UNIVERSITÀ DEGLI STUDI FIRENZE

DOTTORATO DI RICERCA IN SCIENZE CHIMICHE

CICLO XXXII

COORDINATORE Prof. Piero Baglioni

DIVERSITY-ORIENTED SYNTESIS

OF NEW CHEMICAL ENTITIES EXPLOITING

CARBONYL-COUPLING REACTIONS

Settore Scientifico Disciplinare CHIM/06

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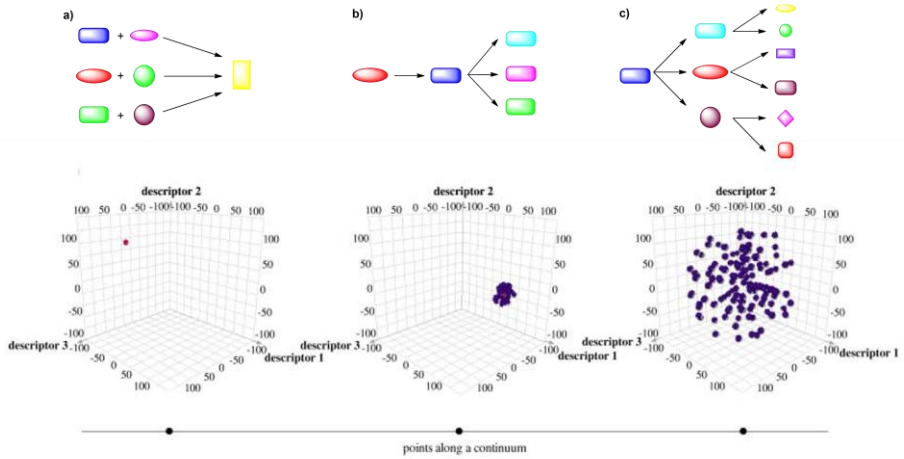
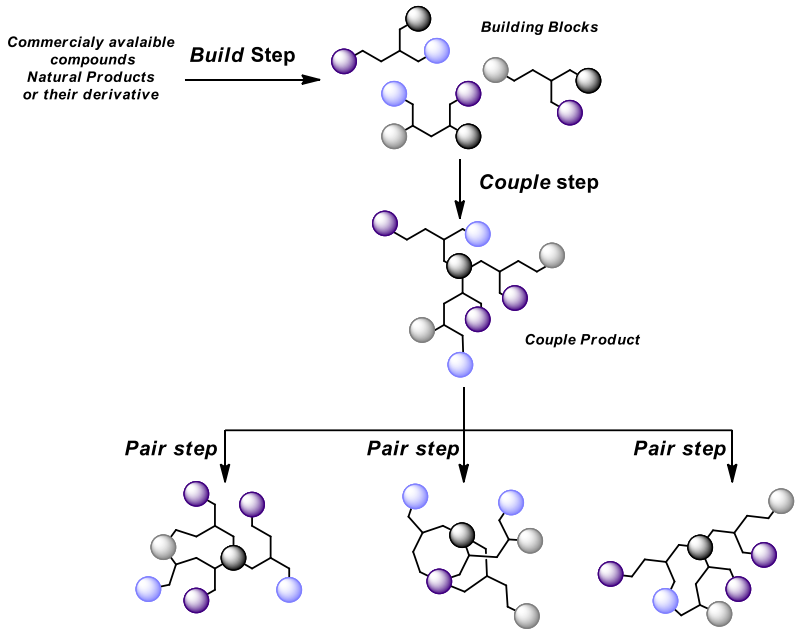
Abstract

The research of New Molecular Entities (NME) with a biological activity is one of the most important topics in modern Drug Discovery, because after an impressive growth at the end of the last Century, the number of NME launched on the drug-market dramatically decreased in recent years. The application of Diversity-Oriented-Synthesis (DOS)[1] has been placed as a new paradigm for the revival of drug discovery, and has received great interest in the biomedical field during last years. DOS consists of generating structurally diverse compounds from a complexity generating reaction followed by cyclization steps and appendage diversity .

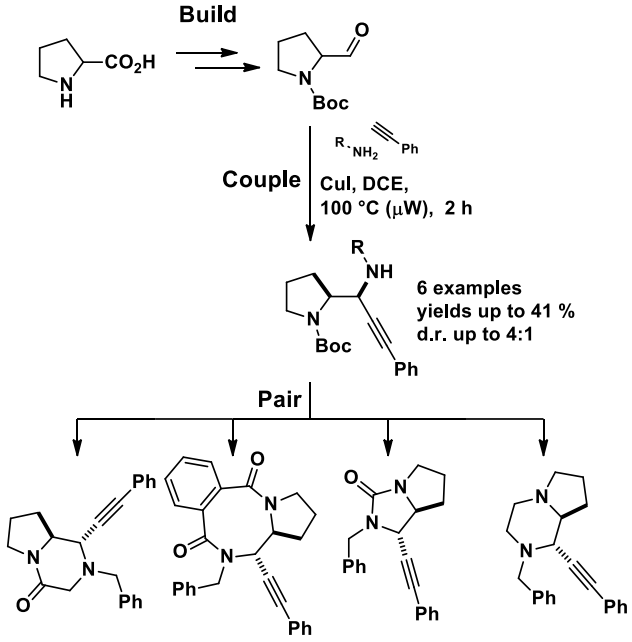


The Build Couple Pair (B/C/P) strategy is one of the most used approaches, and it is based on three different steps. The first is the build phase and comprises all the reactions necessary to transform a natural product derivative into a building block. The "Couple" consists of intermolecular coupling reactions that join the selected building blocks. The "Pair" is a series of intramolecular coupling reactions that join pairwise combinations of functional groups incorporated in the “Build” phase. In this type of approach the "Couple" step represents the core of the strategy; indeed based on the chemical approach used in this phase suitable the building blocks are required, and consequently the functional groups available for the pair step.



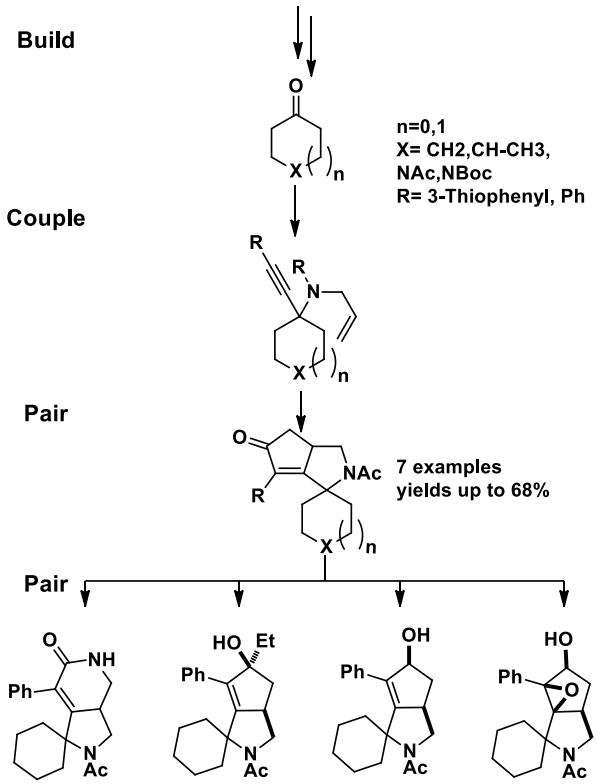
To obtain a suitable strategy, the couple step requires some properties: the reaction needs to be chemo- and regioselective to avoid the use of many protecting groups and to obtain a quick and efficient synthetic pathway with a good tolerance of many functional groups. The second important point for a couple reaction is to have the control of all the possible stereochemical outcomes; this indeed gives the possibility to synthesize all the possible stereoisomers of a compound to increase the possibilities to find a bioactive molecule. The Aldehyde-Amine-Alkyne (A^3) coupling reaction[3] is a copper-catalyzed multicomponent reaction. This is interesting for being applied as a couple reaction in a B/C/P strategy[4], because the reaction products are highly functionalized and the reaction can be conducted in a stereoselective way. The reaction starts with the imine formation and it evolves with the attack of the imine carbon by the copper acetilyde in situ, pre-formed by the usual mechanism of copper catalysis, to give a propargylamine with a mono-substituted α-carbon. For our strategy we decided to use α-amino aldehydes as building blocks, because they are of special interest due to their ready availability in both enantiomeric forms from natural sources as well as their pronounced versatility. Indeed, the amino and aldehyde functionalities are two orthogonal groups that can be used, in a selective way, one for the couple step and the other in the pairing phase. Among all the possible amino aldehydes we decided to focus on N-Boc-prolinal, because the presence of a cyclic framework helps the reactions proceeding with better stereoselectivity and the presence of a cycle before the pairing step allows to obtain a product with higher structural

complexity. The aldehyde was synthesized starting from the commercial L-prolinol in the Build step. Then, optimization of the A^3 (Couple step) reaction resulted in finding the best condition employed for this process, specifically using CuI as catalyst, 1,2-dichloroethane as solvent and heating the reaction at 100°C for two hours using microwave irradiation. The scope of the reaction was studied with several amines all proceeding with satisfying yield and d.r.. Then, we used 4 different bidentate reagents to obtain different intramolecular cyclization from the two nitrogen atoms of the couple adduct for the Pairing step.



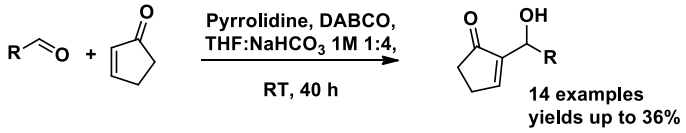
The Ketone Amine Alkyne coupling (KA^2) reaction[5] is a variation of the A^3 coupling, where the aldehyde is replaced with a ketone. The reaction starts with the imine formation and evolves with the attack of the imine carbon by the copper acetylide in situ, pre-formed by the usual mechanism of copper catalysis, to give a propargylamine with a bi-substituted α-carbon. This reaction usually needs more drastic conditions to give good results, and this is probably correlated to the less reactivity of the ketone as compared to the aldehyde. However, when a cyclic ketone is used, the product of the reaction gives the unique possibility to create a spirocyclic compound using the alkyne functionality and a functional group added to the amine. For our strategy we decided to install an alkene functionality with the KA^2 reaction (Couple step) for creating a spirocyclic moiety for the subsequent Pauson-Khand reaction[6] (Pair step). To meet this issue, we used different cyclic ketones in a KA^2 reaction using allylamine and aromatic alkynes, followed by the conversion of

the amine functionality to an amide. Such substrate was successfully applied to the cyclization step. The KA[2] and acylation reactions was performed with good results, and so as for the final Pauson-Khand reaction. In order to increase the diversity of the products synthesized, other four scaffolds were obtained from a one of the spirocyclic compounds.

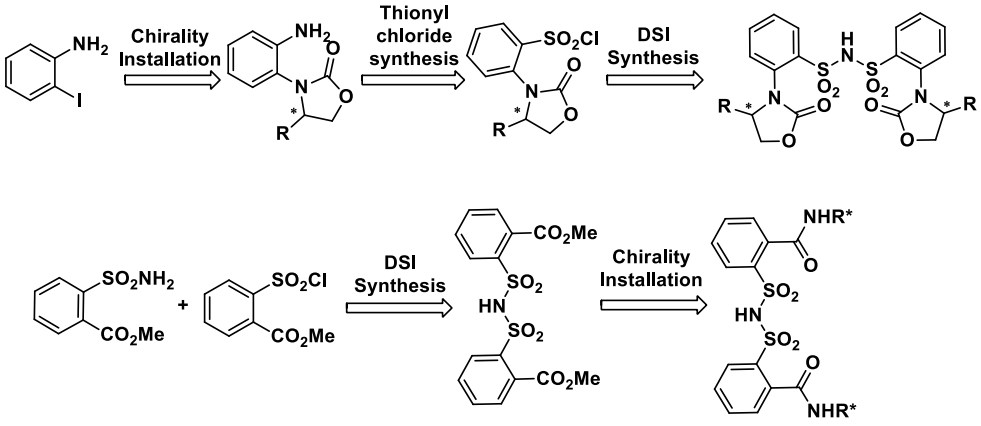


The Morita-Baylis-Hillman[7] reaction is an atom-economic carbon-carbon bond-forming reaction between the β-position of an electron poor alkene and different electrophilic carbon atoms under the influence of a catalytic system. The product of a MBH reaction is quite interesting for DOS approaches because of its polyfunctional character. These properties make it an excellent compound for subsequent reactions in the pair phase, thus the MBH reaction can be used as a couple reaction in B/C/P strategies. Several electron poor alkenes have been used in this reaction such as acrylic acid derivatives, nitro alkenes, α,β unsaturated ketones, and cyclic analogues, Nevertheless, cyclic enones, and in particular the cyclopent-2-enone proved to be a challenging substrate, as only few examples of efficient catalytic systems working on this compound have been reported in the literature[8]. Cyclopent-2-enones is indeed a quite represented moiety in many natural product compounds, making it a suitable building block for a DOS strategy . In our work we found a new mild catalytic

system based on the concomitant presence of an iminium catalyst, derived from a secondary amine, and a basic water solution of $NaHCO_3$ for the reaction of cyclopent-2-enone with various aldehydes.



The aryl disulfonimide (DSI) compounds proved to be a powerful catalyst for many of suchreactions[9]. Unfortunately, the synthesis of the common catalysts are lengthy and the starting material usually is derived from expensive compounds. This represents a limitation both in their applicability and in the possibility of easily synthesizing different catalysts, to find the most suitable for each reaction. During my secondment research period in Oxford University under the supervision of prof. Darren J. Dixon, the aim of my project was the synthesis of these catalyst using a short synthetic pathway and their application in several reactions to test their efficiency. In our strategy we decided to install several chiral side chains, such as oxazolidone derived from aminoalcohols, enantiopure amides and various chiral amines on the achiral skeleton of the disulfonimide. Unfortunately, the direct attack of various oxazolidinones on halogen substituted aryl disulfonimides did not work under the standard conditions of the Ullmann coupling. Even though the acid NH was replaced by various alkyl and aryl side chains, to solve this problem we performed the coupling on different compounds which contained a functional group that was converted into a sulfonyl chloride. So, starting from *o*- halogen substituted anilines, we obtained the desired compounds in good yields. After the conversion of the amine functionality we achieved the chiral sulfonyl chloride that could be directly transformed in the DSI catalysts with a simple disulfinylation reaction with ammonium chloride. In the second generation of catalysts, we started from commercially available thiosalicylic acid derivatives. After a protection of the thiol functionality, we attached several chiral amines using a common amide bond formation reaction, and after the conversion of sulfonyl chloride the catalyst that contained a primary amide evolved into the saccharin derivative. We solved this problem keeping the methyl ester group until the formation of the DSI catalyst and also we converted the methyl ester functionality into the desired amide by a trans-amidation reaction. This last reaction unfortunately worked only with primary amines, and due to this limitation such process does not represent a general synthetic pathway. The next step of this project will be the application of this catalyst in several reactions to test the effective activity of these compounds.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Bibliography

1. “Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology”, Trabocchi, A., Ed.; Wiley and Sons, **2013**
2. Schreiber, S. L.; *Nature*, **2009**, 457, 153.
3. Peshkov, V.A., Pereshivko, O.P., Van der Eycken, E.V., *Chem. Soc. Rev.*, **2012**, 41, 3790
4. Knapp, J.; Kurth, M. J.; Shaw J. T.; Youna, A.; " *Strategic Applications of Multicomponent Reactions in Diversity-Oriented Synthesis*" in " *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology"* Ed. by Andrea Trabocchi, Wiley and Sons, **2013**.
5. *Catalytic Nucleophilic Addition of Alkynes to Imines: The A3 (Aldehyde–Alkyne–Amine) Coupling"*, in "*Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations"*, First Edition. Edited by Trost, B. M.; Li, C. J.; **2015**, Wiley-VCH Verlag GmbH & Co. KGaA
6. Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J.; *Chem. Soc. Rev.*, **2004**, 33, 1, 32
7. Basavaiah, D.; Veeraraghavaiah, G.; *Chem. Soc. Rev.*, **2012**, 41, 68.
8. Gomes; J. C.; Rodrigues Jr.; M. T.; Moyano; A.; Coelho; F.; *Eur. J. Org. Chem.*, **2012**, 6861.
9. James, T.; van Gemmeren, M.; List, B.; *Chem. Rev*., **2015**, 115, 9388.

Part I
Introduction

Chapter 1

Diversity-Oriented Synthesis as a new resource for the Drug Discovery

1.1 The research of New Molecular Entities

The research of new molecules with a biological activity, or New Molecular Entities (NME), has always been one challenging topic for both academics and pharmaceutical industries. This research field usually involves many kind of scientists such as chemists, biologists, clinical scientists and others. The role of the organic chemist in this process is the synthesis of *small molecules*, indeed it is well known that this kind of compounds can modulate protein-protein interactions or have a crucial role in many biological processes[1]. When the biological targets are well known the rational design of ligands indicates which structure is optimal to interact with the target, and the corresponding synthetic strategy is the Target-Oriented synthesis (TOS) (Figure 1 top). The role of the chemist in the traditional discovery process stays at the end, because other informations such as the structure of the enzyme and the mechanism of the interaction are previously required to understand which structure can be the optimal one[2].

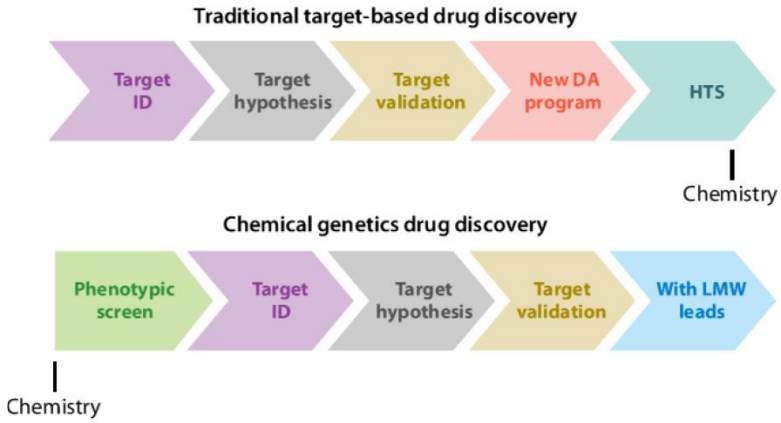


Figure 1 Comparison between the classic "Target based approach" and the "Chemical Genetics" Reproduced from reference 4 with permission from Annual Reviews

Unfortunately, many disorders, such as cancer and neurodegenerative diseases, are often associated with complex interactions between transcription factors, proteins and DNA, targets that have been termed “undruggable”, due to the difficulty in being applied to traditional drug discovery programs[3]. In fact, after

an impressive growth at the end of last Century, the number of NME produced every year dropped down to the levels of 40 years ago, in spite of an exponential growth of investments in the R&D sector[4]. (Figure 2).

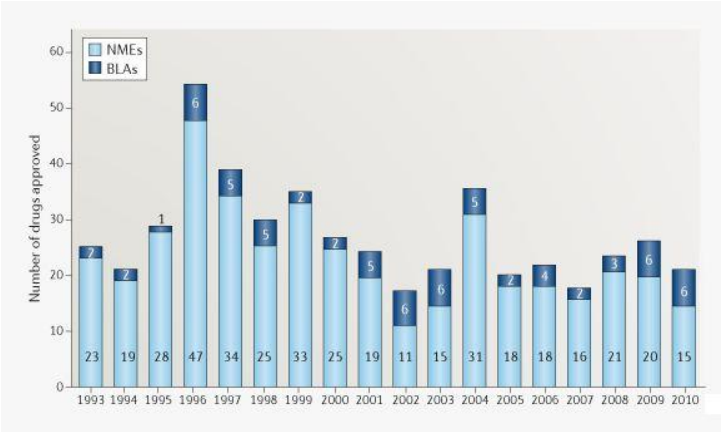


Figure 2 NME launched on market trend.

To address this problem, both academia and pharmaceutical companies must apply new approaches. One of the most promising alternatives for the discovery of new targets and new *lead* compounds is the application of large small molecule libraries in high-throughput screening (HTS)[5] campaigns, phenotypic assays and chemical genetics studies(Figure 1, bottom). Indeed, the relevance of this approach is also highlighted by the advent of international screening initiatives, such as EU-OPENSCREEN[6] or the European Lead Factory[7]. To implement this strategy, several efforts have been devoted to improve the quality and quantity of small molecules representing a library. In particular, during last decades, organic chemists have taken advantage of high-throughput synthetic methods, such as solid-phase techniques,[8] and combinatorial chemistry[9]. Despite the good idea, this approach proved to be unsuitable for the intended purpose[1d], because the libraries generated with these methodologies mainly consisted of compounds having the same central scaffold, and the diversity being focused only on the side chains, resulting in similar behavior in the screening output. Furthermore, combinatorial libraries usually contain flat and simple structures, showing not enough three-dimensional complexity for an efficient interaction with biological macromolecules[10]. A further step forward is represented by Diversity-Oriented Synthesis (DOS). The aim of this synthetic strategy is synthesize the largest number of structurally complex small molecules different from each other as much as possible. For this DOS has revolutionized the construction of libraries for drug discovery issues[11]. Accordingly, DOS has been defined by Spring[12] as “the deliberate,

simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem" in contrast to TOS that is defined as "efforts to identify simultaneously therapeutic protein target and their small molecule regulation"[13].

1.2 Diversity-Oriented Synthesis

1.2.1 Molecular Diversity, the main concept in DOS

Since from the first paperbySchreiber[13] DOS appeared as a synthetic strategy with particular focus on drug discovery and based its strength in creating libraries composed by molecules very much different each other to increase the possibility of finding a new lead compound. So, the center of this concept is the diversity, and over the years the simple word diversity has been developed to arrive to the definition of 4 different categories[14] of diversity that, ideally, should be satisfied in every library:

1. *Appendage diversity*: diversity resulting from the use of different building blocks or achieved by decorating the functional groups of the scaffold with different appendages. This strategy, already used by combinatorial chemistry, is capable of generating thousands of distinct small molecules in few steps, which, however, cover only a small area of the chemical space.
2. *Functional group diversity*: diversity obtained varying the functional groups present in specific sites of scaffolds, giving them different possibilities of interactions with the biomacromolecule.
3. *Stereochemical diversity*: this type of diversity increases the number of relative orientations of the potential interacting elements of the final molecule. It can be achieved best by using enantio- or diastereoselective reactions that proceed in a general way, overriding specific substrate bias.
4. *Scaffold or Skeletal diversity*: diversity resulting in molecules with distinct molecular shapes, obtained by modifying ring structures and other rigidifying elements. This is the most difficult type of chemical diversity to achieve, but also the most attractive one, considering that the scaffold complexity is a tight requisite for the interactions with target biomacromolecules.

*Appendage diversity i*s viewed as the easiest one to achieve but it is the least important when it comes to producing functionally (biologically) diverse compounds, *Scaffold diversity* is by far the most important and most difficult to obtain, because biomacromolecules are (on a molecular scale) large three-dimensional environments with more or less defined binding regions, pockets,

and surfaces and they will interact only with molecules that have a complementary three-dimensional structure. Therefore, it is the overall shape of a molecule that is the most important factor in determining its biological effects, and this is linked intrinsically to the molecular scaffold or skeleton that the molecule possesses[15]. So it is easy to understand that this is the differing feature for the three main synthetic strategies (TOS, Combinatorial Libraries and DOS). Indeed, while for the TOS we do not talk about libraries because it is focused on the synthesis of few selected compounds with a well-defined structure, for the combinatorial libraries the lack of diversity is an intrinsic consequence of the synthetic methodology, as the libraries synthesized with this approach often contains a huge number of compounds but with poor skeletal diversity [5d]. (Figure 3).

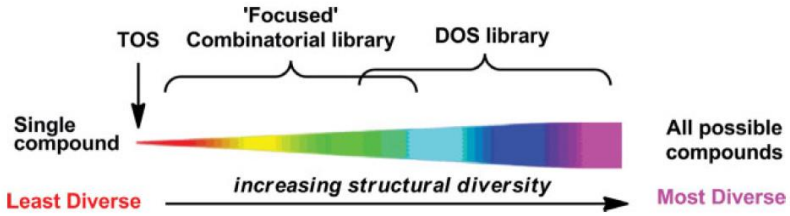


Figure 3 Molecular diversity spectrum a visual comparison from TOF, Combinatorial Chemistry and DOS. Reproduced from reference 5 with the permission of John Wiley and sons.

1.2.2 Chemical space, a tool for the analysis of the diversity inside a library

Despite all the previous definitions of diversity, the concept of diversity is hard to understand and analyze with a proper methodology, therefore the use of the concept called" *Chemical Space*", is of help to visualize the diversity generated in different libraries in a quick, and easy way[16]. The chemical space, or more exactly the *multidimensional descriptor space*, was defined by Dobson, as "the total descriptor space that encompasses all the small carbon-based molecules that could in principle be created"[17]. So, the chemical space is infinite for definition and the only limitation could be represented from the current synthetic knowledge[18]. Using this concept, the difference between TOS, combinatorial chemistry and DOS are easy to understand[19].

- *TOS* do not generate a library but a single compound in a focused region of the chemical space (Figure 4 a)
- *Combinatorial chemistry* aims to generate a large number of structures, but they occupy only a selected region of the chemical space (Figure 4 b)
- DOS uses forward synthetic analysis to explore wide and unknown areas of the chemical space in a much more efficient way (Figure 4 c)

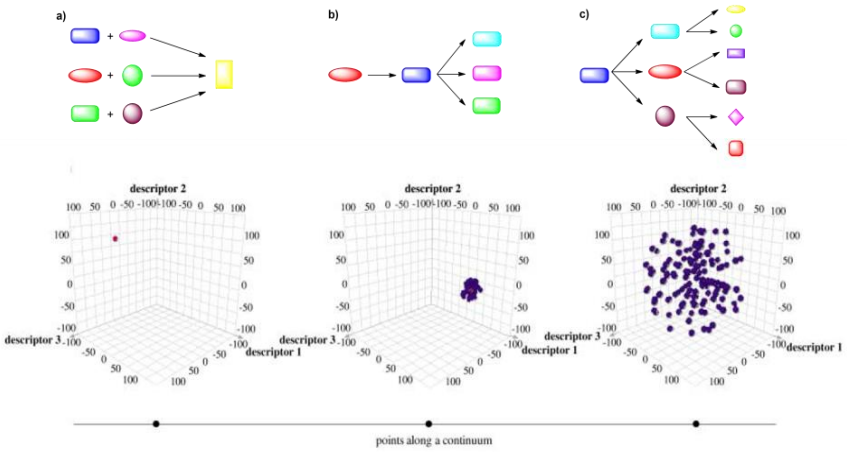


Figure 4 Products distribution in the chemical space of TOS (a), combinatorial (b) and DOS strategies.

The concept of chemical space allow us to understand how large is the diversity of compounds inside a library but also to compare different libraries and to analyze which are the common or the different areas that they occupy inside the chemical space. As an example, this is useful to understand if a synthesized library has points in common with a library composed of known bioactive molecules.

1.2.3 Chemoinformatics methodology to analyze the diversity in the libraries

The goal of representing the chemical space in a easily understandable graph is a hard work, because, as described in the previous paragraph, the chemical space can be defined using all the physical and chemical properties of the molecules. Given that an univocal and right representation of it[20] is not possible, the chemo informatics instruments as *Principal Component Analysis* (PCA)[21] and *Principal Moment of Inertia* (PMI)[22] allow us to organize a selected property of the molecules in a easily readable graph. PCA is a statistical tool used to condense multidimensional chemical properties, such as molecular weight, logP, ring complexity, into single dimensional numerical values, that can be plotted into graphs and superimposed to compare the relative diversity of different molecule collections. Just to give an example, in Figure 5 was reported a PCA analysis by Wyatt et al.[23] Specifically, they compared a library synthesized with a DOS methodology with a focused library and with a database of drugs retrieved from the MDL Drug Data Repository. The first principal component was related to the ratio of aromatic ring atoms towards the

total number of heavy atoms and the number of hydrogen bond donors and acceptors. The second principal component was analyzed considering the ring fusion degree and the number of carbon-sulfur and carbon-halogen bonds. The focused library covers only a limited area in the diversity space and the major part covered by drugs and natural products do not contain any representative compounds of it.

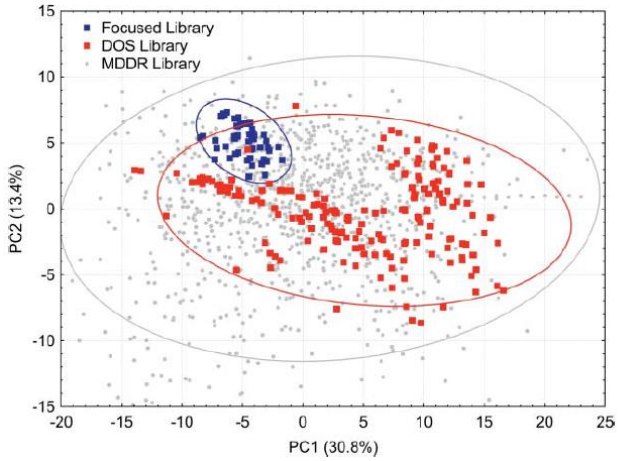


Figure 5 Comparison of a synthesized DOS library (red), a focused one (blue) and MDL Drug Data Repository (grey). Reproduced from ref 23 with the permission of Royal Society of Chemistry

The Principal Moments of Inertia (PMI) analysis employs normalized shape based descriptors to position the minimum energy conformation of each library member in a triangular graph plot, where the vertices represent a perfect rod (acetylene), disc (benzene) and sphere (adamantane), thus describing the chemical space covered by the library members with respect to the molecular shape. Greater shape diversity of a library correlates with increased likelihood of the collection to contain molecules capable of interacting with biological targets. Just to give an example, Menédez[24] and coworkers using the PMI analyzed the distribution of their library containing a series of scaffolds with a pyrrolidine moiety with collections of natural products and drugs. (Figure 6).

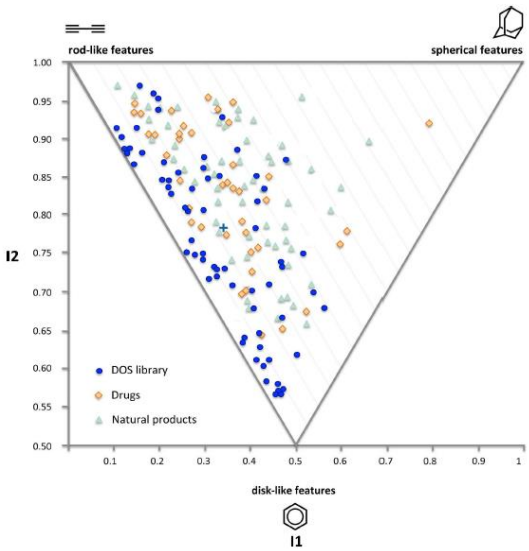


Figure 6 Comparison of a synthesized DOS library(blue), and two libraries composed by natural products (green) and drugs(orange), respectively.

1.2.4 Chemical genetics, the biological application of DOS libraries

The aim of Diversity-Oriented Synthesis (DOS) is the application of the synthesized libraries to find new lead compounds, so we can say that this synthetic strategy was born to be applied on drug discovery. As introduced previously, there are two different approaches to establish the bioactivity of the molecules[25]. The first one is the traditional approach, the high-throughput screening looking for activity against several known biological targets. Although being an old approach, this is still remunerative and attractive thanks to advances in HTS technology and robotics, as demonstrated by the high number of collaborative public or private screening networks[26].

The second one is the phenotypic screening, and in particular the chemical genetics studies in search of *hit* compounds capable of inducing a desired phenotype[29]. In this assay method, the molecules are screened in cellular or animal disease models to identify which compounds give a desirable change in the phenotype. Only after the compounds have been discovered, new efforts are made to determine the biological targets of the identified compounds - a process known as target deconvolution (Figure 7). This ‘forward pharmacology’ process proved to be particularly successful for lead discovery in those complex disorders, such as cancer and neurological or infective pathologies, where multiple targets are involved and/or physiopathological pathways have yet to be discovered.

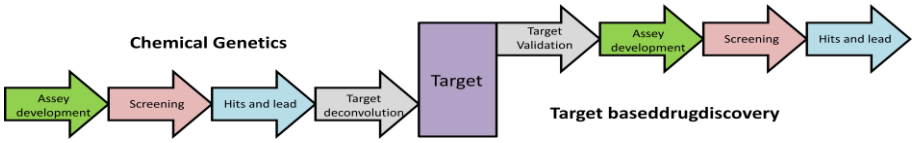
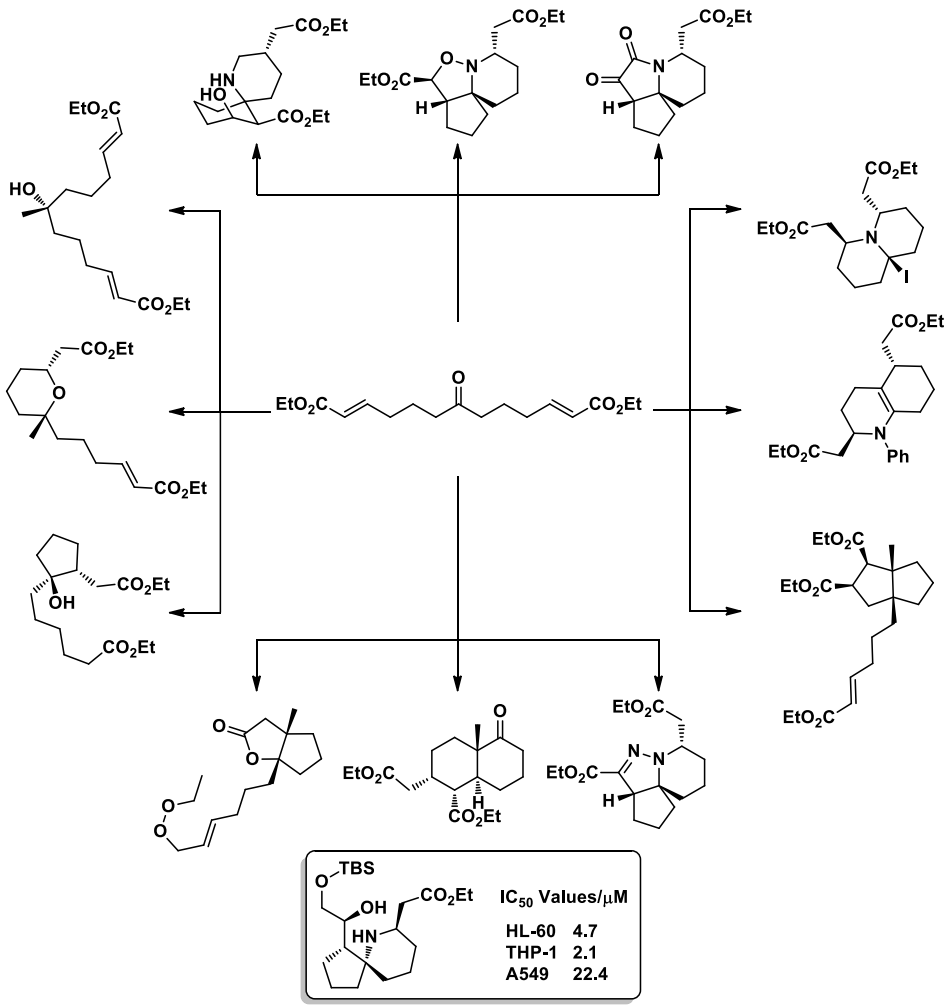


Figure 7 Comparison of the two lead discovery pathways

In this context, chemical genetics is one of the best examples of a methodological development in *lead* generation. Chemical genetics is defined as "analogous to classical genetic screen". In a genetic screening random mutations are introduced in organisms, the phenotype of these mutants is observed, and then the specific gene mutation (genotype) that produced that phenotype is identified. In chemical genetics, the phenotype is perturbed not by the introduction of mutations, but by addition of compounds. Phenotypic screening of chemical libraries is used to identify the activity of a compound directly in a complex biological system, to identify drug targets (forward genetics) or to validate those targets in experimental models of disease (reverse genetics)[28].This approach has been always used in pharmaceutical industries, especially in particular fields[29]. For example, nifedipine, nimodipine, and other calcium channel antagonists were found through the screening of large compound collections by looking at the molecules able to induce vasodilation and blood pressure reduction[30]. However, in the last few years phenotypic screenings have evolved and acquired a precise strategy, taking advantage of robotic and miniaturized technologies and the intrinsic molecular diversity of the libraries generated following Diversity-Oriented Synthesis principles[31].
One of the best example that showed applicability of DOS in drug discovery was reported by Robbins et al. in 2011[32]. In this work the authors transformed a ketone in 12 diverse scaffolds using different cyclization reactions, and the resulting compounds were screened against three different cell lines (HL-60, THP-1, A549), resulting in the identification of several compounds showing micromolar activity against all three celllines, and the best one showing a low µM activity against the first two cell lines (Scheme 1).



Scheme 1 Summary representation of Robbins's work.

1.2.5 The use of privileged scaffold in DOS

As herein defined, the aim of DOS is to synthesize a library containing molecules different from each other without any consideration for the target structure of the products. Nevertheless, diversity oriented synthesis is often focused to the synthesis of different molecules containing specific structure moieties called *Privileged Scaffolds.* This term was defined by Evans[33] as "a set of structures that are able to provide high-affinity ligands for more than one type of receptor". For confirming this property it was found that 35% of bioactive compounds in a large database interacted with more than one protein[34] and 675 proteins from several proteomic families interacted with at least one ligand for another protein within 10-fold of affinity[35]. Many of these structures derived from natural products or heterocyclic compounds (Figure 9)[36].

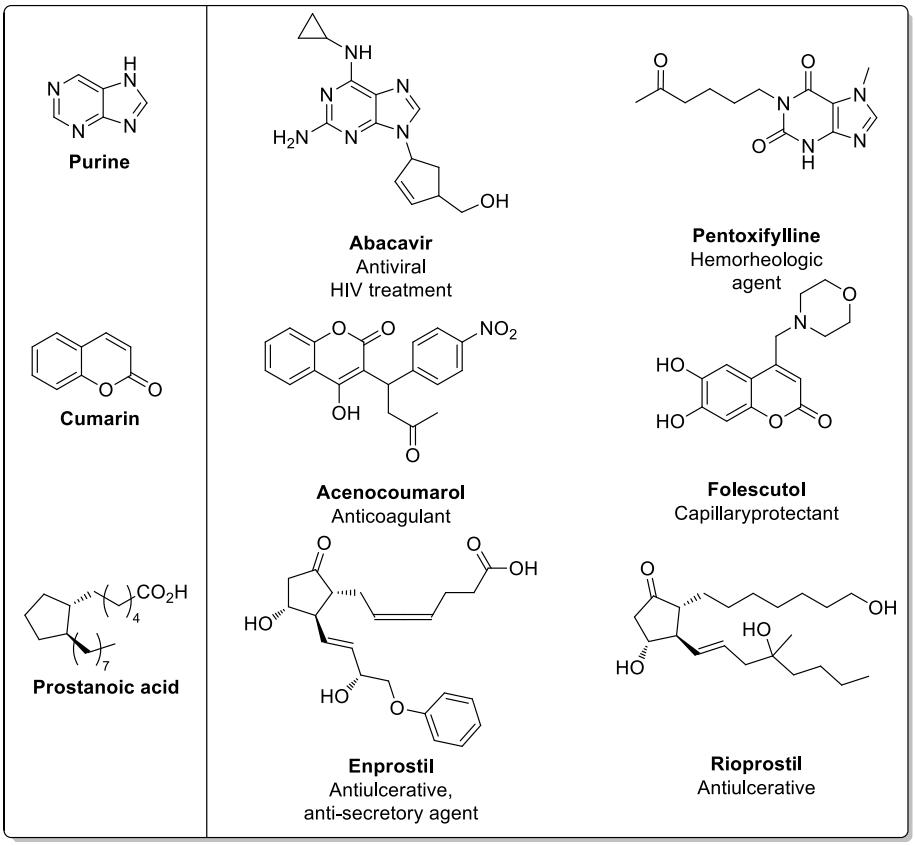
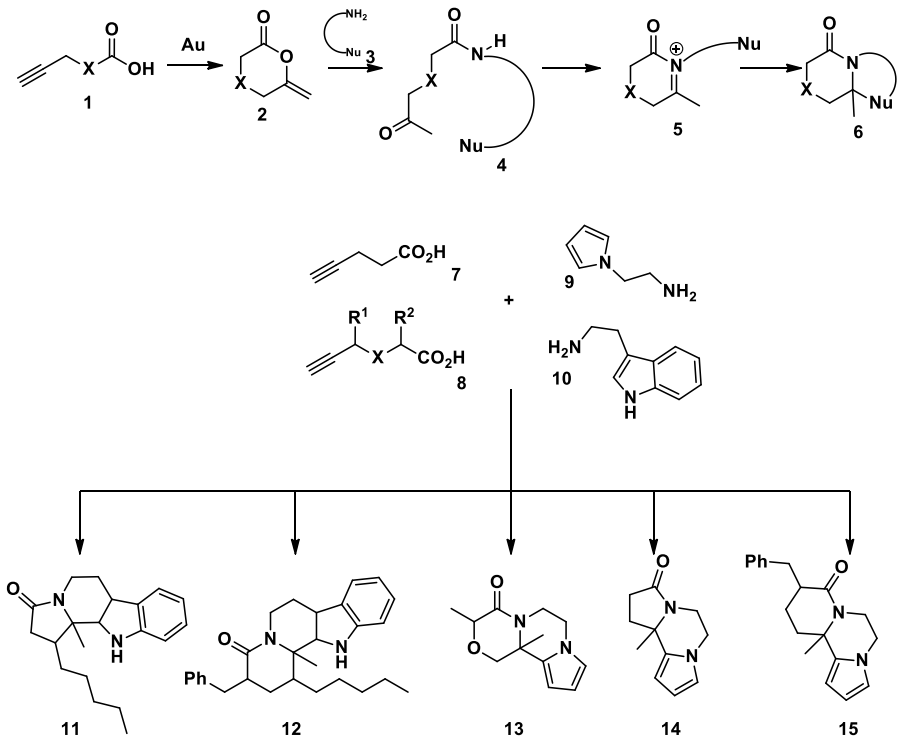


Figure 8 Representative selection of privileged scaffold (left) and bioactive compounds containing this structure moieties.

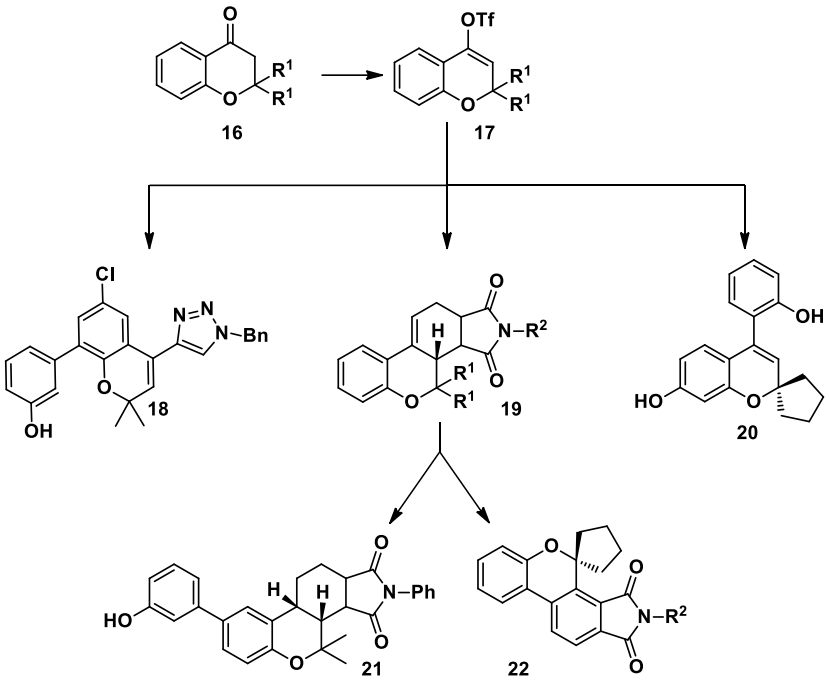
The generation of libraries comprising privileged scaffolds using DOS approach can be divided in two approaches: in the first one the library is synthesized with the aim to obtain compounds that have the structure of a privileged

scaffold; in the second one the privileged scaffolds are used as building blocks for the synthesis of more complex compounds, thus resulting in the structure being a moiety of the final compounds[37]. Often, the first approach is used when the selected privileged scaffold has a complex structure, usually derived from a complex natural product. In the second approach the privileged scaffold has a simple structure, is commercially available or easy accessible by synthesis. A brilliant example of the first case was reported by Dixon et al[38].who used a gold catalyzed cascade cyclization reaction to prepare skeletally diverse alkaloid-like small molecules. The reaction used alkynyl carboxylic acids and amines. In the first step alkynyl carboxylic acids (**1**) gave the corresponding cyclic enol ethers (**2**), subsequently, the attack of amine nucleophiles (**3**) on the cyclic enol ether generated the corresponding ketoamides (**4**). Under these reaction conditions, the cyclization precursor was also converted into an *N*-acyl iminium ion (**5**), which was then trapped by a tethered nucleophile (**6**) (Scheme 2, Top). The scope of the methodology is summarized in Scheme 10. Using combinations of alkynyl carboxylic acids and pyrrole- and indole-tethered amines, a remarkable range of alternative alkaloid-like scaffolds was prepared.



Scheme 2 Summary representation of Dixon's work.

An example of the second case was reported by Oh[39]. They synthesized a library containing a benzopyran moiety, using it as a building block for the synthesis .The vinyl triflates **17**, prepared from the corresponding ketones **16**, were the key intermediates in the synthesis (Scheme 3). The final compounds **20** were prepared by Suzuki coupling, followed by release from the solid support. Alternatively, ethynylation, followed by a Cu-catalyzed "click" reaction, yielded the triazoles **18**. In a similar vein, Pd-catalyzed vinylation of the vinyl triflates **8**, followed by a Diels–Alder reaction, yielded the adducts **19**; it was either reduced (**21**) or aromatized (**22**) to yield final compounds with related scaffolds.



Scheme 3 Summary representation of Oh's work.

DOS proved during the years to be a strong strategy of synthesis, especially in the context to synthesize molecules for drug discovery applications.

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1.3 Bibliography

1. a) Schreiber, S. L.; *Biorg. Med. Chem.,* **1998**, 6, 1127; b) Schreiber, S. L.; *Chem. Eng. News*, **2003**, 81, 51; c) Stockwell, B. R.; *Nat. Rev. Genet.*, **2000**, 1, 116; d) O' Connor, C. J.; Laraia, L; Spring, D. R.; *Chem. Soc. Rev.*,**2011**, 40, 4332.
2. "The Logic of Chemical Synthesis" Corey, E. J.; Cheng, X. M. Ed.; John Wiley & Sons Inc., **1995**, New York. 436 pp
3. Altmann, K. H.; Buchner, J.; Kessler, H.; Diederich, F.; Krautler, B.; Lippard, S.; Liskamp, R.; Muller, K.; Nolan, E. M.; Samorì, B.; Schneider, G.; Schreiber, S. L.; Schwalbe, H.; Toniolo, C.; van Boeckel, C. A. A.; Waldmann, H.; Walsh, C. T. *ChemBioChem.* **2009**, *10*, 16.
4. Cong, F.; Cheung, A. K.; Huang, S.-M. A. *Annu. Rev. Pharmacol. Toxicol.* **2012**, *52*, 57
5. a) Stockwell, B. R. *Nat. Rev. Genet.* **2000**, *1*, 116; b) Stockwell, B. R. *Nature* **2004**, *432*, 847; c) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476; d) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem* **2008**, *6*, 1149; e) Walters, W. P.; Namchuk, M. *Nat. Rev. Drug Discov.* **2003**, *2*, 259
6. http://www.eu-openscreen.eu/ .
7. a) https://www.europeanleadfactory.eu; b) Karawajczyk, A.; Giordanetto, F.; Benningshof, J.; Hamza, D.; Kalliokoski, T.; Pouwer, K.; Morgentin, R.; Nelson, A.; Müller, G.; Piechot, A.; Tzalis, D. *Drug Discov. Today* **2015**, *20*, 1310.
8. a) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 10997; b) De Witt, S. H.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909; c) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149; d) Camps, F.; Castells, J.; Ferrando, M. J.; Font, J. *Tetrahedron Lett.* **1971**, *12*, 1713; e) Patchornik, A.; Kraus, M. A.; *J. Am. Chem. Soc.* **1970**, *92*, 7857; f) Crowley, J. I.; Rapoport, H. *J. Am. Chem. Soc.* **1970**, *92*, 6363.
9. a) Balkenholh, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C.; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; b) Plumkett, M. J.; Ellman, J. A.; *J. Am. Chem. Soc.* **1995**, *117*, 3306.
10. a)Lovering, F.; Bikker, J.; Humblet, C.; *J. Med. Chem.* **2009**, *52*, 6752; b) Lovering, F.; *Med. Chem. Commun.* **2013**, 4, 515; c) Chuprina, A.; Lukin, O.; Demoiseaux, R.; Buzko A.; Shivanyuk, A.; *J. Chem. Inf. Model.* **2010**, *50*, 470; d) Nadin, A.; Hattotuwagama C.; Churcher, I.; *Angew. Chem. Int. Ed.* **2012**, *51*, 1114.

11. “Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology”, Trabocchi, A., Ed.; Wiley and Sons, **2013**.
12. Spring, D. R.; *Org. Biomol. Chem.* **2003**, *1*, 3867.
13. Schreiber, S. L.; *Science* **2000**, *287*, 1964
14. Galloway, W. R. J. D.; Lobet, A. I.; Spring, D. R.; *Nay.Commun.*,**2010**, 1, 80
15. a) Lipinsky, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J.; *Adv. Drug Deliv. Rev.*, **1997**, 23, 3; b) Schreiber, S. L.; *Nature*, **2009**, 457, 153.
16. Oprea, T. I.; Gottfries, J. *J. Comb. Chem.* **2001**, *3*, 157.
17. Dobson, C. M. *Nature* **2004**, *432*, 824.
18. Medina-Franco, J. L.;Mayorga, K. M.; Giulianotti, M. A.; Houghten; Pinilla, C.; *Curr. Comput. Aided Drug Des.* **2008**, *4*, 322.
19. Burke, M. D.; Schreiber, S. L.; *Angew. Chem. Int. Ed.*, **2004**, 43, 46.
20. Akella, L. B.; DeCaprio, D.; *Curr. Opin. Chem. Bio.*,**2010**, 14, 325.
21. Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74.
22. Sauer, W. H. B.; Schwarz, M.K. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 987.
23. Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. J.; Jessiman, A. S.; Welchd, M.; Spring, D. R.; *Chem. Commun*., **2006**, 3296.
24. Leonardi, M.; Estévez, V.; Villacampa, M., Menedéz, J. C.; *Adv Synth .Catal.*,https://doi.org/10.1002/adsc.201900044.
25. a) Macarron, R.; Banks, M. N.; Bojanic, D.; Burns, D. J.; Cirovic, D. A.; Garyantes, T.; Green, D. V. S.; Hertzberg, R. P.; Janzen, W. P.; Paslay, J. W.; Schopfer, U.; Sittampalam, G. S. *Nat. Rev. Drug. Discovery* **2011**, *10*, 188; b) Heeres, J. T.; Hergenrother, P. J. *Chem. Soc. Rev.* **2011**, *40*, 4398; (d) Mishra, K. P.; Ganju, L.; Sairam, M.; Banerjee, P. K.; Sawhney, R. C. *Biomed. Pharmacother.* **2008**, *62*, 94.
26. a) Moffat, J. G.; Rudolph, J.; Bailey, D. *Nat. Rev. Drug Discov.* **2014**, *13*, 588; (b) Koh, M.; Park, J.; Koo, J. Y.; Lim, D.; Cha, M. Y.; Jo, A.; Choi, J. H.; Park, S. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5102; (c) Gregori-Puigjané, E.; Setola, V.; Hert, J.; Crews, B. A.; Irwin, J. J.; Lounkine, E.; Marnett, L.; Roth, B. L.; Shoichet, B. K. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 11178.
27. Mullard, A. *Nat. Rev. Drug Discov.* **2015,** *14*, 807
28. "The Value of Chemical Genetics in Drug Discovery" Kubinyi, H.; Muller, G.; Ed. **2004** Wiley-VCH Verlag GmbH & Co. KGaA.
29. Swinnery, D. C.; Anthony, J. *Nat. Rev. Drug Discov.* **2011**, *10*, 507 .

30. a) Elliott, W.J.; Ram, C.V. *J. Clin. Hypertens.* **2011**, *13*, 687; b) Triggle, D.J. *Biochem. Pharmacol*. **2007**, *74*, 1.
31. a) Schirle, M.; Jenkins, J. L. *Drug Discov. Today* **2016**, *21*, 82; b) Gonzalez-Munoz, A. L.; Minter, R. R.; Rust, S. J. *Drug Discov. To*day **2016**, *21*, 150; c) Zheng, W.; Thorne, N.; McKew, J. C. *Drug Discov. Today* **2013**, *18*, 1067
32. Robbins, D.; Newton, A. F.; Gignoux , C.; Legeay, J.-C; Sinclair, A.; Rejzek, M.; Laxon, C.A.; Yalamanchili, S. K.; Lewis, W.; O'Connell, M.; Stockman, R. A., *Chem. Sci.*, **2011**, 2 , 2232.
33. Evans, B. E.; Rittle, K. E.; Bock, M. G.; *J Med Chem*, **1988**, 31, 2235.
34. Paolini, G. V.; Shapland, R. H. B.; van Hoorn, W. P.; Mason, J. S.; Hopkins, A. L.; *Nat. Biotech.***, 2006,** 24, 805.
35. Hopkins, A. L.; *Nat. Biol.*, **2008**, 4, 682.
36. for a list and a review on privileged scaffolds see:a) Welsch, M. E.; Snyder, S. A.; Stockwell, B. R; *Curr. Opin. Chem. Biol.*, **2010**, 14, 347; b) Zhao, H.; Dietrich, J.; *Expert Opin. Drug Discov*, **2015**, 7, 781.
37. Cordier, C.; Morton, D.; Murrison, S.; Nelson, A; O'Leary-Steele, C.; *Nat. Prod. Rep*., **2008**, 25, 719.
38. Yang, T.; Campbell, L.; Dixon, D. J.*; J. Am. Chem. Soc.,* **2007**, 129, 12070.
39. (a) S. Oh, H. J. Jang, S. K. Ko, Y. Ko, S. B. Park, *J. Comb. Chem.* **2010**, *12*, 548–558;(b) S. Oh, S. W. Cho, J. Y. Yang, H. J. Sun, Y. S. Chung, C. S. Shin, S. B. Park, *Med.Chem. Commun.* **2011**, *2*, 76–80.

Chapter 2

Synthetic Approach for the construction of Diversity-Oriented Synthesis library.

2.1 Synthetic approach for DOS

2.1.1 The synthetic pathway planning for a DOS strategy

As introduced in the previous chapter, the plan of a synthetic strategy for a DOS library is a crucial topic to address the aim of creating a library of compounds with a broad distribution of compounds in the chemical space to increase the possibilities of discovering new lead compounds[1]. One of the features required for each compound synthesized by a DOS strategy is the structure complexity, because the molecules that show a biological activity as the natural products or other privileged scaffolds own a complex structure. This suggests the possibility that the structural complexity may be positively correlated with the likelihood of perturbing the state of a macromolecule[2]. How DOS use the parameter of complexity is what diversifies the plan of synthetic pathway compared to a classic approach. Indeed, also for a TOS synthetic strategy the aim is to obtain a complex compound but in TOS they have a target structure, therefore the synthetic pathway is linear and convergent, it is planned in the reverse synthetic way following a retrosynthetic analysis where the goal is moving the complexity of the compound from complex → simple[3]. Conversely, in a DOS plan where a specific target structure is not addressed, the goal is to access the diversity of the compounds using a diversity and complex generating process, thus the aim of a strategy must move the structure of compounds from simple and similar → complex and diverse[4] (Figure 1). Indeed, in an ideal DOS pathway, all the products of a step can be substrates for the subsequent ones[5].

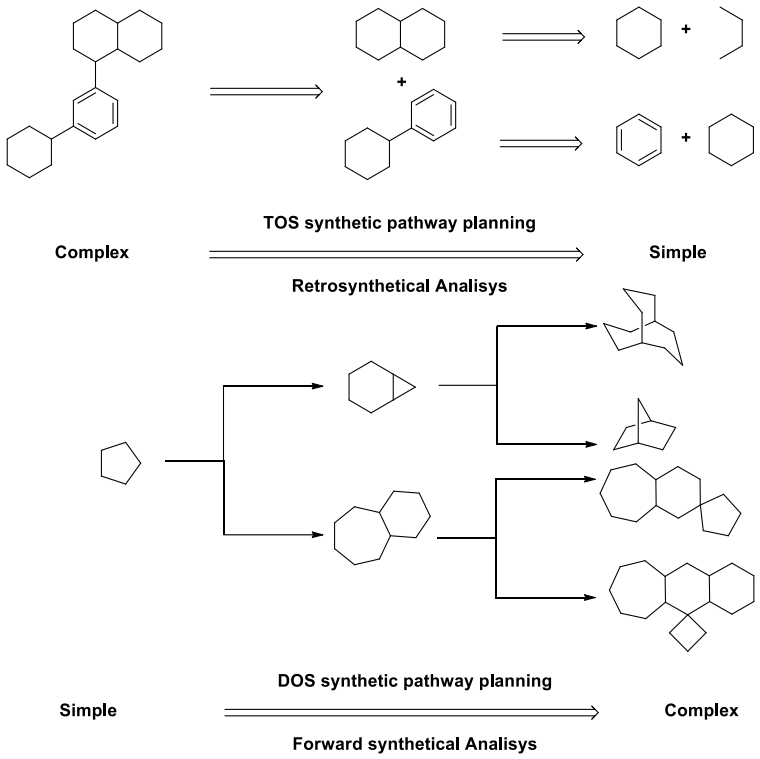


Figure 1 Different strategy planning for TOS and DOS

Since the beginning of DOS two different strategies for the generation of libraries containing complex and diverse compounds (where the goal is to obtain the skeletal diversity) have been identified in the literature. The reagent-based approach and the substrate-based approach[5,6]. These two strategies are complementary to each other and several DOS works contain aspects of both[7]approaches. Accordingly, over the years they have been condensed and rationalized into a new strategy called build/couple/pair[8].

2.1.2 Substrate-based approach

The substrate-based approach, also known as *branching reaction pathway* is the strategy where a number of different starting materials containing appendages with "pre-encoded" skeletal information react in same conditions to give different products (Figure 2). So, in this kind of strategy all the informations to produce the skeletal diversity are contained in the structure of the reagent or substrate. For this reason, to have a good level of complexity in the final structure, starting with substrates that have a good level of structural complexity is required.

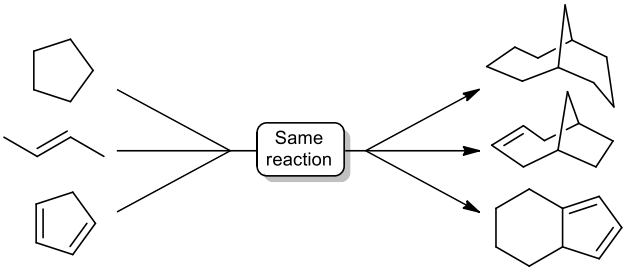


Figure 2 A schematic representation of Substrate-Based Approach

Thus, the substrate-based diversification is generally used in the late stage of DOS strategy (when a mixture of approaches are used) and it is also called *folding reaction pathway* When this approach is exclusively applied using commercially available starting materials, such building blocks require a high level of structural complexity to propagate the skeletal information to the product, and for this end usually the natural products or their derivatives are a good solution[9]. One of the best examples of pure substrate-based approach was published by Nelsonet al. in 2009. In this work, they attached various unsaturated and functionalized building blocks (called "propagating" and "capping") to a fluorous-tagged linker to obtain various linear intermediates that contained several functional groups. Finally, they applied these functional groups in a series of metathesis cascade reactions to obtain 96 final products from 86 linear compounds, of which 84 can be classified as scaffolds. Indeed, all these molecules contain a high degree of stereochemical and skeletal diversity. The level of structural complexity obtained allow us to define this library as a "Natural-product like" one.

2.1.3 Reagent Based Approach

The reagent-based approach is a branching strategy where a common molecule with a simple structure is involved in a series of different reactions, also following different synthetic pathways to give different products, that stands out with a high degree of structural complexity and with a significant skeletal

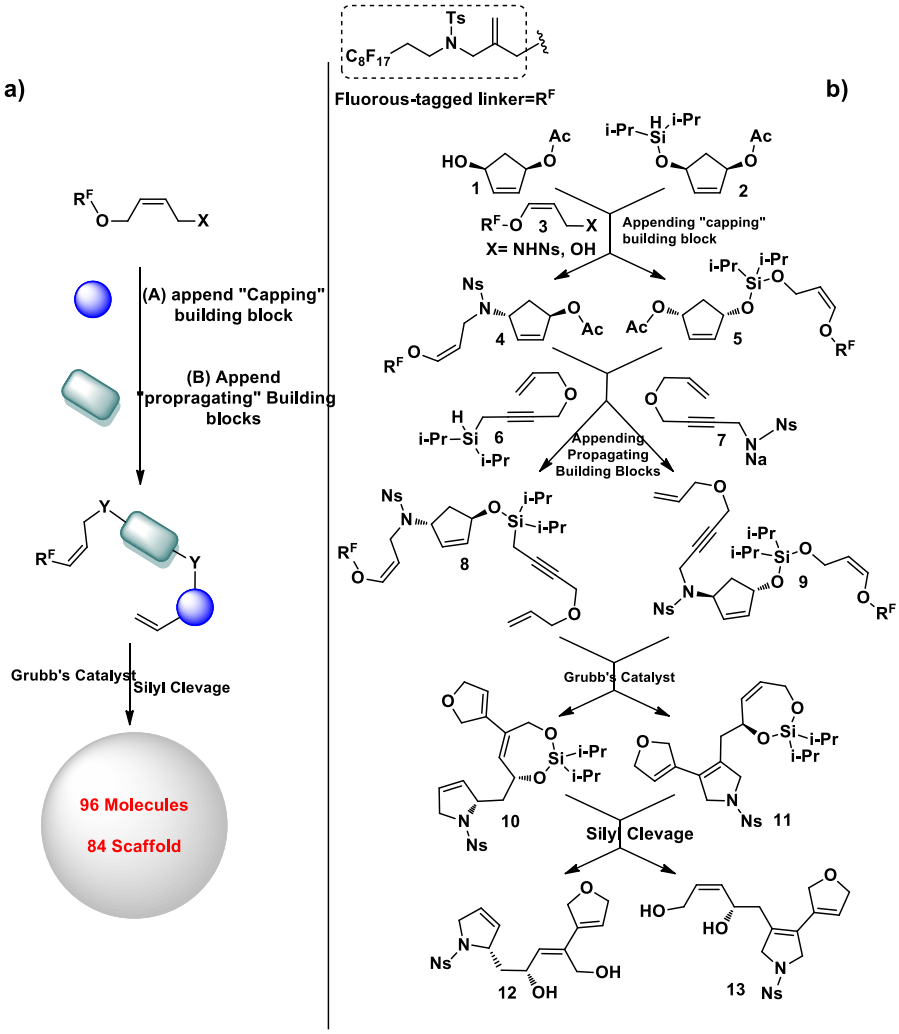


Figure 3 Schematic strategy of Morton's work; b) Example of a synthetic pathways with two different starting materials.

diversity. In this process, the complexity, as the diversity, is generated in every step using different reagents. (Figure 4).This type of approach is also classified in two different subtypes according to the nature of the starting material.

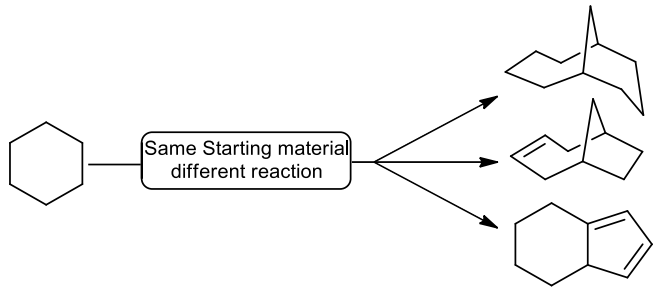
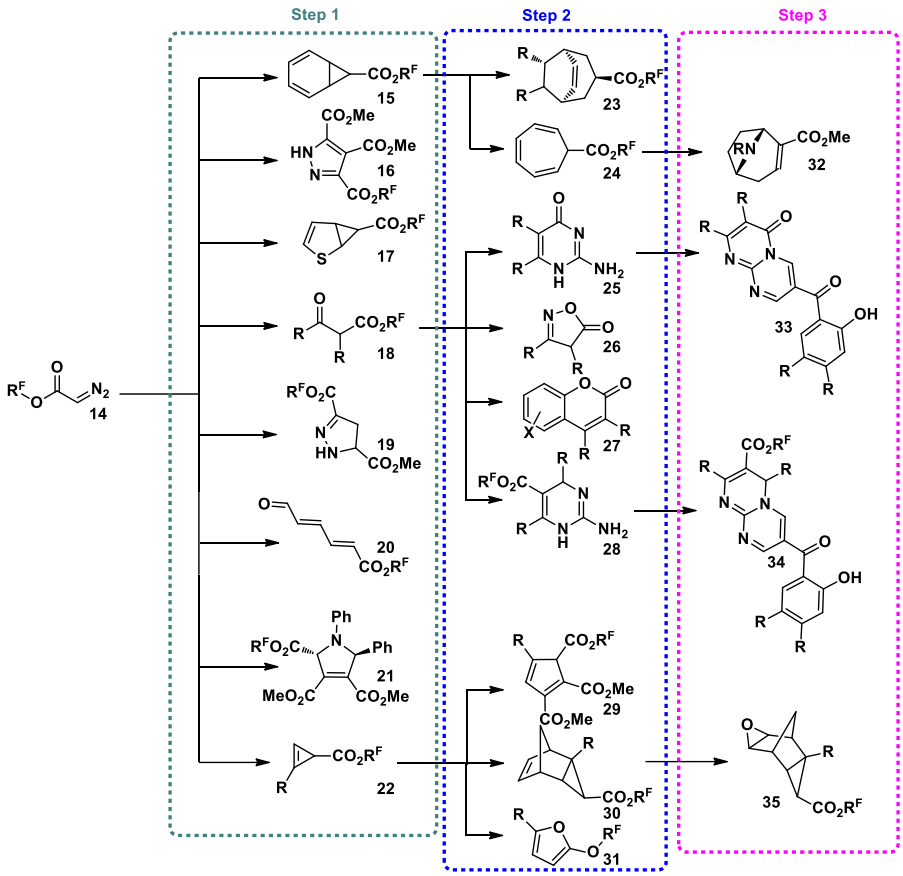


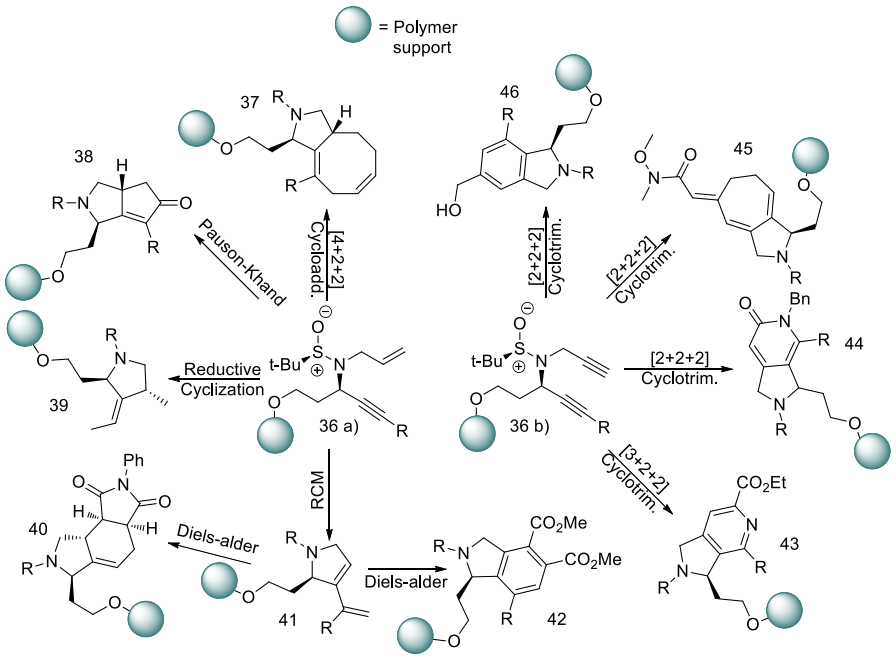
Figure 4 A schematic representation of Reagent-Based Approach

The first one is called *Reagent-based approach using pluripotent functional groups*; here the starting material owns a functional group that can be involved in different types of reactions. This leads to the synthesis of molecules with a high skeletal diversity. One of the more brilliant examples of this approach was reported by Springet al.[11] . In this synthesis they used a fluorous-tagged diazo-compound as a starting material. This compound represents perfectly the concept of pluripotent reagent as it can react both as a nucleophile and as an electrophile. Starting from this simple molecule and using different synthetic pathways, though not exceeding the 3 steps each, Spring obtained a library of 223 small molecules based around 30 distinct molecular skeletons (Scheme 1). This library was screened for the effects against three different UK epidemic *Staphylococcus aureus, the* methicillin-susceptible *S.aureus* (MSSA), and two strains of methicillin resistant (EMRSA 15-16) *S. aureus* .Out of the 223 compounds tested, 64 were found able to modulate the growth of EMRSA15 and EMRA 16 at concentrations comprised from 10 to 100μM. In the *Reagent approach based on densely functionalized molecules* we use again simple molecules, but the difference with the other one is that the molecule contains a series of different functional groups that can be used in an orthogonal way to give different intramolecular cyclization reactions.



Scheme 1 A representative scheme of the library of scaffolds generated by Spring et al.

So, in this approach the starting material contains almost all the reagents and the atoms of the future products. A good example of possible applications of this approach is the paper published by Tan et al.[12] In this work they synthesized the solid supported sulfonamide **36a-b**, and using several different pericylic reactions they obtained a alkaloid/terpene-inspired library containing 190 compounds and comprising 10 polycyclic structures (Scheme 2).



Scheme 2 Representative scheme of Tan's work based on different cyclizations using different pericyclic reactions.

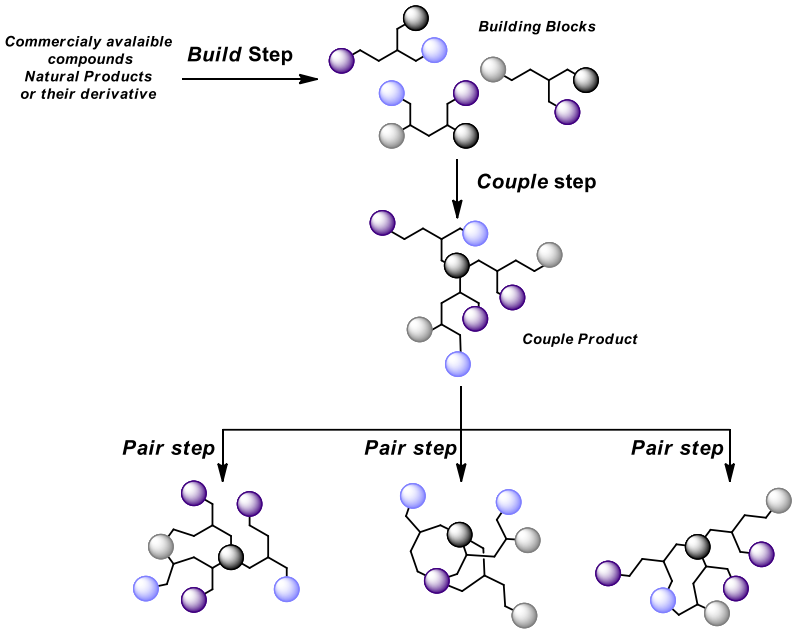


Figure 9 Schematic representation of the Build/Couple/Pair approach.

2.1.4 Build/Couple/Pair (B/C/P) approach

The B/C/P strategy is an innovative 3-6 steps approach for the efficient and systematic generation of skeletally and stereochemically diverse small organic molecule libraries suitable for biological screening. This strategy was formulated by Schreiber at the beginning of this Century, it mixed the main concepts of the two previous strategies, *the reagent- and the substrate-based approach*, using the principles of both in a series of encoded steps[5]. This is not really a new approach as other works showed a mixed strategy based on both approaches. Indeed, the real novelty introduced by the build/couple/pair approach (B/C/P) was the formulation of a well-encoded synthetic pathway in order to maximize the single strengths of both to increase the effectiveness of the overall strategy[9]. The aim of a B/C/P approach is to obtain a dense matrix of stereochemically and skeletally different compounds using a quick[13] synthetic pathway, basically divided into three different steps (Figure 4):

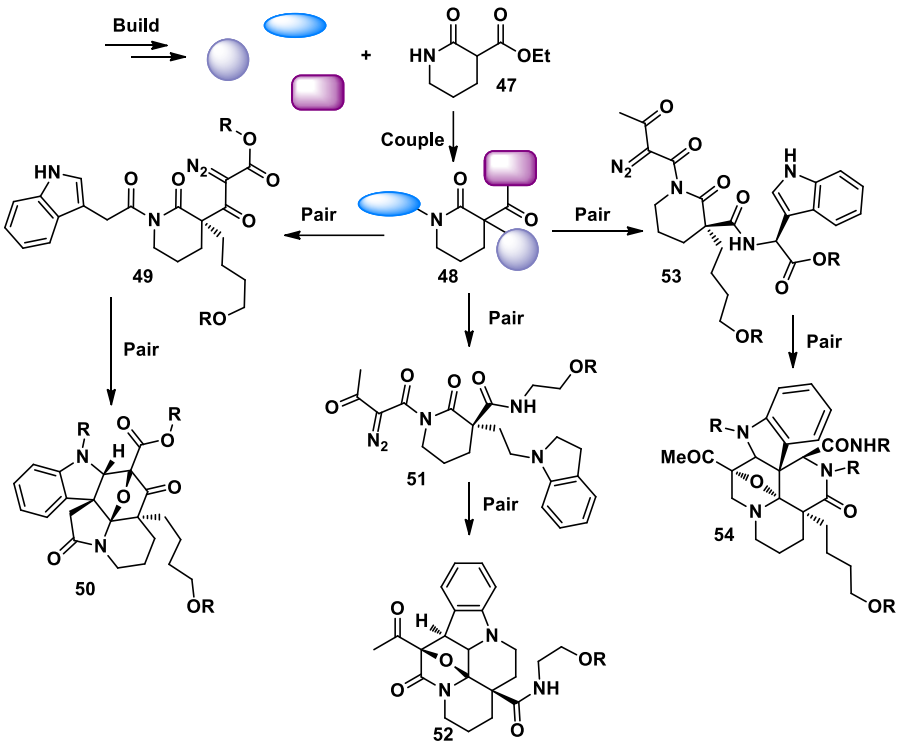
- The *Build step* is defined as*:" Asymmetric syntheses of chiral building blocks, or synthetic transformation of commercially available chiral compounds, that contain orthogonal sets of functionality suitable for subsequent coupling and pairing steps, are performed"*
- The *Couple steps* is defined as: *" Intermolecular coupling reactions that join the building blocks are performed – ideally either without stereochemical consequences or with complete control of all possible stereochemical outcomes".*
- The *Pair step* is defined as: *" An intramolecular coupling reaction that joins pairwise combinations of different functional groups incorporated in the build phase are performed. This last step is the one that provides to create the skeletal diversity from the different compounds deriving from the same couple product".*

The request of chiral building blocks or compounds with a complex structure is a crucial point. Indeed, in the *build step* the major part of the structure that will be included in the final products is introduced, and as anticipated in the previous chapter, the 3D structure complexity is a parameter required in a DOS library to increase the possibility of finding biological active molecules. For this reason, the choice of an appropriate building block is an important point for the success of a DOS strategy. The ideal building block has a well-defined 3D structure (and if possible all the stereoisomers are taken into account to satisfy the stereochemical diversity) and many functional groups that could be used for the next step of the synthesis. The satisfaction of all these

requirements is usually given using natural products or their derivatives. Indeed, they are compounds with a well defined complex 3D structure, they usually possess many different functional groups, some of the possible stereoisomers are usually commercially available and often their structures contain a privileged scaffold[14]. The *couple step* is the stage where all the building blocks are connected together in a single reaction that involves only selected functional groups and leaves the others unreacted to be used next in the pairing step. During the pair step the skeletal diversity is created using selected reactions from suitable functional groups. The possible reactions that can be performed in this step are usually divided by the functional group involved. They are divided in two different categories, *polar* and *non polar,* so all the possible reaction combinations are:

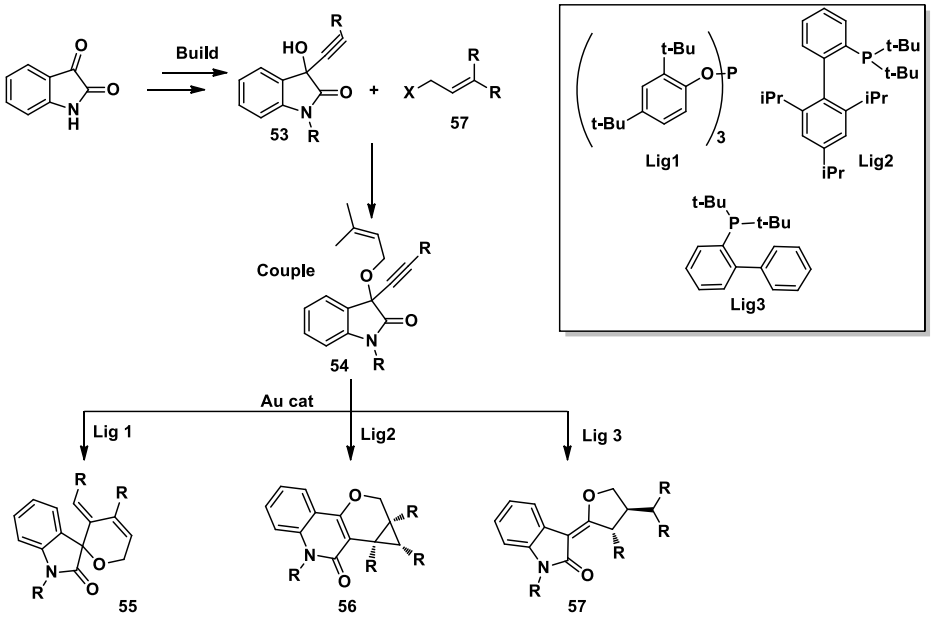
- *Polar/polar;* such as for an example the Mitsunobu reaction between two hydroxyl groups to form a cyclic ether
- *Nonpolar/nonpolar*; such as for example the alkene/alkyne ring-closing metathesis to generate a cycloalkene
- *Polar/nonpolar;* such as for example the hydroamination reaction from an amine and an alkene.

In some B/C/P strategies the couple molecule before the pair step is appended with other functional groups to increase the number of possible pair reactions. An example of B/C/P approach was reported by Padwa[15] and co-workers. In this work, the consecutive rhodium- catalyzed cyclization an cyclo addition reactions were used to synthesize an indole alkaloid-inspired library. In the coupling phase, many combinations of α-diazaketocarbonyl and indole moieties were incorporated at well-defined positions around the common template **48** (Scheme 3).



Scheme 3 Summary representation of Padwa's work

Another and recent example was reported by Waldmann et al. [16] In this work, starting from isatine, they synthesized the building block **56** that, after a simple couple reaction, an oxygen alkylation the product of the couple step (**52**) was involved in three different pair reactions. The particularity of this work stays in the pair step. Indeed, Waldmann and co workers are able to generate three different scaffolds using the same functional group and the same catalyst but changing only the ligand (Scheme 4). This new approach is called *ligand-directed divergent catalytic approach* and promises to be a great tool for DOS strategies.



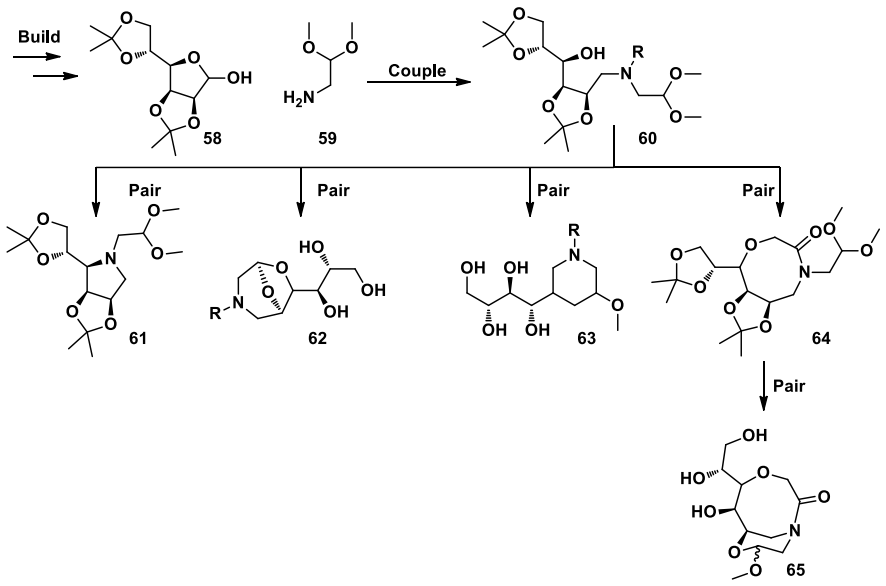
Scheme 4 Representation of Waldmann's work.

2.2 The Couple step at the heart of the B/C/P strategy

The importance of the couple in a B/C/P is crucial and the choice of the reaction characterizes the nature of building blocks both for the type of the groups that must react and also for the tolerance of the reaction to the other functional groups of the molecules .To increase the possibility to generate a good library of compounds the couple reactions need to be[5]:

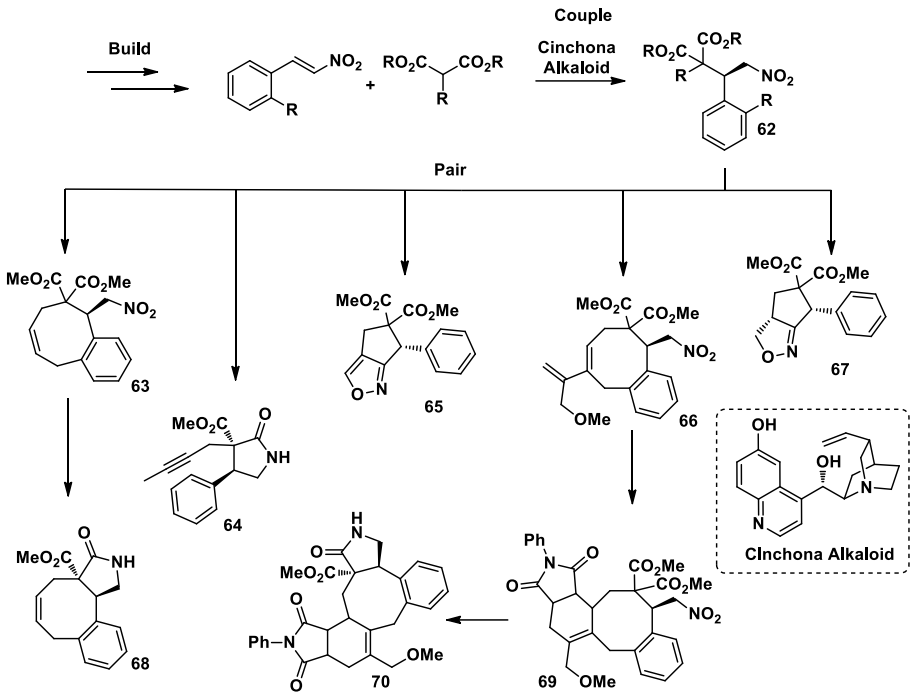
- Able to connect many compounds together, to increase the structure complexity degree and to insert as much functional groups as possible to generate high diversity in subsequent steps.
- Highly chemo- and regioselective to allow working with the contemporary presence of different functionalities without using protective groups (or just a limited number) in order to obtain a short synthetic pathway.
- capable of not generating new stereogenic elements or if they do it, it should be able to control every possible stereoisomeric outcome.

Many type of reaction are used in different works, Trabocchi[17]et al. used a reductive amination to connect a mannose derived building block (**58**) with the dimethoxy protected amino aldehyde **59** derived from glicine (Scheme 5).



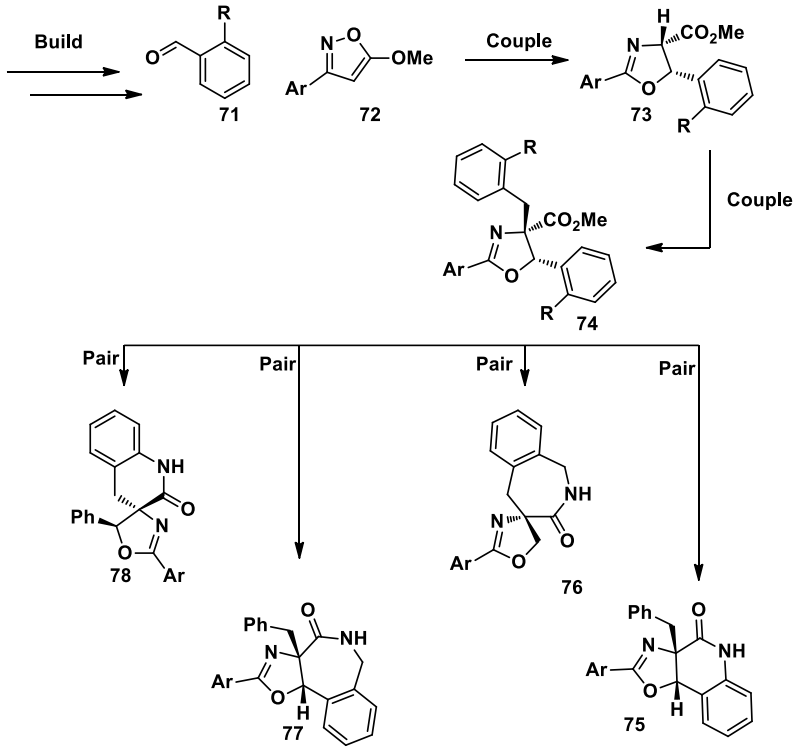
Scheme 5 Representation of Trabocchi's work

Porco et al. in 2007[18] performed a cinchona alkaloid catalyzed Michael reaction as a couple reaction (Scheme 6). From a mechanistic point of view, the catalyst allowed to control the stereochemical outcome of the reaction, thus obtaining only one of the possible stereoisomers, suggesting a perfect stereochemical control to obtain the stereochemical diversity in the couple step. Indeed, without a catalyst, this approach would not have fully satisfied the requirements to be applied as couple reaction.



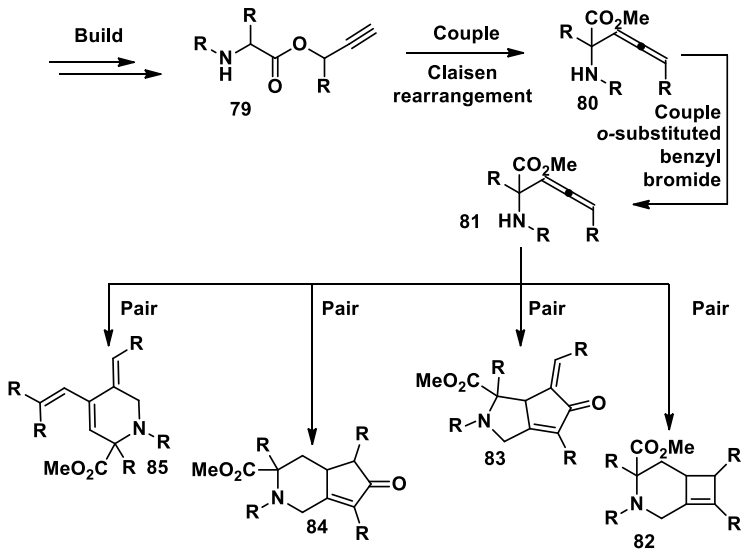
Scheme 6 Representative scheme of Porco's work.

In some B/C/P strategies there is more than one couple step, and this is generally pursued for particular synthetic requirements or to increase the functionalization degree of the couple product. For example Shaw and Mitchell[19] performed an Al-catalyzed enantioselective Suga-Ibata reaction of oxazole (**72**) with several ortho-substituted aromatic aldehydes, followed by an alkylation with various *ortho*-substituted benzyl bromides to obtain the final couple product **74** to be used in the pair phase(Scheme 7).



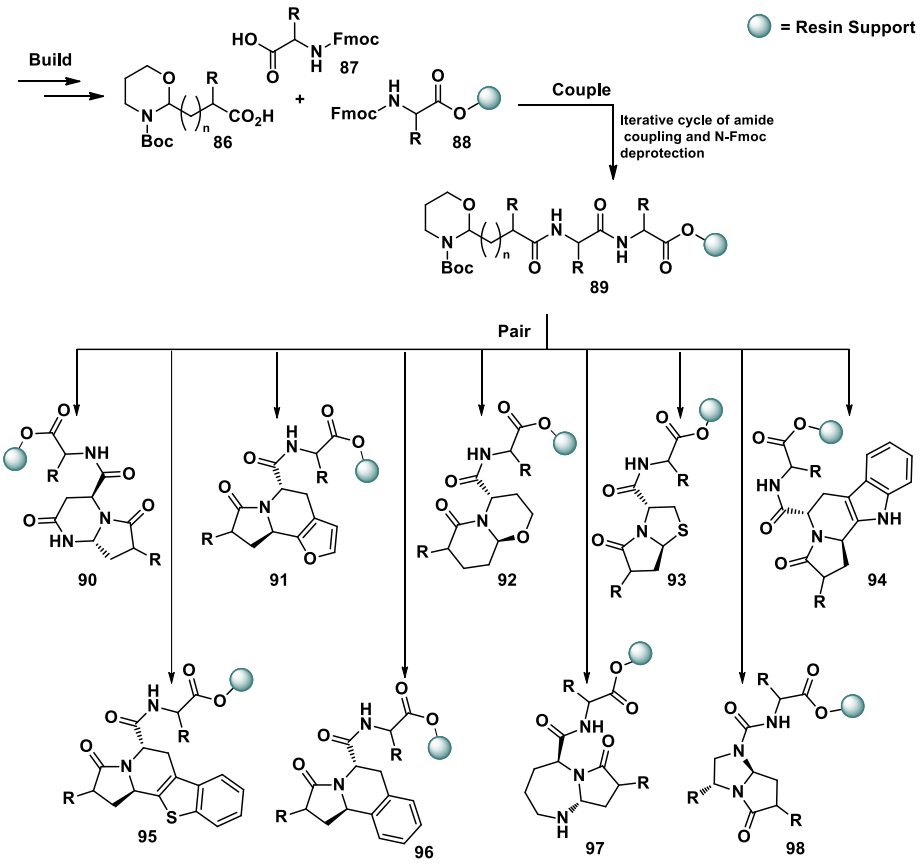
Scheme 7 Representation of Mitchell's work**.**

Brummond[20] and coworkers divided the couple step in two different reactions: in the first one a propargyl amino ester was converted into a quaternary allene amino acid (**80**) by a Claisen rearrangement, then the product was functionalized by an alkylation at the nitrogen atom with propargyl bromide (**81**) (Scheme 8).



Scheme 8 Representation of Brummond's work.

Starting from the concept of couple step as a single reaction but thinking it as the process that connects all building blocks in a single molecule, even the iterative synthetic methodology can be used as replacement of the coupling reaction. In this context, Meldal reported the synthesis of several macrocyclic peptides using as "couple step" a series of reactions consisting of amide coupling formation and nitrogen deprotection[21] (Scheme 9).



Scheme 9 DOS application mixed with peptide synthesis.

The use of such iterative process in this work is remarkable because the synthesis on solid phase was performed, and this work is the first reported B/C/P approach on solid phase.

2.2.1 Application of the Multicomponent reactions in the couple step.

Every couple reaction described in the precedent paragraph is able to connect only two compounds each, if we exclude the iterative process. This could represent a limitation in DOS where the efficiency of the synthetic pathway is a crucial point. A particular class of reactions which can solve this problem is the multicomponent reaction (MCR). They are defined as "convergent reactions, in which three or more starting materials react, without a precise control of the order of addition, to form high selective products, where basically all or most of the atoms contribute to the newly formed product. In a MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally flow into an irreversible step yielding the product"[22]. In this kind of reactions, in contrast with the classic

ones, all the reactants are mixed together at the same time (Figure 5)and the formation of a single product is driven from the irreversible step.[23]

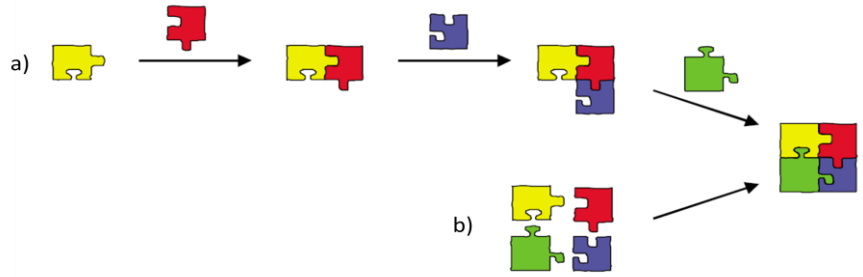


Figure 10 Comparison from a the classic synthetic pathway (a) with the ones derived from multicomponent reactions (b) Reproduced with permission from (23), Copyright © 2005 Elsevier Ltd.

From the definition it became clear that MCRs are a powerful tool to be applied for the couple step in a B/C/P strategy:

- They can connect many compounds at the same time in a single reaction.
- These kind of reactions are highly chemo and regioselective and for this they can tolerate the presence of many functional groups which do not react in this process.
- The stereochemistry of the product could be driven from the presence of a single stereoisomer, from the reagents, or by catalysis.

All these proprieties can be converted in a DOS concept.[24] Indeed, for the possibility of connecting more reactants together, they offer a unique possibility of creating *appendage diversity*. The *stereochemical diversity* could be created using different stereoisomers of the building blocks or by catalysis. Even though we cannot fully address the scaffold diversity because the MCRs are convergent reactions that give only a product, this product can be highly functionalized and this gives the possibility to introduce this type of diversity in the *Pair step* (Figure 6).

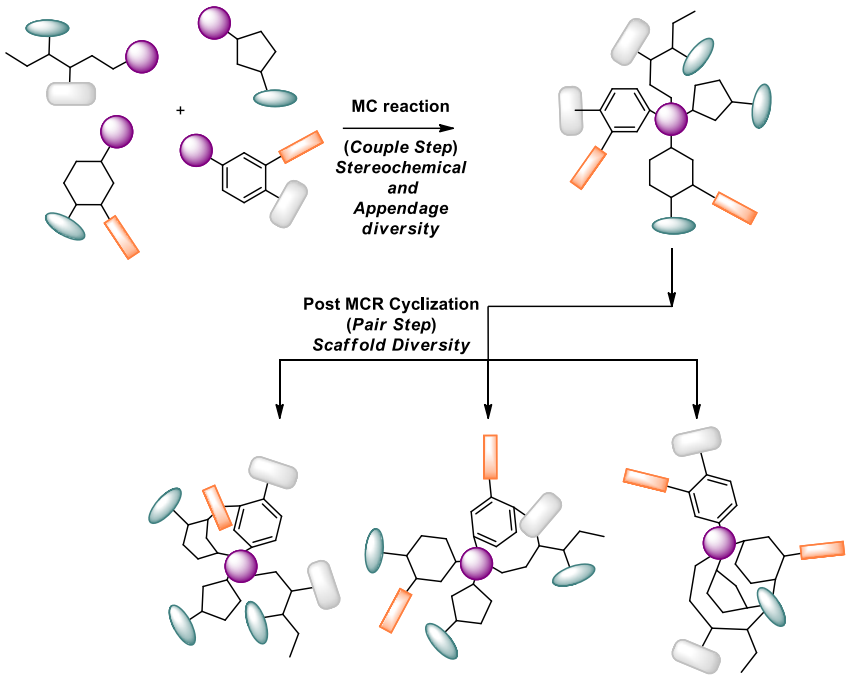
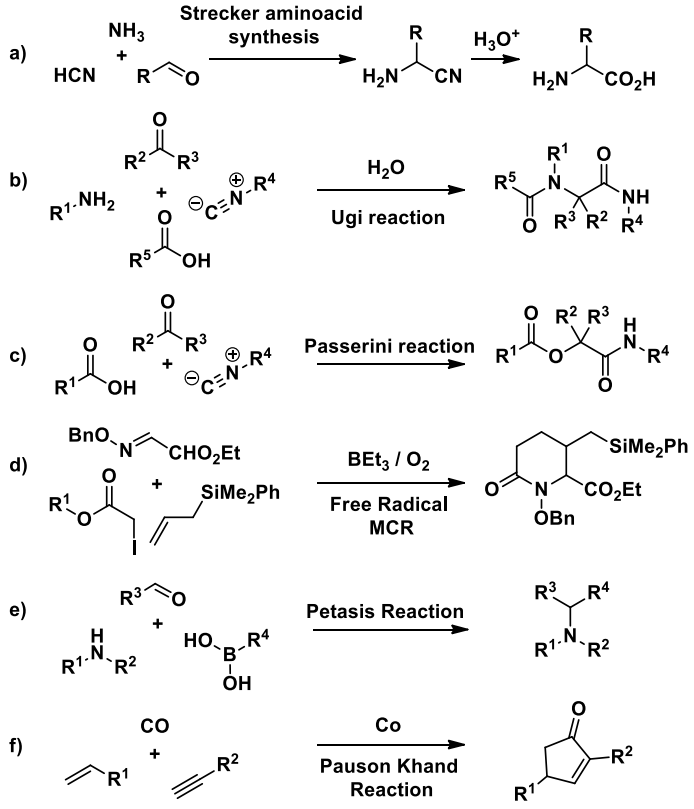


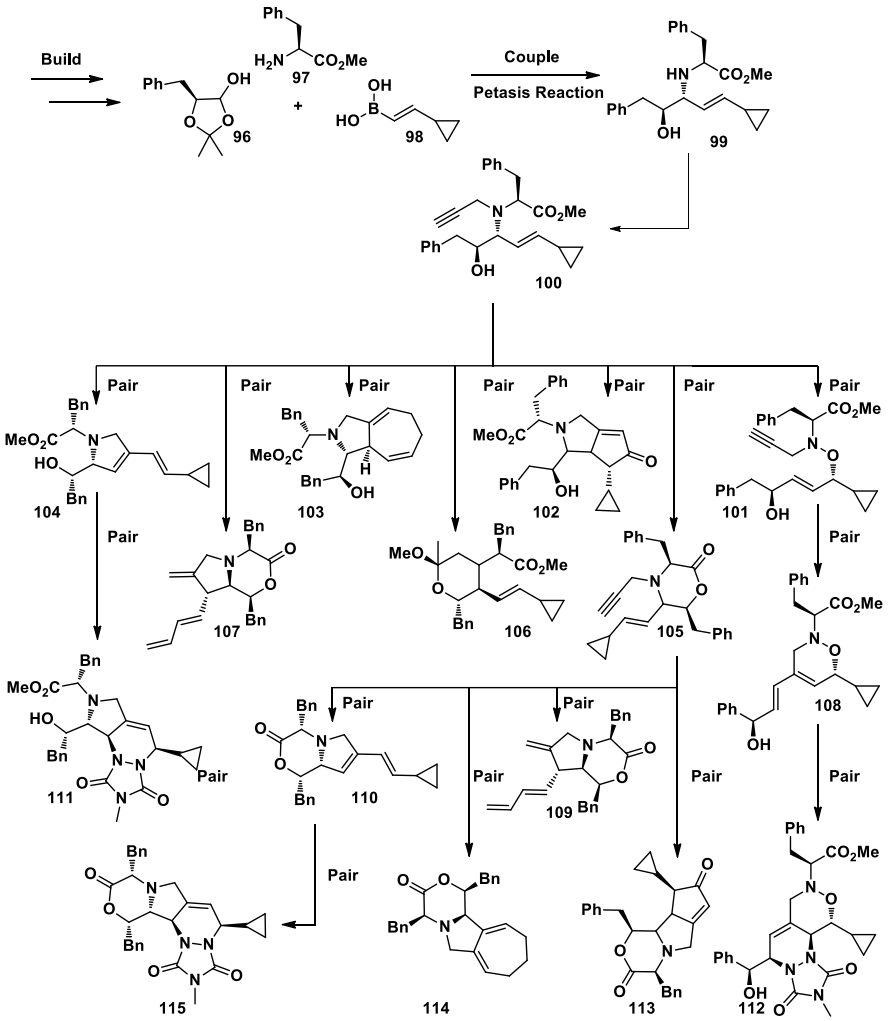
Figure 6 B/C/P synthetic pathway includes MCR as "*Couple step*".

The first documented multicomponent reaction was the Strecker[25a]synthesis of α-amino cyanides in 1850 from which α-amino acids could be obtained (Scheme 10 a). A multitude of MCRs exists today, including isocyanide-based MCRs (Scheme 10 b e c)[25b,c], free-radical mediated MCRs (Scheme 10 d)[25d], MCRs based on organoboron compounds (Scheme 10 e)[25e] and metal-catalyzed MCRs (Scheme 10 f).[25f]Most of these have been also applied in *Build/Couple/Pair* approach for the creation of scaffold libraries.



Scheme 10 Selected examples of MC reactions.

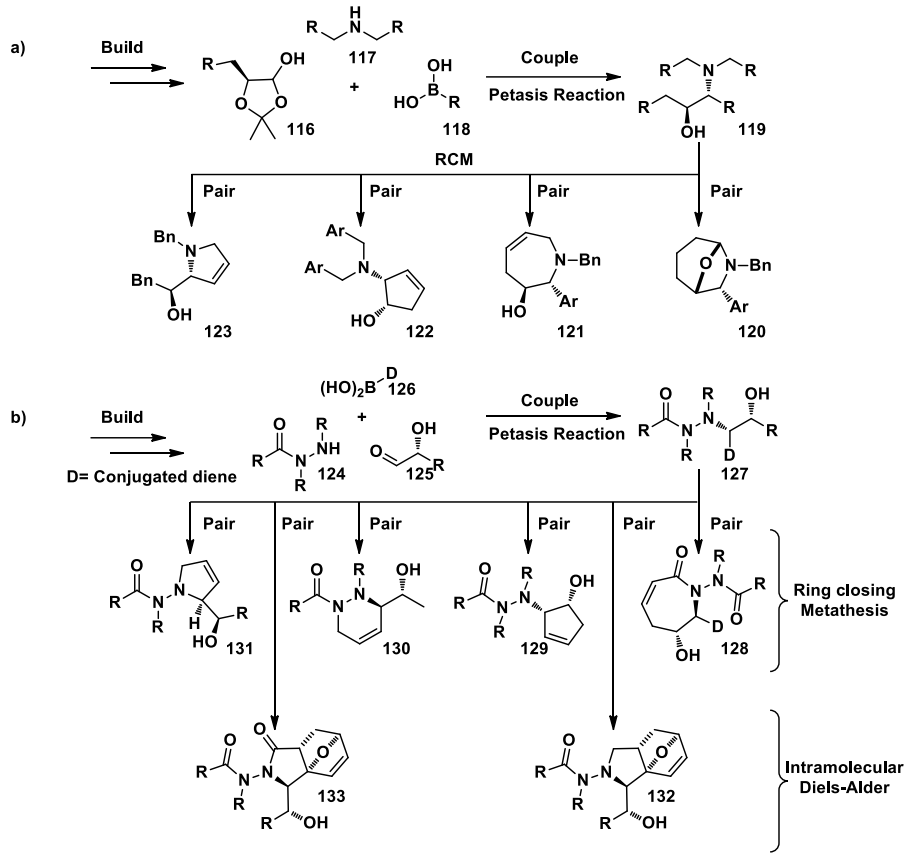
To address how the MCRs are useful for the *Build Couple Pair* approach, it is worth mentioning the first paper that explicitly report the use of MCRs in a B/C/P approach, published by Schreiber et al. in 2006[26]. For the first time, in this work the authors arrange the B/C/P approach in three distinct steps using the Petasis reaction for the couple step (Scheme 11).



Scheme 11 Application of Petasis reaction in B/C/P strategy.

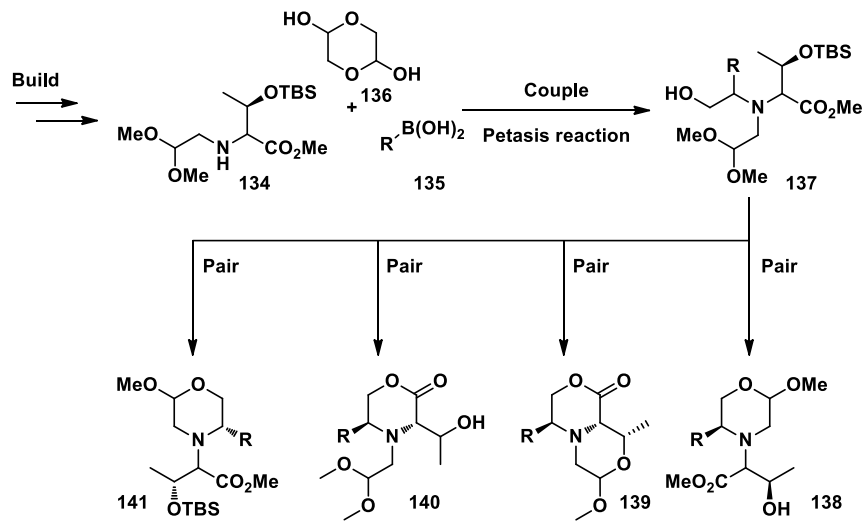
Starting from the aldehyde **96**, the phenylalanine methyl ester **97**, and the boronic acid **98**, they performed a Petasis reaction that gave the compound **99**, that was further appended by a propargylic function to give the compound **100**. Such coupling adduct was used in several cyclization reactions. The Petasis reaction has been used in several papers over the years, probably due to the high stereoselectivity. Specifically, it has been demonstrated[27] that the use of chiral that the use α hydroxy aldehyde. brings to only one of all the possible stereoismers . The Petasis reaction has been used in several papers can be high ted two different works based on this reaction[28,29]. In the first work (Scheme 12 a) they used the Petasis reaction to connect together various aryl/vinyl boronic acid with a series of amines and aldehydes, and then, using the alkene

functionality in the couple product, they obtained four different scaffolds using RCM.



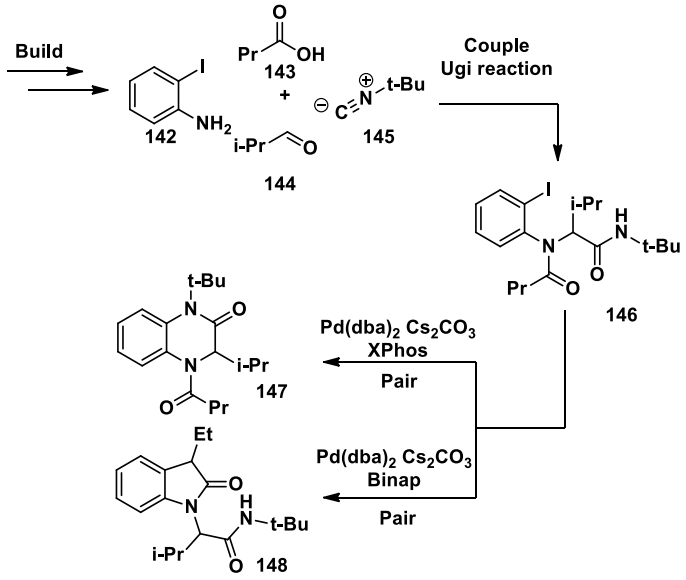
Scheme 12 Schematic summary of Nielsen's work

In the second one, they used different boronic acids appended with a conjugated alkene moiety, and the product **127** resulting from the couple step was cyclized using a RCM or an intramolecular Diels-Alder reaction (Scheme 12 b). One last recent work on Petasis reaction was published by Trabocchi and co workers[30].In this paper, using as starting material a N-alkyl Treonine methyl ester (**134**), they synthesized various scaffolds containing a morpholine ring, given the interest of this particular heterocycle as an efficient privileged scaffold (Scheme 13).



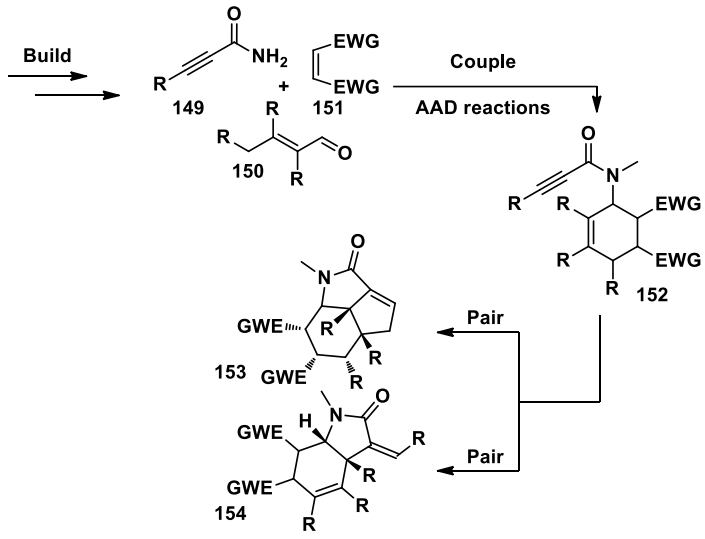
Scheme 13 Summary report of Trabocchi's work.

A nice example of the application of the Ugi reaction was reported by Zhu[31]. In this work, the combination of MCR as a couple reaction followed by the *ligand-directed divergent catalytic approach* for the pair step was applied. Interestingly, the type of scaffold generated changed depending on the choice of the Pd-ligand (Scheme 14).



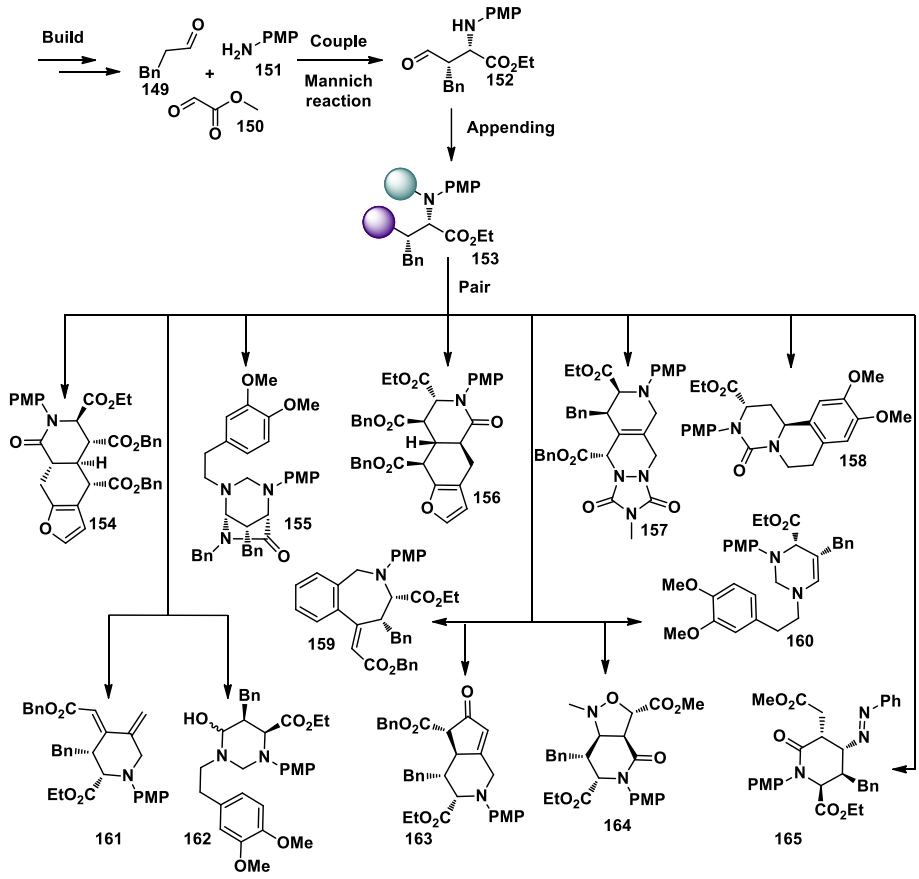
Scheme 14 Representation of Zhu's work based on Ugi reaction.

Beller and co-workers applied the Aldehyde/Amide/Dienophile (AAD) reaction[32] as a couple step to obtain a product containing an enyne (**152**) functionality, which was used in the pair step to produce two different scaffolds(**153** and **154**), (Scheme 15).



Scheme 15 Beller's application of AAD reaction in B/C/P strategy.

A last example was reported by Schreiber in 2009[33]. In this work they applied a Mannich reaction to obtain the couple product, then using a series of appending reactions and subsequent pairing they obtained a library of 12 different scaffolds, suggesting a high quality of the strategy given by the chemoselectivity of the reaction (Scheme 16).



Scheme 16 Schreiber B/C/P strategy based on Mannich reaction.

It is worth noting that in the couple product an aldehyde functionality is still present thus, as this group is often reactive, only a high chemoselective reaction can maintain unaltered this functionality.

In conclusion, as evinced in this paragraph, the MCRs represent a great tool in the context of B/C/P approach, and for this reason the application of known MCR approaches in B/C/P strategies or the discovery of new MCRs are two important and fascinating research fields.

2.3 Bibliography

1. Schreiber, S. L.; *Science* **2000**, *287*, 1964.
2. “Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology”, Trabocchi, A., Ed.; Wiley and Sons, **2013**.
3. "Tandem Organic Reactions", Ho, T-L.; **1992** Wiley, New York.
4. Spaller, M. R.; Burger, M. R.; Fardis, M.; Bartlett, P. A.; *Curr. Opin.Chem.Biol.*, **1997**, 1, 47.
5. Burke, M. D.; Schreiber, S. L.; *Angew. Chem. Int. Ed.*, **2004**, 43, 46.
6. Galloway, W. R. J. D.; Bender, A.; Weich, M.; Spring, D. R., *Chem. comm.*, **2009**, 2446.
7. a) Spandl, R. J.; Bender, A.; Spring, D. R.; *Org. Biomol. Chem.*, **2008**, *6*, 1149; b) Spandl, R. J.; Gavilan, M. D.; O' Connel, K. M.; Thomas, G. L.; Spring, D. R.; *Chem. Rec.*, **2008**, 8, 129.
8. Nielsen, T. E.; Schreiber, S. L.; *Angew. Chem. Int. Ed.*,**2008**, 47, 48.
9. Galloway, W. R. J. D.; Lobet, A. I.; Spring, D. R.; *Nat.Commun.*, **2010**, 1, 80.
10. Morton , D.; Leach , S.; Cordier , C.; Warriner , S.; Nelson, A.; *Angew. Chem. Int. Ed.*, **2009**, 48,104.
11. Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. J.; Jessiman, A. S.; Welchd, M.; Spring, D. R.; *Chem. Commun*., **2006**, 3296.
12. Letts, G. M.; Di Biasi, C. M.; Bauer, R. A.; Tan, D. S.; *Proc. Natl. Acad. Sci.*, **2011**, 108, 6745.
13. Pizzirani, D.; Kaya,T.; Clemons, P. A.; Schreiber, S. L.; *Org. Lett.*, **2010**, 12, 2822.
14. Welsch, M. E.; Snyder, S. A.; Stockwell, B. R; *Curr. Opin. Chem. Biol.*, **2010**, 14, 347.

15. Oneto, J. M. M.; Padwa, A.; *Org. Lett.*, **2004**, 6, 3241.
16. Lee, J. L; Patil, S.; Golz, C.; Strohmann, C.; Ziegler, S.; Kumar, K.; Waldmann, H.; *Nat. Comm.*, **2017**, 8, 14043.
17. Lenci, E.; Menchi, G.; Guarna, A. Trabocchi, A.;*J. Org. Chem.*, **2015**, 80, 4, 2182.
18. Co*mer, E.; Roh*an, E.; Deng, L.; Porco, J. A.; *Org. Lett.*, **2007**, 9 2123.
19. a) Mit*chell, J. M.;* S**haw,** J. T.; *Angew. Chem. Int. Ed.*, **2006**, 118, 3717; b) Mitchell, J. M.; Shaw, J. T.; *Angew. Chem. Int. Ed.*, **2006**, 45, 1722.
20. Brummond, K. M.; Mitasev, B.; *Org. Lett.*, **2004**, 6, 2245.
21. Nielsen, T. E.; Meldal, M.; *J. Org. Chem,*. **2004**, 69, 3765.
22. Domling, A.; Ugi, I.; *Angew. Chem. Int. Ed.*, **2000**, 39, 3168.
23. For recent review on multicomponent reactions see a) Muller, T. J. J.; *Beilstein J. Org. Chem.*, **2016,***12*, 1269; b) Domling, A.; Wang, W.; Wang, K.; *Chem. Rev.*, **2012**, 112, 6, 3083.
24. Scheffelaar, R.; Ruijter, E.; Orru, R. V. A.; *Top. Heterocycl. Chem.*, **2010**, 25, 95.
25. a) Strecker, A.; *Justus Liebigs Ann. Chem*., **1850**, 75, 27; Ugi, I; Meyr, R.; Fetzer, U.; Steinbrückner, C; *Angew. Chem.*,**1959**, 71, 11, 386; c)Passerini, M.; Simone, L.; *Gazz. Chim. Ital.*,**1921**, 51, 126; d) Godineau, E.; Landais, Y.; *J. Am. Chem. Soc.*, **2007**, 129, 12662-12663; e) Petasis, N. A.; Akritopoulou, I.; *Tetrahedron Lett.*,**1993**,34, 4, 583; f) Pauson, P. L.; Khand, I. U.; *Ann. N. Y. Acad. Sci.*, **1977**, 295, 2.
26. Kumagai, N.; Muncipinto, G.; Schreiber, S. L.; *Angew. Chem. Int. Ed.*, **2006**, 45, 3635.
27. Candeias, N. R.; Montalbano, F.; Cal, P.M.S.D.; Gois, P.M.P.; *Chem. Rev.*,**2010**, 110, 6169.
28. Ascic, E.; Le Quement, S. T.; Ishoey, M.; Daugaard, M.; Nielsen, T. E.; *ACS Comb. Sci.*, **2012**, 14, 253.
29. Flagstad, T.; Hansen, M. R.; Le Quement, S. T., Givskov, M.; Nielsen, T. E.; *ACS Comb. Sci.*, **2015**, 17,19.
30. Lenci, E.; Rossi, A.; Menchi, G., Trabocchi, A.; *Org. Biomol. Chem*., **2017**, 15, 9710.
31. Erb, W.; Neuville, L.; Zhu, J.; *J. Org. Chem.*, **2009**, 74 3109.
32. Strubing, D.; Neumann, H.; Klaus, S.; Hurbner, S.; Beller, M; *Tetrahedron*, **2005**, 61, 11333.
33. Uchida, T.; Rodiquez, M.; Schreiber, S. L.; *Org. Lett.*, **2009**, 11, 1559.

Work Overview

The screening of small molecule libraries represents a powerful approach for *lead* discovery, especially in those complex disorders, such as cancer and infectious diseases, where the lack of validated targets makes conventional drug discovery programs difficult to succeed. Accordingly, this thesis work aims to apply the principles of Diversity Oriented Synthesis in the generation of novel molecular scaffolds for library development. In a first work, we initially studied the metal-based multicomponent reaction called Aldehyde Amine Alkyne (A^3) coupling reaction using as a substrate the α-amino aldehyde derived from proline, phenylacetylene and several amines. Following the optimization of reaction conditions, the study of stereoselectivity of the reaction and of the scope of the method, we used one of the A^3 adducts for the generation of a small library of scaffolds using the B/C/P approach where the Couple step was represented by the A^3reaction. Thus, we obtained four different scaffolds containing the phenylethynyl moiety, a structure fragment which is considered a privileged scaffold for the biological interaction with many enzymes involved in many neurological diseases. To obtain this, we performed four different reactions on the same compound derived from the A^3 reaction. As a second application, we used a variation of the A^3 reaction called Ketone Amine Alkyne (KA^2) coupling reaction to obtain, a library of spirocyclic compounds still using a B/C/P approach. After the optimization of reaction conditions, we tried two different functional groups for the pairing step, that we installed with the KA^2 coupling reaction, namely the hydroxyl and a terminal alkyne, so as to perform the spirocyclization reaction (Pairing reaction).Despite several attempts, the hydration reaction failed in all the conditions we tried, but the Pauson-Khand reaction between the alkene and the alkyne groups allowed us to obtain the desired spirocyclic compound. After setting up the synthetic method, we analyzed the scope of the methodology and in order to expand the number of scaffolds generated we performed a second stage of modifications starting from a selected spirocyclic compound, and resulting to the achievement off our other structurally different scaffolds. As last part of my work in the University of Florence, we also studied the Morita Baylis Hillman reaction. Indeed, this reaction can be applied as a couple step because it generates an adduct with many functionalities which can be used for the pairing step. Specifically, we decided to explore the synthesis of the cyclopent-2-en-

1-one, as this scaffold has interesting proprieties in medicinal chemistry. The synthesis of such compounds proved to be harder than expected, as all the classic catalytic systems did not bring to the MBH adduct. Following a long study, we found that the concomitant use of a secondary and a tertiary amine in the presence of a biphasic solvent was an efficient catalytic system for this unreactive substrate, so we analyzed the scope of the reaction including different starting materials and obtaining satisfying yields. In the last part of my Ph.D. work I moved to the Oxford University for a five-months secondment under the supervision of Prof. Darren J. Dixon. In this period I worked on the synthesis of new chiral acid catalysts, the chiral disulfonimides (DSI). Over the years, they proved to be able of catalyzing many interesting reactions, also in stereoselective fashion, that can be applied as a couple step in B/C/P strategies. Unfortunately, the usual synthesis of them resulted rather lengthy and the structural diversity that could be produced was limited thus restricting the evaluation of the DSI catalyst in a large number of different reactions. So, to meet this issue, I optimized two different and fast synthetic pathways for the synthesis of these catalysts, that allowed us to obtain the final chiral catalyst in only three steps starting from cheap starting materials.

Part II

B/C/P strategies base on copper catalyzed Multicomponent reactions

Chapter 4

Copper-Catalyzed A^3-Coupling for the Diversity-Oriented Synthesis of Proline-Derived Alkynyl-Substituted Peptidomimetic Scaffolds

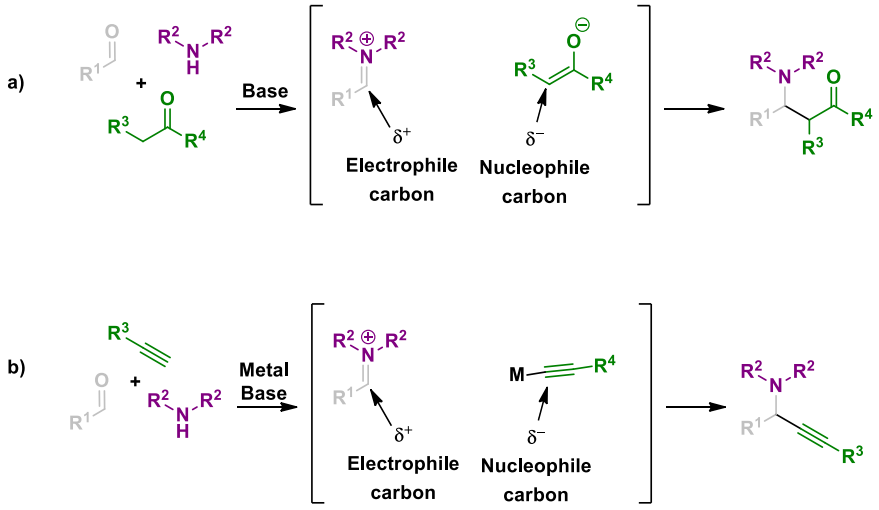
3.1 Introduction

As well explained in the introduction chapters the multicomponent reaction is a unique and powerful tool to be applied as couple step in a B/C/P strategy[1]. Indeed, these reactions bring a series of advantages[2] such as the combination of many starting materials together in a single reaction, they are usually compatible with many functional groups and the reactions are chemo and regioselective. Because of this, as previously reported, many of these reactions have been applied on a B/C/P strategy[3]. Nowadays, the multicomponent reactions[4] is a very studied topic for their applicability in many fields, for their ability to produce complex molecules from easy starting materials with a quick process. Also, for this reason the research of new multicomponent reactions or the conversion of a multi-step synthetic pathway in one of them is a fast developing research field in recent years. The advantages of converting more reactions in a single multicomponent are numerous, such as:

- The possibility of adding all the starting materials at the same time without a particular addition order and therefore obtaining an easier process from a practical point of view;
- The possibility to avoid many intermediate purification steps, thus obtaining a reduction of the synthesis time;
- MCRs reduce waste generated by a process by incorporating a highly resource efficient step in the synthesis, and often shortening the overall number of steps. Their excellent chemo- and regio-selectivity minimize the generation of side-products, and by-products are typically simple small molecules such as water, alcohols, amines or common salts, resulting in not only a reduced amount of waste, but the waste itself is generally

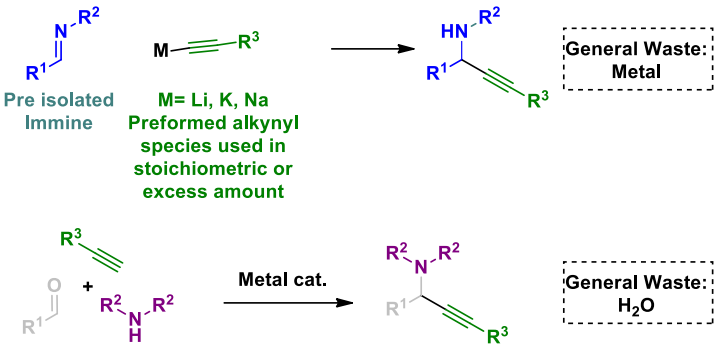
benign, thus allowing for their applicability to large scale synthesis;

For all these reasons many works have been published in this field, and new MCRs have been discovered in recent years. The Aldehyde Amine Alkyne coupling, or A^3 reaction is one of them[5]. This reaction can be considered as a Mannich reaction[6](Scheme 1a) because it consists of the attack on an electrophilic carbon atom of an imine by a nucleophilic species derived from an organometallic compound to give a α substituted propargyl amine as a reaction product (Scheme 1b).



Scheme 1 Comparison from the classic Mannich reaction (a) and the A^3 coupling reaction (b).

This reaction was known as a multistep process[7] before the discovery of the A^3 reaction (Scheme 2 a).In this process, an organometallic compound attacks a preformed, and usually pre-isolated, imine to give the resulting compound. This kind of reaction has many disadvantages, such as the use of stoichiometric or excess amount of organometallic compound that is usually a salt of the first group, thus particularly unstable. Also, the presence of the metal is an unavoidable presence in the reaction waste, and usually so as to obtain good results the imine needs to be pre-isolated and stable (Scheme 2a), Nevertheless, the A^3 reaction works in catalytic conditions and the catalyst can be ideally recovered, and more importantly, all the species are in situ generated (Scheme 2b).



Scheme 2 Comparison between the multi step process using preformed alkynyl compound (a) and the A^3 reaction (b).

To be more specific we can consider this multicomponent reaction as a middle ground between the precedent reaction and the Sonogashira[8] coupling reaction. Certainly, in the reaction mechanism for the A^3 reaction the alkynylide is formed with the same mechanism involved in the Sonogashira reaction. The reaction mechanism[9] (Figure 1) starts with the coordination of the metal compound and the alkyne (Figure 1, step I) to form the π complex (Figure 3, intermediate **I**).This kind of coordination makes the proton of the alkyne more acidic, and this catalyzes the deprotonation by a base, usually by the amine itself, (Figure 1, step II) to form the σ complex (Figure 1, intermediate **II**). Then, the nucleophilic carbon atom of this species(Figure 1, step IV) attacks the electrophilic one from an in situ pre-formed imine (Figure 1, step III and Intermediate **III**), to give the final product (Figure 1, Intermediate **IV**) and the free copper species, which return in the catalytic cycle.

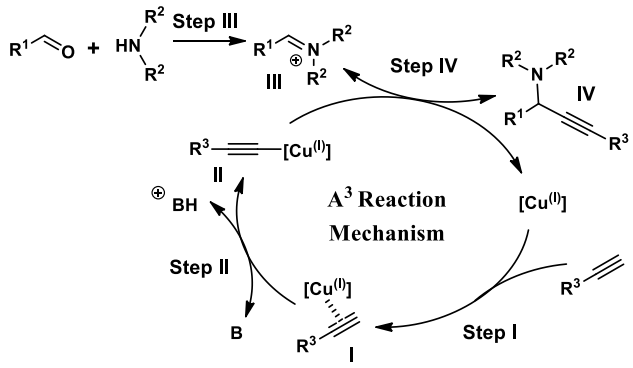
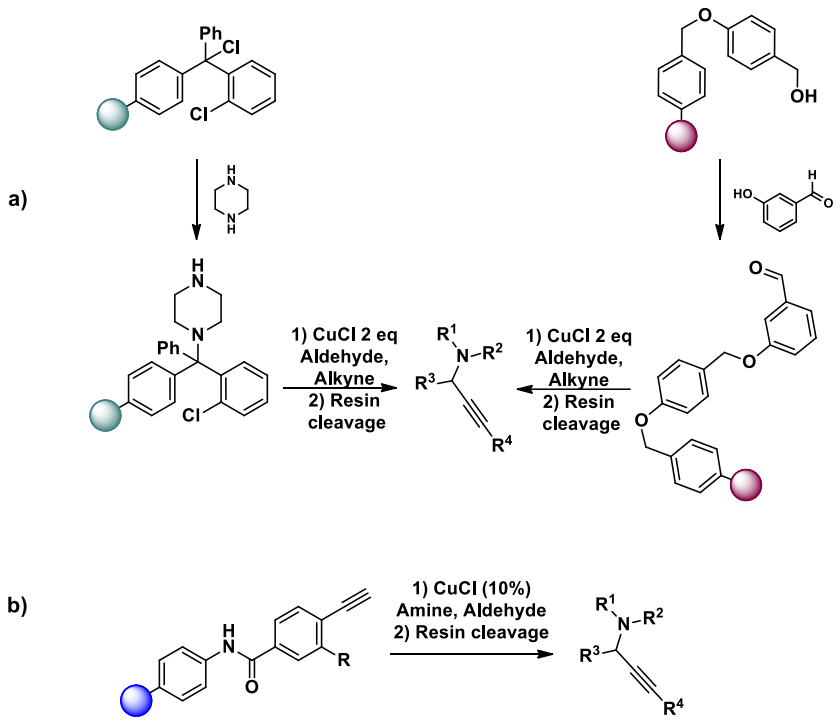


Figure 1 Accepted mechanism for the A^3 reaction.

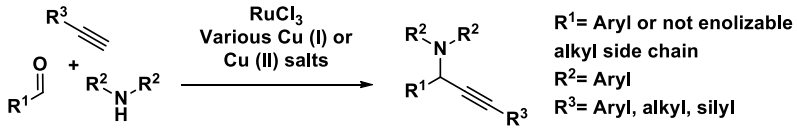
The first example that showed almost all the characteristics of the A^3 reaction was reported by Dax[10] in 1998. In this work, they performed the

propargylamine synthesis promoted by two equivalents of CuCl where either the amine or aldehyde component could be attached to the resin (Scheme 3a). In the same year, Rivero[11] described a complementary protocol employing polymer-supported aryl alkynes and variously substituted aldehydes and secondary amines to form propargyl amines in the presence of a catalytic amount of CuCl (Scheme 3b).



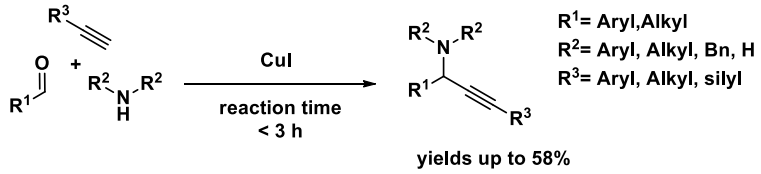
Scheme 3 Comparison between Dax work (a) using an excess amount of CuCl and Rivero's work using catalytic amounts of Cu-catalyst.

Starting from these pioneering works, many studies were reported at the beginning of this century, many interesting works reported the use of several copper salts such as CuCl, $CuCl_2$, CuBr, CuI etc. all showing catalytic activity even in the absence of a co-catalyst, although the addition of $RuCl_3$[12] dramatically increased the yield of the desired propargylamine from 30% to 90%. In all these works the reactions gave good results with both aromatic and aliphatic alkynes, but, unfortunately, the scope of this procedure was limited to the use of anilines and aromatic or aliphatic aldehydes without α-hydrogens (Scheme 4).



Scheme 4 Summary representation of several works using Cu(I) or Cu(II) salts and $RuCl_3$ to perform the A^3 coupling reaction.

The change of the metal species expanded the scope of the reaction. Indeed, using Au(I) or Au(III) salts the reaction gave good results also using secondary amines[13], where as the use of Ag(I) salts allowed to include aliphatic aldehydes to the possible starting materials of this reaction[14]. The main unsolved problem included the long reaction times at high temperatures, a condition that did not allow the use of more delicate molecules as the starting material. Tu and co-workers reported in 2004 a catalytic method based on CuI to solve this issue, that proved to be able of performing the A^3 reaction in short time and also with a broad scope including both aromatic and aliphatic aldehydes and alkynes, as well as secondary amines, aniline and tert-butyl amine[15](Scheme 5).



Scheme 5 Summary representation of Tu's work.

More recently, other metal catalysts, such as Fe(III), In(III), Zn(II), Ni(II) and Hg(I) were used to expand the scope of the reaction, to make the reaction conditions milder, and include particular substrates[16]. The high number of works published on this topic proved the great interest not only on this reaction but also on the reaction products. The general structure of the product can be described as a propargylamine, this compound a being of interest for several reasons. Indeed, this compound is an interesting starting material for the synthesis of many heterocyclic compounds that are usually involved in a wide range of applications[23].

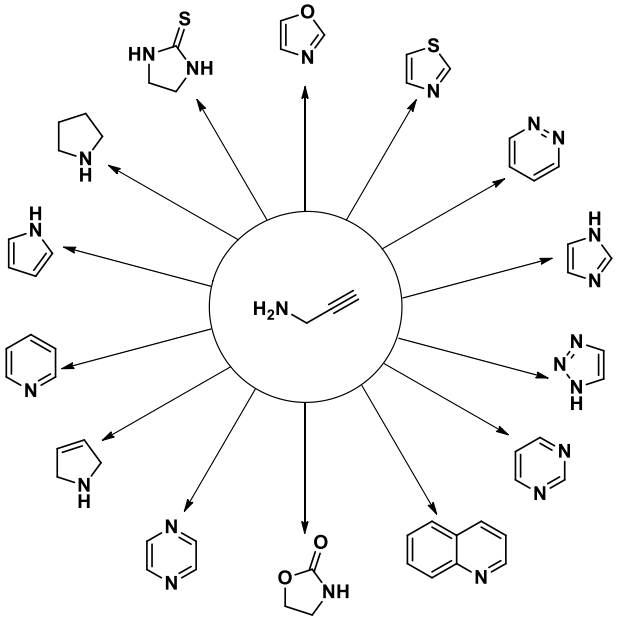


Figure 2 Schematic representation of the heterocycles obtainable from propargylamine.

Also, propargylamine has been considered as a substrate of many cross-coupling reactions such as the Pauson-Khand[18], Metathesis[19], Sonogashira[20], tandem Heck-Suzuki[21], Chloropalladation[22], etc... Propargylamine-derived compounds play a key role also in modern drug discovery, as this structure is the starting material for the synthesis of many bioactive compounds such as heterocycles (Figure 2),[23] key role also in mode all restricted peptides, isosteres, natural products etc...[24].Also this, many other compounds with a biological activity containing the propargylamine moiety, and this fragment proved to play an important role in the interactions between the biological target and the compound[25]. The major number of active molecules that contain this fragment are used for treatment many neurological diseases such as Parkinson' s, Alzheimer' s and Huntington' s diseases[26]. Accordingly, many compounds containing the propargyl fragment have been approved as drugs, such as l-Deprenil, PF960IN, Rasagiline, Ladostigil, etc.[27](Figure 3 a). From all the possible alkynyl fragments that show biological activity, the phenylacetylene fragment represents one of the more interesting ones. Many compounds, especially the ones where the nitrogen is contained in a cyclic structure, are promising drug candidates [28](Figure 3 b).

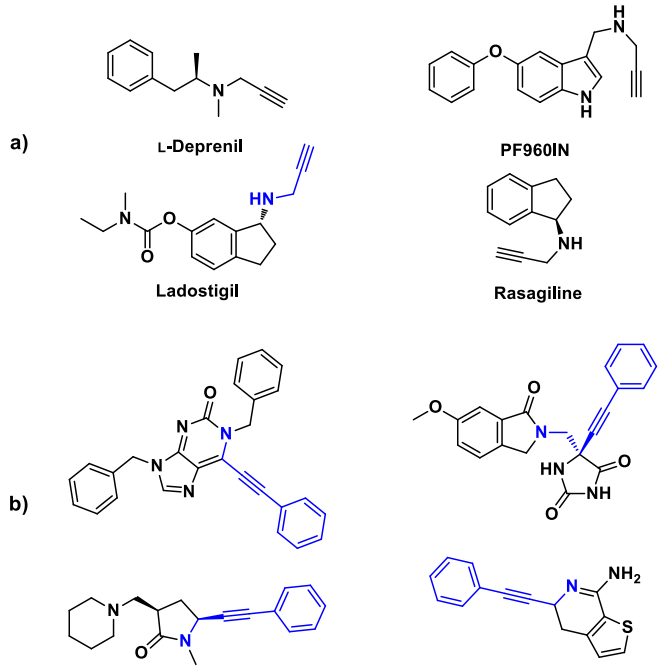


Figure 3 (a) Selected approved drugs containing the propargylamine moiety (highlighted in blue); (b) Selected compounds containing 3-phenylprop-2-yn-1-amine moiety(highlighted in blue) that have biological activity.

From a chemical point of view the installation of this moiety is not easy to be obtained, and the usual strategy is represented from a post synthesis modification of a terminal alkyne using metal cross-coupling reactions, thus limiting the production of different structures as a basic requirement for modern drug discovery strategies. In this field, the A^3 coupling reaction represents a unique tool to obtain in only one step compounds possessing the 3-phenylprop-2-yn-1-amine moiety (Figure 4). Indeed, this reaction allows to work directly with phenylacetylene as the alkyne source, and this is usually one of the best substrates for this reaction.

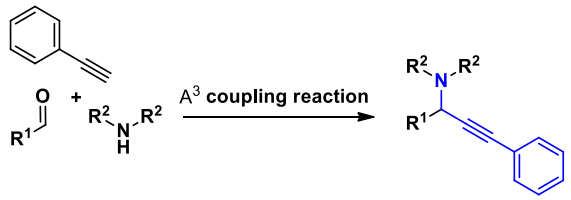


Figure 4 General representation of the A^3 adduct containing the 3-phenylprop-2-yn-1-amine moiety.

3.2 Results and discussions

In order to obtain a series of different scaffolds containing this fragment, a B/C/P pair strategy using the A^3 reaction as the couple step represents the most easy and quick solution. The scaffolds that contain the 3-phenylprop-2-yn-1-amine moiety and give the best results are the ones where the N are included in a heterocyclic structure. In order to obtain this result in our B/C/P strategy, we included as other starting materials some compounds possessing additional functional groups. Such additional arm was conceived to create the heterocyclic moiety and to give access to a complex 3D structure to maximize the diversity and complexity of the final compounds. An interesting class of compounds for this aim are the N protected α- amino aldehydes. These compounds are derived from the natural amino acids and show a series of interesting proprieties for our aim, such as the presence of a secondary functional group other than the aldehyde (that is involved in the A^3 reaction) to be used in the pairing step.(Figure 5).

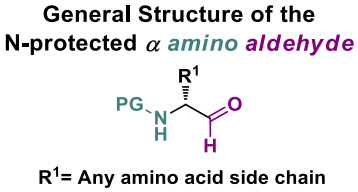


Figure 5 General structure of the N-Protected α-amino aldehyde

So, we decided to apply the A^3 reaction for our B/C/P strategy using α- amino aldehydes, phenylacetylene and other primary amines to give access to the concomitant presence of two nitrogen atoms to create the heterocyclic moiety. From all the possible amino aldehydes we chose the one derived from proline because the presence of a pre-installed cycle allowed to obtain more complex structures in the final products (Figure 6).

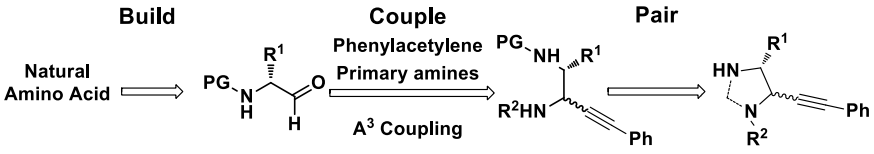
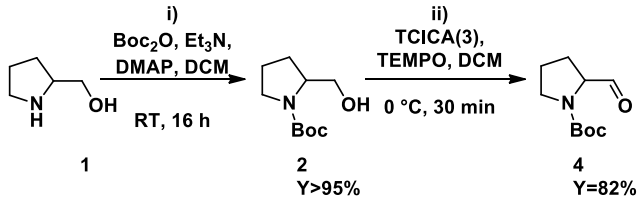


Figure 6 Representative scheme of the B/C/P strategy for the synthesis of heterocyclic compounds containing 3-phenylprop-2-yn-1-amine moiety using N-protected α-amino aldehydes, primary amines and phenylacetylene.

Our B/C/P strategy started as usual from the "Build phase". In this application it consisted in the preparation of the N-protected α-amino aldehyde derived from proline. The Boc group was selected as a protecting group for the nitrogen because:

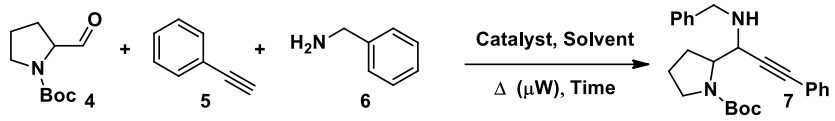
- It can be installed selectively on the nitrogen atom despite the concomitant presence of the hydroxyl group;
- It is stable under basic conditions of the A^3 reaction as opposed to the FMOC;
- It can be removed without modifying the alkyne functionality as opposed to the CBz;

Thus, starting from the commercially available racemic prolinol (**1**) the nitrogen was protected using a classical procedure with Boc_2O (Scheme 6 reaction i) to give the corresponding N-protected aminoalcohol (**2**) in pure form and quantitative yield. Then, Boc-prolinal (**4**) was obtained conveniently from the oxidation (Scheme 6 reaction ii) of the corresponding alcohol (**2**) with trichloroisocyanuric acid (TCICA) (**3**) and TEMPO in 82 % yield.



Scheme 6 i) Boc_2O (1.3 eq), DMAP (0.5 eq), Et_3N (2 eq), DCM (4 mL/mmol), RT, 16 h;**ii)** TCICA (1 eq), TEMPO (10%), DCM (5 mL/mmol), 0 °C, 30 min.

Once having this starting material in hands, we moved on the study of the "Couple phase". Thus, we optimized the A^3 reaction using compound **4**, phenylacetylene (**5**) and benzylamine (**6**) (Tab. 1).

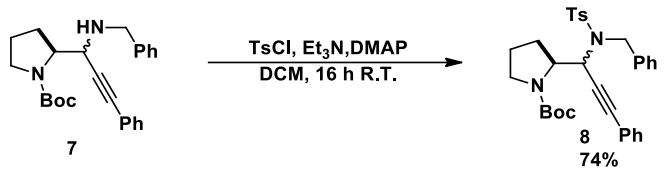


Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)[a]	d.r.[b]
1	AcCN	AgOTf	100	2	0	
2	AcCN	PPh_3AuCl	100	2	0	
3	AcCN	CuBr	100	2	25	3:1
4	AcCN	$(CuOTf)_2$Benzene	100	2	17	2:1
5	AcCN	$Cu(OTf)_2$	100	2	25	2:1
6	AcCN	CuI	100	2	72[c]	3:1
7	AcCN	CuI	60[d]	20	19	3:1
8	AcCN	CuI	150	0.4	17	2.5:1
9	AcCN	CuI	100	1	28	3:1
10	MeOH	CuI	100	2	31	2.5:1
11	DCE	CuI	100	2	85	4:1
12	Toluene	CuI	100	2	60	3:1
13	Water	CuI	100	2	37	3:1

Tab.1 All the reactions were performed using: compound **4** (1 eq), benzylamine (1.2 eq), phenylacetylene (1.2 eq), catalyst (0.2 eq), solvent (2 mL/mmol), and were warmed at the indicated temperature by μW irradiation for the indicated time. a) Yields were obtained by HPLC; b) Determined by HPLC; c)Yield was determined on isolated compound d)Reaction was warmed using oil bath.

The reaction was tested initially in acetonitrile as the solvent and at 100 °C under microwave irradiation. The catalyst screening showed that when we used Ag- or Au-based catalysts the reaction failed to give the desired product (Tab. 1,entries 1–2). Among copper derivatives, CuI proved to be superior with respect to the corresponding bromide or triflate salts (Tab. 1, entries 3–6). The reaction conditions were also studied as regarding to temperature and reaction time. On prolonging the reaction time at reduced temperature (entry 7) or reducing the reaction time at higher temperature a positive effect on the reaction yield was not achieved (Tab. 1, entry 8), nor by reducing the time to 1 h at100 °C (Tab. 1, entry 9). Finally, we screened several solvents, and acetonitrile was

compared with other polar and non-polar solvents (Tab 1, entries 10–13), irrespective of their interaction with microwave irradiation. Indeed, the reaction in toluene was still possible taking advantage of the concentration of the reagents (0.5M) and the presence of CuI as a strong microwave interacting species. The best performance was achieved with acetonitrile and 1,2-dichloroethane as solvents (Tab. 1, entries 6 and 11, respectively), with significantly higher yield as compared to protic solvents such as water and methanol. Moderate stereoselectivity was observed in all cases and with similar extent, suggesting a substrate effect towards stereoselectivity. In the end we found that the optimal conditions were selected as those employing CuI in 1,2-dichloroethane (DCE) and reacting for 2 h at 100 °C under microwave irradiation. After optimizing the reaction conditions, we investigated the geometry of our couple product (**7**) to understand which diasteroisomer was obtained in major amounts. The structure of **7**did not allow to obtain this information directly from the NMR spectra because the new stereocenter was not embedded in a constrained structure. To solve this problem we derivatized the basic nitrogen of **7** with tosyl chloride (Scheme **7**) to obtain the corresponding sulfonamide **8**.



Scheme 7 Et_3N (4 eq), **7** (1 eq), DMAP (0.5 eq), TsCl (3 eq) in dry DCM (4 mL/mmol), RT, 16 h.

The major diastereoisomer was easy crystallized from the mixture of both using a 10:1 diethyl ether/EtOAc, and the X-ray crystallographic analysis allowed us to assign the structure of **8** and consequently those of the corresponding precursors **7** (Figure 7).

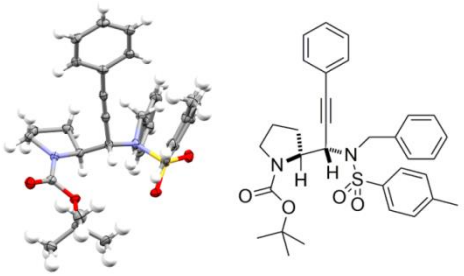


Figure 7 X-Ray crystallographic analysis of **8**, for the assignment of the relative configuration of the two stereocenters.

From this analysis we found the major diastereoisomer formed in A^3 reaction being the *syn*, and this selectivity of the A^3 adducts can be explained by the Cram chelate model (Figure 8).

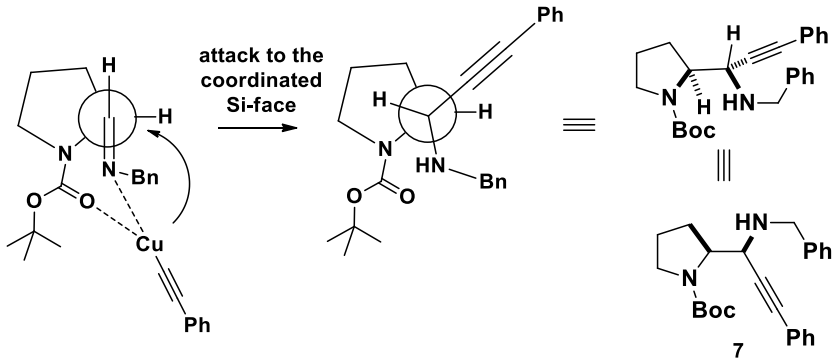
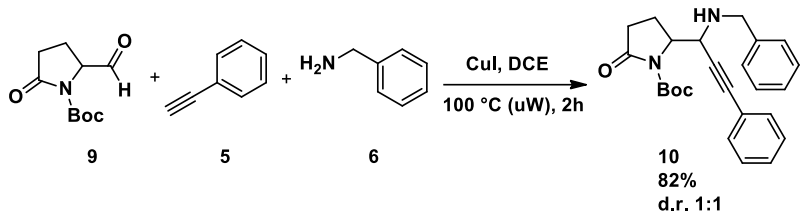


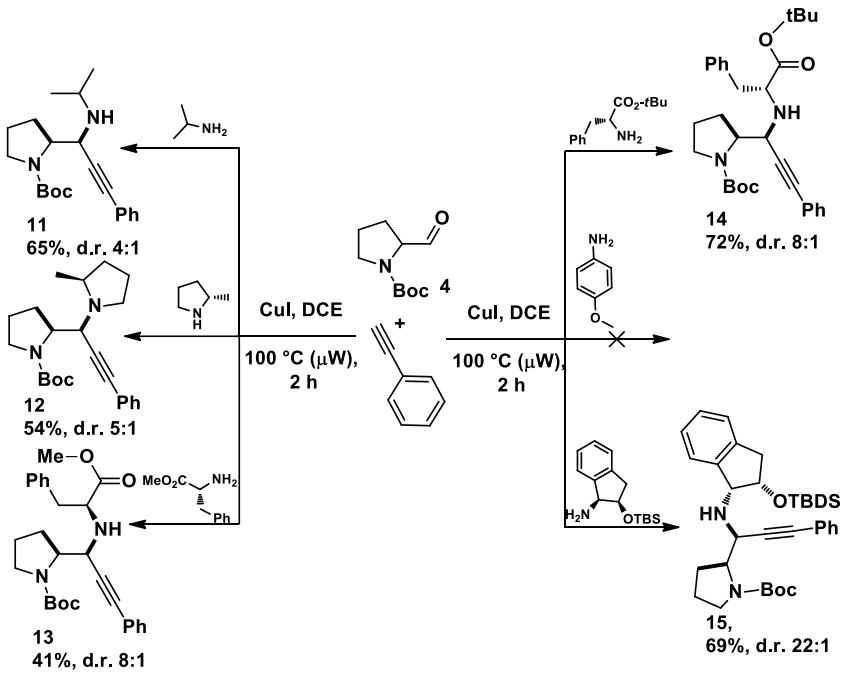
Figure 8 Hypothesized mechanism for the stereoselectivity resulting from the A^3-coupling to the coordinated Si-face of intermediate imine derived from Boc-prolinal

The nucleophilic addition by the acetylide takes place through acyclic transition state attacking the C=N group of the imine from the less hindered coordinated Si-face in a conformation where the steric interaction between the N-benzyl substituent and the bulky Boc group is minimized, providing the *syn* 1,2-diamine as the major stereoisomer. Such hypothesis was verified by carrying out the A^3 reaction under the same reaction conditions and using Boc-pyrrolidone-carbaldehyde (**9**).This compound was synthesized according to the literature, and its use in place of Boc-prolinal resulted in the coupling adduct **10** with 82 % yield and no diastereoselectivity. Accordingly, we reasoned this loss of stereo selectivity could be due by the presence of the C=O bond, which reduced the asymmetric conformational environment of the five-membered ring and inhibited the correct coordination of the Cu-alkyne species according to the Cram chelate model(Scheme 8).



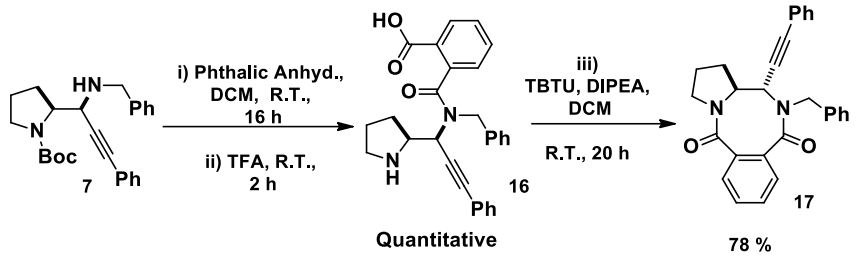
Scheme 8 Compound **9** (1 eq), benzylamine (1.2 eq), phenylacetylene (1.2 eq), CuI (0.2 eq), DCE (2 mL/mmol), 100 °C (μW), 2 h. Diastereoselectivity was determined by HPLC

In order to prove the tolerability of the A^3 reaction for other substrates containing different functional groups useful in a second phase to increase the number of possible scaffolds, we performed the A^3 with several amines. We carried out the reaction with the more sterically hindered *i*-propylamine (Scheme 9 product **11**), obtaining comparable yield and diastereoselectivity to that of benzylamine, and suggesting no significant effect of the steric hindrance of the amine substituent and the stereochemestry was assigned for similarity to the previous one, because no other factors can influence the attack mechanism. Similar results were obtained by using a chiral secondary amine(Scheme 9 product **12**), and a modest increase in the stereoselectivity was ascertained using phenylalanine esters, giving the corresponding products **13** and **14** with similar diastereoselectivity of 8:1. The low yield of product **13** was attributed to the side homo-coupling reaction. This problem was by-passed using the corresponding *t*-butyl ester for the achievement of **14**, which proved to be more resistant to the reaction conditions and not experiencing such side reaction. The use of the chiral (+)-cis-1-amino-2-indanol, containing two stereogenic centers, gave the highest diastereoselectivity ratio of 22:1 for the achievement of **15**. No reaction was experienced with *p*-methoxyaniline, possibly due to the low nucleophilicity of this amine.



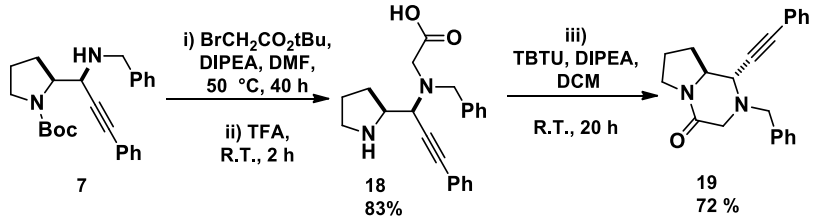
Scheme 9 Compound **4** (1 eq), amine (1.2 eq), phenylacetylene (1.2 eq), CuI (0.2 eq), DCE (2 mL/mmol), 100 °C (μW), 2 h. Diastereoselectivity was determined by HPLC.

After testing the tolerability of our couple reaction for several amines we focused on the study of the "Pairing" phase, using the 1,2, diamine moiety created with the A^3 reaction. Initially, we performed the reaction of **4** with phthalic anhydride, followed by Boc deprotection and concomitant lactamization upon addition of a base and TBTU, resulting in the achievement of the corresponding [6,8,5]-tricyclic compound **17** in 78 % yield, and having a *trans* geometry at the two stereocenters, as expected from the structural analysis on the acyclic adduct (Scheme 10).



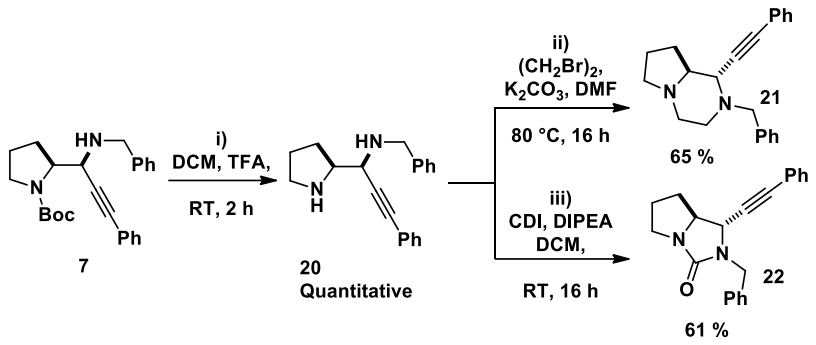
Scheme 10 i)Compound **7** (1 eq), Phthalic anhydride (1 eq), DCM dry(4 mL/mmol), RT, 16 h; **ii**) DCM:TFA 3:1 (5.2 mL/mmol), RT, 2 h; **iii**) 16 (1 eq), TBTU (3 eq), DIPEA (6 eq), DCM dry (10 mL/mmol).

A similar approach for the generation of bicyclic compounds of 6,5 size was obtained by treating compound **7** with tert-butyl bromoacetate, resulting to the achievement of **18** after tert-butyl removal, and subsequent intramolecular amide bond formation to obtain the corresponding bicyclic lactam **19** in 72 % yield (Scheme 11).



Scheme 11 i) Compound **7** (1 eq),tert-Butylbromoacetate (1 eq), DIPEA(4 eq), DMF dry(2 mL/mmol), 50 °C, 40 h; **ii**) DCM:TFA 3:1 (5.2 mL/mmol), RT, 2 h; **iii**)**18** (1 eq), TBTU (3 eq), DIPEA (6 eq), DCM dry (20 mL/mmol).

For the last two scaffolds we removed initially the *t*-Boc protecting group to obtain the intermediate compound containing a 1,2-diamino moiety, followed by a cyclization with two different bidentate reagents, namely 1,2 di-bromo-ethane and carbonyldimidazole, to afford respectively the bicyclic 6,5 and 5,5, compounds **21** and **22** (Scheme 12).



Scheme 12 i) Compound **7** (1eq), DCM:TFA 4:1 (12 mL/mmol), RT 2 h; **ii**) **20** (1 eq) 1,2 dibromoethane (1 eq), K_2CO_3 (10 eq), DMF dry (20 mL/mmol), 80 °C 16 h; **iii**) **20** (1 eq), CDI (1 eq), DIPEA (10 eq), DCM dry (20 mL/mmol), RT, 16 h.

In order to analyze the difference inside the small library of produced compounds using this B/C/P strategy, we carried out a shape analysis in the context of the chemical space using principal moments of inertia(PMI) analysis. This chemoinformatic tool was used to assess the 3D molecular shape analysis of the major diastereoisomers of A^3-coupling products **4**–**19** as compared to a reference set of BB (blockbuster) drugs (Figure 9 The PMI analysis was carried out by calculating the lowest energy conformation of each representative compound of the library of proline-derived A^3 -coupling products, and of each molecule from the reference set using VegaZZ software. Then, the three principal moments of inertia (Ixx, Iyy, Izz) and the corresponding normalized principal moments of inertia were determined according to Sauer and Schwarz for all the compounds and the reference blockbuster drugs.

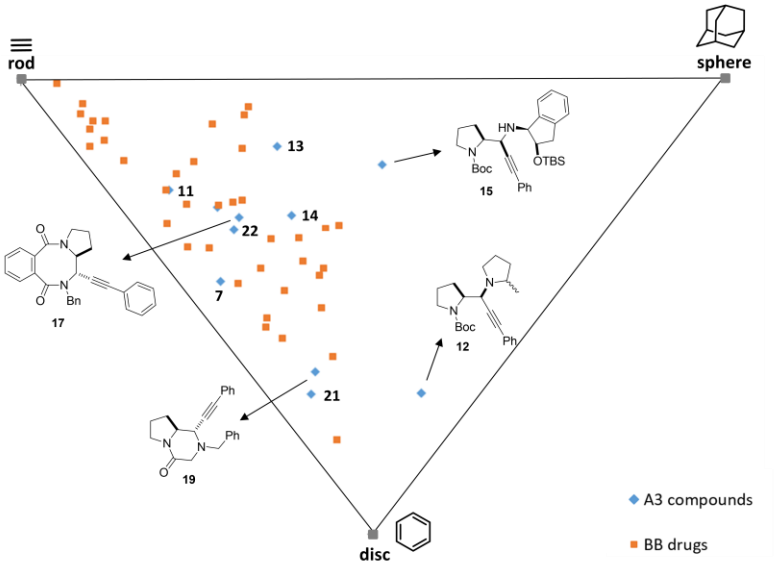


Figure 9 PMI plot showing the skeletal diversity of A^3-coupling products (blue diamonds) with respect to the reference set of brand-name blockbuster drugs (orange squares).

All the normalized PMI ratios were plotted on a triangular graph where the vertices (0,1), (0.5,0.5),and (1,1) represent a perfect rod (i.e., 2-butyne), disc (i.e., benzene), and sphere (i.e., adamantane), respectively. The A^3-coupling products were found to lie along the center-left side of the triangle, with a preference for the rod–disc side. Such positioning showed A^3-coupling products possessing lower tendency to stay in the rod side of the triangle and major dispersion in the space, as compared to BB drugs, suggesting higher shape diversity for these compounds as compared to BB drugs, which showed higher tendency to lie along the rod-disc axis. Interestingly, bi- and tricyclic scaffolds**17**, **19**, **21** and **22** proved to shift more towards the disc corner of the triangle, demonstrating a quite diverse shape as compared to BB drugs. Also, compounds **12** and **15** proved to be positioned to the sphere-disc region, indicating good coverage within shape diversity as a function of the appendage extent of the A^3 coupling intermediate. The PMI analysis suggested that the skeletal diversity coming from the exploitation of prolinal using the A^3-coupling reaction and follow-up cyclization reactions according to the Build-Couple-Pair approach resulted in an array of molecules spanning the chemical space despite the limited number of representatives, as compared to brand-name blockbuster drugs.

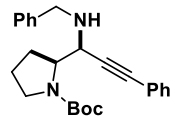
3.3 Conclusions

In conclusion we proved that the A^3 reaction can be used as couple step in a B/C/P strategy using α amino aldehydes as the aldehyde source to generate a good library of scaffolds using fast and efficient synthetic pathways. The reaction proved to work with good substrate scope, and interesting results were also obtained as regarding to diastereoselectivity, obtaining *syn* selectivity of the A^3 adducts explained by the Cram chelate model. Intramolecular cyclization performed in the "Pair step" of the 1,2-diaminechemical moiety enabled the synthesis of a range of representative bi- and tricyclic pyrrolidines with an alkynyl containing the phenylacetylene moiety, with good coverage of the chemical space, as shown by PMI chemoinformatic tool. Specifically, the A^3adducts differed in the chemical space positioning with respect to bi- and tricyclic compounds obtained under the pairing stage, suggesting the importance of including all the compounds in a developing library. The future development of this work will consist in the generation of other scaffolds using other amines which proved to be reactive in the A^3 reaction to increase the library of compounds. These molecules will be tested using phenotypic assays on selected biological targets such as those involved in the Alzheimer's disease and others using the principles of Chemical genetics.

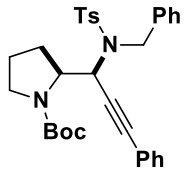
3.4 Experimental Part

General: All commercially available reagents and solvents were used as received, unless otherwise specified. Microwave heated reactions were performed on an automated single-mode microwave synthesizer (InitiatorSixty, Biotage AB) using sealed reaction vessels and built-in internal pressure and temperature sensors. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), or a Varian Gemini 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz). The chemical shifts (δ) and coupling constants (J) are expressed in parts per million (ppm) and hertz (Hz), respectively. Flash column chromatography (FCC) purifications were performed manually using glass columns with Merck silica gel (0.040–0.063 mm), or using the BiotageIsolera system and SNAP silica cartridges. TLC analyses were performed on Merck silica gel 60 F254 plates. Elemental analyses were performed on a CHN- S Flash E1112 Thermofinnigan analyzer. ESI-MS spectra were recorded on a Thermo Scientific LCQ fleet ion-trap double quadrupole mass spectrometer using electrospray (ES^{+}) ionization techniques. The diastereomeric ratio was calculated by HPLC using a chiral column Phenomenx Lux 5u Cellulose-1 (250x4.60 mm) an isocratic elution program (80% CH_3CN, 20% H_2O) to enhance separation of diastereomeric peaks.

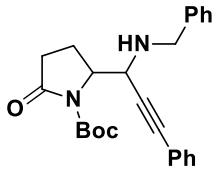
General Procedure for the A^3 coupling reaction. CuI (0.2 eq) and a solution of Boc-prolinal (1 eq), prepared as reported,[17] in dry dichloroethane (2 mL/mmol) were added in a dry microwave flask under nitrogen flow. Then, phenylacetylene (1.2 eq) and amine (1.2 eq) were added to the stirring solution under nitrogen flow. Successively, the mixture was heated under microwave irradiation at 100 °C for 2 h. Then, EtOAc was added and the organic phase was washed with 5% NH_4OH (3 x 20 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the indicated solvent mixture as eluant.



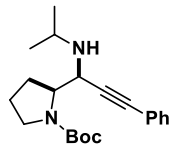
***rac*-(*S*)-*tert*-butyl 2-((*S*)-1-(benzylamino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (7).** Compound **7** was obtained following the general procedure using Boc-prolinal (140 mg, 0.7 mmol), dichloroethane (1.4 mL), phenylacetylene (92 µL, 0.84 mmol), CuI (27 mg, 0.14 mmol) and benzylamine (91 µL, 0.84 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant (Rf 0.25), to give **7** (197 mg) as a yellow oil in 72% yield. The product was obtained as a 4:1 mixture of two inseparable racemic diastereomers.^{1}H NMR (400 MHz, $CDCl_3$) 2:1 mixture of rotamersδ 7.43-7.22 (m, 10H), 4.29-3.85 (m, 3H), 3.61-3.39 (m, 2H), 2.07 (m, 4H), 1.78 (m, 1H) 1.53 and 1,44 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 2:1 mixture of rotamers δ 155.0 and 154.4, 140.2 and 139.6, 131.7(2C), 131.6 (2C), 128.6 and 128.4 (2C), 128.3(2C), 128.1,126.9, 123.1, 89.2 and 88.6, 85.0 and 84.7, 79.5 and 79.3, 60.9 and 60.4, 53.3 and 52.5, 52.2 and 51.7, 47.3 and 46.9, 28.6 and 28.4 (3C), 27.8 and 27.3, 24.2 and 23.7 ppm. MS (ESI) *m*/*z* (%): 391.22 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{25}H_{30}N_2O_2$: C, 76.9; H, 7.7; N, 7.2. Found: C, 77.4; H, 7.9; N, 6.9.



***rac*-(*S*)-*tert*-butyl 2-((*S*)-1-(*N*-benzyl-4-methylphenylsulfonamido)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (8)**. To a stirred solution of **7**(950 mg, 2.44 mmol) in dry dichloromethane (10 mL) was added triethyl amine (1.35 mL, 9.76 mmol) and DMAP (149 mg, 1.22 mmol). Successively, the mixture was kept to 0 °C and tosyl chloride (1.388 g, 7.30 mmol) was added portionwise, then the reaction was allowed to room temperature and left under stirring for 20 h. The mixture was diluted with EtOAc (30 mL) and washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution (3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography with a mixture of 1:1 hexane-EtOAc (Rf 0.63), to give the pure product (982 mg) in a yield of 74%. The pure compound was recrystallized from a mixture of 10:1 diethyl ether-EtOAc. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.84-7.05 (m, 14H), 5.58-5.54 (m, 1H), 4.72 (d, J = 16.9 Hz, 1H), 4.59-4.17 (m, 1H), 4.03 (m, 1H), 3.60-3.17 (m, 2H), 2.36 (s, 3H), 2.05-1.75 (m, 2H), 1.65-1.26 (m, 2H), 1.62 and 1.51 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 155.0, 143.5, 137.9, 136.0, 131.4 (2C), 129.6 (2C), 129.5, 129.2, 129.0, 128.7, 128.6 (3C), 128.5, 128.4, 128.3, 121.9, 87.9, 83.5, 80.8, 61.1, 53.7, 49.3, 46.7, 28.7 (3C), 23.7, 21.4 (2C) ppm. MS (ESI) *m*/*z*(%): 545.32 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{32}H_{36}N_2O_4S$: C, 70.6; H, 6.7; N, 5.1. Found: C, 70.6; H, 6.7; N, 5.1.

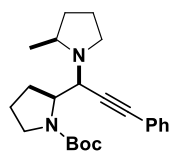


***rac-tert*-butyl 2-(1-(benzylamino)-3-phenylprop-2-yn-1-yl)-5-oxopyrrolidine-1-carboxylate (10).** Compound **10** was obtained following the general procedure using *tert*-butyl 2-formyl-5-oxopyrrolidine-1-carboxylate (**9**) (450 mg, 2.11 mmol), dry dichloroethane (4.2 mL), phenylacetylene (277 µL, 2.53 mmol), CuI (80 mg, 0.42 mmol) and benzylamine (279 µL, 2.53mmol). The reaction was heated for two hours under microwave irradiation, and the crude product was purified by flash chromatography with 2:1 hexane-diethyl ether as eluant to separate the two diastereomers as racemic mixtures (Rf_1 0.52, Rf_2 0.43). The two diastereoisomers were isolated (337 mg + 343 mg) in 80% combined yield. Diastereomer **10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.22 (m, 10H), 4.34 (m, 1H), 4.10(d, *J* = 12.9 Hz, 1H), 4.09 (d, *J* = 4.3 Hz, 1H), 3.91 (d, *J* = 13.0 Hz, 1H), 2.86 (dt, *J* = 18.0, 10.1 Hz, 1H), 2.46 (ddd, *J* = 17.9, 10.0, 3.0 Hz, 1H), 2.29-2.11 (m, 2H), 1.43 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 149.8, 139.4, 131.8 (2C), 131.7 (2C), 128.8, 128.5 (2C), 128.4 (2C), 127.3, 122.3, 87.0, 85.7, 83.1, 60.6, 52.5, 52.0, 32.0, 27.9 (3C), 19.4. MS (ESI) *m*/*z* (%): 405.52 [$(M+H)^+$, 100]. Diastereomer **10b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 10H), 4.10 (d, *J* = 13.4 Hz, 1H), 3.70 (d, *J* = 12.9 Hz, 1H), 3.58 (dd, *J* = 13.2, 7.1 Hz, 2H), 2.73-2.65 (m, 1H), 2.57-2.25 (m, 3H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 150.1, 139.3, 139.0, 128.9 (3C), 128.4 (3C), 128.3 (2C), 127.2, 127.1, 86.2, 82.7, 62.1, 60.2, 51.2, 50.8, 33.0, 28.1 (3C), 18.5. MS (ESI) *m/z* (%): 405.54 [$(M+H)^+$, 100].

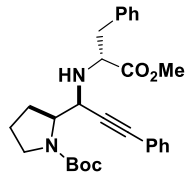


***rac*- (*S*)-*tert*-butyl 2-((*S*)-1-(isopropylamino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (11).** Compound **11** was obtained following the general procedure using Boc-prolinal (60 mg, 0.30 mmol), dry dichloroethane (600 µL), phenylacetylene (40 µL, 0.36 mmol), CuI (11 mg, 0.15 mmol) and isopropylamine (30 µL, 0.360 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography with 2:1 hexane-EtOAc as eluant (Rf 0.48), to give product **5** (67 mg) in a yield of 65% as a 4:1 mixture of two inseparable racemic diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.39-7.35 (m, 2H), 7.33-7.23 (m, 3H), 4.41-4.17 (m, 1H), 4.06-3.83 (m, 1H), 3.66-3.42 (m, 1H), 3.41-3.27 (m, 1H), 3.19-3.05 (m, 1H), 2.13-1.93 (m, 3H), 1.85-1.69 (m, 1H), 1.47 and 1.45 (s, 9H), 1.12 and 1.05 (d, *J* = 6.3 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) major rotamerδ 154.4, 131.6 (2C), 128.3 (3C), 123.1, 89.1, 84.2, 79.6, 60.8, 50.7, 47.0, 46.4, 28.6 (3C), 27.5, 24.0, 23.7, 21.9 ppm. MS (ESI) *m*/*z* (%): 365.18 [$(M+Na)^+$,

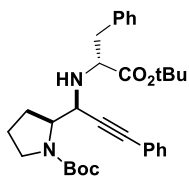
100]. Anal. Calcd. for $C_{21}H_{30}N_2O_2$: C, 73.6; H, 8.8; N, 8.2. Found: C, 74.0; H, 9.0; N, 8.1.



***rac*- (*S*)-*tert*-butyl 2-((*S*)-1-((*S*)-2-methylpyrrolidin-1-yl)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (12).** Compound **12** was obtained following the general procedure using Boc-prolinal (131 mg, 0.6 mmol), dry dichloroethane (1.2 mL), phenylacetylene (79 µL, 0.72 mmol), CuI (22 mg, 0.12 mmol) and (*S*)-2-methylpyrrolidine (73 µL, 0.73 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography eluted with 1.5:1 hexane-ethyl ether (Rf 0.28) to give the product (119 mg) in a yield of 54%. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.50-7.35 (m, 2H), 7.35-7.14 (m, 3H), 4.35 (m, 1H), 3.96 (m, 1H), 3.69-3.20 (m, 2H), 3.01-2.67 (m, 3H), 2.31-1.92 (m, 3H), 1.92-1.64 (m, 5H), 1.48 (s, 9H), 1.11 (d, *J* = 5.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 154.6, 131.6 (2C), 128.2 (2C), 127.9, 123.2, 87.1, 85.3, 79.7, 61.3, 57.8, 55.1, 48.9, 46.5, 32.1, 28.7 (3C), 24.0, 22.3, 19.7 (2C) ppm. MS (ESI) *m*/*z* (%): 391.51 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{23}H_{32}N_2O_2$: C, 75.0; H, 8.8; N, 7.6. Found: C, 75.3; H, 9.0; N, 7.4.

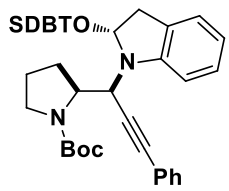


***rac*- (*S*)-*tert*-butyl 2-((*S*)1-(((*R*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)amino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (13).** Compound **13** was obtained following the general procedure using Boc-prolinal (152 mg, 0.76 mmol), dry dichloroethane (1.52 mL), phenylacetylene (100 µL, 0.92 mmol), CuI (30 mg, 0.20 mmol) and d-phenylalanine methyl ester (164 mg, 0.92 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography eluted with 2:1 hexane-ethyl ether (Rf 0.28) to give the product (143 mg) in a yield of 41%. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.38-7.33 (m, 2H), 7.31-7.15 (m, 8H), 4.01 (m, 1H), 3.89-3.40 (m, 6H), 3.39-3.28 (m, 1H), 3.09-2.83 (m, 2H), 2.17-1.93 (m, 4H), 1.45 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 174.9, 154.4, 137.5, 131.9, 131.6 (3C), 129.3 (2C), 128.5, 128.2 (3C), 126.6, 88.04, 85.1, 79.7, 61.7, 60.2, 52.8, 51.9, 46.9, 39.7, 28.5 (3C), 28.4, 28.0 ppm. MS (ESI) *m*/*z*(%): 485.29 [$(M+Na)^+$, 100]. Anal.Calcd. for $C_{28}H_{34}N_2O_4$: C, 72.7; H, 7.4; N, 6.1. Found: C, 73.1; H, 7.5; N, 5.9.

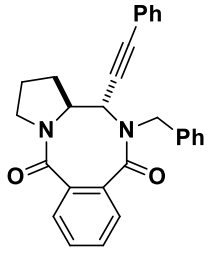


***rac*- (*S*)-*tert*-butyl 2-((*S*)-1-(((*R*)-1-(*tert*-butoxy)-1-oxo-3-phenylpropan-2-yl)amino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (14)**. Compound **14** was obtained following the general procedure using Boc-prolinal

(144 mg, 0.72), dry dichloroethane (1.5 mL), phenylacetylene (94 µL, 0.86 mmol), CuI (27 mg, 0.14 mmol) and d-phenylalanine *tert*-butyl ester (220 mg, 0.86 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography eluted with 3:1 hexane-ethyl ether (Rf 0.42), to give the pure product (262 mg) in a yield of 72%. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.40-7.33 (m, 2H), 7.30-7.17 (m, 8H), 4.03-3.98 (m, 1H), 3.78-3.60 (m, 1H), 3.72-3.58 (m, 1H), 3.42-3.32 (m. 2H) 2.94-2.81 (m, 2H), 2.13-1.83 (m, 4H), 1.48 and 1.46 (s, 9H), 1.34 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) major rotamer δ 173.5, 154.4, 137.5, 131.6 (3C), 129.7 (2C), 128.2 (4C), 126.4, 123.0, 88.0, 85.1, 79.6, 61.7, 60.1, 52.5, 51.8, 46.9, 39.6, 28.5 (3C), 28.4 (3C), 27.5, 23.5 ppm. MS (ESI) *m*/z(%): 527.33 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{31}H_{40}N_2O_4$: C, 73.8; H, 8.0; N, 5.6. Found: C, 73.9; H, 8.1; N, 5.5.

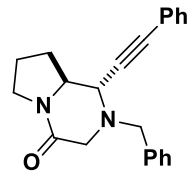


***rac*-(*S*)-*tert*-butyl 2-((*S*)-1-(((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1*H*-inden-1-yl)amino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate (15)**. Compound **15** was obtained following the general procedure using Boc-prolinal (215 mg, 1.07 mmol), dry dichloroethane (2.50 mL), phenylacetylene (141 µL, 0.92 mmol), CuI (41 mg, 0.22 mmol) and (1*S*,2*R*)-2-(TBS)-2,3-dihydro-1*H*-inden-1-amine (340 mg, 1.29 mmol). The reaction was heated for 2 h and the crude product was purified by flash chromatography with 2:1 hexane-ethyl ether (Rf 0.28). To give the product (403 mg) in a yield of 69%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.12 (m, 9H), 4.73-4.48 (m, 1H), 4.29 (d, J = 4.2 Hz, 1H), 4.24 (d, J = 5.6 Hz, 1H), 3.90-3.87 (m, 1H), 3.64-3.56 (m, 1H), 3.46-3.33 (m, 1H), 3.17-2.92 (m, 2H), 2.23-1.98 (m, 4H), 1.48 and 1.46 (s, 9H), 0.92 and 0.87 (s, 9H), 0.15 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 143.0, 140.7, 131.6 (2C), 128.4 (2C), 128.2, 128.0, 127.8, 126.3, 125.3, 123.3, 89.1, 85.0, 79.4, 74.4, 62.0, 60.4, 50.8, 47.0, 39.3, 28.4 (3C), 27.4, 25.8 (3C), 23.8, 18.1, -4.8 (2C) ppm. MS (ESI) *m*/*z* (%): 569.37 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{33}H_{46}N_2O_3Si$: C, 72.5; H, 8.5; N, 5.1. Found: C, 72.6; H, 8.5; N, 5.0.



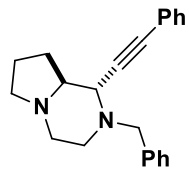
***rac*-(3a*S*,4*S*)-5-Benzyl-4-(phenylethynyl)-1,2,3,3a,4,5hexahydrobenzo[f]pyrrolo[1,2-a][1,4]diazocine-6,11-dione (17).** To a stirred solution of **7** (276 mg, 0.71 mmol) in dry dichloromethane (2.83 mL) was added portionwise phthalic anhydride (104 mg, 0,71 mmol) at 0 °C under a N_2 flow, then the mixture was kept at room temperature and left under stirring for 24 h. TFA was

added (0.95 mL) and the mixture was left under stirring for 2 h, then the solvent and the TFA were removed by evaporation under vacuum and crude **13** dissolved in dry dichloromethane (7 mL). To this solution was added diisopropylethylamine (688 µL, 4.26 mmol) and TBTU (635 mg, 2.13 mmol), and the mixture was left under stirring for 24 h. Successively, the mixture was diluted with dichloromethane (30 mL) and washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution (3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography with EtOAc as eluant (Rf 0.51), to give the pure product **17** (200 mg) in 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 17.7, 8.2 Hz, 1H), 7.53-7.43 (m, 3H), 7.41-7.22 (m, 10H), 5.74 (d, *J* = 14.5 Hz, 1H), 3.99 (d, *J* = 14.5 Hz, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.72-3.59 (m, 1H), 3.31 (td, *J* = 11.4, 7.5 Hz, 1H), 3.05-2.88 (m, 1H), 1.93-1.76 (m, 1H), 1.69-1.60 (m,, 2H), 0.99-0.77 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.7, 136.6, 135.1, 134.5, 131.7 (2C), 130.4, 130.1, 129.2 (2C), 129.0 (2C), 128.9 (2C), 128.4, 128.2 (2C), 126.4, 121.7, 85.5, 84.4, 63.8, 54.7, 51.3, 45.6, 29.7, 21.8 ppm. MS (ESI) *m*/*z*(%): 421.19 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{28}H_{24}N_2O_2$: C, 80.0; H, 5.8; N, 6.7. Found: C, 80.1; H, 5.8; N, 6.6.

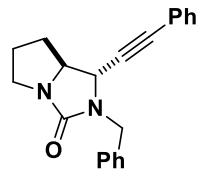


***rac*-(1*S*,8a*S*)-2-Benzyl-1-(phenylethynyl)hexahydropyrrolo[1,2-a]pyrazin-4(1*H*)-one (19).** To a mixture of **7** (260 mg, 0.66 mmol) and dry diisopropylethylamine (470 µL, 2.68 mmol) was added *tert*-butyl 2-bromoacetate (98 µL, 0.66 mmol) at 0 °C and under N_2 flow. The mixture was heated at 50 °C for 40 h, then it was diluted with EtOAc (30 mL) and washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution (3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude was purified by flash chromatography with 5:1 hexane-diethyl ether as eluant (Rf 0.61), to give 276 mg of pure (*rac*-(*S*)-*tert*-butyl 2-((*S*)-1-(benzyl(2-(*tert*-butoxy)-2-oxoethyl)amino)-3-phenylprop-2-yn-1-yl)pyrrolidine-1-carboxylate) in 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.45-7.05 (m, 10H), 4.19-4.08 (m, 2H), 3.92-3.76 (m, 2H), 3.59-3.52 (m, 2H), 3.47-3.28 (m, 2H), 2.36-2.03 (m, 2H), 2.00-1.69 (m, 2H), 1.49 and 1.48 (s, 9H), 1.45 (s, 9H) ppm.MS (ESI) *m*/*z* (%): 527.26 [$(M + Na)^+$, 100]. Suchintermediate (130 mg 0.25 mmol) was dissolved in dry dichloromethane (2.5 mL), then TFA (0.75 mL) was added, and the mixture was stirred at room temperature for 3 h. Successively, the solvent was removed by evaporation under vacuum and the resulting crude **15** was dissolved in dry dichloromethane (5 mL). To this suspension diisopropylethylamine (430 µL, 2.5 mmol) and TBTU (160 mg, 0.5

mmol) were successively added. The mixture was stirred at room temperature for 20 h, then the solvent was evaporated and the crude dissolved with EtOAc (30 mL), washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution (3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography with EtOAc as eluant (Rf 0.43) to give pure compound **19** (60 mg) in 72% yield.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.25 (m, 10H), 4.40 (d, *J* = 13.2 Hz, 1H), 3.83-3.77 (m, 1H),3.66 (d, *J* = 12.9 Hz, 1H), 3.57-3.39 (m, 1H), 3.45 (d, *J* = 17.2 Hz, 1H), 3.32 (d, *J* = 9.1 Hz, 1H), 2.91 (d, *J* = 17.1 Hz, 1H), 2.31 (dt, *J* = 11.6, 5.7 Hz, 1H), 2.02 (dt, *J* = 14.3, 7.3 Hz, 1H), 1.96-1.78 (m, 1H), 1.69-1.61 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 136.5, 131.7 (3C), 129.3 (2C), 128.8, 128.4 (3C), 127.4, 122.2, 87.8, 84.8, 62.1, 58.0, 57.3, 54.6, 45.2, 30.8, 21.9 ppm. MS (ESI) *m*/*z* (%): 331.20 [$(M+H)^+$, 100].Anal. Calcd. for $C_{22}H_{22}N_2O$: C, 80.0; H, 6.7; N, 8.5. Found: C, 80.4; H, 6.8; N, 8.4.



***rac*-(1*S*,8a*S*)-2-Benzyl-1-(phenylethynyl)octahydropyrrolo[1,2-a]pyrazine (21).** To a stirred solution of **7** (500 mg, 1.28 mmol), in anhydrous dichloromethane (12 mL) was added TFA (3 mL) and the mixture was stirred for 2 h. Then, the solvent was removed by evaporation under vacuum and the resulting crude **17** was dissolved in dry DMF (25 mL). To this suspension K_2CO_3 (1.766 g, 12.8 mmol) and 1.2 dibromoethane (240 mg, 1.28 mmol) were successively added. The mixture was stirred at 100 °C for 20 h. Successively, the solvent was evaporated and the crude was dissolved with EtOAc (30 mL) and washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution (3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography with 40:1 dichloromethane-MeOH as eluant (Rf0.39), to give pure **21** (260 mg) in a yield of 65%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.18 (m, 10H), 4.41 (d, *J* = 13.4 Hz, 1H), 3.62 (d, *J* = 13.4 Hz, 1H), 3.15-3.02 (m, 2H), 2.98-2.89 (m, 1H), 2.87-2.77 (m, 1H), 2.36-2.19 (m, 4H), 2.16-2.05 (m, 1H), 1.91-1.71 (m, 2H), 1.71-1.58 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.7 (2C), 129.6 (2C), 128.3, 128.2 (2C), 128.1 (2C), 127.1, 123.0, 87.4, 85.5, 67.2, 59.3, 58.9, 53.8, 51.1, 50.4, 28.3, 21.0 ppm. MS (ESI) *m*/*z*(%): 317.22 [$(M+H)^+$, 100]. Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.5; H, 7.6; N, 8.9. Found: C, 84.0; H, 7.7; N, 8.8.



***rac*- (1*S*,7a*S*)-2-Benzyl-1-(phenylethynyl)tetrahydro-1*H*-pyrrolo[1,2-c]imidazol-3(2*H*)-one (22).** Similarly to the procedure for **21**, to a stirred solution of **7** (190 mg, 0.48 mmol), in anhydrous dichloromethane (4.8 mL) was added TFA (1.21 mL) and the mixture was stirred for 2 h. Then, the solvent was removed by evaporation under vacuum and the resulting crude **17** was dissolved in dry THF (10 mL). To this suspension were added diisopropylethylamine (817 µL, 4.70 mmol) and 1,1′-carbonyldiimidazole (77 mg, 0.47 mmol). The mixture was stirred at room temperature for 24 h, then the mixture was diluted with EtOAc (30 mL) and washed with 1M HCl (3 x 15 mL), satd Na_2CO_3 solution(3 x 15 mL), brine (15 mL) and dried with Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by flash chromatography eluted with a mixture of 1:1 hexane-EtOAc (Rf 0.47), to give pure **22** (90 mg) in a yield of 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.23 (m, 10H), 4.94 (d, *J* = 14.9 Hz, 1H), 4.19-4.11 (m, 2H), 3.87-3.68 (m, 2H), 3.21-3.07 (m, 1H), 2.10-1.76 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 136.7, 131.8 (2C), 131.7, 128.6 (2C), 128.3 (2C), 128.2 (2C), 127.5, 122.1, 85.8, 85.4, 63.6, 49.7, 45.8, 45.6, 30.0, 24.7 ppm. MS (ESI) *m*/*z* (%): 329.14 [$(M+Na)^+$, 100]. Anal. Calcd. for $C_{21}H_{20}N_2O$: C, 79.7; H, 6.4; N, 8.8. Found: C, 80.1; H, 6.5; N, 8.7.

X-Ray crystallographic analysis. Compound **8** was crystallized by slow evaporation from a 10:1 diethyl ether-EtOAc solvent mixture, then suitable dried crystals were subjected to X-ray analysis.A colourless prismatic shaped crystal (0.09x0.05x0.04) was used for collection and single crystal diffraction measurement was carried out with an Oxford Diffraction Xcalibur2 diffractometer using the Mo/K radiation (40mA/-40KV) at 100 °K. Data collection was performed with the program CrysAlis CCD. $C_{32}H_{36}N_2O_4S$, M=544.69, Monoclinic, space group P 2_1/c, *a*=11.311(2), *b*=12.587(2), *c*=20.405(3)Å, β=94,560(1) V=2895.9(8)Å^3, Z=4 D_c=1.249, µ=0.151 mm^{-1}, F(000)= 1160.CCDC 1839011 contains the supplementary crystallographic data for this paper. Data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

PMI Analysis. Principal moment of inertia analysis was carried out by calculation of the lowest energy conformation of each compound **7, 8, 10**-**15**, **17**, **19, 21**, **22** and each compound from the reference set of 40 brand-name blockbuster (BB) drugs. The conformation calculation was performed using the built-in AMMP molecular mechanics algorithm with default parameters of the VEGA ZZ molecular modeling software package v.3.0.1. Once the lowest

energy conformer was calculated, the three principal moments of inertia (Ixx, Iyy, Izz) and normalized principal moments of inertia, npr1 (Ixx/Izz) and npr2 (Iyy/Izz) were determined, and PMI ratios were calculated for **7, 8, 10**-**15**, **17**, **19, 21**, **22** and each compound from the reference set of BB drugs, as reported by Sauer and Schwarz.The ratios were plotted on a triangular graph with the vertices (0,1), (0.5,0.5), and (1,1) representing a perfect rod, disc, and sphere, respectively

3.5 Bibliography

1. Schreiber, S. L.; *Nature*, **2009**, 457, 153
2. Sanderhaus, J. D.; Martin, S. F.; *Chem.: Eur. J.*, **2009**, 15, 6, 1300.
3. Knapp, J.; Kurth, M. J.; Shaw J. T.; Youna, A.; " *Strategic Applications of Multicomponent Reactions in Diversity-Oriented Synthesis*" in " *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology"* Ed. by Andrea Trabocchi, Wiley and Sons, **2013**.
4. "*Multicomponent reactions"* Ed. by Zhu, J.; Bienayme, H.; Wiley VCH, **2005**
5. Peshkov, V.A., Pereshivko, O.P., Van der Eycken, E.V. (2012) *Chem. Soc. Rev.*, **41**, 3790; Yoo, W.-J.; Zhao, L.; Li, C.-J.; *Aldrichim. Acta*, **2010** 44, 43; Li, C.-J.; *Acc. Chem. Res.*, **2010**, 43, 581; Zani, L.; Bolm, C.; *Chem. Commun.*, **2006**, 4263; Wei, C., Li, Z.; Li, C.-J.; *Synlett*, **2004**, 1472.
6. Thompson, B. B.; *J. Pharm. Sci.*, **1968**, 57, 5, 715.
7. Magueur, G.; Crousse, B.; Delpon, D. B.; *Tetrahedron Lett*., **2005**, 46, 2219; Ma, Y.; Lobkovsky, E.; Collum, D. B.; *J. Org. Chem.*, **2005**, 70, 2335; Aubrecht, K.B.; Winemiller, M. D.; Callum, B; *J. Am. Chem. Soc*., **2000**, 122, 11084.
8. Chinchilla, R.; Najera, C.; *Chem. Soc. Rev.*, **2011**, 40, 50840.
9. Yoo, W.J.; Zhao, L.; Li, C. J. *Aldrichim. Acta*, **2011**, 44, 43.
10. McNally, J. J.; Youngman, M. A; Dax, S. L., *Tetrahedron Lett.* **1998**, *39*, 967.
11. Diatkin, A. B.; Rivero, R. A.; *Tetrahedron Lett.*, **1998**, 39, 3647.
12. Li, C. J.; Wei, C.; *Chem. Commun*., **2002**, 268.; Kuninobu, Y.; Inoue, Y.; Takai, K.; *Chem. Lett.*, **2006**, 35, 1376; Roy, B.; Raj, R.,; Mukhopadhyay, B.; *Tetrahedron Lett.*, **2009**, 50, 5838; Shao, Z.; Chan, A.; *Synthesis*, **2008**, 2868; Bieber, L.W.; da Silva, M.F.; **2004,** *Tetrahedron Lett*., 45, 8281.
13. We, C.; Li, C. J.*; J. Am. Chem. Soc.*, **2003**, 125, 9584.
14. Bloch, R.; *Chem. Rev.*, **1998**, 98, 1407.
15. Shi, L.; Tu, Y. Q.; Wang, M.; Zhang, F. M.; Fan, C. A.; *Org. Lett*., **2004**, 6, 1001.
16. Li, P.; Zhang, Y.; Wang, L.; *Chem.–Eur. J*., **2009**, 15, 2045; Chen, W. W.; Nguyen, R. V.; Li, C. J. *Tetrahedron Lett*., **2009**, 50, 2895; Zhang, Y.; Li, P.; Wang, M.; Wang, L.*; J. Org. Chem*., **2009**, 74, 4364; Ramu, E.; Varala, R.; Sreelatha, N.; Adapa, S. R.; *Tetrahedron Lett*., **2007**, 48,

7184; Samai, S.; Nandi, G. C.; Singh, M. C.; *Tetrahedron Lett.*, **2010**, 51, 5555Li, P.; Wang, L.; *Chin. J. Chem*., **2005**, 23, 1076.
17. Zindo, F. T.; Jacques, J.; Sarel, F.; *Future Med. Chem.*, **2015,** 7, 609.
18. Lauder, K.; Toscani, A.; Scalacci, N.; Castagnolo, D. *Chem. Rev*. **2017**, 117, 1409.
19. Smulik, J. A.; Diver, S. T.; *Org. Lett.*, **2000**, 2, 2271; Castagnolo, D.; Renzulli, M. L.; Galletti, E.; Corelli, F.; Botta, M.; *Tetrahedron: Asymmetry*, **2005**, 16, 2893. Castagnolo, D.; Giorgi, G.; Spinosa, R.; Corelli, F.; Botta, M.; *Eur. J. Org. Chem*., **2007**, 3676
20. Chinchilla, R.; Nájera, C.; *Chem. Rev*. **2007**, 107, 874; Chinchilla, R.; Najera, C. Re; *Chem. Soc. Rev*. **2011**, 40, 5084; Gotteland, J.-P.; Dax, C.; Halazy, S.; *Bioorg. Med. Chem. Lett*. **1997**, 7, 1153; Conn, C.; Shimmon, R.; Cordaro, F.; Hargraves, T.-L.; Ibrahim, P.*; Bioorg. Med. Chem. Lett*. **2001**, 11, 2565; Merkul, E.; Müller, T. J.; *Chem. Commun*. **2006**, 4817; Ghaudhuri, G.; Kundu, N. G. *J. Chem. Soc. Perkin Trans*, **2000**, 775.
21. Peshkov, A. A.; Peshkov, V. A.; Pereshivko, O. P.; Van Hecke, K.; Kumar, R.; Van Der Eycken, E. V., *J. Org. Chem*. **2015**, 80, 6598.
22. Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J.; *Org. Lett*., **2003**, 5, 983.
23. Bhaskaruni, S.V.H.S.; Maddila, S.; Gangu, K.K.; Jonnalagadda, S.B.; *Arab. J. Chem*., **2017**, https://doi.org/10.1016/j.arabjc.2017.09.016.
24. Yogev, M. & Amit, T.; Youdim, M.; *FASEB J*., **2004** 17. 2325.
25. *"Privileged Structures in Drug Discovery: Medicinal Chemistry and Synthesis"* Ed. by Yet, L. Wiley and sons, **2018**
26. Crossman, A. R,; *J. Anat*. **2000,** 196, 519; "*Experimental and Clinical Neurotoxicology"*. Ed. by Spencer P. S.; Schaumburg H. H.; Ludolph A.C.. Oxford University Press, Oxford, UK **2000**.
27. Xu, Y. X..; Wang, H.; Li, X.-k.; Dong, S.; Liu, W.; Gong, Q.; Wang, T. D. Y.; Tang, Y.; Zhu, J.; Li, J.; Zhang, H.-y.; Mao, F.. *Eur. J. Med. Chem.* **2018**, *143*, 33
28. Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X.-M.; Paterson, I. A.; Yu, P. H.*; Drug Dev. Res*. **1997**, 42, 150; Bar-Am, O.; Amit, T.; Weinreb, O.; Youdim, M. B.; Mandel, S.; *J. Alzheimer's Dis*. **2010**, 21, 361; Mao, F.; Li, J.; Wei, H.; Huang, L.; Li, X. Tacrine, *J. Enzyme Inhib. Med. Chem*, **2015**, 30, 995−1001.

Chapter 4

Application of Ketone-Amine-Alkyne (KA^2) reaction in a Build Couple Pair strategy for the generation of a library of spirocyclic compounds.

4.1 Introduction

During our study on A^3 reaction we found in the literature an interesting variation of it. This reaction called KA^2 is still a multicomponent reaction catalyzed by metal salts (usually copper), although in this case the substrate involved are amines and alkynes, as usual, and a ketone to give propargyl amines with the α-carbon disubstituted as reaction products (Scheme 1)[1].

Scheme 1 Representation of a general Ketone, Amine, Alkyne (KA^2) reaction.

Also in this case the reaction of a nucleophilic carbon atom, generated by acetylide formation, and an electrophilic one from a ketimine was already known. The novelty in this work, as for the A^3, is the possibility of generating all the substrates in situ, thus working under multicomponent reaction conditions. The first work that reported this reaction is the one published by Van der Eycken[2] and co-workers in 2010. In this brilliant work they hypothesized a reaction mechanism that comprised all the steps of a normal A^3 reaction (Figure 1).

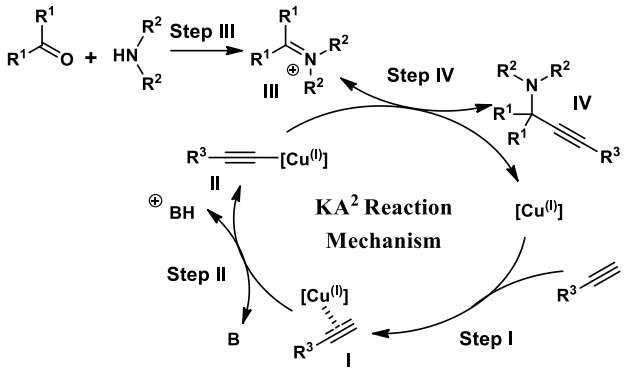


Figure 1 KA^2 reaction mechanism proposed by Van der Eycken.

Indeed, the reaction mechanism starts with the generation (Figure 1, Step I & II) of the metal acetylide **II** and evolves to the attack (Figure 1, Step IV) of its nucleophilic carbon atom on the electrophile formed from an in situ generated (Figure 1 step III) iminium ion **III**, to give the product of reaction **IV** and the free copper that returns in the catalytic circle. The principal differences between KA^2 and A^3 reactions in the nature of the product and the reactivity. The product indeed has the α carbon disubstituted because coming from a ketone (Figure 2a).This variant brings many opportunities that will be discussed later[2]. The second aspect differing in this reaction is the reactivity of the system, as the carbonyl carbon atom results less electrophilic as compared with the A^3 reaction for the additional substitution from the second alkyl group (Figure 2b).

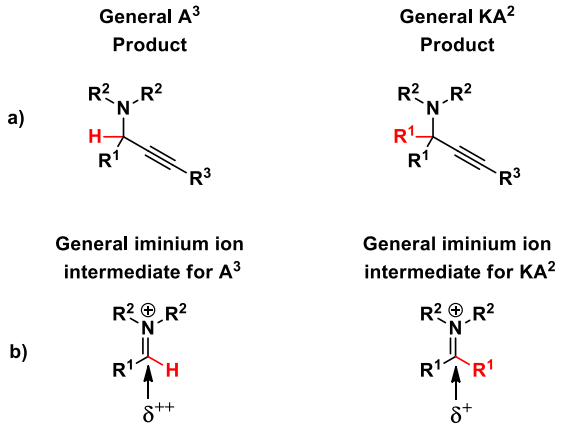
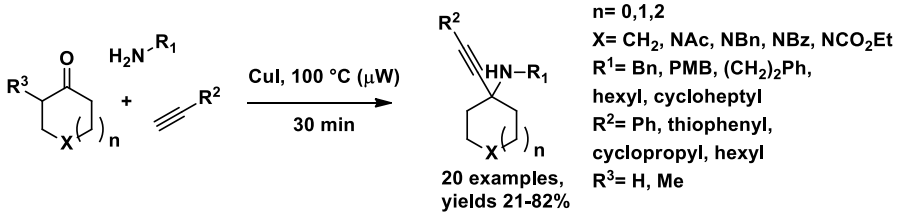


Figure 2 Comparison between different characteristics of A^3 and KA^2 reaction.

Due to this different reactivity, the reaction conditions result more drastic as compared to those of A^3 and the catalytic systems are usually less versatile. Also, changing the substrate nature, especially for the ketone, brings to a dramatic decrease of the yield. The less versatile profile is showed in the first works published on this reaction, where the aim of the initial studies was to find different catalytic systems in order to make this transformation accessible to the largest number of substrates. In the first work[2] Van der Eycken and co-workers (Scheme 2) used only primary amines for the reaction with various cyclic ketones and alkynes. The catalytic system proved to be really efficient when benzylic amines and aromatic alkynes were involved in the reaction (yield > 50%).



Scheme 2 Summary of Van der Eycken's work.

When aliphatic amines and alkynes are used the yield decreases(31-48%), and the presence of an heteroatom in the ketone does not affect the yields, except for the basic nitrogen (38%). Another limitation are the substitution of the α carbon of ketone, as using 2 methyl-cyclo-hexanone the yield dramatically decreased (21%). This can be explained focusing on the formation of an intermediate step. Indeed, the reactive imine intermediate is in equilibrium with the enamine species. As showed by Knochel, the presence of a metal moves the equilibria to the imine form, but however the increase of the substitution stabilizes the enamine form, over increment the steric hindrance near to the reactive center[3] (Figure 3).

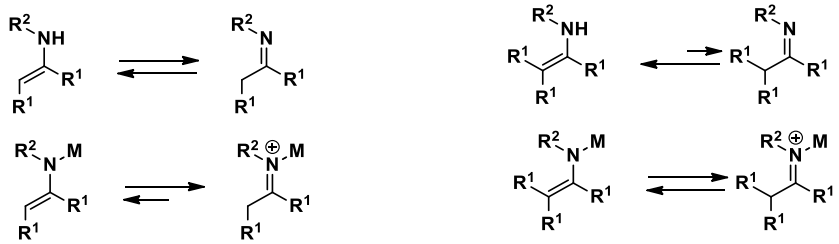
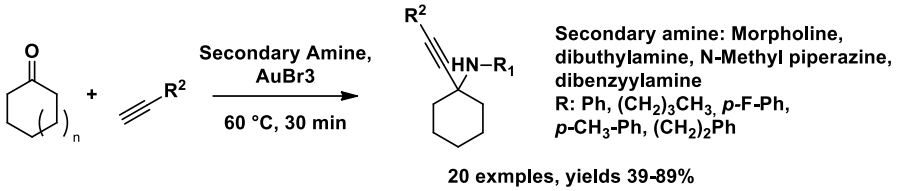


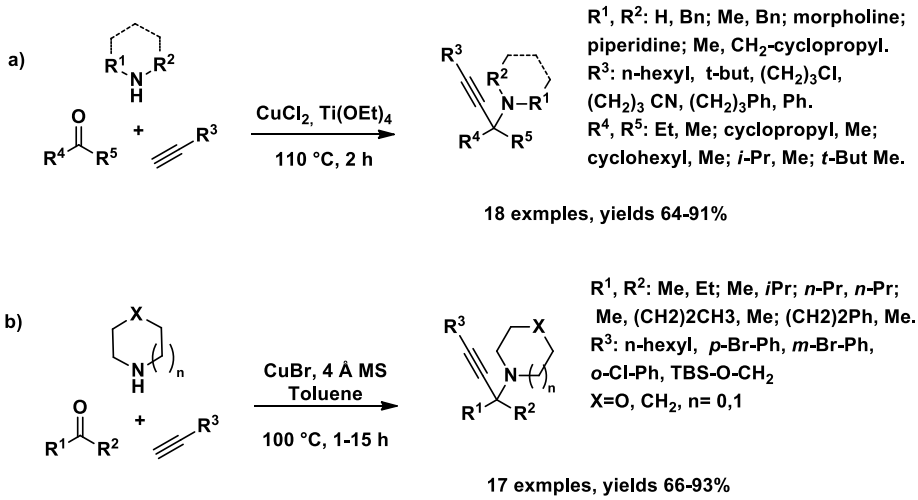
Figure 3 The role of the metal presence and of the substitution of α carbon.

Hu et al[4] found that the $AuBr_3$ is able to catalyze the KA^2reaction using several cyclic and acyclic ketones, aromatic alkynes and various secondary aliphatic cyclic and acyclic amines with satisfactory yields. (Scheme 3). This methodology has as a main limitation the nature of the alkyne, as only the aromatic ones produce good results, and the cost and stability of the catalyst as compared with the CuI.



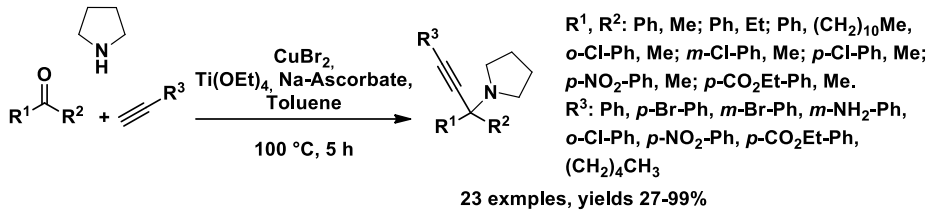
Scheme 3 Summary scheme of Hu's work.

The use of acyclic ketones proved to be hard substrates for the common methodologies. Larsen[5] and Ma[6] reported in two separate works two different catalytic methods to include acyclic ketones as substrates (Scheme 4 a e 4 b).These methodologies gave good results with several alkynes, but unfortunately they worked only with secondary amines and did not involve any aromatic or cyclic ketones. This substrate resulted less reactive as compared with the aliphatic because the electrophile carbon of their imine resulted to be less reactive for the presence of the adjacent aromatic ring.



Scheme 4 Summary scheme of Larsen's (a) and Ma's (b) works based on acyclic and aliphatic ketones.

Only in 2016 Ma[7] reported a methodology to perform the KA[2] reaction with these substrates, using a catalytic system formed by $CuBr_2$/sodium ascorbate and $Ti(OEt)_4$,giving good results and the reaction working with a broad number of aromatic ketones (Scheme 5).



Scheme 5 Summary scheme of Ma's work using acyclic aromatic ketones.

As easy to understand from all these examples, the KA[2] reaction proves to be less versatile as compared to the A[3] reaction. Despite this, this reaction gives the unique possibility of generating in one step a propargyl amine with a tetra-substituted sp^3 carbon atom. As explained in the previous chapter, the propargyl amines are interesting compounds that are involved in many applications and for this the possibility to generate different substrates remain an interesting topic. For example, tetra substituted carbon atoms bearing amines can provide much higher levels of activity than the corresponding less substituted analogues. Accordingly, fentanyl is an anesthetic that is 100 times more powerful as morphine and carfentanyl is over 10,000 stronger (Figure 4).

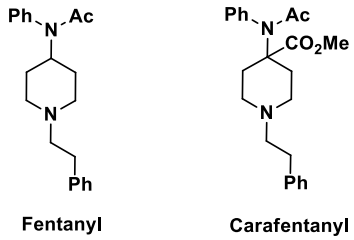
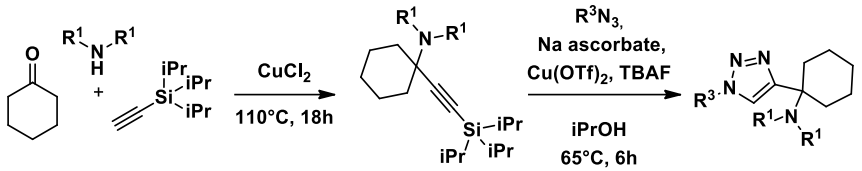


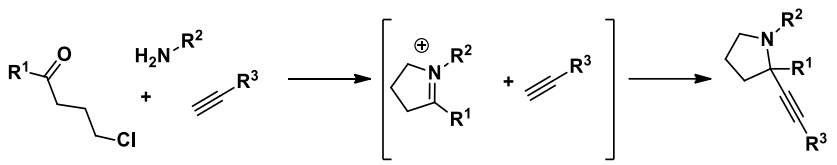
Figure 4 Structures of fentanyl and carafentanyl.

An application of this field was reported by Larsen[8] and co-workers, describing the use of alkynes present in KA[2] adducts to synthesize alpha tetra-substituted triazoles (Scheme 6). These molecules were reported as bioactive compounds for the treatment of Chagas' disease [9] and many inflammation involved in autoimmune disorders[10].



Scheme 6 Representative scheme of Ellman's work.

Another interesting application of this reaction is the synthesis of heterocyclic compounds containing a tetra substituted carbon atom. These compounds are usually hard to be synthesized, and an example of this was reported by Van Beek et al.[11]. In this work, they synthesized several pyrrolidines with a tetra substituted α carbon using the KA^2 coupling reaction as the only step. To obtain this they performed this reaction using several ω chloro-ketones, for generating a cyclic ketiminium ion in situ that evolved to the heterocyclic compound following the acetylide attacks(Scheme 7)



Scheme 7 General scheme of the synthesis of pyrrolidines with α quaternary carbon atom.

Apart from this important application the more fascinating property of this reaction appears when cyclic ketones are used as starting materials. Indeed, using building blocks containing additional functional groups present in the side chain of the amine, or functionalizing the amine with a moiety containing an additional functional group, a pairing reaction with the alkyne can produce a spirocyclic compound (Figure 5).

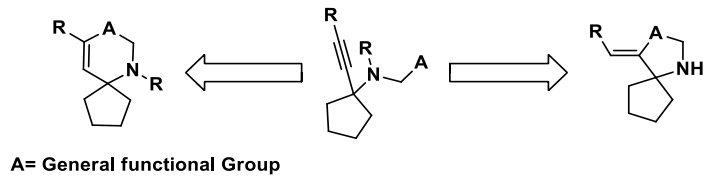


Figure 5 Representative cyclization reactions

Spiro compounds[12] are bicyclic organic compounds with comprise rings connected through one atom that present peculiar 3D structural properties,

related to their inherent rigidity. This structure moiety are present in many natural products (Figure 6).

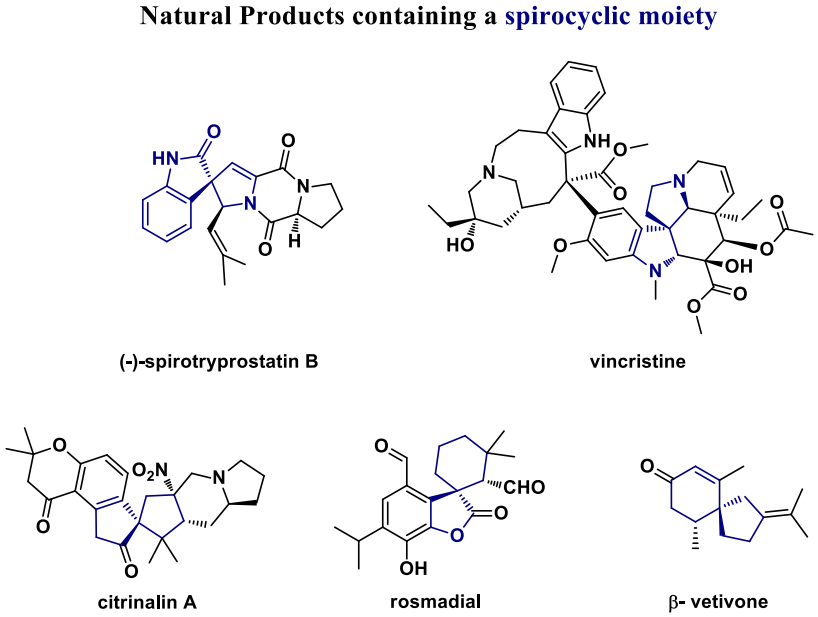


Figure 6 Representative selection of natural products containing spirocyclic moiety.

The synthesis of this moiety represents a synthetic challenge and it is an essential issue in drug discovery, as these compounds display a broad range of biological activities. These proprieties derived from intrinsic complexity and, more importantly, rigidity contribute to many spirocyclic compounds having a marked biological activity[13] (Figure 7).

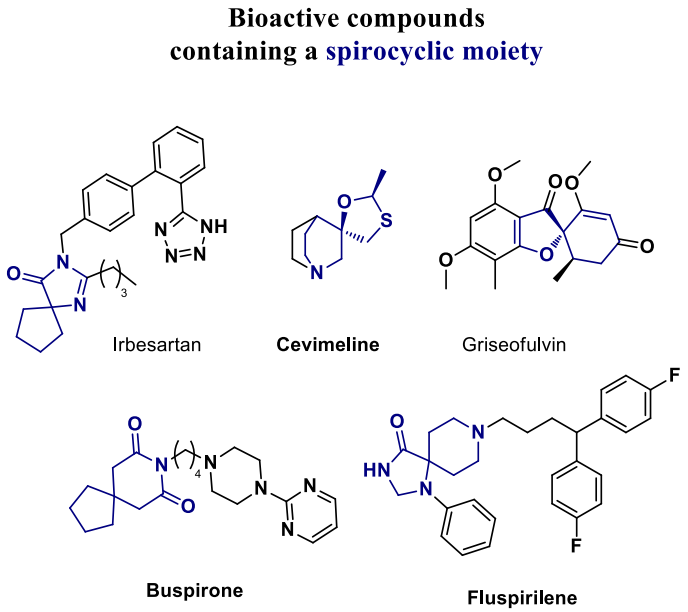
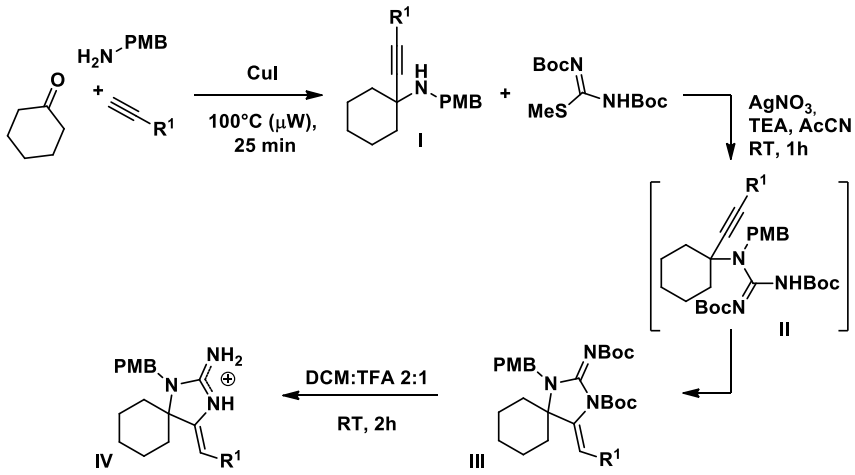


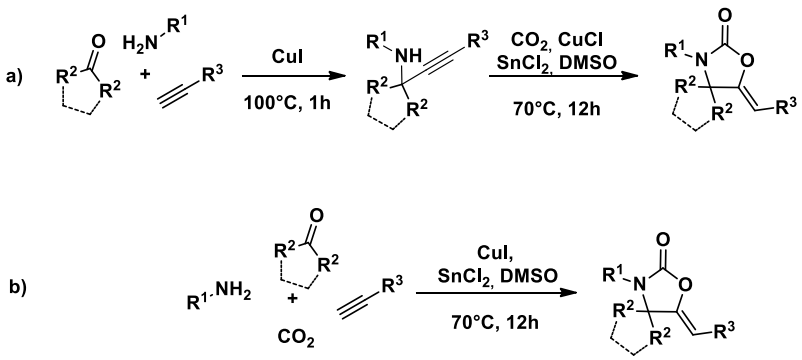
Figure 7 Representative selection of compounds with biological activity containing a spirocyclic moiety.

The first application of the KA^2 in this methodology was reported by Van der Eycken in 2011. In this work the KA^2 adduct was used to synthesize several spiro-2-aminoimidazoles[14]. Initially, the intermediate **I** was synthesized using KA^2 reaction then it was transformed directly in the bis-Boc-spiro-2-iminoimidazolines **III** by a one pot procedure that comprised installing the basic nitrogen to form, in situ, the guanidine intermediate **II**, followed by the use of the second nitrogen for the spirocyclization. The final deprotection converted **III** in the final spiro-2-aminoimidazoles **IV** (Scheme 8).



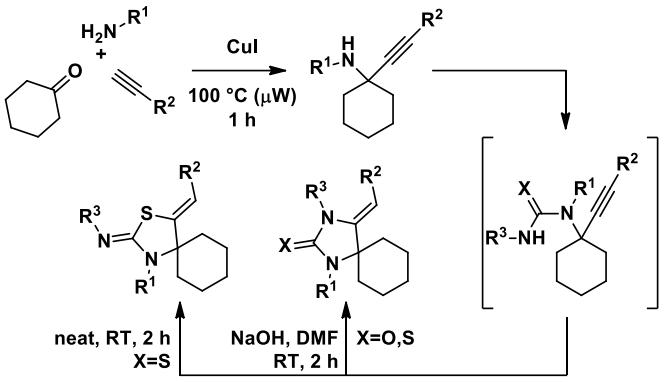
Scheme 8 General synthetic pathway for the synthesis of spiro-2-aminoimidazoles.

Jiang and co-workers[16] reported the synthesis in a single step of several spiro-oxazolidinones combining together the KA^2 reaction with the additional copper catalyzed spirocyclization, thus obtaining in this way a 4-component multicomponent reaction. To meet this issue, they performed the KA^2 reaction under CO_2 atmosphere, thus obtaining the usual coupling reaction and the additional spirocyclization reaction by incorporation of the CO_2 molecule (Scheme 9).



Scheme 9 Synthesis of spiro-oxazolidinones in a two step process (a) or one pot (b) using a 4 component multicomponent reaction.

In two different works Dethe et al.[16,17] reported the synthesis of two different hetero spirocyclic compounds from the same KA^2 adduct (Scheme 10).



Scheme 10 Diversity synthesis of spiro-thiazolidin-2-ylideneamine(top) and spiro-imidazol-2-one (X= O) spiro-imidazolidine-2-thione (X=S) (bottom).

All these approaches proved that the KA^2 is an interesting starting point for the synthesis of molecules with a high degree of structural complexity from simple starting materials. In all these examples the functional groups using for the cyclization reaction weren't install with the amines but in a post couple phase. This means that the original amine side chain didn't used as reactive group, but only as substituent for generate *Appendage diversity***,** this means using only the half of the possibility that this substrates inherently possess. Indeed, many works showed that several amines containing functional group that could be involved in the spirocyclization reaction with the alkyne are good substrates for the KA^2 reaction. The construction of a B/C/P DOS strategy using this reaction gives the opportunity not only to obtain a library of different scaffolds but also spirocyclic in nature. For this reason the application of the KA^2 reaction in a DOS B/C/P strategy and offers the unique possibility to generate many different spirocyclic compounds with a quick synthetic process.

4.2 Results and Discussion

At the beginning of our work we decided to use as the amine component the amino-alcohols with the idea of using the hydroxyl group to cyclize the KA^2 adduct with an intramolecular hydration of alkynes[18] (Figure 8).

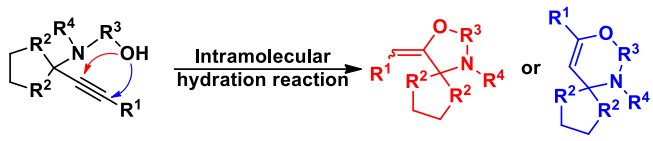
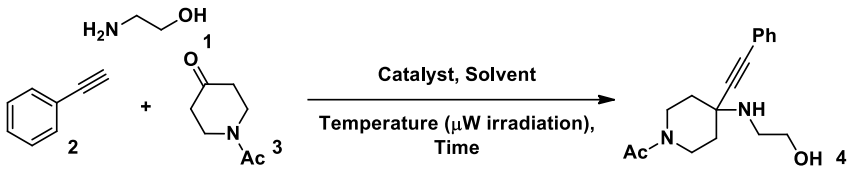


Figure 8 General hydration reaction.

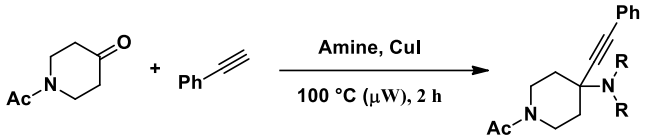
The amino alcohols[19] represent a good starting material because they have two different functional groups with a modular reactivity and also they are derived from the natural amino acid, thus they are often commercially available or easily synthesized. Similarly to the structure of the amino acid, the amino alcohol derivatives are considered privileged scaffolds in drug discovery[20]. As the first step we studied the KA^2 reaction, using aminoethanol (**1**) because of its simplicity, phenyl acetylene (**2**) because it is usually the most versatile alkyne and N-acetyl 4-piperidone (**3**) as ketone, to obtain a product with a high functional degree.

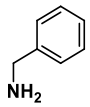
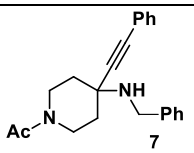
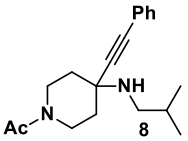
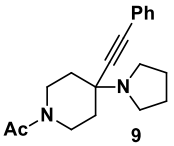
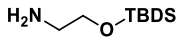
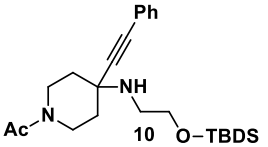
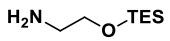
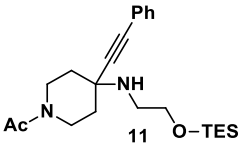


Entry	Solvent	Catalyst	Temp. (°C)	Time (h)	Yield (%)
1	DCE	CuI	100	2	12
2	DMF	CuI	100	2	9
3	Toluene	CuI	100	2	0
4	MeOH	CuI	100	2	5
5	neat	CuI	100	2	33, 7[a]
6	neat	CuBr	100	2	16
7	neat	CuCl	100	2	18
8	neat	Cu(OAc)	100	2	2
9	neat	$AgBF_4$	100	2	0
10	neat	AgOTf	100	2	0
11	neat	CuI	100	16	0[b]
12	neat	CuI	150	0.17	0

Tab.1 All the reactions were performed using aminoethanol (1.2 eq), phenyl acetylene (1,2 eq), catalyst (0.2) eq, solvent (1 mL/mmol) when used, and N-acetyl 4-piperidone (1 eq) under microwave irradiation and nitrogen atmosphere. [a] The reaction was performed in the presence of 3 Å molecular sieves (100 mg/mmol). [b] The reaction was performed by warming with an oil bath.

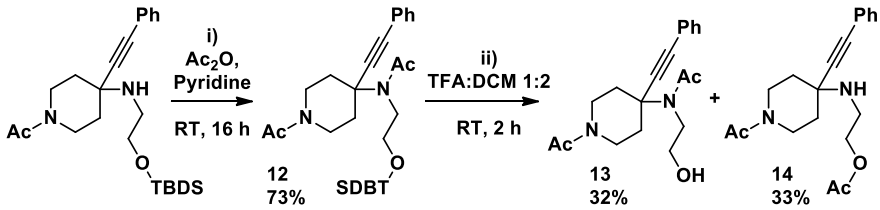
Changing the solvent (Tab.1 entry4) we found that the best condition was working under neat condition, and the best catalyst being CuI (Tab.1 entries 5-10). When we tried to change the condition increasing the time of the reaction or the temperature (Tab.1 entries 11-12) we did not obtain any product. The best condition resulted as in entry 5, but unfortunately the result was still unsatisfactory (33%). We thought that the problem could be the presence of the free hydroxyl group, and to confirm this hypothesis we tried to apply the best conditions (Tab.1 entry 5) with different amines (Tab 2).



Amine	Product	Yield (%)
	 7	78
	 8	71
	 9	88
 5	 10 O–TBDS	68
 6	 11 O–TES	63

Tab.2 All the reactions were performed using amine (1.2 eq), phenyl acetylene (1,2 eq), CuI (0.2) eq, and N-acetyl 4-piperidone (1 eq) under microwave irradiation and a nitrogen atmosphere

As a confirmation of our hypothesis we obtained satisfactory results both with unfunctionalized amines (Tab.2 products **8**-**10**), and with O-silyl protected aminoethanol (Tab.2 amines **5** and **6**), and we did not find a difference between the two protecting groups. So, we decided to continue our synthesis using compound **10** because the TBS group is usually more stable[21] and also this it can be removed not only by treatment with fluoride salt but also under acidic condition. The presence of this protecting group is useful, as well as to increase the yield of KA^2 and for don't have a selectivity problem in the acylation reaction for the amide synthesis. This is necessary for many of the common reaction conditions for the hydration of the alkynes. Thus, after finding the best substrate and conditions for the KA^2 reaction, we converted the basic amine of the compound **10** into the corresponding amide **12** thought reaction with pyridine and acetic anhydride (Scheme 11) on a satisfying yield.



Scheme 11 i) Ac_2O (4 mL/mmol), pyridine (2 mL/mmol) RT, 16 h; **ii**) TFA:DCM 1:2 (3 mL/mmol), RT 2 h.

Then, we tried to deprotect the oxygen functionality using acidic conditions, but we obtained a 1:1 mixture of the desired product **13** and of the by-product **14**, where the acetyl group migrated from the nitrogen to the oxygen (Scheme 11), as showed from the HMBC experiment where the $J^3_{C\text{-}H}$ correlation between the hydrogen atom of the CH_2 group near the oxygen and the carbonyl quaternary carbon is shown (Figure 9).

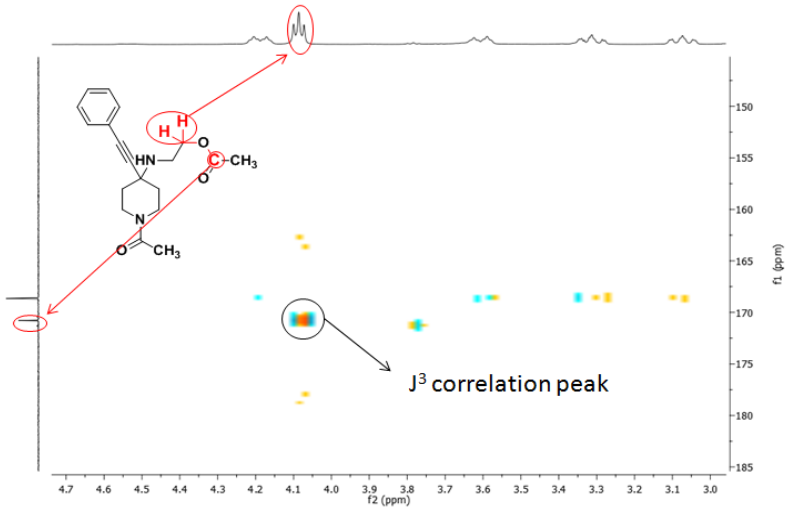
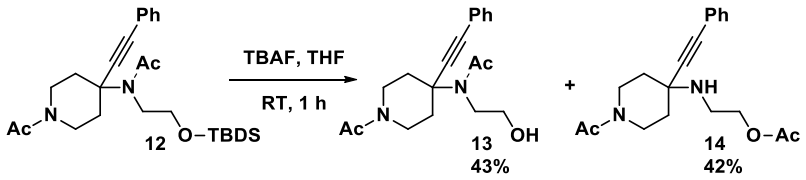


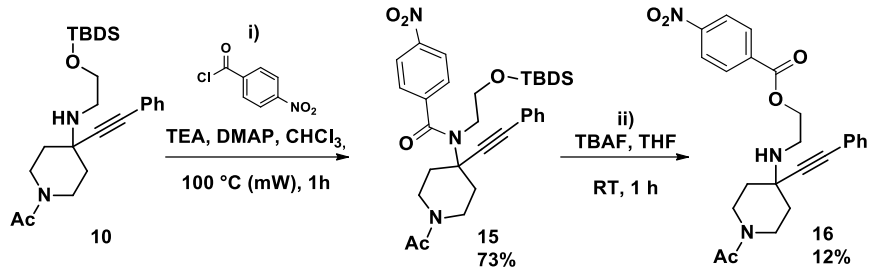
Figure 9 HMBC of the compound**14** showed a ^{3}J correlation from carbonyl carbon and the hydrogen in α position of oxygen.

This side reaction can be promoted due to many factors, such as the instability of the acetyl group, the steric hindrance close to the nitrogen atom and also due to the reaction conditions. In order to avoid this side reaction, we applied classic deprotection conditions of the silyl group with TBAF, but we still obtained the same results although with higher yield (Scheme 12).



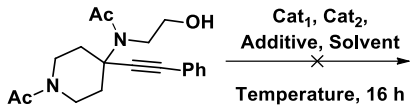
Scheme 12 TBAF 1 M in THF (1.1 eq), THF (3 mL/mmol), RT 1 h.

When we replaced the acetyl group with the more stable *p*-NO_2 benzoyl group (Scheme 13),we obtained only the by-product and with lower yield. Such data can be a proof that the steric hindrance is the major responsible for the side reaction, and with a more stable but also bulkier group the only product of the reaction is the by-product. As the steric hindrance close to the nitrogen atom was difficult to address because intrinsic in the KA^2 adduct, we discontinued the study of this pairing reaction.



Scheme 13 i) *p*-NO_2-Bz-Cl (2 eq), Triethylamine (3 eq), $CHCl_3$ (2 mL/mmol), 100°C (μW), 2h; **ii**) TBAF 1 M in THF (1.1 eq), THF (3 mL/mmol), RT 1 h.

We decided to continue our synthesis using **13** for the cyclization stage, but unfortunately despite the many reaction condition tested (Tab.3) no one of the reactions tried brought to the desired products and in every reaction only starting material was recovered. Therefore, we concluded that unfortunately this cyclization reaction is not suitable to be applied to a pairing step in a DOS strategy.



Entry	Cat. 1	Cat. 2	Additive	Solvent	Temp. (°C)
1	I_2	-	TMS	DCM	25
2	$AuCl_3$	-	K_2CO_3	DMF	25 or 100
3	$AuCl_3$	-	K_2CO_3	DMF	25 or 100
4	PPh_3AuCl	-	-	Toluene	25 or 100
5	PPh_3AuCl	AgOTf		Toluene	25 or 100
6	PPh_3AuCl	AgOTf	*p*-TsOH	Toluene	25 or 100
7	PPh_3AuCl	$AgSBF_6$	*p*-TsOH	Toluene	25 or 100
8	PPh_3AuCl	AgOTf	*p*-TsOH	EtOH	25 or 78
9	PPh_3AuCl	AgOTf	*p*-TsOH	DMF	25 or 100
10	PPh_3AuCl	AgOTf	BzOH	Toluene	25 or 100

Tab.3 13 (1 eq)Catalyst 1 (0.15 eq), Catalyst 2 (0.30 eq) additive entries (3 eq entries 1-3; 0.5 entries 6-10), solvent (20 ml/mmol).

Despite the bad results of the previous method, we continued our study to find a better functional group to be involved as a couple step of B/C/P strategy the KA^2 reaction. In order to simplify the methodology and have less possible side reactions, we chose a different pairing reaction and allylamine as a different substrate . This amine does not need any protecting group for its functional group and can be involved in the Pauson-Khand reaction[22]. This multicomponent reaction between an alkyne, an alkene and

carbon monoxide generates a cyclopentenone moiety. This structure, as stated in the previous chapter, can be considered as a privileged scaffold[23], as the structure of the final product has many functionalities that can be used for further modification to increase the complexity and the diversity of the spirocyclic adducts obtained. (Figure 10).

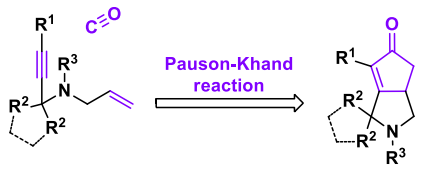
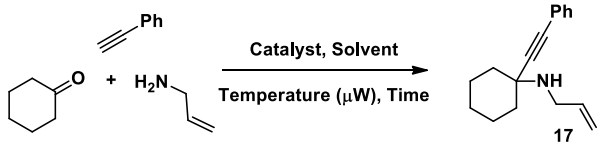


Figure 10 General Pauson-Khand spirocyclization.

In the first stage of our study we decided to use the simplest system to avoid any possible side reactions, and focused our attention only on the synthetic pathway. For this reason, we chose allylamine phenylacetylene and cyclo-hexanone as first substrates.

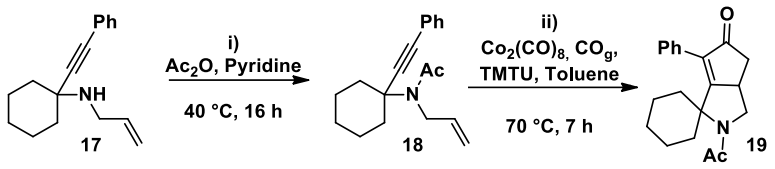


Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	CuI	Toluene	100		50[a]
2	CuI	MeOH	100	2	62[a]
3	CuI	THF	100	2	43[a]
4	CuI	-	100	2	79[a],82[b]
5	CuBr	-	100	2	72[a]
6	$CuBr_2$	-	100	2	35[a]
7	AgOTf	-	100	2	8[a]
8	CuI	-	100	2	73[a]
9	CuI	-	60[c]	4	11[a]
10	CuI	-	150	0.5	28[a]

Tab.4 All the reactions were performed using a allylamine(1.2 eq), phenylacetylene, solvent when it was used (2 mL/mmol), (1,2 eq), catalyst (0.2) eq, and cyclo-hexanone (1 eq) under microwave irradiation and nitrogen atmosphere; [a] the yield was determined by HPLC; [b] yield was calculated on isolated product; [c] the reaction was warmed using oil bath.

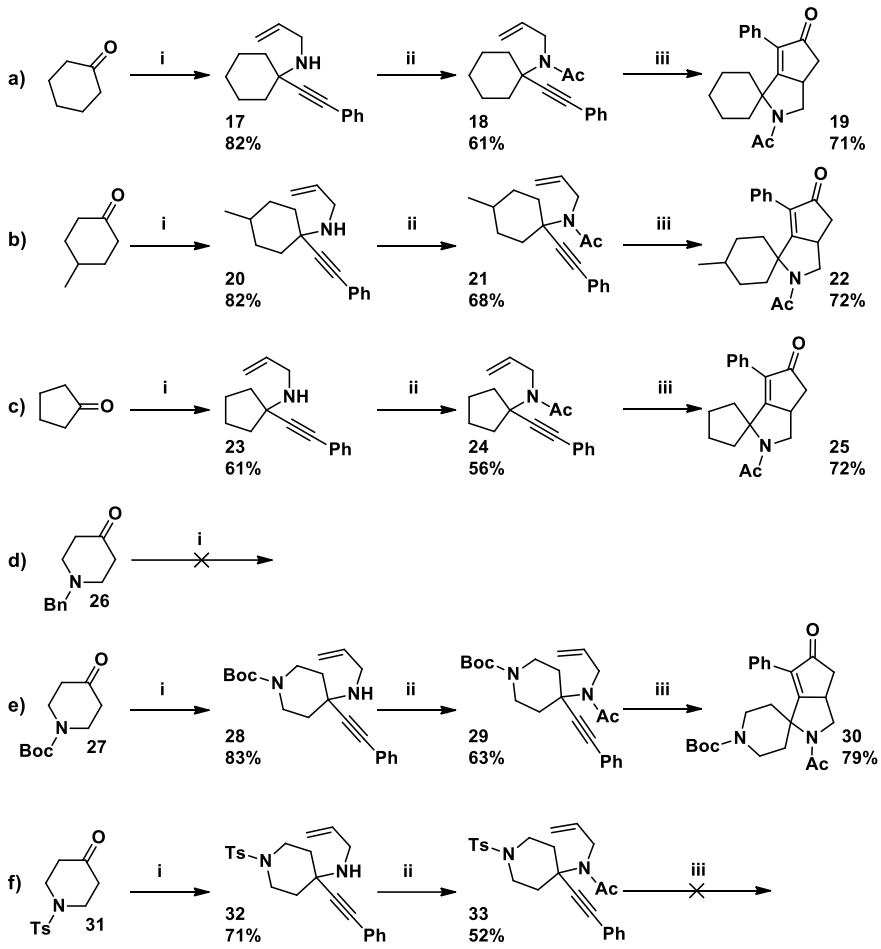
The reaction optimization, as expected, showed that the best condition is the same of the previous reaction (Tab.4). In this case the yields are generally higher. Also in this case, before the Pauson-Khand reaction, we converted the amine to an amide to prevent possible side interactions between the lone pair of the nitrogen and the catalytic system of the Pauson-Khand reaction.

This reaction was performed as previously, giving satisfying results. Compound **18** was converted to the spirocyclic compound **19** using the common condition of the reaction and using carbon monoxide at atmospheric pressure (Scheme 14).



Scheme 14 i) Ac_2O (4 mL/mmol), pyridine (2 mL/mmol) RT, 16 h; **ii**) $Co_2(CO)_8$ (0.15 eq), tetramethylthiourea (0.6 eq), toluene (20 mL/mmol), CO (1 atm), 70 °C, 7 h.

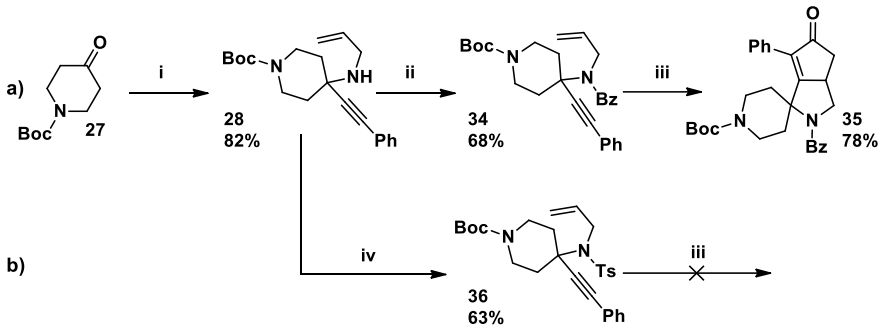
In this case the reactions worked with good results and with satisfying yields, so after this we started to study the scope of our synthetic pathway by changing the ketones.



Scheme 1513 i) Allylamine (1.2 eq), phenylacetylene (1.2 eq), CuI (0.2 eq) ketone (1 eq), 100 °C (μW), 2 h; **ii)** Ac_2O (4 mL/mmol), pyridine (2 mL/mmol) 40 °C, 16 h; **iii)** $Co_2(CO)_8$ (0.1 eq), TMTU (0.6 eq), CO_g (1 atm), 70°C 7 h.

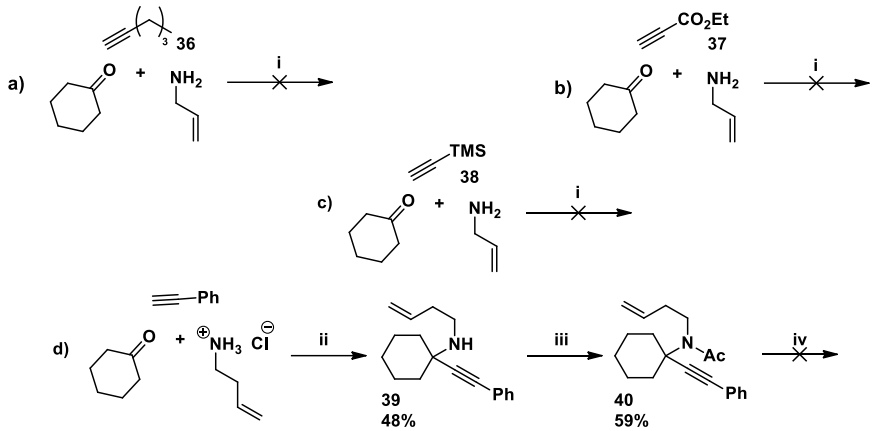
The cyclic alkyl ketones did not present a critical point as the addition of substituents (Scheme 15 b) or the variation of the ring size (Scheme 15 c)did not influence the results. When ketones containing a heteroatom were used, the KA[2] reaction gave satisfying results when the amine was converted into a carbamate (Figure 25 e) or into a sulfonamide (Scheme 15 f) but, in agreement with the literature[2], it failed in presence of a basic nitrogen atom (Scheme 15 d). The subsequent conversion of the amines (**28**, **32**) to the corresponding amide (**29**, **33**) did not show any critical issue but the Pauson-Khand failed for the substrate with the tosyl group **33** (Scheme 15 f), probably due to incompatibility of the sulfonamide moiety with the

Pauson-Khand catalytic system. By using the compound **27** as starting material and changing the acylating reagent for the basic nitrogen atom, the Pauson-Khand reaction with the resulting products still failed when the tosyl group was involved (Scheme 16 b).



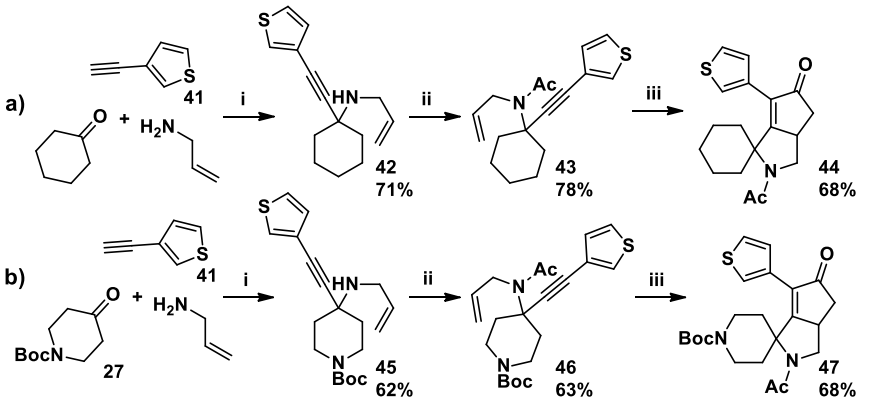
Scheme 16 i) Allylamine (1.2 eq), phenylacetylene (1.2 eq), CuI (0.2 eq), 27 (1 eq), 100 °C (μW), 2 h; **ii)**BzCl, (4 eq), pyridine (2 mL/mmol) 40 °C, 16 h; **iii)** $Co_2(CO)_8$ (0.1 eq), TMTU (0.6 eq), CO_g (1 atm), 70°C 7 h;**iv)**TsCl, (4 eq), pyridine (2 mL/mmol) 40 °C, 16 h

The use of non aromatic alkynes *n*-hexyne, **37**, **38** (Scheme 17 a, b, c) was a problem because the KA^2 reaction did not work with them, and this could be predicted as literature shows that the KA^2 catalytic systems are, usually, not so versatile when the nature of substrates changes. The KA^2 reaction with homo-allylamine (Scheme 17 d) worked well, similarly to the protection of the nitrogen atom, but the Pauson-Khand reaction failed to proceed, and only a messy mixture of by products and starting material were recovered, probably due to the instability of the resulting spirocyclic product.



Scheme 17 i) Allylamine (1.2 eq), alkyne (1.2 eq), CuI (0.2 eq) cyclo-hexanone (1eq), 100 °C (μW), 2 h; **ii)** homo-allylamine (1.2 eq), alkyne (1.2 eq), Triethylamine (1.4 eq) CuI (0.2 eq) cyclo-hexanone (1eq), 100 °C (μW), **iii)** Ac_2O (4 mL/mmol), pyridine (2 mL/mmol) 40 °C, 16 h; **iv)** $Co_2(CO)_8$ (0.1 eq), TMTU (0.6 eq), CO_g (1 atm), 70°C 7 h.

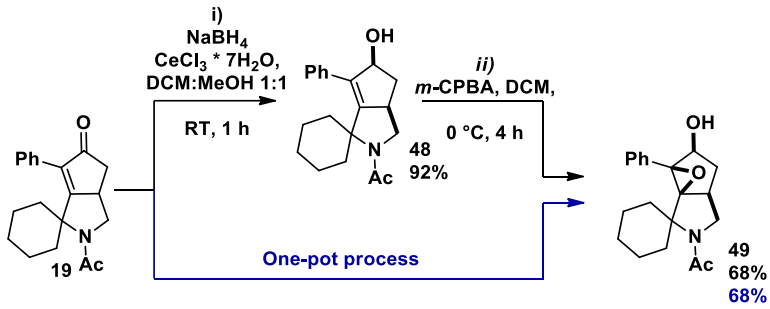
Instead, the use of heteroaromatic alkynes such as **41** did not raise any problem, also when the ketone contained a heteroatom, and the compounds **44** and **47** were obtained with satisfying yields(Scheme 18).



Scheme 18 i) Allylamine (1.2 eq), **41** (1.2 eq), CuI (0.2 eq), 27 (1 eq) 100 °C (μW), 2 h; **ii)**BzCl, (4 eq), pyridine (2 mL/mmol) 40 °C, 16 h; **iii)** $Co_2(CO)_8$ (0.1 eq), TMTU (0.6 eq), CO_g (1 atm), 70°C 7 h; BzCl, (4 eq), pyridine (2 mL/mmol) 40 °C, 16 h

In order to increase the number of generated structures and their complexity, we modified the structure of the spirocyclic compound **19**,by applying representative reactions on the cyclo pent-2-en-1-one motif. Initially, we performed the chemoselective carbonyl reduction to obtain the corresponding allylic alcohol derivative **48** in 92% yield. To obtain a single

diastereoisomer from all the possible variants, we performed the reaction using the Luche's reduction conditions[24], employing $NaBH_4$ and $CeCl_3$ in MeOH-DCM (Scheme 19). This allowed us to obtain the selective formation of the *syn* alcohol as a consequence of the formation of the equatorial alcohol favored by reduced *gauche* interactions[25]. Then, we used the contemporary presence of the free hydroxyl group and the alkene to perform the epoxidation of the double bond, the stereocontrol being directed by the hydroxy group and using *m*-chloro-perbenzoicacid (*m*-CPBA) we obtained the compound **49** in 68% yield. When this process was performed in one pot, the compound **49** was afforded in a total yield of 68 %.



Scheme 19 i) $CeCl_3$* 7 H_2O (2 eq), $NaBH_4$ (2 eq), DMC:MeOH 1:1 (20 mL/mmol), **ii)** *m*-CPBA (1 eq) DCM (6.5 mL/mmol), 0 °C, 4 h.

To assign the structure of compound **48** we used a series of detailed 1D and 2D NMR. NOESY-1D (Figure 11) experiments carried out with a mixing time of 500 ms allowed to identify the unique rotamer possessing a *Z* geometry of the amide bond, as evinced by NOE interaction between H_d and the methyl group.

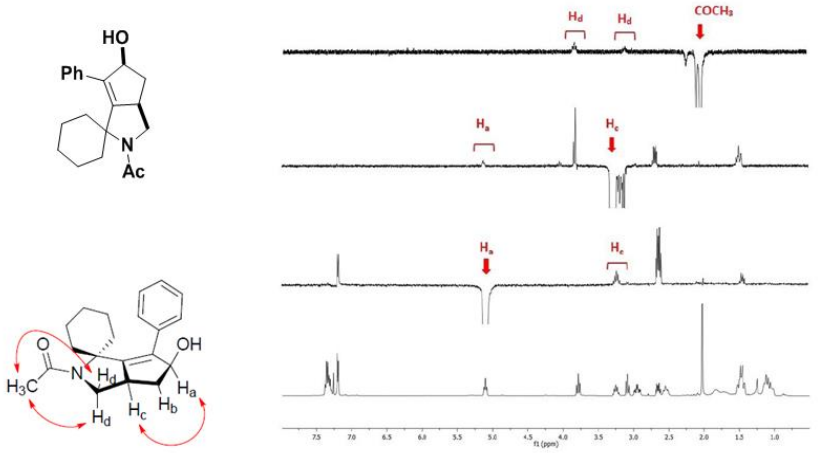


Figure 11 Selection of NOEs spectra of the compound **48**.

The *cis* relationship between the OH group and the pyrrolidine ring, resulting from the chemo- and stereoselective *syn* reduction of the carbonyl group, was evinced by NOESY-1D experiments showing intense NOE effects between H_c and H_a protons, as also shown in NOESY 2D spectrum (Figure 12).

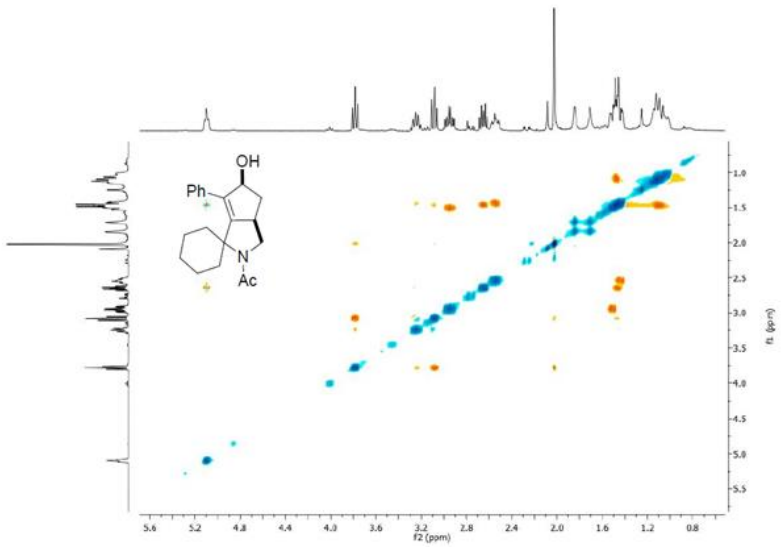
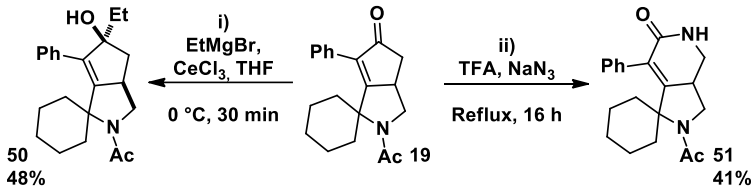


Figure 12 2-D NOESY of compound **48**.

Successively we also obtained two other derivatives. Starting from compound **19** we synthesized the tertiary allylic alcohol [26] **50** by a reaction using ethyl magnesium bromide and $CeCl_3$ in 48% yield. Applying the Schmidt[27] reaction to the same precursor by treatment with sodium azide in TFA we obtained the conversion to the corresponding six-member ring lactam **51** in 41% yield (Scheme 20).



Scheme 20 i) Compound **19** (1 eq), EtMgBr3M in Et_2O (5 eq), THF (6 mL/mmol), 0 °C, 30 min; **ii)** NaN_3 (1.8 eq), TFA (5 mL/mmol) reflux, 16 h.

4.3 Conclusions

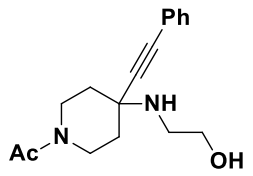
In conclusion of this chapter we proved that also the KA^2 represents a useful reaction to be applied in B/C/P strategy to synthesize a library of highly functionalized spirocyclic compounds. Indeed, this reaction showed a good reactivity for several amines, ketones, and aromatic alkynes and this is an essential requirement for a reaction to be applied as couple step in a DOS strategy. Unfortunately, from the two pairing reactions that we tested here, only the Pauson-Khand reaction gave the desired spirocyclic compounds, but the products of this synthetic pathway proved to be enough functionalized to be a further starting point to obtain other different compounds. The future development of this project will be oriented to increment the number of pairing reactions using different amines or appending side chains containing different functional groups for the application of other different reactions to obtain a larger DOS library with a B/C/P approach based on KA^2 reaction.

4.4 Experimental part

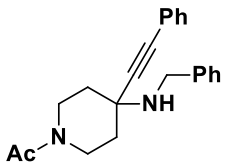
General. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (^{1}H: 400 MHz) or Varian Inova (^{1}H: 400 MHz),13 C spectra were recovered on a Varian Mercury 400 (^{13}C: 100 MHz) or Varian Inova (^{13}C: 400 MHz) or in a Varian Gemini 200 (^{13}C: 50 MHz). The chemical shifts (δ) and coupling constants (J) are expressed in parts per million (ppm) and hertz (Hz), respectively. Chemical shifts are reported relative to TMS (^{1}H: δ = 0.00 ppm) and $CDCl_3$ (^{13}C: δ = 77.0 ppm). Flash column chromatography (FCC) purifications were performed manually using glass columns with Merck silica gel (0.040–0.063 mm). TLC analyses were performed on Merck silica gel 60 F254 plates. Elemental analyses were performed on a Perkin Elmer C, H, N analyzer. ESI-MS spectra were recorded on a Thermo Scientific LCQ fleet ion-trap double quadrupole mass spectrometer using electrospray (ES^{+}) ionization techniques. All commercially available reagents and solvents were used as received, unless otherwise specified.All chemical shifts are reported in parts per million (δ) referenced to residual non deuterated solvent.

General Procedure (A) for the KA2 coupling reaction. CuI (0.2 eq) was added in a dry microwave flask under nitrogen flow. Then Ketone (1eq), phenylacetylene (1.2 eq) and amine (1.2 eq) were added under nitrogen flow. Successively, the mixture was heated under microwave irradiation at 100°C for 2h. Then, EtOAc was added and the organic phase was washed with 5% NH_4OH (3 x 20 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the indicated solvent mixture as eluant.

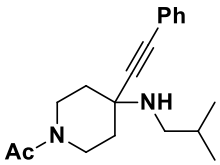
General Procedure (B) for the Amine Protection. The indicate KA2 product was dissolved in pyridine (2 mL/mmol) and the reaction mixture was kept to 0°C and acetic anhydride(4mL/mmol) was added dropwise, after the addition the reaction mixture was heated at 40 °C for 16h. Then, EtOAc was added and the organic phase was washed with HCl 1M (3 x 20 mL), $Na_2CO_{3\ sat}$ (3 x 20 mL) and brine The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the indicated solvent mixture as eluant.



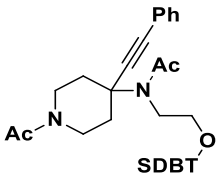
1-(4-((2-hydroxyethyl)amino)-4-(phenylethynyl)piperidin-1-yl)ethanone (4) Compound **4** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (123 µL, 1 mmol), phenylacetylene (131 µL, 1.2 mmol), CuI (38 mg, 0.2mmol) and ethanolamine (73 µL, 1.2mmol). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **4** (94 mg) as a yellow oil in 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 2H), 7.34 – 7.22 (m, 3H), 4.44 – 4.29 (m, 1H), 3.77 – 3.62 (m, 3H), 3.53 – 3.34 (m, 1H), 3.18 – 3.03 (m, 1H), 3.02 – 2.87 (m, 2H), 2.41 (s, br, 1H), 2.07 (s, 3H), 2.00 – 1.88 (m, 3H), 1.59 (dtd, *J* = 17.0, 12.6, 4.0 Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9, 131.7, 128.4, 122.7, 90.6, 86.0, 61.9, 53.5, 45.2, 43.5, 38.6, 38.0, 37.3, 21.4. MS (ESI) *m*/*z*(%): 287.16 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{17}H_{22}N_2O_2$ C 71.30%; H 7.74 %; N 9.78%; O 11.17%, found C 71.52%, H 7.63%, N 9.80%, O 11.05%.



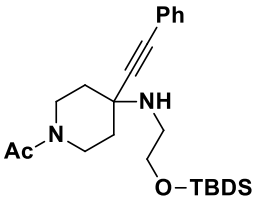
1-(4-(benzylamino)-4-(phenylethynyl)piperidin-1-yl)ethanone (7): Compound **7** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (247 µL, 2 mmol), phenylacetylene (260 µL, 2.4 mmol), CuI (77 mg, 0.4 mmol) and benzylamine (265 µL, 2.4 mmol). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **7** (259 mg) as a yellow oil in 78% yield. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.52 – 7.22 (m, 10H), 4.33 (dt, *J* = 8.5, 4.0 Hz, 1H), 3.99 (s, 2H), 3.83 – 3.70 (m, 1H), 3.48 (ddd, *J* = 13.7, 10.8, 2.9 Hz, 1H), 3.26 (ddd, *J* = 13.6, 8.6, 3.0 Hz, 1H), 2.10 (s, 3H), 2.07 – 1.89 (m, 3H), 1.77 - 1.66 (m, 2H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 185.2, 168.9, 140.0, 131.7, 128.6, 128.5, 128.4, 128.3, 127.2, 122.7, 90.9, 86.0, 77.4, 77.0, 76.7, 54.0, 48.0, 43.3, 38.4, 37.8, 37.0, 21.5. MS (ESI) *m*/*z*(%): 355.23 [(M + Na)$^+$, 100]. Anal. Calcd. for $C_{22}H_{24}N_2O$, C 79.48; H 7.28; N, 8.43; O 4.81 found C 79.31, H 7.25, N 8.52, O 4.92.



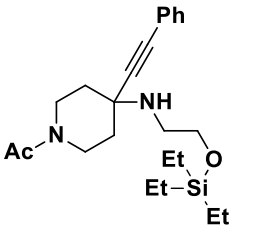
1-(4-(isobutylamino)-4-(phenylethynyl)piperidin-1-yl)ethanone (8): Compound **9** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (123 µL, 1 mmol), phenylacetylene (131 µL, 1.2 mmol), CuI (38 mg, 0.2mmol) and isobuthylamine (120 µL, 1.2mmol). The crude product was purified by flash chromatography with 2:1 hexane-Et_2O as eluant ,to give **8** (211 mg) as a yellow oil in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.32 – 7.26 (m, 3H), 4.27 (dt, *J* = 13.8, 4.0 Hz, 1H), 3.71 (dt, *J* = 13.6, 3.9 Hz, 1H), 3.43 (ddd, *J* = 13.6, 10.7, 2.9 Hz, 1H), 3.22 (ddd, *J* = 13.6, 10.8, 3.0 Hz, 1H), 2.63 – 2.53 (m, 2H), 2.08 (s, 3H), 1.97 – 1.86 (m, 2H), 1.74 – 1.54 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 131.7, 128.3, 128.2, 123.0, 91.5, 85.4, 53.4, 51.3, 43.4, 38.4, 37.9, 37.2, 29.0, 21.4, 20.9. MS (ESI) *m*/*z*(%): 299.12 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{19}H_{26}N_2O$ C, 76.47; H, 8.78; N, 9.39; O 5.36, found C 76.52, H 8.65, N 9.30, O 5.53 .



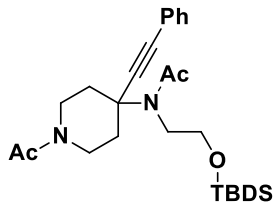
1-(4-(phenylethynyl)-4-(pyrrolidin-1-yl)piperidin-1-yl)ethanone (9) Compound **9** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (184 µL, 1.5 mmol), phenylacetylene (200 µL, 1.8 mmol), CuI (57 mg, 0.3 mmol) and pyrrolidine (150 µL, 1.8 mmol). The crude product was purified by flash chromatography with 3:2 hexane-EtOAc as eluant ,to give **9** (258 mg) as a yellow oil in 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 2H), 7.35 – 7.26 (m, 3H), 4.35 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 3.50 – 3.38 (m, 1H), 3.23 – 3.09 (m, 1H), 2.81- 2.76 (m, 2H), 2.08 (s, 3H), 2.04 – 1.93 (m, 2H), 1.84 – 1.65 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 131.8, 128.3, 128.2, 122.8, 87.88, 87.4, 58.0, 47.1, 43.3, 38.4, 37.7, 36.9, 23.5, 21.4. MS (ESI) *m*/*z*(%): 319.12 [$(M + Na)^+$, 100]. Anal. Calcd. for $C_{19}H_{24}N_2O$ C 76.99; H 8.16; N 9.45; O 5.40 found C 77.12; H 8.01 ; N 9.22 ; O 5.65.



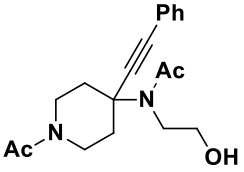
1-(4-((2-((tert-butyldimethylsilyl)oxy)ethyl)amino)-4-(phenylethynyl)piperidin-1-yl)ethanone (10): Compound **10** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (160 µL, 1.3 mmol), phenylacetylene (208 µL, 1.87 mmol), CuI (50 mg, 0.26 mmol) and **5** (200 mg, 1.87 mmol). The crude product was purified by flash chromatography with 3:1 hexane-Et_2O as eluant ,to give **10** (353 mg) as a yellow oil in 68% yield. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.47 – 7.35 (m, 2H), 7.35 – 7.24 (m, 3H), 4.46 – 4.25 (m, 1H), 3.81 – 3.68 (m, 2H), 3.45 (ddd, *J* = 13.8, 11.2, 2.9 Hz, 1H), 3.17 (ddd, *J* = 13.8, 11.2, 2.9 Hz, 1H), 2.89 (dd, *J* = 10.8, 5.9 Hz, 2H), 2.09 (s, 4H), 2.08 – 1.78 (m, 2H), 1.67 - 1.55 (m, , 2H), 0.93 – 0.83 (m, 9H), 0.13 – -0.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 131.6, 128.3, 128.2, 122.8, 90.9, 85.7, 62.5, 53.3, 45.3, 43.4, 38.5, 38.0, 37.1, 25.9, 21.5, 18.3, -5.3. MS (ESI) *m*/*z*(%): 422.99 [(M + Na)$^+$, 100]. Anal Calcd. for $C_{23}H_{36}N_2O_2Si$ C 68.95; H 9.06; N 6.99; O 7.99; Si 7.01% found C 68.65; H 9.12; N 7.11; O 7.58; Si 7.54



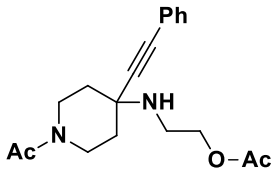
1-(4-(phenylethynyl)-4-((2-((triethylsilyl)oxy)ethyl)amino)piperidin-1-yl)ethanone (11): Compound **11** was obtained following the general procedure (A) using N-Ac-4-piperidone (**3**) (300 µL, 2.46 mmol), phenylacetylene (320 µL, 2.96 mmol), CuI (95 mg, 0.5 mmol) and **6** (320 mg, 2.96 mmol). The crude product was purified by flash chromatography with 3:1 hexane-Et_2O as eluant ,to give **11** (619 mg) as a yellow oil in 63% yield. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.43 – 7.37 (m, 2H), 7.33 – 7.27 (m, 3H), 4.37 (dt, *J* = 13.7, 3.7 Hz, 1H), 3.88 – 3.71 (m, 3H), 3.46 (ddd, *J* = 13.8, 9.6, 2.9 Hz, 1H), 3.25 – 3.11 (m, 1H), 2.91 (dd, *J* = 13.7, 8.6 Hz, 2H), 1.99 - 1.93 (m, 2H), 1.76 – 1.51 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 1H), 0.60 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 168.8, 139.8, 131.6, 128.8, 128.3, 128.2, 122.8, 91.4, 85.9, 62.2, 53.4, 45.3, 43.4, 38.5, 37.9, 37.1, 21.5, 6.8, 4.4. . MS (ESI) *m*/*z*(%): 400.05 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{23}H_{36}N_2O_2Si$ C 68.95; H 9.06; N 6.99; O 7.99; Si 7.01%; found C 69.11; H 9.13; N 7.05; O 8.12; Si 6.59



N-(1-acetyl-4-(phenylethynyl)piperidin-4-yl)-N-(2-((tert-butyldimethylsilyl)oxy)ethyl)acetamide (12): Compound **12** was obtained following the general procedure (B) using compound 10 (200 mg, 0.5 mmol), pyridine (1 mL) and acetic anhydride (2 mL). The crude product was purified by flash chromatography with 4:1 hexane-EtOAc as eluant ,to give **12** (161 mg) as a yellow oil in 73% yield. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.46 – 7.39 (m, 2H), 7.37 – 7.27 (m, 3H), 4.75 – 4.57 (m, 1H), 3.85 – 3.71 (m, 3H), 3.49 (tt, *J* = 14.2, 7.1 Hz, 1H), 3.08 – 2.75 (m, 4H), 2.22 (s, 3H), 2.09 (s, 3H), 2.02 – 1.74 (m, 4H), 0.87 (m, 9 H), 0.04 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 168.7, 131.5, 128.7, 128.4, 122.2, 89.1, 88.2, 62.7, 59.6, 50.0, 44.2, 39.2, 34.4, 33.9, 25.9, 25.8, 25.5, 21.4, 18.2, -5.6. MS (ESI) *m*/*z*(%):443.15 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{25}H_{38}N_2O_3Si$ $C_{25}H_{38}N_2O_3Si$ C 67.83; H 8.65; N 6.33; O 10.84; Si, 6.34 found C 67.58; H 9.12 ; N 6.02; O 10.26; Si 7.02 .

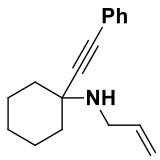


N-(1-acetyl-4-(phenylethynyl)piperidin-4-yl)-N-(2-hydroxyethyl)acetamide (13): To a dry round bottom flask containing **12** (161 mg, 0.37 mmol) atmosphere was added at 0 °C dry THF (1.11 mL) and 1 M TBAF solution (410 µL, 0.41 mmol) in THF under nitrogen flow. The reaction mixture was warm to RT and stirred for 1 h then $NaHCO_3$ (30 mL) satured solution was added. The acqueos solution was extracted with AcOEt (3 x 20 mL) and the collection of organic phases were mixed, washed with BRINE (30 mL). The resulting organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture 3:1 of hexane: Et_2O to give the compound **13** (52 mg) in 43% yield and the side product **14** (50 mg) in 42% of yield. Characterization of compound **13** : ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.41 – 7.33 (m, 2H), 7.33 – 7.20 (m, 3H), 4.54 (d, *J* = 13.5 Hz, 1H), 3.87 – 3.68 (m, 3H), 3.43 (td, *J* = 13.4, 2.5 Hz, 1H), 2.94 (td, *J* = 13.1, 2.3 Hz, 1H), 2.69 (dtd, *J* = 38.5, 12.4, 3.8 Hz, 2H), 2.17 (s, 3H), 2.08 – 1.95 (m, 2H), 2.02 (s, 3H) 1.87 (dd, *J* = 12.6, 1.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 169.1, 131.5, 128.8, 128.4, 122.0, 89.0, 88.0, 61.8, 59.2, 53.5, 49.6, 44.2, 39.3, 34.5, 34.0, 25.3, 21.3. MS (ESI) *m*/*z*(%): 319.19 [(M + H)$^+$, 100]. Anal Calcd for $C_{19}H_{24}N_2O_3$ C 69.49; H 7.37; N 8.53; O 14.62 found C 71.02; H 6.89 ; N 9.21; O 12.88.

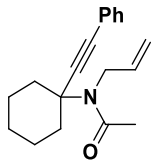


2-((1-acetyl-4-(phenylethynyl)piperidin-4-yl)amino)ethyl acetate (14): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 2H), 7.22 – 7.11 (m, 3H), 4.23 – 4.15 (m, 1H), 4.09 (t, *J* = 5.5 Hz, 2H), 3.59 (dd, *J* = 26.1, 16.2 Hz, 1H), 3.39 – 3.22 (m, 1H), 3.14 – 3.00 (m, 1H), 2.94 (t, *J* =, 5.7 Hz, 2H), 1.96 (s, 3H), 1.93 (s, 2H), 1.88 – 1.75 (m, 2H), 1.65 – 1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 168.6, 131.5, 128.2, 128.2, 122.6, 90.6, 85.7, 64.6, 53.5, 53.2, 43.2, 42.0, 38.3, 37.7, 36.9, 21.3, 20.8. MS (ESI) *m*/*z*(%): 319.21 [$(M + H)^+$, 100]. Anal Calcd for $C_{19}H_{24}N_2O_3$ C 69.49; H 7.37; N 8.53; O 14.62 found C 68.87; H 7.45; N 8.97; O 14.71.

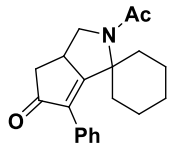
General procedure for the Pauson-Khand (C) reaction. In a dry round bottom flask under nitrogen flow was added $Co_2(CO)_8$ (0,1 eq), N,N, N',N'-tetramethyl-thiourea (0,6 eq) and a solution of the indicate enyne compound (1 eq) in dry toluene (20 mL/mmol), after the addition the reaction mixture was kept under CO atmosphere and stirred at 70°C and monitored by TLC until the startin material was over. Then the mixture was filtered on Celite and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the indicated solvent mixture as eluant.



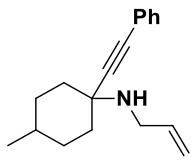
N-allyl-1-(phenylethynyl)cyclohexanamine: Compound **17** was obtained following the general procedure (A) using ciclo-hexanone (235 µL, 2.28 mmol), phenylacetylene (300 µL, 2.73 mmol), CuI (86 mg) and allylamine (200 µL, 273 mL). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **17** (446 mg) as a yellow oil in 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.35 – 7.27 (m, 3H), 6.00 (ddt, *J* = 16.3, 10.2, 6.1 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.46 (d, *J* = 6.1 Hz, 2H), 1.96 (d, *J* = 13.0 Hz, 2H), 1.82 – 1.57 (m, 5H), 1.57 – 1.38 (m, 4H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3(d), 131.6(d), 128.2(d), 127.7(d), 123.6(s), 115.7(t), 93.2(s), 84.8(s), 55.0(s), 46.3(t), 38.2(t), 25.9(t), 23.1(t) ppm. MS (ESI) *m*/*z*(%): 240.12 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84; N, 5.85. Found: C, 85.75; H, 8.91; N, 5.79



N-allyl-N-(1-(phenylethynyl)cyclohexyl)acetamide: Compound **18** was obtained following the general procedure (B) using compound **17** (446 mg, 1.86 mmol), pyridine (3.72 mL) and acetic anhydride (7.44 mL). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **18** (318 mg) as a yellow oil in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.35 – 7.26 (m, 3H), 6.00 – 5.85 (m, 1H), 5.28 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.31 – 4.20 (m, 2H), 2.55 (ps, 2H), 2.15 (s, 3H), 2.00 (d, *J* = 11.8 Hz, 2H), 1.88 – 1.59 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4(s), 135.4(d), 131.5(d), 128.2(d), 128.1(d), 123.2(s), 115.9(t), 90.5(s), 87.7(s), 49.9(t), 34.7(t), 25.2(t), 24.9(q), 24.1(t) ppm. . MS (ESI) *m*/*z*(%): 304.12 [$(M + Na)^+$, 100].].Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.19; H, 8.30; N, 4.89.

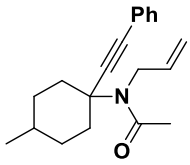


2'-acetyl-6'-phenyl-3a',4'-dihydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-5'(3'H)-one (19): Compound **19** was obtained following the general procedure (C) using compound 18 (318 mg, 1.13 mmol), toluene (22.6 mL) $Co_2(CO)_8$ (38 mg, 0.11 mmol), N, N, N', N' - tetramethyl - thiourea (87 mg 0.66 mmol). The reaction mixture was heated for 7 h and the crude product was purified by flash chromatography with EtOAc as eluant ,to give **19** (240 mg) as a yellow oil in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.31 (m, 3H), 7.11 (dt, *J* = 4.1, 2.3 Hz, 2H), 4.02 (t, *J* = 9.0 Hz, 1H),3.50 - 3.43 (m, 1H), 3.22 – 3.08 (m, 1H), 2.97 (td, *J* = 13.7, 6.0 Hz, 1H), 2.85 – 2.73 (m, 1H), 2.77 (dd, *J* = 18.3, 6.6 Hz, 1H) 2.28 (dd, *J* = 18.3, 3.3 Hz, 1H), 2.10 (s, 3H), 1.67 – 1.53 (m, 4H), 1.30 – 1.07 (m, 4H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.1(s), 177.8(s), 168.9(s), 139.1(s), 129.2(s), 128.7(d), 79.3(s), 65.1(d), 53.2(t), 39.6(t), 38.6t), 31.6(t), 29.1(q), 28.5(t), 24.8(t) ppm. MS (ESI) *m*/*z*(%): 332.06 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 78.01; H, 7.54; N, 4.46.

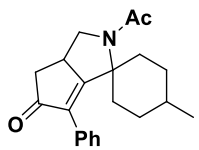


N-allyl-4-methyl-1-(phenylethynyl)cyclohexanamine (20): Compound **20** was obtained following the general procedure (A) using 4- methyl-ciclo-hexanone (200 µL, 1.63 mmol), phenylacetylene (214 µL, 1.95 mmol), CuI (60 mg, 0.32 mmol) and allylamine (145 µL, 1.95 mmol). The crude product was purified by flash chromatography with 3:1

hexane-EtOAc as eluant ,to give **20** (338 mg) as a yellow oil in 82% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 2H), 7.33 – 7.27 (m, 3H), 6.03-5.96 (m, 1H), 5.27 – 5.18 (m, 1H), 5.09 (dd, *J* = 10.2, 1.6 Hz, 1H), 3.47 (d, *J* = 6.1 Hz, 2H), 2.02 (dd, *J* = 26.2, 8.1 Hz, 2H), 1.50 – 1.36 (m, 7H), 0.93 (d, *J* = 5.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 131.6, 128.2, 127.8, 123.6, 115.7, 92.9, 85.1, 55.1, 46.53, 38.3, 32.4, 31.9, 22.2 ppm. MS (ESI) *m*/*z*(%): 276.15 [$(M + Na)^+$, 100]. Anal. Calcd. for $C_{18}H_{23}NO$: C, 85.32; H, 9.15; N, 5.53. Found: C, 85.78; H, 9.24; N, 5.47.

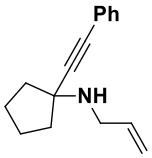


N-allyl-4-methyl-1-(phenylethynyl)cyclohexanamide (21): Compound **21** was obtained following the general procedure (B) using compound **20** (230 mg, 0.9 mmol), pyridine (1.8 mL) and acetic anhydride (3.6 mL). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **21** (180 mg) as a yellow oil in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.40 (m, 2H), 7.34 – 7.28 (m, 3H), 5.93 (ddd, *J* = 15.2, 9.8, 4.6 Hz, 1H), 5.28 (d, *J* = 15.2 Hz, 1H), 5.21 (d, *J* = 10.5 Hz, 1H), 4.28 – 4.23 (m, 2H),), 2.16 (s, 3H), 2.01 (d, *J* = 12.1 Hz, 2H), 1.73 – 1.40 (m, 7H), 0.91 (d, *J* = 5.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 135.5, 131.4, 128.2, 128.1, 123.2, 115.9, 90.6, 87.7, 34.5, 32.6, 31.4, 25.2, 22.3 ppm. MS (ESI) *m*/*z*(%): 296.20 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.89; H, 8.61; N, 4.68.

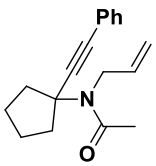


2'-acetyl-4-methyl-6'-phenyl-3a',4'-dihydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-5'(3'H)-one (22): Compound **22** was obtained following the general procedure (C) using compound n (180 mg, 0.62 mmol), $Co_2(CO)_8$ (20 mg, 0.06 mmol), N, N, N', N'-tetramethyl -thiourea (48 mg, 0.36 mmol). The reaction mixture was heated for 8 h and the crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **22**(144 mg) as a yellow oil in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.0 Hz, 3H), 7.17 – 7.07 (m, 2H), 4.02 (td, *J* = 9.2, 3.3 Hz, 1H), 3.56 – 3.41 (m, 1H), 3.15 (t, *J* = 10.5 Hz, 1H), 3.05 (td, *J* = 13.7, 6.0 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.83 – 2.73 (m, 1H), 2.28 (dd, *J* = 18.3, 1.9 Hz, 1H), 2.10 (d, *J* = 7.0 Hz, 3H), 1.65 – 1.19 (m, 8H), 0.51 (d, *J* = 6.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 168.8, 168.7, 138.8, 133.2, 129.4, 129.2, 128.4, 128.2, 67.7, 53.0, 39.8, 38.3, 38.1, 28.6, 28.5, 27.7, 26.3, 21.9 ppm. MS (ESI) *m*/*z*(%): 346.25

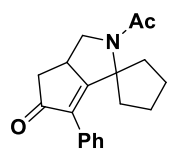
[(M + Na)$^+$, 100]. Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.32; H, 7.86; N, 4.26.



N-allyl-1-(phenylethynyl)cyclopentanamine (23) : Compound **23** was obtained following the general procedure (A) using ciclo-pentanone (100 µL, 1.13 mmol), phenylacetylene (150 µL, 1.36 mmol), CuI (43 mg, 0.23 mmol) and allylamine (100 µL, 1.36 mmol). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant, to give **23** (156 mg) as a yellow oil in 61% yield. ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.40 (dd, *J* = 6.5, 3.2 Hz, 2H), 7.31 – 7.27 (m, 3H), 6.05 – 5.95 (m, 1H), 5.23 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.3 Hz, 1H) 3.44 (d, *J* = 6.0 Hz, 2H), 2.04 (dd, *J* = 13.9, 7.4 Hz, 2H), 1.90 – 1.73 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.1, 131.6, 129.7, 128.3, 128.2, 126.7, 116.5, 89.9, 84.9, 49.9, 48.3, 42.1, 40.6, 23.8 ppm. MS (ESI) *m*/*z*(%): 226.19 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 85.47; H, 8.59; N, 6.14.

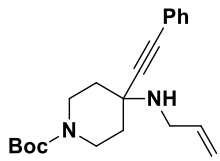


N-allyl-N-(1-(phenylethynyl)cyclopentyl)acetamide (24) : Compound **24** was obtained following the general procedure (B) using compound **23** (150 mg, 0.67 mmol), pyridine (1.34 mL) and acetic anhydride (2.68 mL). The crude product was purified by flash chromatography with 4:1 hexane-EtOAc as eluant ,to give **24** (100 mg) as a yellow oil in 56% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 2H), 7.35 – 7.26 (m, 3H), 6.00 – 5.88 (m, 1H), 5.32 – 5.17 (m, 2H), 4.20 – 4.11 (m, 2H), 2.47 - 2.42 (m, 2H), 2.19 - 2.09 (m, 3H), 2.09 (s, 3H), 1.92 – 1.76 (m, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 151.1, 135.3, 134.7, 131.6, 131.5, 129.7, 128.3, 128.2, 127.9, 126.8, 92.9, 82.9, 63.9, 49.9, 40.2, 29.7, 23.3 ppm. MS (ESI) *m*/*z*(%): 290.23 [(M + Na)$^+$, 100]. Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.17; H, 8.01; N, 5.16.

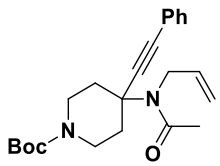


2'-acetyl-6'-phenyl-3a',4'-dihydro-2'H-spiro[cyclopentane-1,1'-cyclopenta[c]pyrrol]-5'(3'H)-one (25) : Compound **25** was obtained following the general procedure (C) using compound **24** (80 mg, 0.29 mmol),$Co_2(CO)_8$ (10 mg, 0.03 mmol), N, N, N', N'-tetramethyl-thiourea (24 mg, 0.18mmol). The reaction mixture was heated for 6 h and the crude product was purified by flash chromatography with

EtOAc as eluant ,to give **25** (61 mg) as a yellow oil in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.29 (m, 3H), 7.14 (dd, *J* = 7.8, 1.6 Hz, 2H), 4.03 (t, *J* = 9.1 Hz, 1H), 3.50 – 3.39 (m, 1H), 3.17 (dd, *J* = 11.2, 9.6 Hz, 1H), 2.81 (dd, *J* = 18.0, 6.6 Hz, 1H), 2.58 (dt, *J* = 13.2, 8.0 Hz, 1H), 2.34 (dd, *J* = 18.0, 3.6 Hz, 1H), 2.24 – 2.13 (m, 2H), 2.08 (s, 3H), 2.01 – 1.88 (m, 2H), 1.75 (ddd, *J* = 13.5, 9.8, 5.6 Hz, 1H), 1.71 – 1.58 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 183.3, 168.2, 136.0, 129.6, 128.3, 72.5, 52.8, 40.9, 40.2, 39.1, 34.9, 27.3, 27.1, 24.5 ppm. MS (ESI) *m*/*z*(%): 318.14 [$(M + Na)^+$, 100]. Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.68; H, 7.26; N, 4.69.

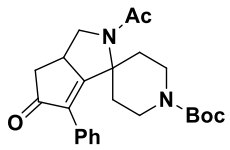


tert-butyl 4-(allylamino)-4-(phenylethynyl)piperidine-1-carboxylate (28) : Compound **28** was obtained following the general procedure (A) using tert-butyl 4-oxopiperidine-1-carboxylate (220 mg, 1.11 mmol), phenylacetylene (146 µL, 1.33 mmol), CuI (42 mg, 0.22 mmol) and allylamine (100 µL, 1.33 mmol). The crude product was purified by flash chromatography with 1:1 hexane-EtOAc as eluant ,to give **28** (313 mg) as a yellow oil in 83% yield^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (ddd, *J* = 4.2, 2.9, 1.7 Hz, 2H), 7.34 – 7.26 (m, 3H), 6.00 - 5.93 (m, 1H), 5.22 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.09 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.97 (pd, *J* = 24.4 Hz, 2H), 3.43 (d, *J* = 6.0 Hz, 2H), 3.18 (ps, 2H), 1.88 (d, *J* = 12.0 Hz, 2H), 1.59 (td, *J* = 12.7, 3.9 Hz, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 137.0, 131.7, 128.3, 128.2, 123.0, 115.9, 91.3, 53.7, 46.3, 40.8, 37.5, 28.5 ppm. MS (ESI) *m*/*z*(%): 341.22 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 74.53; H, 8.37; N, 8.15.

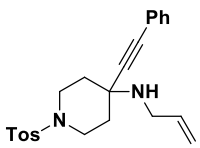


tert-butyl 4-(N-allylacetamido)-4-(phenylethynyl)piperidine-1-carboxylate (29) : Compound **29** was obtained following the general procedure (B) using compound **28** (300 mg, 0.88 mmol), pyridine (1.66 mL) and acetic anhydride (3.32 mL). The crude product was purified by flash chromatography with 1:1 hexane-EtOAc as eluant ,to give **29** (211 mg) as a yellow oil in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.34 – 7.28 (m, 3H), 6.09 – 5.80 (m, 1H), 5.31 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.24 (dd, *J* = 10.5, 1.1

Hz, 1H), 4.24 – 4.21 (m, 2H), 4.17 - 4.06 (m, 2H), 3.17 (ps, 2H), 2.57 (td, *J* = 12.6, 4.4 Hz, 2H), 2.15 (s, 3H), 2.05 (d, *J* = 11.6 Hz, 2H), 1.46 (s, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.51, 152.29, 135.10, 131.62, 128.48, 128.34, 122.63, 116.33, 92.45, 88.22, 79.58, 59.60, 49.58, 41.57, 34.46, 28.49, 24.92 ppm. MS (ESI) *m*/*z*(%): 383.25 [$(M + H)^+$, 100].].Anal. Calcd. for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21. Found: C, 65.31; H, 7.31; N, 7.17.

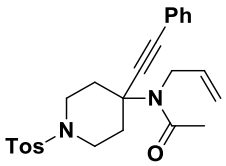


tert-butyl 2-acetyl-5-oxo-6-phenyl-3,3a,4,5-tetrahydro-2H-spiro[cyclopenta[c]pyrrole-1,4'-piperidine]-1'-carboxylat (30): Compound **30** was obtained following the general procedure (C) using compound **29** (203 mg, 0.53 mmol), toluene (10 mL), $Co_2(CO)_8$ (17 mg, 0.05 mmol), N, N, N', N' - tetramethyl - thiourea (40 mg, 0,3mmol). The reaction mixture was heated for 3 h and the crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **30** (171 mg) as a yellow oil in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.36 (m, 3H), 7.15 – 7.06 (m, 1H), 4.04 (t, *J* = 9.1 Hz, 1H), 3.89 – 3.68 (m, 1H), 3.55-3.46 (m, 2H), 3.24 – 3.12 (m, 1H), 2.84 (m, 3H), 2.80 (dd, *J* = 18.3, 6.7 Hz, 1H), 2.34 - 2.29 (m, 1H), 2.19 (s, 3H), 2.09 (s, 1H), 1.85 – 1.56 (m, 3H), 1.39 (d, *J* = 17.3 Hz, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.1, 177.8, 168.9, 139.1, 129.2, 128.7, 79.3, 65.1, 53.1, 39.6, 38.6, 31.6, 29.1, 28.5, 24.8 ppm. MS (ESI) *m*/*z*(%): 433.15 [$(M + Na)^+$, 100].].Anal. Calcd. for $C_{24}H_{30}N_2O_4$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.80; H, 7.45; N, 6.75.

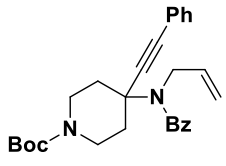


N-allyl-4-(phenylethynyl)-1-tosylpiperidin-4-amine (32): Compound **32** was obtained following the general procedure (A) using 1-tosylpiperidin-4-one (370 mg,0.93 mmol), phenylacetylene (122 µL, 1.12 mmol), CuI (35 mg, 0.19 mmol) and allylamine (85 µL 1.12 mmol). The crude product was purified by flash chromatography with 2:1 hexane-EtOAc as eluant ,to give **32** (259 mg) as a yellow oil in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.25 – 7.21 (m, 2H), 7.16 – 7.12 (m, 3H), 5.93 (ddt, *J* = 16.3, 10.3, 6.0 Hz, 1H), 5.20 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.08 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.61 (dt, *J* = 11.8, 3.7 Hz, 2H), 3.37 (d, *J* = 6.0 Hz, 2H), 2.81 (td, *J* = 11.6, 2.6 Hz, 2H), 2.43 (s, 3H), 1.96 (d, *J* = 12.9 Hz, 2H), 1.82 – 1.73 (m, 2H). . ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 136.7, 133.2, 131.4, 129.7, 129.5,

128.2, 128.2, 127.7, 127.6, 122.6, 116.0, 106.0, 90.3, 86.6, 64.4, 52.9, 46.3, 44.5, 43.2, 36.8, 34.4, 21.5 ppm. MS (ESI) *m*/z(%): 417.26 [$(M + Na)^+$, 100]. Anal. Calcd. for $C_{23}H_{26}N_2O_2S$ C, 70.02; H, 6.64; N, 7.10; O, 8.11; S, 8.13 found C 70.87; H 6.11; N 7.85; O 7.42; S 7.75.

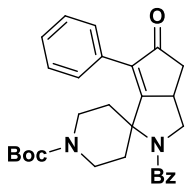


N-allyl-N-(4-(phenylethynyl)-1-tosylpiperidin-4-yl)acetamide (33) : Compound **33** was obtained following the general procedure (B) using compound **32** (259 mg, 0.66 mmol), pyridine (1.32 mL) and acetic anhydride (2.64 mL). The crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **33** (150 mg) as a yellow oil in 52% yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.74 – 7.63 (m, 1H), 7.35 – 7.28 (m, 1H), 7.24 – 7.18 (m, 1H), 5.87 (ddt, *J* = 17.2, 10.4, 4.4 Hz, 1H), 5.29 (dd, *J* = 17.2, 0.9 Hz, 1H), 5.23 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.14 (dt, *J* = 4.0, 1.8 Hz, 2H), 3.78 (d, *J* = 11.8 Hz, 2H), 2.77 (td, *J* = 12.3, 2.3 Hz, 2H), 2.62 – 2.52 (m, 2H), 2.41 (s, 3H), 2.24 – 2.18 (m, 2H), 2.13 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 143., 134.7, 132.5, 131.1, 129.5, 128.3, 128.1, 127.9, 122.2, 116.5, 88.8, 87.9, 57.86, 49.1, 44.1, 33.9, 24.6, 21.5 ppm. MS (ESI) *m*/*z*(%): 437.17 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{25}H_{28}N_2O_3S$ C, 68.78; H, 6.46; N, 6.42; O, 10.99; S, 7.34 found C 69.10; H 6.21; N 6.99; O 10.30; S 7.40.

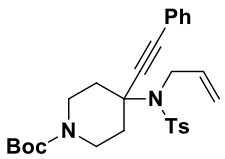


tert-butyl 4-(N-allylbenzylamido)-4-(phenylethynyl)piperidine-1-carboxylate (34) : . Compound **28** (540 mg, 1.58 mmol) was dissolved in pyridine (3.15 mL) and the reaction mixture was kept to 0°c and tosyl chloride (780 µL, 9.45 mmol) was added portionwise, after the addition the reaction mixture was heated at 40 °c for 16h. Then, EtOAc was added and the organic phase was washed with HCl 1M (3 x 20 mL), $Na_2CO_{3\ sat}$ (3 x 20 mL) and brine The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture of hexane: diethyl ether 4:1, to give the pure compound **34** (448 mg) in a yield of 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.41 – 7.35 (m, 5H), 7.32 (dd, *J* = 5.0, 1.8 Hz, 3H), 5.86 (ddt, *J* = 15.9, 10.4, 5.1 Hz, 1H), 5.17 (ps, 2H), 5.14 (dd, *J* = 8.3, 1.1 Hz, 2H), 4.16 (d, *J* = 5.1 Hz, 2H), 3.33 – 3.14 (m, 2H), 2.69 (td, *J* = 12.5, 4.5 Hz, 2H), 2.20 (d, *J* = 12.2 Hz, 2H), 1.47 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 154.7, 138.4, 136.1, 131.6, 129.4, 128.4, 128.3, 128.3, 126.4, 122.6, 116.8, 88.6, 79.6,

59.3, 51.2, 41.2, 34.2, 28.5, 28.4 ppm. MS (ESI) *m*/*z*(%): 467.30 [(M + Na)$^+$, 100]. Anal. Calcd. for $C_{28}H_{32}N_2O_3$: C, 75.65; H, 7.26; N, 6.30. Found: C, 75.89; H, 7.34; N, 6.19.

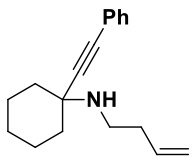


tert-butyl 2-benzoyl-5-oxo-6-phenyl-3,3a,4,5-tetrahydro-2H-spiro[cyclopenta[c]pyrrole-1,4'-piperidine]-1'-carboxylate (35) : Compound **35** was obtained following the general procedure (C) using compound **34** (430 mg, 0.96 mmol), toluene (19.2 mL), $Co_2(CO)_8$ (34 mg, 0.1 mmol), N,N, N',N'-tetramethyl-thiourea (80 mg, 0,6 mmol). The reaction mixture was heated for 3 h and the crude product was purified by flash chromatography with 3:1 hexane-EtOAc as eluant ,to give **35** (353 mg) as a yellow oil in 78% of yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (ps, 8H), 7.14 (d, *J* = 6.8 Hz, 2H), 4.06 - 3.87 (m, 1H), 3.83 (dd, *J* = 9.9, 8.4 Hz, 1H), 3.67 -3.29 (m, 1H), 3.21 (t, *J*= 10.5, 1H), 2.96 - 2.79 (m, 2H), 2.72 (dd, *J* = 18.4, 6.6 Hz, 1H), 2.24 (dd, *J* = 18.5, 3.1 Hz, 1H), 2.16 - 2.05 (m, 1H), 1.92 - 1.77 (m 1H), 1.73 - 1.66 (m, 2H),1.41 (d, *J* = 21.8 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 193.5, 179.5, 169.6, 154.7, 146.7, 137.8, 129.9, 129.1, 128.8, 128.6, 126.3, 79.4, 65.6, 55.3, 38.2, 31.6, 28.4 ppm. MS (ESI) *m*/*z*(%): 473.26 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{29}H_{32}N_2O_4$: C, 73.70; H, 6.83; N, 5.93. Found: C, 74.11; H, 6.92; N, 5.88

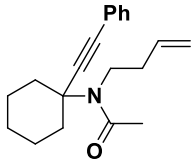


tert-butyl 4-(N-allyl-4-methylphenylsulfonamido)-4-(phenylethynyl)piperidine-1-carboxylate (36): Compound **28** (360 mg, 1.05 mmol) was dissolved in pyridine (2.1 mL) and the reaction mixture was kept to 0°c and tosyl chloride (1200 mg, 6.30 mmol) was added portionwise, after the addition the reaction mixture was heated at 40 °c for 16h. Then, EtOAc was added and the organic phase was washed with HCl 1M (3 x 20 mL), $Na_2CO_{3\ sat}$ (3 x 20 mL) and brine The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture of hexane: diethyl ether 3:1, to give the pure compound **36** (326 mg) in a yield of 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 1H), 7.33 – 7.24 (m, 2H), 7.23 – 7.14 (m, 2H), 6.04 (dq, *J* = 10.6, 5.6 Hz, 1H), 5.31 (d, *J* = 17.3 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.19 (ps, 2H), 4.05 (ps, 2H), 3.06 (s, 1H), 2.33 (ps, 4H), 1.45 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.6, 154.4, 143.2, 138.8, 136.8, 131.5, 129.4, 128.6, 128.2, 127.5, 121.9, 116.9, 87.9, 87.1, 79.8, 60.9, 50.3, 28.4, 21.4 ppm. MS (ESI) *m*/*z*(%): 417.20 [(M

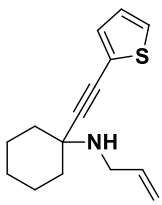
+ Na)$^+$, 100]. Anal Calcd. for $C_{28}H_{34}N_2O_4S$ C, 67.99; H, 6.93; N, 5.66; O, 12.94; S, 6.48 found C 68.35; H, 7.02; N 5.02; O 12.92; S 6.69.



N-(but-3-en-1-yl)-1-(phenylethynyl)cyclohexanamine (39) : Compound **39** was obtained following the general procedure (A) using ciclo-hexanone (160 µL, 1.54 mmol), phenylacetylene (200 µL, 1.84 mmol), CuI (57 mg, 0.30 mmol) and 3-buten-1-amine (168 µL, 1.84 mmol). The crude product was purified by flash chromatography with 2:1 hexane-diethyl ether as eluant ,to give **39** (187 mg) as a yellow oil in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 7.36 – 7.26 (m, 3H), 5.89 – 5.76 (m, 1H), 5.14 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.30 (q, *J* = 6.8 Hz, 2H), 1.95 (d, *J* = 12.4 Hz, 2H), 1.70 - 1.65 (m, 6H), 1.54 – 1.39 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 131.6, 128.2, 127.7, 123.6, 116.4, 93.3, 84.6, 55.0, 42.1, 38.2, 34.2, 27.9, 25.9, 23.1 ppm. MS (ESI) *m*/*z*(%): 276.12 [(M + Na)$^+$, 100]. Anal Calcd. $C_{18}H_{23}N$ C, 85.32; H, 9.15; N, 5.53; found C 86.01; H 9.12; 4.87;

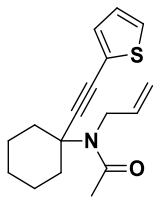


N-(but-3-en-1-yl)-N-(1-(phenylethynyl)cyclohexyl)acetamide (40) : Compound **40** was obtained following the general procedure (B) using compound 39 (187 mg, 0.75 mmol), pyridine (1.5 mL) and acetic anhydride(3 mL). The crude product was purified by flash chromatography with 3:1 hexane-diethyl ether as eluant ,to give **40** (126 mg) as a yellow oil in 59% yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.43 (dd, J = 6.2, 3.0 Hz, 2H), 7.39 – 7.28 (m, 3H), 5.88 – 5.67 (m, 1H), 5.11 - 5.04 (m, 2H), 3.66 (t, J = 7.1 Hz, 2H), 2.77 (2s, 2H), 2.48 (q, J =7.2 Hz, 2H), 2.18 (s, 3H), 1.92 – 1.59 (m, 8H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 145.0, 134.7, 131.5, 128.4, 128.2, 123.1, 116.9, 90.4, 88.0, 62.0, 47.9, 35.6, 34.5, 25.5, 24.9, 24.1 ppm. MS (ESI) *m*/*z*(%): 296.13 [(M + H)$^+$, 100]. Anal. Calcd. $C_{20}H_{25}NO$ C, 81.31; H, 8.53; N, 4.74; O, 5.42 found C 82.03; H 8.10; N 4.95; O 4.92.

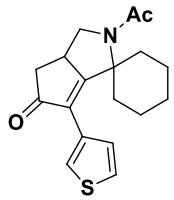


N-allyl-1-(thiophen-2-ylethynyl)cyclohexanamine (42) : Compound **42** was obtained following the general procedure (A) using ciclo-hexanone (88 µL, 0.84 mmol), 3-ethynylthiophene (100 µL, 1.01 mmol), CuI (30 mg, 0.17 mmol) and allylamine (75 µL, 1.01 mmol). The crude

product was purified by flash chromatography with 2:1 hexane-EtOAc as eluant ,to give **42** (152 mg) as a yellow oil in 74% yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.38 (dd, J = 3.0, 1.2 Hz, 1H), 7.25 – 7.24 (m, 1H), 7.09 (dd, J = 5.0, 1.2 Hz, 1H), 6.07 – 5.92 (m, 1H), 5.22 (dq, J = 17.2, 1.6 Hz, 1H), 5.09 (ddd, J = 10.2, 2.8, 1.3 Hz, 1H), 3.46 – 3.41 (m, 2H), 1.94 (d, J = 12.7 Hz, 2H), 1.70 - 1.63 (m, 6H), 1.51 – 1.40 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3(d), 130.1(d), 127.8(d), 125.1(d), 122.6(s), 115.6(t), 93.0(s), 79.6(s), 77.3, 77.0, 76.7, 55.0(s), 46.3(t), 38.2(t), 25.9(t), 23.0(t) ppm. MS (ESI) *m*/*z*(%): 268.22 [$(M + Na)^+$, 100].]. Anal. Calcd. for $C_{18}H_{23}NO$: C, 85.32; H, 9.15; N, 5.53. Found: C, 85.78; H, 9.24; N, 5.47.

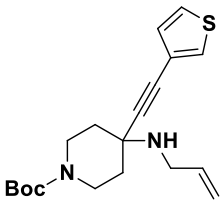


N-allyl-N-(1-(thiophen-2-ylethynyl)cyclohexyl)acetamide (43) : Compound **43** was obtained following the general procedure (B) using compound **42** (150 mg, 0.61 mmol), pyridine (1.1 mL) and acetic anhydride (2.2 mL). The crude product was purified by flash chromatography with 2:1 hexane-EtOAc as eluant ,to give **42** (137 mg) as a yellow oil in 78% yield. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 1H), 7.25 (ddd, *J* = 5.1, 2.9, 0.9 Hz, 1H), 7.09 (dd, *J* = 4.9, 1.1 Hz, 1H), 5.97 – 5.84 (m, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 4.25 – 4.18 (m, 2H), 2.15 (s, 3H), 2.01 (d, *J* = 12.1 Hz, 2H), 1.82 – 1.57 (m, 8H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4(s), 135.4(d), 129.8(d), 128.2(d), 125.5(d), 122.1(s), 115.9(t), 90.0(s), 82.(s)7, 61.6(s), 49.7(t), 34.8(t), 25.2(t), 24.9(q), 24.0(t) ppm. MS (ESI) *m*/*z*(%): 300.20 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{17}H_{21}NOS$: C, 71.04; H, 7.36; N, 4.87. Found: C, 71.10; H, 7.43; N, 4.80

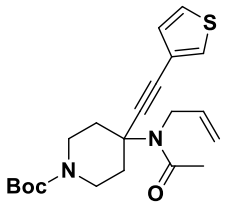


2'-acetyl-6'-(thiophen-3-yl)-3a',4'-dihydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]-5'(3'H)-one (44) : Compound **44** was obtained following the general procedure (C) using compound **43** (130 mg, 0.45 mmol), Toluene (9 mL) ,$Co_2(CO)_8$ (15 mg, $5*10^{-2}$ mmol), N,N, N',N'-tetramethyl-thiourea (40 mg, 0.3 mmol). The reaction mixture was heated for 4 h and the crude product was purified by flash chromatography with EtOAc as eluant ,to give **44** (96 mg) as a white solid in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.09 (dd, *J* = 2.8, 1.0 Hz, 1H), 6.89 (dd, *J* = 4.9, 1.0 Hz, 1H), 4.00 (dd, *J* = 19.4, 10.4 Hz, 1H), 3.50 – 3.37 (m, 1H), 3.22 – 3.06 (m, 1H), 2.97 (td, *J* = 13.4, 5.5 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.31 – 2.22 (m, 1H), 2.08 (s, 3H),

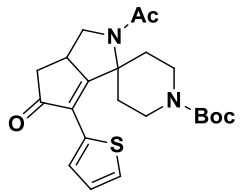
1.59 (t, *J* = 14.9 Hz, 4H), 1.42 – 1.06 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 181.22, 168.8, 134.1, 132.3, 128.7, 126.0, 124.7, 67.8, 52.9, 45.8, 39.8, 38.1, 32.7, 28.9, 25.3, 24.1, 23.4, 21.9 ppm. MS (ESI) *m*/*z*(%): 316.14 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.32; H, 7.86; N, 4.26.



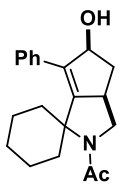
tert-butyl 4-(allylamino)-4-(thiophen-3-ylethynyl)piperidine-1-carboxylate (45) : Compound **45** was obtained following the general procedure (A) using tert-butyl 4-oxopiperidine-1-carboxylate (218 mg, 1.1 mmol),3-ethynylthiophene (130 µL, 1.32 mmol), CuI (41 mg, 0.22 mmol) and allylamine (100 µL, 1.32 mmol). The crude product was purified by flash chromatography with 1:1 hexane-diethyl ether as eluant ,to give **45** (235 mg) as a yellow oil in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.27 - 7.25 (m, 1H), 7.08 (dd, *J* = 5.0, 1.1 Hz, 1H), 5.97 (ddt, *J* = 16.3, 10.2, 6.0 Hz, 1H), 5.23 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.96 (ps, 2H), 3.47 – 3.38 (m, 3H), 3.21 - 3.16(m, 2H), 1.89 (d, *J* = 12.5 Hz, 2H), 1.60 (td, *J* = 12.4, 4.0 Hz, 2H), 1.45 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 136.9, 129.9, 128.4, 125.3, 121.9, 115.9, 90.7, 80.7, 79.5, 53.7, 46.2, 28.4 ppm. MS (ESI) *m*/*z*(%): 347.18 [(M + H)$^+$, 100]. Anal. Calcd. for $C_{19}H_{26}N_2O_2S$: C, 65.86; H, 7.56; N, 8.08. Found: C, 66.01; H, 7.62; N, 8.00.



tert-butyl 4-(N-allylacetamido)-4-(thiophen-3-ylethynyl)piperidine-1-carboxylate (46): Compound **46** was obtained following the general procedure (B) using compound **45** (221 mg , 0.63 mmol), pyridine (1.26 mL) and acetic anhydride (2.52 mL). The crude product was purified by flash chromatography with 2:1 hexane-diethyl ether as eluant ,to give **46** (153 mg) as a yellow oil in 63 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.7 Hz, 1H), 7.27 7.25 (m, 1H), 7.08 (d, *J* = 4.9 Hz, 1H), 5.89 (ddd, *J* = 15.0, 9.9, 4.5 Hz, 1H), 5.29 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.19 -4.05 (m, 4H), 3.14 (ps, 2H), 2.55 – 2.44 (m, 2H), 2.14 (s, 3H), 2.06 (d, *J* = 11.8 Hz, 2H), 1.45 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 154.6, 134.9, 129.8, 128.8, 125.4, 121.5, 116.3, 88.1, 83.3, 79.6, 59.4, 49.4, 34.4, 28.4, 24.9 ppm. MS (ESI) *m*/*z*(%): 411.19 [(M + Na)$^+$, 100]. Anal. Calcd. for $C_{21}H_{28}N_2O_3S$: C, 64.92; H, 7.26; N, 7.21. Found: C, 65.31; H, 7.31; N, 7.17.

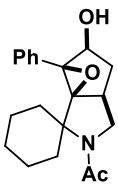


tert-butyl 2-acetyl-5-oxo-6-(thiophen-2-yl)-3,3a,4,5-tetrahydro-2H-spiro[cyclopenta[c]pyrrole-1,4'-piperidine]-1'-carboxylate: Compound **47** was obtained following the general procedure (C) using compound **46** (149 mg, 0.38 mmol), toluene (7.6 mL) $Co_2(CO)_8$ (14 mg, 0.04 mmol), N,N, N',N'-tetramethyl-thiourea (32 mg, 0,24 mmol). The reaction mixture was heated for 3 h and the crude product was purified by flash chromatography with EtOAc as eluant ,to give **47** (108 mg) as a yellow oil in 68% yield. . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 4.9, 3.0 Hz, 1H), 7.09 (dd, J = 2.8, 1.0 Hz , 1H), 6.90 (dd, 4.9, 1.00 Hz, 1H), 4.15 (dd, J = 17.0, 7.9 Hz, 1H), 3.99 - 3.79 (m, 1H), 3.72 - 3.56 (m, 1H), 3.29 (t, J = 10.2 Hz, 1H), 2.90 (dd, J = 18.3, 6.7 Hz, 1H), 2.79 - 2.72 (m, 1H), 2.42 (dd, J = 18.3, 3.2 Hz, 1H), 2.34 - 2.26 (m, 1H), 2.19 (s, 3H), 1.93 - 1.63 (m, 2H), 1.49 (d, J =17.3 Hz, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.7, 183.2, 170.8, 136.1, 134.3, 130.7, 128.0, 126.7.78.3, 64.1, 52.1, 38.6, 37.6, 30.6, 28.1, 27.5, 23.8 ppm. MS (ESI) *m*/*z*(%): 417.20 [$(M + H)^+$, 100]. Anal. Calcd. for $C_{22}H_{28}N_2O_4S$: C, 63.44; H, 6.78; N, 6.73. Found: C, 63.74; H, 6.85; N, 6.68.

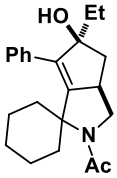


1-((3a'R,5'S)-5'-Hydroxy-6'-phenyl-3',3a',4',5'-tetrahydro-2'H-spiro[cyclohexane-1,1'-cyclopenta[c]pyrrol]- 2'-yl)ethanone (48) : To a solution of **19** (50 mg, 0.162 mmol) in a 1:1 mixture of MeOH - DCM (3.5 mL) were added successively CeCl3 .7*H_2O (120 mg, 0.32 mmol) and NaBH4 (12 mg, 0.32 mmol). The reaction mixture was left stirring at 25 °C for 1 h, then the reaction was quenched with satd. NH_4Cl (4 mL) and 1M HCl (1 mL). The reaction mixture was partitioned between EtOAc and water, and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography 2:1 EtOAc-Petr. Et. to give **48** (46 mg) in 92% yield as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 3H), 7.21 – 7.13 (m, 2H), 5.10 (t, J = 7.1 Hz, 1H), 3.79 (t, J = 8.8 Hz, 1H), 3.32 – 3.16 (m, 1H), 3.09 (t, J = 9.8 Hz, 1H), 2.95 (td, J = 13.5, 5.6 Hz, 1H), 2.65 (dt, J = 12.7, 7.1 Hz, 1H), 2.60 – 2.47 (m, 1H), 2.02 (s, 3H), 1.98 – 1.54 (m, 2H), 1.52 – 1.37 (m, 4H), 1.14 – 1.02 (m, 4H) ppm. 13C NMR (100 MHz, CDCl3) δ 168.8, 148.3, 137.3, 136.5, 129.5, 128.2, 127.4, 84.9, 66.6, 54.5, 43.9, 37.7, 32.6, 28.8, 25.4, 24.3, 23.4, 22.1 ppm.

MS (ESI) m/z (%): 334.27 (100, $[M^{+}Na]^{+}$). Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.14; H, 3.09; N, 4.50. Found: C, 77.50; H, 3.21; N, 4.39.

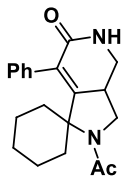


1-((1a'S,2'S,3a'S,6a'S)-2'-Hydroxy-1a'-phenyltetrahydrospiro[cyclohexane-1,6'-oxireno[2',3':1,5]cyclopenta[1,2-c]pyrrol]-5'(1a'H)-yl)ethanone (49) : To a solution of compound **19** (43 mg, 0.154 mmol) in anhydrous DCM(1 mL) *m*CPBA (34 mg, 80%, 0.154 mmol) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with satd. $NaHCO_3$ (2 mL) and the resulting mixture was partitioned between EtOAc and water. The aqueous layer was extracted three times with EtOAc, washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography (1:1 EtOAc-Petr. Et.) to give pure **49** (34 mg, 68% yield) as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 5H), 4.59 (t, J = 7.7 Hz, 1H), 3.69 (t, J = 8.5 Hz, 1H), 3.36 – 3.25 (m, 1H), 2.79 – 2.69 (m, 1H), 2.67 – 2.54 (m, 1H), 2.07 – 2.01 (m, 1H), 2.04 (s, 3H), 1.76 – 1.42 (m, 4H), 1.35 – 1.03 (m, 7H). 13C NMR (100 MHz, $CDCl_3$) δ 169.1, 133.5, 128.5 , 128.4, 127.8, 83.7, 80.0, 73.7, 66.4, 49.9 38.5, 30.9, 28.1, 26.0, 25.3, 23.9, 23.0, 21.9 ppm. MS (ESI) *m*/*z*(%): 350.34 (100, $[M^{+}Na]^{+}$). Anal. Calcd. for $C_{20}H_{25}NO_3$: C,73.37; H, 7.70; N, 4.28. Found: C, 73.78; H, 7.79; N, 4.20.



1-((3a'*R*,5'*S*)-5'-Ethyl-5'-hydroxy-6'-phenyl-3',3a',4',5'-tetrahydro-2'*H*-spiro[cyclohexane-1,1'-cyclopenta[*c*]pyrrol]- 2'-yl)ethanone (50): $CeCl_3$ (40 mg, 0.162 mmol) was dried under vacuum and transferred under a nitrogen atmosphere to a round bottom flask. Then, a solution of compound **19** (50 mg, 0.162 mmol) in THF (1 mL) was added and stirred at room temperature for 1 h. The mixture was cooled to 0 °C before adding dropwise the Grignard reagent as a 3M solution in Et_2O (300 µL, 0.810 mmol). The resulting mixture was left stirring at 0 ° C for 30 min, then quenched by carefully adding a saturated solution of NH4Cl (1 mL). The solution was left under stirring for 30 min before pouring a saturated solution of NH4Cl (15 mL). Then, the resulting mixture was extracted with Et2O, washed with water and brine, dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography 1:1 EtOAc-Petr. Et. to give **50** (26 mg),in 48% yield as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 3H), 7.19 – 7.16

(m, 2H), 3.78 (t, *J* = 8.7 Hz, 1H), 3.24 – 3.12 (m, 1H), 3.06 (t, *J* = 9.6 Hz, 1H), 2.89 (td, *J* = 13.2, 5.6 Hz, 1H), 2.57 (dt, *J* = 12.7, 5.1 Hz, 1H), 2.45 (dd, *J* = 13.0, 7.3 Hz, 1H), 2.03 (s, 3H), 1.75 – 1.61 (m, 4H), 1.58 – 1.40 (m, 4H), 1.36 – 1.25 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 148.9, 137.5, 135.5, 127.9 (3C), 127.5 (2C), 92.4, 66.6, 54.8, 43.8, 40.5, 32.6, 31.9, 28.6, 25.4, 24.2, 23.4, 21.7, 8.53 ppm. MS (ESI) *m*/*z* (%): 362.28 (100, [M + Na]+). Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 78.12; H, 8.70; N, 4.05.



2'-Acetyl-7'-phenyl-3',3a',4',5'-tetrahydrospiro[cyclohexane-1,1'-pyrrolo[3,4-*c*]pyridin] 6'(2'*H*)-one (51): To a stirred solution of compound **19** (50 mg, 0.162 mmol) in TFA (600 μL) was added NaN_3 (19 mg, 0.29 mmol) and the reaction mixture was heated at reflux temperature for 16 h. After completing the reaction, the mixture was cooled to room temperature and evaporated under reduced pressure. The resulting crude was treated with water and extracted with DCM. The combined organic phase was successively washed with satd. $NaHCO_3$, water, and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography EtOAc to give pure **51** (22 mg) in 41% yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 5.56 (br s, 1H), 3.83 – 3.67 (m, 1H), 3.40 (d, *J* = 4.4 Hz, 1H), 3.17 – 3.00 (m, 1H), 2.70 (dd, *J* = 18.7, 6.9 Hz, 1H), 2.34 (d, *J* = 18.7 Hz, 1H), 2.12 – 2.02 (m, 2H), 1.98 (s, 3H), 1.83 – 1.56 (m, 8H) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 165.2, 133.6, 132.5, 132.0, 129.1, 128.0 (2C), 127.8, 59.6, 42.7, 40.2, 39.4, 27.5, 25.7, 23.3, 22.4, 21.6 ppm. MS (ESI) *m*/*z* (%): 347.25 (100, [M + Na]+). Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 3.64. Found: C, 74.56; H, 7.53; N, 3.57.

4.5 Bibliography:

1. For general review on A^3 and KA^2 coupling reaction see: Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V.; *Chem. Soc. Rev.*, **2012**, 41, 3790; Uhlig, N.; Yoo, W. J.; Zhao, L.; Li, C. J.; **2015** "*Catalytic Nucleophilic Addition of Alkynes to Imines: The A3 (Aldehyde–Alkyne–Amine) Coupling"*, in "*Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations"*, First Edition. Edited by Trost, B. M.; Li, C. J.; **2015**, Wiley-VCH Verlag GmbH & Co. KGaA.
2. Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V.; *Org. Lett.*, **2010**, 12, 2638.
3. Koradin, C.; Polborn, K.; Knochel, P.; *Angew. Chem., Int. Ed.* **2002**, *41*, 2535.
4. Cheng, M.; Zhang, Q.; Hu, X.Y.; Li, B. G.; Ji, J. X.; Chan, A. S. C.; *Adv. Synth. Catal.*, **2011**, 353, 1274.
5. Pierce, C. J.; Nguyen, M.; Larsen, C. H.; *Angew. Chem., Int. Ed.*, **2012**, 51, 12289.
6. Tang, X.; Kuang, J.; Ma, S.; *Chem. Commun.*, **2013**, 49, 8976.
7. Cai, Y.; Tang, X.; Ma, S.; *Chem. -Eur J*., **2016**, 22, 2266.
8. Palchak, Z. L.; Nguyen, P. T.; Larsen, C. H.; *Beilstein J. Org. Chem.*, **2015,** 11, 1425.
9. Brak, K.; Doyle, P. S.; McKerrow, J. H.; Ellman, J. A.; *J. Am. Chem. Soc.* **2008,** *130*, 6404.
10. Patterson, A. W.; Wood, W. J. L.; Hornsby, M.; Lesley, S.; Spraggon, G.; Ellman; J. A. *J. Med. Chem.* **2006,** *49*, 6298; Wood, W. J. L.; Patterson, A. W.; Tsuruoka, H.; Jain, R. K.; Ellman, J. A. *J. Am. Chem. Soc.* **2005,** *127*, 15521.
11. Van Beek, W. E.; Van Stappen, J.; Franck, P.; Abbaspour Tehrani, K.; *Org. Lett*., **2016**, 18, 4782.
12. For review on spirocyclic compounds, and their application in drug discovery see: Zheng, Y. J.; Tice, C. M.; Singh, S. B.;*Bioorg. Med. Chem. Lett*., **2014**, 24, 3673; Saraswat, P.; Jeyabalan, G.; Hassan, M. Z.; Rahman, M. U.; Nyola, N. K.; *Synthetic Communications*, **2016**, 46, 1643; Rios, R.; *Chem. Soc. Rev*., **2012**, 41, 1060;
13. Ding, A.; Meazza, M.; Guo, H.; Yang, J. W.; Rios, R.;*Chem. Soc. Rev.*, **2018**, *47*, 5946.

14. Peshkov, V. A.; Pereshivko, O. P.; Ermolat'ev,D. S.; Van Hove, S.; Van Hecke, K.; Van Meervelt, L.;Van der Eycken, E. V.;*Synthesis*, **2011**, 10, 1587.
15. Zhao, J.; Huang, H.; Qi, C.; Jiang, H.; *Eur. J.Org. Chem.*, **2012**, 5666.
16. Ranjan, A.; Yerande, R.; Wakchaure, P. B.;Yerande, S. G.; Dethe, D. H.;*Org. Lett*. **2014**, 16,5788.
17. Ranjan, A.; Deore, A. S.; Yerande, S. G.; Dethe, D. H.;*Eur. J. Org. Chem.*, **2017**, 4130.
18. Hintermann, L.; Labonne, A.; *Synthesis*, **2007**, 8, 1121.
19. Vicario, J.; Badia, D.; Reyes, E.; Echevarria, J.; *Curr. Org. Chem*., **2005**, 9. 219.
20. Lenci, E.; Innocenti, R.; Menchi, G.; Faggi, C.; Trabocchi, A.; *Org. Biomol. Chem.*, **2015**, 13, 7013.
21. Corey, E. J.; Venkateswarlu, A.; *J. Am. Chem. Soc*.**1972**, *94*, 6190.
22. For general literature, review and applications of Pauson Khand reaction see :Pauson, P. L.; Khand, I. U.; *Ann. N. Y. Acad. Sci.*, **1977**, 295, 2.; Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J.; *Chem. Soc. Rev.*, **2004**, 33, 1, 32; Jeong, N.; Hwang, S. H.; Lee, Y.; Chung, Y. K.; *J. Am. Chem. Soc.*, **1994**,116, 7, 3159.
23. Simeonov; S.P.; Nunes; J. P. M.; Guerra; K.; Kurteva; V. B.; Afonso; C. A. M.; *Chem. Rev*.,**2016**, 116, 5744.
24. Luche, J.-L.;*J. Am. Chem. Soc.*, **1978**, 100, 7, 2226.
25. Thede, K.;Diedrichs, N.;Ragot, J. P.;*Org. Lett.* **2004**, **6**, 4595.
26. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima,T.; Kamiya, Y.; *J. Am. Chem. Soc.*, **1989**, 111, 4392.
27. Kawanaka, Y.; Kobayashi, K.;Kusuda, S.; Tatsumi, T.; Murota, M.; Nishiyama, T.; Hisaichi, K.;Fujii, A.; Hirai, K.; Nishizaki, M.; Naka, M.; Komeno, M.;Nakai, H.; Toda, M.; *Bioorg.Med. Chem.* **2003**, 11, 689.

Part III
Study of new reactions for their future application in Build Couple Pair strategies

Chapter 5

Study of new catalytic system for Morita Baylis Hillman reaction

5.1 Introduction

The creation of C-C bond is one of the most studied topics in modern organic chemistry, and also in DOS strategy, because many reactions use in B/C/P approach take advantage of a C-C bond formation[1].For example, in the couple phase, where we connect together the building blocks, the formation of new C-C bonds is a common process[2]. Many reactions to form this kind of bond have been studied over the years, and the formation of aldols[3]probably remains one of the most interesting both from a historical point of view and in terms of actual use. Among all this actions for building C-C bonds (Claisen, Claisen-Schmidt, Knovenagel, Mannich, etc...), the one that gathered much interest in recent years is the Morita Baylis Hillman (MBH)[4], despite being known for long time. This base-catalyzed C-C bond forming reaction was reported initially by Morita[5]. In this work, the authors reported the reaction between acrilonitrile and various aldehydes catalyzed by a basic phosphine(Figure 1).Then, few years later Baylis and Hillman[6] reported the same reaction where the phosphine was replaced with an amine.

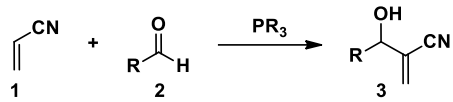


Figure 1 First reported example of MBH reaction by Morita in 1968

This reaction involves electron poor α,β-unsaturated alkenes and aldehydes (the latter being replaced with imines in the so-called aza-MBH), and this combination may sound unusual because these two compounds are usually electrophiles in many reactions. For example, the a α,β-unsaturated compounds are typical electrophiles of Michael reaction[7]. This is possible because in the MBH reaction we have an umpolung of reactivity generated by the base. In the reaction mechanism (Figure 2) the base attacks the electrophilic β position of the α,β electron poor (**I**) alkene to form a

zwitterionic enol compound (**II**). Then, the alpha position becomes a good nucleophilic and can attacks the electrophilic carbon of the aldehyde (**III**) to form the zwitterionic compound (**IV**).

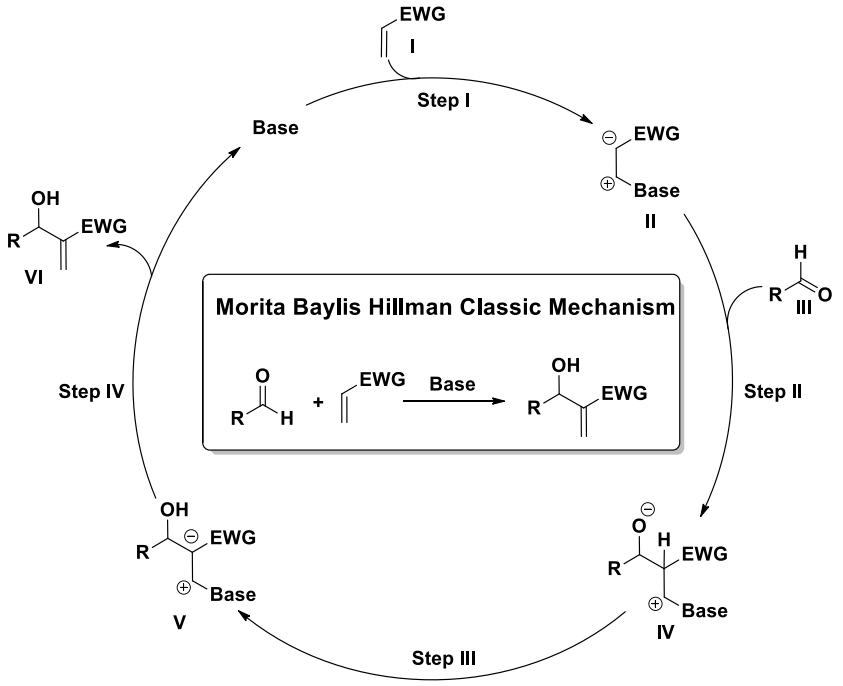
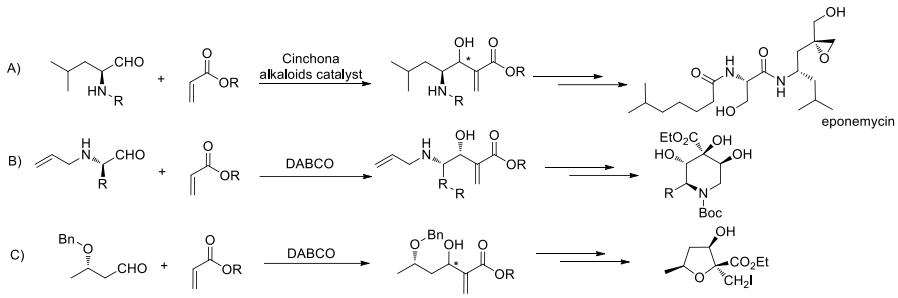


Figure 2 General accepted mechanism for the MBH reaction.

This intermediate **IV** evolves to the MBH adduct (VI) by a H-shift and a sequential elimination of the base, to restore the original double bond[4] and generating the MBH product that includes all the atoms of the reagents in its structure. Over last years, this reaction found many applications, such as the stereo-controlled steps in total synthesis pathways (Scheme 1 A)[8], in the synthesis of bioactive molecules[9] (Scheme 1 B), and in the synthesis of highly functionalized heterocyclic compounds[10] (Scheme 1 C).Another particular property of this reaction lies in the structure of the product, often called MBH adduct.



Scheme 1 Applications of the MBH reaction.

Indeed the MBH adduct possesses many different functionalities in its structure (Figure 3) which can react in a selective way. This property makes the MBH adduct a perfect example of a couple product and consequentially the MBH as a good reaction to be used in the couple step of B/C/Pstrategies[11].

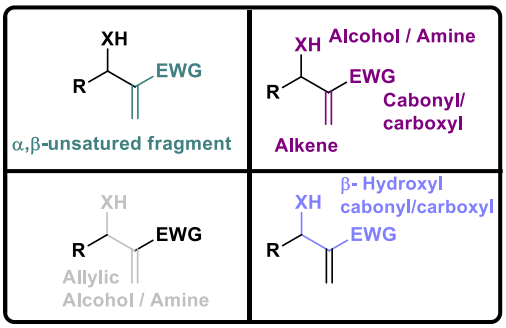


Figure 3 Map of the functional groups in the MBH adduct.

The reactivity of the system depends on the nature of α,β unsaturated compound[4],and in particular, of the electron withdrawing strength of the EWG group. Indeed, is the stronger the EWG, the more electrophile the β carbon will result. This is crucial, because the attack on the electrophilic carbon atom for the formation of the zwitterionic intermediate II (Step I Figure 2) is the step that generates the umpolung of the reaction. The second parameter is the substitution and the nature of the alkene. Indeed, it is well accepted that if a sp^2 carbon is bonded to an alkyl substituent it will result less electrophilic due to the electronic donation of the alkyl group. Also, if the double bond is inside a cyclic structure, the regeneration of the double bound will result harder as compared with an acyclic one. For all these reasons the α,β compounds derived from carboxylic derivatives and nitro

groups are more reactive as compared to the carbonyl compounds and also to the compounds with the β position being substituted, especially the cyclic ones, resulting less reactive with respect to the acyclic ones (Figure 4).

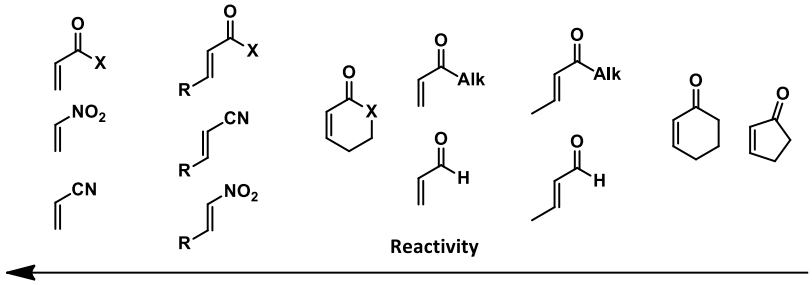
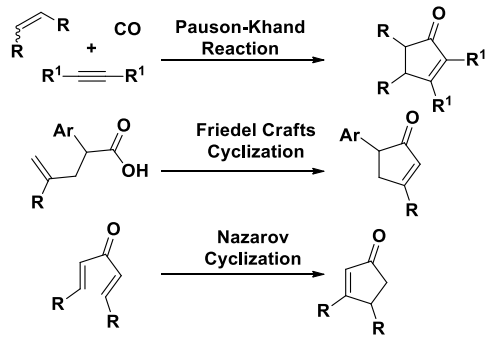


Figure 4 Reactivity scale for α, β conjugated compounds.

Out of all these compounds the hardest substrate for the MBH reaction is the cylopent-2-en-1-one.Accordingly,only few works reported the use of this substrate and only in limited examples in scope tables[12]. Nevertheless, this substrate has several interesting features, as it can be prepared through many synthetic routes, such as the Pauson-Khand reaction[13], Friedel Crafts cyclization[14] and Nazarov[15]reaction (Scheme 2).



Scheme 2 Several examples of reactions used for the synthesis ofcyclopent-2-en-1-one.

Also, this structural moiety is present in many natural products or molecules with a biological activity and for this we can consider it as a privileged scaffold (Figure 5) [16].

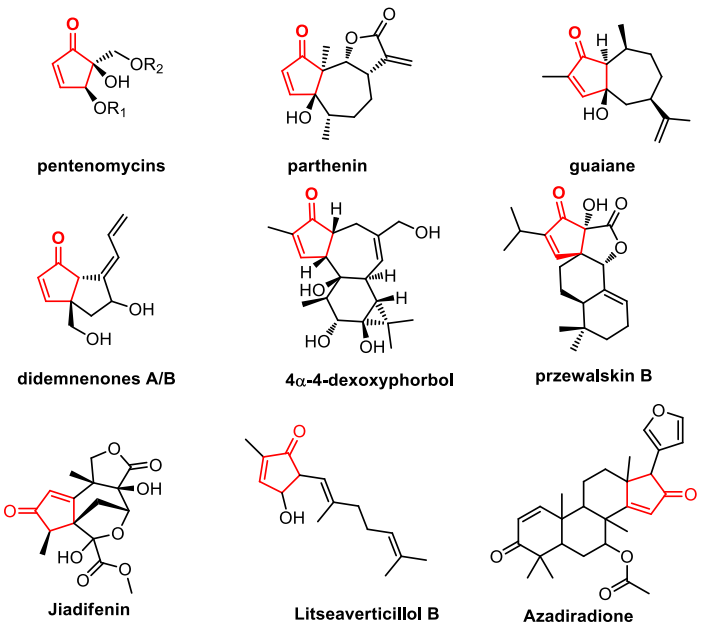
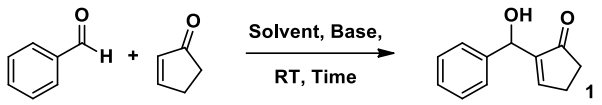


Figure 5 Several natural products or molecules with a biological activity containing the cyclopent-2-en-1one moiety.

The application of cyclop-2-en-1-one in the MBH reaction is an important and challenging goal because this reaction allows us to install an additional stereocenter next to the α-carbon and many substituents by the variation of the aldehyde.

5.2 Results and discussion

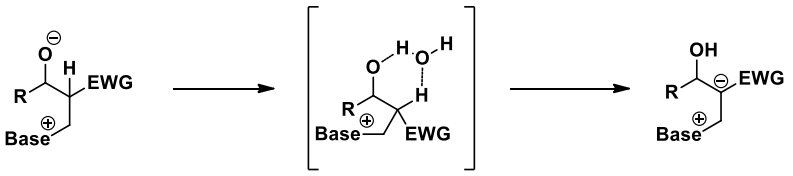
We began our study using benzaldehyde as the electrophile, because this substrate is typically used for this reaction[4] and represents a good starting material: it is stable, commercially available, and the absence of substituents in the aromatic ring allowed us to perform the study on a "neutral" compound without the presence of electron withdrawing/ donating groups. As expected, cyclop-2-en-1-one proved to be a really hard substrate for the Morita Baylis Hillman reaction. In fact when we screened several common bases in an organic polar solvent such as THF no one gave the desired MBH adduct **1**, despite long reaction times (Tab.1 entries 1-7).



Entry	Solvent	Base	Time (h)	Yield (%)
1	THF	N-Methyl-Pyrrolidine	168	0
2	THF	DABCO	168	0
3	THF	Imidazole	168	0
4	THF	Ph_3P	168	0
5	THF	DMAP	168	0
6	THF	Et_3N	168	0
7	THF	Pyrrolidine	168	0
8	THF: H_2O 1:1	N-Methyl-Pirrolidine	168	0
9	THF: H_2O 1:1	DABCO	168	0
10	THF: H_2O 1:1	Et_3N	168	0
11	THF: H_2O 1:1	Ph_3P	168	0
12	THF: H_2O 1:1	Imidazole	168	8
13	THF: H_2O 1:1	DMAP	168	37
14	THF: H_2O 1:1	Pyrrolidine	168	22
15	THF: H_2O 1:1	DMAP	40	35
16	THF: H_2O 1:1	Pyrrolidine	40	23

Tab.1 All the reactions were performed using cyclop-2-en-1-one (1 eq), benzaldehyde (1 eq), a base (0.2 eq) and the indicated solvent (0.25 M).

In the literature were reported many works [4]showing the successful use of a mixture of water and organic solvent, probably because water works as proton shift mediator (Scheme 3) in step III of the reaction mechanism (Figure 2).



Scheme 3 The role of water in the MBH reaction.

Indeed, with this method (Tab.1 entries 8-16) we obtained some good results. Although several bases (Tab.1 entries 8-12) still did not bring to the

desire product **1**, DMAP, pyrrolidine and imidazole proved to promote the reaction in moderate yields (Tab.1 entries 12-14), and a reasonable reaction time (Tab.1 entries 15, 16). Concerning DMAP and imidazole, this result was somewhat expected, because the reactivity of this activated aromatic basic nitrogen base with this substrate was reported in two different works[12a,c;]. Nevertheless, we did not focus our attention on them because the works showed for both catalytic systems some critical points in the reaction scope, showing many limitations involving several aldehydes. For the pyrrolidine the result was more interesting, because such data were not in agreement with the pK_a value of the compound, usually being the main factor for the reactivity. Specifically, pyrrolidine has a higher pKa(11.4) as compared with DABCO (8.93) but not so high as compared with some other bases that did not work with these substrates, such as triethylamine (10.7) and N-methyl pyrrolidine (10.3). This suggested that pyrrolidine works in a different way and, according with the literature[17], we hypothesized a catalytic mechanism involving the formation of an iminium ion from pyrrolidine (Figure 6).

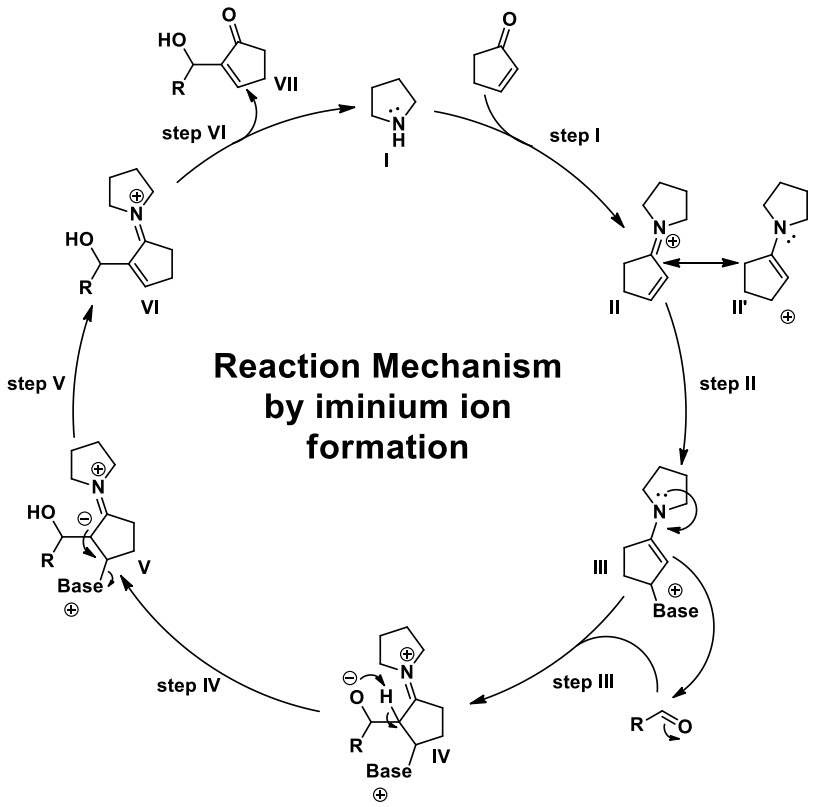


Figure 6 Mechanism of MBH reaction involves by iminium catalysis.

In this mechanistic hypothesis the reaction starts with the iminium ion formation (step I):the corresponding compound **II** has a more electrophilic β carbon for the presence of the resonance with **II'**, indeed in this species the electro withdrawing power of the iminium form is major as compared with a typical ketone. Then, the base attacks the activated carbon atom, forming the Intermediate **III** which evolves by a further activation of the nitrogen to the Intermediate **IV** through the attack of the nucleophilic α carbon to the electrophile aldehyde. Then, the mechanism proceeds as usual with the proton shift (step IV), the elimination of the base (step V) and in the end the hydrolysis gives the final product **VII** and restores the pyrrolidine which returns in the catalytic circle (step VI). To confirm this hypothesis we set up a series of experiments using mass spectrometry as a tool for the analysis (Figure 7). In the first experiment we mixed together the cyclopent-2-en-1-one with the pyrrolidine and after the injection we found the peak of the intermediate **II** in the hydrate form (Figure 7a). In a second experiment,

following the same procedure, we injected a mixture of benzaldehyde and pyrrolidine and also in this case we observed the peak of the corresponding iminium ion (Figure 7 b).Indeed, we obtained the most interesting data with the third experiment, simulating the real reaction conditions mixing together benzaldehyde, cyclopent-2-en-1-one and pyrrolidine. Unexpectedly, in this experiment the peak of the iminium ion derived from the benzaldehyde was not present. This demonstrated that in this system the formation of iminium ion with cyclopent-2-en-1-one was preferred. Also, as we observed the peak of the intermediate VI, it demonstrated that the pyrrolidine not only prefers the cyclopent-2-en-1-one to form the iminium species but also that it remains attached on it until the last step, as hypothesized.

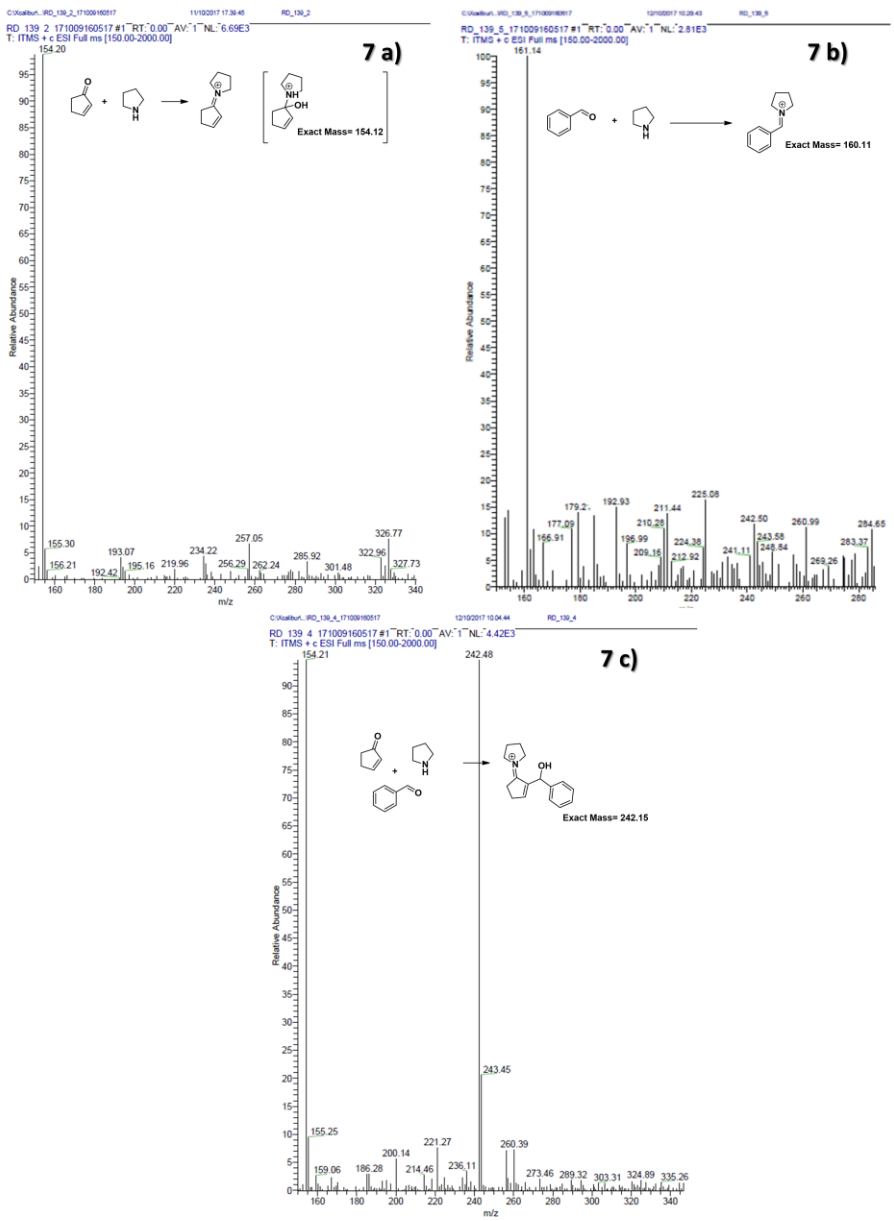
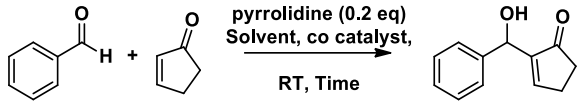


Figure 7 a) The experiment was performed using cyclopent-2-en-1-one (1 eq) and pyrrolidine (0.2 eq). b) The experiment was performed using benzaldehyde (1 eq) and pyrrolidine (0.2 eq). c)) The experiment was performed using benzaldehyde (1 eq), cyclopent-2-en-1-one (1 eq) and pyrrolidine (0.2 eq).

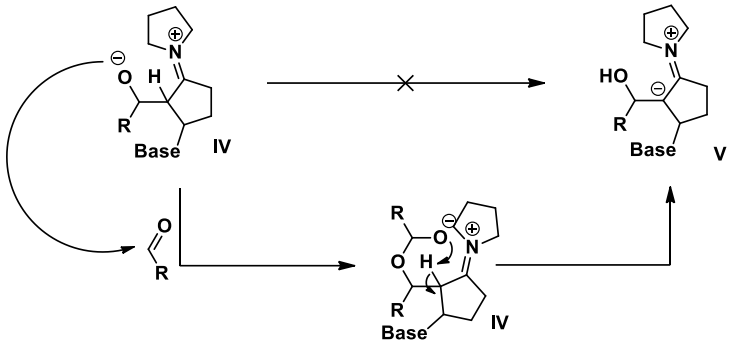
After confirming the role of the pyrrolidine in the reaction we started to optimize the reaction conditions to increase the yield. (Tab.2)



Entry	Solvent (0.25 M)	Co catalyst (0.2 eq)	Time (h)	Yield(%)
1	MeOH	-	168	0[a]
2	MeOH: H_2O 1:1	-	168	0[a]
3	DMF: H_2O 9:1	-	168	0[a]
4	THF: H_2O 1:4	-	40	26[a]
5	THF: $NaHCO_{3\ sol}$ 1M 1:1	-	40	31[a]
6	THF: $NaHCO_{3\ sol}$ 1M 1:4	-	40	43[a], 42[b], 65[c]
7	THF: $NaHCO_{3\ sol}$ 1M 1:4	DABCO	40	75[c]
8	THF: $NaHCO_{3\ sol}$ 1M 1:4	Et_3N	40	40[c]
9	THF: $NaHCO_{3\ sol}$ 1M 1:4	PPh_3	40	0[c]
10	THF: $NaHCO_{3\ sol}$ 1M 1:4	DABCO	16	>10%[c]
11	THF: $NaHCO_{3\ sol}$ 1M 1:4	DABCO	168	76[c]

Tab.2 The reactions were carried out using a) benzaldehyde (1 eq), cyclopent-2-en-1-one (1 eq); b)benzaldehyde (1 eq), cyclopent-2-en-1-one (1.5 eq); c) benzaldehyde (3 eq), cyclopent-2-en-1-one (1 eq).

When we changed the solvent (Tab.2 entries 1-3) the reaction did not work and we observed that by increasing the percentage of water the yield was improved (Tab.2 entry 4),especially when water was replaced with a sodium bicarbonate solution. The study of stoichiometry of the reagent showed that the use an excess of aldehyde gave best results. The role of the aldehyde used in excess was explained by Aggarwal et collab.[17],using a series of kinetics experiments, demonstrating that the MBH reaction is a second order reaction for the aldehyde, as a second molecule is involved in the reaction mechanism. Indeed, the intermediate **IV** (Figure 6) does not evolve to **V** with a simple proton shift. In this step(Figure 6 step **IV**) the anionic oxygen does not take the hydrogen directly but attacks a second molecule of aldehyde to form a new emiacetal compound (intermediate **IV'**, Scheme 4), and only in the sequential hydrolysis the proton shift is complete.



Scheme 4 Representation of the role of the second molecule of aldehyde in MBH reaction.

Obviously the intermediate **IV'** could interact also with water as described previously to proceed in the step easier. In this context, we can also explain the role of bicarbonate that works better than water as intermediate, as previously demonstrated in a series of works[18] in the literature (Figure 8).

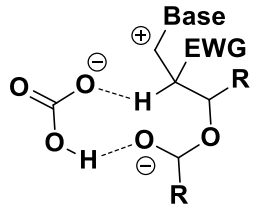
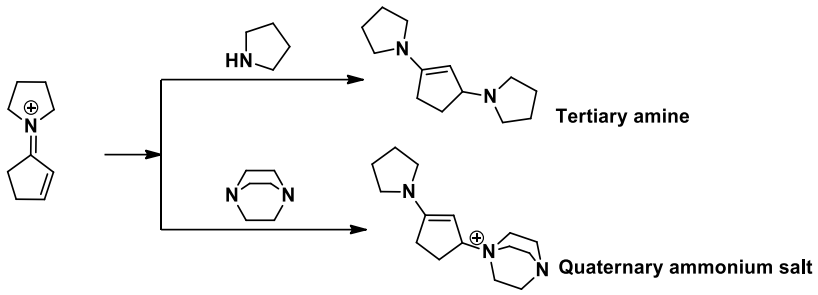


Figure 8 A schematic representation of the role of bicarbonate in the reaction.

We also found that the presence of a co-catalyst dramatically increased the yield of the reaction. This can be explained with two different factors. In first, the presence of a second base species relieves the pyrrolidine from attacking the β carbon. also this the presence of tertiary amine co catalyst give as resulting compound, from the attack of the β carbon, as quaternary ammonium salt a better leaving group compared with the tertiary amine generates from the pyrrolidine attack (Scheme 5) This gets better elimination step (Figure 6 Step V).



Scheme 5 Comparison of the products obtained from the attack on the β-carbon by pyrrolidine (top) and DABCO (bottom).

As a consequence, we hypothesized a new reaction mechanism which included both factors, according to literature[19], the role of bicarbonate and the formation of the iminium ion. (Figure 9).

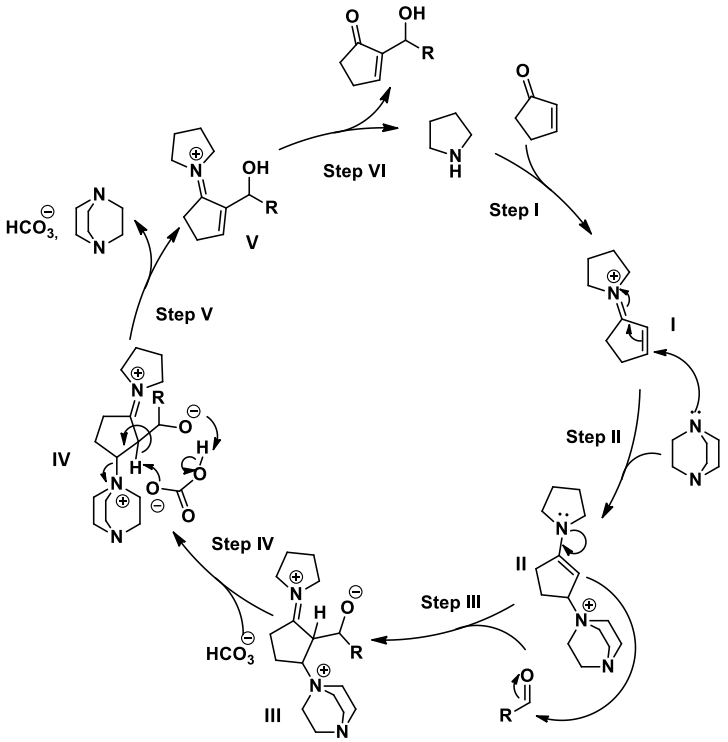
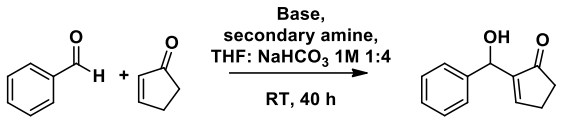
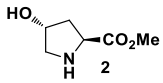
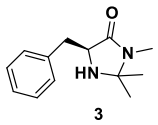
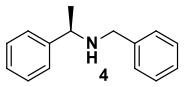


Figure 9 Morita-Baylis-Hillman mechanism involving a secondary amine and bicarbonate.

When we optimized the reaction by screening several secondary amines, we found a direct correlation between the pK_a of they ammonium ions and the yield of the reaction. (Tab.3).

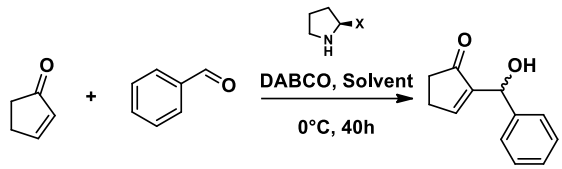


Entry	Secondary amine	pKa[b]	Base	Yield, %[c]
1	Pyrrolidine	11.3	-	68
2			DABCO	75
3	Piperidine	11.1	-	57
4			DABCO	62
5	Diethylamine	11.0	-	58
6			DABCO	64
7	Morpholine	8.0	-	0
8			DABCO	0
9	Proline	10.6	-	20 (17)
10			DABCO	32 (9)
11	Prolinol	10.5	DABCO	52 (25)
12	Proline methyl ester	9.2	-	10 (22)
13			DABCO	20 (10)
14	 2	8.2	-	15 (0)
15			DABCO	24 (0)
16	 3	5.2	-	0
17			DABCO	0
18	 4	10.8	-	0
19			DABCO	0
20	 5	11.4	-	62 (21)
21			DABCO	81 (23 (S))

Tab.3 Screening of several secondary amines. a)The reaction was carried out using cyclopent-2-enone (1 eq),benzaldehyde (3 eq), DABCO (0.2 eq if used), amine (0.2 eq), 1:4

THF-1M $NaHCO_3$, with0.25 M conc. for the cycloenone. b) calculated with ACD/Labs. c) % ee are in parentheses; the values were calculated using GC with chiral BetaDex120 column.

This can be explained by an analysis of step **III** (Figure 9) of the reaction. In this step, the nitrogen donates the doublet to generate a negative charge on the α carbon, then it is used for the attack of the aldehyde. For this reason, the secondary amine with a high pK_a value produced best results with exception for compound **4**, although the less reactivity of this amine depends from the presence of the two bulky side chains. The poor reactivity of the weak bases is correlated to this with their poor activation of this step, that as demonstrated by many studies is the rate-determining step [20]. Another interesting point is the comparison of a moderate ee using chiral secondary amines. This encouraged us to optimize the enantioselectivity of our methodology using (S)-prolinol and (R)-2-methyl pyrrolidine **5** as chiral catalysts following preliminary evidences (Tab.3 entries 9:21).



Entry	Solvent (0.25 M)	X	Yield(%)	ee; R/S
1	THF: $NaHCO_{3\,sol}$ 1M 1:4	CH_3-	80	23, R
2	THF: $NaHCO_{3\,sol}$ 1M 1:4	CH_2OH-	30	25, R
3	THF: H_2O 1:4	CH_3	52	26, R
4	THF: H_2O 1:4	CH_2OH	15	27, R

Tab.4 The reactions were performed using benzaldehyde (3 eq), cyclopent-2-en-1-one (1 eq), the indicated solvent (0.25M) DABCO (0,2 eq), the indicated secondary amine (0.2 eq), at 0°C for 40 h.

Initially, we decreased the reaction temperature to 0 °C (Tab.4 entry 1,2) without obtaining any remarkable improvement in the stereoselectivity. Unfortunately, the temperature represented a limitation for this catalytic system because when we tried to use a lower one we observed the freezing of the aqueous solution. Replacing the bicarbonate solution with water did not improve the results because we obtained the same enantioselectivity but with a dramatically decrease of the yields(Tab.4 entries 3,4).This result suggested that the presence of the hydroxyl group does not influence the stereoselectivity and that the ee is brought only from the steric hindrance of the catalysts.

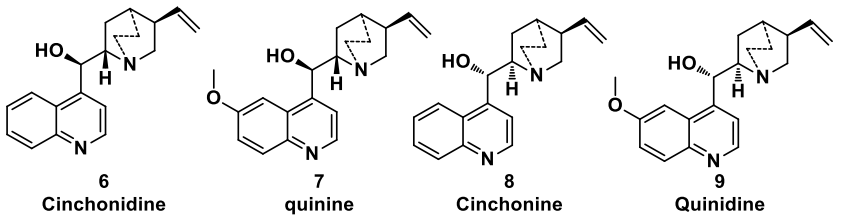
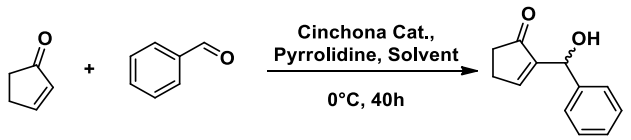


Figure 10 The alkaloids derived from Cinchona

In order to improve the results we decided to use a chiral co-catalyst, and looking at the structure of the DABCO we chose a series of chiral molecules which contained a similar nitrogen and the same bicyclic structure of the cinchona alkaloid (Figure 10). When we screened the co-catalysts **6-9** using the bicarbonate solution in the solvent system (Tab.4 entries 1-4) we obtained more or less the same yields obtained with DABCO, as expected, but the products completely racemic. Instead, when we used pure water (Tab.5 entries 5-8) the yield decreased but we obtained a moderate enantioselectivity, suggesting that this kind of catalyst works a in a different way as compared to the secondary amines.

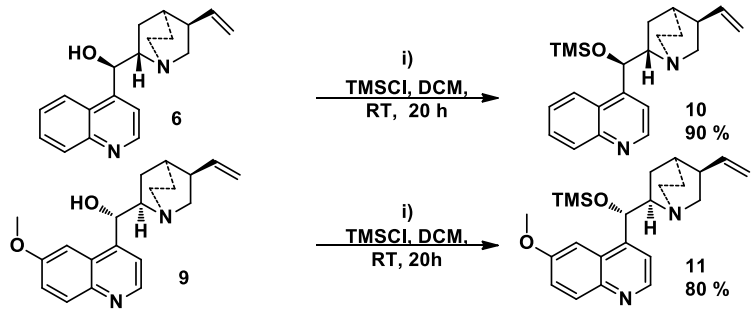


Entry	Solvent (0.25 M)	Cinchona cat.	Yield(%)	ee; R/S
1	THF: $NaHCO_{3\ sol}$ 1M 1:4	6-	82	0
2	THF: $NaHCO_{3\ sol}$ 1M 1:4	7	78	0
3	THF: $NaHCO_{3\ sol}$ 1M 1:4	8	80	0
4	THF: $NaHCO_{3\ sol}$ 1M 1:4	9	83	0
5	THF: H_2O 1:4	6	32	30, S
6	THF: H_2O 1:4	7	28	18, S
7	THF: H_2O 1:4	8	28	19, R
8	THF: H_2O 1:4	9	31	40, R

Tab.5 The reactions were performed using benzaldehyde (3 eq), cyclopent-2-en-1-one (1 eq), the indicated solvent (0.25M)pyrrolidine (0,2 eq), the indicated Cinchona alkaloid (0.2 eq), at 0°C for 40 h.

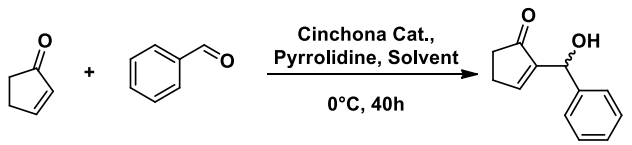
It was postulated that they induced the stereoselectivity using the hydroxyl group, and this could explain why in the bicarbonate solution the catalyst did not show any stereo induction. Indeed, in these experiments the hydrogen bonding that rules the stereo induction is masked by the

bicarbonate. To prove this, we synthesized the TMS derivatives **10** and **11** of the best two catalysts **6** and **9** to inhibit the possibility to establish hydrogen bond interactions (Scheme 6).



Scheme 6. Reactions were performed using Cinchona alkaloid (**6** or **9**) (1 eq), DCM (4 mL/mmol), TMSCl (1.3 eq), RT, 20 h

As expected, the products of the reactions were completely racemic (Tab.6), thus confirming our hypothesis. Probably, the elimination of the water solution from the reaction system could increase the enantioselectivity but, unfortunately, its presence is necessary for the successful outcome of the reaction.

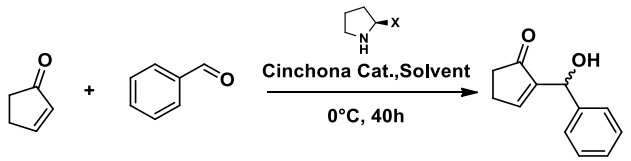


Entry	Solvent (0.25 M)	Cinchona cat.	Yield(%)	ee; R/S
1	THF: H_2O 1:4	10	21	0
2	THF: H_2O 1:4	11	23	0

Tab.6 The reactions were perform using benzaldehyde (3 eq), cyclopent-2-en-1-one (1 eq), the indicates solvent (0.25M)pyrrolidine (0,2 eq), theindicatesCinchona alkaloid (0.2 eq), at 0°C for 40 h.

As the last experiment, we performed the reaction using both chiral secondary amine **5** and chiral co-catalysts **6** and **9**. As expected, when the reaction was performed in sodium bicarbonate media, the missing effect of the co-catalyst was evident, because bicarbonate inhibited their stereo induction (Tab.7 entries 1-4). The unexpected results were the ones from the reactions performed in water, as in this experiments we envisaged a

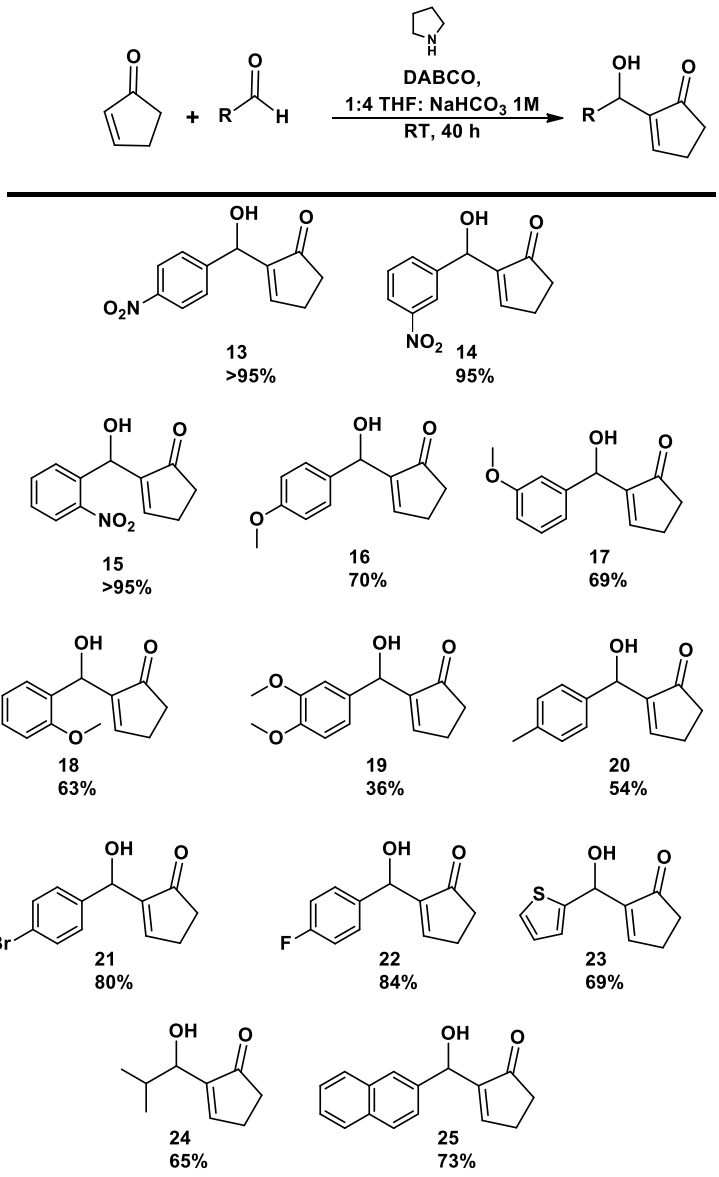
match/mismatch effect derived from the interactions of the two catalytic systems (Tab.7 entries 5-8).



Entry	Solvent (0.25 M)	X	Cinc. cat.	Yield(%)	ee; R/S
1	THF: $NaHCO_{3\ sol}$ 1M 1:4	CH_3	6	73	23, R
2	THF: $NaHCO_{3\ sol}$ 1M 1:4	CH_3	9	75	23, R
3	THF: $NaHCO_{3\ sol}$ 1M 1:4	CH_2OH	6	51	22, R
4	THF: $NaHCO_{3\ sol}$ 1M 1:4	CH_2OH	9	47	25, R
5	THF: H_2O 1:4	CH_3	6	30	21, R
6	THF: H_2O 1:4	CH_3	9	31	25, R
7	THF: H_2O 1:4	CH_2OH	6	12	26, R
8	THF: H_2O 1:4	CH_2OH	9	15	24, R

Tab.7 The reactions were performed using benzaldehyde (3 eq), cyclopent-2-en-1-one (1 eq), the indicated solvent (0.25M)the indicated secondary amine (0,2 eq), the indicated Cinchona alkaloid (0.2 eq), at 0°C for 40 h.

The two experiments gave the same results, both leading to a matched effect, because all the two catalysts should bring to the same enantiomer, (Tab 7 entry 6 and 8) (Tab 7 entry 6 and 8). Moreover, this result is comparable with the ones that we obtained using the chiral secondary amine and DABCO as the base (Tab. 5 entries 3 and 4). This suggested us that the effect brought from the secondary amine is dominant over the other. So, with aim of increasing the stereoselectivity the catalytic system requires further optimization. In the end we studied the scope of the reaction using several aldehydes. The catalytic method proved to be versatile (Scheme 7), giving good results with a range of aldehydes, including the aliphatic ones (**24)** the electron deficient aromatic aldehydes (**13**-**15**, **21**, **22**),and the electron rich ones(**16**-**20**, **23**).Concerning the latter substrates, we obtained satisfying results, despite their usual unreactive character for this reaction. Indeed, compound **19**could not prepared before this method.



Scheme 7 The reactions were perform using the aldehyde (3 eq), cyclopent-2-en-1-one (1 eq), THF: $NaHCO_{3\ sol}$ 1M 1:4 (0.25M)pyrrolidine (0,2 eq), the DABCO (0.2 eq), at 0°C for 40 h.

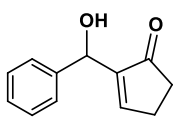
5.3 Conclusions

In conclusion, we reported the study of the MBH on cyclopent-2-enone using the iminium catalysis, demonstrating that a secondary amine is important in activating the poorly reactive enone as the electrophile in the MBH reaction through iminium catalysis. We demonstrated that this methodology tolerates many aldehydes, comprising the ones that usually are unreactive. In addition, we began the study to apply this methodology in a stereoselective fashion, understanding which is the role of the catalyst and which parameters should be changed. The future development of this project will be the conversion of this methodology in a stereoselective version and the application of it as a couple reaction in B/C/P strategy.

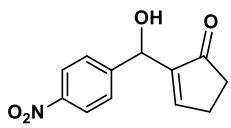
5.4 Experimental Part

General. ^{1}H NMR spectra were recorded on a Varian Mercury 400 (^{1}H: 400 MHz),^{13} C spectra were recovered on a Varian Mercury 400 (^{13}C: 100 MHz) or in a Varian Gemini 200 (^{13}C: 50 MHz). The chemical shifts (δ) and coupling constants (J) are expressed in parts per million (ppm) and hertz (Hz), respectively. Flash column chromatography (FCC) purifications were performed manually using glass columns with Merck silica gel (0.040–0.063 mm). TLC analyses were performed on Merck silica gel 60 F254 plates. Elemental analyses were performed on a Perkin Elmer 240 C, H, N analyzer. ESI mass spectra were recorded on a Thermo LCQ-Fleet. All commercially available reagents and solvents were used as received, unless otherwise specified.

General procedure for the Morita-Baylis-Hillman reaction. In a flask containing a stirring solution of DABCO (0.12 mmol, 14 mg) in THF (0.5 mL) and 1M aqueous solution of $NaHCO_3$ (2 mL), pyrrolidine (0.12 mmol, 10 µL), cyclopent-2-enone (0.6 mmol) and the aldehyde (1.8 mmol) were successively added. The reaction was stirred at room temperature for 40 h. Then, ethyl acetate (20 mL) was added and the organic phase was washed with 1M HCl, satd. $NaHCO_3$ solution and brine. The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and the crude product was purified by flash chromatography column (FCC).

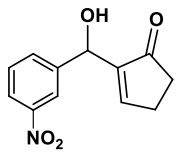


2-[hydroxy(phenyl)methyl]cyclopent-2-enone (4) . Compound **4** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and benzaldehyde (1.8 mmol, 184 µL). The crude product was purified by FCC eluting with 3:1 toluene-ethyl acetate (R_f0.34) to give the pure product as a colorless oil in 75% yield. ^{1} H NMR 400 MHz, CDCl3 δ7.35-7.23 (m, 6H), 5.50 (s, 1H), 2.59-2.46 (m, 2H), 2.46-2.29 (m, 2H); ^{13} C NMR 100 MHz, CDCl3 δ209.6, 159.7, 147.8, 141.5, 128.4, 127.7, 126.3, 69.4, 35.2, 26.7; MS (ESI) m/z (%): 211.08 [$(M + Na)^+$, 100].Anal. Calcd for $C_{12}H_{12}O_2$ (188.22): C, 76.57; H, 6.43. Found: C, 76.71; H, 6.50.

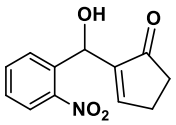


2-[hydroxy(4-nitrophenyl)methyl]cyclopent-2-enone (13): Compound **13** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 4-nitrobenzaldehyde (1,8 mmol, 270 mg). The crude product was purified by a FCC eluting with

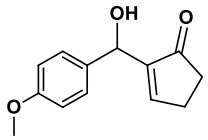
2:1 hexane-ethyl acetate (R_f0.19) to give the pure product as a yellow oil in quantitative yield. NMR data are in according with the literature. ^{1}H NMR 400 MHz, CDCl3 δ8.12 (d, J=8.8 Hz, 2H), 7.53 (d, J=8.8 Hz, 2H), 7.34 (m, 1H), 5.62 (d, J=5.9, 1H), 2.65-2.56 (m, 2H), 2.45-2.39 (m, 2H); ^{13}C NMR 100 MHz, CDCl3 δ209.6, 160.6, 148.8, 147.4, 146.8, 127.1, 123.7, 68.6, 35.2, 26.9; MS (ESI) m/z (%): 256.18 [(M + Na)$^+$, 100].Anal. Calcd for $C_{12}H_{11}NO_4$ (233.22): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.93; H, 4.82; N, 5.90.



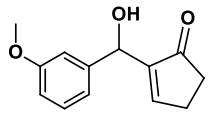
2-[hydroxy(3-nitrophenyl)methyl]cyclopent-2-enone (14).: Compound **14** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 3-nitrobenzaldehyde (1.8 mmol, 270 mg). The crude product was purified by a FCC eluting with 1:1 toluene-diethyl ether (R_f0.24) to give the pure product like a yellow oil in 95% yield. ^{1}H NMR 400 MHz, CDCl3 δ 8.24-8.23 (m, 1H), 8.14-8.10 (m, 1H), 7.74 (t, J=7.8 Hz, 1H), 7.53 (d, J=7.9 Hz, 1 H), 7.35-7.33 (m, 1H), 5.66 (d, J=5.5 Hz, 1H), 2.65-2.63 (m, 2H), 2.49-2.45 (m, 3H); ^{13}C NMR 100 MHz, $CDCl_3$ δ 209.6, 160.6, 146.7, 144.7, 132.6, 131.6, 129.4, 122.7, 121.2, 68.6, 35.2, 26.9; MS (ESI) m/z (%): 256.25 [(M + Na)$^+$, 100].Anal. Calcd for $C_{12}H_{11}NO_4$ (233.22): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.91; H, 4.85; N, 5.91.



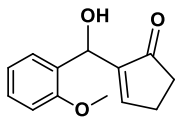
2-[hydroxy(2-nitrophenyl)methyl]cyclopent-2-enone (15) : Compound **15** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 2-nitrobenzaldehyde (1.8 mmol, 270 mg). The crude product was purified by FCC eluting with 1:1 toluene-diethyl ether (R_f0.24) to give the pure product as a yellow oil in quantitative yield. ^{1}H NMR 400 MHz, CDCl3 δ 7.96 (d, J=7.9 Hz, 1 H), 7.86 (d, J=7.8 Hz, 1H), 7.67 (t, J=7.6 Hz, 1H), 7.46 (t, J=7.7 Hz, 1 H), 7.21 (s, 1H), 6.16 (s, 1H), 2.67-2.50 (m, 2H), 2.51-2.43 (m, 2H); □C 13C NMR 100 MHz, CDCl3 δ 209.5, 160.1, 147.7, 145.7, 136.5, 133.7, 128.8, 128.6, 124.6, 65.3, 35.0, 26.7; MS (ESI) m/z (%): 256.22 [(M + Na)$^+$, 100].Anal. Calcd for $C_{12}H_{11}NO_4$ (233.22): C, 61.80; H, 4.75; N, 6.01. Found: C, 61.96; H, 4.88; N, 5.87.



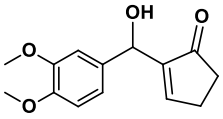
2-**[hydroxy(4-methoxyphenyl)methyl]cyclopent-2-enone (16)** : Compound **16** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 4-methoxybenzaldehyde (1.8 mmol, 218 µL). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.37) to give the pure product as a yellow oil in 70% yield. NMR data are in according with the literature.^{1}H NMR 400 MHz, CDCl3 δ 7.30-7.21 (m, 3H), 6.87 (d, J=8.7 Hz, 2H), 5.50 (s, 1H), 3.78(s, 3H) 2.58 (m, 2H), 2.45 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ209.6, 159.1, 147.9, 133.5, 127.7, 113.9, 69.6, 55.3, 35.3, 26.6; MS (ESI) m/z (%): 241.08 [$(M + Na)^+$, 100].Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.71; H, 6.33.



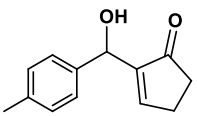
2-[hydroxy(3-methoxyphenyl)methyl]cyclopent-2-enone (17) : Compound **17** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 3-methoxybenzaldehyde (1.8 mmol, 219 µL). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.32) to give the pure product as a yellow oil in 63% yield. ^{1}H NMR 400 MHz, CDCl3 δ7.28-7.22 (m, 2H), 6.94-6.79 (m, 3H), 5.51 (s, 1H) 3.77 (s, 3H), 2.56 (m, 2H), 2.43 (m, 2H); ^{13}C NMR 100 MHz, CDCl3 δ209.6, 159.7, 147.6, 143.0, 129.5 (2C), 118.6, 113.3, 111.8, 69.5, 55.2, 35.2, 26.6; MS (ESI) m/z (%): 241.11 [$(M + Na)^+$, 100].Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.67; H, 6.36.



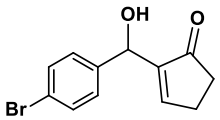
2-[hydroxy(2-methoxyphenyl)methyl]cyclopent-2-enone (18): Compound **18** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 2-methoxybenzaldehyde (1.8 mmol, 217 µL). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.41) to give the pure product as a yellow oil in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 3 H), 6.99-6.94 (m, 1H), 6.89-6.84 (m 1H) 5.84 (s, 1H) 3.82 (s, 3H), 2.58 (m, 2H), 2.45 (m, 2H); ^{13} C NMR (50 MHz, $CDCl_3$) δ 209.9, 159.7, 156.5, 146.9, 130.6, 128.8, 127.4, 120.9 110.1, 65.3, 51.3, 35.3, 26.6; MS (ESI) m/z (%): 241.08 [$(M + Na)^+$, 100].Anal. Calcd for $C_{13}H_{14}O_3$ (218.25): C, 71.54; H, 6.47. Found: C, 71.66; H, 6.35.



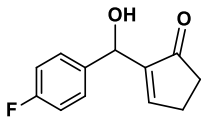
2-[hydroxy(3,4-dimethoxyphenyl)methyl]cyclopent-2-enone (19) : Compound **19** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL), 3,4-dimethoxybenzaldehyde (1.8 mmol, 300 mg). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.46) to give the pure product as a yellow oil in 37% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95-6.81 (m, 4 H), 5.50 (s, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H) 2.58 (m, 2 H), 2.45 (m, 2 H); □C (50 MHz, $CDCl_3$) δ 209.7, 159.3, 149.1, 148.6, 147.8, 133.9, 118.6, 110.9, 109.5, 69.7, 55.9 (2C), 35.3, 26.6; MS (ESI) m/z (%): 271.17 [(M + Na)$^+$, 100].Anal. Calcd for $C_{14}H_{16}O_4$ (248.27): C, 67.73; H, 6.50. Found: C, 67.80; H, 6.58.



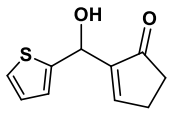
2-[hydroxy(4-methylphenyl)methyl]cyclopent-2-enone (20).: Compound **20** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 4-methylbenzaldehyde (1.8 mmol, 227 µL). The crude product was purified by FCC eluting with 1:1 hexane-diethyl ether (R_f0.26) to give the pure product as a colorless oil in 54% yield. ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.29-7.14(m, 5H), 5.50 (s, 1H), 3.49 (br, 1H), 2.57 (m, 2H), 2.43 (m, 2H), 2.33 (s, 3H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 209.6, 159.3, 147.9, 138.5, 137.5, 129.2, 126.3, 69.6, 35.3, 26.6, 21.1; MS (ESI) m/z (%): 225.17 [(M + Na)$^+$, 100].Anal. Calcd for $C_{13}H_{14}O_2$ (202.25): C, 77.20; H, 6.98. Found: C, 77.42; H, 6.90.



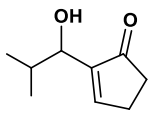
2-[hydroxy(4-bromophenyl)methyl]cyclopent-2-enone (21) : Compound **21** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 4-bromobenzaldehyde (1.8 mmol, 333 mg). The crude product was purified by FCC eluting with 1:1 hexane-diethyl ether (R_f0.14) to give the pure product as a yellow oil in 80% yield. ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.45-7.41 (m, 2H), 7.16 (d, J=7.90 Hz, 2H), 5.45 (s, 1H), 2.55 (m, 2H), 2.39 (m, 2H); ^{13} C NMR (100 MHz, , $CDCl_3$) δ 209.6, 159.8, 147.3, 141.7, 131.6, 128.1, 121.5, 68.9, 35.2, 26.7; MS (ESI) m/z (%): 289.08 [(M + Na)$^+$, 100], 291.17 [(M + 2 + Na)$^+$, 100].Anal. Calcd for $C_{12}H_{11}BrO_2$ (267.12): C, 53.96; H, 4.15. Found: C, 54.11; H, 4.02.



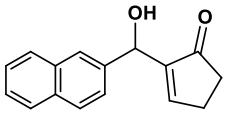
2-[hydroxy(4-fluorophenyl)methyl]cyclopent-2-enone (22).: Compound **22** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 4-fluorobenzaldehyde (1.8 mmol, 192 µL). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.36) to give the pure product as a brown oil in 84% yield ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.29 (m, 3H), 7.03-6.98 (m, 2H), 5.50 (s, 1H), 3.68 (br, 1H), 2.57 (m, 2H), 2.42 (m, 2H); □C 13C NMR 100 MHz, CDCl3 δ209.6, 162.3 (d, J_{C-F}= 246), 159.5,147.7, 137.13 (d, J_{C-F}= 3), 128.1 (d, J_{C-F}= 8), 115.3 (d; J_{C-F}= 22), 69.1, 35.2, 26.7; MS (ESI) m/z (%):229.08[(M + Na)$^+$, 100].Anal. Calcd for $C_{12}H_{11}FO_2$ (206.21): C, 69.89; H, 5.38. Found: C, 69.99; H, 5.29.



2-[hydroxy(2-thienyl)methyl]cyclopent-2-enone (23) : Compound **23** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and thiophene-2-carboxaldehyde (1.8 mmol, 165 µL). The crude product was purified by FCC eluting with 1:1 hexane-diethyl ether (R_f0.34) to give the pure product as a yellow oil in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 1 H), 7.27-7.23 (m, 1H), 7.00-6.95 (m, 2H), 5.81 (s, 1H), 3.68 (br, 1H), 2.65-2.62 (m, 2H), 2.49-2.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 159.6, 146.9, 145.1, 126.7, 125.2 124.7, 66.2, 35.3, 26.7; MS (ESI) m/z (%): 217.08 [(M + Na)$^+$, 100].Anal. Calcd for $C_{10}H_{10}O_2S$ (442.52): C, 61.83; H, 5.19. Found: C, 62.00; H, 5.28.



2-(2-ethyl-1-hydroxybutyl)cyclopent-2-enone (24) : Compound **24** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 2-methylpropionaldehyde (1.8 mmol, 164 µL). The crude product was purified by FCC eluting with 3:1 hexane-ethyl acetate (R_f0.19) to give the pure product as a yellow oil in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 1H), 4.17 (d, J=5.8 Hz, 1 H), 2.79 (br, 1H), 2.60 (m, 2H) 2.44-2.41 (m, 2H), 1.98-1.89 (m, 1H), 0.90-0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 159.2, 146.5, 73.3, 35.2, 32.8, 26.7, 19.0, 17.2; MS (ESI) m/z (%): 177.10 [(M + Na)$^+$, 100].Anal. Calcd for $C_{11}H_{18}O_2$ (430.53): C, 72.49; H, 9.95. Found: C, 72.62; H, 10.01.



2-[hydroxy(2-naphthyl)methyl]cyclopent-2-enone (25). : Compound **14** was synthesized following the general procedure using cyclopent-2-enone (0.6 mmol, 50 µL) and 1-naphthaldehyde (1.8 mmol, 280 mg). The crude product was purified by FCC eluting with 1:1 hexane-ethyl acetate (R_f0.42) to give the pure product as a yellow oil in 73% yield. ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 5H), 7.49-7.47 (m, 3H), 5.74 (s, 1H), 2.57 (m, 2H), 2.46 (m, 2H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 209.7, 159.6, 147.6, 138.6, 133.2, 133.0, 128.3, 128.1, 127.7, 126.2, 126.0, 125.1, 124.3, 70.0, 35.2, 26.7; MS (ESI) m/z (%): 261.17 [$(M + Na)^+$, 100].Anal. Calcd for $C_{16}H_{14}O_2$ (486.56): C, 80.65; H, 5.92. Found: C, 80.78; H, 6.01.

5.5 Bibliography

1. "Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology", Trabocchi, A., Ed.; Wiley and Sons, **2013**.
2. Nielsen, T. E.; Schreiber, S. L.; *Angew. Chem. Int. Ed.,* **2008**, 47, 48.
3. a) Yamashita, Y.; Yasukawa, T.; Yoo, W.-J.; Kitanosono, T.; Kobayashi, S.; *Chem. Soc. Rev.*, **2018,** 47, 4388; b) "Modern Aldol Reactions", Marhwald, R., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA, **2004**
4. For recent reviews on Morita Bayliss Hillman reaction see: a) Basavaiah, D.; Reddy, D. S.; Badsara, S. S.; *Chem. Rev*.**2010**,*110*, 5447; b) Basavaiah, D.; Veeraraghavaiah, G.; *Chem. Soc. Rev.*, **2012**, 41, 68.
5. Morita, K.; Suzuki, Z.; Hirose, H.; *Bull. Chem Soc Jpn,* **1968,** 41, 2815
6. Baylis, A. B.; Hillman, M. E. D.; **1972** German Patent 2155113
7. Galloway, W. R. J. D.; Lobet, A. I.; Spring, D. R.; *Nat. Commun.*,**2010**, 1, 80.
8. Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S.; *Tetrahedron Lett,*. **2001**, 42, 7867.
9. Krishna, P. R.; Reddy; P. S.; *J. Comb. Chem.*,**2008** 10, 3, 426
10. Drewes, S. E.; Njamela, O. L.; Roos, G. H. P. *Chem. Ber.* **1990**, 123, 2455
11. Basavaiah; D.; Veeraraghavaiah; G.; *Chem. Soc. Rev*., **2012**, 41, 68.
12. a)Gatri; R.; El Gaïed; M. M.; *Tetrahedron Lett.*, **2002**, *43*, 7835; b) Ito; H.; Takenaka; Y.; Fukunishi; S.; Iguchi; K.; *Synthesis,* **2005**, 3035. c) Bugarin; A.; Connell; B. T. *J.*; *Org. Chem.*, **2009**, 74, 4638–4641; d) Guerra; K. P.; Afonso; C. A. M.; *Tetrahedron*, **2011**, *67*, 2562. e) Gomes; J. C.; Rodrigues Jr.; M. T.; Moyano; A.; Coelho; F.; *Eur. J. Org. Chem.*, **2012**, 6861.
13. Park; K. H:; Song; S. U.; Chung; J. K.;*Tetrahedron Lett.*, **2003**, 44, 2827.
14. Xu; Y.; McLaughlin; M.; Chen; C. Y.; Reamer; R. A.; Dormer; P.G.; Davies; I. J.;*J. Org. Chem.*, **2009**, 74, 5100
15. Marx; V. M.; Burnell; D. J.;*Org. Lett.*,**2009**, 11, 1229.
16. Simeonov; S.P.; Nunes; J. P. M.; Guerra; K.; Kurteva; V. B.; Afonso; C. A. M.; *Chem. Rev*. **2016**, 116, 5744.

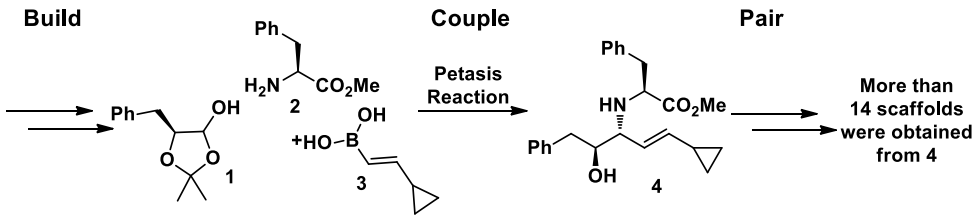
17. Aggarwal; V. K.; Fulford; S. Y.; Jones; G. C. L.; *Angew. Chem. Int. Ed.*, **2005**, 44, 1706
18. Gruttadauria, M.; Giacalone; F. ; Lo Meo, P.; Marculescu; A. M.; Riela; S.; Noto; R.;*Eur. J. Org. Chem.*, **2008**, 1589.
19. a) Shi; M.; Jiang; J. K.; Li; C. Q.; *Tetrahedron Lett.*, **2002**, 43, 127. b) Davies; H. J.; Ruda; A. M.; Tomkinson; N. C- O.;*Tetrahedron Lett.*, **2007**, 48, 1461
20. a)Hoffmann; H. M. R.; Rabe; J.; *Angew. Chem. Int. Ed. Engl*., **1983**, 22, 795; b) Hill; J. S.; Isaacs; N. S. J.; *J. Chem. Res*., **1988**, 330, c) Hill; J. S.; Isaacs; N. S. J.; *J. Chem. Res*., *Phys. Org. Chem*., **1990**, 3, 285.d) Kaye; P. T.; Bode; M. L.; *Tetrahedron Lett*., **1991**, 32, 5611; e) Price; E.; Broadwater; S. J.; Jung; H. M.; McQuade; D. T.; *Org. Lett*., **2005**, 7, 147.

Chapter 6

Synthesis and application of new chiral disulfonimide acid catalysts

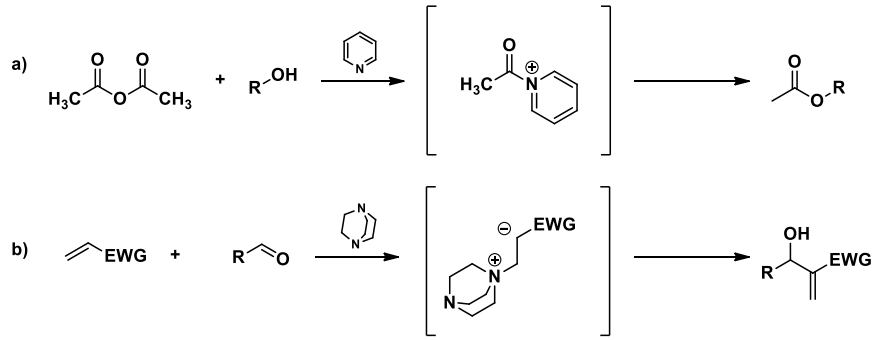
6.1 Introduction

As described in the previous chapter, the Build Couple Pair strategy represents a unique tool to obtain with fast efficient synthetic pathway large libraries of scaffolds composed by many different scaffolds [1]. As also described, the crucial step in this strategy is usually represented by the "Couple Step"[2] because with this reaction we create a poly functionalized compound containing the major part of the functionalities needed to synthesize the final compound. In theory the couple reaction shouldn't create new stereocenters, and when it creates them the total control of all the possible stereochemical outcomes should be maintained[3]. The impossibility to control the stereochemical outcomes make necessary don't create new stereocenter. This is a big limitation in DOS strategy because the number of possible reactions that can be involve for DOS strategy and this is a decrease of its. Many of the reactions resulting more efficient in the B/C/P strategy, such as the multicomponent reactions, provide the transformation of a sp^2 carbon into an sp^3 with the consequent formation of a new stereocenter. In some cases, the geometry of the starting material drives the stereochemistry of the products. An example of this situation was reported by Schreiber by using a Petasis reaction and enantiopure starting materials (**1**, **2**)to obtain a couple reaction with a complete control of the diastereoselectivity (Scheme 1)[4].



Scheme 1 Summary representation of Schreiber's work.

These examples represent only a single solution of this complicated problem because not all the reactions showed such high diastereoselectivity. Moreover, there is no guarantee that all the possible substrates give the same good results and that such strategy is applicable only to diastereoselective reactions, where a stereochemical information is yet contained in the starting materials and does not represent a solution for all the enantioselective ones[5]. Despite all the possibilities of driving and varying the stereochemistry of the products, it remains fundamental in DOS strategies to get what is called stereochemical diversity. A practical solution of this could be represented by the use of stereoselective catalysts. Such compounds catalyze the reaction drive stereochemistry of the products. From all the possible stereo induced catalyst the ones that are among the most preferred choices are called "Organocatalysts"[6]. They are defined as small organic molecules predominantly composed of C, H, O, N, S and P to accelerate chemical reactions[7]. The advantages of organocatalysts include their lack of sensitivity to moisture and oxygen, their ready availability, low cost, and low toxicity, which confers a huge direct benefit in the production of pharmaceutical intermediates when compared with (transition) metal catalysts. Their use in organic chemistry is well known since last century, and for example a typical application is the use of pyridine in esterification reactions, or the use DABCO in the Morita Baylis Hillman reaction[8] (Scheme 2).



Scheme 2 Two classic examples of organocatalysts, a) the activation of acetic anhydride by pyridine, b) the generation of a carboanion from a α,β unsaturated compound promoted by DABCO.

The novelty was represented not in their use as simple catalyst but in their application in the asymmetric synthesis. Indeed, during the past century the use of enantiopure organic molecules as catalysts revolutionized synthetic

chemistry, and the number of works using one of these molecules to direct the stereochemistry of the products increased every year (Figure 1).

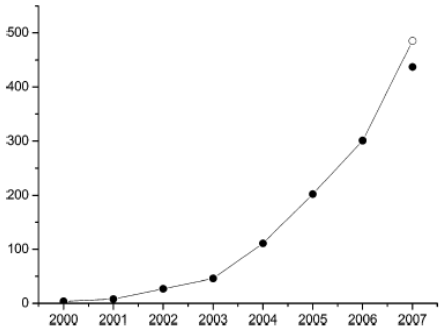
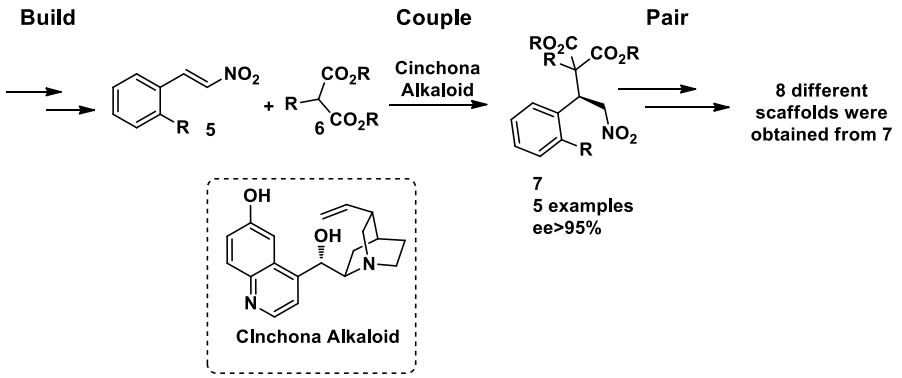


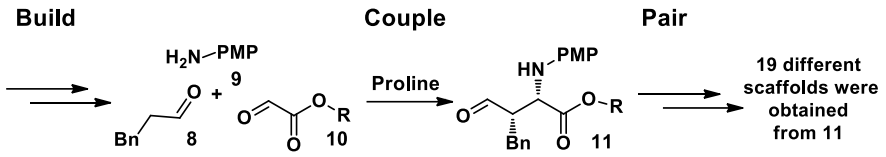
Figure 1 Number of publications using the term "organocatalysis" in the title or abstract since the year 2000: ●, from SciFinder as of November 21, 2007, ○, predicted. Reproduced from reference 12 with the permission of American Chemical Society

Obviously, many works including their use in the crucial step of DOS strategies were published over the years. In 2007 Porco and co workers performed a B/C/P strategy using a couple step a 1,4-addition of substituted dicarbonyls (**6**) to *β*-nitrostyrenes (**5**) catalyzed by cinchona alkaloid to obtain compound **7** with complete control of the stereochemistry[9] (Scheme 3).



Scheme 3 Representation of Porco's B/C/P strategy based on enantioselective couple step by the use of an organocatalyst.

Another example using an organocatalyst in the couple step was reported by Schreiber et al. They performed a diastereoselective Mannich reaction using L-proline as organocatalyst to obtain the couple adduct **11** (Scheme 4)[10].



Scheme 4 The Mannich reaction was performed in a stereoselective way by the use of L-proline as organocatalyst.

It is easy to understand that the use of this kind of catalyst represents a great advantage to perform the couple reaction of a B/C/P strategy. Thus, the discovery, synthesis and application of new catalysts to increase the number of possible reactions obtainable in a stereoselective way is an interesting research field. During last years many new catalysts were synthesized and applied in many reaction as the acid catalysts[11] (Figure 2).

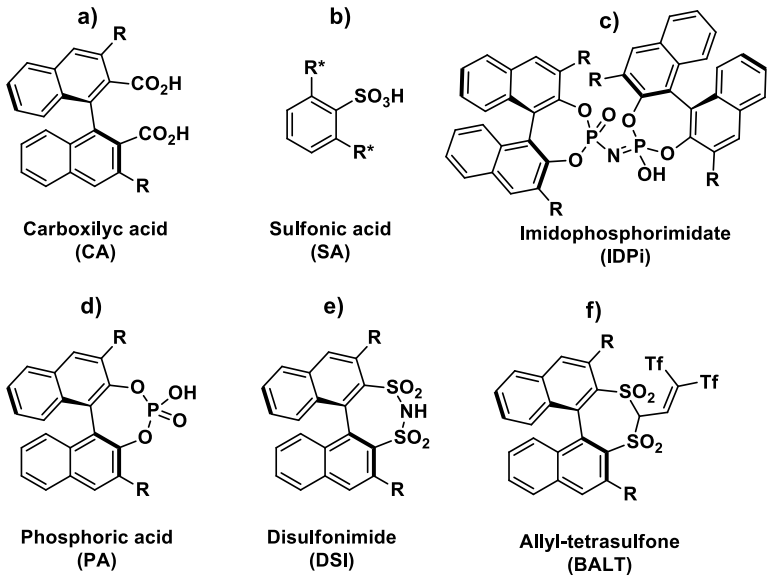
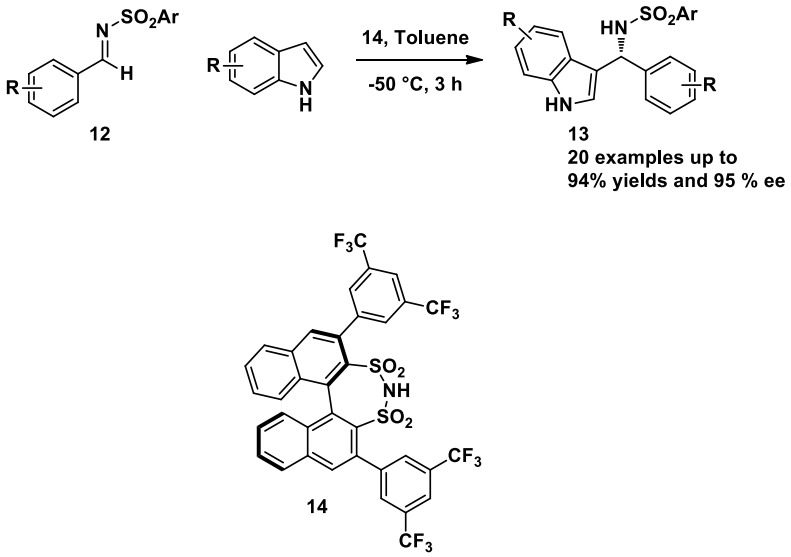


Figure 2 Selection of the most used acid asymmetric organocatalysts.

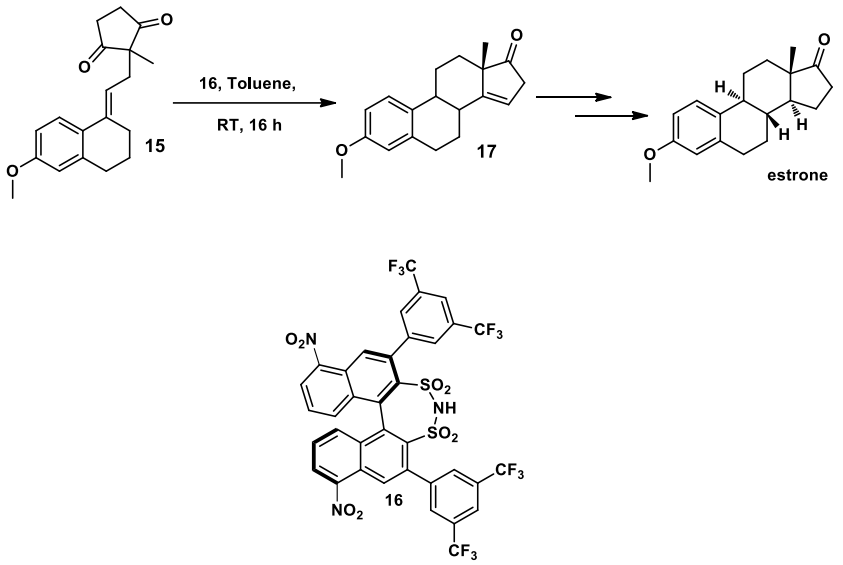
From all of these molecules a novel class that showed success in the last years is the group of disulfonimide (DSI) (Figure 2e) catalysts[12]. These compounds were used in the last years to catalyze many reactions. For example, Lee and co-workers[13] described the enantioselective alkylation reactions mediated by the chiral disulfonimide **14**. The treatment of N-sulfonyl aldimines **12** with several indoles in the presence of disulfonimide

14, in toluene resulted in the formation of secondary sulfonamides **15** in good to excellent yields and with high levels of stereocontrol (Scheme 5).



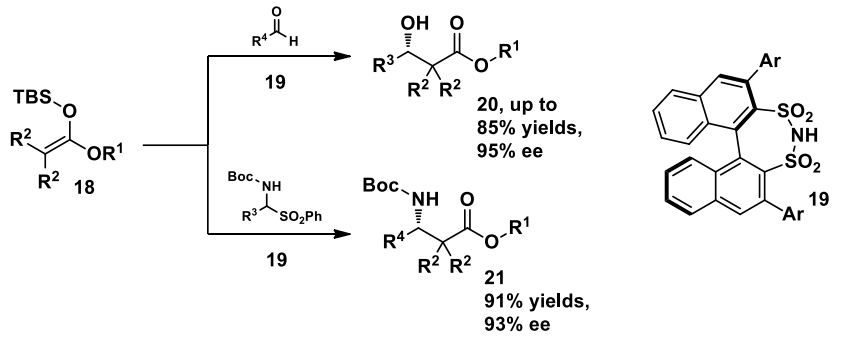
Scheme 5 Summary representation of Lee's work.

In other examples, List and coworkers developed an intramolecular Torgov cyclization of the compound **15** in enantioselective way by the use of enantiopure DSI **16** (Scheme 6). The resulting enantiopure compound **17** was used as starting material in the total synthesis of steroid derived natural products[14].



Scheme 6 List application of DSI **16** for the synthesis of estrone.

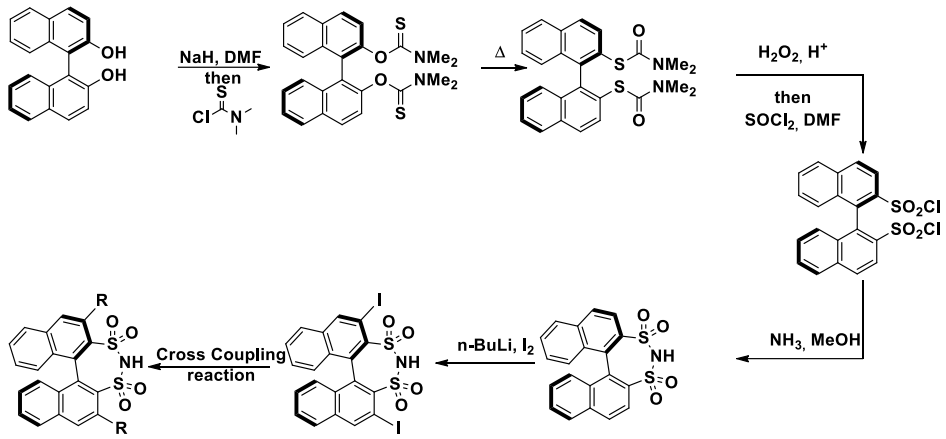
List also reported their application in the Mukaiyama's aldol reaction and its variation Mukayama-Mannich transformation, obtaining excellent results [15, 16, 17] (Scheme 7).



Scheme 7 Representative application of DSI catalyst in the Mukaiyama Aldol and Mukayama-Mannich reactions.

Despite all these interesting applications, this catalyst possesses a crucial limitation for applicability, as the synthetic pathway to obtain it is lengthy and with several steps difficult to be scaled up (Scheme 8). Also, the general structure of these catalysts are almost the same and the variations are focused only in the side chain, thus representing a limitation of their

applicability to many reactions. Indeed, the possibility of modifying easily and quickly the catalyst represents an important improvement[18].



Scheme 8 Classic synthetic pathway for the synthesis of disulfonimide catalysts.

Despite such shortcomings, this new class of catalysts shows many interesting proprieties and also many of the reactions that they are able to catalyze can be applied to DOS strategies. So the improvement of their synthesis represents an incredible opportunity for their application in a larger number of reactions, and for this reason, under the supervision of Prof. Darren J. Dixon from the University of Oxford, I spent four months in this research field focusing my attention to the synthesis of these catalysts and in the research for new reactions they can catalyze.

6.2 Results and Discussion

The first synthetic pathway for the synthesis of our catalyst we hypothesized was based on the synthesis of achiral DSI core by the double sulfonylation of ammonia using aryl halogen sulfonyl chloride and then replacing the alogen with chiral molecules to obtain the DSI catalyst (Figure 3).

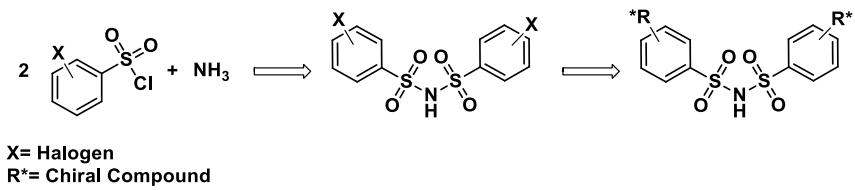
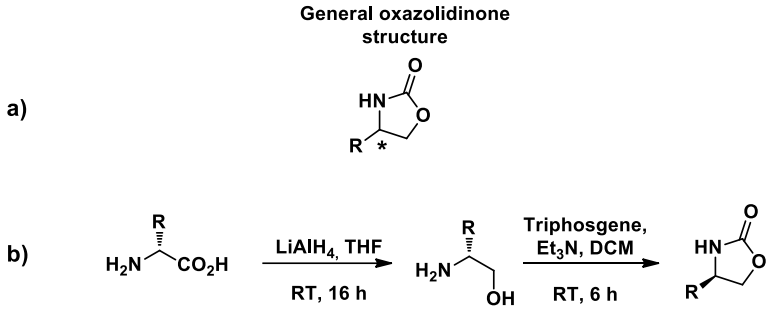


Figure 3 Three-step synthetic pathway to obtain chiral DSI catalysts.

As the chiral side chain we decided to use the chiral oxazolidinones. These compounds are generally used as chiral auxiliary in asymmetric synthesis, because they are commercially available or easy prepared from the corresponding aminoalcohols, thus making it possible to have a large number of different compounds starting from cheap starting materials (Scheme 9).



Scheme 9 a) General structure of oxazolidinone; b) Usual synthetic pathway for the synthesis of chiral oxazolidinones from natural amino acids.

To connect this moiety to our achiral DSI we envisaged to use the classic Ullmann type reaction. This copper catalyzed cross coupling reaction uses amides and aryl halides as general starting materials. The reaction mechanism starts with the creation of the σ complex with the deprotonated amide to give the intermediate **I**; the copper salt performs an oxidative insertion between the aryl and the halide to give the intermediate **II** that evolves by reductive elimination to the Ullmann adduct and to the original copper species(Figure 4).

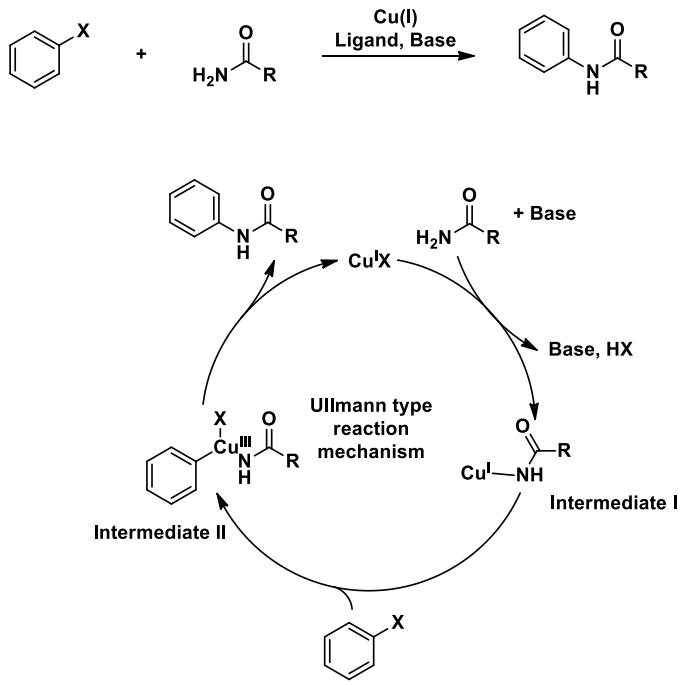
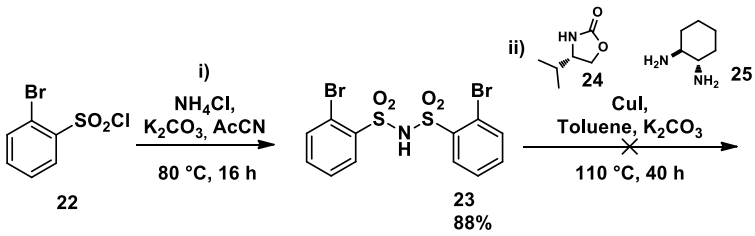


Figure 4 General Ullmann type reaction (Top) and its mechanism (Bottom).

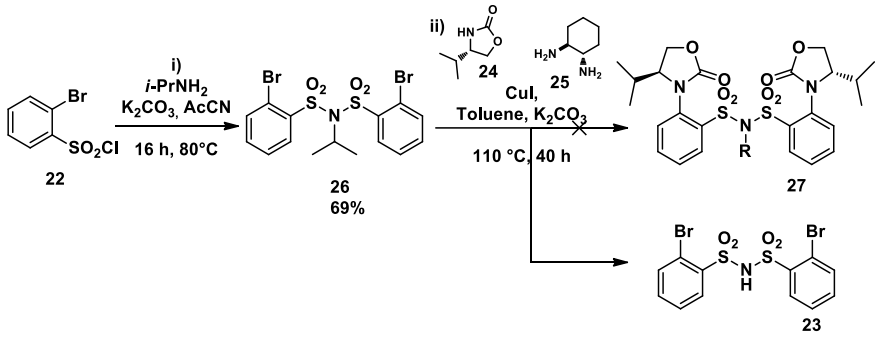
As the starting material we chose the *o*-Br-phenylsulfonyl chloride **22** and following the procedure found in the literature we obtained the desired DSI achiral catalyst **23** in 88% yield. Unfortunately, the successive Ullmann reaction did not give the desired product but only a complex mixture of starting materials and degradation products(Scheme 10).



Scheme10 i) Compound **22** (2.1 eq), K_2CO_3 (3 eq), NH_4Cl (1 eq), AcCN (2 mL/mmol), 80 °C, 16 h; **ii**) **23** (1 eq),), K_2CO_3 (3 eq), **24** (2 eq), (±) *trans*-4-cyclohexane-1,2-diamine (**25**) (1 eq), CuI (1 eq), Toluene (1 mL/mmol), 110 °C, 40 h.

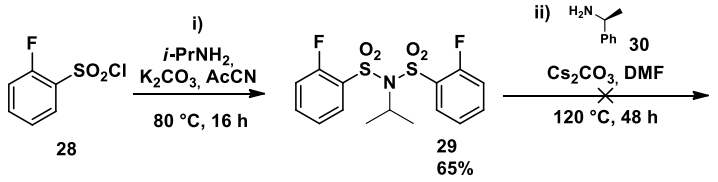
We thought that the problem of this unsuccessful Ullmann reaction could be the presence of the free N-H bond of DSI substrate, as it could interact negatively with the catalytic system. To solve this problem we replaced the

ammonium chloride with *i*-propylamine, and in this way we obtained the N-alkyl sulfonimide (**26**) that was involved in the usual Ullmann coupling. Unfortunately, even in this case we did not obtain the desired compound (**27**) but compound **23,** probably because this "protecting group" was too unstable under the reaction conditions (Scheme 11).



Schem 11 i) Compound **22** (2.1 eq), K_2CO_3 (3 eq), *i*-propilamine(1 eq), AcCN (2 mL/mmol), 80 °C, 16 h; **ii**) **26** (1 eq), K_2CO_3 (3 eq), **24** (2 eq), (±) *trans*-4-cyclohexane-1,2-diamine (**25**) (1 eq), CuI (1 eq), Toluene (1 mL/mmol), 110 °C, 40 h.

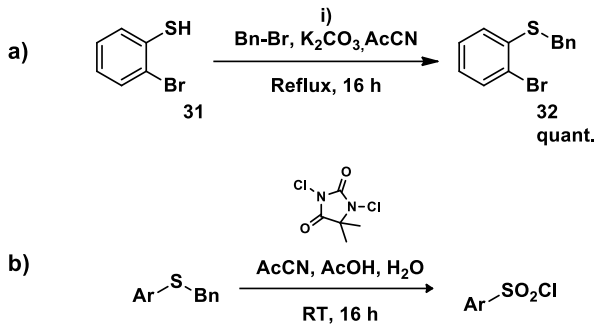
In order to understand if the problem was the coupling reaction we tried to change it and we tried a similar strategy using the ortho-fluorobenzene sulfonyl chloride (**28**) and the chiral (S)-1-phenylethanamine (**30**) using as appending reaction a nucleophilic aromatic substitution, but in this case no reaction was observed (Scheme 12).



Scheme1214 i) Compound **22** (2.1 eq), K_2CO_3 (3 eq), *i*-propilamine (1 eq), AcCN (2 mL/mmol), 80 °C, 16 h; **ii**) **29** (1 eq), Cs_2CO_3 (3 eq), **30** (2 eq), DMF (1 mL/mmol), 120 °C, 48 h.

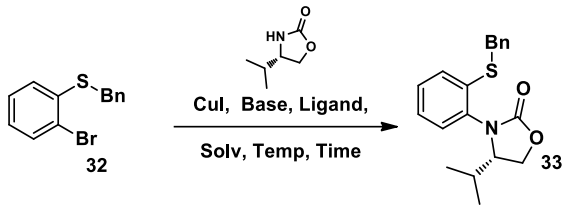
To improve this poor reactivity of our catalytic system we thought that the best way was changing the starting material and installing the chiral side chain before the disulfonylation reaction. Thus, starting from *o*-Br-thiophenol (**31**) we synthesized the S-benzyl (**32**) protected derivative(Scheme 13, a), because in the literature is reported a reaction able

to directly convert this compound into the corresponding sulfonyl chloride(Scheme 13, b).



Scheme 13 a) **i**) BnBr (1.1 eq), **31** (1 eq), K_2CO_3 (1.5 eq), AcCN (4 mL/mmol), reflux, 16 h b) reported example of conversion of. S- Benzyl thiophenol in Aryl sulfonyl chloride

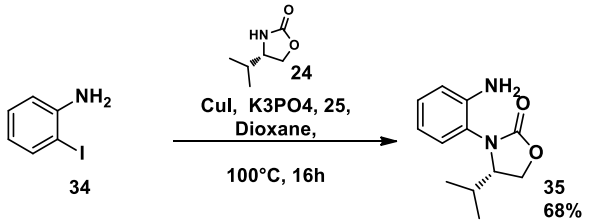
Unfortunately, after several tests performed for the Ullmann coupling, changing the base (Tab.1 entries 1-3), the ligand (Tab.1 entries 4-6) the solvent (Tab.1 entries 7-10) and the reaction timing and temperature (Tab.1 entries 11,12) the best results were achieved by using K_2CO_3, mesitylene, CuI and DMEDA as ligand, a reaction time of 16 h,and150 °C (Tab.1 entry 11) to give the desired product **33** only in 44% yield.



Entry	Base	Solvent	Ligand	Temp. (°C)	Time (h)	Yield(%)
1	K_2CO_3	Toluene	DMEDA	110	16	29
2	K_3PO_4	Toluene	DMEDA	110	16	24
3	Cs_2CO_3	Toluene	DMEDA	110	16	20
4	K_2CO_3	Toluene	Fenantroline	110	16	0
5	K_2CO_3	Toluene	**25**	110	16	12
6	K_2CO_3	Toluene	TMEDA	110	16	0
7	K_2CO_3	DMSO	DMEDA	110	16	0
8	K_2CO_3	DMF	DMEDA	110	16	10
9	K_2CO_3	Dioxane	DMEDA	110	16	19
10	K_2CO_3	Mesitylene	DMEDA	110	16	35
11	K_2CO_3	Mesitylene	DMEDA	150	16	44
12	K_2CO_3	Mesitylene	DMEDA	150	48	0

Tab.12 All the reactions were performed using **32** (1 eq) Base (3 eq), **24** (2 eq), (±) ligand (1 eq), CuI (1 eq), solvent (1 mL/mmol), for indicated time and temperature.

Trying to obtain a better result, we replaced the thiophenol with the corresponding amine **34** and in this case, using the literature reaction conditions, we obtained the desired product **35** in 68% yield (Scheme 14).



Scheme 14 The reaction was performed using **34** (1 eq), **24** (1.5 eq), **25** (1 eq),K_3PO_4 (2 eq) CuI (1 eq), Dioxane (1 mL/mmol), 100 °C, 16 h.

After this cheering results we tried to convert the aniline moiety in the sulfonyl group by a synthetic process called Meerwein process. This methodology is divided in two different steps, in the first one the amine moiety is converted in diazonium salt, then a radical reaction allows to install the sulfonyl chloride moiety (Figure 5).

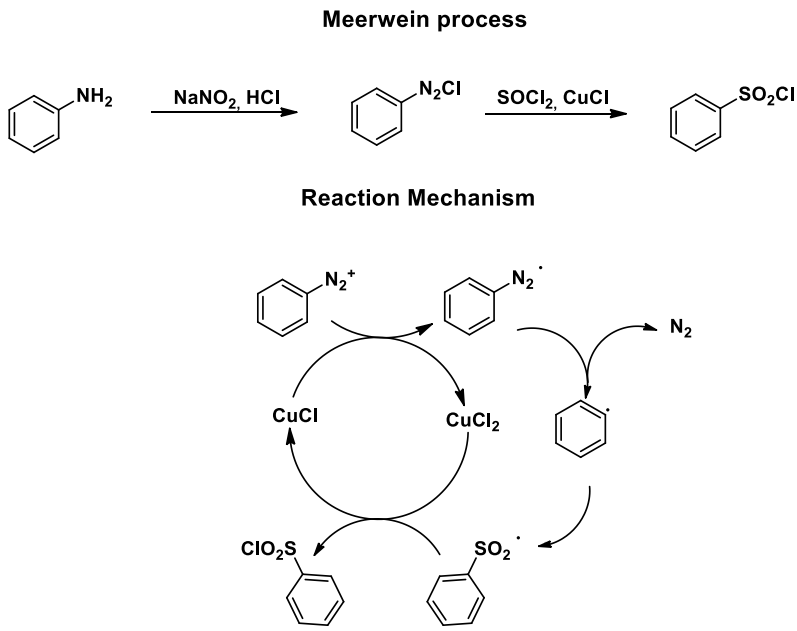
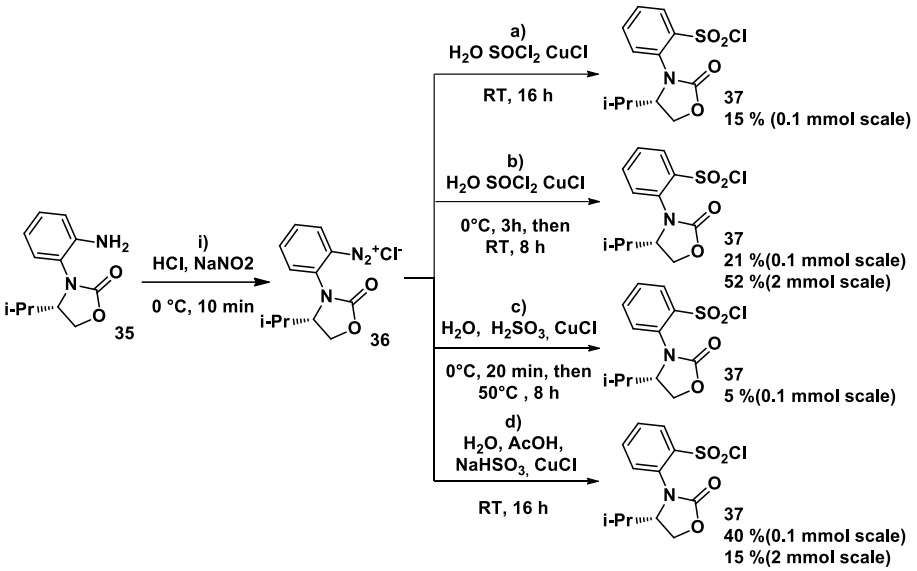


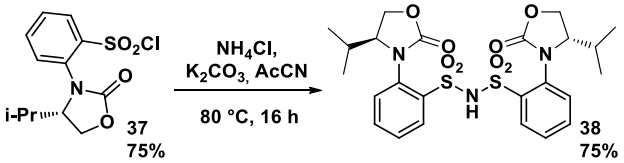
Figure 5 General Meerwein process (Top) and mechanism of the conversion of the diazonium salt in sulfonyl chloride (Bottom).

To perform this reaction we tried different conditions for the installation of the sulfonyl chloride moiety. The process was performed without the isolation of the diazonium salt, because the reaction mixture of the first reaction was directly added to the second one. With surprise, the best reaction performed in 0.1 mmol scale (Scheme 15 reaction **d**), gave a worse result when translated to1 mmol scale, where as the reaction **b** giving bad results at 0.1 mmol scale, proved to be the best one at1 mmol scale.



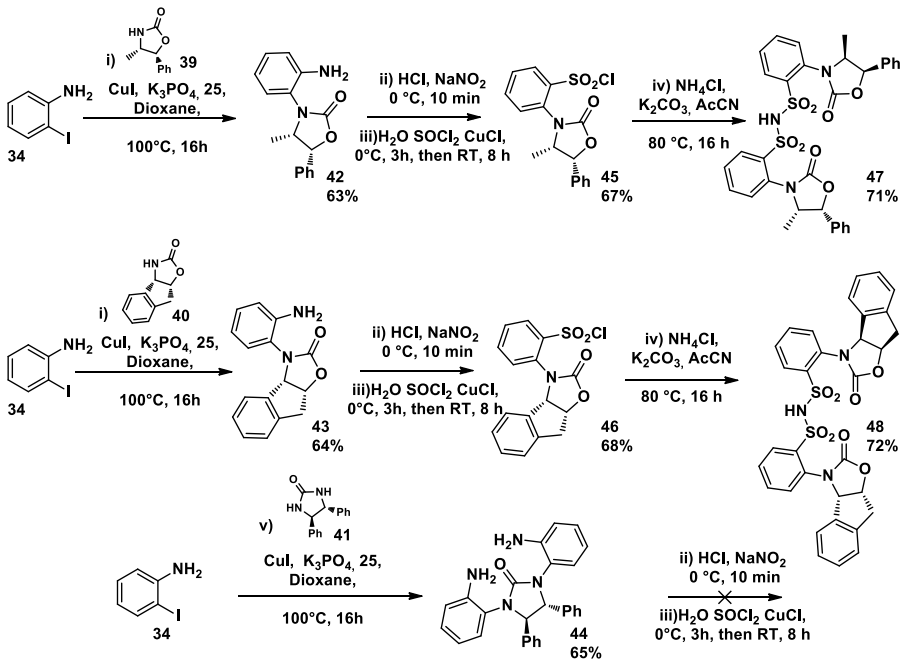
Scheme 15 i) HCl 37% (2,5 mL/mmol), $NaNO_2$ solution 10 M (0,1 mL/mmol), 0°C 15 min; **a**) H_2O (2 mL/mmol), **36** (1 eq), $SOCl_2$ (6 eq), CuCl (0,1 eq), RT, 16 h; **b**) H_2O (2 mL/mmol), **36** (1 eq), $SOCl_2$ (6 eq), CuCl (0,1 eq), 0 °C, 3 h then RT, 8 h; **c**) H_2O (1 mL/mmol), **36** (1 eq), H_2SO_3 (4 eq), CuCl (0,5 eq), 0 °C, 3 h then 50 °C, 8 h; **d**) H_2O (3 mL/mmol), **36** (1 eq), $NaHSO_3$ (8 eq), CuCl (1 eq), RT, 16h;

Following this step, the disulfonylation proceeded without inconveniences to give the desired compound **38** in 75% of yield (Scheme 16).



Scheme 156 37 (2.1 eq), K_2CO_3 (3 eq), NH_4Cl (1 eq), AcCN (2 mL/mmol), 80 °C, 16 h.

In order to expand the nature of the catalyst, we also tried to synthesize the DSI catalyst starting from the compounds **39**-**41**. For the first two catalysts the synthetic pathway proceeded without problems and the catalyst **47** and **48** were obtained, for the compound **41** the Ullmann coupling condition was changed. **41** was used as limiting reagent and *o*-I- aniline in excess because in this case two molecules of *o*-I- aniline were required to obtain the desired product **44** . Unfortunately, the Meerwein reaction using the Ullmann adduct **44** from failed and only a messy mixture of by-products were recovered (Scheme 17).



Scheme 17 i) 34 (1 eq), **39** or **40** (1.5 eq), **25** (1 eq), K_3PO_4 (3 eq), CuI (1 eq), Dioxane (1 mL/mmol), 100 °C, 16 h; **ii)** 37% (2,5 mL/mmol), $NaNO_2$ solution 10 M (0,1 mL/mmol), 0°C 15 min; **iii**) H_2O (2 mL/mmol), **36** (1 eq), $SOCl_2$ (6 eq), CuCl (0,1 eq), 0 °C, 3 h then RT, 8 h; **iv**) **37** (2.1 eq), K_2CO_3 (3 eq), NH_4Cl (1 eq), AcCN (2 mL/mmol), 80 °C, 16 h; **v**) **34** (2.2 eq), **41** (1eq), **25** (1.5 eq), K_3PO_4 (3 eq), CuI (1 eq), Dioxane (1 mL/mmol), 100 °C, 16 h.

Despite this last unsuccessful attempt, we can assert that we found a new rapid synthetic pathway to obtain DSI catalyst from cheap starting materials(Figure 6).

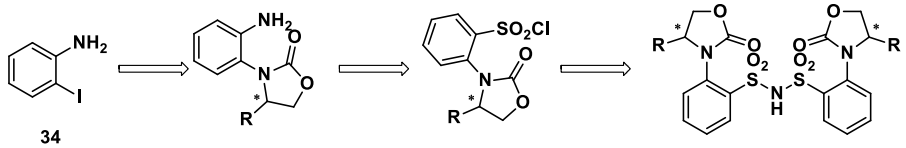
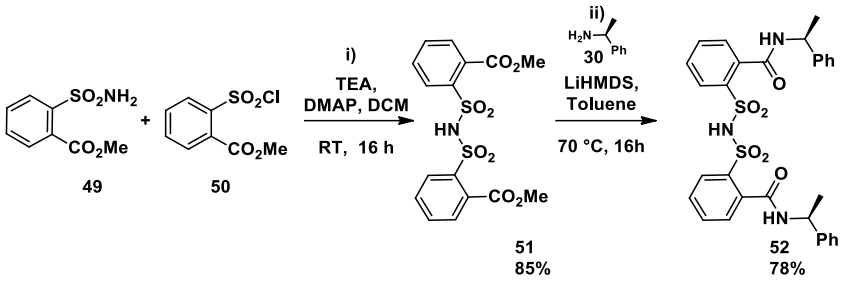


Figure 6 Our synthetic pathway for the synthesis of chiral DSI catalysts.

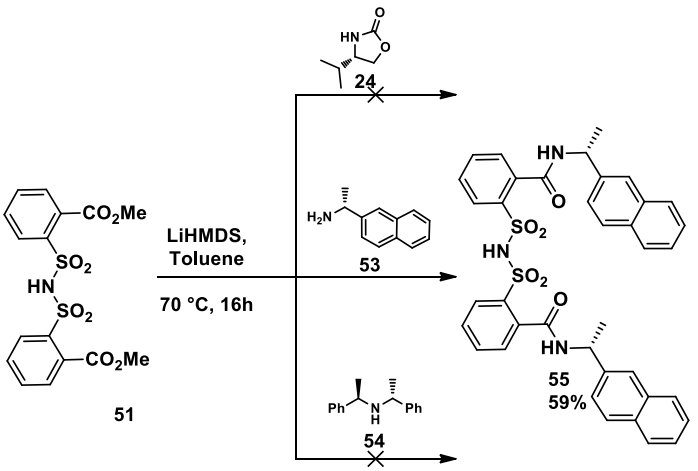
In order to increase the number and the structure diversity of our catalysts we developed another synthetic pathway starting from the methyl 2-sulfamoylbenzoate (**49**). It was involved in a reaction with the sulfonyl chloride **50** in order to obtain the DSI achiral catalyst **51** in 85% yield.

Then, using a recently reported procedure we installed the chiral side chain by an amide bond formation using the chiral amine **30**, thus obtaining the final chiral compounds **52** in 78% yield (Scheme 18).



Scheme 18 i) 49 (1 eq), **50** (1.5 eq), Et_3N (2 eq), DCM (2 mL/mmol), RT, 16 h; **ii) 51** (1 eq), LiHMDS 1 M in toluene (6 eq), **30** (3 eq), Toluene (0,5 mL/mmol), 70 °C, 16 h.

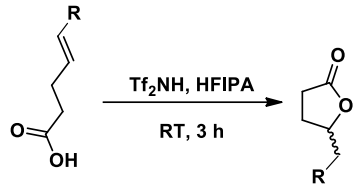
This procedure was interesting, as in only two steps we obtained the final catalyst. Nevertheless, when we tried to expand the scope using amide, or other amines only the primary amine **30** gave the final catalyst. (Scheme 19).



Scheme 19 52 (1 eq), LiHMDS 1 M in toluene (6 eq), indicate nucleophile(3 eq), Toluene (0,5 mL/mmol), 70 °C, 16 h.

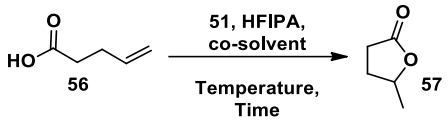
Satisfied by the result obtained, we started to screen several reactions, to understand which reaction could be catalyzed by our catalyst. We studied the reactivity of the trifliimide, because this popular compound has an acidity and a structure moiety similar to our catalysts[19]. The first reaction that we tested with our catalyst is the recently reported Intramolecular

Hydroacyloxylation of unactivated Alkenes and carboxylic acid for the synthesis of lactones (Scheme 20)[20].



Scheme 20 Reported intramolecular cyclization.

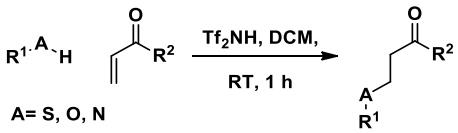
Trying to reproduce this result we started our study using the chiral catalyst **51** and pent-4-enoic acid (**56**) as the substrate. Despite our test that comprised the addition of co-solvent (Tab.2 entry 2) to facilitate the dissolution of **51**, the warming (Tab.2 entry 3), and increase of reaction time(Tab.2 entry 4) no reaction was observed and only starting material was recovered.



Entry	Co- Solvent	Temp. (°C)	Time (h)	Yield (%)
1	-	25	3	0
2	DMF	25	3	0
3	DMF	80	3	0
4	DMF	80	48	0

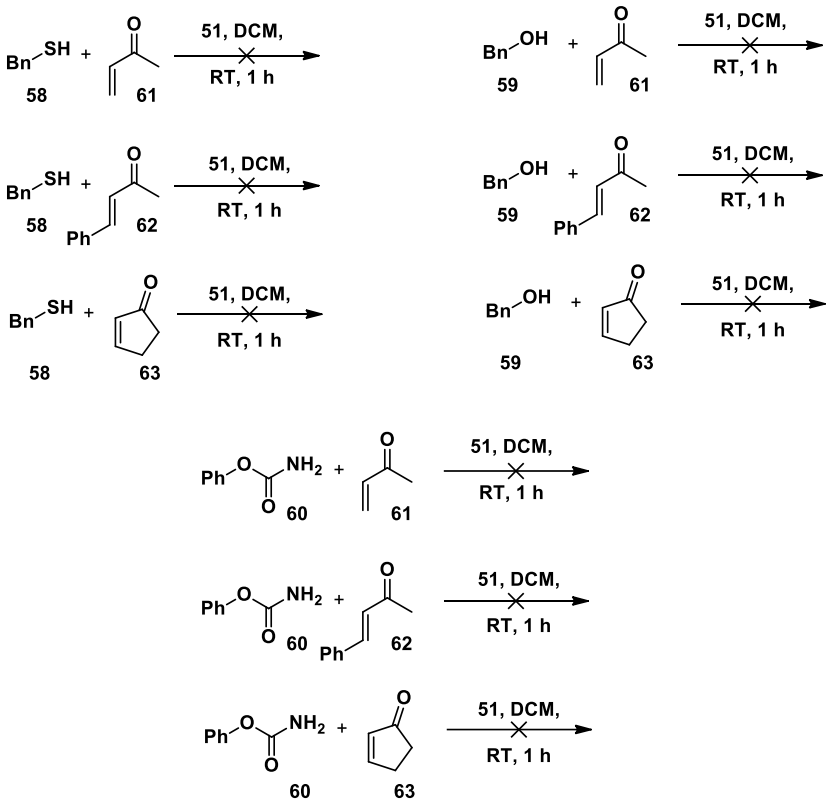
Tab.2 All the reactions are performed using **56** (1 eq), **51** (0,15 eq), HF*i*PA (10 mL/mmol), for the indicate times and temperatures.

Another reported reaction that the Tf_2NH is able to catalyze is the hetero Michael addition of the α,β unsaturated ketones[21] (Scheme 21).



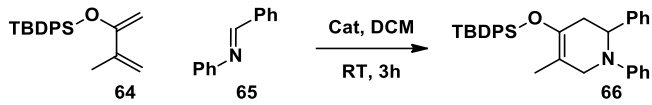
Scheme 21 General scheme of reported Hetero Michael addition catalyzed by Tf_2NH.

Also in this case, despite the use of the more reported reactive nucleophiles (**58- 60**) and ketones (**61-62**), no reaction was observed using the reported conditions (Scheme 22).



Scheme 22 All the reactions were performed using **51** (0,2 eq), ketone (1 eq), nucleophile (1.5 eq) in DCM (1 mL/mmol), RT, 1h.

Instead the reported Hetero Diels-Alder reaction from activated diene (**64**) and aromatic preformed imine (**65**) gave the same results both with triflimide and with our catalyst [22](Tab.3).



Entry	Catalyst	Yield (%)
1	Tf_2NH	68
2	**51**	61
3	-	0

Tab.3 All the reactions were performed using Catalyst (0,2 eq), **64** (1 eq), **65** (1.5 eq) in DCM (1 mL/mmol), RT, 3h.

As preliminary results we can also observe that there was not marked difference in the results obtained from the reported catalyst (Tab.3 entry 1) and ours (Tab.3 entry 2).It can be assessed that the role of the catalyst in this reaction is fundamental as the reaction carried out without catalyst showed the presence of only starting material after the same reaction time (Tab.3 entry 1).

6.3 Conclusions

In conclusion we found two different fast synthetic pathways for the synthesis of new DSI catalysts. Both the synthetic pathways are characterized by being fast and cheap, using commercially available starting materials and giving the final catalyst with acceptable yield (Figure 7).

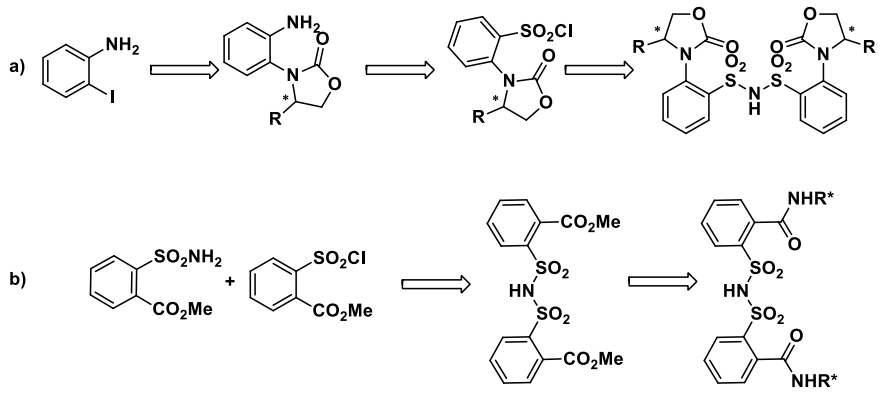


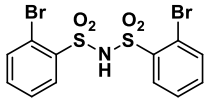
Figure 7 Summarizing representation of our synthetic pathway for the synthesis of chiral DSI catalysts using a) the Ullmann type coupling reaction and b) the amide bond formation to install the chirality.

After this short screening of few reactions we found one where our catalyst was able to reproduce the results from those reported in the literature. Future development of this project will be the synthesis of new chiral DSI catalysts and their application in Hetero Diels Alder reaction and other reactions in which they will show good catalytic activity. After this optimization phase, better reactions will be taken into account as couple step in B/C/P strategy in order to obtain high stereoselective processes.

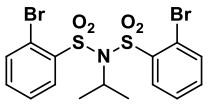
6.4 Experimental Part

General All reagents bought from commercial sources were used as received. Organic solvents were evaporated under reduced pressure using a Büchi rotary evaporator. All solvents were commercially supplied or dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. Petrol ether (PE) refers to distilled light petroleum of fraction 30 - 40 °C. All reactions were followed by thin-layer chromatography (TLC) when practical, using Merck Kieselgel 60 F254 fluorescent treated silica. Visualization was accomplished under UV light (λmax= 254 nm) and by staining with $KMnO_4$ staining dip. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicroTOF mass spectrometer equipped with an ESI source. Infrared absorption spectra (IR) were recorded on a Bruker Tensor 27 FT-IR spectrometer from a thin film on a diamond ATR module. Only selected bands (νmax) are reported in wavenumbers (cm-1). NMR spectra were recorded on Bruker spectrometers operating at 400 (^{1}H resonance). Proton chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance (CDCl3, δ = 7.26 ppm) as internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal. Coupling constants (*J*) are given in Hertz (Hz). ^{13}C-NMR spectra were recorded with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the solvent resonance (CDCl3, δ = 77.16 ppm) as internal standard. Compounds **64** and **65** were prepared in according with the literature [22].

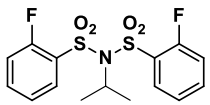
General procedure for disulfinylation reaction (A): Under an argon atmosphere, Amine (1 eq) or (NH_4Cl (1 eq)) and K_2CO_3 (3 eq) was dissolved in AcCN (2 mL/mmol) and to this was added the sulfonyl chloride (2.2 eq) at 0 °C The reaction mixture was warmed to 80 °C for 16 h. Then, EtOAc was added and the organic phase was washed with 2M HCl (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the indicated solvent mixture as eluent, then the pure compound was dissolved in EtOAc and the organic phase was additionally washed with 2M HCl (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure.



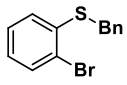
2-bromo-N-((2-bromophenyl)sulfonyl)benzenesulfonamide (23): Compound **23** was obtained following the general procedure (A) using compound **22** (561 mg, 2.20 mmol), NH_4Cl (54 mg, 1 mmol), AcCN (2 mL) and K_2CO_3 (416 mg, 3 mmol) The crude product was purified by flash chromatography with 20:1 DCM:MeOH as eluent ,to give **23** (400 mg) as a yellow solid in 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (br, 1H), 7.92 (dd, *J* = 6.8, 2.1 Hz, 2H), 7.83 – 7.61 (m, 2H), 7.55 – 7.39 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 135.0, 133.8, 132.4, 127.2, 116.0. HRMS (ESI): m/z 451,8265 [(M-H)$^-$, 100%]



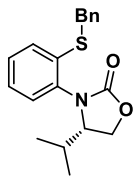
2-bromo-N-((2-bromophenyl)sulfonyl)-N-isopropylbenzenesulfonamide (26) : Compound **26** was obtained following the general procedure (A) using compound **22** (1382 mg, 5.42 mmol), *iso*propylamine(200 µL, 2.46 mmol), AcCN (4.92 mL) and K_2CO_3 (1020 mg, 7.38 mmol) The crude product was purified by flash chromatography with AcOEt as eluent ,to give **26** (843 mg) as a brown solid in 69% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.94 (m, 2H), 7.67 – 7.56 (m, 2H), 7.42 – 7.29 (m, 4H), 4.90 (hept, *J* = 6.9 Hz, 1H), 1.53 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 135.7, 135.0, 134.5, 133.6, 133.0, 131.4, 127.9, 127.7, 120.6, 57.9, 22.4. HRMS (ESI): m/z 495.88831 [M+H$^+$, 60%]$^+$;; 497.88598 [(M+2+H)$^+$, 100%]



2-fluoro-N-((2-fluorophenyl)sulfonyl)-N-isopropylbenzenesulfonamide (26) Compound **29** was obtained following the general procedure (A) using compound **28** (500 mg, 2.57 mmol), *iso*propylamine(95 µL, 1.17 mmol), AcCN (2.34 mL) and K_2CO_3 (485 mg, 3.51 mmol) The crude product was purified by flash chromatography with AcOEt as eluent ,to give **29** (285 mg) as a pink solid in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (qd, *J* = 7.7, 1.7 Hz, 2H), 7.61 – 7.50 (m, 2H), 7.26 – 7.20 (m, 2H), 7.12 (ddd, *J* = 10.2, 8.4, 0.9 Hz, 2H), 4.62 (hept, *J* = 6.9 Hz, 1H), 1.51 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 136.3, 136.2, 132.0, 124.3, 117.3, 117.1, 57.9, 21.8. HRMS (ESI): m/z 376.04840 [(M+H)$^+$, 100%].



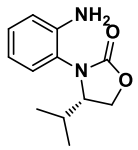
benzyl(2-bromophenyl)sulfane (32) : To a stirred suspension of **31** (960 µL 8 mmol), K_2CO_3 (1656 mg, 12 mmol) in dry AcCN (40 mL) under Argon atmosphere was added in 20 minutes at 0 °C dropwise benzyl bromide (1045 µL 8.8 mmol). Then the reaction was warmed to 80 °C for 16 h, successively the reaction was cooled at RT and HCl 1 M (50 mL) was added, the aqueous phas was extracted with pentane (3 x 40 mL), then the collection of organic phase was mixed and washed with Brine (30 mL), dried with Na_2SO_4 to give the pure compound **32** (2232 mg) in quantitative yield without further purification.. ^{1}H NMR (400.2 MHz, $CDCl_3$) δ, 7.54 (d, J= 8.0 Hz, 1H), 7.35 (d, J= 7.0 Hz, 2H), 7.30 (t,J= 7.5 Hz, 2H), 7.26-7.20 (m, 3H), 7.03-7.00 (m, 1H), 4.14 (s, 2H);13C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.1, 132.9, 128.9, 128.8, 128.6, 127.7, 127.4, 126.9, 123.6, 37.9, HRMS (ESI): m/z 278.9844 [M+H$^+$, 100%].



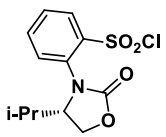
(S)-3-(2-(benzylthio)phenyl)-4-isopropyloxazolidin-2-one (33) : 32 (278 mg, 1 mmol), potassium phosphate (414 mg, 3 mmol), copper(I) iodide (190 mg 1 mmol) and an oxazolidinone **24** (258 mg, 2 mmol) were placed in a dry flask, and 2 sequences vacuum/argon were applied. Under argon, dry mesitylene was added (2 mL), and the suspension was stirred vigorously while *N*,*N*′-dimethylethylenediamine was added in one portion (110 µL, 1 mmol). The resulting dark suspension was warmed for 16 h at 150°C. Then, EtOAc was added and the organic phase was washed with 5% NH_4OH (3 x 20 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using pentane:Et_2O 3:1 to obtain **33** in 44% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 2H), 7.26 – 7.14 (m, 7H), 4.37 (t, *J* = 8.3 Hz, 1H), 4.20 (ddd, *J* = 8.2, 4.9, 3.4 Hz, 1H), 4.14 (dd, *J* = 8.3, 5.0 Hz, 1H), 4.04 (d, *J* = 7.1 Hz, 2H), 1.68 (heptd, *J* = 6.9, 3.5 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 131.1, 129.0, 128.7, 128.6, 127.4, 127.3, 63.8, 61.8, 38.6, 28.9, 18.0, 15.1. HRMS (ESI): m/z 328.13624 [M+H$^+$, 100%].

General procedure for Ullmann coupling of the *o*-iodo-aniline (B): *o*-iodo-aniline (1 eq.), potassium phosphate (2 eq), copper (I) iodide (1 eq) and an oxazolidinone **24** (1.5 eq) were placed in a dry flask, and 2 sequences vacuum/argon were applied. Under argon, dry dioxane was added (1 mL/mmol), and the suspension was stirred vigorously while **25** was

added in one portion (1 eq). The resulting dark suspension was warmed for 16 h at 110°C. Then, EtOAc was added and the organic phase was washed with 5% NH_4OH (3 x 20 mL) and brine. The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using indicated solvent mixture.

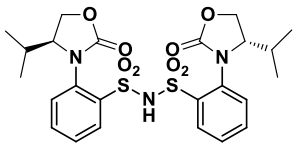


(S)-3-(2-aminophenyl)-4-isopropyloxazolidin-2-one (35): **35** was obtained following the general procedure (B) using compound **34** (219 mg, 1 mmol), **24** (193 mg, 1.5 mmol) potassium phosphate (424 mg, 2 mmol), CuI (190 mg 1 mmol), Dioxane (1 mL) and **25** (120 µL, 1 mmol) The crude product was purified by flash chromatography with pentane: AcOEt 2:1 as eluent ,to give **35** (150 mg) as a pale solid in 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.97 (m, 2H), 6.72 – 6.62 (m, 2H), 4.39 (t, *J* = 8.5 Hz, 1H), 4.25 – 4.18 (m, 1H), 4.15 (dd, *J* = 8.4, 5.9 Hz, 1H), 3.91 (d, *J* = 37.4 Hz, 2H), 1.81 – 1.69 (m, 1H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.9, 143.7, 128.5, 126.6, 122.5, 118.8, 118.0, 64.1, 61.6, 28.7, 17.8, 15.0. HRMS (ESI): m/z 221,12935 [$M+H^+$, 100%].

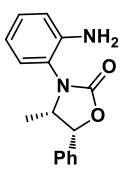


(S)-2-(4-isopropyl-2-oxooxazolidin-3-yl)benzene-1-sulfonyl chloride (37) : In a round bottom flask **35** (440 mg 2 mmol) was dissolved in HCl_{conc} (5 mL) at 0°C, then a solution of $NaNO_2$ (151 mg, 2.2 mmol) in water (1 mL) was added dropwise over 10 minutes, in contemporary to a round bottom flask containing water (10 mL), was added drop by drop $SOCl_2$ (6.27 mL, 12 mmol) at -15 °C. when the addition was complete CuCl (0.1 mmol, 10 mg) and then the first solution was added. The reaction mixture was stirred for 3 h at 0 °C and then warmed to room temperature and left react for 8 h. After this a solution of $NAHCO_{3\ sat}$ (30 mL) was added and the aqueous phase was extracted with DCM (3 x 25 mL) then the collection of organic phase was mixed and washed with BRINE (20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture of pentane Et_2O 2:1 to obtain **37** (315 mg) in 52% yield as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.55 (m, 1H), 7.30 – 7.16 (m, 3H), 4.45 (t, *J* = 8.6 Hz, 1H), 4.29 (dt, *J* = 8.6, 4.3 Hz, 1H), 4.19 (dd, *J* = 8.6, 5.2 Hz, 1H), 1.75 (qd, *J* = 10.6, 6.7 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 135.1, 135.0, 129.8, 129.0,

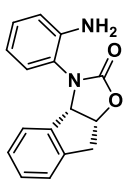
128.5, 64.0, 62.0, 29.1, 18.1, 15.2. HRMS (ESI): m/z 326,02297 [$(M+Na)^+$, 100%]



2-((S)-4-isopropyl-2-oxooxazolidin-3-yl)-N-((2-((S)-4-isopropyl-2-oxooxazolidin-3-yl)phenyl)sulfonyl)benzenesulfonamide (38) : Compound **38** was obtained following the general procedure (A) using compound **37** (1000 mg, 3.3 mmol), NH_4Cl (80 mg, 1.5 mmol), AcCN (3 mL) and K_2CO_3 (620 mg, 4.5 mmol) The crude product was purified by flash chromatography with AcOEt as eluent ,to give **26** (620 mg) as a white solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 16.0, 7.6 Hz, 2H), 7.18 - 7.16 (m, 6H), 4.40 (t, *J* = 8.6 Hz, 2H), 4.24 (dt, *J* = 8.6, 4.2 Hz, 2H), 4.14 (dd, *J* = 8.4, 5.3 Hz, 2H), 1.73 - 1.67 (m, 2H), 0.82 (d, *J* = 6.8 Hz, 6H), 0.71 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 135.1, 135.0, 129.8, 129.0, 128.5, 64.1, 62.0, 29.0, 18.1, 15.2. HRMS (ESI): m/z 551.30693 [$(M)^+$, 100%]

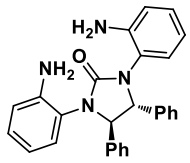


(4S,5R)-3-(2-aminophenyl)-4-methyl-5-phenyloxazolidin-2-one (42): 42 was obtained following the general procedure (B) using compound **34** (438 mg, 2 mmol), **39** (386 mg, 3.0 mmol) potassium phosphate(848 mg, 4 mmol), CuI (380 mg 2 mmol), Dioxane (2 mL) and **25** (240 µL, 2 mmol) The crude product was purified by flash chromatography with pentane: AcOEt 3:2 as eluent ,to give **42** (337 mg) as a brown solid in 63% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.31 (m, 5H), 7.15 – 7.08 (m, 2H), 6.81 – 6.72 (m, 2H), 5.85 (d, *J* = 8.0 Hz, 1H), 4.56 (dq, *J* = 8.1, 6.6 Hz, 1H), 3.93 (br, 2H), 0.69 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 156.6, 144.3, 135.2, 129.0, 128.6, 128.6, 128.5, 128.4, 126.1, 121.9, 118.9, 117.5, 79.2, 57.5, 14.9 HRMS (ESI): m/z 269.12827 [$(M+H)^+$, 100%].

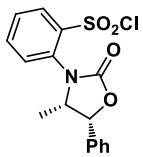


(3aS,8aR)-3-(2-aminophenyl)-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d]oxazol-2-one (43) : 43 was obtained following the general procedure (B) using compound **34** (200 mg, 0.75 mmol), **40** (227 mg, 1.3 mmol) potassium phosphate(480 mg, 2.25 mmol), CuI (140 mg 0.75 mmol), Dioxane (0.75 mL) and **25** (82 µL, 0.75 mmol) The crude product was purified by flash chromatography with pentane: AcOEt 3:2 as eluent ,to give **43** (128 mg) as a brown solid in 64% yield. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.28 (m, 2H), 7.16 (td, *J* = 7.7, 1.5 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.99 (dd, *J*

= 7.8, 1.5 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 5.61 – 5.56 (dd, 1H), 5.52 (ddd, *J* = 7.5, 5.8, 2.7 Hz, 1H), 3.76 (s, 2H), 3.54 – 3.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 144.0, 140.2, 138.6, 129.6, 129.2, 129.1, 127.2, 125.6, 125.5, 122.0, 118.7, 117.3, 65.1, 39.1. HRMS (ESI): m/z 267.11273 [$(M+H)^+$, 100%].

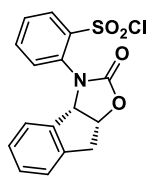


(4R,5R)-1,3-bis(2-aminophenyl)-4,5-diphenylimidazolidin-2-one (44) 44 was obtained following the modified general procedure (B) using compound **34** (959 mg, 2.2 mmol), **41** (476 mg, 1 mmol) potassium phosphate(1272 mg, 6.6 mmol), CuI (380 mg 0.75 mmol), Dioxane (0.75 mL) and **41** (120 µL, 1 mmol) The crude product was purified by flash chromatography with pentane: Et2O4:1 as eluent ,to give **44** (268 mg) as in 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 10H), 7.04 – 6.95 (m, 4H), 6.82 – 6.73 (m, 2H), 6.65 (t, *J* = 7.6 Hz, 2H), 5.25 (ps, 2H), 4.31 – 3.93 (br, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 143.5, 137.8, 128.8, 128.5, 127.5, 127.3, 125.0, 124.3, 118.9, 118.3, 69.8. HRMS (ESI): m/z 421.20225 [$(M+H)^+$, 100%]

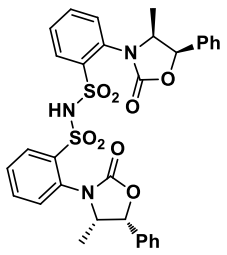


2-((4S,5R)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)benzene-1-sulfonyl chloride In a round bottom flask **42** (402 mg 1.5 mmol) was dissolved in HCl_{conc} (3.75 mL) at 0°C, then a solution of $NaNO_2$ (113 mg 1.65 mmol) in water (300 µL) was added dropwise over 5 minutes, in contemporary to a round bottom flask containing water (3 mL), was added drop by drop $SOCl_2$ (4.70 mL, 9 mmol) at -15 °C. when the addition was complete CuCl (30 mg, 0.15 mmol) and then the first solution was added. The reaction mixture was stirred for 3 h at 0 °C and then warmed to room temperature and left react for 8 h. After this a solution of $NAHCO_{3\ sat}$ (30 mL) was added and the aqueous phase was extracted with DCM (3 x 25 mL) then the collection of organic phase was mixed and washed with BRINE (20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture of pentane Et_2O 2:1 to obtain **45** (352 mg) in 67% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.76 (td, *J* = 7.7, 1.3 Hz, 1H), 7.68 – 7.52 (m, 1H), 7.42 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.40 – 7.26 (m, 5H), 5.87 (t, *J* = 22.3 Hz, 1H), 4.75 – 4.57 (m, 1H), 0.75 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 156.18, 142.78, 136.49, 134.41, 134.24, 130.36, 129.76, 128.70, 125.92, 79.67. HRMS (ESI): m/z 352.04019 [$(M+H)^+$, 100%].

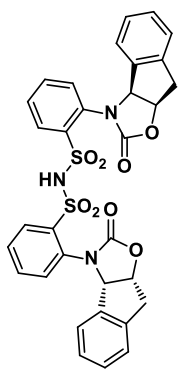


2-((3aS,8aR)-2-oxo-8,8a-dihydro-2H-indeno[1,2-d]oxazol-3(3aH)-yl)benzene-1-sulfonyl chloride (46) : In a round bottom flask **43** (349 mg 1 mmol) was dissolved in HCl_{conc} (2.5 mL) at 0°C, then a solution of $NaNO_2$ (76 mg 1.1 mmol) in water (200 µL) was added dropwise over 5 minutes, in contemporary to a round bottom flask containing water (2 mL), was added drop by drop $SOCl_2$ (3.15 mL, 6 mmol) at -15 °C. when the addition was complete CuCl (10 mg, 0.1 mmol) and then the first solution was added. The reaction mixture was stirred for 3 h at 0 °C and then warmed to room temperature and left react for 8 h. After this a solution of $NAHCO_{3\ sat}$ (30 mL) was added and the aqueous phase was extracted with DCM (3 x 25 mL) then the collection of organic phase was mixed and washed with Brine (20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using a mixture of pentane Et_2O 4:1 to obtain **43** (237 mg) in 68% yield as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 1H), 7.30 – 7.21 (m, 4H), 7.21 – 7.14 (m, 2H), 7.08 – 6.92 (m, 2H), 6.51 (t, *J* = 8.1 Hz, 1H), 5.64 – 5.59 (m, 1H), 5.49 (ddd, *J* = 7.4, 6.4, 2.7 Hz, 1H), 3.51 – 3.33 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.1, 129.7, 129.5, 128.4, 127.1, 125.7, 125.5, 123.4, 122.7, 65.9, 39.1. HRMS (ESI): m/z 350.11856 [$(M+H)^+$, 100%].

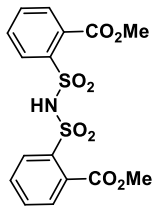


2-((4S,5R)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)-N-((2-((4S,5R)-4-methyl-2-oxo-5-phenyloxazolidin-3-yl)phenyl)sulfonyl)benzenesulfonamide (47) : Compound **47** was obtained following the general procedure (A) using compound **45** (280 mg, 0.8 mmol), NH_4Cl (20 mg, 363 mmol), AcCN (700 µL) and K_2CO_3 (150 mg, 1.09 mmol) The crude product was purified by flash chromatography with AcOEt MeOH 20:1 as eluent ,to give **47** (168 mg) as a pale yellow solid in 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 7.99 (m, 2H), 7.74 – 7.64 (m, 2H), 7.64 – 7.53 (2, 1H), 7.40 – 7.31 (m, 2H), 7.29 – 7.7.16 (m, 10H), 4.74 – 4.61 (m, 2H), 1.53 – 1.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 139.5, 137.6, 136.2, 131.2, 128.8, 127.9, 127.5,

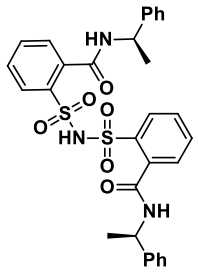
126.3, 123.5, 117.3, 82.1, 58.9, 15.0. HRMS (ESI): m/z 646.13186 [(M-H)$^-$, 100%]



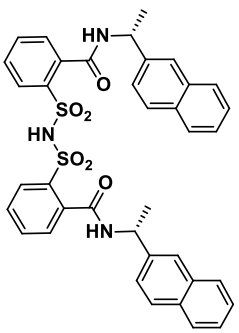
2-((3aS,8aR)-2-oxo-8,8a-dihydro-2H-indeno[1,2-d]oxazol-3(3aH)-yl)-N-((2-((3aS,8aR)-2-oxo-8,8a-dihydro-2H-indeno[1,2-d]oxazol-3(3aH)-yl)phenyl)sulfonyl)benzenesulfonamide (48): Compound **48** was obtained following the general procedure (A) using compound **46** (484 mg, 2.20 mmol), NH_4Cl (54 mg, 1 mmol), AcCN (2 mL) and K_2CO_3 (416 mg, 3 mmol) The crude product was purified by flash chromatography with 20:1 DCM:MeOH as eluent ,to give **23** (461 mg) as a yellow solid in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.05 (m, 2H), 7.72 – 7.57 (m, 4H), 7.44 – 7.32 (m, 2H), 7.28 – 7.11 (m, 8H), 5.87 – 5.77 (m, 2H), 5.67 – 5.53 (m, 2H), 3.32 - 3.19 (m, 4H). ^{13}C NMR (125 MHz, Common NMR Solvents) δ 151.3, 139.2, 139.0, 137.9, 136.9, 132.0, 128.8, 127.6, 127.4, 126.9, 125.4, 123.7, 118.3, 87.6, 67.4, 40.7. HRMS (ESI): m/z 642.08308 [(M-H)$^-$, 100%]



dimethyl 2,2'-((hydrosulfonylamino)sulfonyl)dibenzoate (51): To a solution of compound **49** (500 mg, 2.33 mmol), in dry DCM (4.7 mL) under argon atmosphere was added TEA (650 µL, 4.66 mmol), then the reaction mixture was allowed to 0 °C and **50** (812 mg , 3.48 mmol), was added portionwise over 5 minutes, then the reaction was warmed at RT and stirred for 16 h. Then, EtOAc was added and the organic phase was washed with 2M HCl (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography using the DCM: MeOH 20:1, then the pure compound was dissolved in EtOAc and the organic phase was additionally washed with 2M HCl (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the pure compound **51** (816 mg) in 85% yield as white solid. ^{1}H NMR (400 MHz, DMSO d-6) δ 8.32 (br, 1H), 7.92 – 7.85 (m, 2H), 7.49 – 7.42 (m, 4H), 7.38 – 7.32 (m, 2H), 3.73 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 169.0, 143.8, 132.0, 130.4, 129.8, 128.8, 127.4, 52.7. HRMS (ESI): m/z 412.01639 [(M-H)$^-$, 100%].

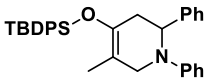


2,2'-((hydrosulfonylamino)sulfonyl)bis(N-((R)-1-phenylethyl)benzamide) (52) : An oven-dried vial equipped with a stir bar was charged with an **51** (600 mg, 1.45 mmol), **30** (560 µL 4.35 mmol) placed under a positive pressure of argon, and subjected to three evacuation/argon cycles. Toluene (700 µL) and LiHMDS 1.0 M in Toluene, (8.7 mL, 8.7 mmol) were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for an indicated time. After the indicated time, the reaction mixture was quenched with NH4Cl (aq., 1.0 M, 1 mL), diluted with EtOAc (10 mL), the organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. Purification was performed by chromatography on silica gel DCM MeOH 5:1 then the pure compound was dissolved in EtOAc and the organic phase was additionally washed with 2M HCl (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure to give the pure compound **52** (668 mg) in 78% yield as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (br, 1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.06 (m, 14H), 5.04 (p, *J* = 6.9 Hz, 2H), 1.42 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 142.4, 136.2, 135.2, 134.0, 130.0, 129.2, 129.1, 128.7, 127.5, 126.4, 49.9, 21.2. HRMS (ESI): m/z 590,14198 [$(M-H)^-$, 100%].



2,2'-((hydrosulfonylamino)sulfonyl)bis(N-((R)-1-(naphthalen-2-yl)ethyl)benzamide) (55): An oven-dried vial equipped with a stir bar was charged with an **51** (289 mg, 0.7 mmol), **53** (329 mg, 2.1 mmol) placed under a positive pressure of argon, and subjected to three evacuation/argon cycles. Toluene (350 µL) and LiHMDS 1.0 M in Toluene (4.2 mL, 4.2 mmol), were sequentially added with vigorous stirring at room temperature, and the reaction mixture was stirred at room temperature for an indicated time. After the indicated time, the reaction mixture was quenched with HCl 1 M, (1 mL), diluted with EtOAc (10 mL), the organic layer was washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. Purification was performed by chromatography on silica gel DCM MeOH 5:1 then the pure compound was dissolved in EtOAc and the organic phase was additionally washed with 2M HCl (3 x 20 mL). The organic phase was dried with

Na_2SO_4 and concentrated under reduce pressure to give the pure compound **52** (285 mg) in 59% yield as white solid. HRMS (ESI): m/z 690.17358 [(M-H)$^-$, 100%]. ^{1}H NMR (400 MHz, DMSO) δ 8.82 (d, *J* = 7.5 Hz, 2H), 7.92 - 7.73 (m, 10H), 7.54 (dt, *J* = 6.4, 3.2 Hz, 2H), 7.50 – 7.42 (m, 4H), 7.39 - 7.21 (m Hz, 4H), 5.15 (m, 2H), 1.48 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, DMSO) δ 167.2, 142.7, 142.3, 135.9, 133.4, 132.5, 130.9, 129.8, 128.9, 128.2, 128.1, 127.8, 126.3, 125.9, 125.7, 124.6, 60.2, 49.7, 21.2, HRMS (ESI): m/z 590,14198 [(M-H)$^-$, 100%].



4-((tert-butyldiphenylsilyl)oxy)-5-methyl-1,2-diphenyl-1,2,3,6-tetrahydropyridine (66): In a dry round bottom flask containing **64** (161 mg, 0.5 mmol) was added under argon atmosphere dry DCM (0.5 mL), **51** (20 mg, 0.05 mmol), and **65** (100 mg, 0.55 mmol). The reaction mixture was stirred for 3 h then $NaHCO_{3\ sat}$ was added, the aqueous phase was extracted with DCM (3 x 10 mL) and the combination of organic phase was mixed and washed with Brine (10 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduce pressure. The crude product was purified by Flash Chromatography on basic alumina using a mixture of pentane Et_2O 10:1 to obtain **63** (153 mg) in 61% yield as a colourless oil. The characterization data were in according with the previous literature [22].

6.5 Bibliography

1. "Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology", Trabocchi, A., Ed.; Wiley and Sons, **2013**.
2. Schreiber, S. L.; *Nature*, **2009**, 457, 153.
3. Wyatt, E. E.; Fergus, S.; Galloway, W. R. J. D.; Bender, A.; Fox, D. J.; Plowright, A. J.; Jessiman, A. S.; Welchd, M.; Spring, D. R.; *Chem. Commun*., **2006**, 3296.
4. Kumagai, N.; Muncipinto, G.; Schreiber, S. L.; *Angew. Chem. Int. Ed*., **2006**, 22, 3635.
5. Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.*, **2008**, *6*, 1149.
6. Buckley, B. R.; Kimber, M. C.; Slater N.H.; *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.*, **2012**, 108, 98.
7. List, B.; *Chem. Rev.*, **2007**, 107, 5413.
8. Basavaiah, D.; Reddy, D. S.; Badsara, S. S.; *Chem. Rev.* **2010**, 110, 5447.
9. Comer, E.*;* Rohan, E.; Deng, L.; Porco, J. A.; *Org. Lett.*, **2007**, 9 2123.
10. Uchida, T.; Rodiquez, M.; Schreiber, S. L.; *Org. Lett.*, **2009**, 11, 7, 1559.
11. Akiyama, T.; Mori, K.; *Chem. Rev.*, **2015**, 115, 9277.
12. James, T.; van Gemmeren, M.; List, B.; *Chem. Rev*., **2015**, 115, 9388.
13. Chen, L.-Y.; He, H.; Chan, W.-H.; Lee, A. W. M.; *J. Org. Chem*. **2011**, 76, 7141
14. Wakchaure, V. N.; Kaib, P. S.; Leutzsch, M.; List, B.; *Angew. Chem. Int. Ed.*, **2015**, 54, 11852.
15. Wang, Q.; Leutzsch, M.; van Gemmeren, M.; List, B.; J. *Am. Chem. Soc*., **2013**, 135, 15334.
16. Gandhi, S.; List, B. *Angew. Chem., Int. Ed*. **2013**, 52, 2573.
17. García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B.; *Angew. Chem., Int. Ed*. **2009**, 48, 4363.
18. Treskow, M.; Neudo, J.; Giernoth, R.*; Eur. J. Org. Chem*., **2009**, 3693.
19. .Zhao, W.; Sun, J.; *Chem. Rev,* .**2018**, 118, 20, 10349.

20. Mukherjee, P.; Woroch, C. P.; Cleary, L.; Rusznak, M.; Franzese, R. W.; Reese, M. R.; Tucker, J. W.; Humphrey, J. M.; Etuk, S. M.; Kwan, S. C.; am Ende, C. W.; Ball, N. D.; *Org*. *Lett*., **2018**, 20, 3943
21. Wabnitz, T. C.; Spencer, J. B.; *Org*. *Lett*. **2003**, 5,2141.
22. Takasu, K.; Shindoh, N.; Tokuyama, H.; Ihara, M.; *Tetrahedron*, **2006**, 62, 11900.

Part IV
Conclusions and appendix

Chapter 7

Conclusions

In conclusion, during my Ph. D I focused my research work tot he study of new reactions that can be applied as a couple step using Build Couple Pair approach in Diversity-Oriented Synthesis strategies for the synthesis of libraries of scaffolds. Initially, we successfully applied the multicomponent copper catalyzed Aldehyde-Amine-Alkyne (A^3) reaction. In our B/C/P strategy we used as starting materials several amines containing different functional groups, the α-amino aldehyde derived from proline and phenylacetylene. The choice of these last two functional groups was based on the fact that both structures are considered privileged scaffolds in drug discovery and indeed these moieties are present in many compounds with interesting biological activity. Also, the choice of using a starting material with a cyclic structure yet present before the "Pair" step allowed us to obtain a higher level of 3D structural complexity in the structure of the final compounds. The study of the reaction allowed us to discover a *syn*-stereoselective preference in the mechanism of the acetylide attack. Finally, starting from only one product of the A^3 reaction we obtained four different bicyclic compounds containing two different privileged scaffold moieties, and we analyzed the structural diversity of the generated compounds using the PMI analysis.

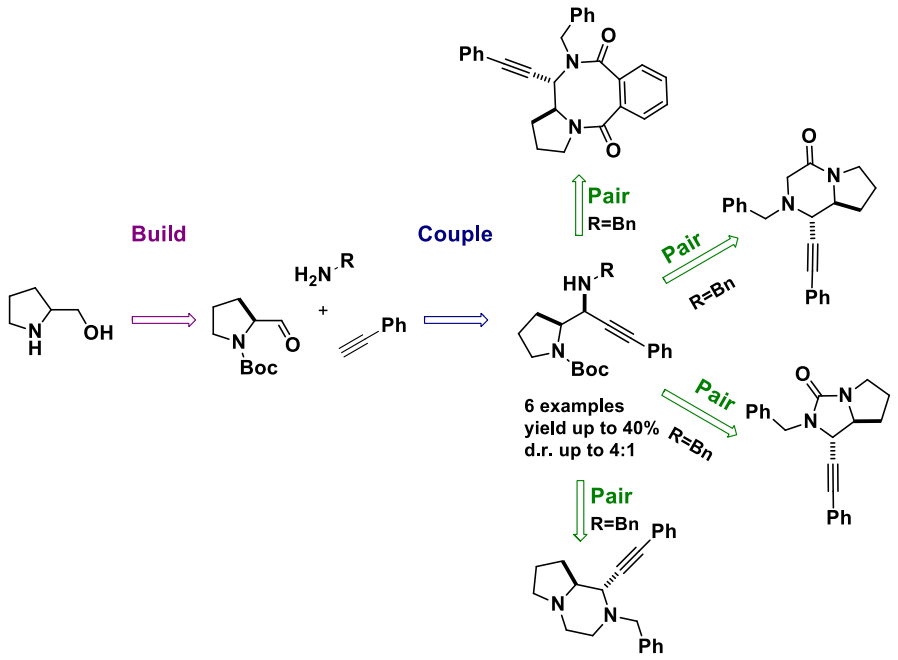


Figure 1 Summarizing report of the A^3 reaction.

The future developments of this project will be the application of other couple products exploiting their functional groups to generate other structures. Also, we used the variation of the A^3 reaction called the Ketone-Amine-Alkyne (KA^2) coupling reaction as couple to obtain a B/C/P strategy able to generate a library of spirocyclic compounds. To obtain this, we tried the hydration reaction of alkynes as pair step without obtaining the desired products, and the Pauson Khand reaction, that successfully resulted to the corresponding spirocyclic compounds. The study of the scope of reaction allowed us to obtain 7 final spirocyclic compounds, and after a second generation of pairing reactions using 4 different reactions we obtained other 4 scaffolds.

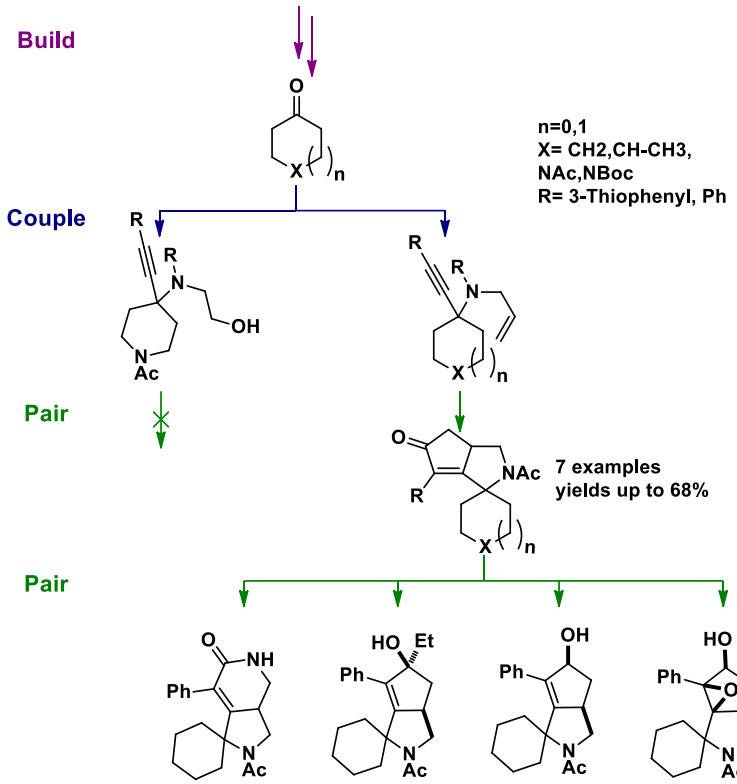


Figure 2 Summarizing report of the KA^2 reaction.

Future developments in this field will be the increase of different pairing reactions to obtain other different spirocyclic compounds. To obtain this, we will use other side chains containing different functional groups or using the same functional groups with different reactions. In order to increase the number of reactions to be used in B/C/P strategy as couple step, we also studied the Morita Baylis Hillman (MBH) reaction using the cyclopent-2-en-1-one as the substrate. Such substrate proved to be one of the hardest to achieve, but after a series of optimization studies, we succeeded in finding a novel iminium based catalytic system able to promote the reaction of this substrate with several aldehydes. The future developments of this project will involve this MBH reaction in a B/C/P using the highly functionalized property of the MBH adduct for the pair step.

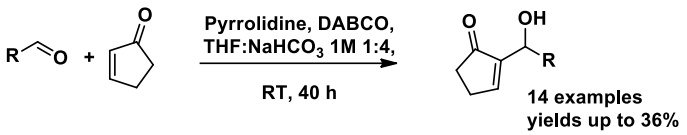


Figure 3 Summarizing report of the MBH reaction.

As last project in collaboration with Prof. Darren J. Dixon I found a novel convenient synthetic strategy to obtain chiral disulfonimide (DSI) catalysts.

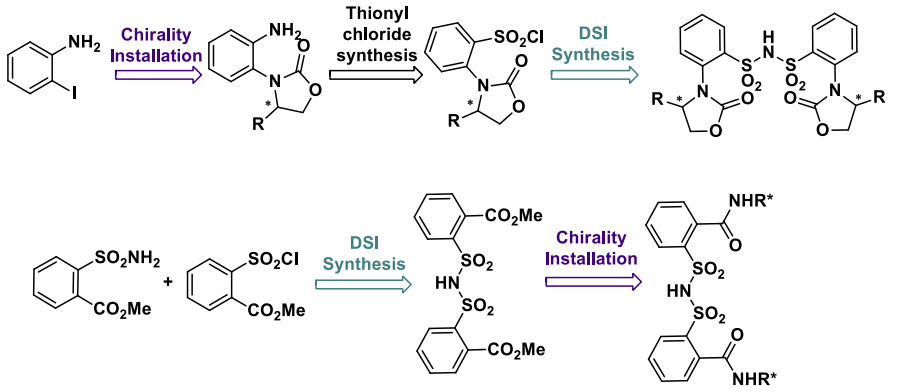


Figure 4 Summarizing report of the synthesis of DSI catalysts.

This catalyst will be tested in several reaction that can be applied as couple step, this can represent a great improvement for a B/C/P strategy because the stereochemical control in the couple step is a good and required property. In the end we obtained two different B/C/P strategies using copper catalyzed reactions and we increased the possibility to obtain other B/C/P strategies thanks to the optimization of the MBH reaction and the synthesis of a new catalyst. After completing the synthesis of all these molecules, such compounds will be delivered to a number of screening versus several targets, especially those concerning phenotypic assays.

Appendix 1
Abbreviations

NME	New Molecular Entities
TOS	Target-Oriented Synthesis
DOS	Diversity-Oriented Synthesis
B/C/P	Build Couple Pair
R&D	Research and Development
HTS	High Throughput Screening
MCR	Multicomponent Reaction
PCA	Principal Component Analysis
PMI	Principal Moments of Inertia
A^3	Aldehyde Amine Alkyne
KA^2	Ketone Amine Alkyne
MBH	Morita Baylis Hillman
PK	Pauson Khand
EWG	Electron Withdrawing Group
EDG	Electron Donating Group
Ac	Acetyl
Ns	Nosyl
Me	Methyl
Et	Ethyl
Pr	Propyl
*i*Pr	*iso*-propyl
*t*Bu	*tert*-buthyl
Ar	Aryl
Ph	Phenyl
Bn	Benzyl
Bz	Benzoyl
Tf	Triflate
Ts	Tosyl
TMS	Trimethylsilyl
TES	Triethylsilyl
TBDS	*tert*-Buthyl dimethylsilyl
TBDPS	*tert*-Buthyl diphenylsilyl
*p*TsOH	*para*-Toluensulfonic acid
PMP	*para*-Methoxyphenyl
PMB	*para*-Methoxybenzyl
Boc	tert-Butoxycarbonyl
CBz	Benzyloxycarbonyl

FMOC	Fluorenylmethoxycarbonyl
TFA	Trifluoroacetic acid
HF*i*PA	1,1,1,3,3,3-Hexafluoroisopropyl alcohol
DMEDA	1,2-Dimethylethylenediamine
TMEDA	1,2-Tetramethylethylenediamine
DABCO	1,4-diazabicyclo[2.2.2]octane
m-CPBA	eta-Chloroperoxybenzoic acid
TMTU	Tetramethylthiourea
TBTU	2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate
TCICA	Trichloroisocyanuric acid
AcOEt	Ethyl Acetate
DCM	Dichloromethane
DCE	1,2 Dichloroethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
AcCN	Acetonitrile

Appendix 2
List of Publications

1. **Innocenti R.**, Lenci E., Menchi G., Trabocchi A.," *Combination of multicomponent KA^2 and Pauson-Khand reactions: short synthesis of spirocyclic pyrrolocyclopentenones*", **2020**, *Beilstein J. Org. Chem.* 16, 200-211.
2. **Innocenti R**., Lenci, L., Baldini, L., Menchi G., Faggi, C., Trabocchi A., *" Copper-catalyzed A^3-coupling for the diversity-oriented synthesis of proline-derived alkynyl-substituted peptidomimetic scaffolds*", **2019**, *Eur. J. Org. Chem*., 6203-6210.
3. Lenci E., **Innocenti R.**, Di Francescoantonio T., Menchi G., Bianchini F., Contini A., Trabocchi A. *Identification of highly potent and selective MMP2 inhibitors addressing the S1' subsite with d-proline-based compounds*, **2019**, *Bioorg. Med. Chem.*, 27, 1891-1902
4. Lenci, E., **Innocenti, R.,** Menchi G., Trabocchi A., *Diversity-Oriented Synthesis and chemoinformatic analysis of the molecular diversity of sp3-rich morpholine peptidomimetics*, **2018**, *Front. Chem.*, 6, 522
5. **Innocenti R**., Menchi G., Trabocchi A., *Dual iminium and Lewis base catalyzed Morita Baylis Hillman reaction on cyclopent-2en-1-one*, **2018**, *Synlett*, 29, 820-824
6. **Innocenti, R.,** Lenci, E.;Menchi, G.; Pupi, A.; Trabocchi, A. *Design and Synthesis of bicyclic acetals as Beta Secretase (BACE1) inhibitors*, **2017,** *Biorg. Med. Chem., 25 ,5077-5083*
7. Lenci, E.; **Innocenti, R**.; Biagioni, A.; Menchi, G.; Bianchini, F.; Trabocchi, A. *Identification of Novel Human Breast Carcinoma (MDA-MB-231) Cell Growth Modulators from a Carbohydrate-Based Diversity Oriented Synthesis Library*, **2016**, *Molecules*, *21*(10), 1405-1423.
8. Lenci, E.; **Innocenti, R**.; Menchi, G.; Faggi, C.; Trabocchi, *A.Two-step one-pot synthesis of dihydropyrazinones as Xaa-Ser dipeptide isosteres through morpholineacetal rearrangement*. *Org. Biomol. Chem.***2015**, 13, 7013-7019.