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CICLO XXXI

Tailored Homogeneous Catalytic Methodologies for the Sustainable Synthesis of Value-Added Chemicals

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Abstract

The work presented in this thesis has as main theme sustainable catalysis. The objective was the development of tailored homogeneous catalytic methodologies for the sustainable synthesis of value added chemicals. A comprehensive overview allows identifying the synthesis and complete characterization of 124 previously unknown molecules. It is also worth to mention the possibility of insert gaseous building block in complex structures by means of continuous flow technology.

In this context, **Chapters 2** and **3** describe the activity of an innovative catalytic system composed of palladium and potassium iodide. This winning combination allows a smooth activation of aryl bromides in coupling chemistry and in C-H activation. The above-mentioned catalytic system was applied to the synthesis of isocoumarins (**Chapter 2**). The procedure involves 2-alo benzoates and easy accessible and abundant ketones, catalyzed by a commercially available palladium source. This method features the α-arylation of the ketone mojety and the intramolecular condensation with the ester group. The use of potassium iodide proved to be essential to boost the selectivity when 2-bromo benzoates were employed. To obtain more insights in the role of KI, we tested 2-iodo benzoates, which were successfully coupled in absence of iodine anions. From a mechanistic point of view, KI can trigger an halogen exchange reaction or promote the in situ formation of highly nucleophilic palladium species able to increase the oxidative addition rate of aryl bromides to Pd(II) complexes. Using 2-iodo benzoates in presence of KI we noticed a remarkable decrease in reaction time (from 24 hours to 8 hours) and, since the so called halogen effect cannot take place, the present result strongly supports that the role of iodide anions is crucial in the coordination of the metal center. The synthetic usefulness of this approach is furthermore demonstrated with the synthesis of Xiridine A, in only two reaction steps.

The same combination was successfully employed in the synthesis of tailor-made functionalized dibenzo[b,f]azepine from commercially available starting materials, as described in **Chapter 3**. The presence of iodide anions that acts as competing ligands is crucial to enhance selectivity and reactivity. The synthetic utility of this protocol was further demonstrated with the formal synthesis of Clomipramine®, prepared in three steps from commercial reagents. The reaction mechanism involves sequential ortho C-H activation and double ortho and ipso functionalization of aryl bromides. Since both staring materials can undergo to oxidative addition to the palladium species, competing experiments were proposed in order to ascertain the most probable pathway. An organometallic intermediate was trapped with the fast Suzuki-Miyaura coupling, so we proved that the aryl bromide, and not the o-bromoaniline, starts the catalytic cycle.

In **Chapter 4**, a highly practical and efficient continuous-flow platform for homogeneous and gas-liquid Catellani-type reactions. The use of gaseous olefins allows significantly expanding the scope of Catellani-like reactions, providing access to a series of relevant ortho-disubstitued styrenes and vinyl arenes in an atom-efficient fashion. A control experiment was also performed to demonstrate the key role of flow technology to enable efficient gas-liquid transformations. When the same gas-liquid reaction was carried out in batch, uncontrolled and inefficient use of the gaseous olefin and the evaporation of norbornene into the headspace resulted in a lower yield for the desired product (12% batch vs 66% flow) along with the formation of several by-products. Furthermore, the use of flow also allows readily scaling the reaction conditions (1.26 g of product).

From the energetic point of view one of the most accessible and greener source of energy is, beyond any doubt, solar energy. The use of visible light to promote a chemical reaction is highly desirable for an environmentally benign chemistry.

In this context, **Chapter 5** describes the development of an innovative photocatalytic strategy for the oxidation and dearomatization of naphtobenzo azepine derivatives using molecular oxygen as oxidant. Different substituents were tested and this methodology proved to tolerate diverse functional groups providing from excellent to good yields. Further studies are ongoing in the laboratory to enlarge the generality of this transformation and to support with experimental evidences the proposed catalytic cycle.

Another interesting aspect in terms of sustainability is the attempt to replace metal catalysts with organic ones especially in the synthesis of active pharmaceutical ingredients (API). **Chapter 6** reports the first base-catalyzed intramolecular hydroamidation to highly substituted imidazolidin-2-ones and imidazol-2-ones. Notable features of this methodology include (i) excellent chemo- and regio-selectivity to 5-membered cyclic ureas, (ii) ample substrate scope and high functional group tolerance, (iii) very mild reaction conditions and short reaction times, (iv) key mechanistic insights on the reaction pathways. Further, the feasibility of the one-pot step-economical protocol starting from propargylic amines and isocyanates was demonstrated.

A complementary approach to the base catalyzed hydroamidation of propargylic ureas was exploited in **Chapter 7**. This silver (I) catalytic procedure allows a smooth activation of propargylic ureas bearing an alkylic fragment unreactive under the previously reported strategy and almost completely unexplored in other methodologies. In literature only another example is reported with one similar substrate achieving low yield with high temperature and catalyst loading. The reported approach involves the use of a cheap source of silver (silver nitrate) employing methanol as a benign reaction media. In this case also, the possibility to obtain these compounds with a one-pot reaction was reported.

1. Introduction

1.1. The origins of catalysis

Nowadays the concept of catalysis is well established and scientists all around the world apply this powerful tool to create new tailored-made catalytic strategies for achieving every kind of target substances with an extremely high selectivity. Mentioning the present accomplishments, it is impossible to leave aside the *"Fathers"* of catalysis[1] (**Figure 1.1** displays the timeline of the beginning of catalysis studies).

Understanding the basis of this phenomenon has been gained gradually. For example, it took 30 years from the first observation by A. A. Parmentier[2] that boiling potato starch in presence of tartaric and acetic acids formed sugar to the recognition in 1811 by Kirckhoff[3,4] that those acids were not consumed. The lead chamber process, i.e. the production of sulfuric acid with saltpeter, was known from the half of 18th century[5]. At the beginning of 19th century C. B. Desormes and N. Clément[6] found that nitrous gases act as oxygen carriers, first with the oxidation of SO_2 by NO_2 and the reoxidation of NO by O_2. In 1812 H. Davy characterized the intermediate[7] as $[(NO)HSO_4]$. It was first recognized that in a homogeneous catalytic reaction the catalyst was directly involved in the reaction mechanism.

During the same period J. Priestley reported the first heterogeneously catalyzed reaction[8]: the dehydratation of alcohol in a heated tobacco pipe. Shortly thereafter, J. R. Deimann discovered that a glass pipe did not induce the reaction, but a glass pipe containing clay fragments did. Several other studies at the beginning of 19th century led first H. Davy to the discovery of the combustion of methane and alcohol on glowing platinum wire[9] followed by J. W. Döbereiner with the disclosure of the oxidation of alcohol into acetic acid on platinum black and with the finding of the inflammation of hydrogen in presence of a platinum sponge both at ordinary temperature[10]. The latter was the basis of Döbereiner's lamp with almost 20 hundreds in use by 1828.

In 1835 J. J. Berzelius in his annual reports [11] summed all the observations done in the previous years and defined the concept of catalysis for the first time.

“It has been demonstrated that many bodies, simple or compound, in solid or dissolved form, possess the property of exerting an influence on compound bodies quite different from conventional chemical affinity, whereby they cause in the body a conversion of the components, without themselves taking part with their components, although this can sometimes be the case. […] I will call it the catalytic force of the bodies, and will call their decomposition catalysis […] The catalytic force seems essentially to consist of the property that bodies, by their mere presence, and not by their affinity, are able to awaken affinities that are dormant at this temperature, …”

This definition has been attacked over the years because *“the creation of a force does not explain the phenomenon”* (Liebig).

In 1894 Ostwald published the definition of catalysis[12], which is firmly recognized in present-day. *“Catalysis is the acceleration of a slow running chemical reaction via the presence of a foreign substance”*. Ostwald won the Nobel Prize in 1909 for his works on catalysis and on the studies about the rate of reactions. *“… the catalyst is not directly involved although the partial reactions contain the catalyst as a major chemical component of the process …”* (Ostwald Nobel Prize lecture, 1909[13]).

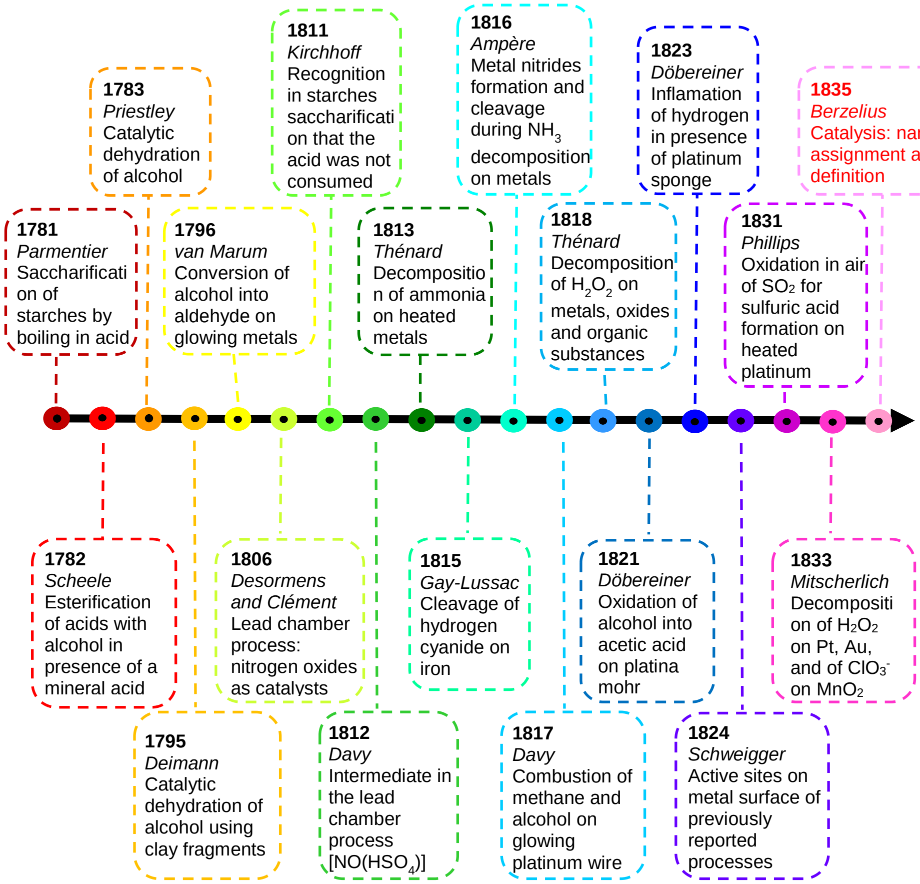


Figure 1.1 Time line of the beginning of catalysis research in chemistry

Historically catalysts have been divided in to two main categories: homogeneous and heterogeneous. The distinction lays in the operation phase of the catalyst[14]: if it exploits its activity in the same phase where the reaction occurs, it is called homogeneous catalyst, on the contrary if the phases are different the catalyst is named heterogeneous. Biocatalysis is often classified apart and it involves the use of enzymes or entire cells as catalysts in organic and industrial reactions.

1.2. Catalysis in industrial applications

Catalysis has always played a fundamental role in chemical industry[15] ranging from reducing the cost of manufacture to the reduction of wastes and pollutants, to the development of new chemical products and to increasing the quality of the existing ones. Nowadays it is estimated that more than 80% of chemical processes involve at some point a catalytic step for a total value of more than 1800 billion of American dollars. Catalysts, as mentioned before, are divided into three main groups: heterogeneous, homogeneous and biocatalysts. Every industrial sector has different requirements on the nature of the catalyst. In refinery processes, 90% of the proceedings include a heterogeneous catalyst, whereas for commodity and fine chemicals the use of a homogeneous catalyst is preferred in order to reach high selectivities requiring little or no further purification.

To underline the importance of catalysis in industrial application[16], it is worth to mention for example the introduction of the catalytic cracking of crude oil in 1936 by Houdry[17]. This new methodology and the subsequent improvements led to an increase in gasoline fuel obtained from a barrel of oil and in the quality by increment the octane rating while reducing sulphur and aromatics. Implementing catalysis can bring also to the discovery of new products and applications especially in the area of polymers. For example in 1933 the first polyethylene was discovered, it consisted in a highly branched flexible and soft polymer (LDPE, Low Density Polyethylene) made by the free radical polymerization of ethylene at high pressure (2000 bar). In the 50’s the addition of catalysts in the polymerization afforded a different type of polyethylene, called HDPE (High Density Polyethylene), that was light, strong, low cost, easy to manufacture and chemically resistant. Another example of the key role played by catalysis is in the synthesis of pharmaceuticals. Knowles[18] developed the asymmetric hydrogenation of the enamide precursor of L-DOPA used to treat Parkinson disease, using a complex of rhodium bearing a chiral phosphine (Monsanto process). The disclosure of a more efficient catalytic route to a product can result in the gradual or complete substitution of one type of feedstock for another. The most clean-cut example is the production of acetic acid[19] over the last 100 years. Nowadays more than 85% of acetic acid is produced via carbonylation of methanol that displays an incredible economic advantage on the two-step ethylene based Wacker route. A large part of this cost reduction can be ascribed to the cost of starting materials: methanol is approximately one third of the price of ethylene. From its very first appearance on the market, the methanol carbonylation process was intensely studied and different catalysts were commercialized. In the 1960's BASF used an iodide promoted cobalt catalyst requiring high pressures and temperatures with only 90% of selectivity. The BASF process was quickly upstaged by the Monstanto process, catalyzed by rhodium/iodide cooperative action allowing lower pressure and temperature in addition to an excellent selectivity (99%). In 1995 the Cativa process was commercialized by BP Chemicals. This new methodology utilized an iridium/iodide catalyst and a ruthenium promoter. The Cativa strategy is more efficient and greener and today it has largely substituted the Monsanto process, often in the same production plants.

The distinct value of applied catalysis for the industrial sector is the disappearence of interdisciplinary barriers and the key of success is a multidisciplinary approach that integrates catalysis, organic chemistry and process engineering.

1.3. Homogeneous transition metal catalysis

In terms of understanding the process on a molecular level, homogeneous catalysis is ahead of heterogeneous catalysis[1]. This advantage combined with the fact that each single catalytic entity can act as single active site ensures to homogeneous catalysis a better activity and selectivity. Moreover employing a transition metal catalyst is possible to tune the electronic and steric proprieties in order to enhance the desired reactivity[20]. The main drawback is the expensive and time-consuming process of catalyst separation and recovery. To address this issue some unique developments and applications of biphasic systems and membrane reactors are rising[21]. Another concern with organometallic catalysts, despite the technologies advantages, is their sensitiveness to oxidation or hydrolysis.

Regardless of these disadvantages, transition metal catalysis plays an important role in industrial synthesis of organic chemicals, especially for fine chemicals[22]. Owing to their versatility, transition metal catalysts can open new reactions pathways that might cause a reduction in synthetic efforts and therefore in process costs[23]. In addition transition metal catalyzed routes are often performed using mild conditions such as atmospheric pressure and moderate temperatures with an increasing energy efficiency[24]. Selectivity assures that reactions proceed with the minimal formation of byproducts. This theme is significant in order to prevent the increase in pollution and in chemical refuse, because these byproducts have to be separated and disposed of. The reasoned choice of the metal center combined with the design of the ligand ensure a high control on selectivity[25] to reduce, and sometimes even to avoid, the formation of byproducts.

One of the most elegant examples of the importance to understand the basis of a process, and thus the reactions involved, is given by the hydroformilation[26]. This reaction, also known as Roelen[27] reaction or oxo synthesis, consists in the addition of syngas (synthesis gas, a mixture of CO and H_2) to olefins using a homogeneous metal catalyst to afford linear or branched (if the feedstock is different from ethylene) aldehydes. This regioselectivity aspect combined with the ratio of the reaction and the possibility to yield other oxygenated by products are important features of this transformation. These parameters have been intensely studied among the years[28] to result in a selective and mild methodology tuning the electronic and steric proprieties of the metal center. The first generation processes follow the original procedure of Roelen employing as catalyst cobalt salts, which in presence of syngas under the reaction conditions generate cobalt carbonyls. The conditions were relatively smooth but the production reached only 10 kt/year. The second generation uses an “unmodified” cobalt catalyst [$HCo(CO)_4$] formed in situ from the cobalt carbonyl $Co_2(CO)_8$ under harsh conditions (130-175 °C, 250 bar). The main disadvantage of this approach was the low ratio between linear and branched products. In order to solve this issue, monodentate phosphine ligands were introduced. However, these ligands resulted also in decreased reaction rate and in the production of a higher amount of alcohols and alkanes as byproducts. The second generation process permitted a working pressure of 50-100 bar. In the late 1960s rhodium catalysis started rising and the third generation processes included a rhodium complex modified with a phosphine ligand ($RhH(CO)(PPh_3)_3$). Rh-catalysts allowed to obtain a high selectivity (no alcohols or alkanes were observed) with the preferential formation of the linear isomer under mild conditions as 25 °C and 1 bar. Due to the expensiveness of rhodium a number of methods for the recycle of this noble metal were also developed. The fourth generation was focused on solving this issue and an aqueous two-phase system was applied to immobilize the metal in the aqueous phase by a sulfonated phosphine ligand.

1.4. Cross-coupling reactions

Among all metal catalyzed reactions, cross-couplings play an important role in organic synthesis[29,30]. More than fifty years ago, carbon-carbon bond formation in organic synthesis was mainly achieved by stoichiometric reactions of, for example, reactive nucleophiles with electrophiles. Then the introduction of palladium into organic chemistry by Richard Heck[31], who developed a coupling reaction in the presence of a catalytic amount of palladium (II), designates a breakthrough toward the fascinating area of palladium catalyzed C-C bond forming reactions. Ever since their introduction in 70’s, cross-coupling reactions have established a new way to conceive the C-C bond formation and have enhanced the possibility to assemble complex molecular frameworks[32].

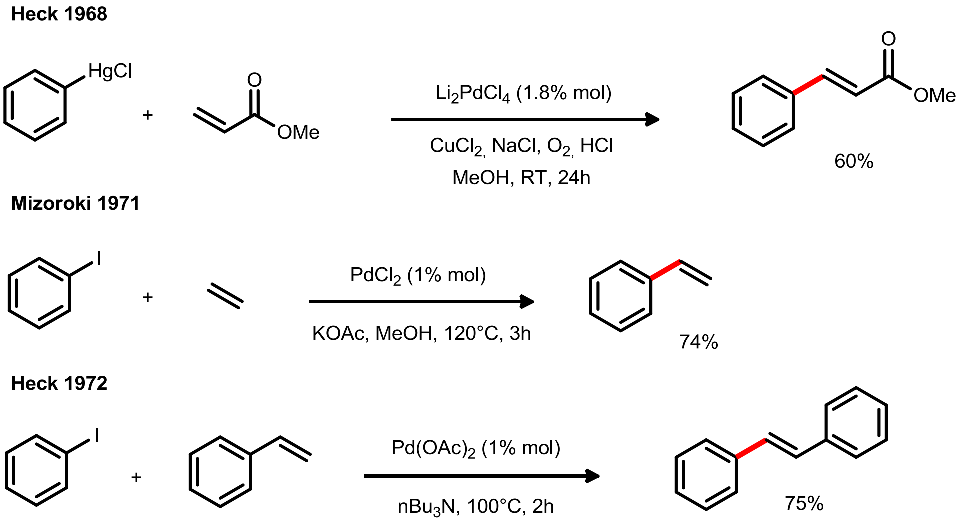
The winning strategy for cross-coupling reactions for the construction of C-C bonds involves an organometallic (or organoboron) nucleophilic specie (R’-Y in

Scheme 1.1) matched with an organohalide as the electrophilic partner (R-X in **Scheme 1.1**) in the presence of a transition metal catalyst.

$$\mathbf{R{-}X} \quad + \quad \mathbf{R'{-}Y} \xrightarrow{\mathbf{TM}} \mathbf{R{-}R'}$$

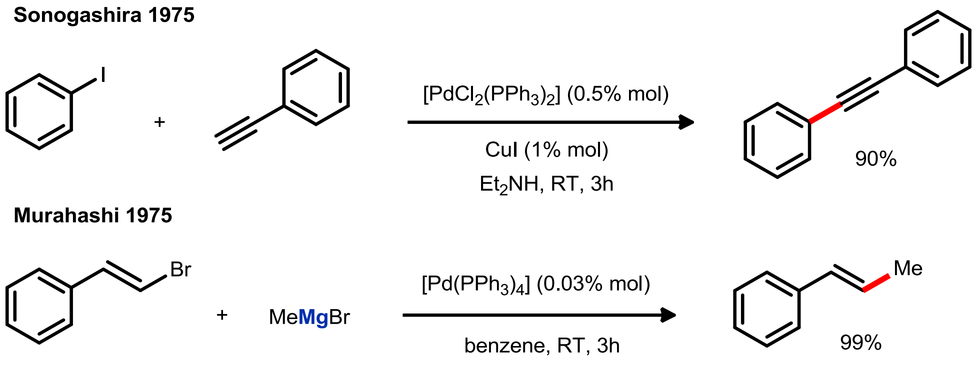
Scheme 1.1 General reaction scheme for cross-couplings

The pioneering discovery of Heck[33], followed by almost independent studies of Mizoroki[34,35], paved the way to the development of coupling chemistry (**Scheme 1.2**).



Scheme 1.2 The first palladium (II) catalyzed coupling reactions

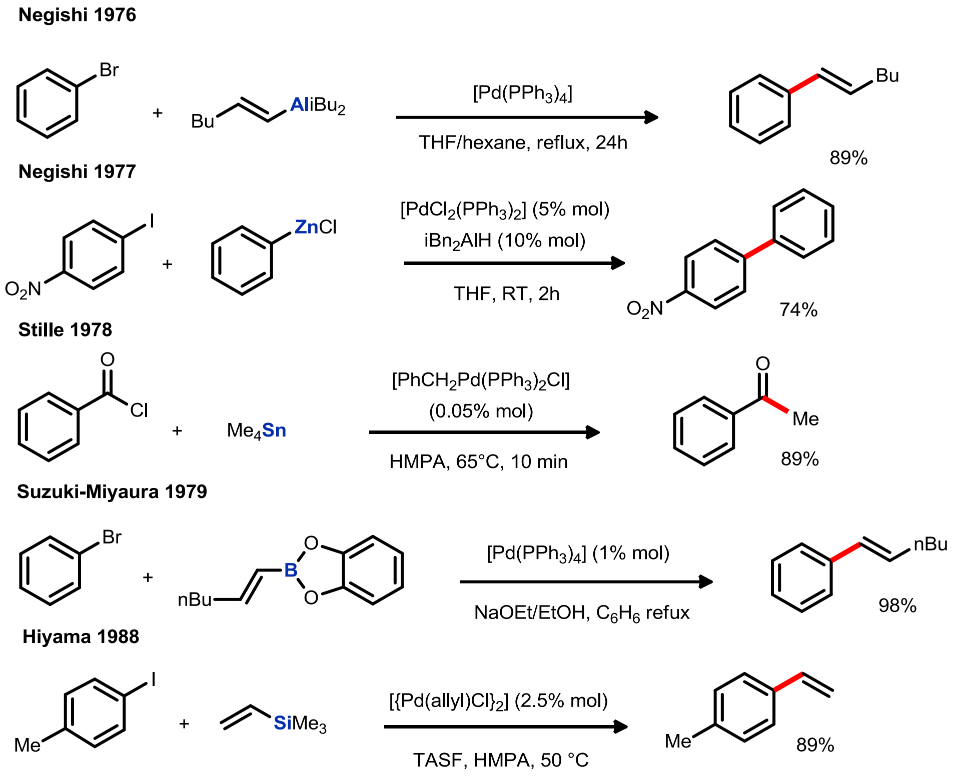
The establishment of palladium upon copper and nickel was achieved with the introduction of Sonogashira coupling[36] and with the contribution of Murahashi[37,38] (**Scheme 1.3**).



Scheme 1.3 Establishment of palladium: Sonogashira and Murahashi reactions

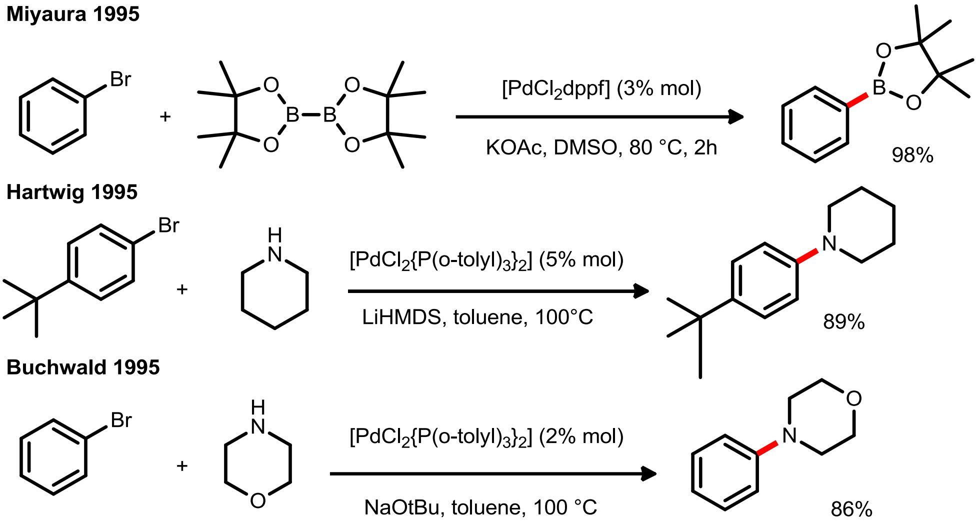
The first allowed to switch from Castro-Stephens coupling[39] that uses a stoichiometric amount of copper acetylide to a palladium-copper cooperative catalysis at room temperature. In 1975 Murahashi reported the first coupling of a Grignard reagent using palladium catalysis broadening the substrate scope of the previously reported nickel catalyzed Corriu-Kumada coupling[40–42].

Once that palladium was confirmed as the most useful and versatile transition metal for coupling reactions, the attention was drawn to the organometallic coupling partner (**Scheme 1.4**). Negishi described first the use of organoaluminum reagents[43] and then employed zinc reagents[44,45] increasing the functional group compatibility in respect to Grignard reagents. The next breakthrough was the use of organotin reagents by Stille[46] that despite the toxicity of organostannates reached a lot of consensus in the chemical community. In 1979 Suzuki[47] reported the palladium cross-coupling of organoboron derivatives. This coupling displays a wide number of advantageous features like mild and convenient reaction conditions, easily handled and stable organoboron starting materials and the facile removal of less toxic inorganic byproducts[48]. Hiyama[49] in 1988 detailed the use of organosilanes with aryl halide in presence of a fluoride source.



Scheme 1.4 Different possibilities for organometallic coupling partner in cross-coupling reactions

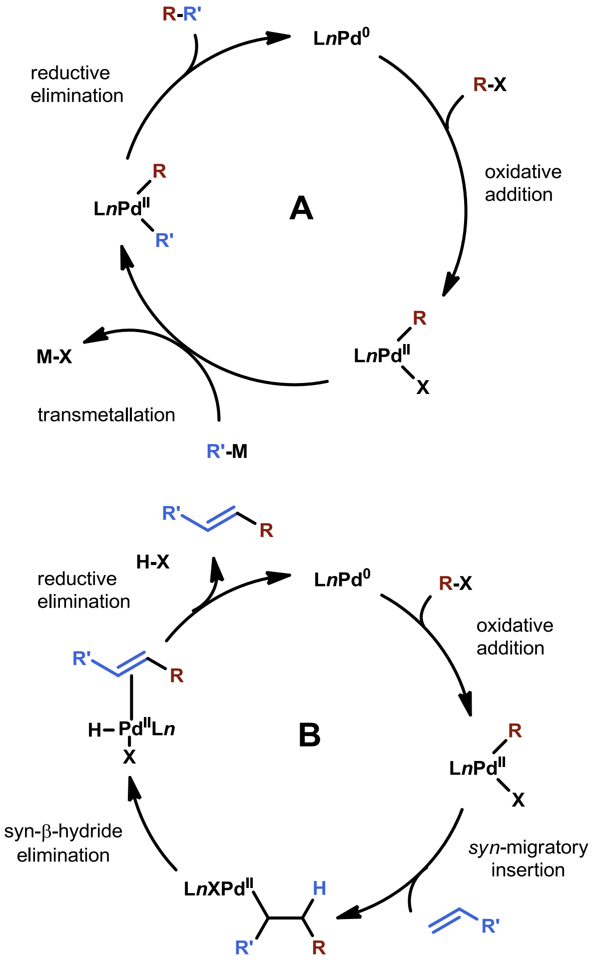
It is worth to mention also the possibility to install a carbon-heteroatom bond (**Scheme 1.5**), like the Miyaura[50] borilation for the formation of a C-B bond or the Buchwald[51]-Hartwig[52] for the C-N bond construction.



Scheme 1.5 Carbon-heteroatom bond formation (Miyaura C-B, Buchwald-Hartwig C-N)

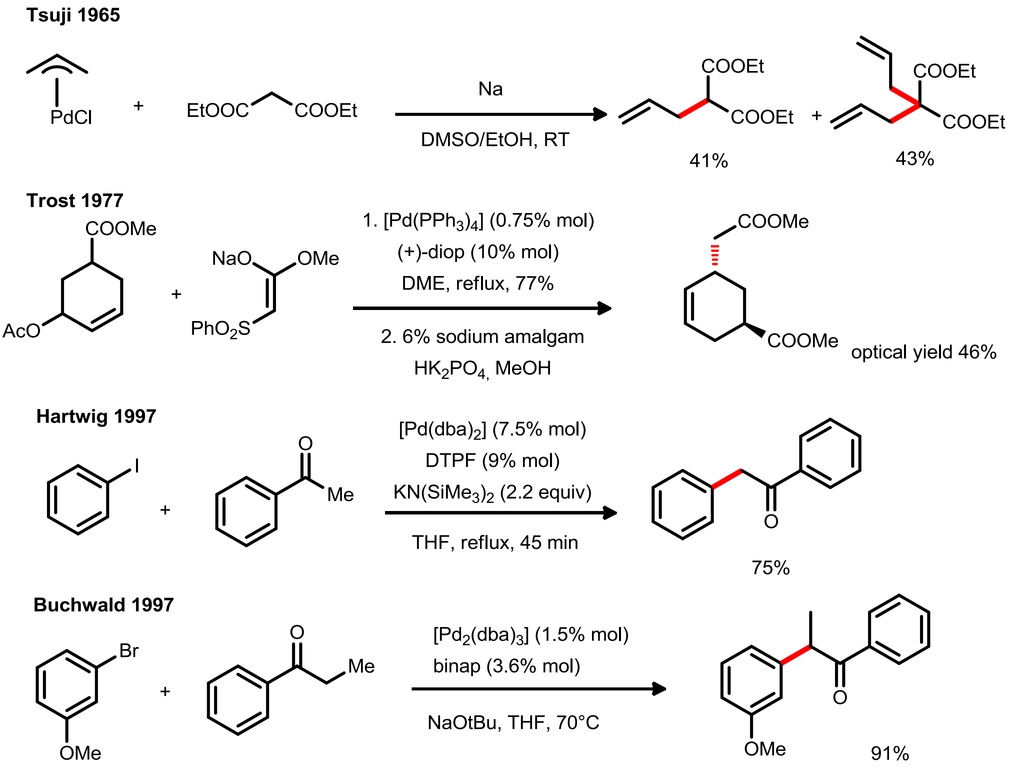
Nowadays this wide number of named reactions are commonly applied in pharmaceutical industry and in material science[53,54].

The general mechanism for cross coupling reactions (Cycle A in **Scheme 1.6**) starts with the oxidative addition of the organo halide (R-X) to a palladium zero specie to form a palladium II complex. Then the transmetallation step occurs generating a palladium complex bearing both the coupling fragments. Finally reductive elimination results in the C-C bond formation with the regeneration of the active specie of Pd(0). In the Heck-Mizoroki reaction (Cycle B in **Scheme 1.6**) after the first step of oxidative addition the catalytic cycle progresses with the coordination of the alkene to the Pd(II) complex followed by a *syn* migratory insertion. The so-formed organopalladium specie undergoes to *syn* β-hydride elimination to form the alkene product. Subsequently base-assisted elimination of H-X from [LnPd(H)(X)] occurs to regenerate the LnPd(0) catalyst[55,56].



Scheme 1.6 General catalytic cycles for cross coupling involved a transmetallation step (A), and for the Heck reaction (B)

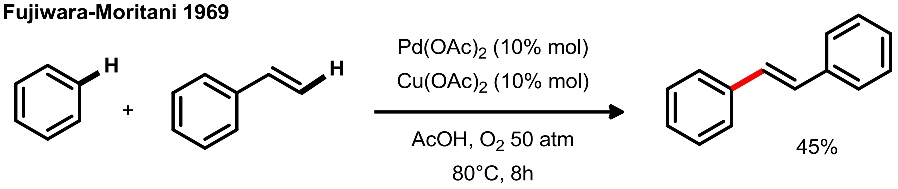
Encourage by these discoveries, other types of coupling reactions involving alternative coupling partners have been exploited. Among them it is important to mention the Tsuji[57]-Trost[58,59] allylation that achieves an allylic substitution via an intermediate π-allyl palladium complex and the α-arylation[60,61] of carbonyl compounds that involves an enolate coupling partner generated in situ from a carbonyl compound and a base (**Scheme 1.7**).



Scheme 1.7 Tsuji-Trost allylation and α-arylation from Hartwing and Buchwald

1.5. C-H activation

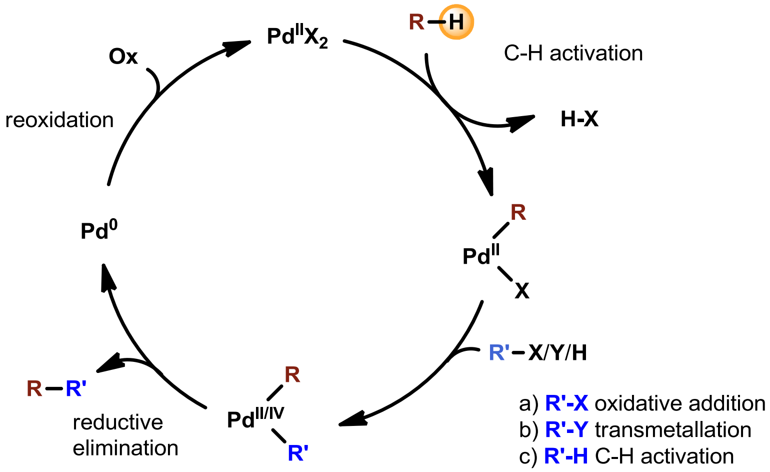
During the 70’s, whilst cross coupling reactions were shaping a new way to conceive C-C bond formation, Fujiwara and Moritani reported the first carbon-carbon bond formation through cleavage of an aromatic C-H bond[62]. Few years later, they improved their methodology introducing an oxidant[63] (**Scheme 1.8**) and this allowed their protocol to become a metal catalyzed C-H activation procedure. In the following years scientists’ attention was drawn to cross coupling reactions mainly for reasons of selectivity[64] despite the evident appealing of this new methodology.



Scheme 1.8 Oxidative Fujitara-Moritani in 1969

Nowadays it is greatly important to consider economic aspect and sustainability in organic synthetic design. In this light C-H activation is a fundamental tool to address atom-economy needs and environmental accepted organic synthesis[65,66]. Despite all the progress done in this field in the last 20 years[67–74], developing an efficient and mild strategy for the C-H activation of a broad variety of organic molecules is still extremely challenging.

Extensive researches[75,76] have established the steps involved in the C-H functionalization. Three different reaction pathways can take place depend on the coupling partner involved (**Scheme 1.9**, for exemplification only palladium C-H activation reactions are displayed).



Scheme 1.9 C-H activation mechanisms depending on the coupling partner

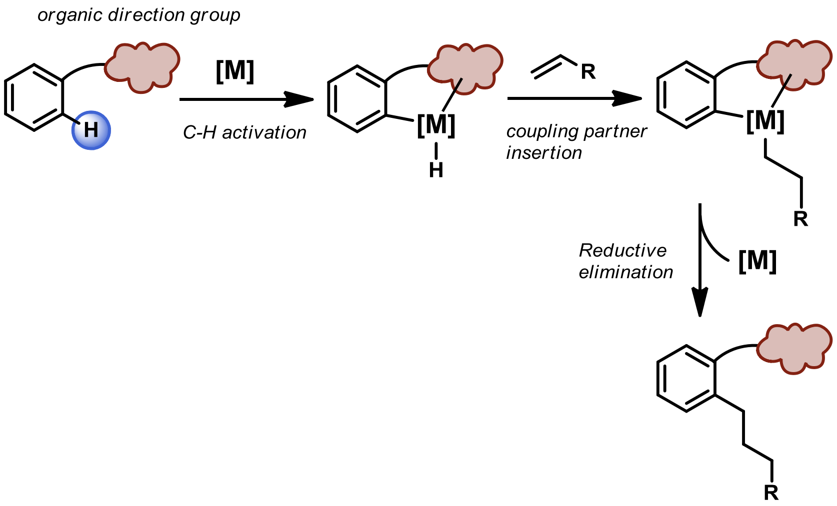
The first step is the C-H activation on the palladium II metal complex then an oxidative addition can take place, forming a specie of palladium IV, followed by a reductive elimination that closes the catalytic cycle regenerating the palladium

II active specie. After the first step of C-H activation it is also possible to incur in a transmetallation or in a further C-H activation on the palladium II species that after the reductive elimination is reduced to Pd (0). In these cases, the use of an oxidant is crucial to close the catalytic cycle. Other studies have proven that the possibility of a first oxidation from palladium II to palladium IV is present and then the C-H activation step occurs on the palladium IV complex[77].

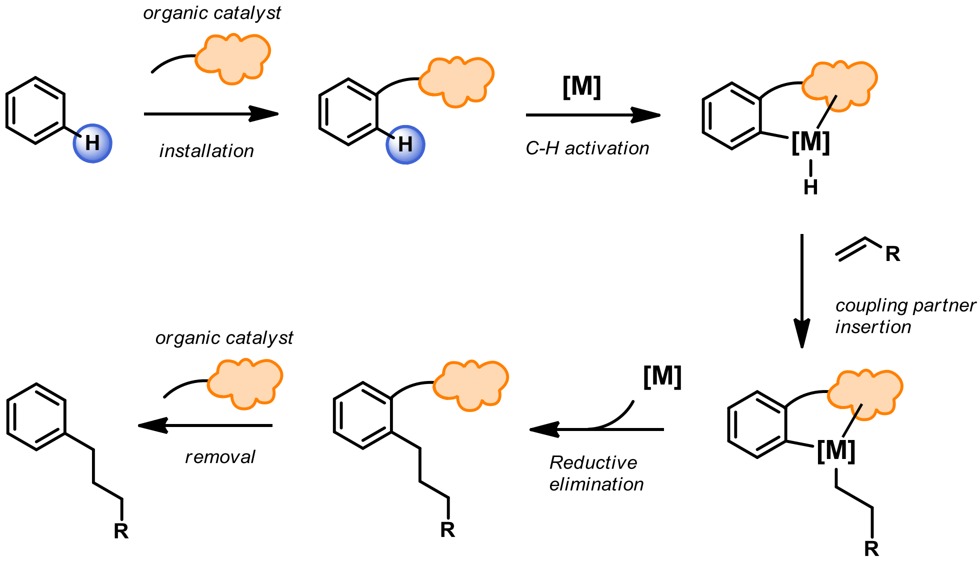
Nevertheless, C-H bond functionalization reactions are restricted by some fundamental challenges: the inert nature of C-H bond requires high activation energies, regioselectivity in the activation of the desired C-H bond and the necessity in some circumstances of an external oxidant. In order to overcome these limitations several approaches have emerged, first of all the chelation assisted protocol[78] utilizing heteroatoms or coordinating organic groups as auxiliaries to solve the problem of substrate direct accessibility to the metal center. The possible strategies are shown in **Schemes 1.10** and **1.11**.

In case **a)** an organic molecule bearing an irremovable directing group is constructed to direct the metal center and after the insertion of the coupling partner, reductive elimination affords the product and the active metal catalyst. The second strategy is the installation of an organic catalyst that directs the metal center in the desired position and after the catalytic cycle is removed to generate the product.

a) unremovable directing group

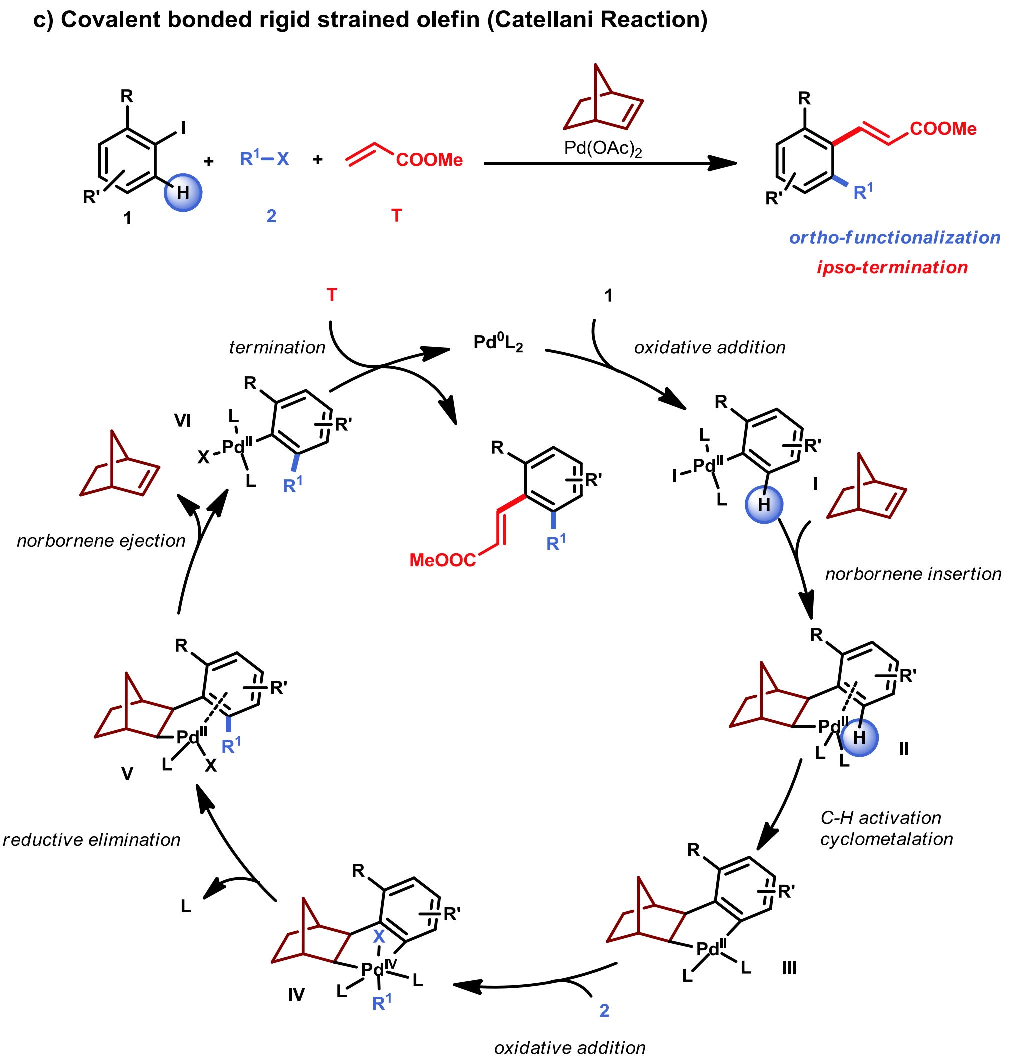


b) temporary installed coordinating organic catalyst



Scheme 10 Chelation assisted C-H activation strategies a) unremovable directing group b) temporary installed coordinating organic catalyst

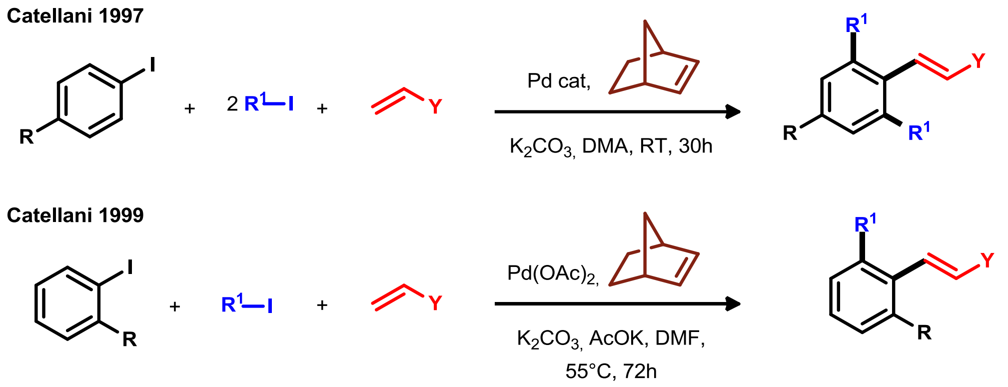
The last approach involves the formation of a covalent bond between a rigid and strained olefin such as norbornene and the substrate; this route is called Catellani reaction. The catalytic cycle[79,80] begins with an oxidative addition of the arylhalide on the palladium 0 specie to afford the palladium II complex **I**. A stereoselective insertion of norbornene generate the *cis,exo* complex **II** bearing a covalently bonded metal directing group. This complex is stable toward hydrogen elimination because it does not possess β-hydrogen atoms *cis* to palladium to be readly eliminated. Then a step of C-H bond activation produces the palladacycle complex **III**. Another oxidative addition leads to the formation of palladium IV metallacycle **IV** that undergoes a reductive elimination to generate the complex **V**. β-carbon elimination produces the mono-functionalized substrate-palladium complex **VI** along with the regeneration of norbornene. Finally the catalytic cycle is terminated by reaction of terminating agent to produce the bis-functionalized product and the regenerated palladium active specie.



c) Covalent bonded rigid strained olefin (Catellani Reaction)

Scheme 1.11 Chelation assisted C-H activation strategies c) covalent bonded rigid strained olefin: Catellani reaction

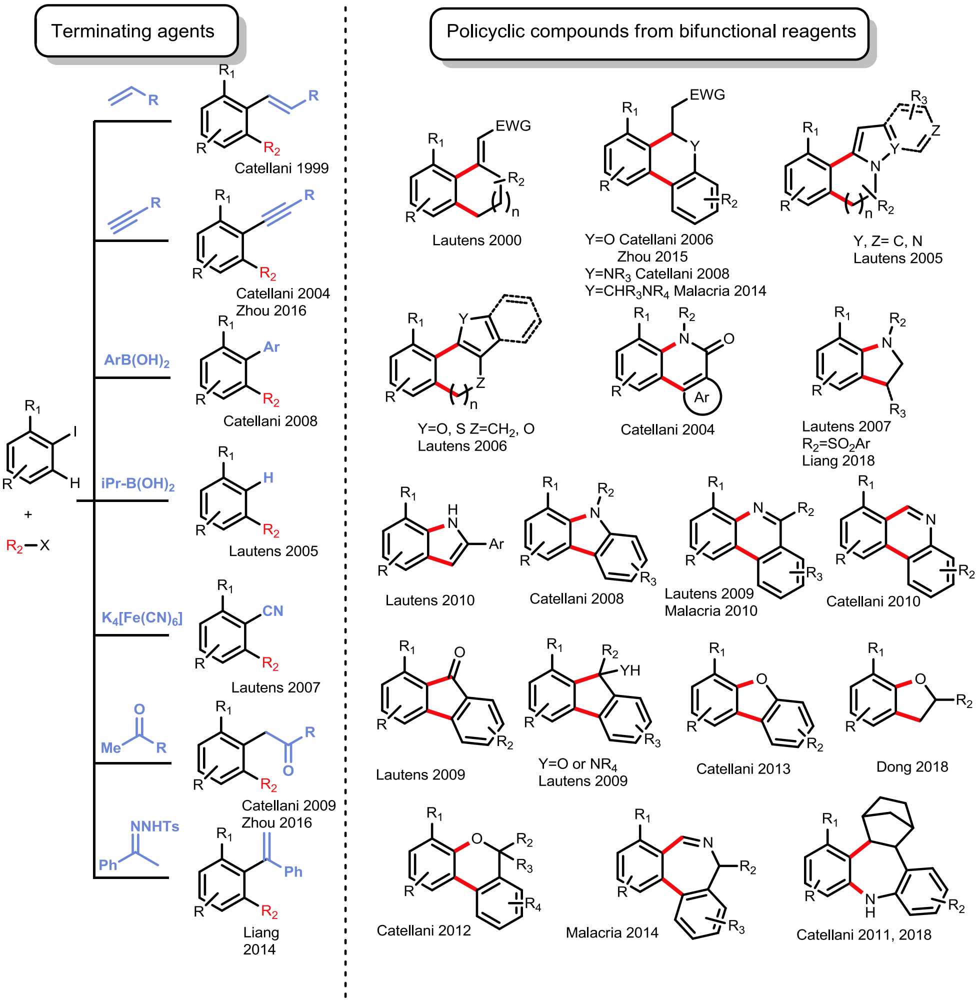
The so-called Catellani reaction is a powerful tool to functionalize both the ortho and the ipso positions of an aryl halide. Over the last two decades the Catellani reaction was intensely investigated[81–83] and a wide variety of compound has been obtained. This palladium catalyzed C-H functionalization reaction mediated by norbornene is a compelling strategy for the construction of complicated molecules including applications in natural product synthesis[81,82]. The initial breakthrough in Pd/norbornene catalysis occurred in 1997[79], when Catellani and coworkers reported the regioselective synthesis of 1,2,3-trialkyl substituted arenes (**Scheme 1.12**).



Scheme 1.12 The breakthrough in Catellani reaction

Scheme 1.12 also shows a variant of the process, describing the formation of unsymmetric 2,6-disubstitued vinylarenes. In the first example the terminating agent is an olefin that ends the catalytic cycle with an Heck-type coupling reaction. During the following years a wide variety of molecules and groups have been employed as terminating agents (**Scheme 1.13**, left side). In addition to these products, carbo- and heterocycles are also obtainable via the Catellani reaction if the electrophile (R^1-X) and the terminating reagent are incorporated into one molecule. **Scheme 1.13** displays some selected examples and shows that using alkyl or aryl halides that possess another functional group as bifunctional reagents, a wide variety of synthetically useful and/or biologically active polycyclic compounds have been prepared.

Despite the many years of research, the Catellani reaction remains a hot topic in C-H functionalization and many research groups are still investigate this powerful methodology. In 2015, Yu[84] and subsequently Dong[85] discolsed a new strategy for allowing the direct *meta* activation of arenes by combining chelation assisted Pd(II) ortho C-H activation and Pd(II)/Pd(IV) norbornene chemistry. The Bach group[86] reported an useful procedure involving Pd(II)/Pd(IV) norbornene catalysis for the synthesis of 2-alkylated indoles employing as starting materials N-unprotected indoles and primary alkyl bromides. In addition electron poor pyrroles proved to be effective in this transformation[87]. Recently Zhou[88] developed the first boron initiated Catellani reaction utilizing arylboronic acids as the substrates instead of aryl halides. The use of 5-norbornene-2-carbonitrile instead of the classic norbornene was also exploited as the main reason for the orthogonal reactivity between this procedure and the classic Catellani reaction.



Scheme 1.13 Selected examples of terminating agents (left side) and polycyclic compounds from bifunctional reagents (right side). References left side from top to bottom[89–97], right side from left to right[98–119]

1.6. Continuous flow as enabling tool

In 2005 an association composed of the America Chemical Society, the Green Chemistry Institute and several pharmaceutical companies was founded[120]. This so-called ACS GCI Roundtable pursues the mission of promoting the implementation of green chemistry and engineering in chemical production starting from pharmaceuticals. To guide this process they published a rank of key research areas[121] in which invest for pursuing a more sustainable chemistry and chemical engineering. Continuous processes were selected as the number one field with the highest potential to positively affect the overall sustainability of pharmaceutical sector.

Nevertheless chemists are conservative towards their laboratory equipment and the traditional round bottom flask is still the fundamental glassware item in every chemical laboratory.

Over the past decade continuous flow has received remarkable attention[122–128] due to several benefits that it can bring. Among these, the better mixing represents an important advantage especially in multiphase systems. Using milli or microflow technologies, the surface area between the liquid phase and the gas phase is increased upon three orders of magnitude (**Table 1.1**). Furthermore, upon formation of Taylor flow regime (**Figure 1.2**), an intensive recirculation within the liquids slugs is obtained, which allows for a fast renewal of the gas boundary layer at the gas-liquid interface. This is translated into shorter reaction time and enhanced selectivity in virtue of the higher contact area between the two phases.

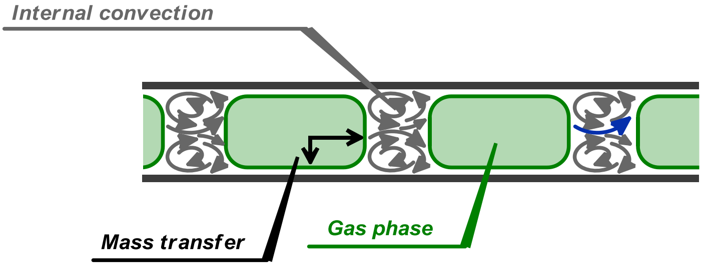


Figure 1.2 Representative imagine of a gas-liquid system under Taylor regime in a microcapillary tubing

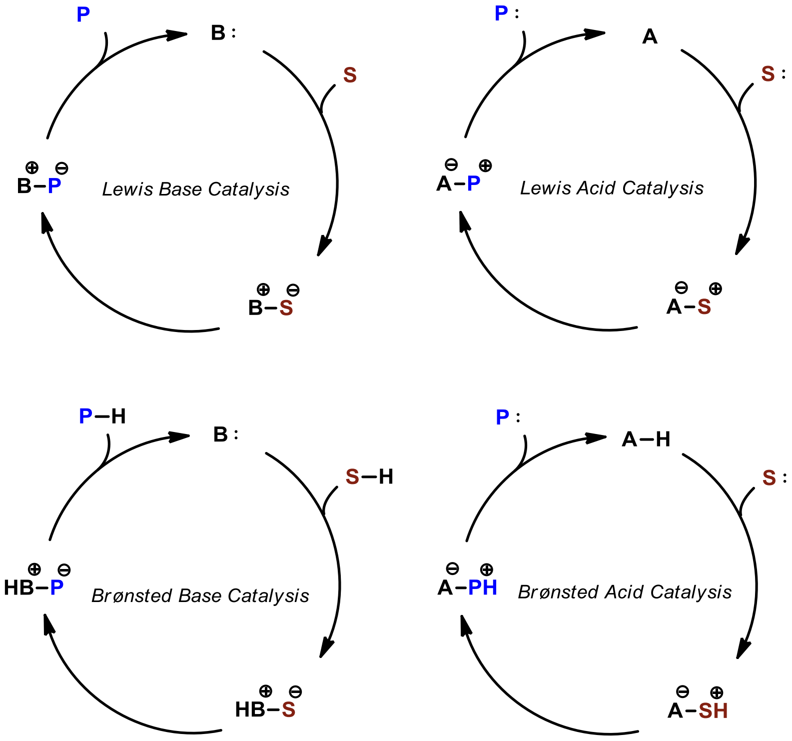
Table 1.1 Interfacial surface areas for various reactors

Reactor vessel	Inner diameter (i.d.)	Surface Area gas:liquid ($m^2.m^{-3}$)
250 mL round-bottom flask	8.6 cm	34
50 mL round-bottom flask	5.0 cm	60
5 mL round-bottom flask	2.8 cm	107
milliflow channel	1.6 mm < i.d. < 1.0 cm	566 – 3536
microflow channel	0.25 mm < i.d. < 1.0 mm	5657 – 22627

Certainly the aspect that can gain more from continuous flow technology is the scale-up process[129,130]. For a batch methodology scale-up means increasing the dimension of the vessel that can results in a lack of control over heating and mixing. Also safety issues[131] can be caused by the large dimensions like hot-spot formation (i.e. ignition source for explosive reaction mixtures) or runaway reactions. On the contrary scaling-up using continuous flow is an easy and straightforward operation resulting in a minimal redesign of reaction conditions and mainly based on increasing the through put of flow reactors, by prolonging the operation time, increasing the tube length or by numbering-up the flow devices in parallel[132]. Flow reactors offer unique heat and mass transfer capabilities decreasing effectively the safety issues. Due to their high surface-to-volume ratios, a fine control over all reactions parameters can be easily achieved and the accumulation of high quantities of hazardous materials can be avoided.

1.7. Organocatalysis

Metal catalysis has always been the undisputed leader in promoting organic reactions with unique activity and selectivity. Despite the large consensus by the chemical community of the important role of metal catalysis in synthesis, it is mandatory to consider also the drawbacks. These flaws include the high cost and efforts for the preparation of the catalyst, the use of toxic metals, which can contaminate the final product even present in traces. Moreover the lack of orthogonality with some functional groups and the limitation in the stability of metal complexes to air and moisture paved the way for the development of organocatalyzed synthesis. Organocatalysis is defined as the catalysis with small organic molecules, predominantly composed of C, H, O, N, S and P, where an inorganic element is not part of the active principle. There are essentially four types of organocatalyst[133]: Lewis bases, Lewis acids, Brønsted bases and Brønsted acids. These catalysts initiate their catalytic cycles by either providing or removing electrons or protons from a substrate or a transition state (**Scheme 1.14**).



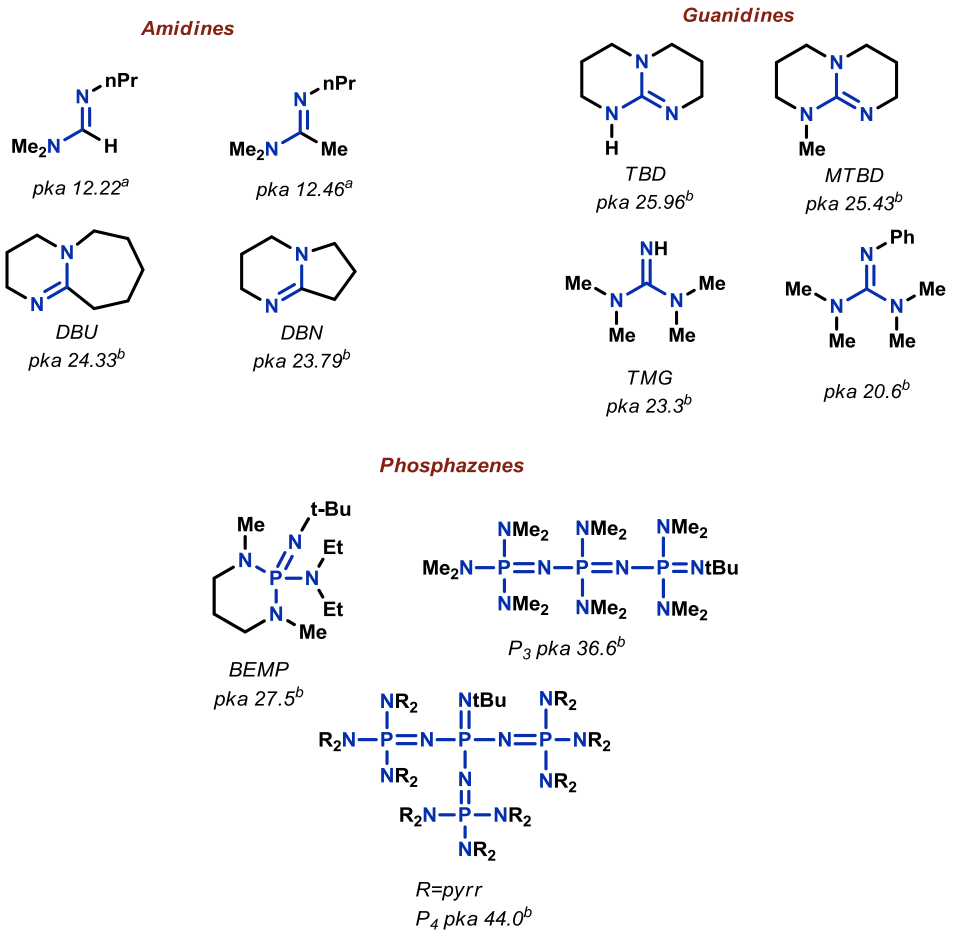
Scheme 1.14 Possible oganocatalytic cycles

Acid catalysis is know from far before the knowledge of catalysis itself. Parmentier reported in 1781[2] the saccharification of starches by boiling in acid.

The first recognized example of organocatalytic reaction is assigned to Von Liebig in 1859 for the synthesis of oxamide from dicyan and water catalyzed by acetaldehyde[134]. Nowadays organocatalysis is mainly applied in the field of asymmetric synthesis[135–137], but many achiral organocatalysts are present in several organic reactions. The late 20th century has experienced a rapid growth in organocatalyzed procedure[138–140], for example it is worth to cite the most famous ones still ongoing in all organic synthetic laboratories like the use of DABCO in the α-hydroxyalkylation of activated olefins (1972)[141] or DMAP that acts as an acyl transfer agent in the esterification of carboxylic acids in 1985[142]. Among all organic catalysts superbases cover a fundamental role due to their strong Brønsted basicity and their versatility as enabling tool in organocatalyzed reactions. As the name may suggest, superbases are a class of nitrogen containing organic molecules that display an exceptional basicity associated with high kinetic activity in proton exchange reactions. The basicity of these derivatives is due to the construction of highly effective coniugation[143,144]. Amidines[145] and guanidines[146] are the most known classes of organo superbases. The first consists in an amine bearing an immine function introduced on the α-carbon of the amine, the latter carries three nitrogen functions: one amine and two immines.

In 1985 Schwesinger introduced phosphazenes[147](triamino immino phosphorene skeleton), which contain a phosphorus atom P(V) bonded to four nitrogen functions: three amines and one imine substituents. They are classified as P*n* bases, based on the number of triamino immino phosphorene units (**Scheme 1.15** for an overview of selected examples of superbases, the scaffold of different classes marked in blue).

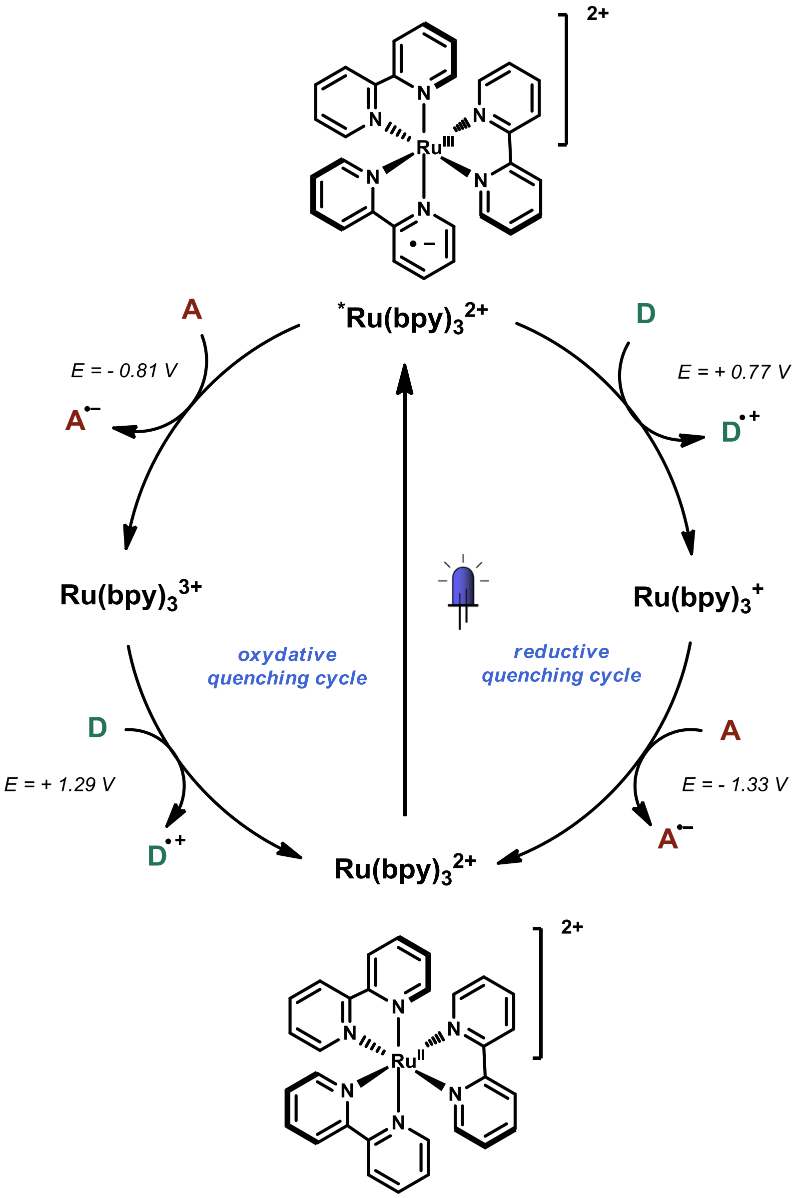
The adoption of phosphazenes as catalyst is reported for various synthesis[147] like the addition of nucleophiles to alkyne, the hydride nucleophile substitution onto aromatic rings (combination between Et_3SiH and tBu-P_4) or the promotion of halogen-zinc exchange reactions.



Scheme 1.15 Different classes of superbases with pka values[148] ^{a} in EtOH, ^{b} in MeCN

1.8. Photocatalysis

Nowadays chemists' efforts are devoted to the development of new sustainable transformations aiming at the reduction of wastes and at the decrease of energy consumption. In this context catalysis plays a pivotal role to enhance the selectivity towards the desired species, maximizing the atom economy of the process[149]. From the energetic point of view one of the most accessible and greener source of energy is, beyond any doubt, solar energy. The use of visible light to promote a chemical reaction is highly desirable for an environmentally benign chemistry. In the last decade photocatalysis, i.e. combining the use of a catalyst and light, has received remarkable attention in chemists community[150–154] due to its capability to enable the construction of non-traditional bond in a sustainable manner. Unfortunately most of organic molecules are not able to absorb visible light and thus to result in a chemical reaction. So an additional species is required to allow the energy transfer from light to the substrate. Photocatalysts, such as polypyridyl complexes of ruthenium and iridium or organic dyes, are able to engage in a single-electron-transfer (SET) with the organic molecule after being excited by visible light. In this brief discussion $Ru(bpy)_3^{2+}$ is take as example to describe the reactivity of photoredox catalysts since it is the most commonly employed and studied (**Scheme 1.16**). $Ru(bpy)_3^{2+}$ absorbs visible light (λ_{abs}=452 nm) and results in a long lived photoexcited state[155] (1100 ns) through the promotion of an electron from one of the t_{2g} orbitals of ruthenium to a π* orbital centered on the ligands. This transformation called metal to ligand charge transfer (MLCT)[156] presents the ruthenium in Ru (III) oxidation state and the ligand scaffold that has undergone to a single-electron reduction. The singlet-type excited state evolves through intersystem crossing (ISC) in the triplet-state possessing the lowest energy. This triplet state is the long-lived excited state of the ruthenium-based photocatalyst due to the prohibited transition to the singlet ground state. $Ru(bpy)_3^{2+}$ in its excited state is both a strong oxidant and reductant compared to the ground state due to the presence of an electron in a high energy orbital and a “hole” in the ground state. This double-edged character can be translated into two different redox pathways: an oxidative or a reductive quenching cycle. The oxidative quenching cycle involves $^*Ru(bpy)_3^{2+}$ that acts as reductant providing one electron to an acceptor. The resulting $Ru(bpy)_3^{3+}$ is a strong oxidant and can receive an electron from a donor species. In the reductive quenching cycle $^*Ru(bpy)_3^{2+}$ functions as an oxidant and it accepts an electron from a donor species providing the reduced species $Ru(bpy)_3^{+}$ that subsequently gives back the electron to an acceptor returning to the ground state. The excited state of Ruthenium bispyridyl complex can also undergo to an energy transfer providing an excited organic molecule.



Scheme 1.16 Oxidative and reductive quenching cycles of $Ru(bpy)_3^{2+}$

1.9. Bibliography

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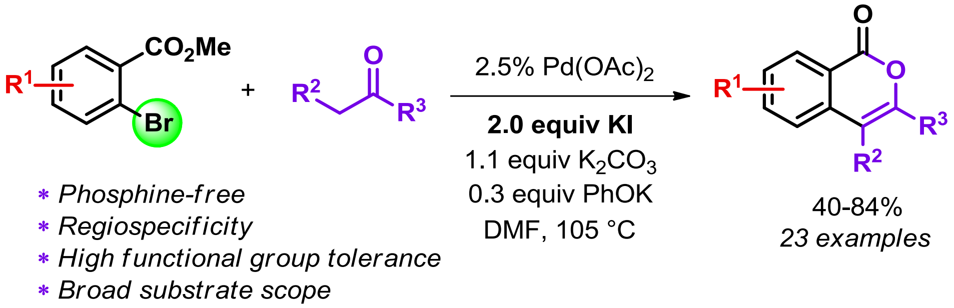
2. Pd-Catalyzed/Iodide-Promoted α-Arylation of Ketones for the Regioselective Synthesis of Isocoumarins



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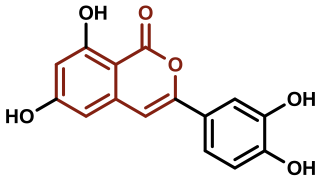
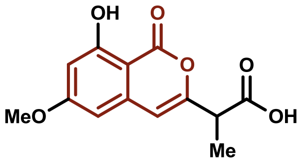
2.1. Introduction

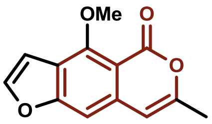
The isocoumarin framework is found in a plethora of natural compounds that display a wide range of biological properties, such as antitumoral, antifungal, antimicrobial, anti-inflammatory and antidiabetic activity[1–3]. Isocoumarins are also employed as chromophores in non-linear optic materials, and as building blocks for the synthesis of a number of medicinally important heterocycles and pharmaceuticals[4–6] (**Figure 2.1** for some selected examples).



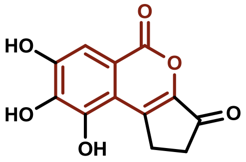
Thuberginol B
antidiabetic



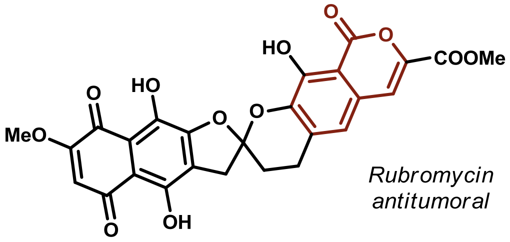
analogue of natural Cytogenin
angiogenesis inibithor



Coriandrin
photoactive



Brevifolin
antioxidant

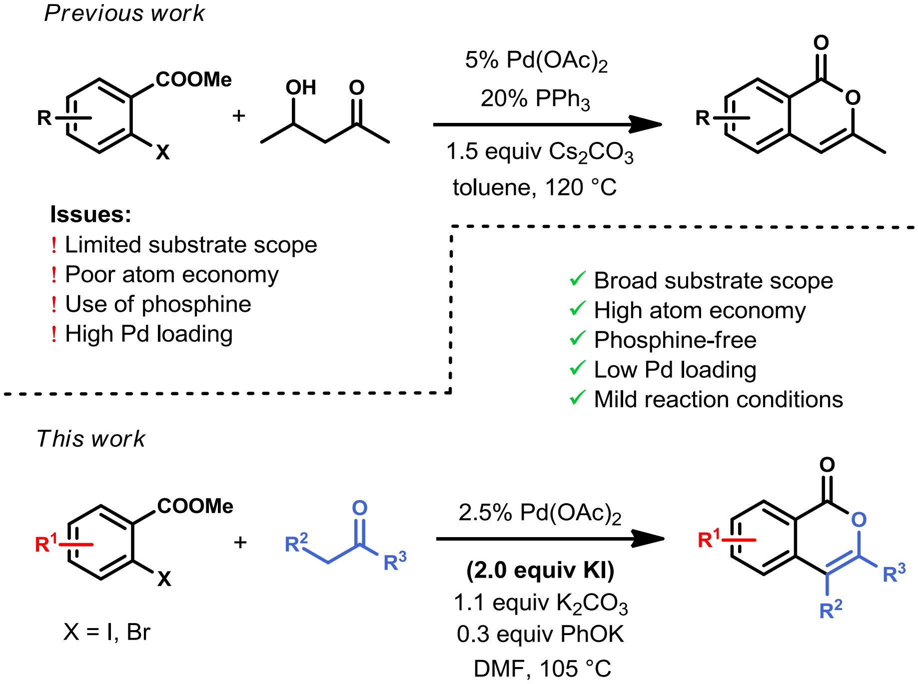


Rubromycin
antitumoral

Figure 2.1 Isocoumarin scaffold in biological active compounds

Traditional and, more recently, transition metal-catalyzed methods have been developed for the construction of isocoumarin scaffold[7–11]. The metal-catalyzed intramolecular annulation of benzoic acid derivatives bearing an alkyne in suitable position is probably the most popular approach[12–15]. The intermolecular version has been extensively investigated and several metals can be active in this transformation[16–19]. The atom economy is particularly high in the Rh or

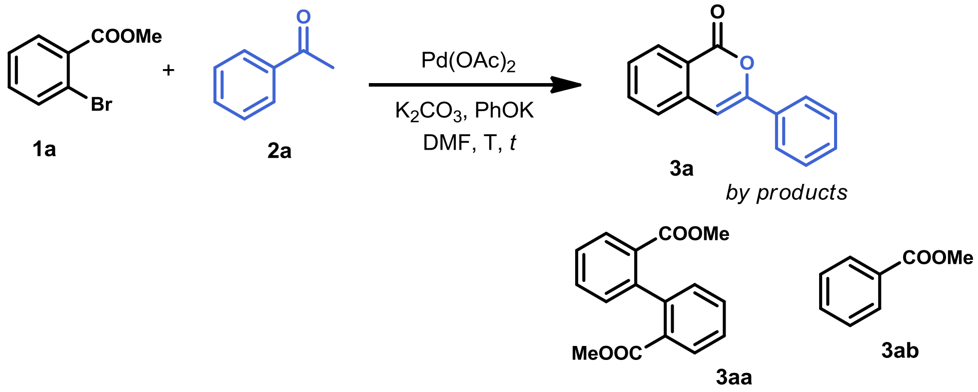
Ru/Cu-catalyzed oxidative annulation of alkynes by non-halogenated carboxylic acids via a direct C−H bond activation[20–24]. However, this approach requires the use of expensive alkynes and manifests regioselectivity issues. Over the years, the use of diketones or vinyl acetates as coupling partners of benzoic acid has also received considerable attention[25–28]. Very recently, Zhang et al. have reported the synthesis of isocoumarins by Pd-catalyzed reaction of β-hydroxy carbonyl compounds with ortho-halobenzoates[29,30]. A palladium catalyzed retro-aldol/α-arylation reaction provides the α-arylated carbonyl intermediates, which undergo intramolecular condensation with the ester moiety to obtain isocoumarin derivatives. Unfortunately this methodology suffers from some limitations, including low atom economy, the use of phosphine, high catalyst loading, and a limited substrate scope (**Scheme 2.1**, previous work).



Scheme 2.1 Pd-Catalyzed syntheses of isocoumarins from 2-halobenzoates and ketone derivatives

2.2. Results and discussion

Taking advantage of our experience[31], we now report a new and practical palladium-catalyzed synthesis of isocoumarins from 2-halobenzoates and ketones. This method features the α-arylation of the ketone and the intramolecular condensation with the ester group. We discuss for the first time the role of iodide anions in the synthesis of isocoumarins. The high accessibility of ketone derivatives together with other evident advantages (**Scheme 2.1**, this work) make this methodology a valuable alternative compared to existing ones. A direct and general route from ketones to isocoumarins is, up to now, unprecedented[32].



Scheme 2.2 Reaction scheme for the optimization studies

Table 2.1 Optimization of iodine source amount and reaction conditions[a]

Entry	KI (equiv.)	T (°C)	t (h)	Conversion (%)[b] 1a	Yield (%)[b] 3a
1		105	24	45	34[c]
2		130	24	96	50
3	0.1	130	24	98	61
4	0.2	130	24	100	66
5	0.5	130	24	100	70
6	1	130	24	100	73
7	2	130	4	100	77
8	2	105	4	100	84[c]
9	2	80	24	37	31
10	2 (tBuNI)	105	4	100	67
11	2 (NaI)	105	4	35	27
12	4	105	4	62	39
13[d]	2	105	24	0	0

[a] Reaction conditions: **1a** (0.4 mmol, 1 equiv), **2a** (5 equiv), $Pd(OAc)_2$ (2.5 mol%, 0.002 M), K_2CO_3 (1.1 equiv), PhOK (0.3 equiv) in DMF (4 mL) under N_2. [b] By GC. [c] Isolated yield. [d] No palladium source was used.

At first, our investigations were focused in exploring the Pd-catalyzed annulation reaction of methyl 2-bromobenzoate **1a** with acetophenone **2a** (**Scheme 2.2**). In an initial experiment, **1a** (0.4 mmol) reacted with 5 equiv of acetophenone in dry DMF with 2.5 mol% of palladium acetate as catalyst and a mixture of K_2CO_3 and PhOK as bases (1.1 and 0.3 equiv. respectively). The two possible byproducts are **3aa**, derived from the Ulmann coupling within two molecules of **3a**, and **3ab** from the hydrogenolysis of the Pd-Ar bond generated after the oxidative addition step (see Scheme 2.6 for reaction mechanism). The molar ratio between **1a** and acetophenone was selected as 1 to 5 to prevent the formation of byproducts, especially **3aa**. Mixtures were heated and samples periodically taken for analyses. The model reaction gave an encouraging 34% isolated yield of **3a** upon 24 h, mostly accompanied by unreacted starting material (**Table 2.1**, entry 1). Increasing the temperature proved beneficial for conversion and marginal for yield (entry 2, 50%), reduction of **1a** to methyl benzoate (**3ab**) and Ullmann-type coupling (**3aa**) being undesired side reactions (25% and 20%, respectively). An ample mix of tertiary phosphines proved ineffective to steer the outcome of this coupling. Similarly, various combinations of carbonates, phosphates, and alcoholates did not improve the yield of **3a**. We then resorted to test the effect of a source of iodide anions. The latter often serves indeed as reagent for metal-catalyzed halogen exchange reactions[33–36]. Iodide anions have been proposed as source of electrons[37,38], which can serve to generate aryl radicals that add then on enolized ketones[39], and might thus enable open-shell mechanisms[40]. Addition of KI proved decisive in our case. Furthermore, our preliminary results strongly suggest that its actual role in these reactions differs from those named above. Sub stoichiometric amounts of KI showed an impact on the yield **3a** (entries 3−5, up to 70%). A further increase is observed increasing its concentration up to 1 equiv. (entry 6, 73%) and then up to 2 equiv. obtaining 77% yield (entry 7). Reactions became significantly faster, achieving complete conversion required only 4 h. This enabled us to reduce back the temperature to 105 °C, delivering **3a** in 84% isolated yield (entry 8). Decreasing the temperature to 80°C resulted in a loss of reactivity (entry 9). Two different sources of iodide anions were tested, tBuNI proved to be slightly less effective than KI providing 67% of yield in 4 hours (entry 10). On the contrary, NaI was considered not suitable for the studied reaction (entry 11, 35% conversion, 27% yield). No reaction took place without palladium (entry 13).

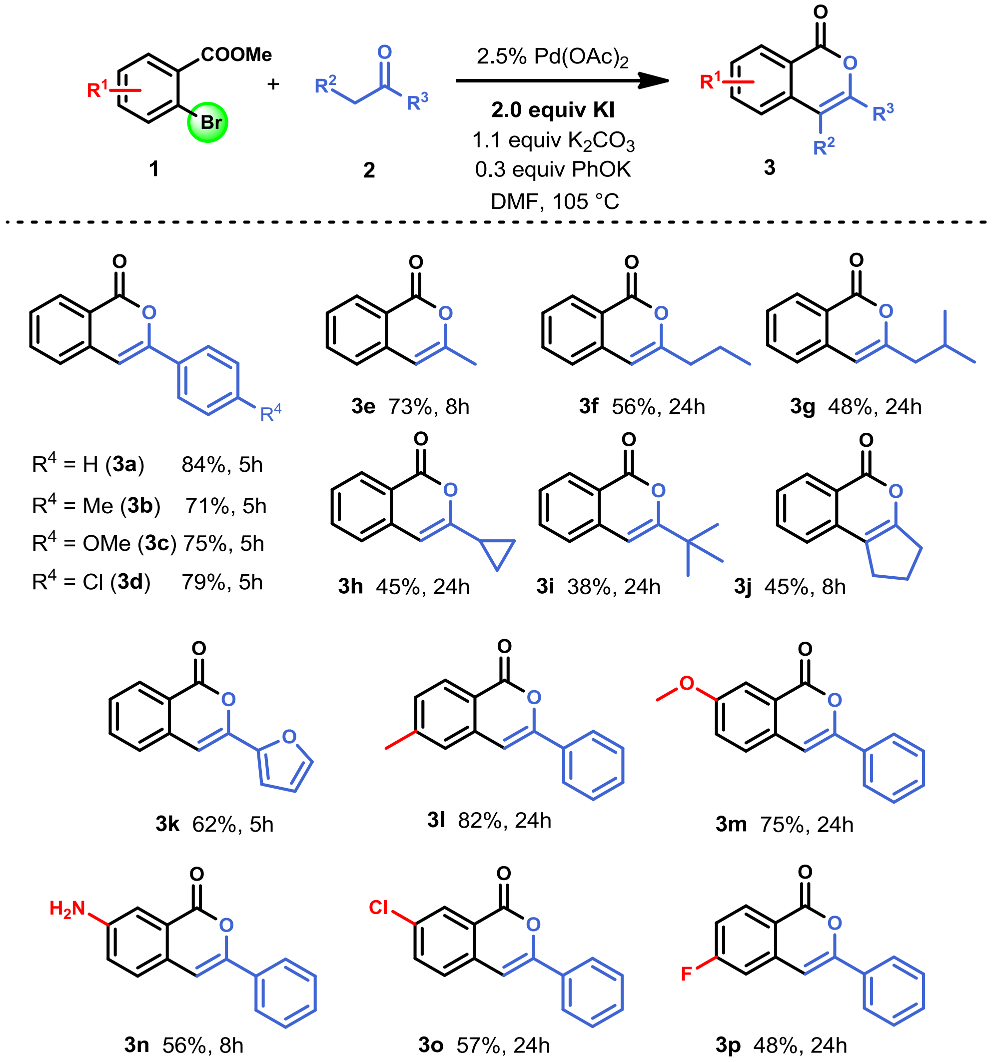
Further modifications, such as different bases proved their inefficiency for the new methodology (**Table 2.2**, entries 1−4). The winning combination between potassium carbonate and potassium phenoxide was established as the best one also compared to potassium phenoxide alone, which ensured a full conversion but a very low yield, providing mostly the Ullmann-type coupling byproduct **3aa** (entry 5). The introduction of triphenyl phosphine increase considerably the reaction time (entry 6), likewise a different source of palladium including two triphenyl phosphines as ligands (after 24 hours the conversion of **1a** was only 26%, entry 9). $PdCl_2$ and $PdCl_2(MeCN)_2$ were almost effective as palladium acetate (73% and 76% yield of **3a** respectively, entries 7−8). Different solvents were found to be not suitable for the transformation (entries 10−12).

Table 2.2 Further optimization of reaction conditions

Entry	Pd source	Base	Solvent	t (h)	Conversion (%)[a] 1a	Yield (%)[a] 3a
1	$Pd(OAc)_2$	K_2CO_3	DMF	8	100	51
2	$Pd(OAc)_2$	Na_2CO_3	DMF	24	100	36
3	$Pd(OAc)_2$	K_3PO_4	DMF	24	100	62
4	$Pd(OAc)_2$	*t-BuOK*	DMF	24	80	12
5	$Pd(OAc)_2$	PhOK	DMF	24	100	9
6	$Pd(OAc)_2$ PPh_3 (5%)	K_2CO_3/ PhOK	DMF	24	57	25
7	$PdCl_2$	K_2CO_3/ PhOK	DMF	4	100	73
8	$PdCl_2(MeCN)_2$	K_2CO_3/ PhOK	DMF	4	100	76
9	$PdCl_2(PPh_3)_2$	K_2CO_3/ PhOK	DMF	24	26	17
10	$Pd(OAc)_2$	K_2CO_3/ PhOK	MeCN	24	0	0
11	$Pd(OAc)_2$	K_2CO_3/ PhOK	DME	24	78	56
12	$Pd(OAc)_2$	K_2CO_3/ PhOK	toluene	24	0	0

Once best conditions were secured, we studied scope and limitations of the reaction. Results are summarized in **Scheme 2.3**.

Acetophenone could be decorated with various donating or withdrawing groups without hampering the outcome of the reactions (**3b−d**, 71−79%). Less acidic aliphatic ketones could be similarly employed, albeit at the expense of yield (**3e−j**, 38−73%). Noteworthy, ketones that have two different enolization sites provided a single regioisomer (**3f**, **3g**). The cyclopropyl ring remained untouched (**3h**). This result rules out mechanisms involving addition of aryl radicals on enolized ketones[39]. Methylene groups of cyclic ketones could be similarly arylated, enabling one to access fused tricycles (**3j**, 45%). Although the arylation of a furan could easily take place under similar conditions[41], we managed to exclude this side reaction to selectively obtain **3k** (62%). Switching to substituents on the bromide partner, electron-rich ones performed better (**3l−n**, 56−82%). Free amino groups are indeed tolerated, offering a valuable handle for further functionalization. Halo-coumarins could also be prepared (**3o−p**, 48−57%).

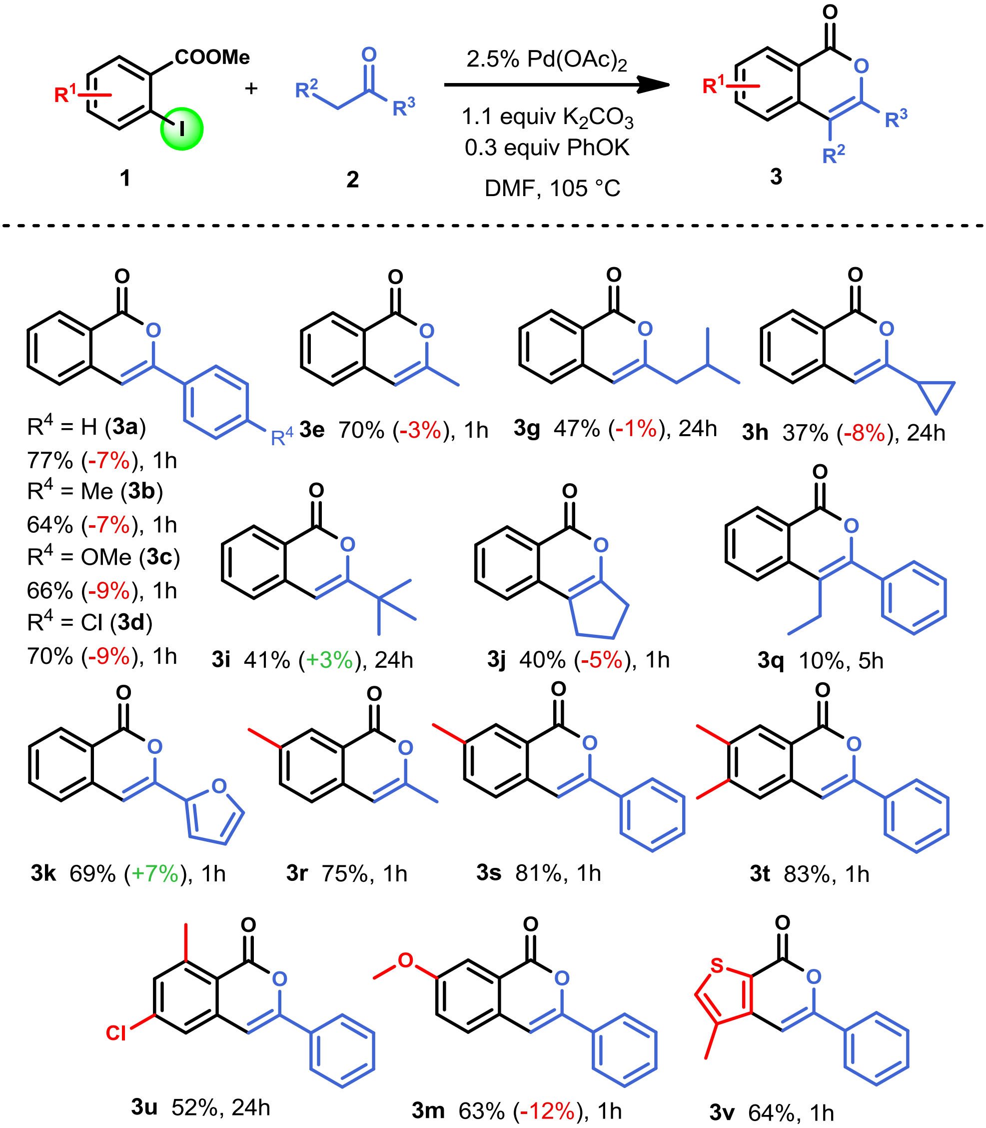


Scheme 2.3 Catalytic synthesis of isocoumarins from 2-bromobenzoates and ketones[a,b]

[a]Reaction conditions: as **Table 2.1**, entry 8. [b]Isolated yield.

Wondering whether KI triggers a halogen-exchange reaction[33–36], we tested methyl 2-iodobenzoates. They can be successfully employed as coupling partners in place of the corresponding bromides without KI (**Scheme 2.4**, values in parenthesis show the relative difference with their bromide peers). In general, slightly lower yields were observed (by 5−9% for **3a-j**). This combines with shortened reaction times, usually within one to a few hours. Pinacolone and 2-

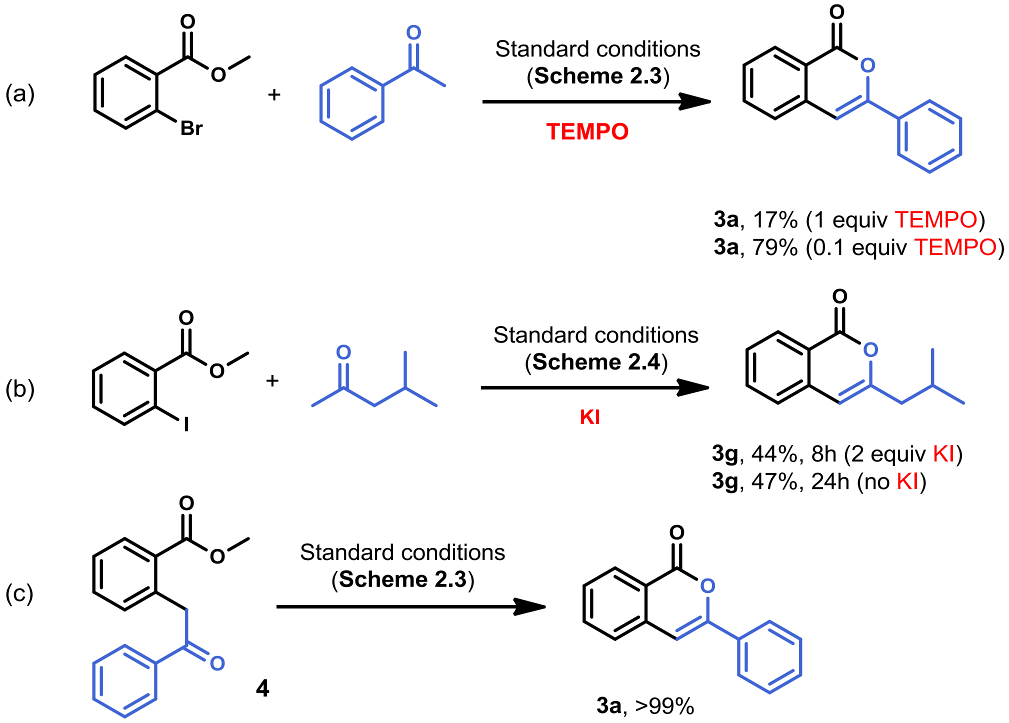
acetylfurane provided **3i** and **3k** with +3% and +7%, respectively. Only traces of products were obtained with butyrophenone (**3q**, 10%). The aryl iodide could be decorated with methyl groups (**3r−t**, 75−83%) and chloride ones (**3u**, 52%). A methoxy substituent para to iodide gave the worst outcome compared with its bromide peer (**3m**, Δ = −12%). Because of the well-known bioisosterism between thiophene and benzene ring thienopyranones have attracted considerable interest in pharmaceutical research. These compounds have been used as alternatives to the benzo derivatives of pyranone and played an important role in the design of new drugs[9]. The benzene ring was invariably replaced by a thiophene moiety in these cases to obtain similar pharmacological activities with reduced side effects. Interestingly, heterocyclic iodides, such as thiophenes, also worked in this new methodology (**3v**, 64%).



Scheme 2.4 Catalytic synthesis of isocoumarins from 2-iodobenzoates and ketones[a,b]

[a]Reaction conditions: as **Table 2.1**, entry 1. [b]Isolated yield.

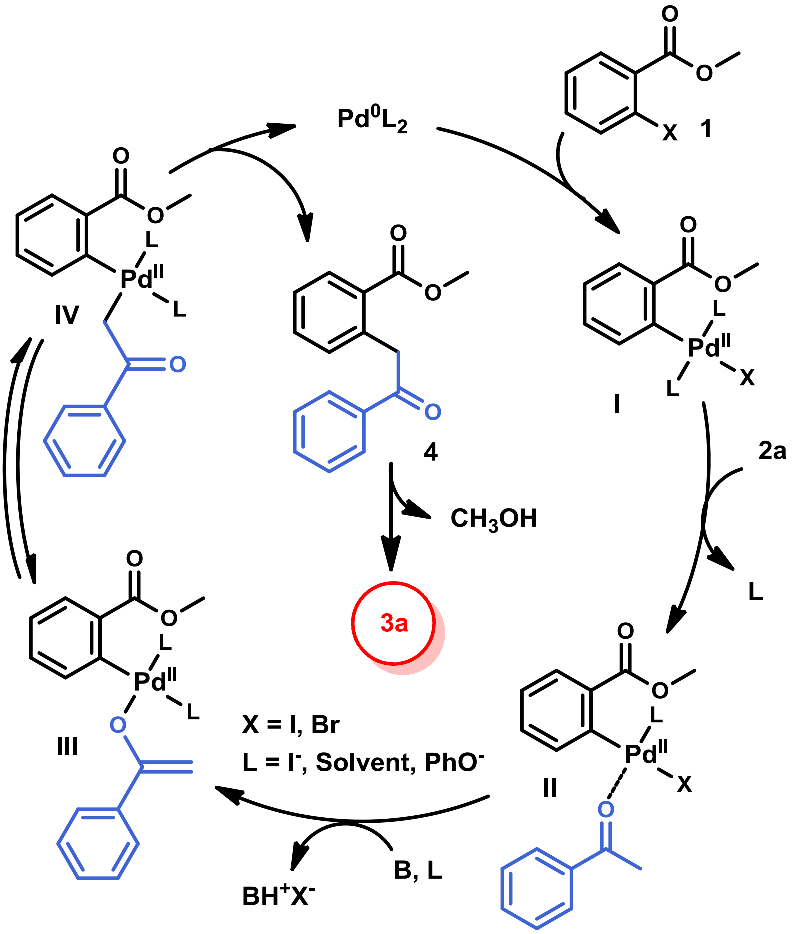
Additional experiments were carried out in order to gain insights on the role of KI in this sequence and the reaction mechanism as well (**Scheme 2.5**).



Scheme 2.5 Experimental findings

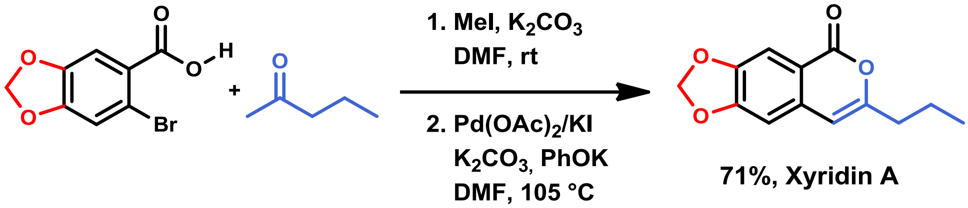
Reactivity is quenched by radical traps, as hindered phenols and TEMPO[40]. The yield of **3a** shrinks down to 17% performing the reaction with 1 equiv. of TEMPO (**Scheme 2.5 a**). This effect blurs at lower concentrations, as witnessed by retrieving 79% of **3a** with 0.1 equiv. of TEMPO. We were however unable to identify any radical recombination product[39,40]. Moreover, the isolation of **3h** using both aryl-bromides and iodides together with the absence of products arising from cyclopropane ring-opening reduce the odds that phenoxide anions act as single electron donor[39] to trigger a radical ketone arylation mediated by DMF. More likely, TEMPO is able to oxidize the in situ formed Pd(0), decreasing the concentration of the active catalyst. Addition of KI to a reaction involving an aryl iodide (**Scheme 2.5 b**) has a negligible impact on yield (44% against 47% without KI), in sharp contrast to observation with aryl bromides. On the contrary, the time required to consume the substrate did change significantly from 24 to 8 h. Since in this case no halogen exchange can be at work, the present result strongly supports that the role of iodide anions is crucial in the coordination of the metal providing anionic species able to increase the apparent reaction rate [42–44]. In addition when a further excess of KI was employed (**Table 2.1**, entry 12) the rate decreased drastically, suggesting that a too high concentration of iodides makes more difficult the coordination of the ketone, allowing side-reactions to take place.

Taken together all these results seem to exclude that KI serves as source of electrons[37,38]. Although the possibility that I^- anions operate as reagent for a halogen-exchange reaction[33–36] prior to ketone arylation cannot be ruled out, the observed acceleration in reactions involving aryl iodides suggests that iodide anions can act as ligands in this palladium-catalyzed phosphine-free synthesis of isocoumarins. According to these considerations, we propose the pathway in **Scheme 2.6**.



Scheme 2.6 Proposed pathway for the Pd-catalyzed synthesis of isocoumarins from 2-halobenzoates and ketones

Oxidative addition of the Pd^{0}L$_n$ with 2-halobenzoates **1a** or **4a** affords the PdII organometallic intermediate **I**. The ketone enters into the coordination sphere of palladium (intermediate **II**) and its subsequent deprotonation/enolization by the bases provides the PdII organometallic intermediate **III**, which is in equilibrium with **IV**[45–49]. Then, reductive elimination from intermediate **IV** gives the α-arylated ketone and regenerates the Pd^{0}L$_n$ catalyst. As we have demonstrated (**Scheme 2.5 c**) and in agreement with literature[50], compound **5** yields isocoumarin **3a** and methanol as coproduct.



Scheme 2.7 Synthesis of Xyridine A

To further demonstrate the synthetic usefulness of our approach, Xyridin A was synthesized in two steps from the corresponding commercial acid in 71% overall yield (**Scheme 2.7**). Xyridine A is extracted from Xyris Indaca L., a tall yellow-eyed grass found throughout Thailand and surrounding areas. In the past in Bengal the plant has been used in folklore medicine as a cure for ringworm, itch and leprosy. In 2003 Saeed reported the only synthetic methodology known in literature[51], in this work he also described its antibacterial and antifungal activities. The synthesis proposed starts with 6-bromo piperonic acid, involves three steps and harsh conditions like dry pyridine at 200 degree. They obtained Xyridine with a yield of 45 %, with an overall yield of 23%.

Our approach starts with a quantitative esterification of 6-bromo piperonic acid with iodomethane that provided the bromoester used for the coupling, which eventually delivered the desired natural product. This result shows that acetals are compatible with present methodology and further witnesses its generality.

2.3. Conclusions

In summary, we have described the first general methodology for the regioselective Pd-catalyzed synthesis of isocoumarins from 2-halobenzoates and ketones. The reaction makes direct use of simple and abundant ketones without the requirement of phosphine ligands or preformed diketones to generate richly decorated isocoumarins. The addition of iodide anions to the reaction mixture was crucial when 2-bromobenzoates were employed as starting materials. This methodology presents excellent regioselectivity, functional group tolerance, and simple protocol without expensive ligands.

2.4. Experimental section

Preparation of starting materials

Methyl 2-bromobenzoate (**1a**)[52], methyl 2-bromo-4-methyl benzoate (**1l**)[53], methyl 2-bromo-5- methoxy benzoate (**1m**)[53], methyl 5-chloro-2-bromo benzoate (**1o**)[53], methyl 2-bromo-4-fluoro benzoate (**1p**)[53], methyl 2-iodo-5-methoxy benzoate (**4m**)[52], methyl 2-iodo-4,5-dimethyl benzoate (**4t**)[53], methyl 4-chloro-2-iodo-6-methyl benzoate (**4u**)[53], and 6-bromobenzo[d][1,3]dioxole-5-carboxylate[53] were prepared from the corresponding benzoic acids according to standard methods. Methyl 2-bromo-5-amino benzoate (**1n**) was obtained from methyl 2-bromo-5-nitro benzoate by hydrogenation as described below.

Methyl 2-bromo-5-amino benzoate (**1n**)

10% Pd/C (0.20 g) was added to a solution of methyl 2-bromo-5-nitro benzoate (1.5 g, 5.7 mmol) in EtOAc (40 mL) and the resulting mixture was stirred for 8 hours at room temperature under 2.5 bar hydrogen pressure. After filtration through a Celite pad and removal of the solvent methyl 2- bromo-5-amino benzoate **1n** (1.3 g, 99%) was obtained as pale yellow oil. Spectroscopic data were consistent with those reported in the literature[54].

General procedure A

Catalyzed synthesis of isocoumarins 3 from methyl 2-bromo benzoates 1 (**Scheme 2.3**). A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with methyl 2-bromo benzoate (**1**, 0.4 mmol), ketone (**2**, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), KI (0.8 mmol, 143 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 5−24 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

General Procedure B

Catalyzed synthesis of isocoumarins **3** from methyl 2-iodo benzoates **4** (**Scheme 2.4**). A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with methyl 2-iodo benzoate (**4**, 0.4 mmol), ketone (2, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 1−24 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using mixtures of hexane-EtOAc as eluent.

3-Phenylisocoumarin (3a): following general procedure A, product **3a** was synthesized starting from methyl 2-bromo benzoate (**1a**, 86 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3a** (75 mg, 84% yield) as white solid. Spectroscopic data of **3a** were consistent with literature values[26]. Compound **3a** was also obtained from methyl 2-iodo benzoate (106 mg) and acetophenone (240 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3a** (69 mg, 77% yield) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.2 Hz, 1H), 7.88-7.83 (m, 2H), 7.71-7.66 (m, 1H), 7.49-7.39 (m, 5H), 6.89 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 153.5, 137.5, 134.9, 131.9, 129.9, 129.6, 128.8, 128.1, 126.0, 125.2, 120.5, 101.8. MS (ESI) calcd for $C_{15}H_{11}O_2$ $[M+H]^+$ *m/z* 223.08, found *m/z* 223.11. IR (neat) 1716 cm^{-1}.

3-(4'-Methylphenyl)isocoumarin (3b): following general procedure A, product **3b** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-methyl acetophenone (268 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3b** (61 mg, 71% yield) as white solid. Spectroscopic data of **3b** were consistent with literature values[55]. Compound **3b** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methyl acetophenone (268 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3b** (61 mg, 64% yield) as white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.29 (d, *J* = 8.2 Hz, 1H), 7.80-7.74 (m, 2H), 7.70 (td, *J* = 7.5, 1.3, 1H), 7.49-7.44 (m, 2H), 7.29-7.23 (m, 2H), 6.89 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 162.4, 153.8, 140.3, 137.7, 134.8, 129.6, 129.5, 129.2, 127.9, 125.9, 125.2, 120.4, 101.1, 21.4. MS (ESI) calcd for $C_{16}H_{13}O_2$ [M+H]$^+$ *m/z* 237.09, found 237.12. IR (neat) 1714 cm^{-1}.

3-(4'-Methoxyphenyl)isocoumarin (3c): following general procedure A, product **3c** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-methoxy acetophenone (300 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3c** (76 mg, 75% yield) as white solid. Spectroscopic data of **3c** were consistent with literature values[26]. Compound **3c** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methoxy acetophenone (300 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3c** (67 mg, 66% yield) as white solid.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24 (d, *J* = 8.2 Hz, 1H), 7.79-7.73 (m, 2H), 7.65 (td, *J* = 7.5, 1.3, 1H), 7.45-7.38 (m, 2H), 6.96-6.89 (m, 2H), 6.77 (s, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 162.4, 161.0, 153.6, 137.9, 134.8, 129.5, 127.6, 126.7, 125.7, 124.4, 120.1, 114.2, 100.2, 55.4. MS (ESI) calcd for $C_{16}H_{13}O_3$ [M+H]$^+$ *m/z* 253.10, found *m/z* 253.15. IR (neat) 1736 cm^{-1}.

3-(4'-Chlorophenyl)isocoumarin (3d): following general procedure A, product **3d** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-chloro acetophenone (308 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3d** (77 mg, 79% yield) as pale yellow solid. Spectroscopic data of **3d** were consistent with literature values[16]. Compound **3d** was also obtained from methyl

2-iodo benzoate (106 mg) and 4-chloro acetophenone (308 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3d** (72 mg, 70% yield) as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.3, 1H), 7.47 (t, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 6.87 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.9, 152.4 137.2, 135.9, 134.9, 130.4, 129.6, 129.1, 128.4, 126.4, 126.0, 120.5, 102.0. MS (ESI) calcd for $C_{15}H_{10}O_2Cl$ $[M+H]^+$ *m/z* 257.04, found *m/z* 257.12. IR (neat) 1722 cm^{-1}.

3-Methylisocoumarin (3e): following general procedure A, product **3e** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and acetone (116 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3e** (47 mg, 73% yield) as white solid. Spectroscopic data of **3e** were consistent with literature values[26]. Compound **3e** was also obtained from methyl 2-iodo benzoate (106 mg) and acetone (116 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3e** (45 mg, 70% yield) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 7.9 Hz, 1H), 7.66 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 154.5, 137.6, 134.7, 129.7, 127.5, 124.9, 119.9, 103.5, 19.6. MS (ESI) calcd for $C_{10}H_9O_2$ $[M+H]^+$ *m/z* 161.06, found *m/z* 161.12. IR (neat) 1714 cm^{-1}.

3-Propylisocoumarin (3f): following general procedure A, product **3f** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and hexan-2-one (200 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3f** (42 mg, 56% yield) as pale colorless oil. Spectroscopic data of **3f** were consistent with literature values[56].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, *J* = 8.0, 0.6 Hz, 1H), 7.67 (td, *J* = 7.8, 1.3 Hz, 1H), 7.45 (td, *J* = 7.9, 1.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 6.26 (s, 1H), 2.51 (t, *J* = 7.5 Hz, 2H), 1.80-1.71 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.0, 158.1, 137.6, 134.7, 129.5, 127.5, 125.0, 120.2, 103.0, 35.4, 20.2, 13.5. MS (ESI) calcd for $C_{12}H_{13}O_2$ $[M+H]^+$ 189.09, found *m/z* 189.20. IR (neat) 1721 cm^{-1}.

3-(2-Methylpropyl)isocoumarin (3g): following general procedure A, product **3g** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 4-methylpentan-2-one (200 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3g** (39 mg, 48% yield) as pale yellow oil. Compound **3g** was also obtained from methyl 2-iodo benzoate (106 mg) and 4-methylpentan-2-one (200 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3g** (39 mg, 47% yield) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.1 Hz, 1H), 7.45 (t, *J* = 7.8, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 6.25 (s, 1H), 2.38 (d, *J* = 7.2 Hz, 2H), 2.20-2.10 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.1, 157.4, 137.6, 134.7, 129.5, 127.6, 125.0, 120.1, 104.0, 42.8, 26.6, 22.2. MS (ESI) calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ *m/z* 203.11, found *m/z* 203.17. IR (neat) 1718 cm^{-1}. Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98; O, 15.82. Found: C, 77.06; H, 7.03.

3-Cyclopropylisocoumarin (3h): following general procedure A, product **3h** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and methyl cyclopropyl ketone (170 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3h** (34 mg, 45% yield) as pale yellow oil. The spectroscopic data of **3h** were consistent with literature values[57]. Compound **3h** was also obtained from methyl 2-iodo benzoate (106 mg) and methyl cyclopropyl ketone (170 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3h** (28 mg, 37% yield) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.67-7.61 (m, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 6.29 (s, 1H), 1.84-1.76 (m, 1H), 1.09-1.03 (m, 2H), 0.95-0.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8, 158.4, 137.9, 134.8, 129.5, 127.1, 124.6, 119.9, 101.4, 13.8, 7.0. MS (ESI) calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ *m/z* 187.08, found *m/z* 187.17. IR (neat) 1715 cm^{-1}.

3-*tert*-Butylisocoumarin (3i): following general procedure A, product **3i** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and pinacolone (200 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3i** (31 mg, 38% yield) as pale yellow oil. Spectroscopic data of **3i** were consistent with literature values[58]. Compound **3i** was also obtained from methyl 2-iodo benzoate (106 mg) and pinacolone (200 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3i** (34 mg, 41% yield) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.6, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 6.32 (s, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 163.0, 137.7, 134.6, 129.4, 127.6, 125.5, 120.1, 99.7, 35.6, 28.0. MS (ESI) calcd for $C_{13}H_{15}O_2$ $[M+H]^+$ *m/z* 203.11, found *m/z* 203.18. IR (neat) 1718 cm^{-1}.

2,3-Dihydro-1*H*-cyclopenta[c]isochromen-5-one (3j): following general procedure A, product **3j** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and cyclopentanone (168 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3j** (34 mg, 45% yield) as white solid. Spectroscopic data of **3j** were consistent with literature values[59]. Compound **3j** was also obtained from methyl 2-iodo benzoate (106 mg) and cyclopentanone (168 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3j** (30 mg, 40% yield) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (further split d, J = 8.0 Hz, 1H), 7.69 (td, J = 7.9, 1.1 Hz, 1H), 7.42 (td, J = 8.1, 1.1 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 2.87-2.78 (m, 4H), 2.22-2.12 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.8, 156.0, 136.4, 134.8, 130.4, 127.0, 122.5, 119.6, 113.3, 31.0, 26.5, 19.8. MS (ESI) calcd for $C_{12}H_{11}O_2$ $[M+H]^+$ 187.08, found *m/z* 187.15. IR (neat) 1716 cm^{-1}.

3-(2-Furanyl)isocoumarin (3k): following general procedure A, product **3k** was synthesized from methyl 2-bromo benzoate (**1a**, 86 mg) and 2-acetylfuran (220 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3k** (52 mg, 62% yield) as orange solid. Spectroscopic data of **3k** were consistent with literature values[58]. Compound **3k** was also synthesized from methyl 2-iodo benzoate (106 mg) and 2- acetylfuran (220 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3k** (59 mg, 69% yield) as orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.2 Hz, 1H), 7.68 (td, J = 7.8, 1.3 Hz, 1H), 7.50 (d, J = 1.7 Hz, 1H), 7.47-7.42 (m, 2H), 6.93 (d, J = 3.4 Hz, 1H), 6.83 (s, 1H), 6.52 (dd, J = 3.4, 1.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.5, 146.9, 146.1, 144.0, 137.3, 135.0, 129.8, 128.0, 126.0, 120.4, 112.1, 110.1, 100.0. MS (ESI) calcd for $C_{13}H_9O_3$ $[M+H]^+$ *m/z* 213.06, found *m/z* 213.14. IR (neat) 1731 cm^{-1}.

6-Methyl-3-phenylisocoumarin (3l): following general procedure A, product **3l** was synthesized from methyl 2-bromo-4-methyl benzoate (**1l**, 92 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3l** (78 mg, 82% yield) as white solid. Spectroscopic data of **3l** were consistent with literature values[16].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.1 Hz, 1H), 7.83 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.47-7.36 (m, 3H), 7.27-7.20 (m, 2H), 6.82 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.2, 153.5, 145.9, 137.6, 132.0, 129.8, 129.51, 129.49, 128.8, 126.0, 125.2, 118.1, 101.5, 21.9. MS (ESI) calcd for $C_{16}H_{13}O_2$ $[M+H]^+$ *m/z* 237.09, found *m/z* 237.17. IR (neat) 1712 cm^{-1}.

7-Methoxy-3-phenylisocoumarin (3m): following general procedure A, product **3m** was synthesized from methyl 2-bromo-5-methoxy benzoate (**1m**, 98 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3m** (76 mg, 75% yield) as pale yellow solid. Spectroscopic data of **3m** were consistent with literature values[58]. Compound **3m** was also synthesized from methyl 2-iodo-5- methoxy benzoate (**4m**, 117 mg) and acetophenone (240 mg) following general procedure B. The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3m** (64 mg, 63% yield) as pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.83 (m, 2H), 7.72 (d, *J* = 2.7 Hz, 1H), 7.48-7.37 (m, 4H), 7.31 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.92 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.5, 159.6, 151.7, 132.1, 131.2, 129.6, 128.8, 127.6, 124.9, 124.7, 121.7, 110.0, 101.6, 55.8. MS (ESI) calcd for $C_{16}H_{13}O_3$ $[M+H]^+$ *m/z* 253.09, found *m/z* 253.17. IR (neat) 1733 cm^{-1}.

7-Amino-3-phenylisocoumarin (3n): following general procedure A, product **3n** was synthesized from methyl 2-bromo-5-amino benzoate (**1n**, 92 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3n** (53 mg, 56% yield) as pale yellow solid. Mp 171−173 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.82 (m, 2H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.47-7.42 (m, 2H), 7.42-7.36 (m, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.89 (s, 1H), 4.05 (br s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 150.4, 146.9, 132.4, 129.2, 128.8, 127.4, 124.7, 122.9, 121.9, 112.7, 102.0. MS (ESI) calcd for $C_{15}H_{11}NO_2$ $[M+H]^+$ *m/z* 237.08, found *m/z* 237.14. IR (neat) 1728 cm^{-1}. Anal. Calcd. for $C_{15}H_{10}NO_2$: C, 75.94; H, 4.67; N, 5.90; O, 13.49. Found: C, 76.11; H, 4.61; N, 5.84.

7-Chloro-3-phenylisocoumarin (3o): following general procedure A, product **3o** was synthesized from methyl 5-chloro-2-bromo benzoate (**1o**, 100 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3o** (59 mg, 57% yield) as pale yellow solid. Spectroscopic data of **3o** were consistent with literature values[58].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 1.8 Hz, 1H), 7.93-7.86 (m, 2H), 7.69 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.53-7.44 (m, 4H), 6.96 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.2, 154.0, 135.9, 135.3, 133.9, 131.6, 130.3, 129.2, 128.9, 127.5, 125.3, 121.7, 101.0. MS (ESI) calcd for $C_{15}H_{10}ClO_2$ $[M+H]^+$ *m/z* 257.04, found *m/z* 257.15. IR (neat) 1722 cm^{-1}.

6-Fluoro-3-phenylisocoumarin (3p): following general procedure A, product **3p** was synthesized from methyl 2-bromo-4-fluoro benzoate (**1p**, 94 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3p** (46 mg, 48% yield) as white solid. Spectroscopic data of **3p** were consistent with literature values[26].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.93-7.86 (m, 2H), 7.52-7.45 (m, 3H), 7.24-7.13 (m, 2H), 6.93 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8 (d, *J*C,F = 256.5 Hz), 161.4, 154.9, 140.24 (d, *J*C,F = 10.8 Hz), 133.03 (d, *J*C,F = 10.4 Hz), 131.6, 130.4, 128.9, 125.4, 117.0, 116.46 (d, *J*C,F = 23.4 Hz), 111.52 (d, *J*C,F = 22.6 Hz), 101.22 (d, *J*C,F = 2.9 Hz). MS (ESI) calcd for $C_{15}H_{10}FO_2$ $[M+H]^+$ *m/z* 241.07, found *m/z* 241.15. IR (neat) 1723 cm^{-1}.

3-Phenyl-4-ethylisocoumarin (3q): following general procedure B, product **3q** was synthesized from methyl 2-iodo benzoate (106 mg) and 1-phenylbutanone (296 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3q** (10 mg, 10% yield) as pale yellow solid. Mp 109−111 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.83 (td, *J* = 8.6, 1.4 Hz, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.62-7.45 (m, 6H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4, 151.3, 137.7, 134.7, 133.5, 130.1, 129.4, 129.0, 128.4, 127.8, 123.4, 121.4, 115.2, 20.1, 14.7. MS (ESI) calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ *m/z* 251.11, found *m/z* 251.21. IR (neat) 1721 cm^{-1}. Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64; O, 12.78. Found: C, 81.43; H, 5.70.

7-Methyl-3-methylisocoumarin (3r): following general procedure B, product **3r** was synthesized from methyl 2-iodo-5-methyl benzoate (110 mg) and acetone (116 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3r** (52 mg, 75% yield) as white solid. Spectroscopic data of **3r** were consistent with literature values[60].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (further split s, 1H), 7.48 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 163.2, 153.6, 137.7, 136.0, 135.2, 129.1, 124.8, 119.8, 103.4, 21.3, 19.5. MS (ESI) calcd for $C_{11}H_{11}O_2$ $[M+H]^+$ 175.08, found *m/z* 175.18. IR (neat) 1712 cm^{-1}.

7-Methyl-3-phenylisocoumarin (3s): following general procedure B, product **3s** was synthesized from methyl 2-iodo-5-methyl benzoate (110 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3s** (76 mg, 81% yield) as white solid. Spectroscopic data of **3s** were consistent with literature values[28].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.83 (d, *J* = 7.6, 2H), 7.51-7.33 (m, 5H), 6.88 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.4, 152.7, 138.5, 136.1, 135.0, 132.0, 129.7, 129.3, 128.8, 125.9, 125.1, 120.4, 101.7, 21.4. MS (ESI) calcd for $C_{16}H_{13}O_2$ $[M+H]^+$ 237.09, found *m/z* 237.18. IR (neat) 1712 cm^{-1}.

6,7-Dimethyl-3-phenylisocoumarin (3t): following general procedure B, product **3t** was synthesized from methyl 2-iodo-4,5-dimethyl benzoate (**4t**, 116 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3t** (87 mg, 83% yield) as white solid. Spectroscopic data of **3t** were consistent with literature values[16].

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.48-7.40 (m, 3H), 7.25 (s, 1H), 6.87 (s, 1H), 2.38 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.5, 152.9, 145.2, 137.8, 135.6, 132.2, 129.7, 129.6, 128.8, 126.6, 125.1, 118.4, 101.6, 20.4, 19.8. MS (ESI) calcd for $C_{17}H_{15}O_2$ $[M+H]^+$ 251.11, found *m/z* 251.20. IR (neat) 1712 cm^{-1}.

6-Chloro-8-methyl-3-phenylisocoumarin (3u): following general procedure B, product **3u** was synthesized from methyl 4-chloro-2-iodo-6-methyl benzoate (**4u**, 124 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3u** (57 mg, 52% yield) as white solid. Mp 158−160 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.86 (m, 2H), 7.52-7.44 (m, 3H), 7.32 (d, *J* = 1.9 Hz, 1H), 7.26 (further split s, 1H), 6.82 (s, 1H), 2.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.8, 154.4, 145.7, 140.5, 140.2, 131.6, 130.9, 130.2, 128.9, 125.3, 123.5, 117.3, 101.3, 23.0. MS (ESI) calcd for $C_{16}H_{12}ClO_2$ $[M+H]^+$ 271.05, found *m/z* 271.15. IR (neat) 1716 cm^{-1}. Anal. Calcd. for $C_{16}H_{11}ClO_2$: C, 70.99; H, 4.10; Cl, 13.10; O, 11.82. Found: C, 71.13; H, 4.15.

3-Methyl-5-phenyl-7H-thieno[2,3-c]pyran-7-one (3v): following general procedure B, product **3v** was synthesized from methyl 3-iodo-4-methylthiophene-2-carboxylate (113 mg) and acetophenone (240 mg). The crude product was purified by flash column chromatography using hexane/ethyl acetate (from 10:0 to 8:2) as eluent to give **3v** (72 mg, 64% yield) as pale orange solid. Mp 136−138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.49-7.41 (m, 4H), 7.00 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.5, 156.3, 147.2, 134.0, 132.4, 132.0, 130.1, 128.9, 125.4, 122.9, 97.6, 13.7. MS (ESI) calcd for

$C_{14}H_{11}O_2S$ [M+H]$^+$ 243.05, found *m/z* 243.15. IR (neat) 1704 cm^{-1}. Anal. Calcd. for $C_{14}H_{10}O_2S$: C, 69.40; H, 4.16; O, 13.21; S, 13.23. Found: C, 69.28; H, 4.09.

Synthesis of Xyridine A

6-Bromobenzo[d][1,3]dioxole-5-carboxylate was synthesized from the corresponding benzoic acids according to literature[53].

A Schlenk-type flask, equipped with a magnetic stirring bar was charged, under nitrogen, with methyl 6-bromobenzo[d][1,3]dioxole-5-carboxylate (122 mg, 0.4 mmol), hexan-2-one (200 mg, 2 mmol), K_2CO_3 (0.45 mmol, 62 mg), PhOK (0.15 mmol, 20 mg), KI (0.8 mmol, 142.8 mg), $Pd(OAc)_2$ (2.5 mol%, 2.2 mg) in DMF (4 mL). The resulting mixture was stirred in an oil bath at 105 °C for 1 h. After cooling to room temperature, the reaction crude was filtered through a sand core funnel and washed with ethyl acetate (20 mL). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using hexane-EtOAc as eluent to afford Xyridine A as white solid (66 mg, 71%). Spectroscopic data were consistent with reported values[51].

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 6.72 (s, 1H), 6.15 (s, 1H), 6.08 (s, 2H), 2.48 (t, J = 7.5 Hz, 2H), 1.79-1.66 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 162.7, 157.1, 153.6, 147.8, 135.3, 114.6, 107.3, 103.6, 103.0, 102.1, 35.3, 20.3, 13.5. MS (ESI) calcd for $C_{13}H_{13}O_4$ [M+H]$^+$ 233.08, found *m/z* 233.18. IR (neat) 1739 cm^{-1}.

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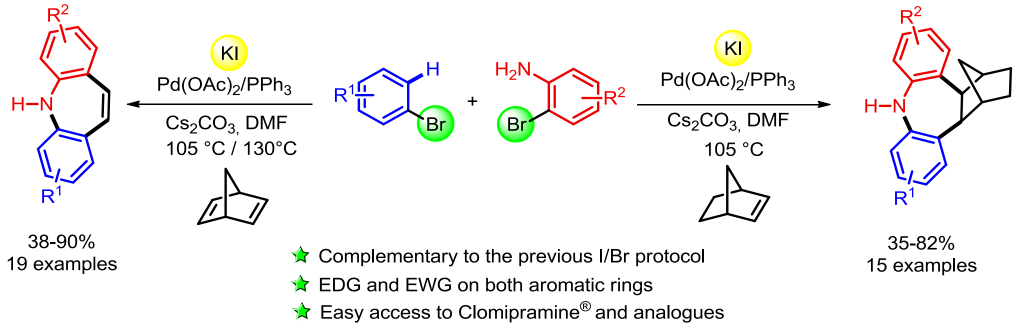
3. Enhancing Reactivity and Selectivity of Aryl Bromides: A Complementary Approach to Dibenzo[b,f]azepine Derivatives



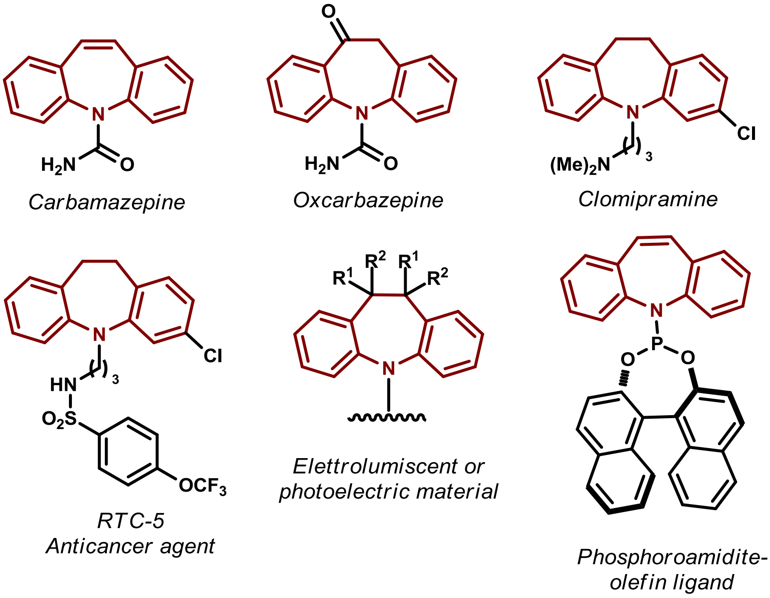
- Complementary to the previous I/Br protocol
- EDG and EWG on both aromatic rings
- Easy access to Clomipramine® and analogues

The main content of this chapter has been published in:

A. Casnati+, M. Fontana+, G. Coruzzi, B. M. Aresta, N. Corriero, R. Maggi, G. Maestri, E. Motti, N. Della Ca'; Enhancing Reactivity and Selectivity of Aryl Bromides: A Complementary Approach to Dibenzo[b,f]azepine Derivatives; *ChemCatChem* **2018**, *10*, 4346 +Both authors contributed equally

3.1. Introduction

Seven-membered nitrogen heterocycles represent an important class of molecules mainly because of their relevance in medicinal chemistry. In particular, 5H-dibenzo[b,f]azepines are attractive targets for synthetic chemists due to their remarkable biological activities[1–3]. In fact, the 5H-dibenzo[b,f]azepine scaffold can be found in pharmaceutically important structures such as carbamazepine, oxcarbazepine and clomipramine, widely used as antiepileptic and anti-anxiety drugs[2] (Figure 1). Molecules containing dibenzo[b,f]azepine nucleus display also antioxidant[4], antiviral[5], antimicrobial[6], antimalarial[7,8] and anticancer[9–12] activities. Moreover, the same tricyclic skeleton is present in chiral bidentate ligands[13,14], electroluminescent[15] and photoelectric[16] materials.



Carbamazepine

Oxcarbazepine

Clomipramine

RTC-5
Anticancer agent

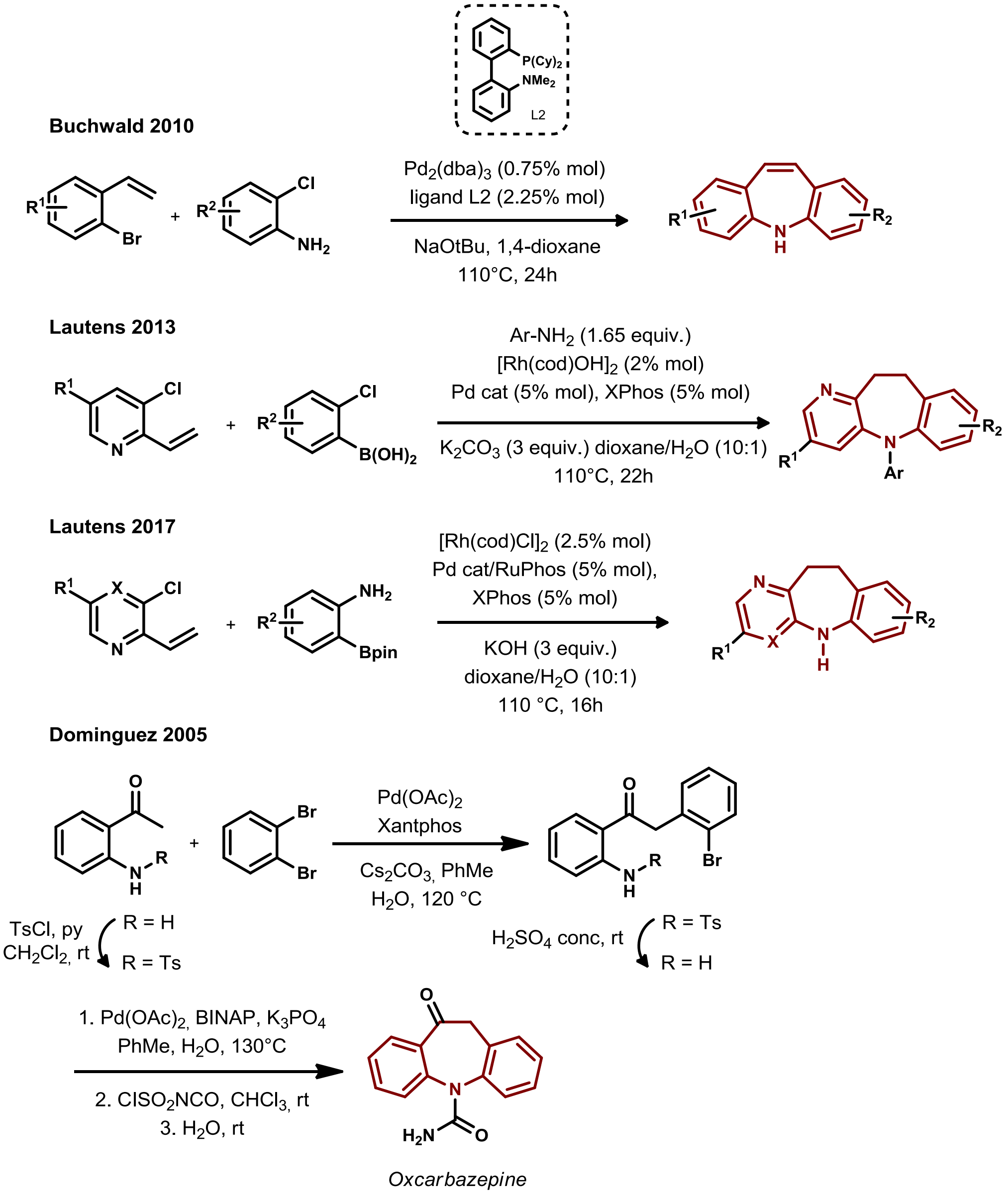
Elettrolumiscent or photoelectric material

Phosphoroamidite-olefin ligand

Figure 3.1 Dihydrodibenzo[b,f]azepine motif in therapeutic agents, advanced materials and metal ligands.

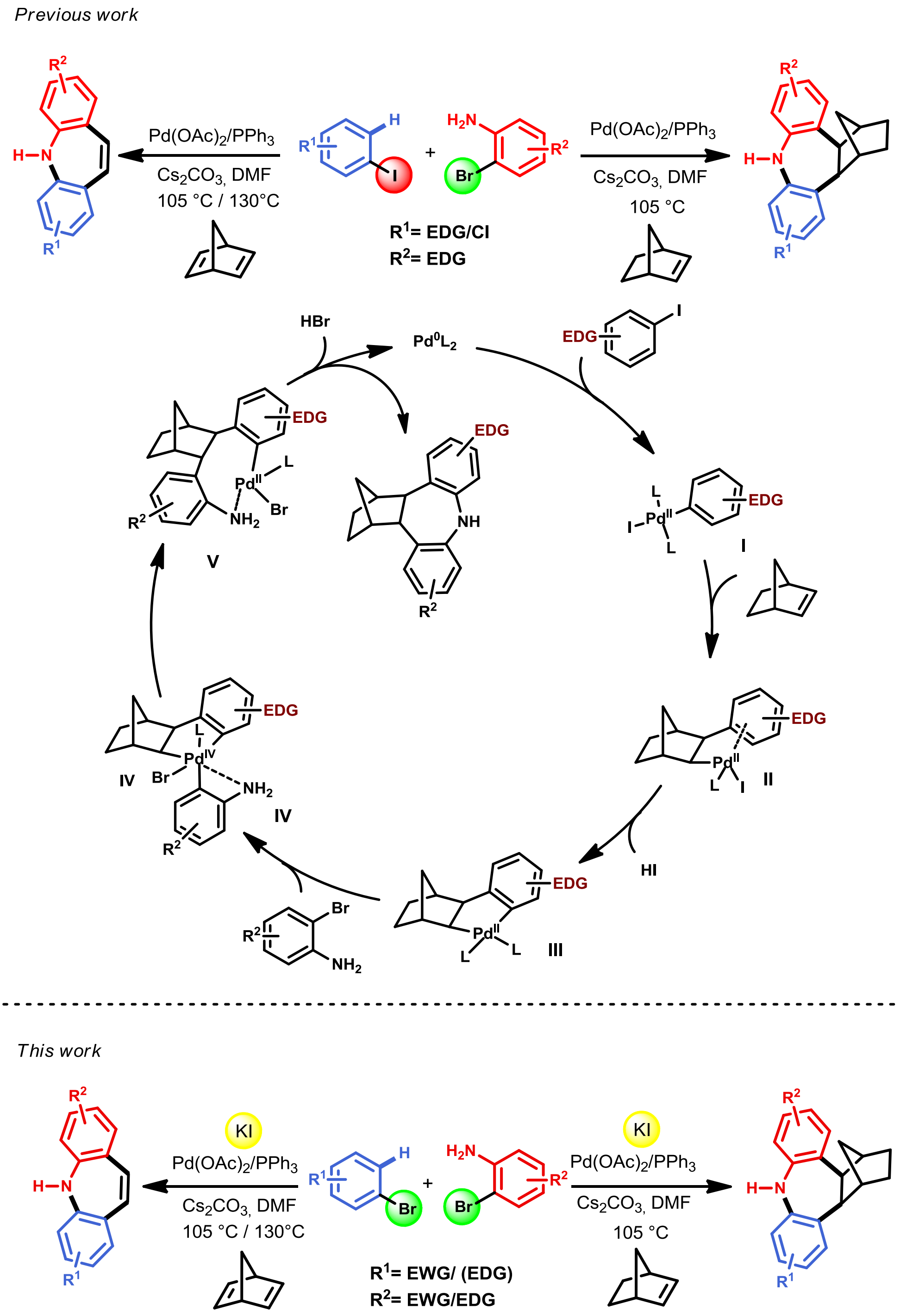
The 10,11-dihydrodibenzo[b,f]azepine framework has traditionally been synthesized through cyclization of o,o'-diaminobibenzyls, which can be dehydrogenated to iminostilbene, for many years considered to be the key intermediate for the production of oxcarbazepine and carbamazepine[1].

Environmental and toxicological drawbacks prompted Novartis to develop a new protocol to specifically produce oxcarbazepine[17] starting from 1,3-dihydro-1-phenyl-2H-indol-2-one with an overall yield around 60% with only three isolated and dried steps (eight steps in total). None of these methods is convenient for the synthesis of tailor-made functionalized structures with different steric and electronic properties. In this view, an interesting synthesis of fluorinated dibenzoazepines, based on a ring expansion reaction starting from isatin, indole and acridine derivatives, has been reported by Stachulski and coworkers[18]. The directed remote metalation (DreM) strategy was exploited by Snieckus et al. in the development of an efficient and regioselective route to dibenzo[b,f]azepinones[19]. In general, the use of transition-metal catalysts guarantees wide generality and high functional group tolerance even in the construction of seven-membered nitrogen heterocycles[20–24]. In this framework, Buchwald[25] and Lautens[26,27] reported versatile Pd- and Pd/Rh-catalyzed methods respectively, starting from ortho-vinyl haloaryls and ortho-substituted anilines. Moreover, transition-metal catalyzed C-H activation strategy can unlock novel and favorable synthetic methodology to access the dibenzoazepine scaffold[28]. As an example, the synthesis of oxcarbazepine (Trileptal), was successfully accomplished by means of palladium-catalyzed intermolecular a-arylation of a ketone as the key step, from commercially available 2’-aminoacetophenone and 1,2-dibromobenzene. However, the very limited scope once more prevented the preparation of analogues.



Scheme 3.1 Examples of synthesis of dibenzo[b,f]azepine derivatives through transition metals catalysis

In recent years, our research group has disclosed new routes to functionalized five, six and seven-membered fused N-heterocyclic compounds by means of the palladium/norbornene system, which allows sequential ortho C-H activation and double ortho and ipso functionalization of aryl halides. This singular methodology, named Catellani reaction, has been widely studied[29–31] by us and other research groups who have significantly contributed to increasing its generality and applicability. In particular, we reported the one-pot synthesis of 10,11-dihydrodibenzo[b,f]azepine and dibenzo[b,f]azepine derivatives through palladium catalysis from aryl iodides, 2-bromoanilines and norbornene/norbornadiene[32]. This process combines the advantages of a C-H activation in the synthesis of the hardly accessible dibenzo[b,f]azepine nucleus, with those deriving from the use of an inexpensive ligand, such as triphenylphosphine, available starting materials and mild reaction conditions (**Scheme 3.2**, previous work).



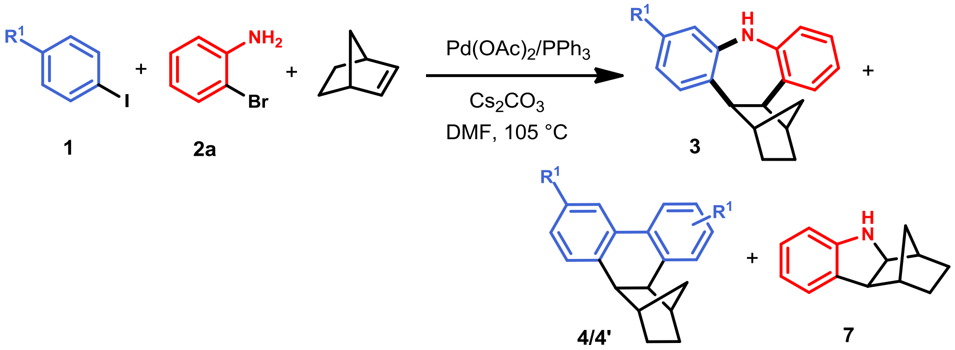
Scheme 3.2 Catellani-type complementary approaches to substituted dibenzo[b,f]azepines

The reaction pathway, proposed on the basis of previous experimental studies and DFT calculations[32–34], is shown in **Scheme 3.2**. Oxidative addition of an aryl iodide to Pd^0L_2 affords the well-known complex I and is followed by norbornene insertion leading to cis,exo-arylnorbornylpalladium intermediate II[35]. For steric reasons this species is prevented from undergoing β-H elimination and in the presence of a base readily forms palladacycle III through activation of the C-H bond in ortho position. Subsequent oxidative addition of o-bromoaniline to III generates complex IV with the assistance of the chelating NH_2 group, which then favors the Csp_2-Csp_3 coupling delivering complex V. Intramolecular Buchwald-Hartwig reductive elimination to form the

C-N bond from V provides dibenzoazepine and concomitantly regenerates the catalytically active Pd(0) species. This protocol is applicable to various substrates and leads to diversely functionalized dibenzoazepines in satisfactory to good yields. Here we report a palladium-catalyzed complementary approach to EWG-substituted 5H-dibenzo[b,f]azepines from aryl bromides, o-bromoanilines and norbornene/norbornadiene (**Scheme 3.2**, this work). The presence of iodide anions is crucial to the enhancement of reactivity and selectivity of the reaction, allowing the synthesis of dibenzoazepines decorated with electron withdrawing groups on both aromatic rings, largely widening the previous reaction scope.

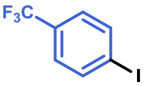
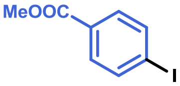
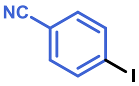
3.2. Results and discussion

Starting from the previous work, we immediately noticed that aryl iodides activated by electron-withdrawing substituents (EWG) were rather little tolerated, mainly because of their high reactivity, thereby preventing or limiting the formation of the products expected (**Scheme 3.3**, **Table 3.1**).



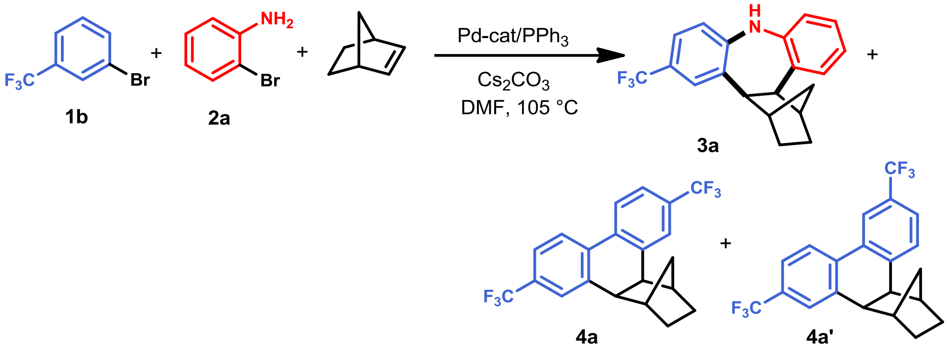
Scheme 3.3 Reactions of EWG-substituted aryl iodides with 2-bromoaniline and norbornene

Table 3.1 Different EWG-substituted aryl iodides and their performances in the reaction[a] with 2-bromoaniline and norbornene

Entry	**1**	**Conversion[b] 1 (%)**	**Conversion[b] 2a (%)**	**Yield[c] 3 (%)**	**Yield[c] 4/4' (%)**	**Yield[c] 7 (%)**
1		100	12	5	78 (5:1)	3
2		100	10	6	83 (6:1)	2
3		100	15	8	69 (5:1)	4

[a] Reaction conditions: **1** (0.48 mmol, 1.1 equiv), **2a** (0.44 mmol, 1.0 equiv), norbornene (0.53 mmol, 1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), Cs_2CO_3 (1 mmol, 2.25 equiv), in DMF (10 mL) under N_2 at 105 °C. [b] Determined by GC analysis. [c] Yields were determined via ^1H NMR analysis with the internal standard method.

In **Table 3.1** different examples are shown. Aryl iodides decorated with EWG groups such as trifluoromethane, methyl benzoate and nitrile in the reaction with o-bromoaniline and norbornene provided full conversion in 24 hours. On the contrary only a low amount of aniline was converted. The main products were methanotriphenylene-type isomers (**4/4’**) with only traces of the desired 5H-dibenzo[b,f]azepine were recovered. The high yield of methanotriphenylene isomers is probably due to the high reactivity of the electron poor aryl iodide. To prevent this reactivity mismatch, we then resorted to aryl bromides in place of the corresponding iodides.



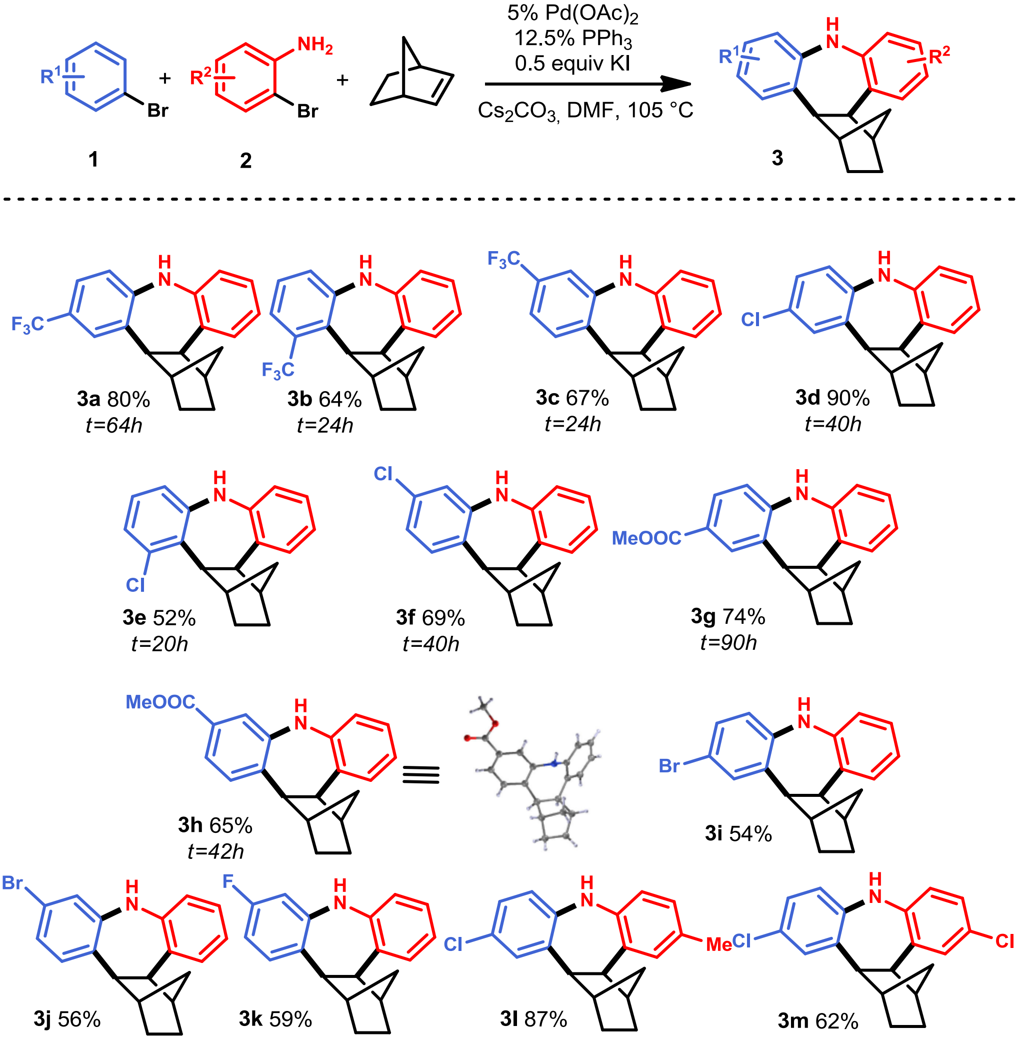
Scheme 3.4 Pd-catalyzed synthesis of dibenzoazepine **3a** from 3-trifluoromethylbromobenzene, 2-bromoaniline and norbornene[a]

Table 3.2 Optimization studies of the reaction in **Scheme 3.4**

Entry	Pd source	Halide salt (equiv)	Time (h)	Conv[b] 1b (%)	Conv[b] 2a (%)	Yield[c] 3a (%)	Yield[c] 4a/4a' (%)
1	$Pd(OAc)_2$	-	40	10	10	5	-
2	PdI_2	-	40	33	31	27	Traces
3	PdI_2	KI (0.25)	40	42	40	36	Traces
4	PdI_2	KI (0.5)	40	52	49	42	2
5	$Pd(OAc)_2$	KI (0.5)	40	73	70	60	3
6	$Pd(OAc)_2$	KI (0.5)	64	100	95	83(80)[d]	4
7	$Pd(OAc)_2$	KI (1)	64	63	58	46	2
8	$Pd(OAc)_2$	NaI (0.5)	64	81	76	62	3
9	$Pd(OAc)_2$	TBAI (0.5)	64	32	29	14	-
10	$Pd(OAc)_2$	KBr (0.5)	64	20	18	11	-
11	$Pd(OAc)_2$	NaBr (0.5)	64	16	14	8	-

[a]Reaction conditions: **1b** (0.48 mmol, 1.1 equiv), **2a** (0.44 mmol, 1.0 equiv), norbornene (0.53 mmol, 1.2 equiv), Pd-cat (5 mol%), PPh_3 (12.5 mol%), Cs_2CO_3 (1 mmol, 2.25 equiv), in DMF (10 mL) under N_2 at 105°C. [b]Determined by GC analysis. [c]Yields were determined via ^1H NMR analysis with the internal standard method. [d]Isolated yield in brackets.

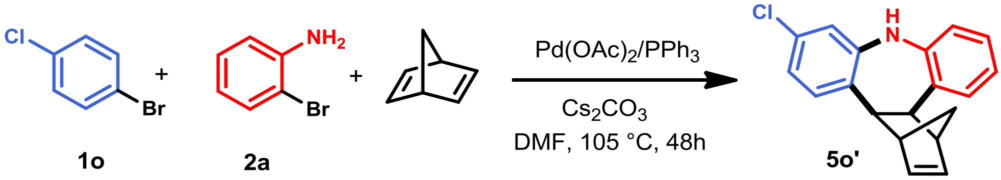
Preliminary studies began with the reaction involving 3-trifluoromethylbromobenzene, o-bromoaniline and norbornene as the reactants, carried out under the previous standard conditions[32]. However, the same reaction led to a very poor yield of the desired dibenzoazepine 3a (**Table 3.2**, entry 1). Higher temperatures or longer reaction times gave worse results. Conversion of the starting materials was quite limited (less than 10%), so several palladium precursors were then tested. PdI_2 was the most active one among them (27%, entry 2), and more importantly, only traces of compounds **4a/4a'** were detected. Dibenzoazepine **3a** was produced in 36% yield by adding an extra source of iodide anions (entry 3). As the amount of KI was doubled (0.5 equiv), the yield of **3a** reached 42% (entry 4). Unexpectedly, when we carried out the reaction using $Pd(OAc)_2$ in conjunction with KI (0.5 equiv), yield of the desired compound **3a** further increased to 60% with 70% of 2-bromoaniline conversion (entry 5). Prolonging the reaction time to 64 h allowed total conversion of the starting materials, achieving 83% yield of **3a** (entry 6). A significant reduction in the reaction rate was observed when the concentration of iodide anions was raised (entry 7), suggesting that an optimal compromise needs to be found for each substrate. Other iodide salts were found to affect the reaction rate. In particular, NaI, used in the same concentration, was slightly less effective (entry 8), while NBu_4I proved to be almost completely inactive (entry 9), as well as inorganic bromides (entries 10 and 11).



Scheme 3.5 Scope of the Pd-catalyzed synthesis of dihydrodibenzoazepines 3 from electron-poor aryl bromides, 2-bromoanilines and norbornene[a,b]
[a]Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol,1.0 equiv), norbornene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105°C. [b]Isolated yield.

Having identified the optimal conditions above (**Table 3.2**, entry 6), we examined the scope of the reaction by reacting electron-poor aryl bromides with 2-bromoanilines and norbornene (**Scheme 3.5**). Aryl bromides bearing electron-withdrawing substituents in ortho, meta or para position in combination with 2-bromoaniline and norbornene gave the corresponding dibenzoazepines **3** in good to excellent yields. The effect of KI was marked in all the examples examined. Various functional groups were tolerated, including CF_3 (products **3a**, **3b** and **3c**), Cl (products **3d**, **3e** and **3f**), CO_2Me (products **3g** and **3h**), Br (products **3i** and **3j**) and F (product **3k**), providing handles for further product diversification. Noteworthily, substituents in meta position on the starting aryl bromide led to better yields of **3** (**3a**, **3d** and **3g**). 2-Bromoanilines bearing an electrondonating or an electron-withdrawing group were found to be suitable substrates, providing the desired products **3l** and **3m** in 87% and 62% yields respectively (**Scheme 3.5**).

The 5H-dibenzoazepine scaffold can be more interesting from a synthetic point of view, so we proceeded to examine the reaction using norbornadiene in place of norbornene, with the aim of accessing the valuable 5H-dibenzo[b,f][azepines by triggering a sequential retro-Diels-Alder. Norbornadiene is more reactive than norbornene and the reaction conditions found for the latter are not often suitable for the former. Indeed, further optimization work was carried out.



Scheme 3.6 Pd-catalyzed synthesis of dibenzoazepine **5o'** from p-clorobromobenzene, 2-bromoaniline and norbornadiene[a]

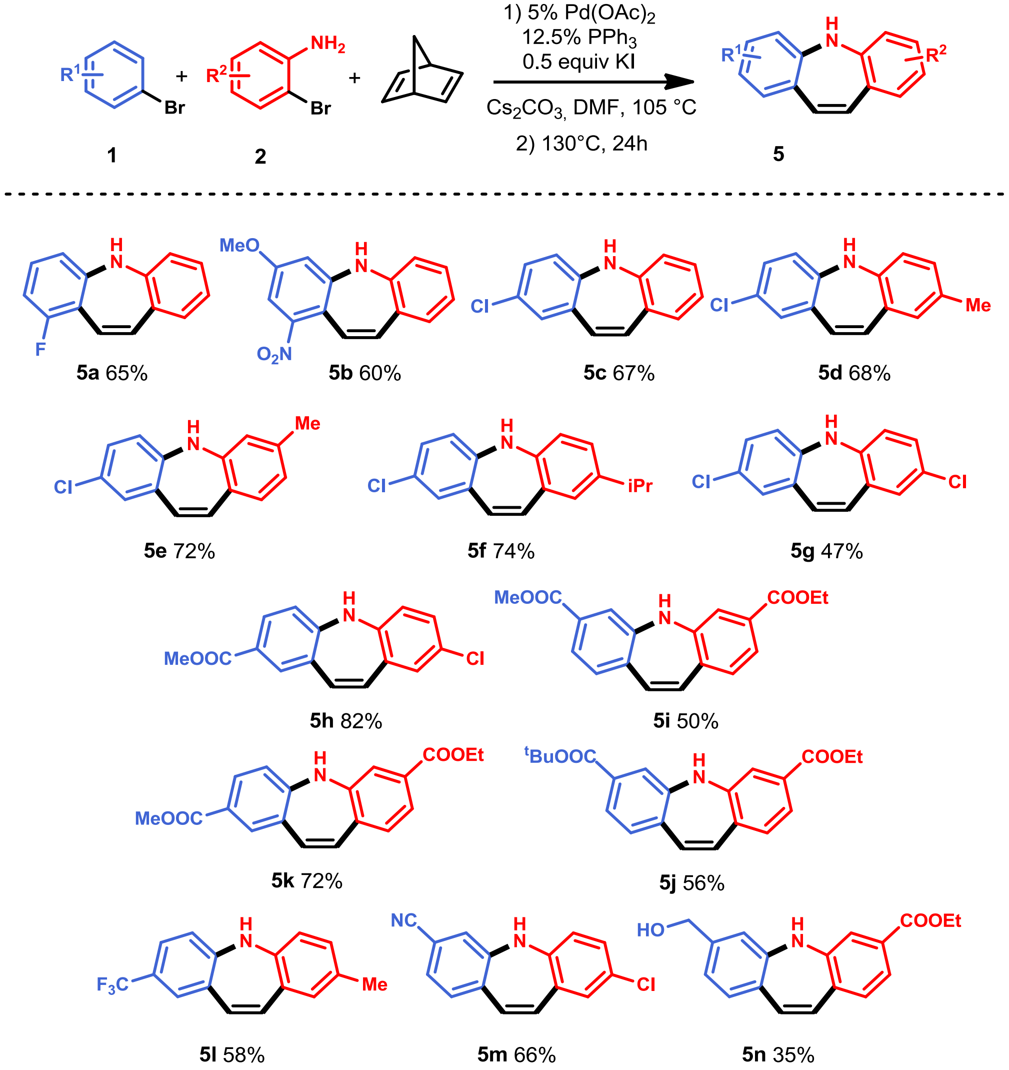
Table 3.3 Screening of the reaction conditions for the palladium-catalyzed reaction of 1-bromo-4-chlorobenzene, 2-bromoaniline and norbornadiene[a]

Entry	Norbornadiene (equiv)	KI (equiv)	Conversion[b] 1o (%)	Conversion[b] 2a (%)	Yield[c] 5o' (%)
1	2	-	44	40	28
2	2	-	95	98	42
3	2	0.5	99	99	64
4	2	0.25	74	72	45
5	2	1	86	87	52
6	1.2	0.5	53	49	31
7	3	0.5	64	61	25

[a]Reaction conditions: **1o** (0.48 mmol, 1.1 equiv), **2a** (0.44 mmol, 1.0 equiv), norbornadiene, Pd(OAc)2 (5mol%), PPh_3 (12.5 mol%), Cs_2CO_3 (1 mmol, 2.25 equiv), in DMF (10 mL) under N_2 at 105 °C for 48 h. [b]Determined by GC analysis. [c]Determined by ^1H NMR analysis of the reaction crude. [d]10 mol% of $Pd(OAc)_2$ was used.

1-Bromo-4-chlorobenzene **1o** was used as model substrate in combination with 2-bromoaniline and norbornadiene. The three reaction components were allowed to react under reported conditions at the standard temperature of 105 °C. For an easier analysis of the sample, after 48 h at 105 °C the reaction was stopped to prevent the retro-Diels-Alder cleavage and so obtaining compound **5o'**, precursor of 5*H*-dibenzo[*b,f*]azepine **5o**. Using our previously reported norbornadiene protocol[32], 1-bromo-4-chlorobenzene **1o** and 2-bromoaniline **2a** gave dihydrodibenzoazepine **5o'** in 28% yield calculated by ^1H NMR analysis on the reaction crude (entry 1). Conversion and yield were increased with 10 mol% of $Pd(OAc)_2$ but at the expense of the selectivity (entry 2). The addition of KI was beneficial to the reaction rate (entries 3-5 vs entry 1) and 0.5 equiv proved to be the optimal compromise, achieving 64% yield of **5o'** with complete conversion of both starting materials (entry 3). The best amount of norbornadiene under these reaction conditions was found to be two equivalents with respect to 2-bromoaniline (entries 3, 6 and 7). As expected, the reaction become sluggish with 1.2 equiv of norbornadiene (entry 6), while a significant reduction of selectivity to **5o'** was observed increasing norbornadiene up to three equivalents (entry 7).

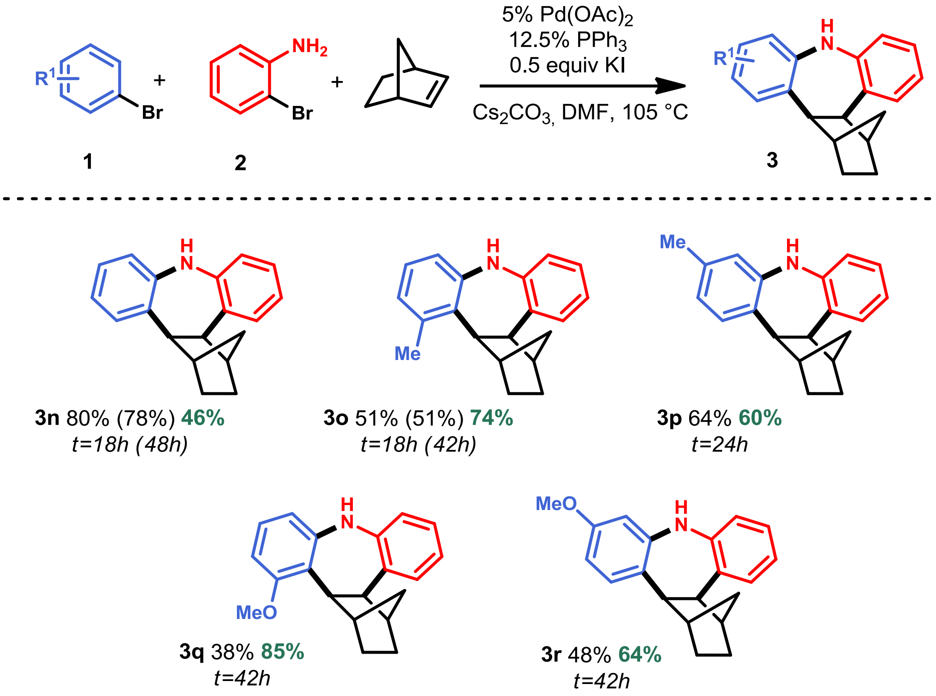
0.5 equivalents of KI and 2 equivalents of norbornadiene allows us to develop a specific protocol for the synthesis of 5H-dibenzo[b,f]azepine derivatives. As previously demonstrated, the final retro-Diels Alder step generally occurs when smoothly increasing the reaction temperature to 130 °C. The reaction scope was then examined and the results are reported in **Scheme 3.7**. Gratifyingly, aryl bromides bearing electron-withdrawing groups readily react with electron-rich and electron-poor 2-bromoanilines and norbornadiene, providing satisfactory to good yields of the 7-membered ring derivatives. A wide variety of functional groups can be successfully employed on both aromatic rings, such as Cl, F, NO_2, CF_3 and CN. Substituents ortho to NH group (located at the C(8)- and C(10)-positions) are normally not allowed, probably for steric reasons. Notably, this one-pot transformation gives access to symmetrical compounds, such as **5g**, useful for enantioselective applications[13,14]. Halogenated dibenzoazepines with reduced ADRs (Adverse Drug Reactions), can be readily prepared in a one-pot fashion (products **5c-h**)[36]. Remarkably the product **5c**, obtained in 67% of yield, is the precursor of Clomipramine. Other electron-withdrawing functional groups, such as CO_2R (R=Me, Et, tBu), can be effectively employed on starting aryl bromides **1** and **2**. It is worth noting that in the absence of KI, compounds **5i–5k** and **5n** with an ester group on the aniline moiety, were not recovered at all. In particular, compounds **5j** and **5n**, precursor of promising imipramine analogous with increased bio selectivity properties, can be obtained in 56 and 35% yield, respectively, through a one-pot reaction from commercially available and readily prepared starting materials.



Scheme 3.7 Scope of the Pd-catalyzed synthesis of 5H-dibenzoazepines 5 from electron-poor aryl bromides, 2-bromoanilines and norbornadiene[a,b]

[a] Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol, 1.0 equiv), norbornadiene (2.0 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105 °C for 46-90 h and at 130 °C for 24 h. [b] Isolated yield.

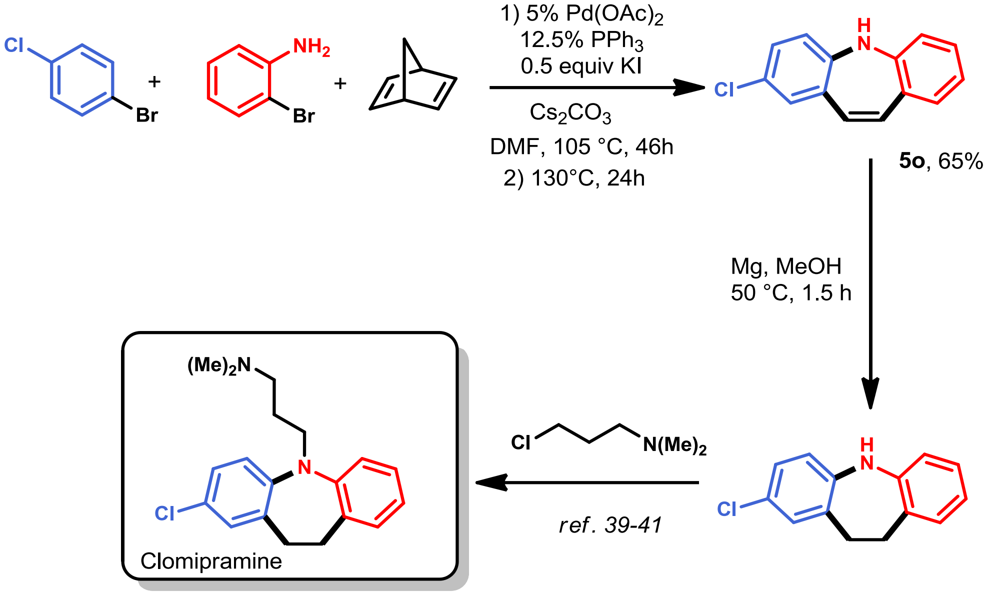
The methodology described can also be applied to electron-rich aryl bromides **1** with satisfactory results (**Scheme 3.8**). 10,11-Dihydrodibenzo[b,f]azepines **3n-r**, previously prepared from aryl iodides (green yields), are now accessible from the corresponding bromides, sometimes with improved yields (**3n** and **3p**). Noteworthy, yields of compounds **3n** and **3o** remained unchanged in the presence of KI (80/78% for **3n** and 51/51% for **3o**), while the reaction time was remarkably reduced (18 vs 48 h for **3n** and 18 vs 42 h for **3o**).



Scheme 3.8 Pd-catalyzed synthesis of 5H-dibenzoazepines 3 from electron-rich aryl bromides, 2-bromoanilines and norbornene[a,b]

[a]Reaction conditions: **1** (1.1 equiv), **2** (0.44 mmol, 1.0 equiv), norbornene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (12.5 mol%), KI (0.5 equiv), Cs_2CO_3 (2.25 equiv), in DMF (10 mL) under N_2 at 105 °C. [b]Isolated yield.

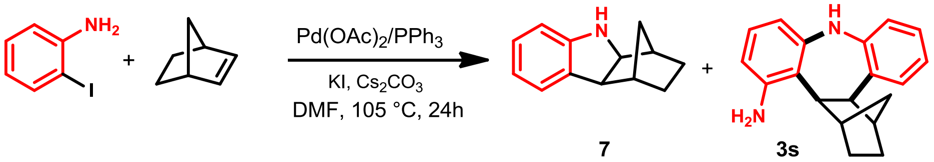
The synthetic utility of this protocol was further demonstrated with the formal synthesis of Clomipramine, prepared in three steps starting from commercial reagents (**Scheme 3.9**). Readily available 4-bromochlorobenzene, 2-bromoaniline and norbornadiene were subjected to the standard reaction conditions to afford the desired 3-chloro-5H-dibenzo[b,f]azepine **5o** in 65% yield, which was readily converted to the corresponding 10,11-dihydrocompound **6o** in 95% yield via a facile reduction of the conjugated double bond through the versatile Mg/MeOH procedure[37,38]. The desired Clomipramine can be finally obtained by a conventional alkylation procedure employing 3-chloro-N,N-dimethylpropan-1-amine[39–41].



Scheme 3.9 3-step formal synthesis of Clomipramine.

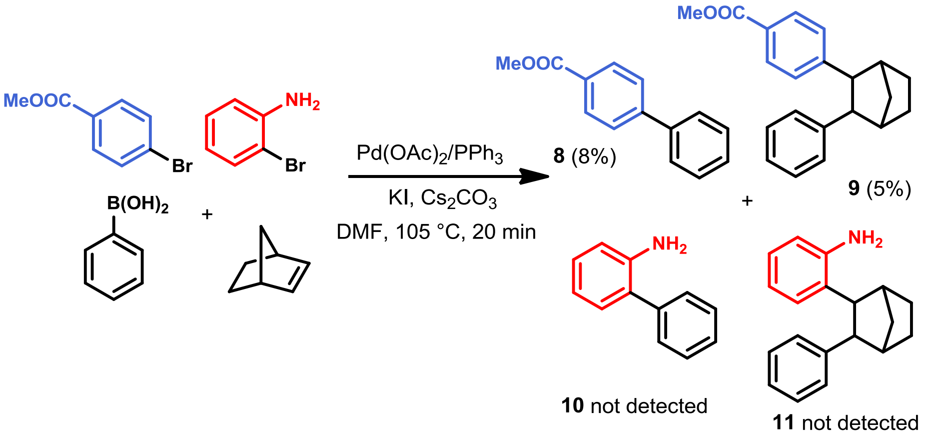
The present cascade sequence leads to several intriguing questions, for example, the singular inertia of this reaction system and the remarkable accelerating effect exerted by iodide anions. Furthermore, from a mechanistic point of view, since both bromides **1** and **2** might start the catalytic cycle, two possible reaction pathways could be proposed. Firstly, the general passivity of the reaction system in the absence of KI might be explained by the inherent presence of aniline derivatives. These NH_2-containing substrates contribute to decreasing the overall reaction rate of the process, probably owing to an easy interaction with palladium, even in the presence of phosphine ligand[42]. Thus, the effect of KI would be crucial to increasing the overall reaction rate, probably by competing with the NH_2 group for the metal coordination[32]. Secondly, the accelerating effect exerted by iodide anions in this transformation can be explained by the in situ formation of highly nucleophilic palladium species able to increase the oxidative addition rate of aryl bromides[43–47]. Otherwise I^- anions can also promote the so called “halogen exchange”[48–51] and we currently cannot exclude this possibility. However, in order to support the “ligand effect” idea for iodide anions, we set up a bromide-free system to prevent any halogen-exchange pathway. We then caused 2-iodoaniline and norbornene to react under standard conditions (**Scheme 3.10**, part a). In the absence of KI, only 20% of the 5-membered ring **7** was obtained (**Scheme 3.10**, part a, entry 1). When 0.5 equiv. of KI were used, yield of **7** raised to 33% and, notably, dibenzoazepine **3s** was also formed with 8% yield (**Scheme 3.10**, part a, entry 2). These values further increased at higher [I_] concentrations, reaching 50 and 32% yield of 7 and 3s respectively, when 1.5 equiv. of KI was employed (**Scheme 3.10**, part a, entries 3 and 4). These results suggest that iodide anions play the role of active ligand in this transformation[52].

a) iodide anions effect on aryliodide substrates



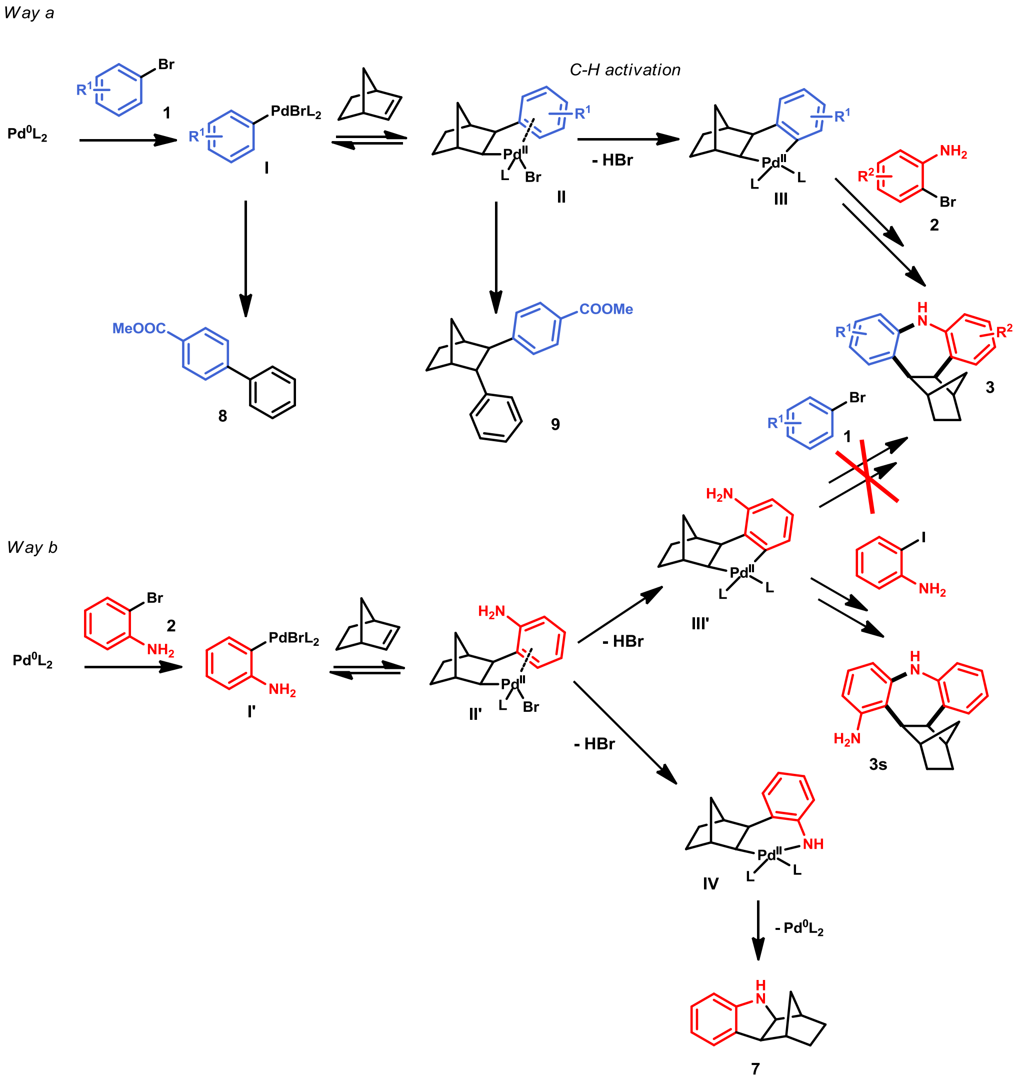
	KI (equiv.)	Yield (%)	Yield (%)
1)	-	20	-
2)	0.5	33	8
3)	1	36	12
4)	1.5	50	32

b) Competitive Suzuki-Miyaura coupling under standard conditions



Scheme 3.10 Experimental findings

Finally, from the mechanistic point of view, two possible reaction pathways can be proposed (**Scheme 3.11**, way a and b). Indeed, both bromides **1** and **2** might start the catalytic cycle since both could provide oxidative addition to palladium(0) species. If **1** begins the sequence (**Scheme 3.11**, way a), the oxidative addition to palladium (0) leads to complex **I**, which, after stereoselective norbornene insertion, affords intermediate **II.** After intramolecular C-H bond activation, an aryl-norbornyl palladacycle **III** is generated and its reaction with 2-bromoaniline **2** provides dibenzoazepine **3** and palladium(0). However, product **3** can also be obtained from way b (**Scheme 3.11**). Thanks to their NH_2 group in ortho position, bromoanilines can compete with **1** for the oxidative addition on Pd(0), leading to complex **I'**. Norbornene insertion would lead to intermediate **II'**, which in turn could undergo C-H activation to palladacycle **III'**. Finally, reaction of **III'** with **1** would provide compound 3. Pathway b would be more plausible for 2-iodoaniline, which is able to start the catalytic cycle providing palladacycle **III'**. The subsequent reaction of **III'** with a second molecule of 2-iodoaniline leads to compound **3s** (**Scheme 3.10**, part a and **Scheme 3.11**). Analogously, hexahydro-1H-1,4-methanocarbazole **7**[53], detected in small amounts when 2-bromoaniline was employed, can arise following way b (**Scheme 3.11**).



Scheme 3.11 Possible reaction pathways: aryl bromide/2-bromoaniline sequence (way a) and 2-bromoaniline/aryl bromide sequence (way b).

In order to ascertain the most probable reaction sequence, we attempted to trap some organometallic intermediates through the fast Suzuki-Miyaura coupling, whose conditions are compatible with those of dibenzoazepine formation[54]. We then caused 4-carbomethoxybromobenzene, 2-bromoaniline and norbornene to react in the presence of phenylboronic acid (**Scheme 3.10**, part b). Upon just 20 min, non-negligible amounts of **8** and **9** were detected, arising from intermediates **I** and **II** with phenylboronic acid respectively, thereby supporting proposed pathway a (**Scheme 3.10**, part b and **Scheme 3.11**, way a). Homologous **10** and **11**, resulting from the corresponding **I’** and **II’** intermediates, were not observed.

3.3. Conclusions

In summary, we have disclosed a complementary protocol to 10,11-dihydrodibenzo[b,f]azepine and dibenzo[b,f]azepine scaffolds from aryl bromides, 2-bromoanilines and norbornene/norbornadiene based on the crucial role of iodide anions. The reaction can tolerate an array of useful functional groups including electron withdrawing ones on the aromatic rings. The methodology described can be exploited in the preparation of Clomipramine and other useful intermediates. Specifically designed experiments allowed us to prove that KI can increase yields and selectivity by acting as competing ligand, and to propose the most plausible reaction pathway by trapping some key organometallic intermediates.

3.4. Experimental section

General procedure for the synthesis of products ***3a-r*** *(**Scheme 3.5** and **3.8**)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with Cs_2CO_3 (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a DMF solution (5 mL) of the aryl bromide **1** (0.48 mmol), 2-bromoaniline **2** (0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added, and then KI (36 mg, 0.22 mmol) was introduced under nitrogen. The resulting mixture was stirred in an oil bath at 105 °C for 20-90 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane/EtOAc as eluent.

*General procedure for the synthesis of products **5a-o** (**Scheme 3.7**)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged under nitrogen with Cs_2CO_3 (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a DMF solution (5 mL) of the aryl bromide **1** (0.48 mmol), 2-bromoaniline **2** (0.44 mmol) and norbornadiene (81 mg, 0.88 mmol) was added, and then KI (36 mg, 0.22 mmol) was introduced under nitrogen. The resulting mixture was stirred in an oil bath at 105 °C for 46-90 h and then at 130 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and extracted three times with a saturated solution of NaCl (25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane/EtOAc as eluent.

*Experimental procedure for the synthesis of compound **6o***[55]

A round-bottom flask, equipped with a magnetic stirring bar, was charged with compound **5o** (68 mg, 0.3 mmol) in methanol (10 mL), then magnesium shavings (72 mg, 3.0 mmol) were added. The mixture was stirred in an oil bath at 50 °C for 1.5 h. After cooling to room temperature, the methanol was decanted from any remaining shavings with 10 mL of methanol as a rinse. The combined methanolic solution was cooled in ice, treated with 5 mL of 6N hydrochloric acid, and diluted with 20 mL of water. The mixture was extracted three times with chloroform (10 mL). The combined chloroform solution was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and product **6o** were isolated in 95% yield (65 mg) by flash column chromatography on silica gel using hexane/EtOAc 90:10 as eluent.

*General procedure for the synthesis of compounds **7** and **3s** from 2-iodoaniline and norbornene (**Scheme 3.10**, part a)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with Cs_2CO_3 (163 mg, 0.5 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a

DMF solution (5 mL) of 2-iodoaniline (0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added, and, when required, KI (0.0-1.5 equiv) was introduced under nitrogen. The resulting mixture was stirred in an oil bath at 105 °C for 24 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Yields reported in **Scheme 3.10**, part a were calculated on the base of ^{1}H NMR spectra with an internal standard (dimethylmaleate). Products were purified by flash column chromatography on silica gel using hexane/EtOAc 90:10 as eluent.

*Experimental procedure for the competitive Suzuki-Miyaura coupling under standard conditions (**Scheme 3.10**, part b)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with Cs_2CO_3 (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a DMF solution (5 mL) of methyl 4- bromobenzoate (103 mg, 0.48 mmol), 2-bromoaniline (76 mg, 0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added, and then phenyl boronic acid (65 mg, 0.53 mmol) and KI (36 mg, 0.22 mmol) were introduced under nitrogen. The resulting mixture was stirred in an oil bath at 105 °C for 20 min. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Compounds **8** and **9** were identified and quantified via GC and GC-MS analysis using the internal standard method. The unknown compound **9** was prepared according to a reported procedure[56] and used for comparison.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6-trifluoromethyl-9H-tribenzo[b,f]azepine (3a): Yield: 80% (116 mg); reaction time: 64 h; white solid; m.p. (hexane): 135–136 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.49 (1H, s), 7.31 (1H, d further split, *J* = 8.2 Hz), 7.26 (1H, d, *J* = 7.5 Hz), 7.11 (1H, td, *J* = 7.6, 1.2 Hz), 6.97 (1H, t further split, *J* = 7.5 Hz), 6.85 (1H, d, *J* = 8.2 Hz), 6.82 (1H, d, *J* = 7.8 Hz), 5.32 (1H, br s), 3.24–3.15 (2H, m), 2.58 (1H, d further split, *J* = 9.8 Hz), 2.35, 2.33 (2H, 2 partly overlapping signals 2 br s), 1.67–1.52 (4H, m), 1.15 (1H, d further split, *J* = 9.8 Hz). ^{13}C NMR (100 MHz): δ 147.2, 143.2, 133.6, 133.4, 132.8, 129.7 (q, *J*C,F = 3.7 Hz), 126.8, 124.5 (q, *J*C,F = 269.6 Hz), 123.6 (q, *J*C,F = 3.6 Hz), 123.5 (q, *J*C,F = 32.2 Hz), 122.4, 120.05, 120.01, 53.3, 52.7, 49.8, 49.5, 37.4, 30.62, 30.57. IR (ATR diamond, cm^{-1}): ν 3367, 2958, 2873, 1585, 1483, 1336, 1254, 1104, 1085, 758. MS: *m/z* 329 (M+, 89), 262 (81), 248 (100). Anal. Calcd. for $C_{20}H_{18}F_3N$: C, 72.93; H, 5.51; F, 17.30; N, 4.25. Found: C, 73.22; H, 5.43.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-5-trifluoromethyl-9H-tribenzo[b,f]azepine (3b): Yield: 64% (93 mg); reaction time: 24 h; white solid; m.p. (hexane): 136–137 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.31 (1H, d, further split, *J* = 7.6 Hz), 7.21 (1H, d further split, *J* = 7.6 Hz), 7.10, 7.06 (2H, 2 partly overlapping signals: t, *J* = 8.0 Hz and t, *J* = 7.2 Hz), 6.98 (1H, d further split, *J* = 7.6 Hz), 6.93 (1H, t further split, *J* = 7.2 Hz), 6.79 (1H, d further split, *J* = 8.0 Hz), 5.10 (1H, br s), 3.51 (1H, d, *J* = 9.4 Hz), 3.18 (1H, d, *J* = 9.4 Hz), 2.87 (1H, d, *J* = 9.8 Hz), 2.33 (1H, br s), 2.27 (1H, br s), 1.66–1.43 (4H, m), 1.14 (1H, d further split, *J* = 9.8 Hz). ^{13}C NMR (100 MHz): δ 146.4, 143.6, 134.2, 132.5, 130.6 (q, *J*C,F = 27.2 Hz), 126.8, 126.2, 124.7 (q, *J*C,F = 272.9 Hz), 124.4, 122.9 (q, *J*C,F = 4.4 Hz), 122.5, 120.5 (q, *J*C,F = 6.7 Hz), 119.9, 53.2, 50.8, 48.9, 45.6, 38.4, 31.2, 29.8. IR (ATR diamond, cm^{-1}): ν 3363, 2954, 2873, 1494, 1308, 1184, 1090, 961, 745. MS: *m/z* 329 (M+, 52), 262 (50), 248 (100). Anal. Calcd. for $C_{20}H_{18}F_3N$: C, 72.93; H, 5.51; F, 17.30; N, 4.25. Found: C, 72.79; H, 5.47.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-trifluoromethyl-9H-tribenzo[b,f]azepine (3c): Yield: 67% (97 mg); reaction time: 24 h; white solid; m.p. (hexane): 130–131 °C. Eluent: Hexane/EtOAc 98:2. ^{1}H NMR (400 MHz): δ 7.34 (1H, d, *J* = 8.0 Hz), 7.28 (1H, dd, *J* = 7.6, 1.6 Hz), 7.19 (1H, dd,*J* = 8.0, 0.8

Hz), 7.13, 7.10 (2H, 2 partly overlapping signals: td, *J* = 7.6, 1.6 Hz and br s),6.99 (1H, td, *J* = 7.6, 1.2 Hz), 6.85 (1H, dd, *J* = 8.0, 1.2 Hz), 5.25 (1H, br s), 3.29–3.18 (2H,m), 2.67 (1H, d further split, *J* = 9.6 Hz), 2.40, 2.37 (2H, 2 partly overlapping signals: 2 br s), 1.70–1.57 (4H, m), 1.19 (1H, d further split, *J* = 9.6 Hz). ^{13}C NMR (100 MHz): δ 144.7, 143.7, 137.5, 133.5, 133.2, 132.7, 128.8 (q, *J*C,F = 32.1 Hz), 126.9, 124.1 (q, *J*C,F = 270.3 Hz), 122.5, 120.1, 118.3 (q, *J*C,F = 3.7 Hz), 116.7 (q, *J*C,F = 3.6 Hz), 53.1, 52.7, 49.6, 49.4, 37.5, 30.68, 30.67. IR (ATR diamond, cm^{-1}): ν 3363, 2944, 2871, 1517, 1473, 1159, 1083, 829, 752. MS: *m/z* 329 (M+, 97), 262 (96), 248 (100). Anal. Calcd. for $C_{20}H_{18}F_3N$: C, 72.93; H, 5.51; F, 17.30; N, 4.25. Found: C, 73.14; H, 5.58.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6-chloro-9H-tribenzo[b,f]azepine (3d): Yield: 90% (117 mg); reaction time: 40 h; white solid; m.p. (hexane): 196–197 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.24–7.17 (2H, m), 7.07 (1H, t further split, *J* = 7.5 Hz), 6.99 (1H, dd, *J* = 8.3, 2.3 Hz), 6.92 (1H, t further split, *J* = 7.2 Hz), 6.78 (1H, d, *J* = 7.8 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 5.07 (1H, br s), 3.14 (1H, d, *J* = 9.4 Hz), 3.07 (1H, d, *J* = 9.4 Hz), 2.60 (1H, d, *J* = 9.7 Hz), 2.33 (2H, br s), 1.65–1.46 (4H, m), 1.12 (1H, d, *J* = 9.7 Hz). ^{13}C NMR (100 MHz): δ 144.1, 143.2, 135.4, 133.4, 132.6, 132.0, 126.7, 126.5, 126.3, 122.2, 121.1, 119.9, 52.9, 52.8, 49.31, 49.26, 37.4, 30.7, 30.6. IR (ATR diamond, cm^{-1}): ν 3368, 2918, 2849, 1580, 1472, 1306, 1129, 954, 895, 745. MS: *m/z* 297 (M+, 35), 295 (99), 230 (36), 228 (100), 216 (36), 214 (99), 191 (15), 179 (10). Anal. Calcd. for $C_{19}H_{18}ClN$: C, 77.15; H, 6.13; Cl, 11.98; N, 4.74. Found: C, 77.25; H, 6.08.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-5-chloro-9H-tribenzo[b,f]azepine (3e): Yield: 52% (67 mg); reaction time: 20 h; white solid; m.p. (hexane): 124–125 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.24 (1H, d, *J* = 7.6 Hz), 7.14–7.06 (2H, m), 6.97 (2H, t, *J* = 7.6 Hz), 6.81 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 7.6 Hz), 5.16 (1H, br s), 3.86 (1H, d, *J* = 9.6 Hz), 3.19 (1H, d, *J* = 9.6 Hz), 2.68 (1H, d further split, *J* = 9.6 Hz), 2.36 (2H, br s), 1.74–1.55 (4H, m), 1.20 (1H, d further split, *J* = 9.6 Hz). ^{13}C NMR

(100 MHz): δ 145.7, 143.7, 136.7, 133.7, 132.6, 131.8, 126.8, 126.6, 123.5, 122.4, 119.8, 118.9, 52.7, 49.8, 48.5, 47.6, 38.3, 31.4,
30.2. IR (ATR diamond, cm^{-1}): ν 3366, 2953, 2866, 1488, 1441, 1295, 1252, 926, 764. MS: *m/z* 297 (M+, 22), 295 (61), 230 (22), 228 (58), 216 (36), 214 (100), 191 (10). Anal. Calcd. for $C_{19}H_{18}ClN$: C, 77.15; H, 6.13; Cl, 11.98; N, 4.74. Found: C, 77.32; H, 6.09.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-chloro-9H-tribenzo[b,f]azepine (3f): Yield: 69% (90 mg); reaction time: 40 h; white solid; m.p. (hexane): 177–178 °C. Eluent: Hexane/EtOAc 98:2.
^{1}H NMR (400 MHz): δ 7.23 (1H, d, *J* = 7.6 Hz), 7.14 (1H, d, *J* = 8.0 Hz), 7.09 (1H, t, *J* = 7.5 Hz), 6.95 (1H, t, *J* = 7.5 Hz), 6.88 (1H, d, *J* = 8.0 Hz), 6.83 (1H, s), 6.80 (1H, d, *J* = 7.6 Hz), 5.09 (1H, br s), 3.14 (2H, m), 2.61 (1H, d, *J* = 9.6 Hz), 2.34, 2.30 (2H, 2 partly overlapping signals: 2 br s), 1.68–1.50 (4H, m), 1.14 (1H, d *J* = 9.6 Hz). ^{13}C NMR (100 MHz): δ 145.4, 143.8, 133.8, 133.6, 132.7, 132.2, 131.3, 126.7, 122.3, 121.8, 120.0, 119.7, 52.8, 52.6, 49.5, 49.3, 37.4, 30.7, 30.6. IR (ATR diamond, cm-1): ν 3359, 2945, 2866, 1577, 1473, 1306, 1244, 746. MS: *m/z* 297 (M+, 32), 295 (87), 230 (36), 228 (100), 216 (36), 214 (99), 191 (15). Anal. Calcd. for $C_{19}H_{18}ClN$: C, 77.15; H, 6.13; Cl, 11.98; N, 4.74. Found: C, 77.40; H, 6.22.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6-carbomethoxy-9H-tribenzo[b,f]azepine (3g)*:* Yield: 74% (104 mg); reaction time: 90 h; Eluent: Hexane/EtOAc 95:5[32].

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-carbomethoxy-9H-tribenzo[b,f]azepine (3h)*:* Yield: 65% (91 mg); reaction time: 42 h; white solid; m.p. (hexane): 170–171 °C. Eluent: Hexane/EtOAc 95:5.
^{1}H NMR (400 MHz): δ 7.56–7.51 (2H, m), 7.26 (1H, d, *J* = 7.6 Hz), 7.21 (1H, dd, *J* = 8.0, 1.2 Hz), 7.07 (1H, td, *J* = 7.2, 1.6 Hz), 6.92 (1H, td, *J* = 7.6, 1.2 Hz), 6.82 (1H, dd, *J* = 7.6, 1.2 Hz), 5.28 (1H, br s), 3.92 (3H, s), 3.20 (1H, d, *J* = 9.6 Hz), 3.15 (1H, d, *J* = 9.6 Hz), 2.63 (1H, d further split, *J* = 9.8 Hz), 2.34, 2.32 (2H, 2 partly overlapping singlets), 1.63–1.49 (4H, m), 1.13 (1H, d further split, *J* = 9.8

Hz). ^{13}C NMR (100 MHz): δ 166.8, 144.5, 144.0, 139.0, 133.4, 132.7, 132.6, 128.3, 126.8, 122.7, 122.2, 121.1, 120.0, 53.2, 52.8, 52.0, 49.6, 49.3, 37.5, 30.7. IR (ATR diamond, cm^{-1}): ν 3356, 2949, 2864, 1696, 1584, 1484, 1368, 1241, 1034, 755. MS: *m/z* 319 (M+, 100), 252 (88), 251 (22), 239 (15), 238 (86), 192 (19). Anal. Calcd. for $C_{21}H_{21}$NO2: C, 78.97; H, 6.63; N, 4.39; O, 10.02. Found: C, 78.09; H, 6.56.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6-bromo-9H-tribenzo[b,f]azepine (3i): Yield: 54% (81 mg); reaction time: 40 h; white solid; m.p. (hexane): 193–194 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.34 (1H, s), 7.20 (1H, d, *J* = 7.6 Hz), 7.13 (1H, d further split, *J* = 8.2 Hz), 7.06 (1H, t, *J* = 7.5 Hz), 6.92 (1H, t, *J* = 7.5 Hz), 6.78 (1H, d, *J* = 7.6 Hz), 6.67 (1H, d, *J* = 8.2 Hz), 5.08 (1H, br s), 3.13 (1H, d, *J* = 9.6 Hz), 3.07 (1H, d, *J* = 9.6 Hz), 2.59 (1H, d, *J* = 9.8 Hz), 2.34, 2.32 (2H, 2 partly overlapping singlets), 1.65–1.45 (4H, m), 1.12 (1H, d, *J* = 9.8 Hz). ^{13}C NMR (100 MHz): δ 144.0, 143.7, 135.8, 134.9, 133.4, 132.6, 129.2, 126.7, 122.2, 121.5, 119.9, 114.0, 52.9, 52.8, 49.4, 49.3, 37.4, 30.7, 30.6. IR (ATR diamond, cm^{-1}): ν 3367, 2964, 2866, 1577, 1473, 1303, 1248, 1127, 814, 745. MS: *m/z* 341 (M+, 100), 339 (98), 276 (75), 274 (77), 260 (80), 258 (78), 191 (25). Anal. Calcd. for $C_{19}H_{18}BrN$: C, 67.07; H, 5.33; Br, 23.48; N, 4.12. Found: C, 67.25 ;H, 5.26.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-bromo-9H-tribenzo[b,f]azepine (3j): Yield: 56% (84 mg); reaction time: 40 h; white solid; m.p. (hexane): 199–200 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.20 (1H, dd, *J* = 7.6, 1.2 Hz), 7.09–7.04 (2H, m), 7.00 (1H, dd, *J* = 8.0, 2.0 Hz), 6.97 (1H, d, *J* = 2.0 Hz), 6.92 (1H, td, *J* = 7.6, 1.2 Hz), 6.78 (1H, dd, *J* = 8.0, 0.8 Hz), 5.07 (1H, br s), 3.15–3.05 (2H, m), 2.58 (1H, d further split, *J* = 9.6 Hz), 2.31, 2.28 (2H, 2 partly overlapping singlets), 1.63–1.46 (4H, m), 1.11 (1H, d, *J* = 9.6 Hz). ^{13}C NMR (100 MHz): δ 145.7, 143.7, 134.0, 133.6, 132.7, 132.6, 126.7, 124.7, 122.5, 122.3, 120.0,

119.1, 52.7, 52.6, 49.4, 49.3, 37.3, 30.7, 30.6. IR (ATR diamond, cm^{-1}): ν 3354, 2943, 2867, 1575, 1471, 1255, 1116, 915, 747. MS: *m/z* 341 (M+, 96), 339 (95), 298 (10), 274 (98), 272 (100), 261 (95), 259 (94), 191 (30), 179 (25), 165 (17). Anal. Calcd. for $C_{19}H_{18}BrN$: C, 67.07; H, 5.33; Br, 23.48; N, 4.12. Found: C, 66.83; H, 5.28.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-fluoro-9H-tribenzo[b,f]azepine (3k): Yield: 59% (72 mg); reaction time: 40 h; white solid; m.p. (hexane): 175–176 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.40 (1H, br s), 7.16–7.09 (2H, m), 7.08–6.98 (2H, m), 6.91 (1H, dd, *J* = 10.8, 2.7 Hz), 6.81 (1H, td, *J* = 7.6, 1.7 Hz), 6.59 (1H, td, *J* = 8.3, 2.7 Hz), 3.10–3.00 (2H, m), 2.44 (1H, d, *J* = 9.4 Hz), 2.10, 2.07 (2H, 2 partly overlapping signals: 2 br s), 1.49–1.36 (4H, m), 0.97 (1H, d *J* = 9.4 Hz). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 160.8 (d, *J*C,F = 240.0 Hz), 146.9 (d, *J*C,F = 9.4 Hz), 144.9, 134.1 (d, *J*C,F = 9.1 Hz), 133.3, 132.7, 129.4 (d, *J*C,F = 2.8 Hz), 126.8, 121.6, 120.4, 107.6 (d, *J*C,F = 20.1 Hz), 106.4 (d, *J*C,F = 21.9 Hz), 52.5, 52.0, 49.9, 49.8, 37.2, 30.4, 30.3. IR (ATR diamond, cm^{-1}): ν 3368, 2956, 1608, 1473, 1184, 986, 752. MS: *m/z* 279 (M+, 97), 212 (90), 198 (100), 183 (8). Anal. Calcd. for $C_{19}H_{18}FN$: C, 81.69; H, 6.49; F, 6.80; N, 5.01. Found: C, 81.51; H, 6.57.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6-chloro-12-methyl-9Htribenzo[b,f]azepine (3l): Yield: 87% (118 mg); reaction time: 48 h; white solid; m.p. (hexane): 228–229 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.21 (1H, s), 7.18 (1H, s further split), 7.05–6.99 (2H, m), 6.94 (1H, d, *J* = 1.5 Hz), 6.91 (1H, d, *J* = 8.0 Hz), 6.80 (1H, dd, *J* = 8.0, 1.5 Hz), 3.04 (1H, d, *J* = 9.3 Hz), 2.98 (1H, d, *J* = 9.3 Hz), 2.45 (1H, d, *J* = 9.4 Hz), 2.17 (3H, s), 2.11 (2H, s), 1.50–1.35 (4H, m), 0.98 (1H, d, *J* = 9.4 Hz). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 145.0, 142.7, 135.3, 133.0, 132.9, 131.7, 130.1, 127.4, 126.4, 124.4, 121.9, 120.4, 52.3, 49.8, 49.7, 37.3, 30.4, 30.3, 20.6. IR (ATR diamond, cm^{-1}): ν 3365, 2957, 1458, 1254, 819, 649. MS: *m/z* 311 (M+, 36), 309 (100), 244 (33), 242 (94), 229 (15), 230 (29), 228 (83), 204 (10). Anal. Calcd. for $C_{20}H_{20}ClN$: C, 77.53; H, 6.51; Cl, 11.44; N, 4.52. Found: C, 77.41; H, 6.57.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-6,12-dichloro-9H-tribenzo[b,f]azepine (3m): Yield: 62% (90 mg); reaction time: 48 h; white solid; m.p. (hexane): 232–233 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.49 (1H, s), 7.20 (2H, s), 7.04 (4H, further split s), 3.03 (2H, s), 2.37 (1H, d, *J* = 9.5 Hz), 2.10 (2H, s), 1.48–1.43 (4H, m), 0.98 (1H, d, *J* = 9.5 Hz). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 144.0, 135.1, 131.8, 126.6, 124.9, 122.1, 51.9, 49.9, 37.3, 30.2. IR (ATR diamond, cm^{-1}): ν 3373, 2949, 1476, 1255, 1129, 818, 635. MS: *m/z* 331 (M+, 65), 329 (100), 264 (65), 262 (97), 250 (62), 248 (94), 227 (13), 213 (12), 190 (17). Anal. Calcd. for $C_{19}H_{17}Cl_2N$: C, 69.10; H, 5.19; Cl, 21.47; N, 4.24. Found: C, 69.33; H, 5.17.

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-9H-tribenzo[b,f]azepine (3n): Yield: 80% (92 mg); reaction time: 18 h; white solid; Eluent: Hexane/EtOAc 98:2[32].

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-5-methyl-9H-tribenzo[b,f]azepine (3o): Yield: 51% (61 mg); reaction time: 18 h; white solid; Eluent: Hexane/EtOAc 98:2[32].

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-7-methyl-9H-tribenzo[b,f]azepine (3p): Yield: 64% (77 mg); reaction time: 24 h; white solid; Eluent: Hexane/EtOAc 98:2[32].

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-5-methoxy-9H-tribenzo[b,f]azepine (3q): Yield: 38% (49 mg); reaction time: 42 h; white solid; Eluent: Hexane/EtOAc 98:2[32].

cis,exo-1,2,3,4,4a,13b-Hexahydro-1,4-methano-9H-tribenzo[b,f]azepine (3r): Yield: 48% (61 mg); reaction time: 42 h; white solid; Eluent: Hexane/EtOAc 98:2[32].

1,2,3,4,4a,13b-Hexahydro-1,4-methano-5-amino-9H-tribenzo[b,f]azepine (3s) Yield: 32% (20 mg); white solid; m.p. (hexane): 192–193 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (400 MHz): δ 7.16 (1H, d, *J* = 7.6 Hz), 7.05 (1H, t further split, *J* = 7.6 Hz), 6.88, 6.86 (2H, 2 partly overlapping signals: t further split, *J* = 7.6 Hz and t, *J* = 8.0 Hz), 6.77 (1H, d, *J* = 7.6 Hz), 6.37 (1H, d, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 8.0 Hz), 5.05 (1H, br s), 3.71 (2H, br s), 3.16–3.06 (2H, m), 2.67 (1H, d further split, *J* = 9.6 Hz), 2.30 (2H, br s), 1.73–1.47 (4H, m), 1.19 (1H, d further split, *J* = 9.6 Hz). ^{13}C NMR (100 MHz): δ 145.9, 144.8, 144.3, 133.1, 132.3, 126.7, 126.5, 121.8, 119.6, 119.4, 111.1, 110.2, 53.1, 48.7, 47.2, 44.9, 38.6, 31.9, 29.7. IR (ATR diamond, cm^{-1}): ν 3352, 3308 2952, 2913, 1601, 1592, 1523, 1476, 1265, 1230, 850, 749. MS: *m/z* 276 (M+, 52), 209 (64), 195 (100), 180 (18). Anal. Calcd. for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.71; H, 7.32.

cis,exo-6,11-bis(trifluoromethyl)-1,2,3,4,4a,12b-hexahydro-1,4-methanotriphenylene (4a) and cis,exo-6,10-bis(trifluoromethyl)-1,2,3,4,4a,12b-hexahydro-1,4-methanotriphenylene (4a'): Yield 67% (total yield **4a**+**4a'**, 61 mg); reaction time: 24 h; yellowish oil; Eluent: Hexane/EtOAc 98:2. Compound **4a** and **4a'** were obtained in 4 to 1 molar ratio. Only the most abundant isomer **4a** has been fully characterized:

^{1}H NMR (400 MHz, CDCl3): δ 7.94 (2H, d, *J* = 8.4 Hz), 7.51 (2H, s), 7.46 (2H, d, *J* = 8.4 Hz), 3.29 (2H, s), 2.41 (2H, s), 1.79–1.72 (2H, m), 1.71–1.64 (2H, m), 1.34 (1H, d, *J* = 10.2 Hz), 1.11 (1H, d, *J* = 10.2 Hz). ^{13}C NMR (101 MHz, CDCl3): δ 139.0, 133.6, 130.7 (q, *J* = 32.4 Hz), 127.3 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 272.2 Hz), 123.4 (q, *J* = 3.7 Hz), 123.2, 49.9, 45.9, 33.4, 30.3. ^{19}F NMR (376 MHz, CDCl3): δ -62.83. MS: *m/z* 382 (M+, 27), 363 (18), 314 (100), 295 (24). Isomer **4a'**: ^{1}H NMR (400 MHz, CDCl3): δ 7.79 (d, *J* = 8.5 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.50–7.39 (m, 3H), 7.35 (dd, *J* = 7.7, 1.1 Hz, 1H), 3.33 (d, *J* = 9.7 Hz, 1H), 3.19 (d, *J* = 9.7 Hz, 1H), 2.50 (s, 1H), 2.19 (s, 1H), 1.83–1.60 (m, 4H), 1.26 (d further split, *J* = 10.3 Hz, 1H), 1.05 (d further split, *J* = 10.3 Hz, 1H). MS: *m/z* 382 (M+, 29), 314 (100), 225 (34).

cis,exo-4,4a,9,13b-Tetrahydro-1H-1,4-methano-7-chloro-tribenzo[b,f]azepine (5o'): Yield: 60% (77 mg); white solid; m.p. (hexane): 185–186 °C. Eluent: Hexane/EtOAc 98:2.

^{1}H NMR (400 MHz): δ 7.24 (1H, br d, *J* = 7.6 Hz), 7.15 (1H, d, *J* = 8.4 Hz), 7.07 (1H, br t, *J* = 7.6 Hz), 6.93 (1H, br t, *J* = 7.6 Hz), 6.87 (1H, dd, *J* = 8.0, 2.0 Hz), 6.81 (1H, d, *J* = 2.0 Hz), 6.78 (1H, br d, *J* = 7.6 Hz), 6.43–6.37 (2H, m), 5.18 (1H, br s), 3.04–2.96 (2H, m), 2.88 (1H, br s), 2.84 (1H, br s), 2.72 (1H, br d, *J* = 8.8 Hz), 1.31 (1H, br d, *J* = 8.8 Hz). ^{13}C NMR (100 MHz): δ 144.4, 142.8, 139.3, 139.0, 134.2, 133.1, 132.2, 131.5, 130.9, 126.7, 122.4, 121.8, 120.0, 119.6, 55.5, 55.4, 46.6, 46.5, 46.4. IR (ATR diamond, cm^{-1}): ν 3371, 2951, 1474, 1259, 1127, 1040, 821. MS: *m/z* 229 ((M-66)+, 46), 227 ((M-66)+, 100), 191 (28), 165 (19). Anal. Calcd. for $C_{19}H_{16}ClN$: C, 77.68; H, 5.49; Cl, 12.07; N, 4.77. Found: C, 77.29; H, 5.44.

1-Fluoro-5H-dibenzo[b,f]azepine (5a): Yield: 65% (60 mg); reaction time: 90 h at 105 °C; yellow solid; m.p. (hexane): 113–114 °C. Eluent: Hexane/EtOAc 95:5. ^{1}H NMR (400 MHz): δ 7.08 (1H, ddd, *J* = 8.0, 6.8, 2.4 Hz), 7.01 (1H, dt, *J* = 8.0, 6.0 Hz), 6.95–6.86 (2H, m), 6.59, 6.58 (2H, 2 overlapping signals: dd, *J* = 12.0, 1.2 Hz and ddd, *J* = 9.6, 8.4, 1.2 Hz), 6.53 (1H, d further split, *J* = 7.6 Hz), 6.45 (1H, d, *J* = 12.0 Hz), 6.32 (1H, d further split, *J* = 8.0 Hz), 5.06 (1H, br s). ^{13}C NMR (100 MHz): δ 160.7 (d, *J*C,F = 246.8 Hz), 151.0 (d, *J*C,F = 5.3 Hz), 148.0, 133.1 (d, *J*C,F = 1.7 Hz), 130.6, 130.1 (d, *J*C,F = 10.7 Hz), 129.8, 129.6, 123.8 (d, *J*C,F = 8.0 Hz), 123.4, 119.6, 118.0 (d, *J*C,F = 14.5 Hz), 114.8 (d, *J*C,F = 2.7 Hz), 109.7 (d, *J*C,F = 22.8 Hz). IR (ATR diamond, cm^{-1}): ν 3365, 2976, 1616, 1437, 1224, 1019, 722. MS: *m/z* 211 (M+, 100), 183 (14). Anal. Calcd. for $C_{14}H_{10}FN$: C, 79.60; H, 4.77; F, 8.99; N, 6.63. Found: C, 79.72; H, 4.72.

1-Nitro-3-methoxy-5H-dibenzo[b,f]azepine (5b): Yield: 60% (71 mg); reaction time: 90 h at 105 °C; red solid; m.p. (hexane): 126–127 °C. Eluent: Hexane/EtOAc 70:30.

^{1}H NMR (400 MHz): δ 7.13 (1H, td, *J* = 6.8, 2.0 Hz), 7.30–6.95 (2H, m), 6.90 (1H, d, *J* = 2.8 Hz), 6.62 (1H, d, *J* = 7.6 Hz), 6.58 (1H, d, *J* = 12.0 Hz), 6.49 (1H, d, *J* = 12.0 Hz), 6.39 (1H, d, *J* = 2.8 Hz), 5.22 (1H, br s), 3.82 (3H, s). ^{13}C NMR (100 MHz): δ 160.1, 153.4, 150.6, 147.5, 133.0, 130.4, 129.9, 129.6, 126.1, 124.1, 119.8, 116.9, 109.9, 103.4, 55.8. IR (ATR diamond, cm^{-1}): ν 3371, 2918, 1526, 1147, 1051, 748. MS: *m/z* 268 (M+, 31), 239 (14), 209 (100), 178 (23).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.25; H, 4.46.

2-Chloro-5H-dibenzo[b,f]azepine (5c): Yield: 67% (67 mg); reaction time: 90 h at 105 °C; yellow solid; m.p. (hexane): 166–167 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 7.04 (1H, ddd, *J* = 7.8, 6.0, 3.0 Hz), 6.96 (1H, dd, *J* = 8.1, 2.7 Hz), 6.87–6.80 (3H, m), 6.47 (1H, d further split, *J* = 8.1 Hz), 6.41 (1H, d, *J* = 8.1 Hz), 6.34 (1H, d, *J* = 11.7 Hz), 6.20 (1H, d, *J* = 11.7 Hz), 4.90 (1H, br s). ^{13}C NMR (100 MHz): δ 148.1, 146.9, 133.4, 131.4, 130.8, 129.9, 129.8, 129.4, 128.9, 128.0, 123.3, 120.4, 119.4. IR (ATR diamond, cm^{-1}): v 3366, 3057, 2976, 1608, 1464, 1247, 1122, 892, 784. MS: *m/z* 229 (M+, 34), 227 (100), 191 (23), 165 (15). Anal. Calcd. for C14H10ClN: C, 73.85; H, 4.43; Cl, 15.57; N, 6.15. Found: C, 74.08; H, 4.39.

2-Chloro-8-methyl-5H-dibenzo[b,f]azepine (5d): Yield: 68% (73 mg); reaction time: 50 h at 105 °C; yellow solid; m.p. (hexane): 193–194 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 6.96 (1H, dd, *J* = 8.4, 2.4 Hz), 6.85, 6.82 (2H, 2 partly overlapping signals: dd, *J* = 7.8, 1.5 Hz and d, *J* = 2.4 Hz), 6.68 (1H, d, *J* = 1.5 Hz), 6.41, 6.39 (2H, 2 partly overlapping signals: d, *J* = 8.4 Hz and d, *J* = 7.8 Hz), 6.32 (1H, d, *J* = 11.7 Hz), 6.21 (1H, d, *J* = 11.7 Hz), 4.85 (1H, br s), 2.18 (3H, s). ^{13}C NMR (100 MHz): δ 147.2, 145.4, 133.4, 132.6, 131.3, 131.2, 130.7, 130.2, 129.9, 129.2, 128.8, 127.8, 120.2, 119.3, 20.3. IR (ATR diamond, cm^{-1}): v 3355, 3025, 2918, 1472, 1253, 1157, 1124, 814, 736. MS: *m/z* 243 (M+, 35), 241 (100), 204 (13). Anal. Calcd. for $C_{15}H_{12}ClN$: C, 74.54; H, 5.00; Cl, 14.67; N, 5.79. Found: C, 74.73; H, 5.08.

2-Chloro-7-methyl-5H-dibenzo[b,f]azepine (5e): Yield: 72% (76 mg); reaction time: 48 h at 105 °C; yellow solid; m.p. (hexane): 188–189 °C. Eluent: Hexane/EtOAc 95:5.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 6.97, 6.97 (2H, 2 overlapping signals: dd, *J* = 8.4, 2.4 Hz and s), 6.78 (1H, d, *J* = 2.4 Hz), 6.63 (1H, d, *J* = 7.6), 6.58 (1H, d, *J*

= 8.4 Hz), 6.51 (1H, d further split, *J* = 7.6 Hz), 6.41 (1H, br s), 6.06 (1H, d, *J* = 12.0 Hz), 5.95 (1H, d, *J* = 12.0 Hz), 2.10 (3H, s). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 149.4, 148.6, 140.0, 133.8, 131.5, 131.2, 130.0, 129.9, 129.2, 126.4, 125.9, 123.1, 120.8, 120.2, 21.0. IR (ATR diamond, cm^{-1}): ν 3352, 3026, 2923, 1470, 1253, 1152, 1126, 826, 731; MS: *m/z* 243 (M+, 34), 241 (100), 204 (15). Anal. Calcd. for $C_{15}H_{12}ClN$: C, 74.54; H, 5.00; Cl, 14.67; N, 5.79. Found: C, 74.69; H, 5.04.

2-Chloro-8-isopropyl-5H-dibenzo[b,f]azepine (5f): Yield: 74% (87 mg); reaction time: 68 h at 105 °C; pale orange solid; m.p. (hexane): 170–171 °C. Eluent: Hexane/EtOAc 97:3.

^{1}H NMR (300 MHz): δ 6.98 (1H, dd, *J* = 8.4, 2.4 Hz), 6.95 (1H, dd, *J* = 8.0, 2.0 Hz), 6.85 (1H, d, *J* = 2.4 Hz), 6.77 (1H, d, *J* = 2.4 Hz), 6.46, 6.43 (2H, 2 partly overlapping signals: d, *J* = 8.0 Hz and d, *J* = 8.4 Hz), 6.39 (1H, d, *J* = 11.6 Hz), 6.25 (1H, d, *J* = 11.6 Hz), 4.91 (1H, br s), 2.79 (1H, heptet, *J* = 6.8 Hz), 1.21 (6H, d, *J* = 6.8 Hz). ^{13}C NMR (100 MHz): δ 147.2, 145.7, 143.9, 133.6, 131.4, 130.6, 129.8, 129.2, 128.8, 128.7, 127.8, 127.6, 120.3, 119.4, 33.1, 23.9. IR (ATR diamond, cm^{-1}): ν 3360, 2958, 1502, 1463, 1256, 1122, 896, 785. MS: *m/z* 271 (M+, 25), 269 (71), 256 (34), 254 (100), 219 (18), 191 (8). Anal. Calcd. for $C_{17}H_{16}ClN$: C, 75.69; H, 5.98; Cl, 13.14; N, 5.19. Found: C, 75.89; H, 5.94.

2,8-Dichloro-5H-dibenzo[b,f]azepine (5g): Yield: 47% (54 mg); reaction time: 66 h at 105 °C; pale orange solid; m.p. (hexane): 151–152 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 6.98 (2H, dd, *J* = 8.4, 2.4 Hz), 6.81 (2H, d, *J* = 2.4 Hz), 6.39 (2H, d, *J* = 8.4 Hz), 6.22 (2H, s), 4.87 (1H, br s). ^{13}C NMR (100 MHz): δ 146.6, 132.1, 131.0, 130.1, 129.2, 128.3, 120.4. IR (ATR diamond, cm^{-1}): ν 3352, 2958, 1466, 1378, 1259, 1243, 1127, 78. MS: *m/z* 263 (M+, 70), 262 (20), 261 (100), 226 (13), 207 (10), 190 (22). Anal. Calcd. for $C_{14}H_{9}Cl_{2}N$: C, 64.15; H, 3.46; Cl, 27.05; N, 4.33. Found: C, 63.97; H, 3.51.

2-Carbomethoxy-8-chloro 5H-dibenzo[b,f]azepine (5h): Yield: 82% (102 mg); reaction time: 46 h at 105 °C; yellow solid; m.p. (hexane): 186–187 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 7.65 (1H, dd, *J* = 8.4, 2.0 Hz), 7.45 (1H, d, *J* = 2.0 Hz), 6.94 (1H, dd, *J* = 8.4, 2.4 Hz), 6.75 (1H, d, *J* = 2.4 Hz), 6.39 (1H, d, *J* = 8.0 Hz), 6.33 (1H, d, *J* = 8.0 Hz), 6.16 (1H, d, *J* = 12.0 Hz), 6.06 (1H, d, *J* = 12.0 Hz), 5.12 (1H, br s), 3.86 (3H, s). ^{13}C NMR (100 MHz): δ 166.3, 152.6, 145.4, 132.8, 132.7, 131.5, 131.2, 130.7, 130.4, 129.2, 128.4, 128.3, 124.6, 120.3, 118.8, 51.9. IR (ATR diamond, cm^{-1}): ν 3361, 2945, 1695, 1475, 1428, 1296, 1118, 752, 690; MS: *m/z* 285 (M+, 100), 254 (16), 226 (29), 190 (17), 95 (10). Anal. Calcd. for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; Cl, 12.41; N, 4.90. Found: C, 67.12; H, 4.30.

3-Carbomethoxy-7-carboethoxy-5H-dibenzo[b,f]azepine (5i): Yield: 50% (71 mg); reaction time: 64 h at 105 °C; red solid; m.p. (hexane): 164–165 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 7.47, 7.46 (2H, 2 overlapping signals: 2 dd, *J* = 7.8, 1.5 Hz), 7.23, 7.22 (2H, 2 overlapping signals: 2 d, *J* = 1.5 Hz), 6.87 (2H, d, *J* = 7.8 Hz), 6.34 (2H, s), 5.45 (1H, br s), 4.33 (2H, q, *J* = 7.2 Hz), 3.87 (3H, s), 1.36 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz): δ 166.6, 166.1, 148.4, 148.3, 134.1, 134.0, 133.4, 133.2, 131.7, 131.2, 130.7, 130.6, 124.4, 120.4, 120.3, 61.1, 52.2, 14.3. IR (ATR diamond, cm^{-1}): ν 3354, 2945, 2918, 2863, 1723, 1710, 1467, 1433, 1381, 1118, 1025, 1098, 746. MS: *m/z* 323 (M+, 100), 295 (65), 236 (21), 190 (15). Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.47; H, 5.27.

3-Carbo-tert-butoxy-7-carboethoxy-5H-dibenzo[b,f]azepine (5j): Yield: 56% (90 mg); reaction time: 64 h at 105 °C; brown solid; m.p. (hexane): 132–133 °C. Eluent: Hexane/EtOAc 95:5.

^{1}H NMR (400 MHz): δ 7.49 (1H, d further split, *J* = 8.0 Hz), 7.44 (1H, d further split, *J* = 8.0 Hz), 7.27 (1H, s further split), 7.18 (1H, s further split), 6.89, 6.87 (2H, 2 partly overlapping signals: d further split, *J* = 8.0 Hz and d further split, *J* = 8.0 Hz), 6.39–6.33 (2H, m), 5.48 (1H, br s), 4.36 (2H, q, *J* = 6.8 Hz), 1.58 (9H, s), 1.38 (3H, t, *J* = 6.8 Hz). ^{13}C NMR (100 MHz): δ 166.1, 165.1, 148.4, 148.2, 134.1, 133.6, 133.4, 133.2, 133.0, 131.5, 130.6, 130.5, 124.33, 124.30, 120.3, 120.2, 81.2, 61.1, 28.2, 14.3. IR (ATR diamond, cm^{-1}): ν 3362, 2976, 1711, 1701, 1382, 1275, 1101, 751. HR-MS: 388.1514 ([$C_{22}H_{23}NO_4$ + Na^+] calcd 388.1519). Anal. Calcd. for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.06; H, 6.25.

2-Carbomethoxy-7-carboethoxy-5H-dibenzo[b,f]azepine (5k): Yield: 72% (102 mg); reaction time: 46 h at 105 °C; red solid; m.p. (hexane): 154–155 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz): δ 7.65 (1H, dd, *J* = 8.0, 2.0 Hz), 7.47–7.41 (2H, m), 7.10 (1H, d, *J* = 1.6 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 6.43 (1H, d, *J* = 8.0 Hz), 6.19 (1H, d, *J* = 12.0 Hz), 6.12 (1H, d, *J* = 12.0 Hz), 5.42 (1H, br s), 4.34 (2H, q, *J* = 7.2 Hz), 3.86 (3H, s), 1.38 (3H, t, *J* = 7.2 Hz). ^{13}C NMR (100 MHz): δ 166.3, 166.0, 152.8, 147.0, 133.8, 133.7, 132.8, 131.7, 131.5, 131.4, 130.8, 128.4, 124.5, 124.4, 120.1, 118.8, 61.1, 51.9, 14.3. IR (ATR diamond, cm^{-1}): ν 3358, 2984, 1700, 1600, 1479, 1289, 1196, 1127, 1103, 1017, 767, 737. MS: *m/z* 323 (M+, 100), 295 (74), 236 (25), 190 (18). Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.32; H, 5.35.

2-Trifluoromethyl-8-methyl-5H-dibenzo[b,f]azepine (5l): Yield: 58% (70 mg); reaction time: 68 h at 105 °C; yellow solid; m.p. (hexane): 202–203 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (400 MHz): δ 7.23 (1H, dd, *J* = 8.4, 1.2 Hz), 7.05 (1H, d, *J* = 1.6 Hz), 6.86 (1H, dd, *J* = 8.0, 1.6 Hz), 6.67 (1H, d, *J* = 1.6 Hz), 6.49 (1H, d, *J* = 8.0 Hz), 6.37 (1H, d, *J* = 8.0 Hz), 6.28 (1H, d, *J* = 11.6 Hz), 6.20 (1H, d, *J* = 11.6 Hz), 5.01 (1H, br s), 2.20 (3H, s). ^{13}C NMR (100 MHz): δ 151.9, 144.6, 133.4, 132.9, 131.5, 130.9, 130.4, 129.6, 129.0, 127.6 (q, *J*C,F = 3.7 Hz), 126.3 (q, *J*C,F = 3.7 Hz), 124.8 (q, *J*C,F = 32.6 Hz), 124.1 (q, *J*C,F = 269.6 Hz), 119.3, 118.9, 20.2. IR (ATR diamond, cm^{-1}): ν 3365, 2927, 1606, 1484, 1321, 1114, 792; MS: *m/z* 275 (M+, 100), 204 (7). Anal. Calcd. for $C_{16}H_{12}F_3N$: C, 69.81; H, 4.39; F, 20.70; N, 5.09. Found: C, 69.69; H, 4.44.

3-Cyano-8-chloro-5H-dibenzo[b,f]azepine (5m): Yield: 66% (73 mg); reaction time: 68 h at 105 °C; red solid; m.p. (hexane): 212–213 °C. Eluent: Hexane/EtOAc 95:5.

^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.35 (1H, br s), 7.13 (1H, dd, *J* = 7.8, 1.6 Hz), 7.06 (1H, dd, *J* = 8.5, 2.5 Hz), 6.94–6.86 (3H, m), 6.57 (1H, d, *J* = 8.5 Hz), 6.21–6.11 (2H, m). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 150.2, 148.0, 134.4, 134.2, 132.4, 132.0, 131.0, 130.6, 130.2, 126.7, 126.4, 121.8, 121.2, 118.9, 112.3. IR (ATR diamond, cm^{-1}): ν 3363, 2923, 2221, 1474, 976, 621. MS: *m/z* 254 (M+, 33), 252 (100), 216 (16), 190 (15), 126 (6). Anal. Calcd. For $C_{15}H_9ClN_2$: C, 71.30; H, 3.59; Cl, 14.03; N, 11.09. Found: C, 69.69; H, 4.44.

3-Carboethoxy-7-hydroxymethyl-5H-dibenzo[b,f]azepine (5n): Yield: 35% (46 mg); reaction time: 72 h at 105 °C; orange solid; m.p. (hexane): 105–106 °C. Eluent: Hexane/EtOAc 60:40.

^{1}H NMR (400 MHz): δ 7.47 (1H, dd, *J* = 7.8, 1.6 Hz), 7.17 (1H, d, *J* = 1.4 Hz), 6.87 (1H, d, *J* = 7.9 Hz), 6.82 (1H, d, *J* = 7.7 Hz), 6.79 (1H, d further split, *J* = 7.8 Hz), 6.56 (1H, s), 6.36 (1H, d, *J* = 11.8 Hz), 6.27 (1H, d, *J* = 11.8 Hz), 5.27 (1H, br s), 4.55 (2H, s), 4.34 (2H, q, *J* = 7.1 Hz), 2.25 (1H, br s), 1.38 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (100 MHz): δ 166.2, 148.4, 148.2, 143.1, 134.4, 134.0, 131.1, 130.9, 130.3, 128.6, 124.3, 121.4, 120.1, 117.8, 64.4, 61.0, 14.3. IR (ATR diamond, cm^{-1}): ν 3298, 2985, 2934, 2905, 2858, 1707, 1469, 1392, 1282, 1210, 1103, 1052, 1026, 901, 809, 764, 729. MS: *m/z* : 295 (M+, 100), 267 (45), 250 (12), 191 (11). Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.05; H, 5.82.

3-Chloro-5H-dibenzo[b,f]azepine (5o): Yield: 65% (65 mg); reaction time: 46 h at 105 °C; yellow solid; m.p. (hexane): 168–169 °C. Eluent: Hexane/EtOAc 90:10.

^{1}H NMR (300 MHz, DMSO-*d6*): δ 7.09 (1H, s), 6.98 (1H, t, *J* = 7.8 Hz), 6.77–6.66 (5H, m), 6.57 (1H, d, *J* = 7.9 Hz), 6.09–5.98 (2H, m). ^{13}C NMR (100 MHz, DMSO-*d6*): δ 151.3, 148.9, 134.3, 132.8, 132.3, 131.3, 131.1, 130.3, 129.3, 128.4, 122.8, 121.8, 119.6, 118.8. IR (ATR diamond, cm^{-1}): ν 3365, 3055, 2977, 1610, 1464, 1247, 1120, 782. MS: *m/z* 229 (M+, 32), 227 (100), 191 (23), 165 (16). Anal. Calcd. for $C_{14}H_{10}ClN$: C, 73.85; H, 4.43; Cl, 15.57; N, 6.15. Found: C, 74.03; H, 4.49.

3-Chloro-10,11-dihydro-5H-dibenzo[b,f]azepine (6o): Yield: 95% (65 mg); reaction time: 1.5 h at 50 °C; pale yellow solid; Eluent: Hexane/EtOAc 90:10. ^{1}H NMR (400 MHz, CDCl3) δ 7.14–7.03 (m, 2H), 6.96 (d, *J* = 8.6 Hz, 1H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H), 6.78–6.70 (m, 2H), 6.00 (br s, 1H), 3.15–2.98 (m, 4H). ^{13}C NMR (100 MHz, CDCl3) δ 143.5, 141.9, 132.0, 131.9, 130.7, 129.0, 127.0, 126.9, 120.2, 119.2, 118.2, 117.5, 34.7, 34.6. MS: *m/z* 229 (M+, 100), 214 (37), 194 (52), 165 (16). Anal. Calcd. for $C_{14}H_{12}ClN$: C, 73.20; H, 5.27; Cl, 15.43; N, 6.10. Found: C, 72.95; H, 5.35.

Cis,exo-2,3,4,4a,9,9a-hexahydro-1H-1,4-methanocarbazole (7): Yield: 50% (41 mg); reaction time: 24 h; Eluent: Hexane/EtOAc 90:10[53].

Methyl [1,1'-biphenyl]-4-carboxylate (8): Yield: 8% (8 mg); reaction time: 20 min; Eluent: Hexane/EtOAc 95:5[57].

Methyl 4-(3-phenylbicyclo[2.2.1]heptan-2-yl)benzoate (9): Compound **9** was detected in 5% (8 mg) from the competitive Suzuki-Miyaura coupling under standard conditions (See the relative experimental procedure). The same compound was prepared by a reported method[56] and then characterized: white solid; m.p. (hexane): 82.4–83.6 °C. Eluent: Hexane/EtOAc 80:20. ^{1}H NMR (400 MHz, CDCl3) δ 7.70–7.64 (m, 2H), 7.03–6.96 (m, 4H), 6.95–6.87 (m, 3H), 3.85 (s, 3H), 3.35–3.33 (m, 2H), 2.63, 2.62 (2 partly overlapping singlets, 2H), 2.27 (d further split, *J* = 9.6 Hz, 1H), 1.85–1.75 (m, 2H), 1.58 (d further split, *J* = 9.6 Hz, 1H), 1.54–1.49 (m, 2H). ^{13}C NMR (100 MHz, CDCl3) δ 167.2, 148.8, 142.4, 128.7, 128.6, 127.6, 126.8, 125.4, 55.0, 54.9, 51.8, 42.1, 42.0, 37.4, 30.7, 30.7; IR (ATR diamond, cm^{-1}): ν 1718 (C=O); MS: *m/z* 306 (100), 275 (22), 215 (35), 129 (53), 117 (64).

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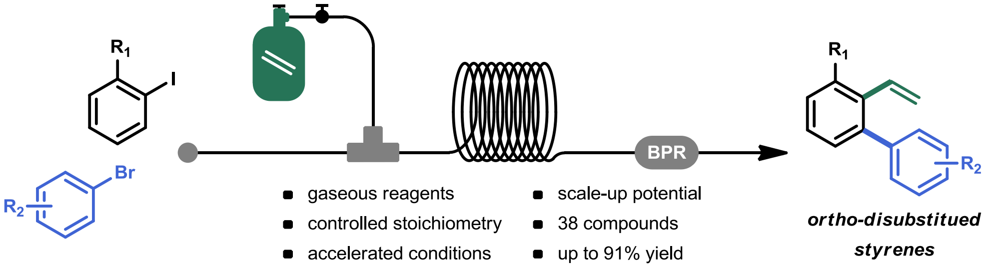
4. Homogeneous and Gas-Liquid Catellani-type Reactions Enabled by Continuous-Flow Chemistry



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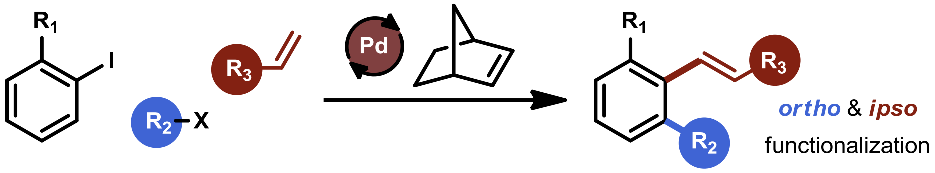
4.1. Introduction

According to the recent guidelines from the US Food and Drug Administration (FDA), the implementation of continuous-flow technology in the pharmaceutical industry will profoundly impact current manufacturing methods[1]. Tangible benefits such as improved safety[2–4], reduced time/energy demand[5,6], reliable scale up[7,8] and, ultimately, cost efficiency[9,10], have drawn considerable attention to flow chemistry as an enabling technology for drug production[11–15]. In this light, different research groups reasoned that current relevant batch methodologies necessitate substantial alterations in order to allow a smooth transition towards continuous manufacturing. Furthermore, the incorporation of flow technology for drug manufacturing enables new, otherwise inaccessible, chemical spaces (e.g. use of gaseous, hazardous/toxic reagents, photochemistry, etc.)[16–19]. From an atom economy perspective, the ultimate goal in modern organic chemistry is to develop efficient and regioselective methodologies by employing readily available hydrocarbon building blocks[20–26]. Site-selective functionalization of the ubiquitous C−H bond via transition metal catalysis (*i.e.* C−H activation) has transformed the way we currently address synthetic challenges, opening new horizons beyond the restriction of conventional synthetic approaches[27–30]. In particular, metal-organic cooperative catalytic systems have emerged as a powerful tool for the development of mild and selective C−H functionalization strategies[31–37]. In this respect, the Pd/norbornene-catalyzed Catellani reaction represents a unique example of a $Pd^{0/II/IV}$ catalytic cycle, combining the effectiveness of cross-coupling with the neatness of C−H functionalization[38–44]. Therefore, Catellani reactions result in the simultaneous functionalization of both *ortho* and *ipso* position of an aryl halide, while circumventing the need for a pre-installed directing group (**Scheme 4.1**).



[1 step bisfunctionalization]

[no directing group required]

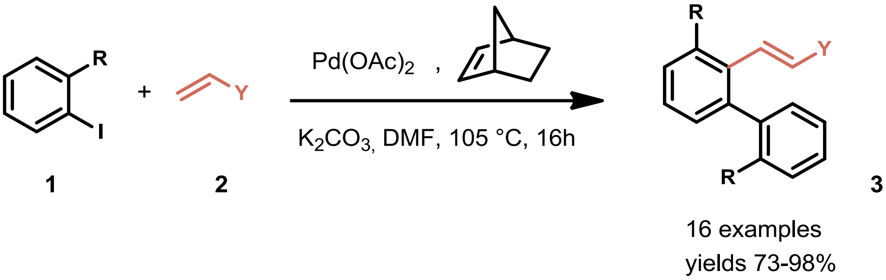
[limited to condensed matter]

Scheme 4.1 Catellani reaction with aryl halide and olefin as terminal reagent

Historically, Catellani reactions have been limited to liquid or solid reagents. This can be ascribed to the fact that the use of gaseous olefins has long been avoided due to safety concerns (*i.e.* pressurized headspace and leakages) and process constraints (*i.e.* gas-liquid mass-transfer limitations). The translation of Catellani-like reactions to a continuous-flow platform would be highly beneficial in terms of safety, reproducibility, scalability, and time-gain. Furthermore, the use of gaseous olefins would expand the scope of Catellani-like reactions, providing direct access to a series of relevant *ortho*-disubstituted styrenes and vinyl arenes in an atom-efficient fashion.

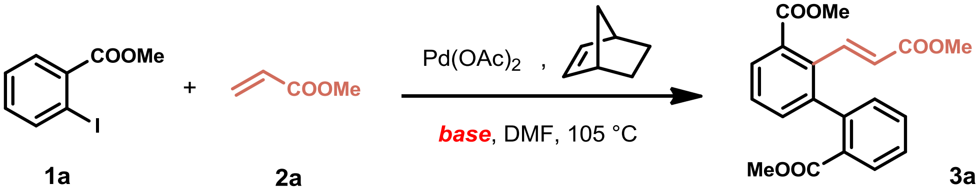
4.2. Results and discussion

We decided to perform in flow one of the first Catellani arylation reactions[44]. An *ortho*-substituted aryl iodide reacted with a terminal olefin in presence of $Pd(OAc)_2$, norbornene, K_2CO_3, in DMF as a solvent at 105 °C for 16 hours (**Scheme 4.2**).



Scheme 4.2 Reaction of ortho-substitued aryl iodide with a terminal olefin

The first challenge was to transform the reaction conditions, which involves K_2CO_3 not completely soluble in the reaction media, into a homogeneous solution for avoiding micro reactor clogging[19,45]. Continuous flow technology, especially micro-flow setups, performs better if solid reagent are avoided, because this ensures an ideal mass transfer. We initially tested different bases (**Table 4.1**), paying special attention to their solubility, to obtain ideal homogenous conditions, using the homo-coupling of methyl 2-iodobenzoate (**1a**) and methyl acrylate (**2a**) as benchmark reaction (**Scheme 4.3**).



Scheme 4.3 Homo-coupling of methyl 2-iodobenzoate and methyl acrylate as benchmark reaction[a]

Table 4.1 Base screening for the reaction in **Scheme 4.3**. Special attention was paid on the solubility of the base in the reaction media

Entry	**Base**	**Conv^b 1a (%)**	**Yield^b 3a (%)**	**Selectivity (%)**	**Homogeneity level**
1	K_2CO_3	>98	94	96	🔴⚪⚪⚪⚪
2	K_2CO_3/tBuNBr	100	91	91	🔴🟠⚪⚪⚪
3	$CH_3COO^-K^+$	95	94	99	🔴🟠🟡⚪⚪
4	$(CH_3)_3CCOO^-K^+$	72	69	96	🔴🟠🟡⚪⚪
5	$KHCO_3$	96	94	98	🔴🟠🟡⚪⚪
6	PhO^-K^+	40	32	80	🔴🟠🟡🟢🟢
7	Et_3N	54	33	61	🔴🟠🟡🟢🟢
8	Et_3N (2 equiv)	60	37	62	🔴🟠🟡🟢🟢
9	TBAA	100	46	46	🔴🟠🟡🟢🟢

[a]Reaction conditions: catalyst 2.5% mol, norbornene 0.3 eq, **1** 1 eq (0.44 mmol), **2** 0.6 eq, base 1.1 eq, solvent (4 mL), 2 hours, performed with Schlenk technique. [b]Determined *via* GC analysis with an internal standard

All inorganic bases, such as K_2CO_3, $KHCO_3$, AcOK, and PivOK (**Table 4.1**, entries 1-5) revealed to be greatly effective for the reaction and showed a high selectivity. However, all these candidates were not soluble in the reaction media, and are therefore considered not suitable. The use of potassium phenoxide (PhOK) or trimethylamine (Et_3N) provided excellent solubility, despite only a fair yield of 32-37% was obtained due to incomplete conversion (entries 6-8). Finally the use of tetrabutylammonium acetate (TBAA) resulted in an improved yield of 46% showcasing excellent solubility and full conversion within 2 hours reaction time, and was considered to be the most suitable candidate (entry 9).

Table 4.2 Conditions screening

Entry	$Pd(OAc)_2$	NB (equiv)	Conversion[a] 1a (%)	Yield[a] 3a (%)
1	2.5% mol	0.3	100	46
2	2.5% mol	0.6	100	55
3	2.5% mol	1	100	48
4[b]	2.5% mol	0.6	100	27
5	5% mol	0.6	100	45
6	5% mol	1.2	100	53

Reaction conditions: **1** 1 eq (0.44 mmol), **2** 0.6 eq, TBAA 1.1 eq, DMF (4 mL), 6 hours, performed with Schlenk technique. [a]Yields determined *via* GC analysis with an internal standard. NB stands for norbornene. [b]2 equivalent of TBAA were employed

After obtaining a suitable base, further reaction optimization was performed by carefully tuning different reaction parameters, *i.e.* catalyst, base and norbornene loadings (**Table 4.2**). Employing 0.6 equivalents of norbornene (entry 2) resulted in an improved yield (55%). However, further increase did not affect the reaction positively (entry 3). Increasing the amount of TBAA (2 equiv., entry 4) led to a remarkable decrease in the yield. An increment of the catalyst loading did not provide improved reactivity (entries 5-6).

Next, different additives or ligands were considered in order to improve the selectivity towards **3a** (**Table 4.3**). We screened some additives; TBAI (entry 2) showed a comparable yield, tBuOK (entry 3) due to its strong basicity promoted side reactions. Using potassium hexafluorophosphate the selectivity increased up to 84% (entry 4), a decreased amount of KPF_6 revealed lower efficiency (entry 5).

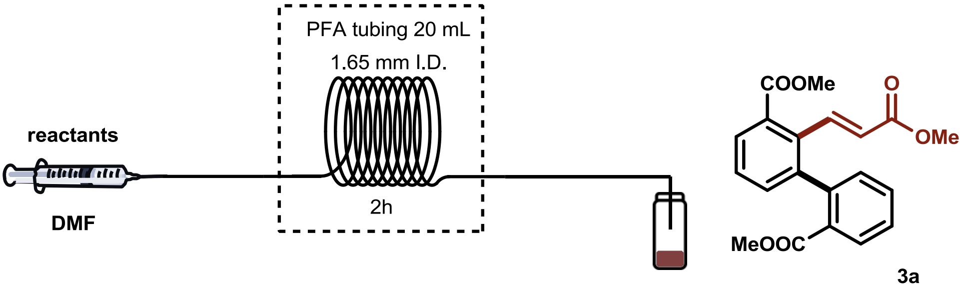
Table 4.3 Additive/ligand optimization[a]

Entry	Additive/Ligand	Conversion[b] 1a (%)	Yield[b] 3a (%)	Selectivity (%)
1	none	100	55	55
2	TBAI (1 equiv)	100	48	48
3	tBuOK (1 equiv)	100	37	37
4	KPF_6 (1 equiv)	100	84	84
5	KPF_6 (0.5 equiv)	82	54	66
6	PPh_3	100	64	64
7	CyJohnPhos	97	56	58
8	XPhos	100	94	94
9	JohnPhos	100	69	69
10	Ac-Val-OH	100	66	66
11	Ac-Ile-OH	100	59	59
12	Boc-Ile-OH	100	48	48

[a] Reaction conditions: $Pd(OAc)_2$ 2.5% mol, ligand 5% mol, **1** 1 eq (0.44 mmol), **2** 0.6 eq, NB 0.6 equiv, TBAA 1.1 eq, DMF (4 mL), overnight, performed with Schlenk technique. [b] Determined *via* GC analysis with an internal standard

However, this salt was not suitable for the translation to continuous flow due to its tendency to foam formation caused by the interaction with TBAA. Furthermore, we investigated various ligands, both phosphine ligands and aminoacids. Triphenyl phosphine increased yield and selectivity to 64% (entry 6), CyJohnPhos and JohnPhos exhibited comparable results (56 and 69% respectively, entries 7-9). XPhos performed better than all other phosphine ligands, obtaining 94% yield of the desired product **3a** (entry 8). Different mono-protected amino acids were explored, but all resulted in moderate yields and selectivities (entries 10-12).

Next, a continuous-flow reactor was constructed, comprising a 20 mL PFA capillary reactor (1.65 mm internal diameter) which was submerged in a heating bath (**Scheme 4.4**).



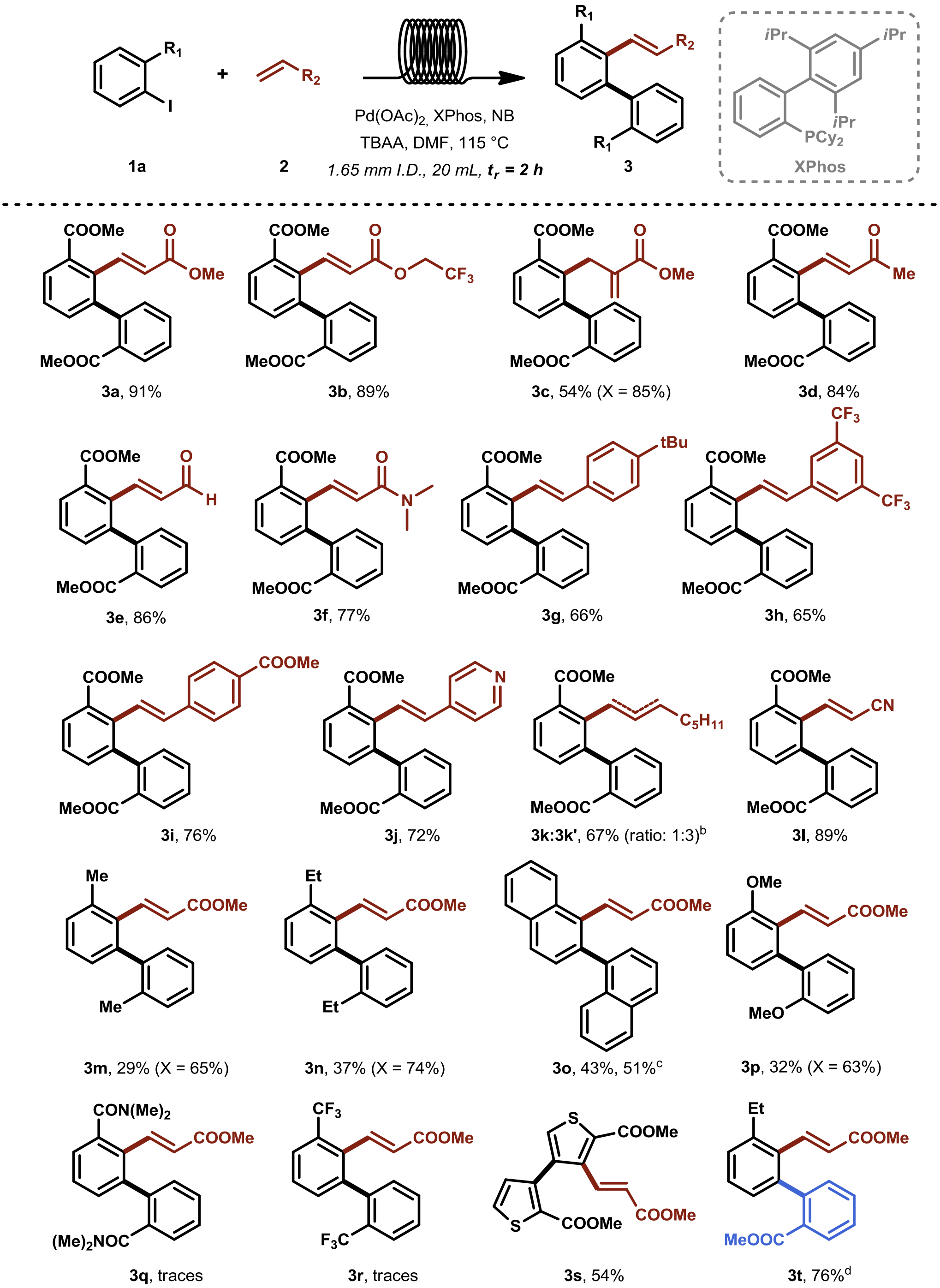
Scheme 4.4 Schematic representation of the continuous flow set-up for liquid phase reactions

Table 4.4 Optimization under continuous flow conditions

Entry	T (°C)	NB (equiv)	2 (equiv)	Conversion 1a^a (%)	Yield 3a^a (%)	Selectivity (%)
1	105	0.6	0.6	62	28	45
2	115	0.6	0.6	83	64	77
3	125	0.6	0.6	100	65	65
4	115	0.3	0.6	71	60	84
5	115	1	0.6	91	58	63
6	115	0.6	0.8	95	69	73
7	115	0.6	1	94	80	85
8^b	115	0.6	1	98	93	95

Reaction conditions: 2.5% mol Pd(OAc)$_2$, 5% ligand, norbornene 0.6 equiv, **1** 1 equiv (1 mmol), **2** 0.6 equiv, TBAA 1.1 equiv, solvent (10 mL), C 0,1 M. Residence time 2 hours, flow rate 0.166 mL/min. ^{a}Yields determined by GC analysis with an internal standard. ^{b}Concentration 0.2 M.

Translating the optimized reaction conditions in flow resulted in a fair yield of 28% with incomplete conversion after 2 hours of residence time (**Table 4.4**, entry 1). A temperature screening revealed that 115°C was optimal in order to accelerate the reaction conditions in order to obtain full conversion (entries 1-3). However, increasing or decreasing the amount of norbornene did not result in an improved yield (entry 4). On the contrary, 1 equivalent of norbornene promoted the formation of norbornene containing byproducts. Then we looked for acrylate (**2a**) stoichiometry; an increased amount of **2a** up to 1 equivalent provided 80% yield of the desired product **3a** (entries 6-7). Finally, it was demonstrated that by employing a concentration of 0.2 M ensured excellent yield of **3a**, within 2 hours residence (94% yield, entry 8).



Scheme 4.5 Substrate scope for the liquid-phase Catellani-type reaction in continuous flow[a]

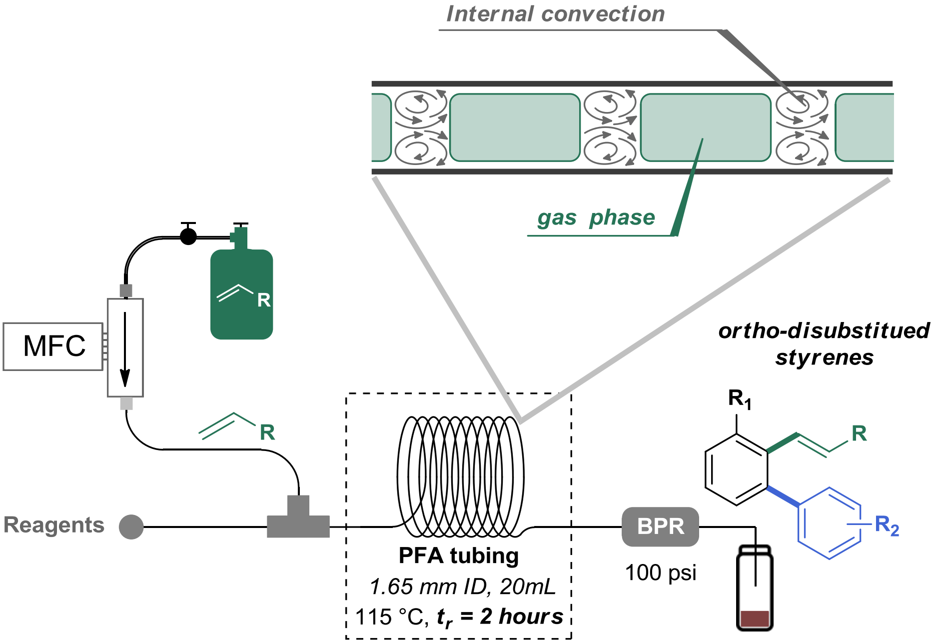
[a]Reaction conditions: 2.5 mol % $Pd(OAc)_2$, 5.0 mol % XPhos, 0.6 equiv norbornene (NB), 1 equiv **1** (1.0 mmol), 0.6 equiv **2**, 1.1 equiv TBAA, 4 mL DMF, performed under Argon atmosphere, flow rate at 0.166 mL/min, added to the reactor via syringe pump. [b]Ratio given as (vinyl : allyl olefin). [c]0.1 M. [d]0.5 mmol of 1-ethyl-2-iodobenzene (**1t**) and 0.5 mmol of methyl 2-bromobenzoate (**4a**).

Subsequently, we set out to explore the reaction scope of the homogeneous Catellani reaction in flow. High reactivity was observed when using activated olefins, such as methyl acrylate (**3a**), α,β-unsaturated ketones/aldehyde (**3d-e**), N,N-dimethylacrylamide (**3f**) and acrylonitrile (**3l**) obtaining good to excellent isolated yields (77-91%). Sterically hindered methyl methacrylate was well tolerated and resulted in a yield of 54% of the most favored isomerization product (**3c**). We then explored the possibility to expand the existing scope of olefins to a fluorine-containing acrylate (**3b**), styrenes (**3g-i**) and a vinyl pyridine (**3j**). To our delight, all styrene reagents could be readily coupled, irrespective of their substitution pattern. Notably, when using 1-octene as terminating reagent, a mixture of compounds (**3k** and **3k'**) was obtained with a ratio of 1:3 favored to the allylic product. This phenomena was attributed to the fact that two *β*-hydride elimination pathways are possible[46].

Next, we varied the aryl iodide substrate using methyl acrylate (**2a**) as benchmark olefin. When employing aryl iodides bearing *ortho*-alkylated substituents (**3m-n**), poor reactivity was observed, with no full conversion obtained within 2 hours of residence time. In the case of 1-iodonaphthalene (**3o**) a slight improved yield was observed (43 to 51%) using more diluted conditions. 2-iodoanisole gave some product (**3p**, 32%), while only traces of product were detected for compounds **3q** and **3r**. Interestingly, the heteroaromatic substrate **1s**, displayed good reactivity obtaining the desired product **3s** in 54% yield.

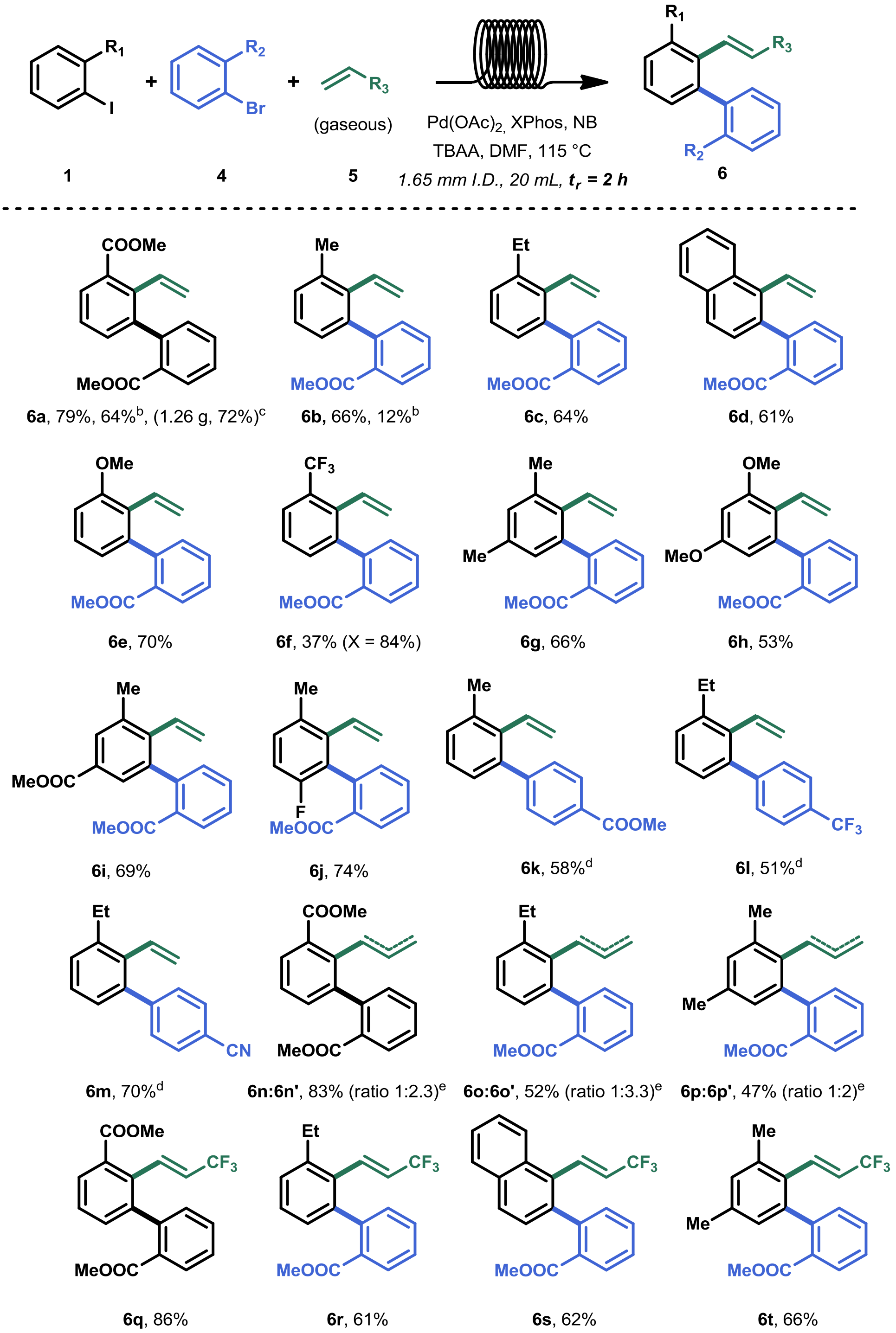
Hence, we speculated that the electron-withdrawing properties of the ortho-methyl ester substituent (**1a** and **1s**) have a significant effect on the second oxidative addition event (*i.e.* Pd^{II} to Pd^{IV}), thus accelerating the reaction[38]. Based on this observation, we predicted that the combination of an electron-rich aryl iodide with an electron-deficient aryl bromide would positively impact the reactivity of the Catellani reaction, thus affording relevant hetero-coupled moieties within a reasonable time frame[47]. To our delight, 1-ethyl-2-iodobenzene was readily coupled with methyl 2-bromobenzoate and methyl acrylate to obtain product **3t** in a good isolated yield of 76%. This promising result demonstrates the efficacy of our continuous platform to enable multi-component reactions yielding complex hetero-coupled biaryl motives.

Having determined a suitable protocol for homogeneous Catellani reactions in flow, we set out to develop a gas-liquid variant utilizing gaseous olefins as coupling partners (**Scheme 4.7**). By employing ethylene, propylene and 3,3,3-trifluoropropene gas, we intended to prepare sterically-hindered *ortho*-disubstituted styrenes building blocks, which are not easily synthesized via traditional methods. In order to accommodate gaseous reagents, the flow reactor was equipped with a mass flow controller (MFC) and a back pressure regulator (BPR) (**Scheme 4.6**).[48] The liquid stream was merged with the olefin gas resulting in a stable Taylor flow regime, which provides an excellent interfacial area between the two phases. Within the liquid segments, toroidal vortices are established which ensure optimal mixing and reduces gas-liquid mass transfer limitations[49].



Scheme 4.6 Continuous-flow reactor set-up for gas-liquid reactions

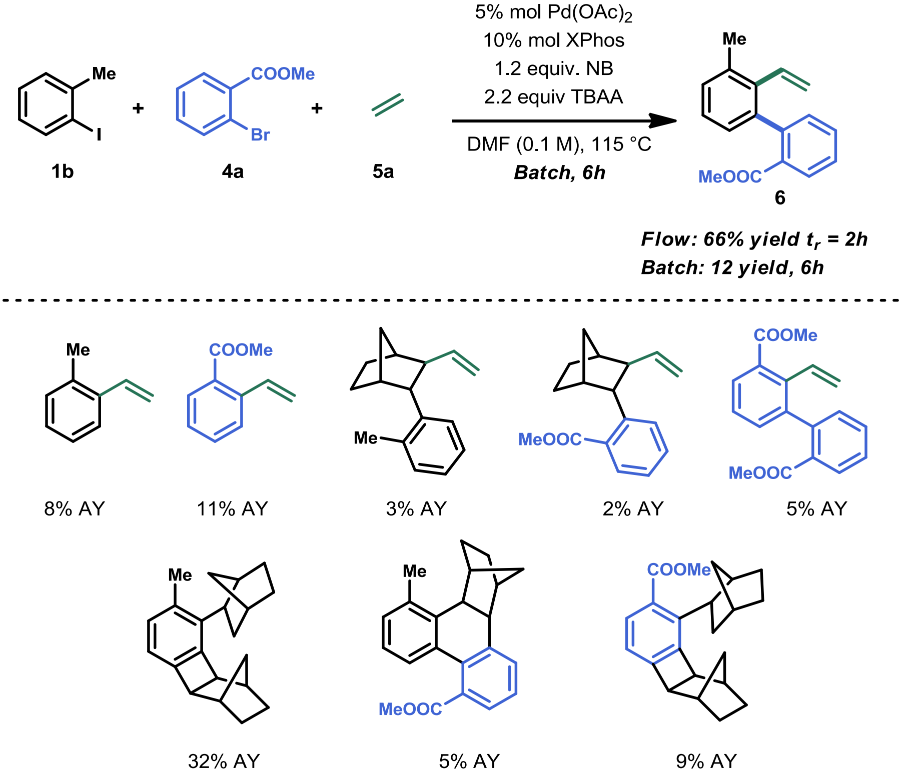
To our delight, when subjecting ethylene gas and the benchmark substrate **1a** to our reaction conditions, we obtained the desired styrene **6a** within 2 hours of residence time in good yield (79%). It should be noted that the formation of undesired Heck-like or norbornene containing by-products is a known complication of the Catellani transformation, which is normally circumvented by carefully balancing the amount of olefin and norbornene. However, regulating the stoichiometry of the gaseous olefin is extremely challenging in batch due a poor control over the interfacial area and diffusion limitations. Indeed, when the same gas-liquid reaction was carried out in batch, uncontrolled and inefficient use of the gaseous olefin and the evaporation of norbornene into the headspace resulted in a lower yield for the desired product **6a** (64% batch vs 79% flow) along with the formation of several by-products. The difference between batch and flow was even more pronounced in more challenging hetero-coupling reactions: *e.g.* **6b** was obtained in 66% yield in flow, while in batch a complex mixture was observed with only 12% of the desired product (**Scheme 4.8**). The latter example highlights the need for a high degree of control over the stoichiometry of gaseous reagents to obtain optimal results. Moreover, this observation demonstrates the key role of flow technology to enable efficient gas-liquid transformations. Furthermore, the use of flow also allows to readily scale the reaction conditions (72% yield, 1.26 g of product **6a**). Next, the scope was determined for the ethylene coupling partner. Aryl iodides bearing *ortho* electron-donating substituents (**6b-c**, **6e**) as well as 1-iodonapthalene (**6d**) all reacted well with methyl 2-bromobenzoate and ethylene, resulting in moderate to good yields (61-70%). A modest yield of 37% was obtained for 1-iodo-2-(trifluoromethyl)benzene (**6f**). More complex *ortho/meta-* and *ortho/para-*disubstituted aryl iodides proved compatible with our method, thus yielding compounds **6g-j** in synthetically useful yields (53-74%). Next, aryl bromides were shown to be competent substrates requiring longer residence times to reach full conversion (3 h, **6k-m**).



Scheme 4.7 Substrate scope for the gas-liquid Catellani-type reaction in continuous flow[a]

[a]Reaction conditions: 5 mol % Pd(OAc)$_2$, 10 mol % XPhos, 1.2 equiv norbornene (NB), 1 equiv **1** (0.5 mmol), 1 equiv **4**, 2 equiv **5** (dosed via a MFC), 2.2 equiv TBAA, 4 mL DMF, performed under Argon atmosphere, liquid flow rate at 0.04 mL/min and gas flow rate at 0.4 mL/min, 100 psi back pressure regulator. [b]Analogous batch experiment with an ethylene balloon. [c]6 mmol scale experiment. [d]3 h residence time. [e]Ratio given as (styrene : terminal olefin).

Finally, we turned our attention towards two more gaseous reagents, *i.e.* propylene and 3,3,3-trifluoropropene. When performing the reaction with **1a** and propylene gas, a mixture of **6n:6n’** was obtained in high yield (83%) in a 1:2.3 ratio in favor of the terminal olefin. Hetero-coupling of 1-ethyl-2-iodobenzene or 2,4-dimethyl-1-iodobenzene with methyl 2-bromobenzoate and propylene, gave the product mixtures **6o:6o’** and **6p:6p’** in moderate yields. When 3,3,3-trifluoropropene gas was introduced into the reactor, a set of *ortho*-disubstituted trifluoromethylated styrenes (**6q-t**) could be obtained in good yield.



Scheme 4.8 Overview of identified by-products for the gas-liquid Catellani reaction in batch (AY=area yield using an internal standard in GC-MS

4.3. Conclusions

In conclusion, we have developed for the first time a highly practical and efficient continuous-flow platform for homogeneous and gas-liquid Catellani-type reactions. The application of flow reactors resulted in reduced reaction times and enabled the use of gaseous olefin reagents (*i.e.* ethylene, propylene and 3,3,3-trifluoropropene) in a safe and scalable manner. This continuous platform provided direct access to valuable *ortho*-disubstituted styrenes and vinyl arenes within 2 hours of residence time.

4.4. Experimental section

Base screening in batch (GP1)

A 25 mL oven-dried glass tube was charged with a magnetic stirring bar and the selected base (0.48 mmol), fitted with a septum and flushed with alternating vacuum and argon backfill. Next, a 5 mL vials were charged with methyl 2-iodobenzoate (**1a**, 115 mg, 0.44 mmol), methyl acrylate (**2a**, 23 mg, 0.26 mmol), norbornene (13 mg, 0.13 mmol), hexadecane (as internal standard, 0.2 mmol) and purged with argon respectively. A second 5mL vial was charged with palladium acetate (2.5 mg, 0.011 mmol). The vials were filled with 2 mL of anhydrous DMF and the two resulting solutions were added via syringe to the 25 mL glass-tube (containing the catalyst and ligand). The reaction mixture was stirred at room temperature for 10 minutes to evaluate the solubility of the base and then heated at 105 °C for 2 hours. The reaction was cooled to room temperature and the crude was analyzed using GC-FID with hexadecane as internal standard.

Batch reactions (GP2)

A 25 mL oven-dried glass tube was charged with a magnetic stirring bar, palladium acetate (2.5 mg, 0.011 mmol) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos, 11 mg, 0.022 mmol), fitted with a septum and flushed with alternating vacuum and argon backfill. Next, a 5 mL vials was charged with methyl 2-iodobenzoate (**1a**, 115 mg, 0.44 mmol), methyl acrylate

(**2a**, 23 mg, 0.26 mmol), norbornene (26 mg, 0.26 mmol), hexadecane (as internal standard, 0.2 mmol) and purged with argon respectively. A second 5mL vial was charged with tetrabutylammonium acetate (146 mg, 0.48 mmol) and was heated with a heat gun under vacuum for 5 min in order to eliminate any residual water content. Both 5mL vials were filled with 2 mL of anhydrous DMF and the two resulting solutions were added via syringe to the 25 mL glass-tube (containing the catalyst and ligand). The reaction mixture was stirred and heated at 105 °C for 16 hours. The reaction was cooled to room temperature and the crude was analyzed using GC-FID with hexadecane as internal standard.

Single phase flow reactions (GP3)

A 25 mL oven-dried glass tube was charged with a magnetic stirring bar, palladium acetate (5.6 mg, 0.025 mmol) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos, 24 mg, 0.05 mmol), fitted with a septum and flushed with alternating vacuum and argon backfill. Next, a 5 mL vials was charged with methyl 2-iodobenzoate (**1a**, 262 mg, 1.0 mmol), methyl acrylate (**2a**, 86 mg, 1.0 mmol), norbornene (56 mg, 0.6 mmol) and purged with argon respectively. A second 5mL vial was charged with tetrabutylammonium acetate (332 mg, 1.1 mmol) and was heated with a heat gun under vacuum for 5 min in order to eliminate any residual water content. Both 5mL vials were filled with 2.5 mL of anhydrous DMF and the two resulting solutions were added via syringe to the 25 mL glass-tube (containing the catalyst and ligand). The reaction mixture was stirred at room temperature for 10 minutes to make the solution homogeneous. The solution was charged in a 5 mL BD Discardit II® syringe. Next, the syringe was fitted to a syringe pump (Fusion 200 Classic) and connected to the inlet of the 20 mL PFA coil (1.65 mm I.D.). The reactor was submerged into a thermostatic oil bath and kept at 115 °C during operation. The syringe pump was operating at 0.16 mL/min (residence time = 2 hours). The outlet of the reactor was fitted to a collection vial via a needle connection. Three extra syringes of each 10 mL anhydrous DMF were pumped after the sample (0.16 mL/min) in order to collect the complete sample. The resulted reaction mixture was monitored using TLC and/or GC-MS. The organic mixture was diluted in ethyl acetate and was introduced into a separation funnel. The organic phase was washed with 1x distilled water and 1x with brine solution respectively. Aqueous phase was backwashed once with ethyl acetate. Collected organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure at the rotavap. Purification was performed via flash chromatography on silica using an EtOAc/cyclohexane eluent mixture. The final product was dried, weighted and characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (if applicable) and melting point analysis (if applicable).

Gas-liquid flow reactions (GP4)

A 25 mL oven-dried glass tube was charged with a magnetic stirring bar, palladium acetate (5.6 mg, 0.025 mmol) and 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos, 24 mg, 0.05 mmol), fitted with a septum and flushed with alternating vacuum and argon backfill. Next, a 5 mL vials was charged with 1-iodo-2-methylbenzene (**1aa**, 116 mg, 0.5 mmol), methyl 2-bromobenzoate (**1b**, 108 mg, 0.5 mmol), norbornene (39 mg, 0.4 mmol) and purged with argon respectively. A second 5mL vial was charged with tetrabutylammonium acetate (332 mg, 1.1 mmol) and was heated with a heat gun under vacuum for 5 min in order to eliminate any residual water content. Both 5mL vials were filled with 2.5 mL of anhydrous DMF and the two resulting solutions were added via syringe to the 25 mL glass-tube (containing the catalyst and ligand). The reaction mixture was stirred at room temperature for 10 minutes to make the solution homogeneous. The solution was charged in a 5 mL BD Discardit II® syringe. Next, the syringe was fitted to a syringe pump (Fusion 200 Classic) and connected to a Tefzel® T-mixer (ID = 500 µm). A Bronkhorst mass flow controller was used to introduce ethylene gas (**4a**) into the reaction mixture via a T-mixer. The gas was added perpendicular to the reaction mixture flow direction in order to produce a stable segmented flow. The syringe pump and mass flow controller were operated at a 1:10 reaction mixture:gas volume flow ratio (liquid flow rate 0.04 mL/min, gas flow rate 0.4 mL/min) in order to ensure a molar ratio 1:2 and a residence time of 2 hours. The reactor consists of a 20 mL PFA coil (1.65 mm I.D.). A 100 psi back pressure regulator was used in order to ensure a stable slug flow regime. The outlet of the reactor was fitted to a collection vial via a needle connection. Three extra syringes of each 10 mL anhydrous DMF were pumped after the sample (0.16 mL/min) in order to collect the complete sample. The resulted reaction mixture was monitored using TLC and/or GC-MS. The organic mixture was diluted in ethyl acetate and was introduced into a separation funnel. The organic phase was washed with 1x distilled water and 1x with brine solution respectively. Aqueous phase was backwashed once with ethyl acetate. Collected organic phase was dried over MgSO4, filtered and concentrated under reduced pressure at the rotavap. Purification was performed via flash chromatography on silica using an EtOAc/cyclohexane eluent mixture. The final product was dried, weighted and characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (if applicable) and melting point analysis (if applicable).

Dimethyl 2'-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (3a)[44] was synthesized following GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (165 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.90 – 7.82 (m, 2H), 7.49 (td, *J* = 7.5, 1.3 Hz, 1H), 7.39 (td, *J* = 7.8, 1.9 Hz, 2H), 7.31 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.16 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.50 (d, *J* = 16.2 Hz, 1H), 3.86 (s, 3H), 3.62 (d, *J* = 0.6 Hz, 6H) ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.2, 166.4, 143.4, 142.0, 141.4, 134.8, 133.0, 131.8, 131.3, 130.3, 130.2, 130.2, 129.3, 127.7, 127.7, 123.5, 52.3, 51.9, 51.5.

Dimethyl 2'-[(1*E*)-3-oxo-3-(2,2,2-trifluoroethoxy)prop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (3b) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 2,2,2-trifluoroethyl acrilate (**2b**, 154 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as pale yellow oil (188 mg, 89% yield). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 16.3 Hz, 1H), 7.94 (ddd, *J* = 7.8, 3.3, 1.3 Hz, 2H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.47 – 7.34 (m, 3H), 7.18 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.51 (d, *J* = 16.2 Hz, 1H), 4.43 (qd, *J* = 8.5, 3.1 Hz, 2H), 3.88 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 167.1, 164.1, 145.9, 142.1, 141.2, 134.4, 133.1, 131.9, 131.3, 130.3, 130.1, 130.0, 129.4, 128.1, 127.8, 121.5, 60.0 (q, *J* = 36.6 Hz), 52.3, 51.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ -73.88 (t, *J* = 8.5 Hz).

Dimethyl 2'-[2-(methoxycarbonyl)prop-2-en-1-yl]biphenyl-2,3'-dicarboxylate (3c)[39] was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and methyl methacrilate (**2c**, 200 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as pale yellow oil (99 mg, 54% yield, 83% conversion). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 1H), 7.91 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48 (td, *J* = 7.5, 1.6 Hz, 1H), 7.42 (td, *J* = 7.6, 1.5 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.18 – 7.13 (m, 1H), 6.05 (dd, *J* = 2.8, 1.6 Hz, 1H), 4.96 (dd, *J* = 3.1, 1.9 Hz, 1H), 3.95 (dt, *J* = 17.3, 1.7 Hz, 1H), 3.82 (s, 3H), 3.65 (s, 3H), 3.62 – 3.56 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.1, 167.1, 143.7, 141.6, 140.0, 136.9, 132.9, 131.5, 130.9, 130.8, 130.4, 129.9, 129.8, 127.7, 125.8, 124.7, 52.0, 51.8, 51.7, 32.4.

Dimethyl 2'-[(1*E*)-3-oxobut-1-en-1-yl]biphenyl-2,3'-dicarboxylate (3d)[44] was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 3-buten-2-one (**2d**, 70 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (142 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (ddd, *J* = 7.8, 4.7, 1.3 Hz, 2H), 7.73 (d, *J* = 16.7 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 – 7.34 (m, 3H), 7.19 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.67 (d, *J* = 16.7 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 167.6, 167.2, 142.4, 141.9, 141.3, 135.2, 133.1, 133.1, 131.8, 131.3, 130.2, 130.2, 129.7, 129.4, 127.8, 127.8, 52.3, 51.9, 26.5.

Dimethyl 2'-[(1*E*)-3-oxoprop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (3e) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and acrylaldehyde (**2e**, 56 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (139 mg, 86% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.42 (d, *J* = 7.8 Hz, 1H), 7.96 (ddd, *J* = 7.3, 5.8, 1.3 Hz, 2H), 7.82 (d, *J* = 16.2 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.36 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.18 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.72 (dd, *J* = 16.2, 7.8 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 193.4, 167.4, 166.9, 151.8, 141.9, 141.2, 134.5, 134.2, 133.3, 131.9, 131.2, 130.5, 129.9, 129.6, 129.5, 128.3, 128.0, 52.3, 52.00.

Dimethyl 2'-[(1*E*)-3-(dimethylamino)-3-oxoprop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (3f) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and N,N-Dimethyl-2-propenamide (**2f**, 99 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as orange oil (141 mg, 77% yield). ^{1}H NMR (400 MHz, MeOD) δ 7.85 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.80 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.65 (d, *J* = 15.7 Hz, 1H), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.28 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.20 (dd, *J* = 7.6, 0.9 Hz, 1H), 5.98 (d, *J* = 15.7 Hz, 1H), 3.81 (s, 3H), 3.55 (s, 3H), 2.80 (s, 3H), 2.59 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 169.6, 169.1, 168.0, 143.5, 143.4, 141.7, 136.7, 134.4, 133.2, 132.9, 132.2, 132.1, 131.3, 130.3, 129.0, 128.9, 125.1, 53.0, 52.7, 37.5, 36.1.

Dimethyl 2'-[(1E)-(4-(tert-butyl)styryl)-biphenyl]-2,3'-dicarboxylate (3g) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 4-tertbutylstirene (**2g**, 320 mg, 2 mmol). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (141 mg, 66% yield). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.70 (dd, *J* = 6.8, 2.3 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.20 – 7.15 (m, 3H), 7.05 – 6.97 (m, 3H), 6.12 (d, *J* = 16.5 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 169.3, 167.6, 150.5, 142.2, 141.7, 136.9, 134.6, 134.5, 132.4, 131.6, 130.7, 130.6, 130.1, 128.9, 127.3, 126.2, 126.1, 125.4, 125.3, 52.2, 51.9, 34.5, 31.2.

Dimethyl [(1E)-2'-(3,5-bis(trifluoromethyl)styryl)-biphenyl]-2,3'-dicarboxylate (3h) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 3,5-bis(trifluoromethyl)stirene (**2h**, 480 mg, 2 mmol). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (165 mg, 65% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 5.7, 3.6 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.57 (s, 1H), 7.47 – 7.40 (m, 3H), 7.34 – 7.26 (m, 4H), 7.18 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.06 (d, *J* = 16.5 Hz, 1H), 3.79 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 167.5, 142.0, 141.9, 139.5, 136.5, 133.1, 132.2, 131.9, 131.7, 131.5, 131.3, 131.2, 131.0, 130.6, 130.1, 129.9, 129.5, 127.5, 127.2, 126.0 (d, *J* = 2.7 Hz), 124.6, 121.9, 120.7 (dt, *J* = 7.6, 3.8 Hz), 52.2, 51.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.04.

Dimethyl [(1E)-2'-(4-(methoxycarbonyl)styryl)-biphenyl]-2,3'-dicarboxylate (3i) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 4-methoxycarbonylstirene (**2i**, 344 mg, 2 mmol). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (163 mg, 76% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 4H), 7.51 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.33 – 7.24 (m, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.17 (d, *J* = 16.5 Hz, 1H), 3.86 (d, *J* = 6.0 Hz, 6H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.4, 166.8, 142.0, 141.8, 142.0, 136.7, 133.5, 132.8, 131.6, 131.5, 130.6, 130.2, 130.0, 129.7, 129.2, 129.0, 128.8, 127.4, 126.7, 126.1, 52.2, 51.9, 51.9.

Dimethyl [(1E)-2'-(2-(pyridin-4-yl)vinyl)-biphenyl]-2,3'-dicarboxylate (3j) was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 4-vinylpyridine (**2j**, 210 mg, 2 mmol). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as orange oil (134 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 7.92 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.88 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.57 (d, *J* = 16.5 Hz, 1H), 7.50 (td, *J* = 7.5, 1.3 Hz, 1H), 7.39 (tt, *J* = 7.6, 4.7 Hz, 3H), 7.22 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.15 (d, *J* = 5.4 Hz, 2H), 6.04 (d, *J* = 16.5 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 167.3, 147.7, 146.7, 141.9, 141.6, 136.0, 134.2, 133.1, 131.7, 131.4, 130.5, 130.4, 130.1, 129.8, 129.5, 127.6, 127.4, 121.4, 52.2, 51.9.

Dimethyl 2'-[(1E)-(oct-1-en-1-yl)-[1,1'-biphenyl]-2,3'-dicarboxylate (3k) and dimethyl (E)-2'-(oct-2-en-1-yl)-[1,1'-biphenyl]-2,3'-dicarboxylate (3k') were synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and 1-octene (**2k**, 224 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (127 mg, 67% yield) ratio vinyl : allyl olefin 1:3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.8, 1.3 Hz, 4H), 7.87 – 7.79 (m, 4H), 7.59 – 7.51 (m, 4H), 7.50 – 7.44 (m, 4H), 7.29 – 7.19 (m, 12H), 5.40 – 5.28 (m, 4H), 5.21 (ddd, *J* = 7.4, 5.9, 4.4 Hz, 2H), 5.00 – 4.91 (m, 1H), 3.91 (t, *J* = 4.4 Hz, 12H), 3.64 – 3.53 (m, 14H), 3.30 (dd, *J* = 14.7, 5.7 Hz, 1H), 2.98– 2.75 (m, 3H), 2.58 (dddd, *J* = 25.9, 12.7, 10.7, 5.4 Hz, 3H), 2.11 – 2.02 (m, 1H), 1.96 (ddd, *J* = 14.3, 7.8, 6.8 Hz, 2H), 1.92 – 1.74 (m, 10H), 1.63 (dd, *J* = 2.8, 1.6 Hz, 3H), 1.58 – 1.54 (m, 1H), 1.33 – 1.07 (m, 22H), 0.94 (dd, *J* = 11.9, 4.4 Hz, 2H), 0.91 – 0.82 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 168.8, 168.7, 167.4, 167.3, 167.2, 143.2, 143.0, 142.9, 142.8, 142.3, 142.2, 142.1, 141.5, 141.4, 141.3, 140.7, 138.6, 132.4, 132.4, 131.7, 131.5, 131.5, 131.4, 131.4, 131.3, 131.3, 131.2, 130.9, 130.8, 130.6, 130.4, 130.3, 130.3, 130.2, 130.2, 130.1, 130.1, 129.8, 129.7, 129.6, 129.5, 129.4, 129.1, 128.1, 127.5, 127.5, 127.4, 125.1, 124.9, 124.8, 124.7, 124.4, 123.5, 51.9, 51.8, 51.7, 34.6, 33.9, 33.8, 32.8, 32.5, 32.3, 32.1, 32.0, 31.6, 31.4, 31.2, 30.8, 30.7, 30.6, 30.5, 30.4, 29.9, 29.5, 29.3, 29.1, 28.9, 28.7, 26.6, 25.5, 22.6, 22.5, 22.1, 17.9, 14.0, 13.9, 13.7, 12.7.

Dimethyl 2'-[(*E*)-2-cyanoethenyl]biphenyl-2,3'-dicarboxylate (3l)[39] was synthesized following the GP 3 from methyl 2-iodo benzoate (**1a**, 262 mg) and acrylonitrile (**2l**, 53 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as white solid (143 mg, 89% yield). Mp. 85.2 – 86.6 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.98 (ddd, *J* = 9.2, 7.9, 1.2 Hz, 2H), 7.74 (d, *J* = 16.8 Hz, 1H), 7.55 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.33 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.03 (d, *J* = 16.8 Hz, 1H), 3.91 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.9, 149.8, 141.9, 140.9, 133.9, 133.3, 132.0, 131.2, 130.5, 129.9, 129.6, 129.6, 128.4, 128.1, 117.3, 102.2, 52.4, 52.0.

Methyl (2*E*)-3-(2',3-dimethylbiphenyl-2-yl)prop-2-enoate (3m)[44] was synthesized following the GP 3 from 2-iodo toluene (**1b**, 218 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (39 mg, 29% yield, conversion 65%). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.62 (d, *J* = 16.4 Hz, 2H), 7.25 (dt, *J* = 10.7, 6.8 Hz, 11H), 7.10 (d, *J* = 7.3 Hz, 2H), 7.05 (d, *J* = 7.2 Hz, 2H), 5.63 (d, *J* = 16.4 Hz, 2H), 3.66 (s, 6H), 2.47 (s, 6H), 2.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 142.5, 142.0, 141.0, 137.3, 135.3, 132.6, 130.1, 129.8, 129.6, 128.5, 128.2, 127.5, 125.7, 122.7, 51.5, 21.3, 20.0.

Methyl (2*E*)-3-(2',3-diethylbiphenyl-2-yl)prop-2-enoate (3n)[44] was synthesized following the GP 3 from 2-ethyl-1-iodo-benzene (**1c**, 232 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (54 mg, 37% yield, 74% conversion). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.3 Hz, 1H), 7.33 – 7.23 (m, 4H), 7.19 (td, *J* = 7.2, 1.8 Hz, 1H), 7.09 – 7.02 (m, 2H), 5.53 (d, *J* = 16.3 Hz, 1H), 3.64 (s, 3H), 2.78 (q, *J* = 7.5 Hz, 2H), 2.33 (ddq, *J* = 22.0, 14.8, 7.4 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H), 1.02 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 143.3, 142.4, 141.5, 141.2, 140.6, 132.2, 129.8, 128.4, 128.4, 128.3, 127.9, 127.7, 125.6, 123.0, 51.5, 27.0, 26.0, 15.5, 14.7.

Methyl (2*E*)-3-(1,2'-binaphthalen-1'-yl)prop-2-enoate (3o)[44] was synthesized following the GP 3 from 1-iodo naphtalene (**1d**, 254 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellowish oil (86 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.99 – 7.95 (m, 1H), 7.95 – 7.89 (m, 4H), 7.64 – 7.57 (m, 2H), 7.54 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.52 – 7.45 (m, 3H), 7.40 – 7.35 (m, 2H), 6.00 (d, *J* = 16.3 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.7, 142.3, 138.6, 138.0, 133.6, 133.1, 131.9, 131.5, 131.3, 129.0, 128.5, 128.5, 128.3, 128.0, 127.9, 127.0, 126.2, 125.9, 125.8, 125.2, 125.2, 124.7, 51.5.

Methyl (2*E*)-3-(2',3-dimethoxybiphenyl-2-yl)prop-2-enoate (3p)[44] was synthesized following the GP 3 from 2-iodo anisole (**1e**, 234 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as white solid (48 mg, 32% yield, conversion 63%). Mp. 101.7 – 102.9 °C. ^{1}H NMR (399 MHz, CDCl$_3$) δ 7.54 (d, *J* = 16.2 Hz, 1H), 7.36 (dt, *J* = 13.9, 6.9 Hz, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.98 – 6.93 (m, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 16.2 Hz, 1H), 3.93 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 168.5, 159.0, 156.4, 141.9, 140.6, 131.2, 130.0, 129.4, 129.3, 123.3, 122.2, 120.8, 120.7, 111.1, 110.0, 55.5, 51.3.

Dimethyl 4'-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]-3,3'-bithiophene-2,5'-dicarboxylate (3s) was synthesized following the GP 3 from methyl 3-iodothiophene-2-carboxylate (**1h**, 268 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (99 mg, 54% yield). Mp 163.2 – 164.1 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.38 – 8.24 (m, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.36 (d, *J* = 0.4 Hz, 1H), 6.98 (d, *J* = 5.0 Hz, 1H), 5.48 (d, *J* = 16.5 Hz, 1H), 3.91 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 167.0, 162.3, 161.9, 141.5, 140.7, 137.1, 136.9, 131.3, 131.2, 131.1, 129.9, 129.3, 122.4, 52.5, 52.2, 51.8.

Methyl 3'-ethyl-2'-[(1*E*)-3-methoxy-3-oxoprop-1-en-1-yl]biphenyl-2-carboxylate (3t)[47] was synthesized following the GP 3 from 2-ethyl-1-iodo-benzene (**1c**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and methyl acrylate (**2a**, 86 mg). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (123 mg, 76% yield). ^{1}H NMR (399 MHz, CDCl$_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.67

(d, *J* = 16.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.23 (m, 2H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 5.59 (d, *J* = 16.3 Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 2.77 (q, *J* = 7.5 Hz, 2H), 1.25 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.9, 142.8, 142.8, 142.6, 141.4, 132.2, 131.6, 131.4, 130.6, 130.1, 128.2, 127.9, 127.3, 127.3, 124.0, 51.9, 51.5, 26.9, 15.4.

Dimethyl 2'-ethenylbiphenyl-2,3'-dicarboxylate (6a) was synthesized following the GP 4 from methyl 2-iodo benzoate (**1a**, 262 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as pale yellow oil (117 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.75 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.22 (dd, *J* = 7.6, 1.0 Hz, 1H), 6.75 (dd, *J* = 17.8, 11.4 Hz, 1H), 5.12 (dd, *J* = 11.4, 1.5 Hz, 1H), 4.89 (dd, *J* = 17.8, 1.5 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 167.4, 142.1, 141.6, 137.4, 134.6, 132.2, 131.5, 131.4, 130.4, 130.4, 130.0, 128.5, 127.2, 126.3, 119.6, 52.0, 51.8.

Methyl 2'-ethenyl-3'-methylbiphenyl-2-carboxylate (6b) was synthesized following the GP 4 from 2-iodo toluene (**1b**, 109 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (83 mg, 66% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.21 (m, 7H), 7.06 (d, *J* = 6.6 Hz, 2H), 6.52 (dd, *J* = 17.9, 11.6 Hz, 2H), 5.27 (d, *J* = 11.5 Hz, 2H), 5.03 (d, *J* = 17.9 Hz, 2H), 3.69 (s, 6H), 2.46 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 143.4, 140.7, 136.0, 135.4, 134.6, 131.6, 131.2, 130.7, 129.7, 129.4, 126.8, 126.3, 120.0, 51.8, 21.0.

Methyl 2'-ethenyl-3'-ethylbiphenyl-2-carboxylate (6c) was synthesized following the GP 4 from 2-ethyl-1-iodo benzene (**1c**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography

(Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (85 mg, 64% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.33 – 7.23 (m, 3H), 7.04 (dd, *J* = 5.4, 3.4 Hz, 1H), 6.57 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.21 (d, *J* = 11.5 Hz, 1H), 5.00 – 4.88 (m, 1H), 3.65 (s, 3H), 2.78 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 143.5, 141.6, 140.7, 135.8, 134.3, 131.6, 131.2, 130.8, 129.7, 127.5, 126.8, 126.7, 126.5, 120.1, 51.8, 26.7, 15.3.

Methyl 2-(1-ethenylnaphthalen-2-yl)benzoate (6d) was synthesized following the GP 4 from 1-iodo naphtalene (**1d**, 127 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (88 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.15 (m, 1H), 7.93 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 – 7.21 (m, 2H), 6.76 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.41 (dd, *J* = 11.5, 2.0 Hz, 1H), 5.20 (dd, *J* = 17.9, 1.9 Hz, 1H), 3.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 143.3, 137.6, 133.8, 133.6, 133.0, 131.8, 131.4, 130.9, 130.0, 128.3, 127.4, 127.1, 126.7, 126.2, 125.7, 125.6, 121.7, 51.9.

Methyl 2'-ethenyl-3'-methoxybiphenyl-2-carboxylate (6e) was synthesized following the GP 4 from 2-iodo anisole (**1e**, 117 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (94 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 7.8, 1.2 Hz, 3H), 7.51 (td, *J* = 7.5, 1.4 Hz, 3H), 7.40 (td, *J* = 7.6, 1.2 Hz, 3H), 7.27 – 7.20 (m, 8H), 6.91 (d, *J* = 8.3 Hz, 3H), 6.75 (d, *J* = 7.6 Hz, 3H), 6.45 (dd, *J* = 17.9, 11.8 Hz, 3H), 5.43 (dd, *J* = 17.9, 2.2 Hz, 3H), 5.18 (dd, *J* = 11.9, 2.2 Hz, 3H), 3.89 (s, 9H), 3.62 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 157.5, 142.6, 142.3, 131.4, 131.4, 131.1, 130.7, 129.9, 127.3, 127.1, 124.7, 121.9, 119.6, 109.7, 55.5, 51.9.

Methyl 2'-ethenyl-3'-(trifluoromethyl)biphenyl-2-carboxylate (6f) was synthesized following the GP 4 from 1-iodo-2-(trifluoromethyl)benzene (**1g**, 136 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (57 mg, 37% yield, 84% conversion). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.68 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.53 (td, *J* = 7.5, 1.3 Hz, 1H), 7.39 (dtd, *J* = 12.0, 7.7, 1.4 Hz, 3H), 7.22 (dd, *J* = 7.6, 1.1 Hz, 1H), 6.72 – 6.55 (m, 1H), 5.22 (dd, *J* = 11.6, 1.5 Hz, 1H), 4.93 (dd, *J* = 17.8, 1.0 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 142.4, 142.0, 136.2, 132.7, 131.9, 131.6, 131.5, 130.3, 130.2, 128.4, 128.1, 127.4, 126.4, 125.7, 124.8 (q, *J* = 5.7 Hz), 122.9, 122.3, 51.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ -58.55 (d, *J* = 1.3 Hz).

Methyl 2'-ethenyl-3',5'-dimethylbiphenyl-2-carboxylate (6g) was synthesized following the GP 4 from 1-iodo-2,4-dimethylbenzene (**1i**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (88 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.49 (td, *J* = 7.5, 1.3 Hz, 1H), 7.37 (td, *J* = 7.6, 1.2 Hz, 1H), 7.25 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.02 (s, 1H), 6.82 (s, 1H), 6.42 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.16 (dd, *J* = 11.5, 1.9 Hz, 1H), 4.92 (dd, *J* = 17.9, 1.9 Hz, 1H), 3.64 (s, 3H), 2.36 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.9, 143.5, 140.6, 135.8, 135.3, 134.5, 133.2, 131.6, 131.2, 130.8, 130.3, 129.7, 127.5, 126.7, 119.5, 51.8, 21.0, 21.0.

Methyl 2'-ethenyl-3',5'-dimethoxybiphenyl-2-carboxylate (6h) was synthesized following the GP 4 from 1-iodo-2,4-dimethoxylbenzene (**1j**, 132 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as white solid (78 mg, 53% yield). Mp 41.3 – 42.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.25 (s, 1H), 6.49 (d, *J* = 2.1 Hz, 1H), 6.35 (dd, *J* = 17.8, 11.9 Hz, 1H), 6.29 (d, *J* = 2.3 Hz, 1H), 5.38 (dd, *J* = 17.8, 2.2 Hz, 1H), 5.07 (dd, *J* = 11.9, 2.1 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 158.8, 158.7, 143.1, 142.7, 131.4, 131.3, 130.8, 130.8, 129.8, 127.2, 118.0, 117.6, 105.9, 97.7, 55.5, 55.3, 52.0.

Dimethyl 6'-ethenyl-5'-methylbiphenyl-2,3'-dicarboxylate (6i) was synthesized following the GP 4 from methyl 4-iodo-3-methylbenzoate (**1k**, 138 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as white solid (107 mg, 69% yield). Mp 81.4 – 82.5 °C. ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 1H), 7.88 (s, 1H), 7.67 (s, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.44 (dd, *J* = 17.9, 11.7 Hz, 1H), 5.26 (d, *J* = 11.7 Hz, 1H), 5.01 (d, *J* = 17.9 Hz, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.1, 142.6, 141.1, 140.9, 135.8, 134.0, 131.6, 131.6, 130.5, 130.3, 130.1, 127.9, 127.8, 127.3, 121.2, 52.0, 51.9, 21.0.

Methyl 2'-ethenyl-6'-fluoro-3'-methylbiphenyl-2-carboxylate (6j) was synthesized following the GP 4 from 4-fluoro-2-iodo-1-methylbenzene (**1l**, 132 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and ethylene (**5a**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellow oil (100 mg, 74% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.36 (dd, *J* = 17.9, 11.6 Hz, 1H), 5.21 (d, *J* = 11.6 Hz, 1H), 4.96 (d, *J* = 17.9 Hz, 1H), 3.68 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.9, 156.5, 137.8, 137.7, 136.6, 134.1, 134.0, 132.2, 131.7, 131.1, 131.1, 130.8, 130.3, 130.2, 130.2, 128.0, 127.9, 127.6, 120.6, 113.3, 113.0, 51.9, 20.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -118.44 – -118.58 (m).

Methyl 2'-ethenyl-3'-methylbiphenyl-4-carboxylate (6k) was synthesized following the GP 4 from 2-iodo toluene (**1b**, 109 mg), methyl 4-bromo benzoate (**4b**, 108 mg) and ethylene (**5a**) with 3 hours of residence time. Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (73 mg, 58% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.28 – 7.25 (m, 2H), 7.15 (dd, *J* = 5.9, 2.8 Hz, 1H), 6.60 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.34 (d, *J* = 11.5 Hz, 1H), 5.06 (d, *J* = 17.9 Hz, 1H), 3.96 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 147.1, 140.3, 136.4, 136.2, 134.7, 130.0, 130.0, 129.1, 128.3, 127.7, 126.8, 120.8, 52.1, 21.1.

2-ethenyl-3-ethyl-4'-(trifluoromethyl)biphenyl (6l) was synthesized following the GP 4 from 2-ethyl-1-iodo benzene (**1c**, 116 mg), 4-bromo benzotrifluoride (**4c**, 113 mg) and ethylene (**5a**), with a 3 hours of residence time. Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as deliquescent white solid (70 mg, 51% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.14 – 7.06 (m, 1H), 6.63 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.30 (d, *J* = 11.5 Hz, 1H), 4.97 (d, *J* = 17.9 Hz, 1H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2, 142.7, 139.9, 136.1, 134.3, 130.3, 128.3, 127.7, 127.2, 124.7 (q, *J* = 3.8 Hz), 121.2, 26.8, 15.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.32.

2'-ethenyl-3'-ethylbiphenyl-4-carbonitrile (6m) was synthesized following the GP 4 from 2-ethyl-1-iodo benzene (**1c**, 116 mg), 4-bromo benzonitrile (**4d**, 91 mg) and ethylene (**5a**), with a 3 hours of residence time. Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellowish solid (81 mg, 70% yield). Mp 45.6 – 46.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.30 – 7.22 (m, 2H), 7.08 (dd, *J* = 5.3, 3.6 Hz, 1H), 6.63 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.29 (dd, *J* = 11.4, 1.3 Hz, 1H), 4.92 (dd, *J* = 17.9, 1.3 Hz, 1H), 2.73 (d, *J* = 7.5 Hz, 2H), 1.22 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 142.8, 139.4, 135.9, 134.1, 131.6, 130.8, 128.6, 127.5, 127.3, 121.5, 119.0, 110.2, 26.7, 15.2.

Dimethyl 2'-prop-2-en-1-ylbiphenyl-2,3'-dicarboxylate (6n) was synthesized following the GP 4 from methyl 2-iodo benzoate (**1a**, 262 mg) and propylene (**5b**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.47 – 7.40 (m, 1H), 7.31 – 7.18 (m, 3H), 5.76 (ddt, *J* = 12.2, 10.2, 3.9 Hz, 1H), 4.81 (d, *J* = 10.1 Hz, 1H), 4.57 (dd, *J* = 17.2, 1.6 Hz, 1H), 3.87 (d, *J* = 1.9 Hz, 3H), 3.66 – 3.54 (m, 4H), 3.41 – 3.28 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 167.2, 166.4, 143.4, 142.0, 141.4, 134.8, 133.0, 131.8, 131.3, 130.3, 130.2, 130.2, 129.3, 127.7, 127.7, 123.5, 52.3, 51.9, 51.5.

Dimethyl 2'-[(1*E*)-prop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (6n') was synthesized following the GP 4 from methyl 2-iodo benzoate (**1a**, 262 mg) and propylene (**5b**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellowish oil. The combined yield of **6n** and **6n'** is 83% (128 mg) with a **6n**:**6n'** ratio of 7:3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.8 Hz, 1H), 7.70 (dd, *J* = 6.3, 2.3 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.32 – 7.26 (m, 2H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.34 (d, *J* = 15.9 Hz, 1H), 5.32 (dq, *J* = 13.1, 6.5 Hz, 1H), 3.85 (s, 3H), 3.60 (s, 3H), 1.57 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 167.8, 142.3, 141.6, 137.2, 132.2, 131.8, 131.5, 131.5, 130.9, 130.6, 129.9, 128.5, 127.7, 127.1, 125.9, 52.0, 51.9, 18.7.

Methyl 3'-ethyl-2'-prop-2-en-1-ylbiphenyl-2-carboxylate (6o) and methyl 3'-ethyl-2'-[(1*E*)-prop-1-en-1-yl]biphenyl-2-carboxylate (6o') were synthesized following the GP 4 from 2-ethyl-1-iodo benzene (**1c**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and propylene (**5b**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (73 mg, 52% yield), with a **6o**:**6o'** ratio of 10:3. ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.7 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 0.3H), 7.54 (t, *J* = 7.5 Hz, 1.3H), 7.46 (t, *J* = 7.6 Hz, 1.3H), 7.42 – 7.38 (m, 0.3H), 7.35 – 7.20 (m, 4H), 7.09 – 7.03 (m, 0.3H), 6.99 (d, *J* = 6.9 Hz, 1H), 6.18 (d, *J* = 16.0 Hz, 0.3H), 5.78 (dq, *J* = 10.9, 5.7 Hz, 1H), 5.34 (dq, *J* = 13.0, 6.6 Hz, 0.3H), 4.93 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 17.1 Hz, 1H), 3.65 (d, *J* = 10.2 Hz, 4H), 3.32 (dd, *J* = 15.8, 5.5 Hz, 1H), 3.18 (dd, *J* = 16.1, 5.5 Hz, 1H), 2.81 – 2.71 (m, 2.6H), 1.63 (d, *J* = 6.5 Hz, 1H), 1.35 – 1.26 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 167.8, 143.8, 143.2, 142.6, 142.0, 141.7, 140.8, 136.9, 135.8, 134.2, 131.7, 131.7, 131.3, 131.1, 131.1, 130.4, 129.9, 129.6, 128.1, 127.4, 127.4, 127.1, 126.8, 126.8, 126.5, 126.2, 125.6, 114.9, 112.7, 89.7, 89.1, 51.8, 51.7, 34.1, 26.8, 25.7, 18.7, 15.2.

Methyl 3',5'-dimethyl-2'-prop-2-en-1-ylbiphenyl-2-carboxylate (6p) and methyl 3',5'-dimethyl-2'-[(1*E*)-prop-1-en-1-yl]biphenyl-2-carboxylate (6p') were synthesized following the GP 4 from 1-iodo-2,4-dimethylbenzene (**1i**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and propylene (**5b**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (66 mg, 47% yield), with a **6p:6p'** ratio of 2:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.2 Hz, 0.35H), 7.51 – 7.46 (m, 1.35H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 7.34 (td, *J* = 7.6, 1.3 Hz, 0.35H), 7.25 – 7.21 (m, 1.35H), 6.99 (s, 1.35H), 6.83 (s, 0.35H), 6.76 (s, 1H), 6.03 (d, *J* = 14.6 Hz, 0.35H), 5.69 (ddt, *J* = 16.0, 10.2, 5.8 Hz, 1H), 5.31 (dq, *J* = 16.0, 6.5 Hz, 0.35H), 4.88 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.71 (dd, *J* = 17.1, 1.9 Hz, 1H), 3.64 – 3.61 (m, 4.05H), 3.19 (dd, *J* = 16.0, 5.9 Hz, 1H), 3.07 (dd, *J* = 16.0, 5.7 Hz, 0.35H), 2.33 – 2.29 (m, 8.1H), 1.59 (dd, *J* = 6.5, 1.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 167.7, 143.7, 143.3, 141.7, 140.5, 136.6, 136.3, 135.3, 134.7, 133.3, 131.9, 131.7, 131.3, 131.2, 131.1, 130.4, 130.3, 130.3, 129.8, 129.5, 127.8, 127.6, 127.5, 127.0, 126.5, 114.8, 51.8, 34.5, 21.0, 21.0, 20.9, 19.8, 18.8.

Dimethyl 2'-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]biphenyl-2,3'-dicarboxylate (6q) was synthesized following the GP 4 from methyl 2-iodo benzoate (**1b**, 262 mg) and 3,3,3-trifluoroprop-1-ene (**5c**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (156 mg, 86% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.96 (t, *J* =

8.4 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 (dd, *J* = 11.4, 4.7 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 1H), 5.29 (dq, *J* = 16.3, 6.4 Hz, 1H), 3.88 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 167.2, 142.0, 141.2, 136.2 (q, *J* = 7.3 Hz), 134.0, 133.0, 131.8, 131.3, 130.3, 130.2, 129.9, 129.4, 127.8 (d, *J* = 3.2 Hz), 124.0, 121.3, 121.0 (q, *J* = 33.6 Hz), 52.2, 52.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.93 (dd, *J* = 6.4, 2.0 Hz).

Methyl 3'-ethyl-2'-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]biphenyl-2-carboxylate (6r) was synthesized following the GP 4 from 2-ethyl-1-iodo benzene (**1c**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and 3,3,3-trifluoroprop-1-ene (**5c**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (102 mg, 61% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 13.9 Hz, 2H), 5.38 (dq, *J* = 12.9, 6.3 Hz, 1H), 3.65 (s, 3H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 142.3, 142.2, 141.0, 135.1 (q, *J* = 7.2 Hz), 131.5, 131.4, 130.5, 130.0, 128.2, 127.7, 127.4, 127.1, 126.8, 124.1, 122.5, 122.2, 121.9, 121.6, 121.4, 51.9, 26.7, 15.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.75 (d, *J* = 6.3 Hz).

Methyl (E)-2-(1-(3,3,3-trifluoroprop-1-en-1-yl)naphthalen-2-yl)benzoate (6s) synthesized following the GP 4 from 1-iodo naphtalene (**1d**, 127 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and 3,3,3-trifluoroprop-1-ene (**5c**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as yellowish oil (111 mg, 62% yield). ^{1}H NMR (399 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 18.3, 7.9 Hz, 2H), 7.90 (dd, *J* = 17.0, 8.1 Hz, 2H), 7.62 – 7.52 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 13.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 5.73 (dq, *J* = 16.3, 6.4 Hz, 1H), 3.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 142.1, 138.7, 134.8 (q, *J* = 7.1 Hz), 132.8, 131.7, 131.5, 131.0, 130.5, 130.3, 128.9, 128.6, 128.3, 127.7, 127.4, 127.0, 126.0, 124.6, 124.1, 123.9, 123.5, 123.2, 122.9, 121.5, 52.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.62 (d, *J* = 6.3 Hz).

Methyl 3',5'-dimethyl-2'-[(1*E*)-3,3,3-trifluoroprop-1-en-1-yl]biphenyl-2-carboxylate (6t) was synthesized following the GP 4 from 1-iodo-2,4-dimethylbenzene (**1i**, 116 mg), methyl 2-bromo benzoate (**4a**, 108 mg) and 3,3,3-trifluoroprop-1-ene (**5c**). Purification by flash chromatography (Biotage KP SIL, gradient: 1-10 % Ethyl acetate in hexanes) to afford the product as colorless oil (110 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 6.97 (d, *J* = 16.4 Hz, 1H), 6.86 (s, 1H), 5.55 – 5.25 (m, 1H), 3.67 (s, 3H), 2.36 (d, *J* = 14.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 142.3, 141.3, 137.9, 136.0, 135.2 (q, *J* = 7.1 Hz), 131.6, 131.3, 130.6, 130.5, 130.0, 128.8, 127.9, 127.4, 124.4, 121.7, 121.0 (q, *J* = 33.1 Hz), 51.9, 21.1, 20.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ -64.43 (d, *J* = 6.2 Hz).

4.5. Bibliography

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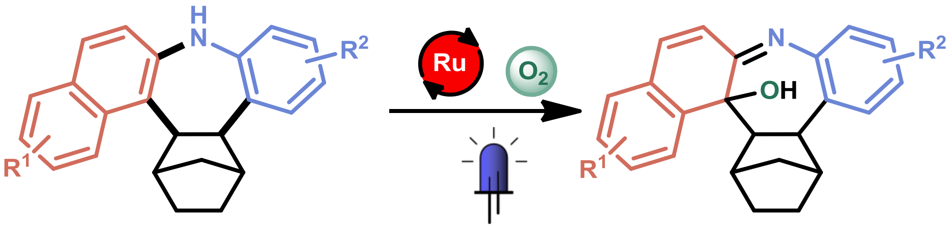
5. Dearomatization and Oxidation of Benzonaphthoazepine Derivatives by Photocatalysis

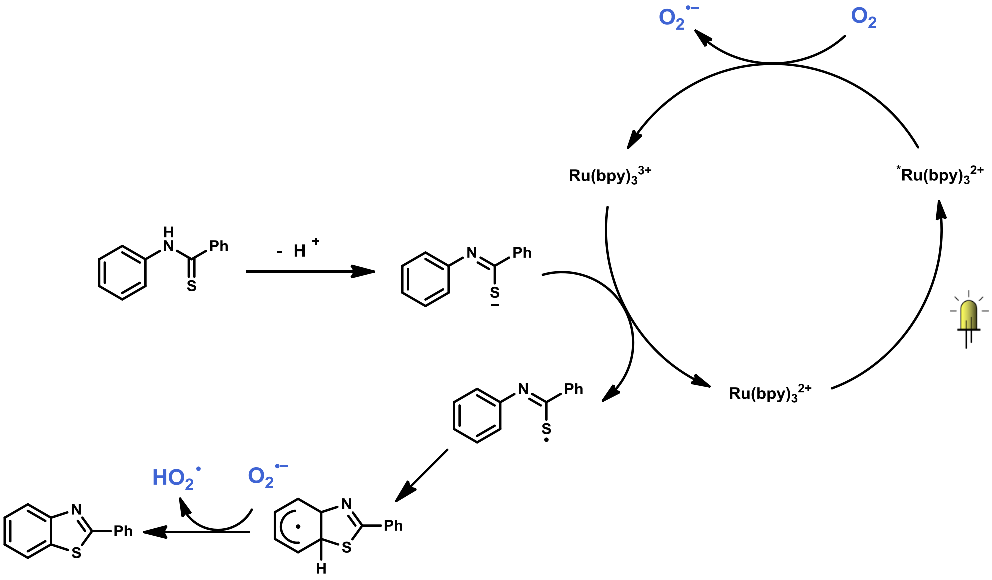


The main content of this chapter will be submitted asap:

A.Casnati, R. Maggi, G. Maestri, E. Motti, N. Della Ca’, *manuscript in preparation*

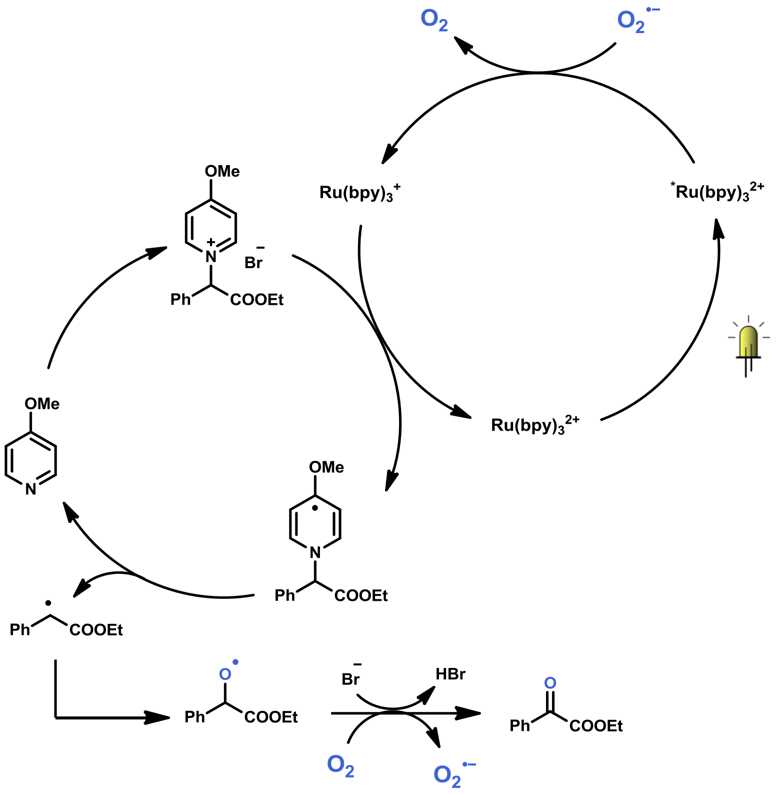
5.1. Introduction

Molecular oxygen is an abundant and benign chemical substance; the atmosphere is composed for the 21% of this valuable chemical indispensable for life on earth. Oxygen is widely employed in chemical applications, especially in the industrial sector[1], for its oxidation proprieties. However, O_2 is relatively stable and often requires high temperature and pressure to be activated in synthetically useful time. Thus, the adoption of molecular oxygen as well established reagent in laboratory scale synthesis remains a challenging goal for organic chemists[2,3]. The last ten years have witnessed a rise in the development of photochemical approaches to construct molecules in a sustainable manner[4–6]. The understanding of these light promoted reactions have allowed the disclosure of new chemical pathways, previously unexplored. The use of molecular oxygen as oxidant in photoredox catalysis is highly desirable due to the highly sustainable nature of this approach [7–11]. Oxygen, under photoredox conditions, can result in a single electron reduction[12–14] to form $O_2^{\cdot-}$ a superoxide radical anion. This step is found both in reductive or oxidative quenching cycles; in the first case oxygen oxidizes the catalyst to produce the active species. On the contrary, in the latter oxygen closes the photoredox catalytic cycle to restore the initial catalyst from its reductive form. In all of these examples oxygen is a sacrificial agent to promote diverse reactions. Li and coworkes[15] in 2011 reported the formation of C-S bond in the synthesis of benzothiazoles under aerobic conditions. In their mechanism oxygen acts as oxidative quencher of the Ru catalyst in the excited state, then the so formed superoxide radical anion abstract an hydrogen atom from an intermediate to afford the final product. Moreover molecular oxygen can also be incorporated in the final molecule when the product contains an oxygen atom.



Scheme 5.1 Benzothiazole formations via aerobic photoredox catalysis

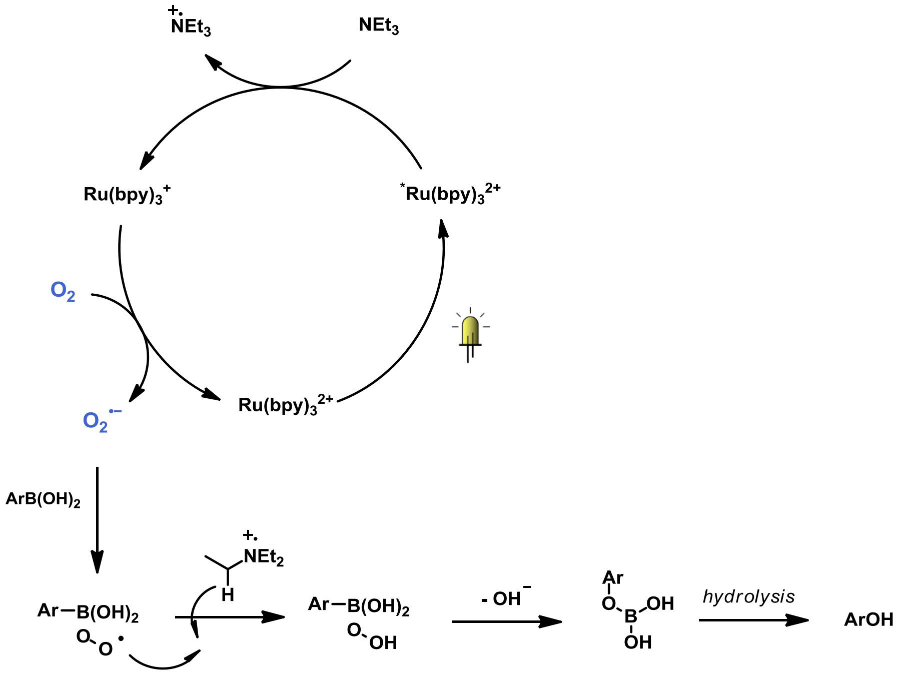
In 2011 Jiao[16] published an aerobic oxidation of benzyl halides under solar light, in his research oxygen appears in different step during the catalytic cycle; of course it represents the O source in the final ketones through the reaction of the preformed benzyl radicals with molecular oxygen. The superoxide radical anion is formed during the oxidation/deprotonation step to afford the final ketone and this strong reductant acts as reductive quencher in the Ru photoredox cycle.



Scheme 5.2 Aerobic oxidation of benzyl halides under solar light

In 2012 Xiao[17] reported the synthesis of phenols from arylboronic acids. In his publication molecular oxygen displays the oxidant role to afford $O_2^{\cdot -}$ and the so-formed superoxide can react with arylboronic acids due to its Lewis acidity and then provides the phenol after a series of rearrangements.

Inspired by these brilliant examples we envisioned the possibility to develop an oxidation and a consequent dearomatization of naphtobenzoazepine derivatives combining the effect of molecular oxygen and photocatalysis.



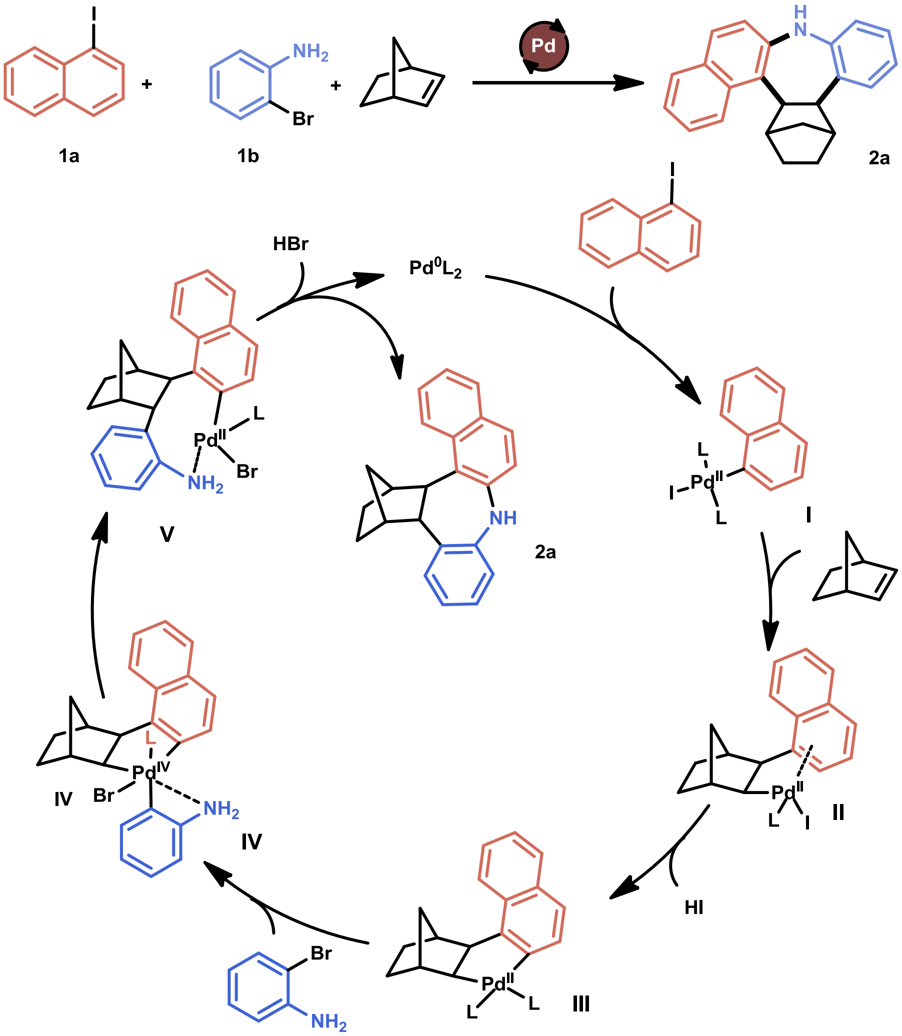
Scheme 5.3 Aerobic Oxidative Hydroxilation of aril boronic acids using photocatalysis

5.2. Results and discussion

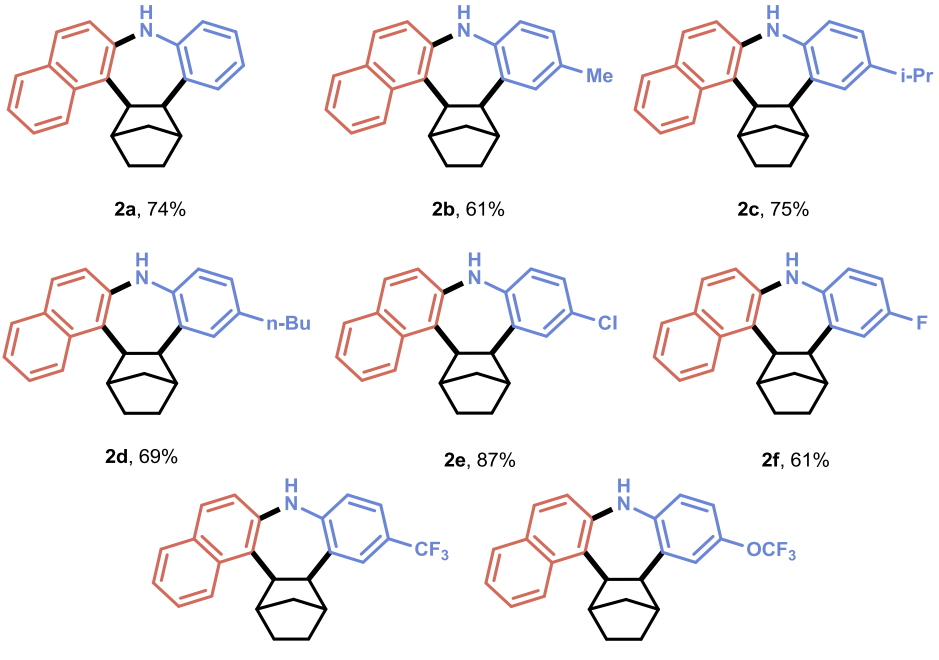
We started our investigation with the synthesis of naphtobenzoazepine derivatives taking advantage from our previously reported strategies[18,19]. The Catellani reaction is a powerful tool to achieve these complex molecules. The reaction involves the use of 1-iodonaphtalene and 2-bromoaniline as starting materials, in presence of a stoichiometric amount of norbornene and cesium carbonate, 5 mol% of palladium acetate and 12.5 mol% of triphenyl phosphine. The catalytic cycle begins with the oxidative addition of 1-iodonaphtalene on a palladium zero species, followed by the stereoselctive insertion of norbornene resulting in the cis,exo-arylnorbonyl palladium intermediate **II**. β-elimination is discouraged for steric reasons so the presence of a base promotes the C-H activation of the bond in *ortho* position with the formation of the palladacycle **III**. Then also the 2-bromoaniline undergoes to oxidative addition to form the complex **IV** where the NH_2 group acts as chelator for the palladium. This chelating effect facilitates the bond formation between the norbornene and C-sp_2 of the aniline providing complex **V**. The formation of the azepine derivatives is due to the intramolecular Buchwald-Hartwig reductive elimination together with the regeneration of the catalyst active species.

According to the above-described methodology, eight different azepine derivatives were successfully synthesized, bearing both electron withdrawing and electron donating groups. The derivatives **2a** was obtained with a satisfactory yield of 74%, while the presence of a Cl group in para position on the aniline ring, led to 87% yield of the corresponding azepine **2b**.

Alkyl fragments as methyl (**2e**), isopropyl (**2c**) and butyl (**2d**) provided good yield (respectively 61%, 75% and 69%). Fluorine containing 2-bromoanilines were also coupled providing the corresponding azepines **2f**, **2g** and **2h** in useful yields (61, 57 and 72 % of isolated yields).



Scheme 5.4 Catalytic cycle for the synthesis of naphtobenzo azepine derivatives



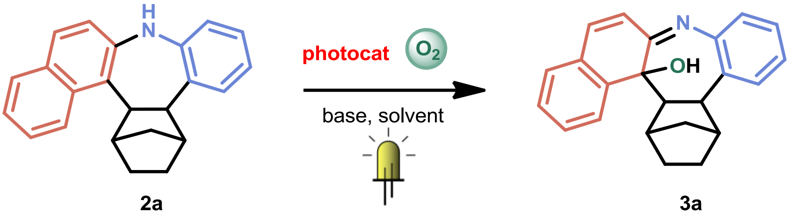
2a, 74% **2b**, 61% **2c**, 75%

2d, 69% **2e**, 87% **2f**, 61%

2g, 57% **2h**, 72%

Scheme 5.5 Aniline scope for the synthesis of naphtobenzo azepine derivatives; reaction conditions: $Pd(OAc)_2$ 5% mol, PPh_3 12.5% mol, Cs_2CO_3 (1 mmol), 1-iodonaphtalene (0.48 mmol), aniline derivative (0.44 mmol) and norbornene (0.53 mmol) in DMF (5 mL), 105 °C, 18h

Intrigued by the possibility to combine molecular oxygen with photocatalysis, we commenced our experiments with the substrate **2a** using different types of photocatalysts under oxygen (1 atm) and visible light. The initial conditions included 0.1 mmol of **2a**, 5% mol of photocatalyst, 2 equivalents of DIPEA with a concentration of 0.1 M. All reactions were run for 24 hours under oxygen atmosphere and visible light provided with white LEDs. A carful screening of solvents was conducted and aprotic polar solvents such as CH_3CN (**Table 5.1**, entry 1), DMF (entry 2) and DMSO (entry 4) provided encouraging results, obtaining the best performance with DMSO (70% of **3a** with 97% of selectivity). The observed byproduct was identified as the idroperoxide, coming from a competitive photoredox pathway (see **Scheme 5.8**). DCM (entry 5), toluene (entry 7) and a mixture of acetonitrile and hydrochloric acid (entry 3) were found not suitable for this transformation. Only 11% of product **3a** was detected using DCE. The amount of the base and the concentration resulted to play a fundamental role; a higher amount of DIPEA (entry 8) despite the high selectivity provided only 25% of yield. Increasing the concentration was detrimental for the selectivity (only 57%, entry 9), on the other hand lowering the concentration affected the productivity (27% of conversion, entry 10). Different catalysts were less effective than $[Ru(bpy)_3]Cl_2$, iridium complexes provided 11 and 33% yield of **3a** respectively (entries 11-12) while an organic dye such as methylene blue produced only traces of the expected product (entry 13). To confirm the effectiveness of this photoredox methodology, blank experiments were performed. In the absence of light (entry 14), base (entry 16) or catalyst (entry 17) only traces of product **3a** were detected. Replacing pure oxygen with air provided only 12% yield of **3a** (entry 15).



Scheme 5.6 Reaction scheme for the optimization study

Table 5.1 Optimization studies

Entry	**Photocatalyst (5% mol)**	**Solvent**	**Conv (%)[b] 2a**	**Yield (%)[b] 3a**	**Selectivity 3a (%)**
1	$[Ru(bpy)_3]Cl_2$	CH_3CN	31	24	77
2	$[Ru(bpy)_3]Cl_2$	DMF	54	46	85
3	$[Ru(bpy)_3]Cl_2$	CH_3CN:HCl[c]	-	-	-
4	$[Ru(bpy)_3]Cl_2$	DMSO	72	70	97
5	$[Ru(bpy)_3]Cl_2$	DCM	-	-	-
6	$[Ru(bpy)_3]Cl_2$	DCE	17	11	65
7	$[Ru(bpy)_3]Cl_2$	Toluene	-	-	-
8[d]	$[Ru(bpy)_3]Cl_2$	DMSO	26	25	96
9	$[Ru(bpy)_3]Cl_2$	DMSO (0.2 M)	42	24	57
10	$[Ru(bpy)_3]Cl_2$	DMSO (0.05 M)	27	26	96
11	$Ir(phpy)_3$	DMSO	16	11	69
12	$[Ir(dF(CF_3)ppy)_2(dbpy)]PF_6$	DMSO	42	33	78
13	methylene blue	DMSO	2	traces	-
14[e]	$[Ru(bpy)_3]Cl_2$	DMSO	8	traces	-
15[f]	$[Ru(bpy)_3]Cl_2$	DMSO	15	12	80
16[g]	$[Ru(bpy)_3]Cl_2$	DMSO	5	traces	-
17	-	DMSO	8	traces	

[a] Reaction conditions: **2a** (0.1 mmol), photocatalyst (5% mol), DIPEA (2 equiv), 0.1 M (1 mL solvent), 24 hours; [b] GC conversion and yield with an internal standard (C16); [c] no base present, HCl 1N, ratio 2.5:1; [d] 4 equivalents of DIPEA [e] absence of light; [f] air instead of pure oxygen; [g] no base present

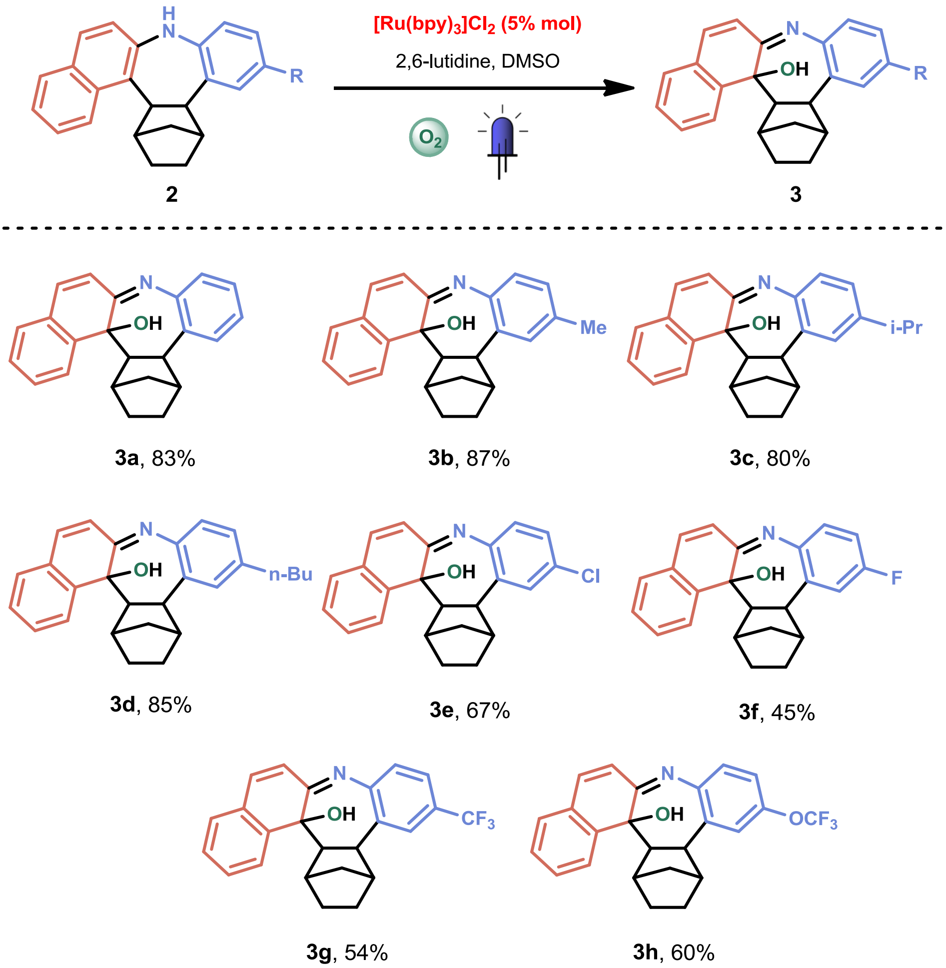
Table 5.2 Base screening

Entry	**BASE**	**Conversion (%)[b] 2a**	**Yield (%)[b] 3a**	**Selectivity 3a (%)**
1	DIPEA	72	70	97
2	Et_3N	69	67	98
3	DBU	63	61	98
4	2,6-dimetoxypyridine	43	43	100
5	2,6-lutidine	75	63	83
6	Ethyldicyclohexylamine	76	72	96
7	Diethylciclohexylamine	77	64	84
8	BEMP	27	24	90
9	MTBD	-	-	-
10	TMEDA	48	46	96
11[c]	DIPEA	76	74	99
12[c]	2,6-lutidine	86	83	96
13[c]	Ethyldicyclohexilammine	75	75	100

[a] Reaction conditions: **2a** (0.1 mmol), $[Ru(bpy)_3]Cl_2.6H_2O$ (5% mol), DIPEA (2 equiv), 0.1 M (1 mL solvent), 24 hours; [b] GC conversion and yield with an internal standard (C16); [c] blue LEDs were used

Then different bases were tested, Et_3N provided similar results to DIPEA (67% compared to 70%, **Table 5.2**, entries 1-2), also ethyldicyclohexylamine and diethylcyclohexylamine behaved almost the same with good yield (72 and 67% respectively, entries 6-7). DBU proved its effectiveness in the reaction conditions with 61% of yield combined with excellent selectivity (entry 3). Lower yield was obtained using the phophazene BEMP and the bifunctional ammine TMEDA (24 and 46% yield respectively, entries 8 and 10). MTBD was found not suitable for this transformation (entry 9). Pyridine derivatives, such as 2,6 dimethoxypiridine and 2,6 lutidine (entries 4-5), were also adequate for the oxidation/dearomatization reaction, especially the latter providing 63% of **3a**. DIPEA, 2,6-lutidine and ethyldicyclohexylamine were also tested using blue LEDs (entries 11-13) and 2,6-lutidine was selected as optimum yielding 83% isolated yield of **3a**.

Once that the optimized conditions were secured, the scope for the aniline fragment was investigated.



3a, 83% **3b**, 87% **3c**, 80%

3d, 85% **3e**, 67% **3f**, 45%

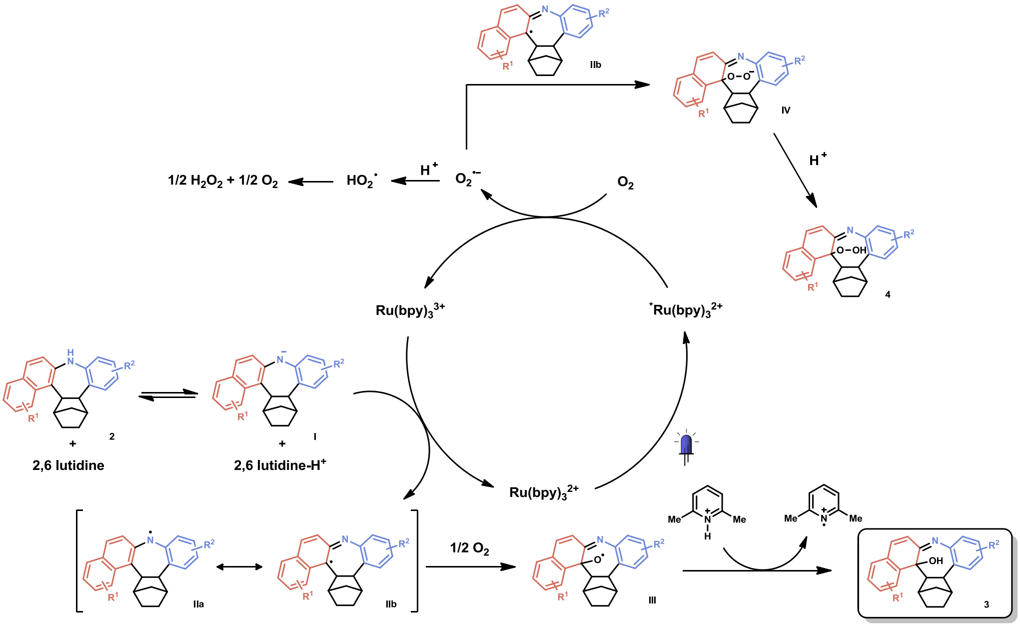
3g, 54% **3h**, 60%

Scheme 5.7 Scope for the aniline fragment in the photocatalytic oxidation and dearomatization of naphtobenzo azepine derivatives

Reaction conditions: **2** (0.1 mmol), [Ru(bpy)$_3$]Cl$_2$.6H$_2$O (5% mol), 2,6-lutidine (2 equiv), 0.1 M (1 mL DMSO), oxygen (1 atm), blue LEDs, 24 hours

Alkylic fragments proved to be highly tolerated in these reaction conditions resulting in good yields (**3b**, **3c**, **3d**). Azepine bearing halogen atoms such as chlorine (**3e**) and fluorine (**3f**) proved to be effective providing respectively 67% and 45% yields. Trifluoromethyl and trifluoromethoxy groups were also compatible and the products **3g** and **3h** were obtained in 54% and 60% yield.
According to blank experiments that ensured the necessity of photocatalyst, base and light for the reaction to take place, here a proposed mechanism is described. Experiments that will clarify in detail the mechanism are still ongoing in our research group.

The photoredox catalytic cycle is initiated by light from bleu LEDs that allows the transition of the $Ru(bpy)_3^{2+}$ to its excitated state $^*Ru(bpy)_3^{2+}$. Then oxygen acts as oxidative quencher to afford the oxidized $Ru(bpy)_3^{3+}$, providing also the superoxide radical anion $O2^{\cdot-}$. The catalyst is restored to its initial form through the single electron oxidation of the deprotonated substrate **I**. The deprotonation is an equilibrium between the initial azepine and the 2,6-lutidine and the intermediate **I** and the protonated 2,6-lutidine. This single electron oxidation step produces intermediate **IIa** with the radical centered on the nitrogen atom and its resonance structure **IIb** with the loss of the aromaticity on the adjacent aromatic ring of the naphthalene moiety and the radical on the carbon 15b. Intermediate **IIb** reacts with molecular oxygen to form the alkoxyradical [20–23] **III**, which affords product **3** by the protonated 2,6-lutidine. This species loses a proton and then an electron to afford the single electron oxidized 2,6-lutidine. Both the proton and the electron are captured by the intermediate **III** to afford **3**. The superoxide radical anion $O2^{\cdot-}$ can react with the intermediate **IIb** to generate the species **IV** which after protonation, gives the hydroperoxide byproduct **4**.



Scheme 5.8 Proposed photoredox mechanism

5.3. Conclusions

In summary, we have reported an efficient photocatalyzed methodology for the subsequent dearomatization and oxidation of naphtobenzo azepine derivatives. We tested different substituents on the aniline aromatic ring. Further studies are ongoing in our laboratory to enlarge the generality of this transformation and to support with experimental evidences the proposed catalytic cycle.

5.4. Experimental section

*Synthesis of 2-bromo anilines (**1**)*

A 250 mL round bottom flask equipped with a stirring bar, charged with 30 mL of CH_3CN was cooled down to 0 °C by ice-bath and aniline derivative (5 mmol) was then dissolved to afford a homogeneous solution. N-bromosuccinimide (6.2 mmol, 1.1 g) was added in portions during 1 hour to the mixture. The reaction was followed via TLC and after the complete consumption of the starting material, the solvent was removed under reduced pressure. The residue was redissolved in 50 mL of CH_2Cl_2 and washed three times with water and then 2 times with NaCl (sat). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane/EtOAc as eluent.

*General procedure 1: Synthesis of naphtobenzoazepine derivatives (**2a-h**)*

A Schlenk-type flask, equipped with a magnetic stirring bar, was charged, under nitrogen, with Cs_2CO_3 (326 mg, 1.0 mmol), PPh_3 (14 mg, 0.055 mmol) and $Pd(OAc)_2$ (5 mg, 0.022 mmol) in DMF (5 mL). After 10 minutes under stirring, a DMF solution (5 mL) of the 1-iodonaphtalene (0.48 mmol, 70 μL), 2-bromoaniline **1** (0.44 mmol) and norbornene (50 mg, 0.53 mmol) was added. The resulting mixture was stirred in an oil bath at 105 °C for 18 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL) and washed with a saturated solution of NaCl (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane/EtOAc as eluent.

*General procedure 2: Photocatalytic procedure (products **3a-h**)*

An oven-dried test tube, equipped with a magnetic stirring bar, was charged, under nitrogen, with the naphtobenzoazepine derivative (0.1 mmol) and $Ru(bpy)_3Cl_2{\cdot}6H2O$ (5% mol, 0.005 mmol, 3.7 mg). The tube was sealed with a rubber stopper, evacuated and backfilled with nitrogen for three times, then dry DMSO (1 mL) was added under nitrogen. Then the internal atmosphere was changed removing nitrogen under vacuum and replacing it with oxygen. A balloon full of the same gas was added as a reservoir. The solution was stirred at room temperature under irradiation with visible light for 24 hours. The crude was then diluted with CH_2Cl_2 (20 mL) and washed with a saturated solution of NaCl (3 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure and the products were isolated by flash column chromatography on silica gel using mixtures of hexane/EtOAc as eluent.

11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2a): 2a was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromoaniline. The product **2a** was obtained as orange solid (Yield 74%, 108 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.37 – 7.26 (m, 2H), 7.17 (d, *J* = 6.7 Hz, 1H), 7.11 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.03 (td, *J* = 7.8, 1.4 Hz, 1H), 6.79 (td, *J* = 7.4, 1.1 Hz, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.20 (d, *J* = 9.3 Hz, 1H), 2.66 – 2.65 (m, 1H), 2.41 (d, *J* = 9.3 Hz, 1H), 2.10 (d, *J* = 11.0 Hz, 2H), 1.75 – 1.65 (m, 1H), 1.64 – 1.56 (m, 1H), 1.56 – 1.41 (m, 2H), 0.98 (d, *J* = 9.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 144.1, 141.6, 133.7, 132.5, 132.0, 129.3, 128.5, 126.9, 126.5, 126.3, 123.6, 123.0, 122.7, 122.4, 120.6, 119.6, 52.0, 49.0, 49.0, 45.4, 37.0, 31.0, 28.8.

10-methyl-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2b): 2b was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-methylaniline. The product **2b** was obtained as orange solid (Yield 61%, 87 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.36 – 7.25 (m, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 3.90 (d, *J* = 9.4 Hz, 1H), 3.14 (d, *J* = 9.1 Hz, 1H), 2.41 (d, *J* = 9.2 Hz, 1H), 2.18 (s, 1H), 2.12 (s, 1H), 2.07 (s, 1H), 1.73 – 1.65 (m, 1H), 1.59 (t, *J* = 8.9 Hz, 1H), 1.55 – 1.39 (m, 1H), 0.97 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 141.9, 133.8, 132.4, 129.3, 129.2, 128.5, 126.9, 126.8, 126.6, 123.4, 123.0, 122.6, 122.4, 119.7, 52.0, 49.1, 49.0, 45.6, 37.0, 31.1, 28.8, 20.2.

10-isopropyl-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2c): 2c was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-isopropilaniline. The product **2c** was obtained as dark orange solid (Yield 75%, 116 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.38 – 7.24 (m, 3H), 7.09 – 6.99 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.91 (d, *J* = 9.2 Hz, 1H), 3.17 (d, *J* = 9.2 Hz, 1H), 2.75 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.45 (d, *J* = 9.0 Hz, 1H), 2.13 (s, 1H), 2.07 (s, 1H), 1.73 – 1.56 (m, 2H), 1.54 – 1.38 (m, 2H), 1.16 – 1.12 (m, 5H), 0.97 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 142.2, 141.9, 140.6, 133.8, 132.3, 129.8, 129.3, 128.5, 126.8, 126.5, 124.0, 123.4, 122.9, 122.6, 122.4, 119.7, 52.2, 49.0, 45.5, 37.0, 32.7, 31.1, 28.9, 24.2, 24.0.

10-butyl-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2d): 2d was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-butylaniline. The product **2d** was obtained as dark yellow solid (Yield 69%, 111 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 1H), 7.31 – 7.24 (m, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 1H), 3.92 (d, *J* = 9.4 Hz, 1H), 3.17 (d, *J* = 9.3 Hz, 1H), 2.48 – 2.37 (m, 3H), 2.09 (d, *J* = 20.4 Hz, 2H), 1.76 – 1.57 (m, 2H), 1.55 – 1.42 (m, 4H), 1.29 – 1.20 (m, 2H), 0.98 (d, *J* = 9.1 Hz, 1H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 142.0, 141.9, 134.4, 133.8, 132.3, 131.8, 129.3, 128.5, 126.8, 126.5, 126.2, 123.4, 123.0, 122.6, 122.4, 119.6, 52.0, 49.0, 49.0, 45.5, 37.0, 34.0, 33.4, 31.1, 28.9, 21.7, 13.8.

10-chloro-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2e): 2e was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-chloroaniline. The product **2e** was obtained as orange solid (Yield 87%, 132 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.75 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.63 – 7.58 (m, 2H), 7.53 – 7.47 (m, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.06 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.91 (d, *J* = 9.3 Hz, 1H), 3.20 (d, *J* = 9.3 Hz, 1H), 2.34 (d, *J* = 9.5 Hz, 1H), 2.13 (d, *J* = 2.3 Hz, 1H), 2.07 (d, *J* = 2.3 Hz, 1H), 1.74 – 1.56 (m, 2H), 0.99 (d, *J* = 9.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 143.2, 141.1, 134.6, 133.7, 131.1, 129.5, 128.6, 127.1, 126.7, 126.1, 124.0, 123.6, 123.1, 122.9, 122.3, 121.4, 51.6, 49.1, 49.0, 45.3, 37.1, 30.9, 28.7.

10-fluoro-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2f): 2f was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-fluoroaniline. The product **2f** was obtained as light brown solid (Yield 61%, 88 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.06 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.7 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.44 (s, 1H), 7.35 – 7.27 (m, 2H), 7.12 (dd, *J* = 8.7, 5.4 Hz, 1H), 7.02 (dd, *J* = 9.9, 2.8 Hz, 1H), 6.87 (td, *J* = 8.4, 2.9 Hz, 1H), 3.89 (d, *J* = 9.3 Hz, 1H), 3.15 (d, *J* = 9.3 Hz, 1H), 2.43 (d, *J* = 9.3 Hz, 1H), 2.15 (s, 1H), 2.07 (s, 1H), 1.71 – 1.55 (m, 2H), 1.53 – 1.36 (m, 2H), 0.98 (d, *J* = 9.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 156.6 (d, *J* = 236.8 Hz), 141.7, 141.0, 134.5 (d, *J* = 6.7 Hz), 133.7, 129.4, 128.5, 127.0, 126.6, 123.6, 122.9 (d, *J* = 18.9 Hz), 122.3, 121.0 (d, *J* = 7.9 Hz), 117.7, 117.5, 113.0, 112.8, 51.7, 49.0, 48.9, 45.3, 37.2, 31.0, 28.7. ^{19}F NMR (376 MHz, DMSO) δ -123.92.

10-(trifluoromethyl)-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2g): 2g was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-trifluoromethylaniline. The product **2g** was obtained as light brown solid (Yield 57%, 95 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.08 (d, *J* = 8.8 Hz, 1H), 7.83 (s, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.36 – 7.30 (m, 3H), 7.07 (d, *J* = 7.8 Hz, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.27 (d, *J* = 9.2 Hz, 1H), 2.30 (d, *J* = 9.5 Hz, 1H), 2.09 (d, *J* = 8.1 Hz, 2H), 1.73 – 1.55 (m, 2H), 1.54 – 1.37 (m, 2H), 0.97 (d, *J* = 9.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 144.5, 140.6, 136.8, 133.6, 133.1, 129.5, 128.6, 127.2, 126.7, 124.7 (d, *J* = 271.8 Hz), 123.9, 123.1, 123.0, 122.2, 116.9 (d, *J* = 3.8 Hz), 116.6 (d, *J* = 3.8 Hz), 51.9, 49.3, 49.0, 45.0, 37.1, 30.8, 28.7. ^{19}F NMR (376 MHz, DMSO) δ -60.94.

10-(trifluoromethoxy)-11b,12,13,14,15,15a-hexahydro-7H-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepine (2h): 2h was synthesized according to general procedure 1 from 1-iodonaphtalene and 2-bromo-4-

trifluoromethylaniline. The product **2g** was obtained as light brown solid (Yield 72%, 125 mg); ^{1}H NMR (400 MHz, DMSO) δ 8.07 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.67 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 1H), 3.92 (d, *J* = 9.3 Hz, 1H), 3.23 (d, *J* = 9.1 Hz, 1H), 2.37 (d, *J* = 9.3 Hz, 1H), 2.13 (s, 1H), 2.07 (s, 1H), 1.71 – 1.57 (m, 2H), 1.54 – 1.38 (m, 2H), 0.99 (d, *J* = 9.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 144.0, 142.2, 141.5, 134.6, 134.1, 129.9, 129.0, 127.5, 127.1, 124.7, 124.2, 123.5, 123.4, 122.7, 121.3, 120.7 (q, *J* = 254.8 Hz), 119.6, 52.1, 49.6, 49.4, 45.6, 37.6, 31.2, 29.2. ^{19}F NMR (376 MHz, DMSO) δ -57.07.

12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3a): 3a was synthesized according to general procedure 2 from **2a**. The product **3a** was obtained as yellow solid (Yield 83%, 27 mg; conversion 86%); ^{1}H NMR (400 MHz, DMSO) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.31 – 7.24 (m, 2H), 7.16 – 7.09 (m, 3H), 7.06 (d, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 9.7 Hz, 1H), 5.49 (s, 1H), 3.17 (d, *J* = 9.7 Hz, 1H), 2.69 (d, *J* = 9.7 Hz, 1H), 2.03 (d, *J* = 3.6 Hz, 1H), 1.79 (d, *J* = 9.9 Hz, 1H), 1.70 (s, 1H), 1.53 – 1.44 (m, 1H), 1.38 – 1.24 (m, 2H), 0.91 – 0.81 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 168.6, 147.4, 146.4, 136.2, 135.6, 131.2, 130.6, 129.4, 128.9, 128.1, 127.5, 127.2, 127.1, 125.6, 124.6, 73.7, 69.6, 55.1, 49.4, 37.4, 34.3, 31.5, 29.9.

10-methyl-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3b): 3b was synthesized according to general procedure 2 from **2b**. The product **3b** was obtained as yellow solid (Yield 87%, 30 mg; conversion 88%); ^{1}H NMR (400 MHz, DMSO) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.20 (m, 3H), 7.07 (d, *J* = 9.7 Hz, 1H), 6.94 (s, 3H), 6.37 (d, *J* = 9.7 Hz, 1H), 5.41 (s, 1H), 3.11 (d, *J* = 9.7 Hz, 1H), 2.65 (d, *J* = 9.7 Hz, 1H), 2.26 (s, 3H), 2.01 (d, *J* = 3.4 Hz, 1H), 1.75 (d, *J* = 9.9 Hz, 1H), 1.68 (s, 1H), 1.53 – 1.41 (m, 1H), 1.38 – 1.23 (m, 2H), 0.88 (d, *J* = 8.5 Hz, 1H), 0.82 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.8, 146.5, 145.1, 136.2, 135.0, 133.6, 131.7, 130.7, 129.7, 128.8, 128.3, 127.5, 127.2, 127.1, 126.3, 73.7, 69.4, 55.1, 49.4, 37.4, 34.2, 31.5, 29.9, 20.6.

10-isopropyl-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3c): 3c was synthesized according to general procedure 2 from **2c**. The product **3c** was obtained as yellow solid (Yield 74%, 27 mg; conversion 81%); ^{1}H NMR (400 MHz, DMSO) δ 7.64 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.29 – 7.25 (m, 2H), 7.07 (d, *J* = 9.7 Hz, 1H), 7.04 – 6.96 (m, 3H), 6.39 (d, *J* = 9.7 Hz, 1H), 5.44 (s, 1H), 3.16 (d, *J* = 9.6 Hz, 1H), 2.84 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.67 (d, *J* = 9.7 Hz, 1H), 2.01 (d, *J* = 3.6 Hz, 1H), 1.76 (d, *J* = 9.9 Hz, 1H), 1.70 (d, *J* = 2.2 Hz, 1H), 1.54 – 1.41 (m, 1H), 1.39 – 1.26 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H), 0.92 – 0.85 (m, *J* = 8.4 Hz, 1H), 0.82 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 167.8, 146.5, 145.4, 144.6, 136.1, 134.9, 130.7, 129.7, 129.1, 128.8, 128.4, 127.5, 127.2, 127.1, 123.4, 73.7, 69.3, 55.3, 49.5, 37.5, 34.1, 33.0, 31.6, 29.9, 24.1, 24.0.

10-butyl-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3d): 3d was synthesized according to general procedure 2 from **2d**. The product **3d** was obtained as yellow solid (Yield 85%, 32 mg; conversion 86%); ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.30 – 7.22 (m, 2H), 7.07 (d, *J* = 9.7 Hz, 1H), 7.01 – 6.89 (m, 3H), 6.38 (d, *J* = 9.7 Hz, 1H), 5.43 (s, 1H), 3.13 (d, *J* = 9.7 Hz, 1H), 2.66 (d, *J* = 9.6 Hz, 1H), 2.56 – 2.50 (m, *J* = 8.8, 7.1 Hz, 2H), 2.00 (d, *J* = 3.4 Hz, 1H), 1.75 (d, *J* = 9.8 Hz, 1H), 1.68 (s, 1H), 1.56 (dt, *J* = 15.4, 7.6 Hz, 2H), 1.51 – 1.42 (m, 1H), 1.34 (dd, *J* = 14.9, 7.5 Hz, 3H), 1.29 – 1.21 (m, 1H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.88 – 0.78 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 168.2, 146.9, 145.7, 139.0, 136.5, 135.4, 131.4, 131.2, 130.1, 129.2, 128.8, 127.9, 127.6, 127.5, 125.9, 74.1, 69.8, 55.6, 49.9, 37.9, 34.9, 34.5, 33.7, 31.9, 30.3, 22.4, 14.3.

10-chloro-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3e): 3e was synthesized according to general procedure 2 from **2e**. The product **3e** was obtained as dark yellow solid (Yield 67%, 24 mg; conversion 74%); ^{1}H NMR (400 MHz, DMSO) δ 7.62 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.32 – 7.25 (m, 2H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.19 – 7.12 (m, 2H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 9.7 Hz, 1H), 5.58 (s, 1H), 3.14 (d, *J* = 9.8 Hz, 1H), 2.66 (d, *J* = 9.7 Hz, 1H), 2.05 (d, *J* = 3.8 Hz, 1H), 1.75 (d, *J* = 10.2 Hz, 1H), 1.69 (d, *J* = 2.9 Hz, 1H), 1.51 – 1.41 (m, 1H), 1.36 – 1.23 (m, 2H), 0.85 (d, *J* = 10.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.8, 147.0, 146.7, 139.0, 136.6, 131.0, 130.8, 130.0, 129.6, 129.5, 128.6, 128.0, 127.8, 127.5, 125.9, 74.2, 69.9, 54.9, 49.7, 37.8, 34.9, 31.7, 30.3.

10-fluoro-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol *(*3f): 3f was synthesized according to general procedure 2 from **2f**. The product **3f** was obtained as dark yellow solid (Yield 45%, 16 mg; conversion 61%); ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.23 (m, 3H), 7.15 – 7.03 (m, 2H), 7.02 – 6.91 (m, 2H), 6.38 (d, *J* = 9.7 Hz, 1H), 5.54 (s, 1H), 3.15 (d, *J* = 9.7 Hz, 1H), 2.66 (d, *J* = 9.7 Hz, 1H), 2.05 (d, *J* = 3.6 Hz, 1H), 1.75 (d, *J* = 10.0 Hz, 1H), 1.69 (s, 1H), 1.51 – 1.41 (m, 1H), 1.39 – 1.20 (m, 2H), 0.84 (d, *J* = 9.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 168.9, 159.4 (d, *J* = 241.8 Hz), 146.7, 144.6, 139.4 (d, *J* = 7.2 Hz), 136.0, 131.1, 130.3, 130.2, 129.8, 129.4, 128.0, 127.7, 127.6, 117.4 (d, *J* = 21.7 Hz), 112.6 (d, *J* = 21.6 Hz), 74.1, 69.7, 55.1, 49.7, 37.8, 34.7, 31.8, 30.2. ^{19}F NMR (376 MHz, DMSO) δ -119.46.

10-(trifluoromethyl)-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3g): 3g was synthesized according to general procedure 2 from **2g**. The product **3g** was obtained as yellow solid (Yield 54%, 21 mg; conversion 56%); ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.42 – 7.26 (m, 6H), 7.21 (d, *J* = 9.7 Hz, 1H), 6.42 (d, *J* = 9.7 Hz, 1H), 5.65 (s, 1H), 3.25 (d, *J* = 9.7 Hz, 1H), 2.70 (d, *J* = 9.6 Hz, 1H), 2.07 (s, 1H), 1.77 (d, *J* = 9.8 Hz, 1H), 1.71 (s, 1H), 1.54 – 1.43 (m, 1H), 1.41 – 1.27 (m, 2H), 0.88 (d, *J* = 9.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 170.7, 148.1, 146.2, 140.9, 137.0, 132.3, 130.5, 129.3, 128.9, 127.7, 127.6, 127.1, 124.1 (d, *J* = 3.8 Hz), 120.6 (d, *J* = 3.4 Hz), 73.9, 69.7, 54.8, 49.3, 37.4, 34.6, 31.3, 29.9. ^{19}F NMR (376 MHz, DMSO) δ -60.85.

10-(trifluoromethoxy)-12,13,14,15,15a,15b-hexahydro-11bH-12,15-methanodibenzo[b,d]naphtho[1,2-f]azepin-15b-ol (3h): 3h was synthesized according to general procedure 2 from **2h**. The product **3h** was obtained as dark yellow solid (Yield 60%, 25 mg; conversion 84%); ^{1}H NMR (400 MHz, DMSO) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.24 (m, 3H), 7.21 – 7.04 (m, 4H), 6.40 (d, *J* = 9.6 Hz, 1H), 5.61 (s, 1H), 3.18 (d, *J* = 9.8 Hz, 1H), 2.67 (d, *J* = 9.7 Hz, 1H), 2.04 (d, *J* = 3.4 Hz, 1H), 1.75 (d, *J* = 10.0 Hz, 1H), 1.69 (s, 1H), 1.49 – 1.42 (m, 1H), 1.38 – 1.25 (m, 2H), 0.86 (d, *J* = 9.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 169.7, 146.8, 146.3, 144.6, 138.5, 136.4, 130.6, 129.4, 129.1, 127.7, 127.4, 127.1, 123.2, 120.3 (d, *J* = 255.5 Hz), 118.1, 73.8, 69.4, 54.6, 49.4, 37.4, 34.5, 31.4, 29.8. ^{19}F NMR (376 MHz, DMSO) δ -56.64.

5.5. Bibliography

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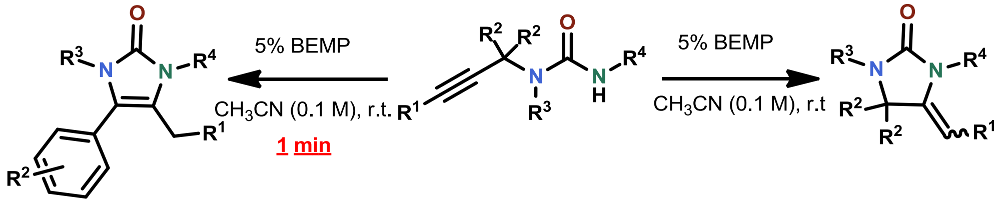
6. Expeditious Synthesis of Imidazolidin-2-ones and Imidazol-2-ones via Base-Catalyzed Intramolecular Hydroamidation of Propargylic Ureas under Ambient Conditions

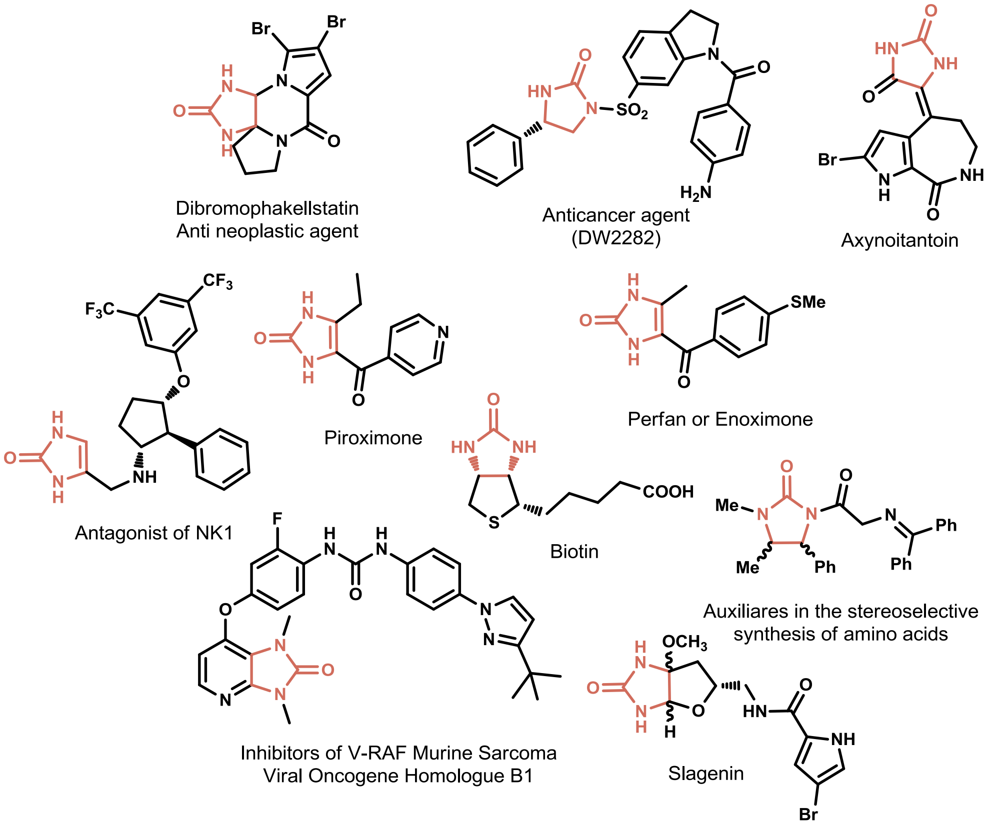


The main content of this chapter has been submitted for pubblication:

A. Casnati, A. Perrone, P. P. Mazzeo, A. Bacchi, R. Mancuso, B. Gabriele, R. Maggi, G. Maestri, E. Motti, A. Stirling and N. Della Ca'; Expeditious Synthesis of Imidazolidin-2-ones and Imidazol-2-ones via Base-Catalyzed Intramolecular Hydroamidation of Propargylic Ureas under Ambient Conditions; *submitted*

6.1. Introduction

Imidazol-2-ones and their analogues play an important role in pharmaceutical and medicinal chemistry due to the presence of this moiety in a wide variety of biologically active compounds[1–6]. They exhibit antitumor, antiviral and antibacterial proprieties; moreover they can act as inhibitor for different human receptors. 5-member cyclic ureas have been used also as intermediates in the synthesis of many natural product[7–9] such as Biotin and Slagenin. Their importance is also displayed in the chiral synthesis of amino acid[10–12] where they serve as stereoselectivity inductors.



Dibromophakellstatin
Anti neoplastic agent

Anticancer agent
(DW2282)

Axynoitantoin

Piroximone

Perfan or Enoximone

Antagonist of NK1

Biotin

Auxiliares in the stereoselective
synthesis of amino acids

Inhibitors of V-RAF Murine Sarcoma
Viral Oncogene Homologue B1

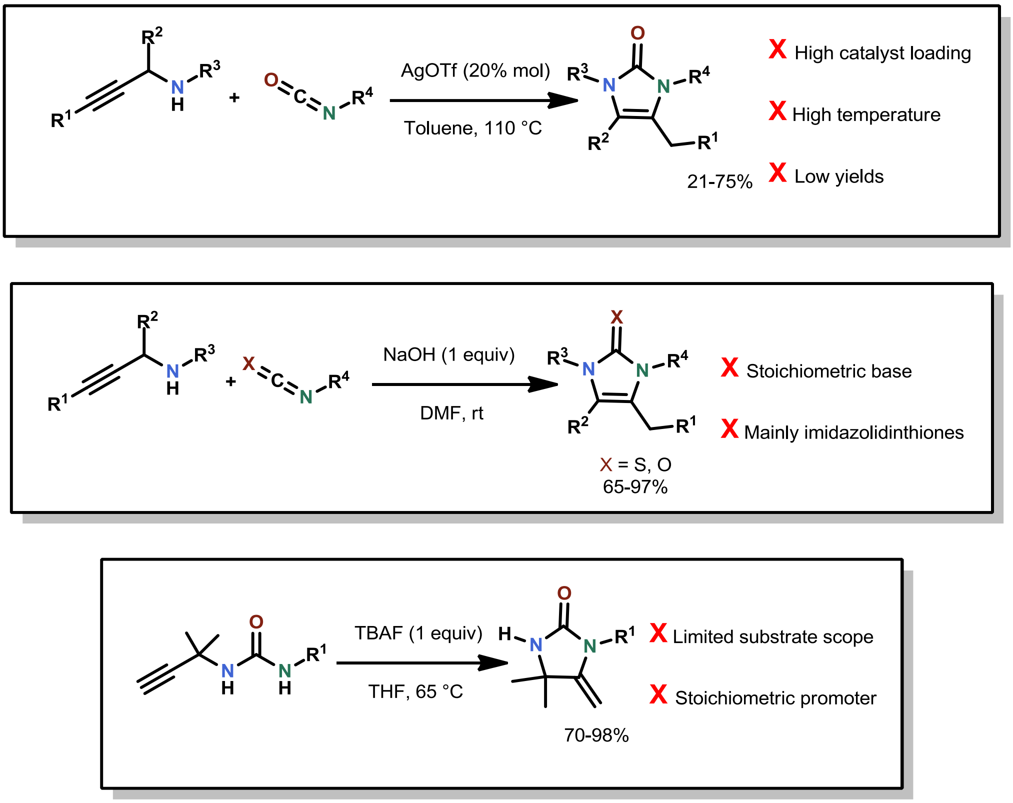
Slagenin

Figure 6.1 Selected bioactive 2-imidazol(idin)one derivatives

The high value of heterocyclic compounds for synthetic and pharmaceutical chemistry has driven the continuous efforts in the development of sustainable and more efficient protocols. Traditional synthetic routes to imidazolin-2-ones and imidazolidin-2-ones include (1) carbonylation/carboxylation of amines[13–29], (2) metal-catalyzed diamination of olefins[30,31], (3) and aziridine ring expansion[32–34]. In addition, intramolecular hydroamidation of propargylic ureas[35–46] represents an environmentally friendly and sustainable strategy to easily access 5-membered cyclic ureas. Transition metal-catalysts are generally employed to control the chemo- (O *vs* N cyclization) and regio- (Markovnikov *vs* anti-Markovnikov) selectivity of the urea cyclization step[35,40,47].

An Ag(I)-catalyzed one-pot protocol for the synthesis of 2-imidazolones through cycloisomerization of an *in situ* formed propargylic urea, was disclosed by Van der Eycken[36]. More recently, Reddy[48] and coworkers have reported the synthesis of indole-cyclic urea fused derivatives through an Ag-catalyzed sequence that involves an elegant double intramolecular hydroamidation process. Although interesting, these methods are limited by the high catalyst loading (20 to 30%), harsh reaction conditions and low reaction yields.

The selective *5-exo-dig* cyclization of propargylic ureas to imidazol-2-ones and imidazolidin-2-ones has also been achieved with metal-free protocols that employ stoichiometric amount of bases or salts. Recently, NaOH[39] and NaH[41] were employed for the regio-selective synthesis of imidazole-2-thione and *N*-amino-imidazolin-2-ones, respectively, under mild conditions and large substrate scope. In 2014 Huguenot[42] and coworkers reported a synthetic strategy for the cyclization of the preformed propargylic urea using a stoichiometric amount of tetrabutylammonium fluoride in THF at 65 degrees. Unfortunately, the authors reported only few substrates that undergo to this cyclization.

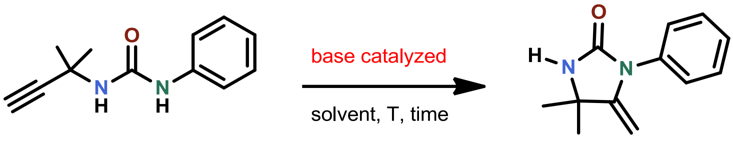


Scheme 6.1 Examples of synthesis of imidazolin-2-ones and imidazolidin-2-ones

Despite the usefulness of these methods, a base-catalyzed intramolecular hydroamidation to imidazol-2-one derivatives is of high demand and, to date is totally unprecedented.

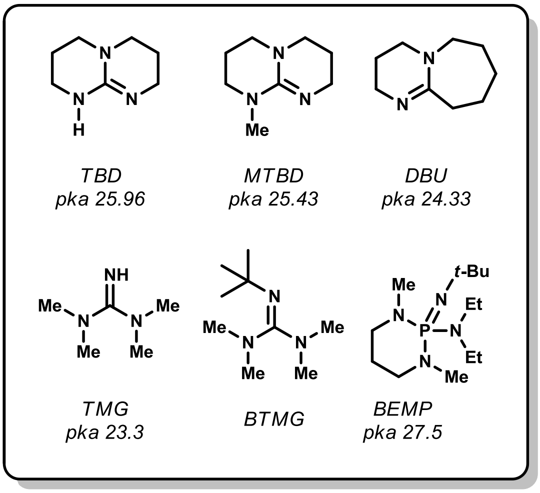
6.2. Results and discussion

Herein, we wish to disclose the first base-catalyzed intramolecular hydroamidation to highly substituted imidazolidin-2-ones and imidazol-2-ones. Notable features of our methodology include (i) excellent chemo- and regio-selectivity to 5-membered cyclic ureas, (ii) ample substrate scope and high functional group tolerance, (iii) very mild reaction conditions and short reaction times, (iv) key mechanistic insights on the reaction pathways. Further, we demonstrated the feasibility of the one-pot step-economical protocol starting from propargylic amines and isocyanates. Inspired by recent studies published by our research group [49], we started to investigate the base-catalyzed intramolecular hydroamidation reaction of propargylic urea **1a**, prepared from 2-methylbut-3-yn-2-amine and phenyl isocyanate according to the literature [43]. The guanidine base TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene), which turned out to be the catalyst of choice in the synthesis of imidazolidinones from propargylic amines, primary amines and CO_2, was initially considered. In the presence of 10% of TBD at 100 °C in dry acetonitrile, propargylic urea **1a** converted quantitatively to imidazolidinone **2a** (**Table 6.1**, entry 1). To our delight, excellent results were equally achieved at lower temperatures (entries 2 and 3) and, therefore, all subsequent experiments were tested at r.t.



1a **2a**

Scheme 6.2 Reaction scheme for the optimization studies



Scheme 6.3 Bases tested with their pka in MeCN pKa is referred to its conjugate acid in MeCN[50]. ^{e} Not determined, but a value within 23.5 and 24.5 could be assigned[51,52].

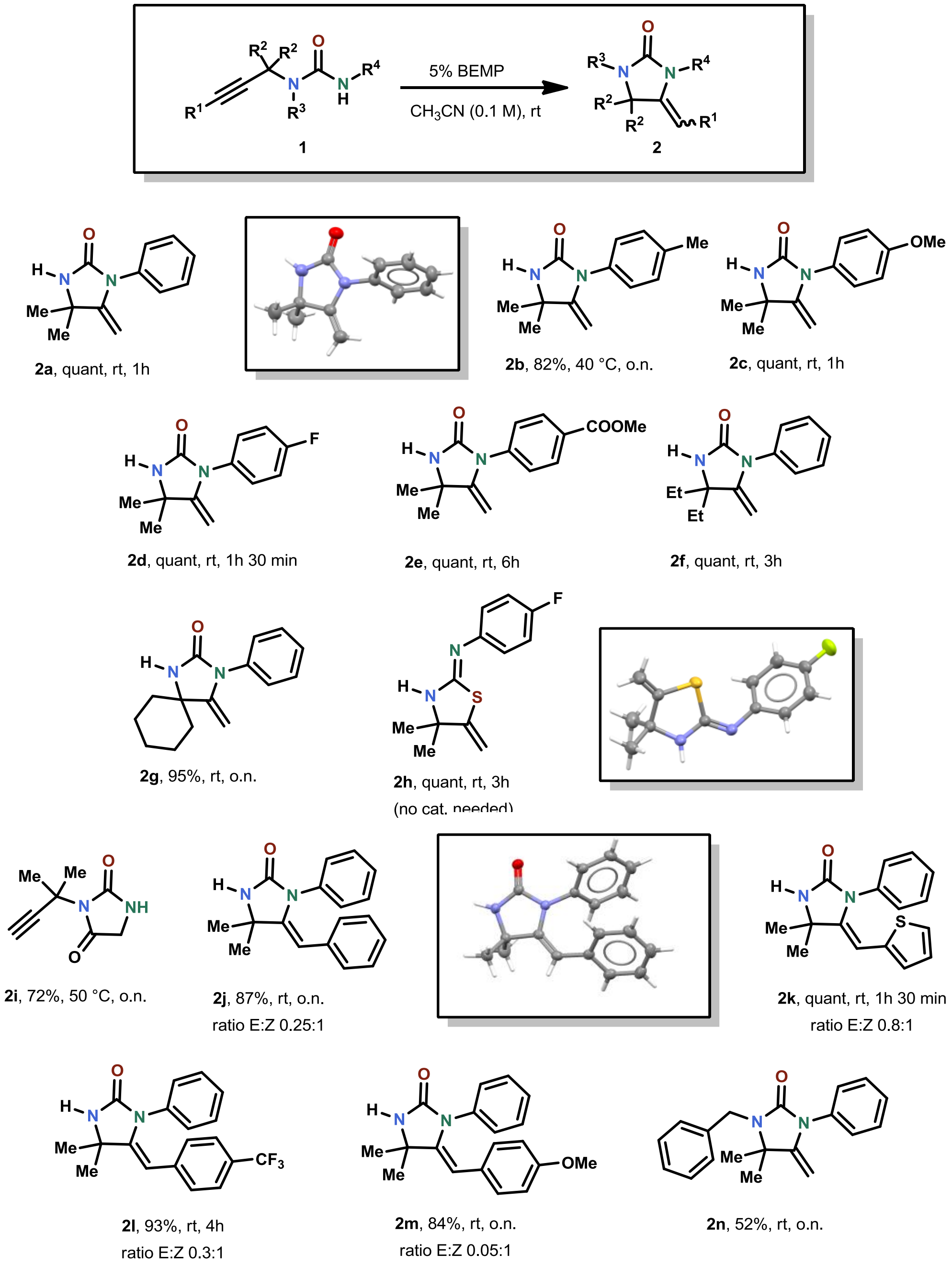
A series of organic basis presenting different *pka* values were then evaluated (entries 4-7). MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) was found to be less effective since 48 h were needed for the full conversion (entry 4), while less basic DBU, TMG and BTMG turned out to be totally inactive in promoting the cyclization step (entries 5-7). Remarkably, the catalytic activity seemed to follow the strength of the bases. We then resorted to a phosphazene-type base, called BEMP, displaying a higher *pKa* value, which demonstrated its usefulness in other hydroamination reactions[53]. With our pleasure, the use of 10 mol% of BEMP afforded **2a** with quantitative yield and, more important, reaction time was dramatically reduced to 30 min (entry 8). This result was not obvious since, as we have previously reported, steric hindrance and hydrogen bridges together with basicity can influence the reaction course. This significant improvement let us to decrease the amount of catalyst up to 1 mol% preserving a high performance (entries 9 and 10). Other solvent were then tested (entries 11-13), and we found that MeCN was crucial under this reaction conditions. Notably, the presence of water in the mixture, detrimental for other protocols, did not affected the outcome (entry 14 to be compared with entry 9). Finally, a control experiment in the absence of catalyst was performed (entry 15).

Table 6.1 Optimization studies. Reaction conditions: **1a** (0.4 mmol), base (1-10 mol%), solvent (4 mL). [b] Yields of **2a** were determined via ^{1}H NMR analysis using methylbenzoate as internal standard. [c] H_2O

Entry	Base (mol %)	Solvent	T (°C)	t (h)	Yield (%)[b] 2a
1	TBD (10)	MeCN	100	24	99
2	TBD (10)	MeCN	50	24	99
3	TBD (10)	MeCN	r.t.	24	99
4	MTBD (10)	MeCN	r.t.	48	99
5	DBU (10)	MeCN	r.t.	48	-
6	TMG (10)	MeCN	r.t.	48	-
7	BTMG (10)	MeCN	r.t.	48	-
8	BEMP (10)	MeCN	r.t.	0.5	99
9	BEMP (5)	MeCN	r.t.	1	99
10	BEMP (1)	MeCN	r.t.	7	99
11	BEMP (5)	EtOAc	r.t.	24	-
12	BEMP (5)	THF	r.t.	24	-
13	BEMP (5)	MeOH	r.t.	24	-
14	BEMP (5)	MeCN[c]	r.t.	1	99
15	-	MeCN	r.t.	24	-

Under optimal conditions (**Table 6.1**, entry 9) various propargylic ureas having electron-donating or –withdrawing groups or heteroaromatic substituents reacted smoothly to give imidazolidin-2-ones in excellent yields (**Scheme 6.4**). Remarkably, valuable functional groups (OMe, F, CO_2Me, CF_3) were successfully tolerated by this simple and robust methodology. Reaction times were, however, significantly influenced by both electronic and steric effects. For instance, the increased hindrance on the quaternary sp^3 carbon, in between the N and the triple bond, consistently slowed down the reaction rate (**Scheme 6.4**,

2a, **2f**, **2g**). Unexpectedly, thiourea **1h** underwent selective intramolecular S-cyclization to thiazolidin-2-imine **2h** without catalyst. Structure of **2h** was confirmed by X-ray diffraction. Urea **1i** bearing an ester group in suitable position led to hydantoin **2i**, where the triple bond remained untouched. Ureas with an internal triple bond led to the corresponding imidazolidin-2-ones (**2j**, **2k**, **2l**, **2m**) in high yield but with a limited stereo-selectivity. In all cases, *Z* configuration, attributed by X ray crystallography (**2j**) and NOESY experiments, was the preferred one. An additional substituent on the nitrogen (R^3 = Bn) was less tolerated, leading to product **2n** in only 52% yield.



2a, quant, rt, 1h

2b, 82%, 40 °C, o.n.

2c, quant, rt, 1h

2d, quant, rt, 1h 30 min

2e, quant, rt, 6h

2f, quant, rt, 3h

2g, 95%, rt, o.n.

2h, quant, rt, 3h
(no cat. needed)

2i, 72%, 50 °C, o.n.

2j, 87%, rt, o.n.
ratio E:Z 0.25:1

2k, quant, rt, 1h 30 min
ratio E:Z 0.8:1

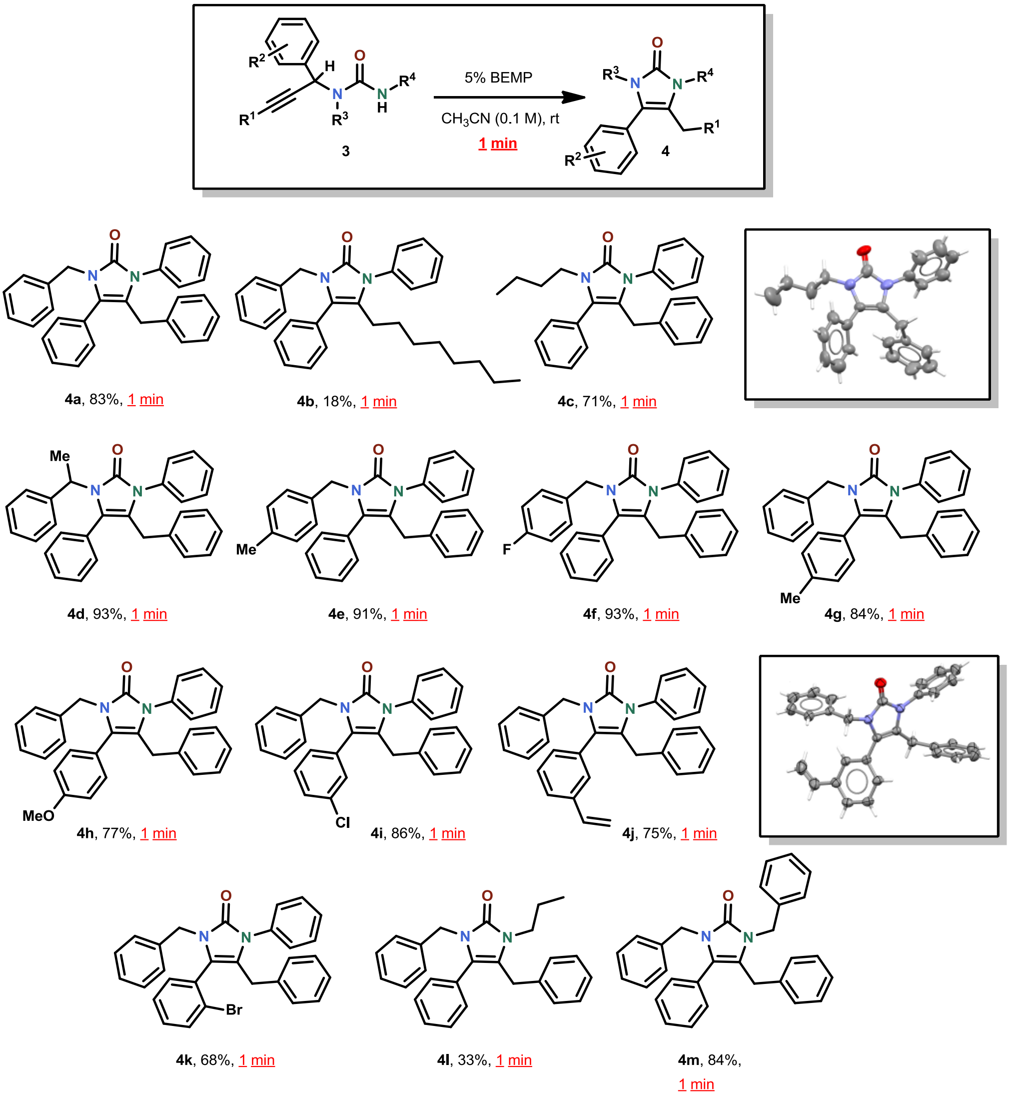
2l, 93%, rt, 4h
ratio E:Z 0.3:1

2m, 84%, rt, o.n.
ratio E:Z 0.05:1

2n, 52%, rt, o.n.

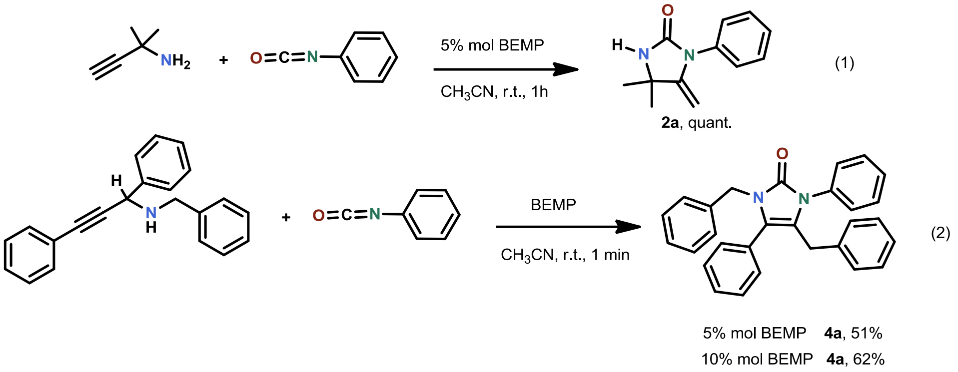
Scheme 6.4 Scope of the BEMP-catalyzed synthesis of imidazolidin-2-ones. Reaction conditions: **1** (0.4 mmol), BEMP (5 mol%), MeCN (4 mL), room temperature. Isolated yields of **2**.

We then explored the substrate scope of the transformation by employing a variety of propargylic ureas **3** having a C-H bond in *alpha* to the nitrogen (**Scheme 6.5**). In these cases, imidazol-2-ones **4**, displaying an internal double bond, were by far the preferred products and reaction times were impressively shortened to 1 minute, close to a *click reaction* performance. Our protocol was again characterized by a remarkable tolerance of valuable functional groups, as illustrated for chloro, bromo, fluoro, methoxy or vinyl substituents. Alkyl substituents in R^1 or R^4 gave, however, very poor results, achieving only 18% and 33% of **4b** and **4l** respectively. Contrary to what we observed with **2n** (**Scheme 6.4**), alkyl or benzyl substituents in R^3 led to excellent yield of product **4**, even when the steric hindrance on the carbon in *alpha* position increased (**4d**).



Scheme 6.5 Reaction conditions: **3** (0.4 mmol), BEMP (5 mol%), MeCN (4 mL), room temperature, 1 min. Isolated yields of **4**.

To further demonstrate the applicability of this protocol, the one-pot synthesis of imidazol-2-one derivatives starting from propargylic amines and isocyanates was performed under standard conditions. Gratifyingly, compound **2a** and **4a** were successfully prepared directly from the corresponding propargylic amines and isocyanates in high yield and very short reaction times (**Scheme 6.6**).



Scheme 6.6 Representative examples of the one-pot synthesis of imidazolidinin-2-ones and imidazolin-2-ones from propargylic amines and isocyanates.

Intrigued by the complete chemo- and site selectivity features as well as by the unexpected fast formation of imidazol-2-ones **4** under very mild conditions, we carried out computational studies to gain insights into the reaction mechanism.

Investigation begun employing the Gaussian03 package[54] using the range separated, hybrid ωb97xd functional[55]. The geometry optimizations, frequency calculations and the calculations of the Gibbs free energy contributions have been done using the 6-31+G* basis set (B_1). The solvent corrected energy of the optimized structures has been recalculated using the larger 6-311++G (3df,3pd) basis set (B_2) employing the SMD implicite solvation model[56]. The final Gibb free energy values for constructing the energy profiles have been obtained by $\Delta G_{solv} = \Delta G_{vrt}^{B_1} + E_{SMD}^{B_2}$, where $\Delta G_{vrt}^{B_1}$ is the sum of the vibrational, rotational, and translational thermal corrections to Gibbs free energy (harmonic oscillator, rigid rotor, ideal gas approximation, calculated on the smaller basis set B_1) while $E_{SMD}^{B_2}$ is the electronic energy calculated with SMD model (employing B_2). For the integrations, the *Ultrafine* grid point density has been selected. The nature of the optimized states has been verified by inspecting the vibrational spectrum of the structures (zero imaginary frequency for reactants, products and intermediates whereas 1 imaginary frequency for transition states). IRC and subsequent optimizations have been performed to verify that the TS-s connect the corresponding intermediate states.

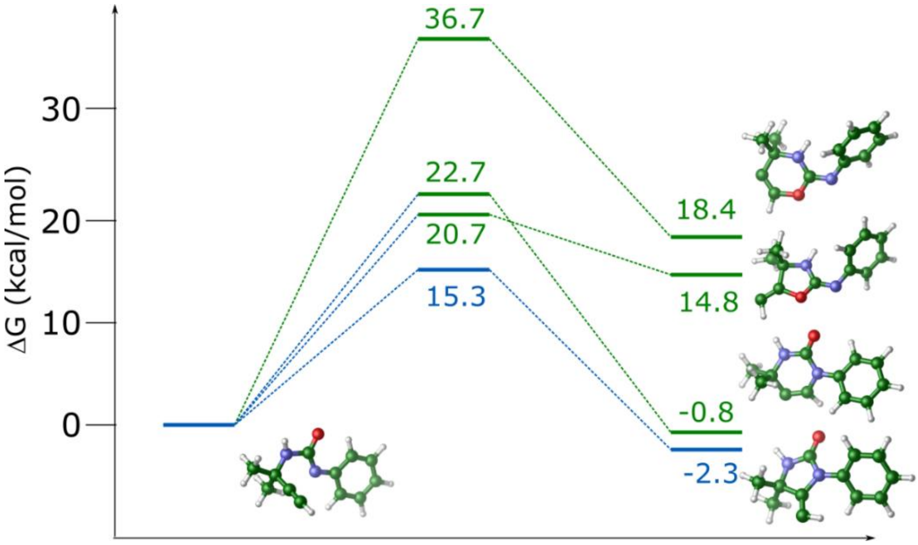


Figure 6.2 Comparison of the Gibbs free energy profiles of the possible cyclization routes. Blue profile: N-5-exo-dig route. Green profiles from top to bottom at the product states: O-6-endo-dig, O-5-exo-dig, N-6-endo-dig cyclizations. Note that the barriers shown here do not contain the free energy investments to reach the deprotonated state of molecules 1a (eg. with BEMP it is 5.3 kcal/mol) which would shift the levels upwards by that value.

In **Figure 6.2** we compare the possible 4 routes starting from the deprotonated **1a**. The Gibbs free energy levels are referenced to this deprotonated state. This can be done as we have seen that the protonated base and the deprotonated substrate prefer the separated state to association. For instance, the associated BEMPH$^+$/**1a**$^-$ state is 15.2 kcal/mol higher than the initial state where the base BEMP and the substrate **1a** are separated. The reaction free energy profiles show that both thermodynamically and kinetically the N-5-exo-dig cyclization is the most favorable route.

Figure 6.3 shows the most feasible mechanism to generate imidazolidinin-2-one **2a** from propargylic urea **1a**. The reaction starts with the abstraction of the urea proton by the base, which is a slightly endergonic process. We obtained good correlation between the pK_a of the bases and the energonicity of the deprotonation step[57]. The levels obtained with the strongest base (BEMP) are shown in blue. The deprotonation yields **1a-D-BEMPH+** (ΔG +5.5 kcal/mol). We note that after the proton transfer took place, the protonated base/deprotonated substrate pair prefers to be separated although the interaction between the two ionic species is also favorable. We explained this by the entropy penalty of the association of the two ions[58]. The deprotonated urea can then react with the triple bond in 4 different ways depending on the cyclization fashion: N- or O-carbon bond formation via 5-exo- or 6-endo-dig cyclization modes (as shown in **Figure 6.2**). We obtained that formation of the anionic form of product **2a** (**2a-D-N5**) is the most favorable path both kinetically and thermodynamically. Ultimately, the cyclization is followed by the strongly exergonic protonation yielding the product **2a** (ΔG -35.0 kcal/mol). The rate determining step is the cyclization which requires a moderate 20.8 kcal/mol activation free energy (from **1a** to **TS-N5**) in the presence of BEMP, which is fully compatible with the observed reaction rate[59]. Indeed, the stronger the base, the more effective it is as a catalyst, which correlates well with the experimental results listed in **Table 6.1**.

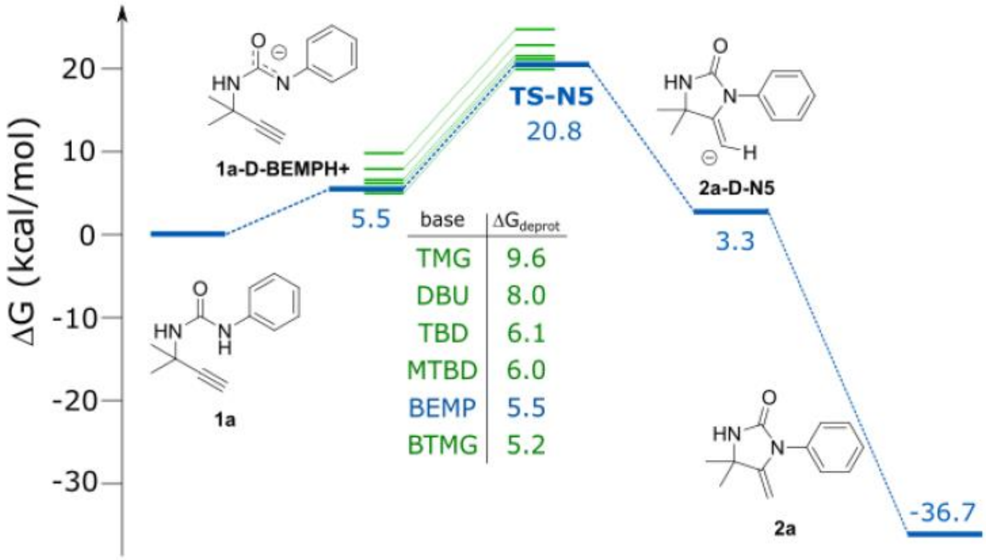


Figure 6.3 Gibbs free energy profile of the formation of imidazolidin-2-one **2a** (N-5-exo-dig cyclization pathway). Color code used for the effect of bases: blue: BEMP as base; green, from top to bottom: TMG, DBU, TBD, MTBD, BTMG as base. Note that for clarity we indicated the level-shifts only for the first two stages of the reactions although the next level is also shifted by the variation of the base. The initial and final state is not affected because the base is not protonated in these states (ie. a spectator).

Secondly, formation of imidazol-2-one **4a** from **3a** was investigated. The initial base-catalyzed isomerization of the triple bond to allene was the most favored pathways to imidazol-2-ones **4a** (**Figure 6.3**, blue pathway). Indeed, as shown in **Figure 6.4**, C-H moiety on **3a** (in red) is more acidic than the urea proton. An important consequence is that an initial allene formation is preferred to the direct deprotonation of the urea moiety (**Figure 6.4**, green pathway). Hence, the resting state under the reaction conditions is the allene structure. Then the N-H deprotonation leads to the formation of the imidazol-2-one ring (**4a-D-2**) and the final protonation yields the neutral product in a highly exergonic step. The calculations revealed that the central carbon of the allene moiety is the most electron-deficient, which explains the preference for the 5-membered ring formation. The barrier of this process is only 12.5 kcal/mol (from **I_1-D** to **TS$_{3-4}$**), which indicates a very fast reaction, in agreement with the experimental observations. Moreover, isomerization of the triple bond to allene moiety is highly plausible under strongly basic conditions[60] while similar intramolecular hydroamidation reactions are known under gold[61,62] and palladium[63] catalysis.

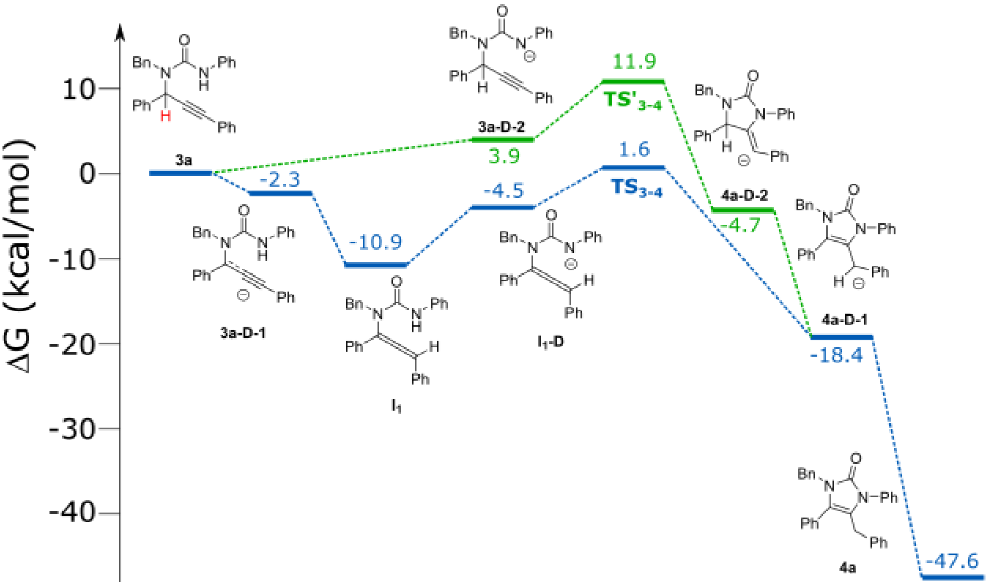


Figure 6.4 Gibbs free energy profile of the formation of imidazol-2-one **4a**, employing BEMP as catalyst. Blue profile: allene-route; green profile: mechanism analogue to the one presented in **Figure 6.2**.

When R^1, R^2 and R^3 substituents were all H (**Scheme 6.5**) the reaction did not proceed under the optimized reaction conditions. We have calculated both routes featuring either allene as intermediate or the direct C-N bond formation. The Gibbs free energy profiles are displayed in **Figure 6.5**.

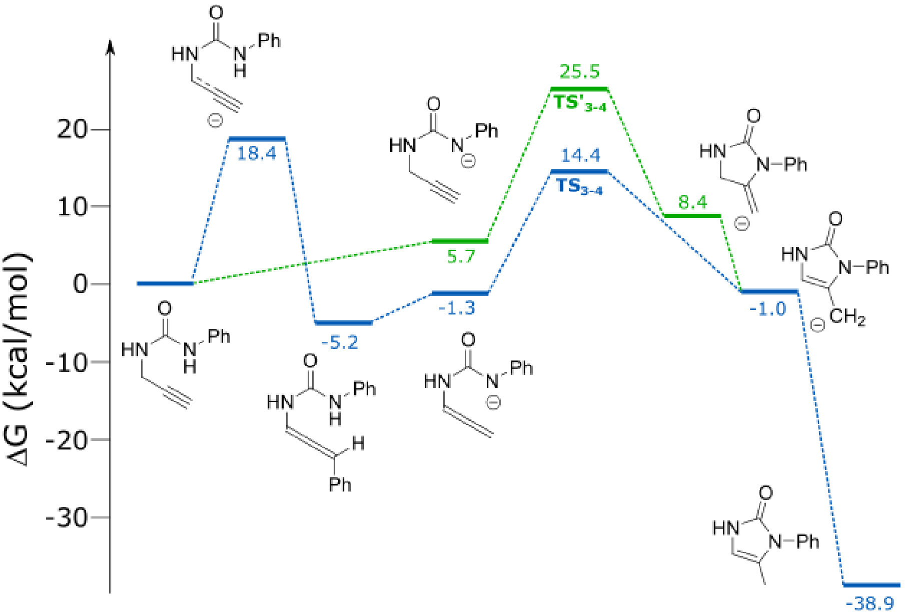


Figure 6.5. Gibbs free energy profiles for two possible ring closure mechanisms of 1-phenyl-3-(prop-2-yn-1-yl)urea **3n** employing BEMP as catalyst. Blue profile: allene-route; green profile: mechanism analogue to the one presented in **Figure 6.4**

We observed that the profiles feature generally higher barriers than the corresponding reactive routes (**Figures 6.3** and **6.4**). In particular the allene route is the preferred one, although we have a remarkably higher initial barrier compared to the one in **Figure 6.4**. The resting state is at level -5.2 kcal/mol as seen in the blue profile. For the green profile the barrier referenced to the resting state (-5.2 kcal/mol) is 30.7 kcal/mol which is too high for a reaction occurring at room temperature. We however noticed that the calculated barrier of the allene (blue) route is still compatible with a reaction occuring at the employed conditions albeit at a considearbly slower rate than what deduced from **Figure 6.4**. We speculated that additional factors not included into the computational model could play a role in the unreactivity of this compound (solubility issues, aggregation, not detected complex formations, etc.). An additional useful insight in these calculations is that the profiles demonstrate the favorable influences of the electron donating substituents (e.g aryl, benzyl) on these urea compounds.

Both the CH and NH acidities are enhanced, and the reactivity of the alkynyl chain is considerably increased.

6.3. Conclusions

In summary, we have developed the first organo-catalyzed method to access imidazolidin-2-ones and imidazol-2-ones from propargylureas under ambient conditions. The protocol is simple and provides 5-membered cyclic ureas in good to excellent yields. DFT calculations provided strong support for the non-assisted cyclization of deprotonated urea in the imidazolidin-2-one formation, and revealed the involvement of an allene intermediate in the imidazol-2-one pathway. The one-pot protocol starting from propargylic amines and isocyanates was also demonstrated.

6.4. Experimental section

General procedure 1: Synthesis of α-disubstituted propargylic urea[43]

A dry 2-necked flask containing a magnetic stir bar was charged with the selected isocyanate (2.5 mmol or 1 mmol), the selected α-disubstituted propargylic amine (2.5 mmol or 1 mmol) and dry THF (25 mL or 10 mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The yield is quantitative and the corresponding α-disubstituted propargylic urea was employed without need of purifications.

Sonogashira procedure for α-disubstituted propargylic urea[64]

To a Schlenk type flask equipped with a magnetic stirred was added $Pd(PPh_3)_2Cl_2$ (2%, 0.02 mmol) and CuI (7%, 0.07 mmol). The flask was purged with N_2 and Et_3N (5 mL) was added under N_2. The aryl iodide (1 equiv, 1 mmol) and the propargylic urea (1.2 equiv.) were dissolved in dry CH_2Cl_2 (7 mL) and then added. The reaction mixture was stirred at room temperature overnight. The crude mixture was filtered through a medium frit, the solid residue washed with CH_2Cl_2, and the combined organics were concentrated under reduced pressure. Purification via flash column chromatography yielded the desired aryl propargyl urea.

Synthesis of N-benzyl-2-methylbut-3-yn-2-amine[65]

A solution of 2-methylbut-3-yn-2-amine (519 µL, 5 mmol) and benzaldehyde (507 µL, 5 mmol) in MeOH (10 mL) was stirred at room temperature overnight. After that, sodium borohydride (378 mg, 10 mmol) was added to the solution. The reaction mixture was stirred at 0°C for 1 hour. Then the reaction was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (Eluent Hexane:Ethyl Acetate 7:3) to afford N-benzyl-2-methylbut-3-yn-2-amine (**1n**) in 55% yield (476 mg)

Synthesis of α-mono substituted secondary propargylic amine[66]

In a typical experiment, CuI (30% mol, 0.6 mmol) was charged in a test tube with a magnetic stirrer. The test tube was sealed and flushed with N2 and then was charged with alkyne (2 mmol), aldehyde (2 mmol), and amine (2 mmol). The test tube was then placed in an oil bath of 75 °C and was allowed to stir overnight. The crude reaction mixture was purified by silica gel column chromatography with a mixture of Hexane and Ethyl Acetate (95:5, 90:10, and 80:20) to provide the desired secondary propargylic amine.

General procedure 2: Synthesis of α-mono substituted propargylic urea[43]

A dry 2-necked flask containing a magnetic stir bar was charged with the selected isocyanate (1 mmol), the selected α-monosubstituted propargylic amine (1 mmol) and dry THF (10 mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The yield is quantitative and the corresponding α-disubstituted propargylic urea was employed without need of purifications. For alkylic and benzylic isocyanate a purification by silica gel column chromatography was required to afford the pure product.

General procedure 3: Catalytic reactions

A test tube equipped with a magnetic stirrer was charged with propargylic urea (0.4 mmol) and CH_3CN (4 mL). Then BEMP (5% mol, 6μL) was added. The reaction mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography with a mixture of hexane and ethyl acetate.

1-(2-methylbut-3-yn-2-yl)-3-phenylurea (1a): 1a was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1a** was obtained as white solid; m.p. (hexane) 116.3–117.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5H), 4.33 (bs, 2H), 2.28 (s, 1H), 1.54 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 139.5, 128.6, 127.4, 127.1, 87.8, 69.9, 46.7, 44.1, 30.2. MS (ESI) calcd for $C_{12}H_{14}N_2NaO$ (M-Na)$^+$ *m/z* 225.10, found *m/z* 225.21.

1-(2-methylbut-3-yn-2-yl)-3-(p-tolyl)urea (1b): 1b was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1b** was obtained as white solid; m.p. (hexane) 144.4–146.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J*=8.2 Hz, 2H), 7.04 (d, *J*= 8.2 Hz, 2H), 2.35 (s, 1H), 2.27 (s, 3H), 1.58 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 136.1, 133.1, 129.7, 120.8, 87.7, 69.8, 47.0, 30.0, 20.9. MS (ESI) calcd for $C_{13}H_{16}N_2NaO$ (M-Na)$^+$ *m/z* 239.13, found *m/z* 239.24.

1-(4-methoxyphenyl)-3-(2-methylbut-3-yn-2-yl)urea (1c): 1c was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1c** was obtained as white solid; m.p. (hexane) 188.6–189.7 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.73 (bs, 1H), 7.83 (d, *J*=8.8 Hz, 2H), 7.49 (d, *J*=8.8 Hz, 2H), 6.58 (bs, 1H), 3.80 (s, 3H), 3.14 (s, 1H), 1.54 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 165.9, 153.4, 144.9, 130.4, 121.8, 116.7, 88.3, 70.9, 51.7, 46.2, 29.2. MS (ESI) calcd for $C_{13}H_{16}N_2NaO_2$ (M-Na)$^+$ *m/z* 255.11, found *m/z* 255.24.

1-(4-fluorophenyl)-3-(2-methylbut-3-yn-2-yl)urea (1d): 1d was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1d** was obtained as light purple solid; m.p. (hexane) 174.1–174.8 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.33 (bs, 1H), 7.41–7.30 (m, 2H), 7.09–7.01 (m, 2H), 6.38 (bs, 1H), 3.11 (s, 1H), 1.53 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 156.9 (d, *J*=237.2 Hz), 153.9, 136.6 (d, *J*=2.3 Hz), 119.1 (d, *J*=7.5 Hz), 115.1 (d, *J*=22.0 Hz), 88.6, 70.8, 46.0, 29.4. ^{19}F NMR (376 MHz, DMSO) δ -122.40. MS (ESI) calcd for $C_{12}H_{13}FN_2NaO$ (M-Na)$^+$ *m/z* 243.09, found *m/z* 243.20.

Methyl 4-(3-(2-methylbut-3-yn-2-yl)ureido)benzoate (1e): 1e was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1e** was obtained as white solid; m.p. (hexane) 189.6–190.9 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.73 (bs, 1H), 7.86–7.81 (m, 2H), 7.52–7.48 (m, 2H), 6.58 (bs, 1H), 3.79 (s, 3H), 3.10 (s, 1H), 1.55 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 166.0, 153.4, 144.9, 130.4, 121.9, 116.7, 88.3, 70.8, 51.6, 46.2, 29.2. MS (ESI) calcd for $C_{14}H_{16}N_2NaO_3$ (M-Na)$^+$ *m/z* 283.10, found *m/z* 283.25.

1-(3-ethylpent-1-yn-3-yl)-3-phenylurea (1f): 1f was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1f** was obtained as white solid; m.p. (hexane) 122.3–123.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.35 (d, *J*=7.6 Hz, 2H), 7.21 (t, *J*=7.9 Hz, 2H), 6.97 (t, *J*=7.4 Hz, 1H), 5.85 (bs, 1H), 2.32 (s, 1H), 1.96 (dq, *J*=14.7, 7.4 Hz, 2H), 1.84 (dq, *J*=14.7, 7.4 Hz, 2H), 0.99 (t, *J*=7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 139.2, 128.9, 122.8, 119.8, 85.8, 71.8, 55.6, 31.4, 8.5. MS (ESI) calcd for $C_{14}H_{18}N_2NaO$ (M-Na)$^+$ *m/z* 253.13, found *m/z* 253.26.

1-(1-ethynylcyclohexyl)-3-phenylurea (1g): 1g was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1g** was obtained as white solid; m.p. (hexane) 157.2–157.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dt, *J*=8.7, 1.7 Hz, 2H), 7.31–7.25 (m, 2H), 7.08–7.02 (m, 1H), 2.54 (s, 1H), 2.20–2.10 (m, 2H), 1.73–1.54 (m, 7H), 1.34–1.20 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 138.8, 129.2, 123.4, 120.3, 86.1, 72.9, 51.4, 38.0, 25.3, 22.4. MS (ESI) calcd for $C_{15}H_{18}N_2NaO$ $(M-Na)^+$ *m/z* 265.13, found *m/z* 265.28.

Ethyl 2-(3-(2-methylbut-3-yn-2-yl)ureido)acetate (1i): 1i was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1i** was obtained as white solid; m.p. (hexane) 83.2–84.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J*=7.1 Hz, 2H), 4.01 (s, 2H), 2.42 (s, 1H), 1.59 (s, 6H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 157.2, 87.5, 70.4, 61.4, 46.9, 42.2, 30.1, 14.3. MS (ESI) calcd for $C_{10}H_{16}N_2NaO_3$ $(M-Na)^+$ *m/z* 235.10, found *m/z* 235.24.

1-(2-methyl-4-phenylbut-3-yn-2-yl)-3-phenylurea (1j): 1j was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1j** was obtained as a yellowish solid; m.p. (hexane) 182.3–183.7 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (bs, 1H), 7.45–7.30 (m, 7H), 7.23 (t, *J*=7.9 Hz, 2H), 6.90 (t, *J*= 7.3 Hz, 1H), 6.53 (bs, 1H), 1.66 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 153.8, 140.2, 131.2, 128.6, 128.4, 128.1, 122.6, 121.0, 117.5, 94.5, 79.6, 46.6, 29.4. MS (ESI) calcd for $C_{18}H_{18}N_2NaO$ $(M-Na)^+$ *m/z* 301.13, found *m/z* 301.28.

1-(2-methyl-4-(thiophen-2-yl)but-3-yn-2-yl)-3-phenylurea (1k): 1k was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1k** was obtained as a yellowish solid; m.p. (hexane) 210.3–211.4 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (bs, 1H), 7.51 (d, *J*=4.9 Hz, 1H), 7.41 (d, *J*=7.9 Hz, 2H), 7.26–7.18 (m, 3H), 7.04–6.99 (m, 1H), 6.91 (t, *J*=7.3 Hz, 1H), 6.55 (bs, 1H), 1.65 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 153.9, 140.2, 131.8, 128.7, 127.7, 127.4, 122.4, 121.2, 117.6, 98.3, 73.1, 46.8, 29.4. MS (ESI) calcd for $C_{16}H_{16}N_2NaOS$ $(M-Na)^+$ *m/z* 307.08, found *m/z* 307.24.

1-(2-methyl-4-(4-(trifluoromethyl)phenyl)but-3-yn-2-yl)-3-phenylurea (1l): 1l was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1l** was obtained as a white solid; m.p. (hexane) 183.9–185.2 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.38

(bs, 1H), 7.68 (d, *J*=8.3 Hz, 2H), 7.58 (d, *J*=8.2 Hz, 2H), 7.43 (d, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.9 Hz, 2H), 6.90 (t, *J*=7.3 Hz, 1H), 6.58 (bs, 1H), 1.68 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 153.9, 140.2, 132.0, 128.6, 128.3 (q, *J* = 32.1 Hz), 127.1 (d, *J* = 1.2 Hz), 125.4 (q, *J* = 3.6 Hz), 121.2, 117.7, 97.4, 78.5, 46.6, 29.3. ^{19}F NMR (376 MHz, DMSO) δ -61.47. MS (ESI) calcd for $C_{19}H_{17}F_3N_2NaO$ (M-Na)$^+$ *m/z* 369.12, found *m/z* 369.28.

1-(4-(4-methoxyphenyl)-2-methylbut-3-yn-2-yl)-3-phenylurea (1m): 1m was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1m** was obtained as pale yellow solid; m.p. (hexane) 178.2–178.6 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.35 (bs, 1H), 7.41 (d, *J*=7.8 Hz, 2H), 7.32 (d, *J*=8.7 Hz, 2H), 7.23 (t, *J*=7.8 Hz, 2H), 6.95–6.86 (m, 3H), 6.51 (bs, 1H), 3.74 (s, 3H), 1.66 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 159.1, 153.9, 140.3, 132.8, 128.7, 121.1, 117.6, 114.7, 114.1, 93.0, 79.6, 55.1, 46.8, 29.6. MS (ESI) calcd for $C_{19}H_{20}N_2NaO_2$ (M-Na)$^+$ *m/z* 331.14, found *m/z* 331.28.

1-benzyl-1-(1,3-diphenylprop-2-yn-1-yl)-3-phenylurea (3a): 3a was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3a** was obtained as yellow solid; m.p. (hexane) 96.2–97.7 °C. The spectroscopic data of **3a** were consistent with literature values[67]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2H), 7.54–7.37 (m, 13H), 7.33–7.25 (m, 4H), 7.15 (s, 1H), 7.08 (tt, *J*=7.2, 1.8 Hz, 1H), 6.59 (bs, 1H), 4.76 (d, *J*=17.1 Hz, 1H), 4.57 (d, *J*=17.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 138.7, 138.0, 137.1, 131.6, 129.1, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 127.0, 123.1, 122.3, 119.7, 86.9, 86.0, 51.3, 48.5. MS (ESI) calcd for $C_{29}H_{25}N_2O$ (M-H)$^+$ *m/z* 417.20, found *m/z* 417.31.

1-benzyl-3-phenyl-1-(1-phenylundec-2-yn-1-yl)urea (3b): 3b was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3b** was obtained as orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J*=7.5 Hz, 2H), 7.48–7.35 (m, 8H), 7.24 (dt, *J*=17.3, 5.4 Hz, 4H), 7.03 (t, *J*=7.1 Hz, 1H), 6.75 (s, 1H), 6.52 (s, 1H), 4.68 (d, *J*=16.8 Hz, 1H), 4.48 (d, *J*=16.9 Hz, 1H), 2.35 (t, *J*=6.7 Hz, 2H), 1.63–1.52 (m,2H), 1.51–1.25 (m, 10H), 0.99 (t further split, *J*=6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 138.8, 138.6, 137.4, 128.9, 128.7, 128.6, 128.0, 127.9, 127.6, 127.2, 123.0, 119.7, 87.8, 76.7, 51.1, 48.6, 31.8, 29.2, 29.1, 28.9, 28.5, 22.6, 18.7, 14.1. MS (ESI) calcd for $C_{31}H_{37}N_2O$ $(M-H)^+$ *m/z* 453.29, found *m/z* 453.47.

1-butyl-1-(1,3-diphenylprop-2-yn-1-yl)-3-phenylurea (3c): 3c was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3c** was obtained as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 2H), 7.55–7.50 (m, 2H), 7.44–7.33 (m, 8H), 7.32–7.27 (m, 2H), 7.08–7.02 (m, 1H), 6.67 (s, 1H), 6.58 (s, 1H), 3.48–3.30 (m, 2H), 1.87–1.73 (m, 1H), 1.61–1.43 (m, 1H), 1.42–1.26 (m, 2H), 0.91 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 139.0, 138.1, 131.8, 129.0, 128.8, 128.7, 128.5, 128.2, 127.5, 123.2, 122.6, 120.0, 86.8, 86.1, 51.3, 45.5, 31.5, 20.4, 13.9. MS (ESI) calcd for $C_{26}H_{27}N_2O$ $(M-H)^+$ *m/z* 383.21, found *m/z* 383.35.

1-(1,3-diphenylprop-2-yn-1-yl)-3-phenyl-1-(1-phenylethyl)urea (3d): 3d was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3d** was obtained as transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=7.6 Hz, 2H), 7.79 (d, *J*=8.0 Hz, 2H), 7.55–7.45 (m, 5H), 7.45–7.30 (m, 7H), 7.29– 7.22 (m, 3H), 7.14 (t, *J*=7.8 Hz, 2H), 7.03 (t, *J*=7.3 Hz, 1H), 6.92 (bs, 1H), 6.36 (s, 1H), 5.52 (d further split, *J*=6.5 Hz, 1H), 1.44 (d, *J*=7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 141.0, 138.8, 138.3, 131.7, 129.1, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 127.2, 122.9, 122.3, 119.5, 86.9, 86.6, 52.1, 50.7, 17.3. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M-H)^+$ *m/z* 431.21, found *m/z* 431.38.

1-(1,3-diphenylprop-2-yn-1-yl)-1-(4-methylbenzyl)-3-phenylurea (3e): 3e was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3e** was obtained as orange solid; m.p. (hexane) 109.8–111.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85

(d, *J*=7.5 Hz, 2H), 7.55–7.48 (m, 4H), 7.45 (d, *J*=7.2 Hz, 1H), 7.41–7.35 (m, 5H), 7.32–7.29 (m, 4H), 7.26 (d, *J*=7.9 Hz, 2H), 7.18 (s, 1H), 7.10–7.04 (m, 1H), 6.67 (bs, 1H), 4.72 (d, *J*=16.9 Hz, 1H), 4.52 (d, *J*=16.9 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 138.8, 138.0, 137.6, 134.0, 131.6, 129.7, 128.7, 128.6, 128.5, 128.2, 128.1, 127.6, 127.0, 123.0, 122.3, 119.6, 86.8, 86.1, 51.2, 48.1, 21.0. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M\text{-}H)^+$ *m/z* 431.21, found *m/z* 431.39.

1-(1,3-diphenylprop-2-yn-1-yl)-1-(4-fluorobenzyl)-3-phenylurea (3f): 3f was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3f** was obtained as light orange solid; m.p. (hexane) 125.6–126.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=7.6 Hz, 2H), 7.51–7.45 (m, 4H), 7.44–7.36 (m, 6H), 7.32–7.23 (m, 4H), 7.13–7.04 (m, 3H), 7.00 (s, 1H), 6.53 (bs, 1H), 4.70 (d, *J*=17.0 Hz, 1H), 4.54 (d, *J*=17.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, *J*=246.7 Hz), 155.4, 138.7, 137.9, 133.0 (d, *J*=3.1 Hz), 131.7, 128.7 (d, *J*=7.8 Hz), 128.8, 128.7, 128.4, 127.7, 123.4, 122.3, 119.9, 116.0 (d, *J*=21.5 Hz), 87.1, 85.9, 51.5, 48.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.93. MS (ESI) calcd for $C_{29}H_{24}FN_2O$ $(M\text{-}H)^+$ *m/z* 435.19, found *m/z* 435.36.

1-benzyl-3-phenyl-1-(3-phenyl-1-(p-tolyl)prop-2-yn-1-yl)urea (3g): 3g was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3g** was obtained as light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.61 (m, 2H), 7.54–7.46 (m, 6H), 7.45–7.37 (m, 5H), 7.33–7.25 (m, 5H), 7.12–7.05 (m, 2H), 6.60 (bs, 1H), 4.78 (d, *J*=17.0 Hz, 1H), 4.59 (d, *J*=17.1 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 138.8, 138.4, 137.9, 137.2, 131.6, 129.1, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.1, 124.8, 123.1, 122.4, 119.7, 86.8, 86.2, 51.3, 48.5, 21.5. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M\text{-}H)^+$ *m/z* 431.21, found *m/z* 431.39.

1-benzyl-1-(1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl)-3-phenylurea (3h): 3h was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3h** was obtained as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.67 (m, 2H), 7.47–

7.40 (m, 6H), 7.39–7.32 (m, 4H), 7.29–7.24 (m, 2H), 7.22–7.18 (m, 2H), 7.07–6.97 (m, 4H), 6.48 (bs, 1H), 4.71 (d, *J*=17.0 Hz, 1H), 4.52 (d, *J*=17.0 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.6, 138.8, 137.3, 131.7, 130.2, 129.2, 129.1, 128.8, 128.6, 128.4, 128.1, 127.2, 123.2, 122.5, 119.8, 114.1, 86.8, 86.4, 55.3, 50.8, 48.5. MS (ESI) calcd for $C_{30}H_{27}N_2O_2$ $(M-H)^+$ *m/z* 447.21, found *m/z* 447.38.

1-benzyl-3-phenyl-1-(3-phenyl-1-(3-vinylphenyl)prop-2-yn-1-yl)urea (3i): 3i was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3i** was obtained as orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.69 (d, *J*=7.4 Hz, 1H), 7.50–7.43 (m, 8H), 7.42–7.35 (m, 5H), 7.30–7.25 (m, 2H), 7.22 (dd, *J*=8.6, 1.4 Hz, 2H), 7.09 (s, 1H), 7.08–7.03 (m, 1H), 6.83 (dd, *J*=17.6, 10.9 Hz, 1H), 6.53 (bs, 1H), 5.87 (d, *J*=17.6 Hz, 1H), 5.36 (d, *J*=11.2 Hz, 1H), 4.73 (d, *J*=17.0 Hz, 1H), 4.54 (d, *J*=17.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 138.7, 138.4, 138.1, 137.1, 136.5, 131.7, 129.2, 129.0, 128.8, 128.6, 128.4, 128.1, 127.8, 127.2, 127.1, 126.0, 125.8, 123.3, 122.4, 119.8, 114.6, 87.1, 85.9, 51.4, 51.3, 48.6. MS (ESI) calcd for $C_{31}H_{27}N_2O$ $(M-H)^+$ *m/z* 443.21, found *m/z* 441.36.

1-benzyl-1-(1-(3-chlorophenyl)-3-phenylprop-2-yn-1-yl)-3-phenylurea (3j): 3j was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3j** was obtained as orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.69 (t, *J*=4.2 Hz, 1H), 7.51–7.44 (m, 6H), 7.42–7.35 (m, 6H), 7.32–7.23 (m, 4H), 7.13 (s, 1H), 7.10–7.05 (m, 1H), 6.62 (bs, 1H), 4.73 (d, *J*=17.2 Hz, 1H), 4.53 (d, *J*=17.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 140.2, 138.5, 136.8, 134.6, 131.6, 130.0, 129.1, 128.8, 128.7, 128.4, 128.3, 128.1, 127.8, 126.9, 125.9, 123.4, 122.0, 120.0, 87.4, 85.2, 50.8, 48.3. MS (ESI) calcd for $C_{29}H_{24}ClN_2O$ $(M-H)^+$ *m/z* 451.16, found *m/z* 451.33.

1-benzyl-1-(1-(2-bromophenyl)-3-phenylprop-2-yn-1-yl)-3-phenylurea (3k): 3k was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3k** was obtained as yellow solid; m.p. (hexane) 124.7–126.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J*=7.7, 1.6 Hz, 1H), 7.68 (dd, *J*=7.9, 1.2 Hz, 1H), 7.55–7.51 (m, 2H), 7.41–7.34 (m, 6H), 7.33–7.24 (m, 8H), 7.09 (s, 1H), 7.06–7.01 (m, 1H), 6.59 (bs, 1H), 4.62 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 138.8, 137.2, 136.6, 133.6, 131.8, 130.8, 130.1, 129.1, 128.8, 128.7, 128.4, 127.9, 127.6, 126.9, 124.6, 123.1, 122.3, 119.7, 87.0, 85.8, 52.2, 48.3. MS (ESI) calcd for $C_{29}H_{24}BrN_2O$ (M-H)$^+$ *m/z* 495.11, found *m/z* 495.27.

1-benzyl-1-(1,3-diphenylprop-2-yn-1-yl)-3-propylurea (3l): 3l was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3l** was obtained as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H), 7.44–7.24 (m, 13H), 6.98 (bs, 1H), 4.54 (d, *J*=17.1 Hz, 1H), 4.37 (t, *J*=5.4 Hz, 1H), 4.31 (d, *J*=17.1 Hz, 1H), 3.26–3.04 (m, 2H), 1.40–1.25 (m, 2H), 0.69 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 138.6, 137.9, 131.7, 128.9, 128.7, 128.5, 128.4, 128.1, 127.8, 127.7, 126.9, 122.7, 86.7, 86.56, 51.4, 48.3, 42.8, 23.2, 11.1. . MS (ESI) calcd for $C_{26}H_{27}N_2O$ (M-H)$^+$ *m/z* 383.21, found *m/z* 383.32.

1,3-dibenzyl-1-(1,3-diphenylprop-2-yn-1-yl)urea (3m): 3m was synthesized according to the general procedure 2. The crude was dried under vacuum and used without purification and the product **3m** was obtained as yellowish oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77–7.70 (m, 2H), 7.48–7.30 (m, 12H), 7.28–7.22 (m, 3H), 7.06–7.00 (m, 3H), 4.84 (t, *J*=5.5 Hz, 1H), 4.63 (d, *J*=17.2 Hz, 1H), 4.54–4.35 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.1, 138.4, 137.6, 131.7, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 127.1, 127.0, 126.9, 122.6, 86.8, 86.3, 51.5, 48.3, 44.9. MS (ESI) calcd for $C_{30}H_{27}N_2O$ (M-H)$^+$ *m/z* 431.21, found *m/z* 431.36.

4,4-dimethyl-5-methylene-1-phenylimidazolidin-2-one (2a): 2a was obtained from **1a** in 1 hour of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2a** (80 mg, quant. yield) as white solid; m.p. (hexane) 127.5–130.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.35–7.30 (m, 3H), 6.23 (bs, 1H), 4.00 (2s, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 154.68, 135.2, 129.4, 127.7, 127.6, 79.6, 56.7, 29.9. MS (ESI) calcd for $C_{12}H_{15}N_2O$ $(M-H)^+$ *m/z* 203.12, found *m/z* 203.24.

4,4-dimethyl-5-methylene-1-(p-tolyl)imidazolidin-2-one (2b): 2b was obtained from **1b** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2b** (69 mg, 82% yield) as pale orange solid; m.p. (hexane) 195.2–197.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J*=8.3 Hz, 2H), 5.83 (bs, 1H), 4.02 (d, *J*=2.1 Hz, 1H), 3.97 (d, *J*=2.3 Hz, 1H), 2.39 (s, 3H), 1.48 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 154.9, 137.6, 132.5, 130.1, 127.6, 79.5, 56.7, 29.9, 21.3. MS (ESI) calcd for $C_{13}H_{17}N_2O$ $(M-H)^+$ *m/z* 217.13, found *m/z* 217.21.

1-(4-methoxyphenyl)-4,4-dimethyl-5-methyleneimidazolidin-2-one (2c): 2c was obtained from **1c** in 1 hour of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2c** (92 mg, quant. yield) as white solid; m.p. (hexane) 213.4–215.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 2H), 7.47–7.41 (m, 2H), 5.88 (bs, 1H), 4.19 (d, *J*=2.6 Hz, 1H), 4.05 (d, *J*=2.6 Hz, 1H), 3.92 (s, 3H), 1.47 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 156.5, 153.5, 139.6, 130.8, 128.8, 127.0, 80.7, 56.8, 52.3, 29.9. MS (ESI) calcd for $C_{13}H_{17}N_2O_2$ $(M-H)^+$ *m/z* 233.13, found *m/z* 233.22.

1-(4-fluorophenyl)-4,4-dimethyl-5-methyleneimidazolidin-2-one (2d): 2d was obtained from **1d** in 1 hour and 30 minutes of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2d** (88 mg, quant. yield) as orange solid; m.p. (hexane) 165.6–167.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 7.17–7.08 (m, 2H), 5.89 (bs, 1H), 4.00–3.97 (m, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 160.5, 157.1, 154.7, 131.10 (d, *J* = 3.1 Hz), 129.60 (d, *J* = 8.6 Hz), 116.5, 116.3, 79.9, 56.8, 29.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.93. MS (ESI) calcd for $C_{12}H_{14}FN_2O$ $(M-H)^+$ *m/z* 221.11, found *m/z* 221.23.

Methyl 4-(4,4-dimethyl-5-methylene-2-oxoimidazolidin-1-yl)benzoate (2e): 2e was obtained from **1e** in 6 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2e** (104 mg, quant. yield) as yellowish solid; m.p. (hexane) 218.0–220.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.07 (m, 2H), 7.48–7.40 (m, 2H), 6.34 (bs, 1H), 4.17 (dd, *J*=2.6, 0.8 Hz, 1H), 4.04 (d, *J*=2.6 Hz, 1H), 3.91 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 156.6, 153.5, 139.6, 130.7, 128.6, 127.0, 80.6, 56.8, 52.3, 29.8. MS (ESI) calcd for $C_{14}H_{17}N_2O_3$ $(M\text{-}H)^+$ *m/z* 261.12, found *m/z* 261.28.

4,4-diethyl-5-methylene-1-phenylimidazolidin-2-one (2f): 2f was obtained from **1f** in 3 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2f** (92 mg, quant. yield) as orangish solid; m.p. (hexane) 120.5–122.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.36–7.31 (m, 1H), 7.30–7.27 (m, 2H), 5.32 (bs, 1H), 4.13 (dd, *J*=2.3, 0.8 Hz, 1H), 3.87 (d, *J*=2.3 Hz, 1H), 1.75–1.57 (m, 4H), 0.97 (t, *J*=7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 150.9, 135.2, 129.5, 127.8, 127.7, 80.2, 63.6, 34.1, 7.8. MS (ESI) calcd for $C_{14}H_{19}N_2O$ $(M\text{-}H)^+$ *m/z* 231.15, found *m/z* 231.27.

4-methylene-3-phenyl-1,3-diazaspiro[4.5]decan-2-one (2g): 2g was obtained from **1g** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2g** (92 mg, 95% yield) as white solid; m.p. (hexane) 175.2–176.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2H), 7.34–7.29 (m, 3H), 6.07 (bs, 1H), 4.07 (d, *J*=2.3 Hz, 1H), 3.96 (d, *J*=2.3 Hz, 1H), 1.92–1.83 (m, 2H), 1.81–1.70 (m, 2H), 1.59 (td, *J*=13.2, 3.5 Hz, 2H), 1.49–1.35 (m, 2H), 1.35–1.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 154.5, 135.1, 129.4, 127.7, 127.6, 80.2, 59.5, 38.6, 25.0, 22.4. MS (ESI) calcd for $C_{15}H_{19}N_2O$ $(M\text{-}H)^+$ *m/z* 243.15, found *m/z* 243.22.

1-(2-methylbut-3-yn-2-yl)-3-phenylthiourea (1h): 1h was synthesized according to the general procedure 2.1. The thiourea was not detected and *(*Z)-N-(4,4-dimethyl-5-methylenethiazolidin-2-ylidene)-4-fluoroaniline (**2h**) using general procedure 2.1 after 3 hours of reaction time. The crude did not require purification and the product **2h** was recovered in quant. yield (1 mmol, 235 mg) as yellow solid; m.p. (hexane) 223.3–224.6 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.30 (bs, 1H), 7.55 (bs, 2H), 7.13–7.03 (m, 2H), 5.23 (d, *J*=1.5 Hz, 1H), 5.16 (s, 1H), 1.38 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 158.3, 155.9, 155.1, 149.1, 119.7, 115.2, 115.0, 102.2, 30.1. ^{19}F NMR (376 MHz, DMSO) δ -121.82. MS (ESI) calcd for $C_{12}H_{14}FN_2S$ (M-H)$^+$ *m/z* 237.09, found *m/z* 237.23.

3-(2-methylbut-3-yn-2-yl)imidazolidine-2,4-dione (2i): 2i was obtained from **1i** in 16 hours of reaction time at 60 °C. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2i** (48 mg, 72% yield) as white solid; m.p. (hexane) 81.1–82.6 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.33 (bs, 1H), 3.88 (d, *J*=1.2 Hz, 2H), 2.47 (s, 1H), 1.89 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.9, 158.1, 85.5, 71.2, 52.3, 46.2, 29.0. MS (ESI) calcd for $C_8H_{11}N_2O_2$ (M-H)$^+$ *m/z* 167.08, found *m/z* 167.20

(Z)-5-benzylidene-4,4-dimethyl-1-phenylimidazolidin-2-one (2j): 2j was obtained from **1j** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2j** (97 mg, 87% yield, ratio Z:E; 1:0.25) as yellowish solid; m.p. (hexane) 216.5–217.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.06–6.95 (m, 5H), 6.88–6.80 (m, 3H), 6.68 (dd, *J*=7.2, 1.9 Hz, 2H), 5.81 (bs, 1H), 5.59 (s, 1H), 1.57 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.8, 145.0, 135.9, 134.6, 128.3, 128.1, 127.0, 126.2, 126.1, 125.2, 99.0, 57.6, 30.1. MS (ESI) calcd for $C_{18}H_{19}N_2O$ (M-H)$^+$ *m/z* 279.15, found *m/z* 279.24.

(Z/E)-4,4-dimethyl-1-phenyl-5-(thiophen-2-ylmethylene)imidazolidin-2-one (2k): 2k was obtained from **1k** in 1 hour and 30 minutes of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2k** (113 mg, quant yield, ratio Z:E; 1:0.8) as pale yellow solid; m.p. (hexane) 220.3–222.0 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (m, 1H(Z)+1H(E)), 7.43–7.31 (m, 2H+2H), 7.19–7.14 (m, 1H+2H), 7.14–7.06 (m, 1H+1H), 6.96–6.85 (m, 1H+1H), 6.77 (d, *J*=3.4 Hz, 1H(Z)), 6.48 (dd, *J* = 5.0, 3.7

Hz, 1H(E)), 6.13 (bs, 1H), 6.01 (bs, 1H), 5.98 (d, *J* = 3.5 Hz, 1H (Z)), 5.57 (s, 1H(E)), 5.51 (s, 1H(Z)), 1.57 (s, 1H(Z)), 1.55 (s, 1H(E)). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.6, 156.8, 150.1, 145.6, 137.5, 136.8, 135.7, 134.9, 129.7, 128.7, 128.2, 127.3, 126.8, 126.6, 126.5, 126.5, 126.3, 124.8, 123.8, 93.1, 91.5, 57.9, 57.7, 29.9, 28.4. MS (ESI) calcd for $C_{16}H_{17}N_2OS$ (M-H)$^+$ *m/z* 285.11, found *m/z* 285.24.

(Z/E)-4,4-dimethyl-1-phenyl-5-(4-(trifluoromethyl)benzylidene)imidazolidin-2-one (2l): 2l was obtained from **1l** in 4 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2l** (129 mg, 93% yield, ratio Z:E; 1:0.3) as white solid; m.p. (hexane) 208.5–211.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54–7.47 (m, 4H), 7.38 (m, 3H), 7.29 (d, *J*=8.6 Hz, 2H), 5.61 (s, 1H), 5.49 (bs, 1H), 1.42 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.6, 149.3, 139.9, 134.8, 130.2, 129.7, 128.5, 128.1, 125.7 (q, *J*=234.6 Hz), 124.9 (q, *J*=3.8 Hz), 99.8, 57.6, 29.1. ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.44. MS (ESI) calcd for $C_{19}H_{18}F_3N_2O$ (M-H)$^+$ *m/z* 347.14, found *m/z* 347.23.

(Z/E)-5-(4-methoxybenzylidene)-4,4-dimethyl-1-phenylimidazolidin-2-one (2m): 2m was obtained from **1m** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2m** (103 mg, 84% yield, ratio Z:E; 1:0.75) as white solid; m.p. (hexane) 182.4–184.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08–6.96 (m, 5H), 6.59 (d, *J*=8.7 Hz, 2H), 6.39 (d, *J*=8.7 Hz, 2H), 5.92 (bs, 1H), 5.54 (s, 1H), 3.65 (s, 3H), 1.55 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.9, 157.3, 143.9, 135.9, 129.3, 128.0, 127.2, 126.1, 126.0, 112.6, 98.7, 57.5, 55.3, 30.1. MS (ESI) calcd for $C_{19}H_{21}N_2O_2$ (M-H)$^+$ *m/z* 309.16, found *m/z* 309.31.

3-benzyl-4,4-dimethyl-5-methylene-1-phenylimidazolidin-2-one (2n): 2n was obtained from **1n** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to give **2n** (61 mg, 52% yield) as colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, *J*=7.2 Hz, 2H), 7.39–7.25 (m, 5H), 7.20–7.16 (m, 2H), 7.06–7.00 (m, 2H), 4.64

(d, *J*=3.3 Hz, 1H), 4.63 (s, 2H), 4.20 (d, *J*=3.3 Hz, 1H), 1.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 149.2, 147.0, 139.0, 128.6, 128.5, 127.8, 127.3, 123.8, 122.3, 83.3, 61.1, 44.4, 27.6. MS (ESI) calcd for $C_{19}H_{20}N_2O$ (M-H)$^+$ *m/z* 293.16, found *m/z* 293.24.

1,4-dibenzyl-3,5-diphenyl-1H-imidazol-2(3H)-one (4a): 4a was obtained from **3a** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4a** (139 mg, 83% yield) as pale yellow oil. The spectroscopic data of **4a** were consistent with literature values[39]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.36 (m, 3H), 7.35–7.23 (m, 8H), 7.20–7.15 (m, 2H), 7.14–7.08 (m, 5H), 6.81–6.72 (m, 2H), 4.92 (s, 2H), 3.71 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 138.2, 137.9, 135.2, 130.4, 129.1, 129.0, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.8, 127.3, 126.3, 122.3, 119.1, 45.5, 29.8. MS (ESI) calcd for $C_{29}H_{25}N_2O$ (M-H)$^+$ *m/z* 417.20, found *m/z* 417.26.

1-benzyl-4-nonyl-3,5-diphenyl-1H-imidazol-2(3H)-one (4b): 4b was obtained from **3b** in 1 minute of reaction time (it was tested also overnight but the yield remained the same, conversion 30%). The crude was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to give **4b** (33 mg, 18% yield) as orangish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.45 (m, 2H), 7.42–7.40 (m, 1H), 7.40–7.38 (m, 1H), 7.38–7.34 (m, 4H), 7.23–7.15 (m, 5H), 7.06–7.02 (m, 2H), 4.81 (s, 2H), 2.35–2.31 (m, 2H), 1.27–1.20 (m, 3H), 1.17–1.07 (m, 4H), 1.09–0.98 (m, 3H), 0.99–0.91 (m, 4H), 0.85 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 138.0, 135.7, 130.6, 129.5, 129.3, 128.6, 128.4, 128.4, 127.9, 127.8, 127.3, 121.1, 120.8, 45.4, 31.9, 29.3, 29.2, 28.9, 28.7, 28.4, 23.5, 22.7, 14.2. MS (ESI) calcd for $C_{31}H_{37}N_2O$ (M-H)$^+$ *m/z* 453.29, found *m/z* 453.32.

4-benzyl-1-butyl-3,5-diphenyl-1H-imidazol-2(3H)-one (4c): 4c was obtained from **3c** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to give **4c** (108 mg, 71% yield) as transparent solid; m.p. (hexane) 112.6–113.7 °C. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.48–7.36 (m, 5H), 7.31–7.23 (m, 3H), 7.14–7.05 (m, 5H), 6.73 (dd, *J*=6.6, 2.8 Hz, 2H), 3.75–3.70 (m, 2H), 3.68 (s, 2H), 1.56–1.47 (m, 2H), 1.28–1.17 (m, 2H), 0.81 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 138.3, 135.2, 130.0, 129.4, 128.9, 128.8, 128.5, 128.2, 128.0, 127.9, 127.7, 126.2, 122.2, 118.7, 41.5, 31.3, 29.7, 19.8, 13.6. MS (ESI) calcd for $C_{26}H_{27}N_2O$ $(M-H)^+$ *m/z* 383.21, found *m/z* 383.37.

4-benzyl-3,5-diphenyl-1-(1-phenylethyl)-1H-imidazol-2(3H)-one (4d): 4d was obtained from **3d** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4d** (160 mg, 93% yield) as orangish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 3H), 7.35–7.26 (m, 8H), 7.24–7.20 (m, 2H), 7.15 (dd, *J*=7.9, 1.4 Hz, 2H), 7.13–7.08 (m, 3H), 6.74 (dd, *J*=6.4, 2.6 Hz, 2H), 5.29 (q, *J*=7.2 Hz, 1H), 3.72–3.56 (m, 2H), 1.86 (d, *J*=7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 141.7, 138.2, 135.0, 131.0, 129.3, 128.8, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.6, 127.1, 127.0, 126.2, 122.3, 119.0, 53.0, 29.8, 18.6. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M-H)^+$ *m/z* 431.21, found *m/z* 431.30.

4-benzyl-1-(4-methylbenzyl)-3,5-diphenyl-1H-imidazol-2(3H)-one (4e): 4e was obtained from **3e** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4e** (156 mg, 91% yield) as orange solid; m.p. (hexane) 146.3–148.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.36 (m, 3H), 7.35–7.27 (m, 5H), 7.18–7.14 (m, 2H), 7.12–7.04 (m, 5H), 7.01 (d, *J*=8.1 Hz, 2H), 6.75 (dd, *J*=6.3, 2.7 Hz, 2H), 4.88 (s, 2H), 3.70 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 138.2, 136.8, 135.1, 134.9, 130.4, 129.1, 128.9, 128.7, 128.5, 128.2, 128.0, 127.9, 127.8, 127.7, 126.2, 122.3, 119.0, 45.2, 29.7, 21.1. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M-H)^+$ *m/z* 431.21, found *m/z* 431.38.

4-benzyl-1-(4-fluorobenzyl)-3,5-diphenyl-1H-imidazol-2(3H)-one (4f): 4f was obtained from **3f** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4f** (161 mg, 93% yield) as dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38

(m, 3H), 7.35–7.24 (m, 5H), 7.15 (dd, *J*=7.7, 1.4 Hz, 2H), 7.12–7.03 (m, 5H), 6.93 (t, *J*=8.7 Hz, 2H), 6.72 (dd, *J*=6.2, 2.7 Hz, 2H), 4.86 (s, 2H), 3.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 160.8, 153.4, 138.0, 135.0, 133.6 (d, *J* = 3.2 Hz), 130.3, 129.6 (d, *J* = 8.1 Hz), 128.9, 128.7, 128.6, 128.2, 128.0, 127.9, 127.8, 126.2, 122.0, 119.2, 115.3, 115.1, 44.7, 29.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.09. MS (ESI) calcd for $C_{29}H_{24}FN_2O$ $(M\text{-}H)^+$ *m/z* 435.19, found *m/z* 435.28.

1,4-dibenzyl-3-phenyl-5-(p-tolyl)-1H-imidazol-2(3H)-one (4g): 4g was obtained from **3g** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4g** (144 mg, 84% yield) as dark yellow solid; m.p. (hexane) 125.8–127.3 °C. The spectroscopic data of **4g** were consistent with literature values[68]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 7H), 7.23–7.15 (m, 5H), 7.15–7.10 (m, 4H), 7.07 (s, 1H), 6.79 (dd, *J*=6.7, 2.3 Hz, 2H), 4.93 (s, 2H), 3.74 (s, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 138.2, 138.0, 135.2, 131.1, 129.3, 128.9, 128.8, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.4, 127.2, 126.2, 122.5, 118.8, 45.5, 29.7, 21.3. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M\text{-}H)^+$ *m/z* 431.21, found *m/z* 431.29.

1,4-dibenzyl-5-(4-methoxyphenyl)-3-phenyl-1H-imidazol-2(3H)-one (4h): 4h was obtained from **3h** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4h** (137 mg, 77% yield) as white solid; m.p. (hexane) 166.6–168.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.24 (m, 6H), 7.24–7.15 (m, 6H), 7.15–7.09 (m, 3H), 6.95–6.89 (m, 2H), 6.79 (dd, *J*=7.1, 2.2 Hz, 2H), 4.91 (s, 2H), 3.82 (s, 3H), 3.71 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 153.3, 138.2, 137.9, 135.1, 131.7, 128.8, 128.3, 128.1, 127.9, 127.8, 127.6, 127.1, 126.1, 121.9, 121.0, 118.6, 114.0, 55.2, 45.3, 29.6. MS (ESI) calcd for $C_{30}H_{27}N_2O_2$ $(M\text{-}H)^+$ *m/z* 447.21, found *m/z* 447.32.

1,4-dibenzyl-3-phenyl-5-(3-vinylphenyl)-1H-imidazol-2(3H)-one (4i): 4i was obtained from **3i** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4i**

(133 mg, 75% yield) as pale yellow solid; m.p. (hexane) 143.8–145.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J*=7.8 Hz, 1H), 7.38–7.32 (m, 4H), 7.32–7.26 (m, 4H), 7.23–7.16 (m, 5H), 7.15–7.11 (m, 3H), 6.80 (dd, *J*=6.8, 2.2 Hz, 2H), 6.66 (dd, *J*=17.6, 10.9 Hz, 1H), 5.62 (d, *J*=17.6 Hz, 1H), 5.27 (d, *J*=10.9 Hz, 1H), 4.93 (s, 2H), 3.74 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 138.2, 138.0, 137.9, 136.1, 135.1, 129.5, 128.9, 128.5, 128.2, 128.0, 127.9, 127.7, 127.3, 126.5, 126.2, 122.2, 119.1, 114.8, 45.6, 29.8. MS (ESI) calcd for $C_{31}H_{27}N_2O$ (M-H)$^+$ *m/z* 443.21, found *m/z* 441.28.

1,4-dibenzyl-5-(3-chlorophenyl)-3-phenyl-1H-imidazol-2(3H)-one (4j): 4j was obtained from **3j** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4j** (155 mg, 86% yield) as orange solid; m.p. (hexane) 130.5–132.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (m, 8H), 7.22 (t, *J*=1.4 Hz, 1H), 7.18–7.09 (m, 8H), 6.73 (dd, *J*=6.5, 2.4 Hz, 2H), 4.89 (s, 2H), 3.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 137.6, 137.5, 134.8, 134.4, 130.7, 130.2, 129.9, 128.9, 128.6, 128.4, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.3, 126.3, 120.9, 119.7, 45.5, 29.6. MS (ESI) calcd for $C_{29}H_{24}ClN_2O$ (M-H)$^+$ *m/z* 451.16, found *m/z* 451.26.

1,4-dibenzyl-5-(2-bromophenyl)-3-phenyl-1H-imidazol-2(3H)-one (4k): 4k was obtained from **3k** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (7:3) as eluent to give **4k** (134 mg, 68% yield) as dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J*=7.3, 1.8 Hz, 1H), 7.39–7.31 (m, 3H), 7.30–7.19 (m, 8H), 7.14 (dd, *J*=6.7, 2.5 Hz, 1H), 7.10–7.06 (m, 3H), 7.05–7.01 (m, 2H), 6.79 (dd, *J*=6.4, 2.7 Hz, 2H), 5.12 (d, *J*=15.2 Hz, 1H), 4.60 (d, *J*=15.2 Hz, 1H), 3.61 (q, *J*=16.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 137.5, 137.4, 135.0, 133.8, 132.9, 130.7, 130.1, 128.9, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.3, 127.2, 126.4, 126.1, 120.4, 119.7, 45.6, 30.0. MS (ESI) calcd for $C_{29}H_{24}BrN_2O$ (M-H)$^+$ *m/z* 495.11, found *m/z* 495.23.

1,4-dibenzyl-5-phenyl-3-propyl-1H-imidazol-2(3H)-one (4l): 4l was obtained from **3l** in 1 minute of reaction time (it was tested also overnight but the yield remained the same, conversion 58%). The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4l** (69 mg, 45% yield) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5H), 7.27–7.21 (m, 4H), 7.20–7.16 (m, 2H), 7.15–7.11 (m, 2H), 7.05 (dd, *J*=7.8, 1.6 Hz, 2H), 4.87 (s, 2H), 3.81 (s, 2H), 3.48–3.43 (m, 2H), 1.60–1.49 (m, 2H), 0.85 (t, *J*=7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 138.4, 138.2, 130.2, 129.2, 128.8, 128.6, 128.4, 128.3, 127.8, 127.4, 127.2, 126.8, 121.7, 118.1, 45.4, 43.45, 29.6, 22.8, 11.3. MS (ESI) calcd for $C_{26}H_{27}N_2O$ $(M\text{-}H)^+$ *m/z* 383.21, found *m/z* 383.29.

1,3,4-tribenzyl-5-phenyl-1H-imidazol-2(3H)-one (4m): 4m was obtained from **3m** in 1 minute of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **4m** (144 mg, 84% yield) as yellow oil. The spectroscopic data of **4m** were consistent with literature values[67]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.25 (m, 12H), 7.24–7.18 (m, 4H), 7.14–7.07 (m, 4H), 4.96 (s, 2H), 4.72 (s, 2H), 3.65 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 138.1, 138.0, 137.9, 130.1, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 127.8, 127.4, 127.3, 127.2, 127.1, 126.8, 122.2, 118.0, 45.6, 44.9, 29.5. MS (ESI) calcd for $C_{30}H_{27}N_2O$ $(M\text{-}H)^+$ *m/z* 431.21, found *m/z* 431.31.

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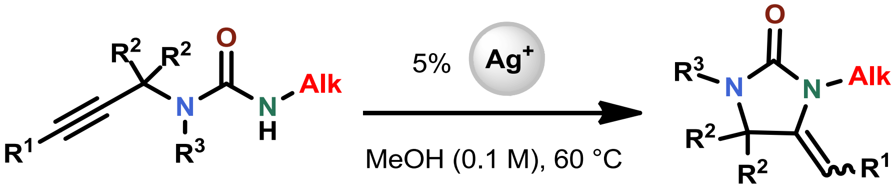
7. Highly Selective Ag(I) Catalyzed N-5-exo-dig Cyclization of Alkylic Propargylic Ureas to 2-Imidazolidinones



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A. Casnati, A. Voronov, P.P. Mazzeo, A. Bacchi, R. Maggi, G. Maestri, E. Motti and N. Della Ca'; Highly Selective Ag(I)- catalyzed N-5-exo-dig Cyclization of Alkylic Propargylic Ureas to Imidazolidin-2-ones; *submitted*

7.1. Introduction

N-hydroamination represents a robust methodology for the construction of C-N bonds[1–3]. This approach consists in the nucleophilic addition of a nitrogen on a C-C unsaturated bond and it involves the cleavage of an N-H bond with the formation of C-N and C-H bonds. From the thermodynamic point of view, this reaction is slightly exothermic but mainly thermoneutral; on the other hand, the kinetic is unfavorable due to the presence of the nucleophile electron density and the π-electrons of the C-C unsaturated bond[4,5]. Hence, a great amount of energy has to be provide to the system in order to overcome the high activation barrier. To solve this issue both a strong acid[6,7] or base[8–10] can be employed. The first one protonates the double or triple bond generating a carbocation more prone to undergo to nucleophilic attack, while a strong base is required to deprotonate the nitrogen and create a stronger nucleophile. Metal catalysts[11–16] can coordinate the unsaturated bond subtracting electronic density or replace the hydrogen in the N-H bond.

Indeed the nature of the nucleophile greatly affects the required reaction conditions. Amides and related compounds, such as ureas, carbamates, amidines …, possess a less nucleophilic nitrogen due to the presence of diverse resonance structures. If these compounds are engaged in the same transformation, called N-hydroamidation, harsher reaction conditions are expected.

In this context, propargylic ureas[17] are relevant substrates allowing the formation, after N-hydroamidation, of biological active cyclic ureas. Imizazol(idin)ones[18,19] and pirimidinones[20,21], respectively deriving from 5-exo or 6-endo ring closure, display important biological and pharmaceutical activities due to the presence of their scaffold in a wide variety of intermediates or active pharmaceutical ingredients (APIs).

In order to tune the chemo and regio selectivity, a number of methods involving different transition metals have been reported[22–33].

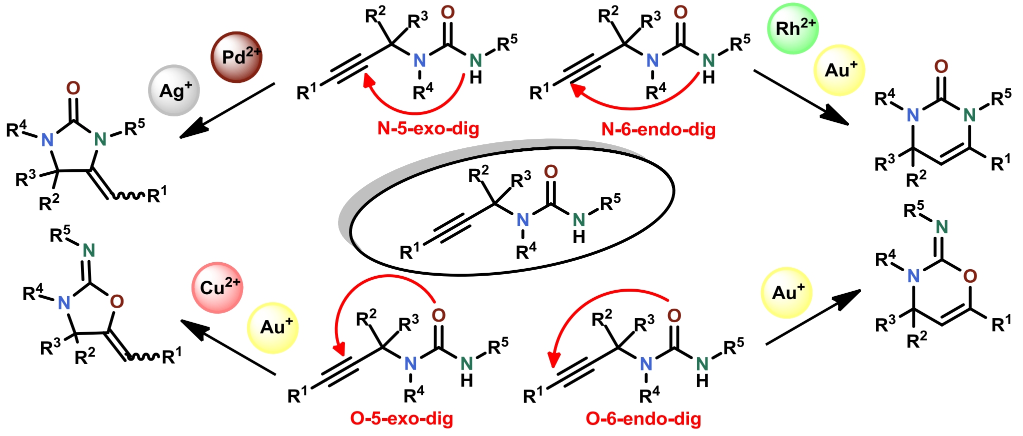
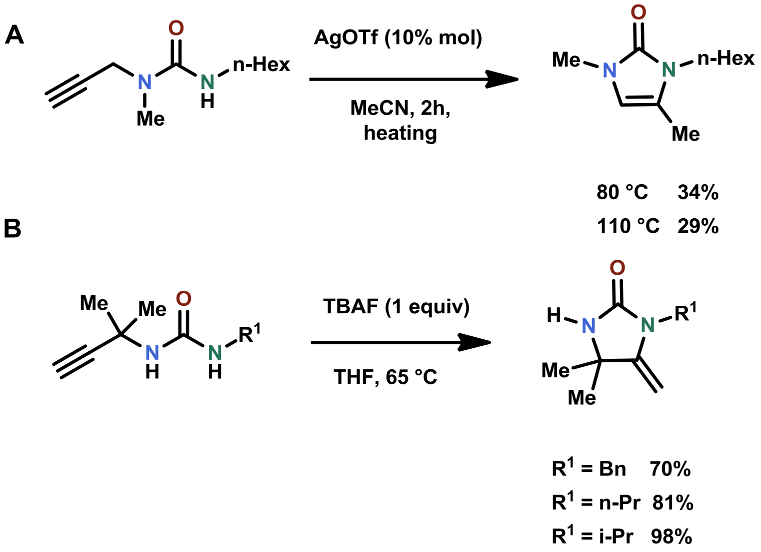


Figure 7.1 Possible cyclization pathways for propargylic ureas

Figure 7.1 depicts the four cyclization events that can occur employing the propargylic urea scaffold. At the top the N-hydroamination pathways are described; in this case ensuring a high regioselectivity is not trivial. For terminals alkynes several approaches have been proposed to afford selectively the Markovnikov or anti Markovnikov product. In intramolecular hydroamidation the selectivity is mainly influenced by the thermodynamics and kinetic of the process. 5-member rings are usually kinetically favored and the nitrogen driven ring closure products display higher stability (Chapter 6, **Figure 6.2**).

As already mentioned in Chapter 6, significant efforts have been devoted to the synthesis of imidazol(idin)one scaffold due to the importance of this moiety in medicinal chemistry. The proposed strategies involve the use of transition metals, such as silver[32] or palladium[25], or a stoichiometric amount of bases (i.e. NaH[24,34] or NaOH[33]) or salts (TBAF[26]). In this context propargylic ureas bearing an alkylic fragment on the nitrogen in position 1 are poorly investigated. Van der Eycken and coworkers in their Ag(I) catalytic procedure reported in 2011 discussed only one example employing a hexyl substituent (**Scheme 6.1**, A). Under the presented optimized conditions (see **Scheme 6.1**, A) they recovered only 34% yield of the desired product, increasing the temperature did not provide them better outcomes. Huguenot in 2014 published a TBAF mediated synthetic strategy for the construction of imidazolidinones scaffold. He showed three different groups such as benzyl, propyl and isopropyl that were successfully employed providing the desired products from good to excellent yields (**Scheme 6.1**, B).

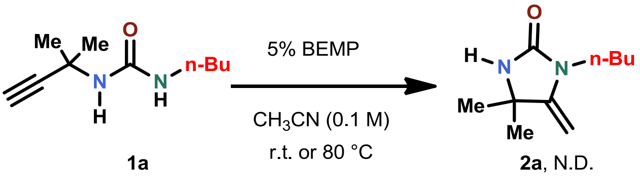


Scheme 7.1 Selected examples of propargylic ureas bearing alkylic fragments cyclization

Despite these spare examples, an easy and handy methodology to access imidazol(idin)ones bearing alkylic fragments has never been described.

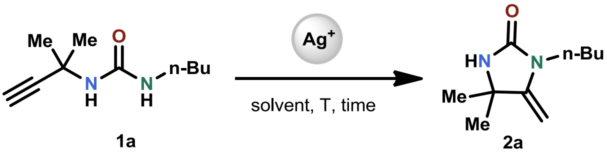
7.2. Result and Discussion

More intrigued by catalytic methodologies compared to mediated ones, initially we were willing to apply the same methodology presented in Chapter 6. Unfortunately using 5% mol of BEMP we did not observe the formation of the desired product, also increasing the temperature up to 80 °C.



Scheme 7.2 Attempt to synthesize **2a** using the base catalyzed approach discussed in Chapter 6

Then taking advantage from the previously descripted approaches [32,35], we decided to investigate silver salts. We caused to react 1-butyl-3-(2-methylbut-3-yn-2-yl)urea (**1a**) in presence of silver triflate (5% mol) in acetonitrile at 50 °C (**Scheme 7.3**). After 24 hours **2a** was obtained in 90% of yield (**Table 7.1**, entry 1). Encouraged by the possibility to trigger this cyclization using nontoxic and abundant silver salts as catalyst we run a carful optimization study. Silver nitrate proved to be greatly effective in our transformation ensuring 94% of yield after 24 hours (entry 2). Ag_2CO_3 and Ag_2O were found not effective to promote the formation of the 5-members cyclic urea (entries 3, 4), on the contrary silver salts possessing a bulky anion, such as $AgPF_6$, $AgBF_4$ and $AgSbF_6$ resulted in good yields respectively 68, 79 and 57% (entries 5-7). Once silver nitrate was confirmed as the most active, we turned our attention to the reaction media. We tested again acetonitrile increasing the temperature up to 60 °C, and thus resulted in quantitative yield of **2a** in 18 hours of reaction time (entry 8). Other polar aprotic solvents, such as DMF and THF afforded quantitative yields in 36 and 16 hours (entries 9, 12). In addition, chlorinated solvents were suitable providing quantitatively **2a** in 18 hours using DCE (entry 10) and 83% of yield over 24 hours with $CHCl_3$ (entry 11). To our delight protic solvents dramatically decreased the reaction time to 4 hours obtaining quantitative yield with methanol (entry 13) and 74 and 66% with ethanol and isopropyl alcohol respectively (entries 14-15). Further modifications, i.e. decreased amount of catalysts or lower concentration (entries 17, 18) did not provide better outcomes. Finally, a control experiment was performed without catalyst resulting only in the recovery of the untouched starting material **1a**.



Scheme 7.3 Reaction scheme for the optimization study

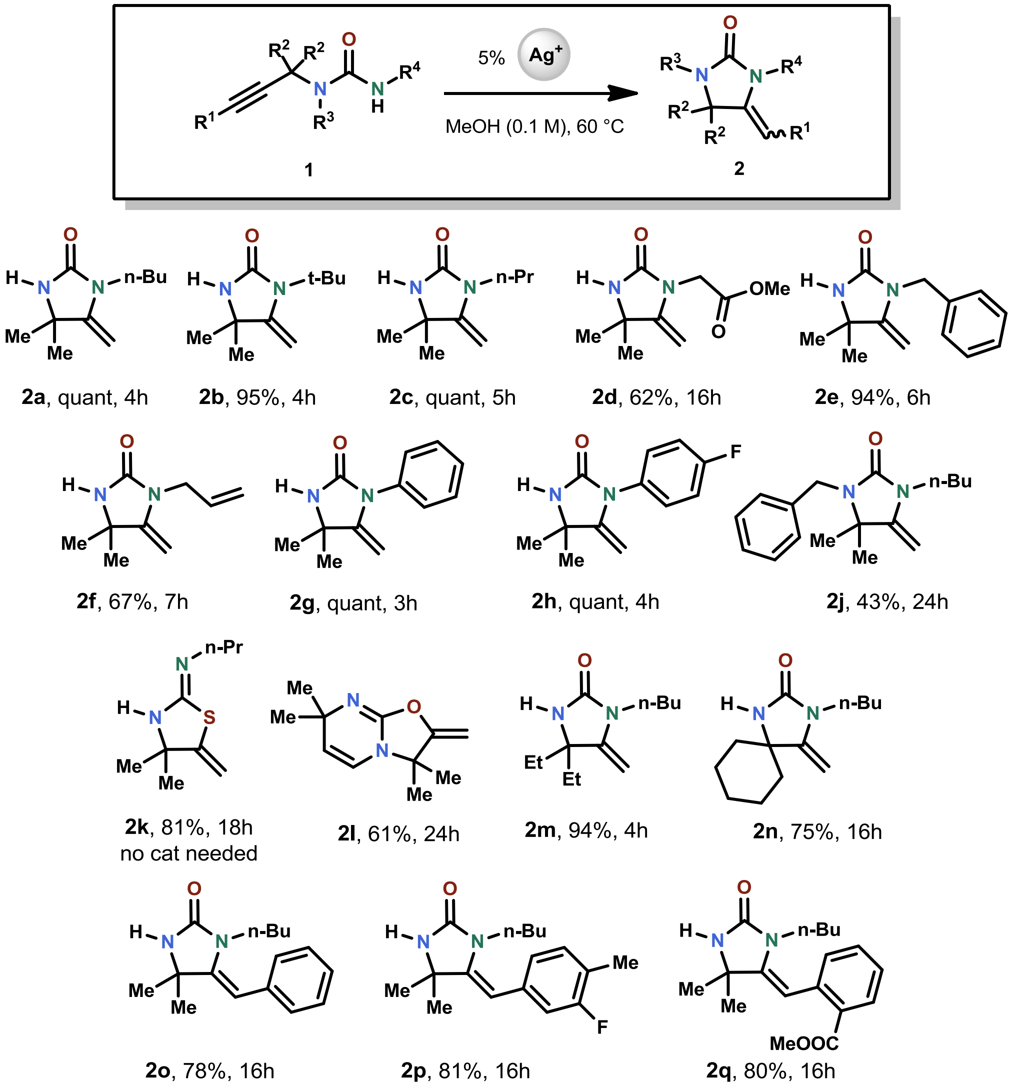
Table 7.1 Optimization studies

Entry	Ag^+ (5 mol %)	Solvent	T (°C)	t (h)	Yield (%)[b] 2a
1	AgOTf	CH_3CN	50	24	90
2	$AgNO_3$	CH_3CN	50	24	94
3	Ag_2CO_3	CH_3CN	50	24	traces
4	Ag_2O	CH_3CN	50	24	traces
5	$AgPF_6$	CH_3CN	50	24	68
6	$AgBF_4$	CH_3CN	50	24	79
7	$AgSbF_6$	CH_3CN	50	24	57
8	$AgNO_3$	CH_3CN	60	18	quant
9	$AgNO_3$	DMF	60	36	quant
10	$AgNO_3$	DCE	60	18	quant
11	$AgNO_3$	$CHCl_3$	60	24	83
12	$AgNO_3$	THF	60	16	quant
13	$AgNO_3$	CH_3OH	60	4	quant
14	$AgNO_3$	ethanol	60	4	74
15	$AgNO_3$	isopropyl alcohol	60	4	66
16	-	CH_3OH	60	16	0
17[c]	$AgNO_3$	CH_3OH	60	4	86
18[d]	$AgNO_3$	CH_3OH	60	7	quant

[a] Reaction condition: 1a (0.4 mmol), Ag^+ (5% mol), solvent 4 mL (C 0.1 M); [b] Yields of **2a** were determined via ^1H NMR analysis using methylbenzoate as internal standard; [c] $AgNO_3$ 2.5% mol; [d] C 0.05 M

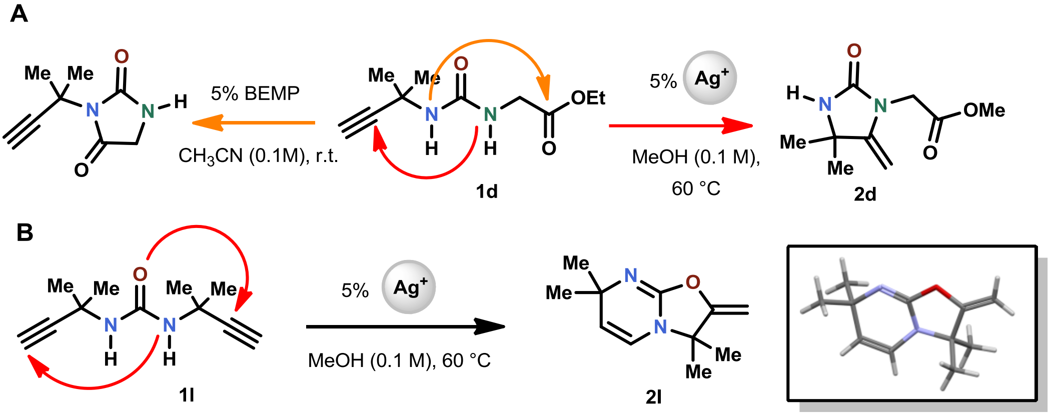
Having the optimized conditions in hand (**Table 7.1**, entry 13), we investigate the reaction scope introducing different substituent on the propargylic urea (**Scheme 7.4**). Alkylic fragments on the nitrogen in position 1 (marked in green in **Scheme**

7.4), like tert-butyl or propyl resulted in excellent yields with short reaction time (**2b** and **2c**). The modification of the alkylic chain with an ester moiety resulted in the formation of **2d** confirming the high chemoselectivity of this protocol preserving the carbonyl function untouched (see **Scheme 7.5 A** for a comparison with the procedure proposed in Chapter 6 using the same substrate as starting material). Placing a benzyl or an allylic substituent, we obtained products **2e** and **2f** respectively in 94 and 67% of yield. The allylic fragment did not react under these reaction conditions enhancing once again the chemoselectivity and the functional group tolerance of the presented methodology.



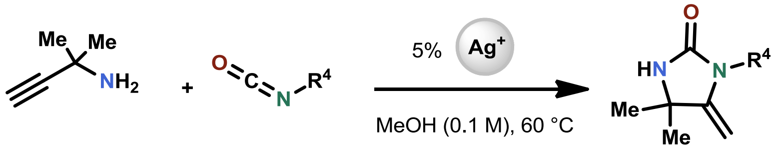
Scheme 7.4 Scope for the propargylic urea for the synthesis of imidazolidinones derivatives. Reaction condition: **1** (0.4 mmol), $AgNO_3$ (5% mol), MeOH 4 mL (C 0.1 M). Isolated yields.

Indeed, it was also possible to convert propargylic ureas bearing a phenyl ring in position N-1, obtaining quantitative yields (**2g** in 3 hours and **2h** in 4 hours). The introduction of an additional substituent on the nitrogen marked in blue (R^3=Bn) provided **2j** in 43% of yield. Increasing the steric hindrance of the propargylic alpha carbon results in good yields with longer reaction time (comparison between **2m** obtained in 4 hours and **2n** in 16 hours). Attempting to synthesize a propargylic thiourea, we observed the formation of product **2k**, the corresponding thiazolidin-2-imine, produced *via* an intramolecular sulphur driven cyclization. The symmetric propargylic urea **1l** resulted in the fused bicyclic product **2l** (see **Scheme 7.5 B** for an explanation of the subsequent cyclization events). Ureas bearing an internal triple bond lead to the formation of products **2o**, **2p** and **2q** with a complete stereoselectivity towards Z isomer.



Scheme 7.5 A Different cyclization pathways tuning the reaction conditions **B** Graphical representation for the formation of product **2l**

To further demonstrate the applicability of our protocol, we performed one-pot experiments starting from the corresponding propargylic amine and isocyanate (**Scheme 7.6**). The products **2a** and **2c** were both recovered in quantitative yield after 6 hours.

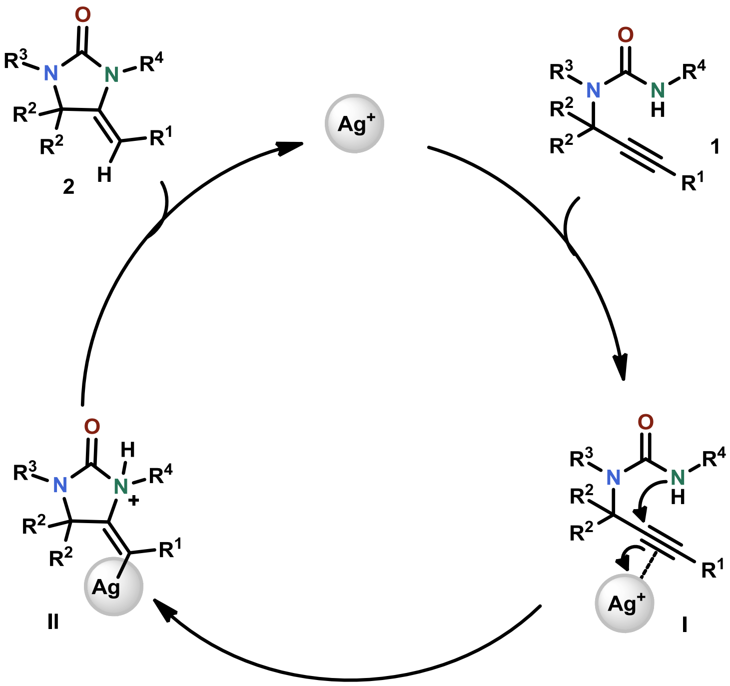


R^4 = n-Bu, **2a** quant yield

R^4 = n-Pr, **2c** quant yield

Scheme 7.6 One-pot experiments

In **Scheme 7.7** is shown the mechanism for the silver catalyzed formation of imidazolidinones. Ag (I) can coordinate the triple bond[36] thanks to its Lewis acid proprieties (intermediate **I**). This type of coordination facilitates the hydroamidation step that results in the formation of a five members ring bearing an exocyclic double bond (intermediate **II**). Finally, a proton transfer leads to the formation of the desired product **2**. The stereoselective formation of the Z alkene can be explained through the formation of intermediate **II** that can only result in *cis* double bonds.



Scheme 7.7 Reaction mechanism

7.3. Conclusions

In summary, we have reported an easy and handy methodology for the N-5-exo-dig cyclization of propargylic ureas bearing an alkylic group in N-1 position. The same approach can be expanded also to different N-1 substituents. We employed a cheap source of silver (silver nitrate) and methanol as benign reaction media. The applicability of this protocol was further demonstrated with the one-pot reaction starting from propargyl amines and isocyanates.

7.4. Experimental section

General procedure 1: Synthesis of α-disubstituted propargylic urea[37]

To a dry 2-necked flask containing a magnetic stir bar was charged with the selected isocyanate (1 mmol), the selected α-disubstituted propargylic amine (1 mmol) and dry THF (10 mL). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The yield is quantitative and the corresponding α-disubstituted propargylic urea was employed without need of purifications.

General procedure 2: Sonogashira procedure for α-disubstituted propargylic urea[38]

To a Schlenk type flask equipped with a magnetic stirred was added $Pd(PPh_3)_2Cl_2$ (2%, 0.02 mmol) and CuI (7%, 0.07 mmol). The flask was purged with N_2 and Et_3N (5 mL) was added under N_2. The aryl iodide (1 equiv, 1 mmol) and the propargylic urea (1.2 equiv.) were dissolved in dry CH_2Cl_2 (7 mL) and then added. The reaction mixture was stirred at room temperature overnight. The crude mixture was filtered through a medium frit, the solid residue washed with CH_2Cl_2, and the combined organics were concentrated under reduced pressure. Purification via flash column chromatography yielded the desired aryl propargyl urea.

*Synthesis of **1j***[39]

A solution of 2-methylbut-3-yn-2-amine (519 µL, 5 mmol) and benzaldehyde (507 µL, 5 mmol) in MeOH (10 mL) was stirred at room temperature overnight. After that, sodium borohydride (378 mg, 10 mmol) was added to the solution. The reaction mixture was stirred at 0°C for 1 hour. Then the reaction was diluted with water (25 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (Eluent Hexane:Ethyl Acetate 7:3) to afford N-benzyl-2-methylbut-3-yn-2-amine (**1j**) in 55% yield (476 mg).

General procedure 3: Catalytic reactions

A test tube equipped with a magnetic stirrer was charged with propargylic urea (0.4 mmol) and MeOH (4 mL). Then $AgNO_3$ (5% mol) was added. The reaction mixture was stirred at 60 °C and monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude was purified by silica gel column chromatography with a mixture of hexane and ethyl acetate.

*Synthesis of **2k***[37]

To a dry 2-necked flask containing a magnetic stir bar was charged with 1-isothiocyanatopropane (1 mmol, 108 μL), 2-methylbut-3-yn-2-amine (1 mmol, 105 μL) and dry THF (10 mL). The resulting mixture was stirred at room temperature and monitored by TLC. After 18 hours, the solvent was removed under reduced pressure The crude reaction mixture was purified by silica gel column chromatography (Eluent Hexane:Ethyl Acetate 1:1) to afford N-(4,4-dimethyl-5-methylenethiazolidin-2-ylidene)propan-1-amine (**2k**) in 81% yield (149 mg).

1-butyl-3-(2-methylbut-3-yn-2-yl)urea (**1a**)**: 1a** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1a** was obtained as light yellow solid; m.p. (hexane) 79.5–81.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.18 (t, J = 7.1 Hz, 2H), 2.38 (s, 1H), 1.56 (s, 6H), 1.50 – 1.42 (m, 2H), 1.37 – 1.29 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 87.8, 70.2, 46.8, 40.1, 32.3, 30.3, 20.2, 13.9.

1-(tert-butyl)-3-(2-methylbut-3-yn-2-yl)urea (**1b**): **1b** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1b** was obtained as white solid; m.p. (hexane) 204.1–205.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 1H), 1.54 (s, 6H), 1.33 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 87.6, 70.6, 50.7, 46.8, 30.3, 29.5.

1-(2-methylbut-3-yn-2-yl)-3-propylurea (**1c**): **1c** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1c** was obtained as white solid; m.p. (hexane) 80.3–81.6 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.12 (t, *J* = 7.1 Hz, 2H), 2.34 (s, 1H), 1.55 (s, 6H), 1.47 (dt, *J* = 14.5, 7.3 Hz, 2H), 0.88 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.9, 88.0, 69.8, 46.6, 42.0, 30.2, 23.5, 11.5.

Ethyl 2-(3-(2-methylbut-3-yn-2-yl)ureido)acetate (**1d**): **1d** was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1d** was obtained as white solid; m.p. (hexane) 83.2–84.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.19 (q, *J*=7.1 Hz, 2H), 4.01 (s, 2H), 2.42 (s, 1H), 1.59 (s, 6H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 171.3, 157.2, 87.5, 70.4, 61.4, 46.9, 42.2, 30.1, 14.3.

1-benzyl-3-(2-methylbut-3-yn-2-yl)urea (**1e**): **1e** was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1e** was obtained as white solid; m.p. (hexane) 112.7–113.8 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.20 (m, 5H), 4.29 (s, 2H), 2.22 (s, 1H), 1.52 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.8, 139.6, 128.5, 127.3, 127.0, 88.0, 69.5, 46.6, 43.9, 30.1.

1-allyl-3-(2-methylbut-3-yn-2-yl)urea (**1f**): **1f** was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1f** was obtained as yellow solid; m.p. (hexane) 83.8–85.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.82 (ddd, *J* = 22.4, 10.4, 5.3 Hz, 1H), 5.58 (t, *J* = 5.2 Hz, 1H), 5.35 (s, 1H), 5.16 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.05 (dd, *J* = 10.3, 1.4 Hz, 1H), 3.79 (s, 2H), 2.33 (s, 1H), 1.56 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.7, 135.6, 115.4, 87.9, 69.8, 46.7, 42.6, 30.2.

1-(2-methylbut-3-yn-2-yl)-3-propyl-1-(propylcarbamoyl)urea (**1g**): **1g** was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1g** was obtained as yellow solid; m.p. (hexane) 45.8–46.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.85 – 3.78 (m, 2H), 3.13 (td, *J* = 6.8, 4.1 Hz, 2H), 2.36 (s, 1H), 1.68 – 1.59 (m, 2H), 1.56 (s, 6H), 1.52 – 1.44 (m, 2H), 0.90 (q, *J* = 7.5 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 157.7, 149.1, 87.7, 70.0, 46.6, 44.4, 41.9, 30.1, 23.3, 21.1, 11.4, 11.1.

1-(2-methylbut-3-yn-2-yl)-3-phenylurea (**1h**): **1h** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1h** was obtained as white solid; m.p. (hexane) 116.3–117.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.17 (m, 5H), 4.33 (bs, 2H), 2.28 (s, 1H), 1.54 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 139.5, 128.6, 127.4, 127.1, 87.8, 69.9, 46.7, 44.1, 30.2.

1-(4-fluorophenyl)-3-(2-methylbut-3-yn-2-yl)urea (**1i**): **1i** was synthesized according to the general procedure 1. The crude was dried under vacuum and used without purification and the product **1i** was obtained as light purple solid; m.p. (hexane) 174.1–174.8 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.33 (bs, 1H), 7.41–7.30 (m, 2H), 7.09–7.01 (m, 2H), 6.38 (bs, 1H), 3.11 (s, 1H), 1.53 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 156.9 (d, J=237.2 Hz), 153.9, 136.6 (d, J=2.3 Hz), 119.1 (d, J=7.5 Hz), 115.1 (d, J=22.0 Hz), 88.6, 70.8, 46.0, 29.4. ^{19}F NMR (376 MHz, DMSO) δ -122.40.

1-butyl-3-(3-ethylpent-1-yn-3-yl)urea (**1m**): **1m** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1m** was obtained as viscous colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (bs, 1H), 4.73 (bs, 1H), 3.15 (dd, J = 12.7, 6.7 Hz, 2H), 2.40 (s, 1H), 1.89 (dq, J = 14.7, 7.4 Hz, 2H), 1.76 (dq, J = 14.5, 7.4 Hz, 2H), 1.50 – 1.39 (m, 2H), 1.37 – 1.26 (m, 2H), 0.95 (t, J = 7.4 Hz, 6H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 86.0, 72.4, 55.4, 40.0, 32.3, 31.8, 20.2, 13.9, 8.6.

1-butyl-3-(1-ethynylcyclohexyl)urea (**1n**): **1n** was synthesized according to general procedure 1. The crude was dried under vacuum and used without purification and the product **1n** was obtained as white solid; m.p. (hexane) 71.1–73.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (bt, J = 5.0 Hz, 1H), 4.91 (bs, 1H), 3.17 (td, J = 7.0, 5.7 Hz, 2H), 2.45 (s, 1H), 2.12 – 2.01 (m, 2H), 1.64 – 1.50 (m, 7H), 1.49 – 1.40 (m, 2H), 1.37 – 1.28 (m, 2H), 1.27 – 1.16 (m, 1H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 86.4, 72.6, 50.8, 40.0, 38.2, 32.4, 25.3, 22.4, 20.2, 13.9.

1-butyl-3-(2-methyl-4-phenylbut-3-yn-2-yl)urea (**1o**): **1o** was synthesized according to the general procedure 2 from **1a**. The crude was purified by silica gel column chromatography to obtain the product **1o** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.35 (m, 2H), 7.32 – 7.24 (m, 3H), 3.21 (t, *J* = 7.0 Hz, 2H), 1.63 (s, 6H), 1.50 – 1.40 (m, 2H), 1.36 – 1.26 (m, 2H), 0.84 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 131.7, 128.5, 128.4, 122.5, 92.6, 82.7, 47.5, 40.1, 32.3, 30.4, 20.2, 13.8.

1-butyl-3-(4-(3-fluoro-4-methylphenyl)-2-methylbut-3-yn-2-yl)urea (**1p**): **1p** was synthesized according to the general procedure 2 from **1a**. The crude was purified by silica gel column chromatography to obtain the product **1p** as yellow solid; m.p. (hexane) 77.9–79.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 6.97 (m, 3H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.24 (d, *J* = 1.9 Hz, 3H), 1.63 (s, 6H), 1.50 – 1.40 (m, *J* = 7.5, 6.6, 2.9 Hz, 2H), 1.37 – 1.25 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.03, 159.59, 157.77, 131.44 (d, *J* = 5.7 Hz), 127.39 (d, *J* = 3.4 Hz), 125.87 (d, *J* = 17.2 Hz), 121.51 (d, *J* = 9.5 Hz), 118.13 (d, *J* = 23.9 Hz), 92.73, 81.68, 47.48, 40.10, 32.34, 30.40, 20.20, 14.62 (d, *J* = 3.4 Hz), 13.84. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.22.

Methyl 2-(3-(3-butylureido)-3-methylbut-1-yn-1-yl)benzoate (**1q**): **1q** was synthesized according to the general procedure 2 from **1a**. The crude was purified by silica gel column chromatography to obtain the product **1q** as transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.45 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.37 (td, *J* = 7.6, 1.4 Hz, 1H), 7.28 (td, *J* = 7.6, 1.4 Hz, 1H), 6.09 (s, 1H), 5.41 (s, 1H), 3.83 (s, 3H), 3.19 (dd, *J* = 12.8, 6.9 Hz, 2H), 1.60 (s, 6H), 1.47 – 1.38 (m, 2H), 1.29 – 1.19 (m, 2H), 0.78 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 158.1, 134.1, 131.7, 131.4, 130.2, 127.9, 123.2, 97.6, 81.0, 51.9, 47.2, 39.9, 32.3, 30.0, 20.0, 13.7.

1-butyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2a**): **2a** was obtained from **1a** in 4 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2a** (72 mg, quant. yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (d, *J* = 2.8 Hz, 1H), 4.06 (d, *J* = 2.8 Hz, 1H), 3.60 (bs, 1H), 3.20 (t, *J* = 7.1 Hz, 2H), 1.52 (dt, *J* = 14.9, 7.4 Hz, 2H), 1.38 – 1.30 (s, 1.32, 6H; m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 156.5, 80.9, 67.0, 42.5, 31.9, 30.6, 20.0, 13.9.

1-(tert-butyl)-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2b**): **2b** was obtained from **1b** in 4 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2b** (72 mg, 95%) as yellowish solid; m.p. (hexane) 177.6–179.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (d, *J* = 2.7 Hz, 1H), 4.01 (d, *J* = 2.7 Hz, 1H), 1.31 (s, 8H), 1.29 (s, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.7, 154.4, 80.2, 67.5, 51.0, 30.5, 29.1.

1-propyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2c**): **2c** was obtained from **1c** and **1g** in 5 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2c** (67 mg, quant. yield) as transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (d, *J* = 2.8 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 3.93 (s, 1H), 3.16 (t, *J* = 7.2 Hz, 2H), 1.55 (dt, *J* = 14.6, 7.3 Hz, 2H), 1.32 (s, 6H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 156.5, 80.9, 67.0, 44.4, 30.5, 23.0, 11.3.

Methyl 2-(4,4-dimethyl-5-methylene-2-oxoimidazolidin-1-yl)acetate (**2d**): **2d** was obtained from **1d** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2d** (49 mg, 62%) as white solid; m.p. (hexane) 82–84.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (s, 1H), 4.50 (d, *J* = 2.9 Hz, 1H), 4.08 (d, *J* = 2.9 Hz, 1H), 4.00 (s, 2H), 3.74 (s, 3H), 1.31 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 168.0, 156.0, 81.4, 66.9, 52.4, 44.1, 30.3.

1-benzyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2e**): **2e** was obtained from **1e** in 6 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2e** (81 mg, 94%) as white solid; m.p. (hexane) 93.3–94.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 4H), 7.27 – 7.22 (m, 1H), 4.97 (s, 1H), 4.48 (d, *J* = 2.8 Hz, 1H), 4.37 (s, 2H), 4.08 (d, *J* = 2.8 Hz, 1H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 156.6, 138.5, 128.6, 127.6, 127.5, 81.0, 66.9, 46.6, 30.4.

1-allyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2f**): **2f** was obtained from **1f** in 7 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2f** (44 mg, 67%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.20 (ddd, *J* = 17.2, 3.1, 1.7 Hz, 1H), 5.12 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.48 (d, *J* = 2.8 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 3.96 (bs, 1H), 3.82 (dt, *J* = 5.5, 1.6 Hz, 2H), 1.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 156.3, 134.3, 116.3, 81.1, 67.1, 45.0, 30.5.

4,4-dimethyl-5-methylene-1-phenylimidazolidin-2-one (**2h**): **2h** was obtained from **1h** in 3 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2h** (80 mg, quant. yield) as white solid; m.p. (hexane) 127.5–130.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2H), 7.35–7.30 (m, 3H), 6.23 (bs, 1H), 4.00 (2s, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 154.68, 135.2, 129.4, 127.7, 127.6, 79.6, 56.7, 29.9.

1-(4-fluorophenyl)-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2i**): **2i** was obtained from **1i** in 4 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2i** (88 mg, quant. yield) as orange solid; m.p. (hexane) 165.6–167.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.25 (m, 2H), 7.17–7.08 (m, 2H), 5.89 (bs, 1H), 4.00–3.97 (m, 2H), 1.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 160.5, 157.1, 154.7, 131.10 (d, *J* = 3.1 Hz), 129.60 (d, *J* = 8.6 Hz), 116.5, 116.3, 79.9, 56.8, 29.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.93.

3-benzyl-1-butyl-4,4-dimethyl-5-methyleneimidazolidin-2-one (**2j**): **2j** was obtained from **1j** in 24 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (6:4) as eluent to give **2j** (47 mg, 43%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 4.48 (s, 2H), 3.99 (d, *J* = 2.3 Hz, 1H), 3.91 (d, *J* = 2.4 Hz, 1H), 3.53 – 3.46 (m, 2H), 1.61 (dt, J = 15.0, 7.5 Hz, 2H), 1.39 (dd, J = 15.1, 7.5 Hz, 2H), 1.24 (s, 6H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 153.1, 139.7, 128.5, 127.7, 127.2, 76.9, 60.3, 43.1, 40.3, 28.8, 27.9, 20.2, 13.9.

N-(4,4-dimethyl-5-methylenethiazolidin-2-ylidene)propan-1-amine (**2k**): **2k** was obtained in 18 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2k** (149 mg, 81%) as yellow solid; m.p. (hexane) 61.2–62.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (dd, J = 6.0, 1.4 Hz, 2H), 4.32 (s, 1H), 3.18 (dd, J = 13.2, 6.1 Hz, 2H), 1.63 – 1.46 (m, 2H), 1.38 (s, 6H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 154.4, 101.7, 77.7, 46.5, 30.4, 23.2, 11.4.

3,3,7,7-tetramethyl-2-methylene-3,7-dihydro-2H-oxazolo[3,2-a]pyrimidine (**2l**): **2l** was obtained from **1l** in 24 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2l** (46 mg, 61%) as yellow solid; m.p. (hexane) 121.8–123.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (d, J = 7.8 Hz, 1H), 4.70 (d, J = 7.8 Hz, 1H), 4.57 (d, J = 3.2 Hz, 1H), 4.14 (d, J = 3.3 Hz, 1H), 1.36 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 151.0, 118.4, 111.7, 83.6, 60.7, 54.8, 32.6, 26.9.

1-butyl-4,4-diethyl-5-methyleneimidazolidin-2-one (**2m**): **2m** was obtained from **1m** in 2 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2m** (79 mg, 94%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, J = 2.6 Hz, 1H), 4.14 (bs, 1H), 3.91 (d, J = 2.6 Hz, 1H), 3.18 (t, J = 7.1 Hz, 2H), 1.66 (dq, J = 14.6, 7.3 Hz, 2H), 1.50 (dt, J = 14.9, 7.3 Hz, 2H), 1.44 – 1.36 (m, 2H), 1.31 (dt, J = 14.5, 7.4 Hz, 2H), 0.87 (t, J = 7.3 Hz, 3H), 0.74 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 156.6, 81.4, 74.7, 42.4, 34.5, 31.9, 19.9, 13.8, 8.1.

3-butyl-4-methylene-1,3-diazaspiro[4.5]decan-2-one (**2n**): **2n** was obtained from **1n** in 16 hours of reaction time. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2n** (66 mg, 75%) as transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (d, J = 2.7 Hz, 1H), 4.09 (d, J = 2.7 Hz, 1H), 3.79 (bs, 1H), 3.20 (t, J = 7.1 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.67 – 1.54 (m, 6H), 1.52 – 1.44 (m, 3H), 1.39 – 1.29 (m, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 156.4, 81.4, 69.7, 42.5, 39.5, 32.1, 25.6, 22.3, 20.0, 13.9.

(Z)-5-benzylidene-1-butyl-4,4-dimethylimidazolidin-2-one (**2o**): **2o** was obtained from **1o** in 16 hours of reaction time using 10% of $AgNO_3$. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2o** (80 mg, 78%) as white solid; m.p. (hexane) 135.4–137.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.47 (m, 2H), 7.34 – 7.28 (m, 2H), 7.19 – 7.10 (m, 1H), 5.39 (s, 1H), 3.29 (t, *J* = 7.2 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.46 – 1.36 (m, 8H: 1.42, s, 6H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 156.5, 135.2, 128.5, 127.8, 126.0, 98.1, 68.8, 42.7, 31.9, 30.5, 20.1, 13.9.

(Z)-1-butyl-5-(3-fluoro-4-methylbenzylidene)-4,4-dimethylimidazolidin-2-one (**2p**): **2p** was obtained from **1p** in 16 hours of reaction time using 10% of $AgNO_3$. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2p** (94 mg, 81%) as white solid; m.p. (hexane) 123.9–125.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, *J* = 7.7, 6.4 Hz, 1H), 7.10 – 7.05 (m, 2H), 5.33 (s, 1H), 3.29 (t, *J* = 7.2 Hz, 2H), 2.25 – 2.22 (m, 3H), 1.64 – 1.54 (m, 2H), 1.43 – 1.36 (m, 8H; 1.40, s, 6H), 0.96 – 0.91 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 160.5 (d, *J* = 79.7 Hz), 156.7, 134.5 (d, *J* = 8.4 Hz), 131.1 (d, *J* = 5.6 Hz), 123.3 (d, *J* = 2.9 Hz), 122.3 (d, *J* = 17.5 Hz), 113.9 (d, *J* = 23.6 Hz),97.4, 68.4, 42.6, 31.8, 30.4, 20.0, 14.3 (d, *J* = 3.5 Hz), 13.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.34.

(Z)-methyl 2-((3-butyl-5,5-dimethyl-2-oxoimidazolidin-4-ylidene)methyl)benzoate (**2q**): **2q** was obtained from **1q** in 16 hours of reaction time using 10% of $AgNO_3$. The crude was purified by flash column chromatography using hexane/ethyl acetate (1:1) as eluent to give **2q** (101 mg, 80%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.81 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.47 (td, *J* = 7.7, 1.4 Hz, 1H), 7.27 – 7.20 (m, 1H), 6.41 (s, 1H), 3.89 (s, 3H), 3.28 (t, *J* = 7.2 Hz, 2H), 1.58 (dd, *J* = 8.2, 6.3 Hz, 2H), 1.47 (s, 6H), 1.37 (dd, *J* = 10.4, 4.8 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 168.1, 160.2, 158.2, 135.4, 131.9, 130.8, 129.8, 128.0, 126.2, 97.3, 67.8, 52.1, 42.7, 32.1, 31.0, 20.0, 13.8.

7.5. Bibliography

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8. List of abbreviations

$[Ru(bpy)_3]Cl_{2*}6H_2O$	Tris(2,2′-bipyridyl)dichlororuthenium(II) hexahydrate
Ac-Ile-OH	N-Acetyl-L-isoleucine
AcOH	Acetic acid
ACS	American Chemical Society
Ac-Val-OH	N-α-Acetyl-L-valine
APIs	Active Pharmaceutical Ingredients
Ar	Aryl
BEMP	2-tert-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
binap	1,1′-Binaphthalene-2,2′-diyl-bis(diphenylphosphine)
Boc-Ile-OH	N-(tert-Butoxycarbonyl)-L-isoleucine
bpy	Bipyridine
BTMG	2-tert-Butyl-1,1,3,3-tetramethylguanidine
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM or CH_2Cl_2	Dichloromethane
DFT	Density Functional Theory
diop	2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino)butane
DIPEA	N,N-Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBPF	1,1′-Bis(di-tert-butylphosphino)ferrocene
e.g.	*exempli gratia*
EDG	Electron Donatin Group
EtOAc	Ethyl Acetate
EWG	Electron Withdrawing Group
GC	Gas Chromatography
GC-FID	Gas Chromatography-Flame Ionization Detector
GCI	Green Chemistry Institute
GC-MS	Gas Chromatoragphy-Mass Spectrometry
HMPA	Hexamethylphosphoramide
i.d. or I.D.	internal diameter

i.e.	*id est*
IRC	Intrinsic Reaction Coordinate
KI	Potassium Iodide
KOAc or AcOK	Potassium Acetate
L-DOPA	L-3,4-dihydroxyphenylalanine
LEDs	Light Emitting Diodes
m.p.	melting point
MeCN or ACN	Acetonitrile
MeOH	Methanol
MFC	Mass Flow Controler
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
nBu	normal Butyl
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PFA	Perfluoroalkoxy alkanes
PhOK	Potassium phonoxide
PivOK	Potassium pivalate
RT or rt	room temperature
SMD	Solvation Model based on Density
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAA	TetraButylAmmonium Acetate
TBAF	TetraButylAmmonium Fluoride
TBAI	TetraButylAmmonium Iodide
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
t-BuOK	Potassium *tert*-butoxide
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	N,N,N′,N′-Tetramethylethylenediamine
TMG	N,N,N′,N′-Tetramethylguanidine
TS	Transition State
Xphos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
ΔG	Gibbs Free Energy

9. Acknowledgements

Finally it is time for the best part of this thesis: acknowledgments.
This long and intimidating word for me means share my gratitude to those who contributed to my personal and scientific growth during these three years.
Here I am, sitted in my office looking back at this experience. The air is still filled with the power of scientific knowledge since this room was Marta Catellani office. I am also using her chair, the most confortable of all the office that now it is hosting new generations of scientists.

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