J_2$= 4 Hz, 1H), 3.80 (bs, 1H), 3.78 (s, 3H), 3.27 (dd, $J_1$= 13.6 Hz, $J_2$= 4 Hz, 1H), 3.08 (dd, $J_1$= 13.2 Hz, $J_2$= 8.4 Hz, 1H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 167.2, 160.0, 146.6, 139.3, 139.2, 138.4, 130.1, 129.9, 129.0, 128.4, 127.0, 126.5, 121.4, 120.6, 118.3, 113.6, 111.6, 70.6, 55.3, 37.7; Anal. Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53; Found: C, 80.36; H, 6.13; N, 8.52.




**4-(4-bromophenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*] [1,4]diazepine:** Yellow solid; Mp: 136-138 °C; IR (KBr): 3347, 3056, 2933, 2854, 1606, 1558, 1473, 1452, 1072, 1008, 823, 759 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 7.69 (d, *J*= 8.8 Hz, 2H), 7.50 (d, *J*= 8.8 Hz, 2H), 7.44 (, *J*= 6.4 Hz, 2H), 7.39-7.33 (m, 4H), 7.13- 7.05 (m, 2H), 6.84 (dd, $J_1$= 7.6 Hz, $J_2$= 1.6 Hz, 1H), 5.21 (dd, $J_1$= 8 Hz, $J_2$= 3.6 Hz, 1H), 3.82 (bs, 1H), 3.21 (dd, $J_1$= 13.6 Hz, $J_2$= 3.6 Hz, 1H), 3.05 (dd, $J_1$= 13.6 Hz, $J_2$= 8 Hz, 1H); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 166.0, 144.6, 138.9, 138.5, 138.0, 131.5, 129.1, 128.9, 128.6, 128.2, 126.8, 126.0, 124.8, 121.4, 120.6, 70.5, 37.7; Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.96; H, 4.53; N, 7.44.

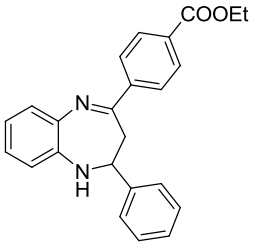



**2-(4-bromophenyl)-4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine:** Yellow solid; Mp**:** 141-143 °C; IR (KBr): 3363, 3056, 2962, 2892, 1614, 1469, 1407, 1326, 1068, 1004, 823, 754 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.83 (d, *J*= 6.8 Hz, 2H), 7.48-7.37 (m, 7H), 7.32 (d, *J*= 8.4 Hz, 2H), 7.12-7.06 (m, 2H), 6.83 (dd, $J_1$= 6.8 Hz, $J_2$= 2 Hz, 1H), 5.20 (dd, $J_1$= 8 Hz, $J_2$= 4 Hz, 1H), 3.73 (bs, 1H), 3.22 (dd, $J_1$= 13.2 Hz, $J_2$= 4 Hz, 1H), 3.04 (dd, $J_1$= 13.6 Hz, $J_2$= 8.4 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 167.0, 143.7, 139.5, 139.0, 138.0, 131.9, 130.3, 128.9, 128.4, 127.8, 127.0, 126.5, 121.8, 121.7, 120.7, 70.2, 37.4; Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.75; H, 4.52; N, 7.42.

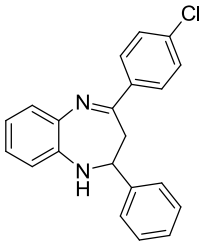



**2-(3-bromophenyl)-4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine** Yellow solid; Mp: 89-91 °C; IR (KBr): 3330, 3062, 2854, 1604, 1567, 1467, 1351, 1294, 1114, 1068, 854, 748 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.84 (d, *J*= 6.4 Hz, 2H), 7.59 (s, 1H), 7.46-7.34 (m, 7H), 7.21 (t, *J*= 8 Hz, 1H), 7.13-7.06 (m, 3H), 6.85 (dd, $J_1$= 7.2 Hz, $J_2$= 2 Hz, 1H), 5.19 (dd, $J_1$= 8.4 Hz, $J_2$= 4 Hz, 1H), 3.76 (bs, 1H), 3.23 (dd, $J_1$= 13.6 Hz, $J_2$= 4 Hz, 1H), 3.05 (dd, $J_1$= 13.2 Hz, $J_2$= 8.4 Hz, 1H); $^{13}C$ NMR (100.6

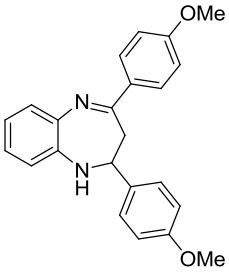
MHz) ($CDCl_3$) δ 167.1, 147.0, 139.4, 139.0, 137.9, 131.0, 130.4, 130.3, 129.2, 128.9, 128.4, 127.0, 126.6, 124.7, 122.8, 121.7, 120.7, 70.1, 37.3; Anal. Calcd. for $C_{21}H_{17}BrN_2$: C, 66.85; H, 4.54; N, 7.43; Found: C, 66.75; H, 4.53; N, 7.44.




**ethyl 4-(2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepin-4-yl)benzoate** Yellow solid; Mp: 129-131 °C; IR (KBr): 3357, 3029, 2992, 2900, 1689, 1600, 1481, 1284, 1103, 1010, 850, 755 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 8.04 (d, *J*= 8.4 Hz, 2H), 7.87 (d, 8.4 Hz, 2H), 7.45-7.29 (m, 6H), 7.13-7.04 (m, 2H), 6.84 (d, *J*= 7.6 Hz, 1H), 5.22 (dd, $J_1$= 8.0 Hz, $J_2$= 3.6 Hz, 1H), 4.41 (q, *J*= 6.8 Hz, 2H), 3.89 (bs, 1H), 3.26 (dd, $J_1$= 13.6 Hz, $J_2$= 3.6 Hz, 1H), 3.09 (dd, $J_1$= 13.6 Hz, $J_2$= 8.4 Hz, 1H), 1.44 (t, *J*= 6.8 Hz, 3H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 166.3, 166.0, 144.6, 143.1, 138.65, 138.60, 131.5, 129.5, 128.9, 128.1, 127.0, 126.8, 126.0, 121.2, 120.5, 70.3, 61.1, 38.1, 14.3; Anal. Calcd. for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56; Found: C, 77.89; H, 5.98; N, 7.54.

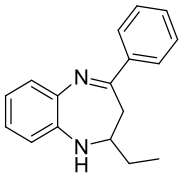



**4-(4-chlorophenyl)-2-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine** Brown solid; Mp: 123-125 °C; IR (KBr) 3347, 3060, 2854, 1606, 1587, 1473, 1095, 1010, 825, 761 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.76 (d, , *J*= 8.4 Hz, 2H), 7.45 (d, , *J*= 6.8 Hz, 2H), 7.39-7.33 (m, 6H), 7.13-7.05 (m, 2H), 6.84 (dd, $J_1$= 7.6 Hz, $J_2$= 1.6 Hz, 1H), 5.21 (dd, , $J_1$= 8.4 Hz, $J_2$= 4 Hz, 1H), 3.82 (bs, 1H), 3.22 (dd, $J_1$= 13.6 Hz, $J_2$= 4.0 Hz, 1H), 3.05 (dd, $J_1$= 14 Hz, $J_2$= 8.4 Hz, 1H); $^{13}C$ NMR (100.6 MHz) ($CDCl_3$) δ 165.9, 144.7, 138.9, 138.5, 137.6, 136.2, 129.1, 128.9, 128.5, 128.3, 128.1, 126.7, 126.0, 121.4, 120.6, 70.5, 37.7; Anal. Calcd. For $C_{21}H_{17}ClN_2$: C, 75.78; H, 10.65; N, 8.42; Found C, 75.88; H, 10.66; N, 8.43.




**2,4-bis(4-methoxyphenyl)-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine** Brown solid; Mp: 98-100 °C; IR (KBr) 3353, 3052, 2956, 2832, 1664, 1600, 1509, 1230, 1172, 1033, 840, 750 $cm^{-1}$; $^1H$ NMR (400 MHz) ($CDCl_3$) δ 7.86 (d, *J*= 8.8 Hz, 2H), 7.37-7.35 (m, 3H), 7.07-06 (m, 2H), 6.98-6.89 (m, 4H), 6.82-6.80 (m, 1H), 5.14 (dd, $J_1$= 8.8 Hz, $J_2$= 3.6 Hz, 1H), 3.87 (s,

1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.20 (dd, $J_1$= 13.2 Hz, $J_2$= 3.6 Hz, 1H), 3.00 (dd, $J_1$= 13.6 Hz, $J_2$= 8.8 Hz, 1H ); $^{13}$C NMR (100.6 MHz) ($CDCl_3$) δ 166.7, 161.4, 159.3, 139.6, 138.2, 137.4, 131.8, 128.7, 128.6, 127.1, 126.0, 121.4, 120.7, 114.1, 113.7, 70.2, 55.4, 37.5; Anal. Calcd. For $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82; Found: C, 77.12; H, 6.18; N, 7.83.




**2-ethyl-4-phenyl-2,3-dihydro-1*H*-benzo[*b*][1,4]diazepine**
brown oil; IR (neat): 3345, 2965, 2875, 1608, 1446, 1384, 1049, 1024, 873, 755 $cm^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$) δ 8.03 (m, 2H), 7.39-7.33 (m, 4H), 7.07-7.01 (m, 2H), 6.80 (d, *J*= 6.8 Hz, 1H), 4.01-3.95 (m, 1H), 3.05 (dd, $J_1$= 13.2 Hz, $J_2$= 4 Hz, 1H), 2.72 (dd, $J_1$= 13.2 Hz, $J_2$= 8.4 Hz, 1H), 1.64 (q, *J*= 7.2 Hz, 2H), 1.02 (t, *J*= 7.6 Hz, 3H); $^3$C NMR (100.6 MHz) ($CDCl_3$) δ 167.3, 139.8, 139.7, 138.2, 130.1, 128.7, 128.5, 127.0, 126.2, 121.3, 120.9, 68.0, 34.7, 30.7, 10.4; Anal. Calcd. For $C_{23}H_{22}N_2O_2$ : C, 77.07; H, 6.19; N, 7.82; O, 8.93; Found : C, 77.07; H, 6.19; N, 7.82; O, 8.93;

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