TESE DE DOUTORAMENTO

THREE-DIMENSIONAL PRINTING IN CATALYSIS: DEVELOPMENT OF REUSABLE METAL-SILICA MONOLITHIC CATALYSTS AND CATALYTIC DEVICES FOR SOLUTION PHASE CHEMISTRY AND DRUG DISCOVERY

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Three-dimensional printing in catalysis: Development of reusable metal-silica monolithic catalysts and catalytic devices for solution phase chemistry and drug discovery

D. Alberto José Coelho Cotón

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Todo lo que escuchamos es una opinión, no un hecho.
Todo lo que vemos es una perspectiva, no es la verdad.

-Marco Aurelio

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Abbreviations index

- 3D: three-dimensional.
- AAPTS: [3- (2-aminoethylamino)-propyl]trimethoxysilane.
- ABS: Acrylonitrile Butadiene Styrene.
- AcOEt: Ethyl acetate.
- APTS: (3-aminopropyl)trimethoxy- silane.
- ATRP: atomic-transfer radical polymerization.
- BCT: body-centered tetragonal.
- BE: binding energies.
- BET: Brunauer−Emmett−Teller.
- CAD: computer-aided design.
- CAE: constant analyzer energy mode.
- CuAAC: copper alkyne−azide cycloaddition.
- DCM: dichloromethane.
- DIPEA: *N*,*N*-Diisopropylethylamine.
- DLP: Digital Ligh Processing.
- DMF: N,N-dimethylformamide.
- DMSO: dimethyl sulfoxide.
- EDS: energy-dispersive X-ray spectroscopy.
- EDX: energy-dispersive X-ray spectroscopy.
- EPR: electro paramagnetic resonance.
- FDM: fused deposition modeling..
- FT-IR: fourier transform Infrared Spectra.
- HR-MS: high-resolution mass spectra.
- ICP-MS: inductively coupled plasma mass spectrometry
- ICP-OES: inductively coupled plasma-optical emission spectroscopy.
- IR: infrared.
- MC: maximum signal counts.
- MCRs: multicomponent reactions.
- MeCN: acetonitrile.
- MeOH: methanol.
- MMCRs: multicatalytic multicomponent reactions.

- MOFs: metal−organic frameworks.
- NCs: nanocomposites.
- NMR: nuclear magnetic resonance.
- NPs: Nanoparticles.
- PCCC: palladium catalyzed cross-coupling.
- Pd: palladium.
- PEG: polyethylene glycol.
- PHC: palladium hydroxy-compounds.
- PI: polyimide.
- PI/Pd: polyimide-palladium.
- PLA: polylactic acid.
- PC: polycarbonate
- PCCCR: palladium catalyzed cross-coupling reaction.
- PMOs: periodic mesoporous organo- silicas.
- PP: polypropylene.
- PS-DIEA: diethylamine on polystyrene.
- PS-TBD: polystyrene-supported 1,5,7-triazabicyclo[4.4.0]- dec-5-ene.
- Ps-TsOH: p-toluenesulfonic acid.
- PVB-PVA- PVAc: poly(vinyl butyral-co-vinyl alcohol-co-vinyl acetate).
- PZC: potencial of zero charge.
- SEA: strong electrostatic adsorption.
- SEM: scanning electron microscopy.
- SLA: stereo-lithography.
- SPOS: Solution phase organic synthesis.
- TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
- tBuOH: *tert*-Butyl alcohol.
- TC: total counts.
- TEA : Triethylamine.
- TEM: transmission electron microscopy.
- TLC: Thin-layer chromatography.
- TMCRs: transition metal-catalyzed reactions.
- TOF-SIMS: Time of flight secondary ions mass spectrometry.

- UV: ultraviolet.
- VSM: vibrating simple magnetometer.
- WD-XRF: wavelength dispersive X-ray fluorescence.
- WI: wet impregnation.
- XPS: X-ray photoelectron spectroscopy.
- XRD: X-ray diffraction.
- ZP: zeta potential.

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SUMMARY

The work developed in this Doctoral Thesis has studied the development and application of the 3D-printing technology in catalytic synthetic chemical processes, at laboratory scale. The main objective was the manufacture of catalytic devices applicable todrug synthesis, mainly aimed at the Pharmaceutical Industry, contributing at the same time to the development of Sustainable Chemistry. On the one hand, heterogeneous monolithic catalysts were synthesized, provided with channels and pores and containing immobilized species of metals (specifically palladium or copper) on their surface. These catalysts were manufactured using three-dimensional printing technology (3D-printing), via direct ink writing technique of a silica support (SiO_2), followed by sintering and subsequent modification of the monolith surface by different surface functionalization techniques for ceramics. Chemical processes described herein are characterized by their speed and efficiency to immobilize metal species on the surface of the ceramic material. The 3D monoliths obtained by the different techniques developed ensure a structure with high catalytic efficiency with negligible levels of metal leaching, adequate mechanical resistance, controlled porosity and easy recyclability/ reusability as catalysts. On the other hand, this Doctoral Thesis addresses the manufacture of other polypropylene devices through 3D printing and its application in catalytic reactions.

The first chapter describes the study of the the surface functionalization of the silica monolith via silanization and subsequent metallization with copper (I) and palladium (0) species. These prepared monolithic catalysts were satisfactorily evaluated in palladium (0) or copper (I) catalyzed reactions by Solution Phase Organic Synthesis, (SPOS) to obtain variously substituted 1,2,3-triazoles. Specifically, the Suzuki, Sonogashira or Stille reactions were evaluated as well as the “click” reaction of copper (I)-catalyzed alkyne-azide cycloaddition, CuAAC. In this work, the catalytic evaluation and reusability of monolithic catalysts in complex multicatalytic/multicomponent transformations were first approached, combining the previously mentioned reactions.

The second chapter describes the study of the surface functionalization of the silica monolith with a polyimide polymer and palladium species, forming a surface composite. Complementarily, the 3D printing of a porous polypropylene capsule that encloses a supported resin loaded with copper (II) species, as well as the synthesis of copper (I) magnetic nanoparticles was addressed. The key objective was to use these

catalysts and devices together in one pot compartmentalized multicatalytic transformations in which two or more heterogeneous catalysts are used in the same reaction medium: The Chan-Lam coupling sequence catalyzed by copper species (II), CuAAC and Suzuki reaction for the synthesis of variously decorated 1,2,3-triazoles was successfully carried out in one-pot version. The design of the catalysts and the transformation itself allows the simple extraction of them, as well as their reusability in new reactions.

The last chapter describes the direct functionalization of the silica monolith with palladium nanoparticles (0) through the wet impregnation (WI) technique via strong electrostatic adsorption (SEA) as well as the evaluation of the catalytic activity and the reusability of the catalyst in Suzuki and Sonogashira reactions. In addition, a custom polypropylene reactor was synthesized by 3D printing and its resistance was evaluated under reaction conditions.

In short, the techniques and methodologies described in this Thesis allow the custom manufacturing of robust and efficient catalysts and catalytic devices, enabling the possibility of a perfect prototyping.

Keywords: 3D printing, Heterogeneous Catalysis, Polyimide, Palladium, Copper Reusability, Sustainable Chemistry, Multicatalysis, Catalyst compartmentalization.

RESUMEN

El trabajo desarrollado en esta Tesis Doctoral, ha pretendido profundizar en el desarrollo y aplicación de la tecnología de impresión en tres dimensiones (3D) en procesos químicos sintéticos catalíticos, a escala de laboratorio. El principal objetivo consistió en la fabricación de dispositivos catalíticos aplicables a la síntesis de fármacos, principalmente dirigidos a la Industria Farmacéutica, contribuyendo a la vez al desarrollo de una Química Sostenible.

Se sintetizaron, por una parte, catalizadores heterogéneos de tipo monolítico, provistos de canales y poros y que contienen especies de metales inmovilizadas (específicamente paladio o cobre) sobre su superficie. Estos catalizadores se fabricaron empleando la tecnología de impresión en tres dimensiones (3D-printing), vía técnica de escritura directa de un soporte de sílice (SiO_2), seguida de sinterizado y posterior modificación de la superficie del monolito mediante diferentes técnicas de funcionalización de superficies cerámicas. Los procesos químicos que se describen en esta memoria se caracterizan por su rapidez y eficiencia para inmovilizar especies metálicas en la superficie del material cerámico. Los monolitos 3D obtenidos por las diferentes técnicas desarrolladas aseguran una estructura con alta eficiencia catalítica, niveles despreciables de lixiviación de metal, una resistencia mecánica adecuada, porosidad controlada y fácil reciclabilidad / reusabilidad como catalizadores.

En esta Tesis Doctoral se aborda también la fabricación de otros dispositivos mediante impresión 3D empleando polipropileno y su aplicación en reacciones catalíticas.

En el primer capítulo se describe el estudio de la estrategia de funcionalización de la superficie de monolitos de sílice vía silanización y posterior metalización con especies de cobre (I) o paladio (0). Estos catalizadores monolíticos preparados se evaluaron de forma satisfactoria en reacciones catalizadas por paladio (0) o cobre (I) mediante química en disolución (Solution Phase Organic Synthesis, SPOS) para la obtención de 1,2,3-triazoles diversamente sustituidos. Concretamente se evaluaron las reacciones de Suzuki, Sonogashira o Stille así como la reacción “click” de cicloadición 1,3-dipolar catalizada por cobre (I), CuAAC. En este trabajo se abordó por primera vez la evaluación catalítica y reusabilidad de catalizadores monolíticos en transformaciones complejas tipo

multicatalíticas / multicomponente, combinando las reacciones previamente mencionadas.

En el segundo capítulo se describe el estudio de la funcionalización de la superficie del monolito de sílice con un polímero de poliimida y especies de paladio, formando un composite superficial muy robusto. Complementariamente se abordó la impresión 3D de una cápsula porosa en polipropileno que encierra una resina polimérica de poliestireno cargada con especies de cobre (II), así como la síntesis de nanopartículas magnéticas que contienen especies de cobre (I). El objetivo clave fue emplear conjuntamente estos catalizadores y dispositivos en transformaciones multicatalíticas compartimentadas de tipo *one pot* en las cuales se emplean dos o más catalizadores heterogéneos en el mismo medio de reacción: La secuencia acoplameinto de Chan-Lam catalizado por especies de cobre (II), CuAAC y reacción de Suzuki para la síntesis de 1,2,3-triazoles diversamente decorados fue llevado a cabo exitosamente. El diseño de los catalizadores y de la propia transformación en sí misma permite tanto la síntesis acelerada de los compuestos finales como la extracción sencilla de los catalizadores, así como su reusabilidad y recuperación individualizada para poder llevar cabo nuevas reacciones.

En el último capítulo se describe la funcionalización directa del monolito de sílice con nanopartículas de paladio (0) mediante la técnica de impregnación húmeda (WI), vía fuerte adsorción electrostática (SEA) así como la evaluación de la actividad catalítica y la reusabilidad del catalizador en reacciones de Suzuki y Sonogashira. Además, se sintetizó un reactor a medida en polipropileno mediante impresión 3D y se evaluó su resistencia en diferentes condiciones de reacción.

En definitiva, las técnicas y metodologías descritas en esta memoria permiten la fabricación a medida de catalizadores metal-cerámicos así como dispositivos catalíticos robustos y eficientes, sentando las bases para un perfecto prototipado a nivel industrial.

Palabras clave: Impresión 3D, Catálisis heterogénea, Poliimida, Paladio, Cobre Reusabilidad, Química Sostenible, Multicatálisis, Compartimentación de catalizadores.

1. INTRODUCTION

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1.1. Catalysis. A brief historical review.

Catalytic phenomena have been known since ancient times, but without knowing their action. In the oldest chemical experiment of Humanity, the obtaining of fire, catalytic phenomena play a role through water vapor, which allows the formation of flame. After this, perhaps the oldest catalytic phenomenon used by man is the enzymatic processes, such as obtaining wine, the formation of vinegar from alcoholic liquids, processes in which nature itself, without the need of man, provides the catalyst.

During the alchemist era, even without reaching any practical result and in a way very deviant from reality, the catalytic idea plays a preponderant role in the chemical thought of that time. In this period, the word catalysis is used for the first time in the works of Libavius, although with a different meaning from the current one.

Gathering many isolated experiments from previous times, Berzelius was able, in 1836, to launch a new fundamental concept, that of catalysis, although still with misconceptions, since he believed that the catalyst aroused sleeping affinities. Accordingly, Berzelius defines them as follows: “The catalytic power essentially appears to consist in the fact that substances are capable, by their mere presence and not by their affinity, of eliciting the affinities which are dormant at this temperature, so that, because of them, the elements within a composite substance arrange themselves in other relationships by which greater electrochemical neutralization is produced” [1]. The most accurate definition of the catalytic phenomenon is that given by the german chemist Alwin Mittasch [2], according to which: «Catalysis is understood as the variation of speed, the production or deviation of thermodynamically possible transformations, by the presence of substances that are chemically not altered, or only very little».

Figure 1. Jöns Jacob Berzelius and Alwin Mittasch (1928).

1.1.1 Homogeneous and heterogeneous catalysts

The modern concept of catalysis assumes that during the catalytic process the catalyst acts cyclically, recovering the initial form after its transformation. The effectiveness of the catalyst depends on the number of cycles can it complete, before deactivation, producing the desired molecule. The industry has a great interest in the production of active and selective catalysts, due to the need to improve chemical processes from an economic and environmental point of view. Depending on the phase in which the reagents and the catalyst are found, two major types of catalysis are distinguished (Figure 2):

- **Homogeneous catalysis:** reagents and catalysts are in the same phase, either liquid or gas. This type of catalysis allows easy access to the reaction mechanism and the absence of poisoning effect. It has a drawback, the difficulty of separating the catalyst from the reaction medium, which entails even greater expense.

- **Heterogeneous Catalysis:** in this case reagents and catalysts are in different phases. Reagents are usually found in the liquid or gas phase and the catalyst is usually solid. The heterogeneous catalyst has an "active site" that is, a specific point or regions where the chemical reaction between the catalyst and the reactive system-products takes place. Among the disadvantages of these catalysts are the surface deactivation, reducing the surface area and the catalytic activity and irreversible poisoning. The thermal process is not limited, increasing the reaction rate. In addition, it is easy to separate the catalyst from the products.

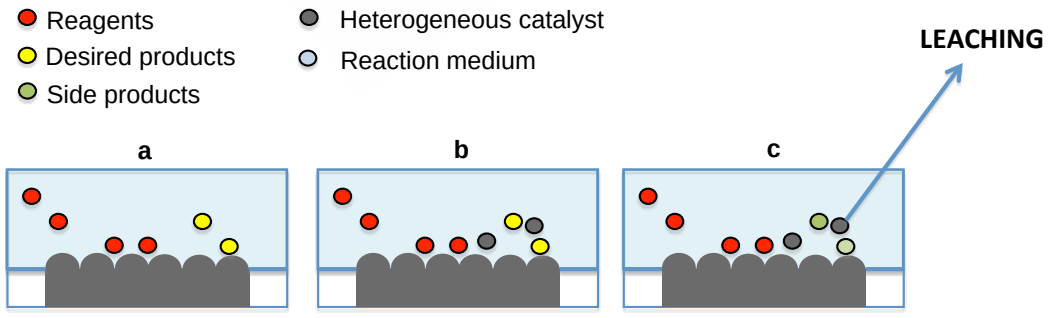


Figure 2: Catalytic events on solid supports.

According to the literature, heterogeneous catalysts can be composed of metals or molecules on a particular support in which metal particles can:

- No leaching or detachment of metal particles or soluble metal species. These catalysts are considered truly heterogeneous (Figure 2a).

- Detach and not interact in the reaction process (Figure 2b).

- Release to the reaction medium and participate in the reaction process as a heterogeneous catalyst, producing collateral products (Figure 2c).

1.1.2 Sustainable Chemistry

The increase of industrial chemical activity in the United States during the 1990s gave rise to a new concept in the industrial and scientific field: Sustainable chemistry or green chemistry. The created institution was called the EPA (Environmental Protection Agency). The main mission was to eliminate or reduce the pollution of industrial processes without diminishing the advantages it provides. Paul Anastas and Jonh Warner established twelve postulates in this regard (1998) [3]:

1. It is better to prevent the waste formation than to try to clean it after its formation.
2. Synthetic methods must be designed to achieve maximum incorporation into the final product of all the materials used in the process.
3. As far as possible, synthetic methodologies should be designed for the use and generation of substances with low human and environmental toxicity.
4. Chemical products must be designed that, while preserving the effectiveness of their function, have low toxicity.
5. Auxiliary substances (solvents, separating agents, etc.) should be unnecessary as far as possible and at the very least, they should be harmless.
6. Energy needs must be considered in relation to their environmental and economic impacts, and minimized. Synthetic methods must be carried out at room temperature and pressure.
7. The starting materials must be renewable and non-extinguishable.
8. The unnecessary formation of derivatives (groups for protection/deprotection, temporary modification of physical/chemical processes) should be avoided as soon as possible.
9. Catalytic reagents (as selective as possible) are superior to stereochemical.
10. Chemical products must be designed so that, at the end of their function, they do not persist in the environment, but rather fragment into inert degradation products.
11. Analytical methodologies that allow real-time monitoring during the process and control prior to the formation of hazardous substances should be developed.

12. The substances and their use in a chemical process must be chosen in a way that minimizes the possibility of accidents.

The postulates of Anastas and Warner as well as other scientists have given ideas on how to carry out environmentally friendly chemical processes that remain efficient ways to achieve a final product without endangering life and ecosystems on the planet. Sustainable Chemistry or Green Chemistry is perhaps the most important area of knowledge within Organic Chemistry today, perhaps because making clean chemistry is no longer a choice, but a historical obligation.

1.2. The importance of the palladium and copper chemistry in Drug Discovery

The pharmaceutical industry generates annual profits of up to 1,105.2 million dollars in 2016, thus becoming one of the most powerful and beneficial markets. This industry has a very important role in the maintenance of human and animal welfare but it is also one of the most polluting, producing in 2016 more than 37 million kilograms of waste and between 25 and 100 kilograms of waste per active ingredient (drug) manufactured [4].

Medicines are special industrial products. Drugs are molecules that produce pharmacological effect that require several synthetic steps for their manufacture. Its levels of purity and analytical controls (table 1) are defined by organizations such as the European Medicines Agency [5].

	Concentration (ppm)	
Metal	Oral	Parenteral
Pt, Pd, Ir, Rh, Ru, Os	5	0.5
Mo, V, Ni, Cr	10	1
Cu, Mn	15	1.5
Zn, Fe	20	2

Table 1. Exposure class and concentration limits for individual metal catalysts and metal reagents.

As can be seen in table 1, the concentration levels of metals allowed in the final products are quite restrictive. For instance, for the oral administration of a drug, a maximum of only 5 ppm is allowed for metals such as palladium or platinum. In the case of copper, the permitted levels can be raised to 15 ppm. In parenteral administration, these restrictions are even greater, with levels of 0.5 ppm for palladium and 1.5 ppm for copper, to name two examples. These data are very important from the point of view of the

manufacture of the drug since as will be addressed in the following sections of this Doctoral Thesis, both palladium and copper are very valuable elements for their catalytic properties and therefore are present in numerous powerful methodologies of chemical synthesis that constitute a true paradigm in Chemistry. Due to these toxicity problems derived from the presence of these metals in human organism, the pharmaceutical manufacturing processes carried out by pharmaceutical companies, companies have to take into account some of the following alternatives:

- To eliminate the metal species present in the final reaction mixtures (in the case of reactions catalyzed by these transition metals),
- To immobilize these species as solid catalysts (heterogeneous catalysis) or
- To propose a different synthetic route avoiding the reactions that imply the presence of transition metals that may have toxicity.

1.2.1 Stille, Suzuki and Sonogashira reactions in drug discovery

Palladium-catalyzed cross-coupling reactions (PCCCRs) constitute a group of catalytic transformations that have led to a profound advance in chemical synthesis today. As a whole, they represent a fundamental pillar in organic synthesis for the formation of carbon-carbon bonds: the reactions of Suzuki [6-11], Sonogashira [12-14], Stille [15-18], Heck [19-22], Negishi [23, 24], Hiyama [25], are named for their respective discoverers. All of them developed methodologies for the preparation of complex organic molecules from simple raw materials, using palladium as a catalyst. These generic cross-coupling reactions were developed and made known in the 1970s. Another important discovery about the chemistry of palladium was the easy formation of carbon-nitrogen bonds by the Butchwald-Hartwig reaction, in more recent days.

Proof of the importance of these transformations was the award of the Nobel Prize in Chemistry 2010 [26], to three of the inventors cited above (Richard. F. Heck, Eiichi Negishi and Akira Suzuki), whose work falls in the field of organometallic chemistry and homogeneous catalysis (Figure 3).

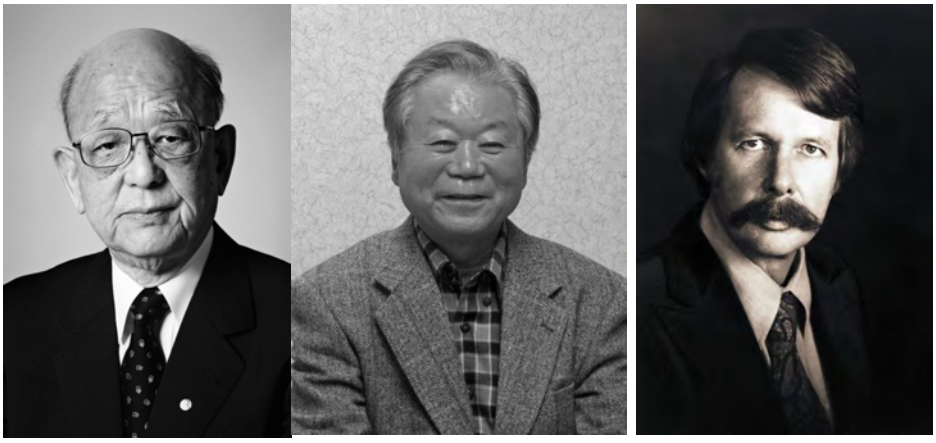
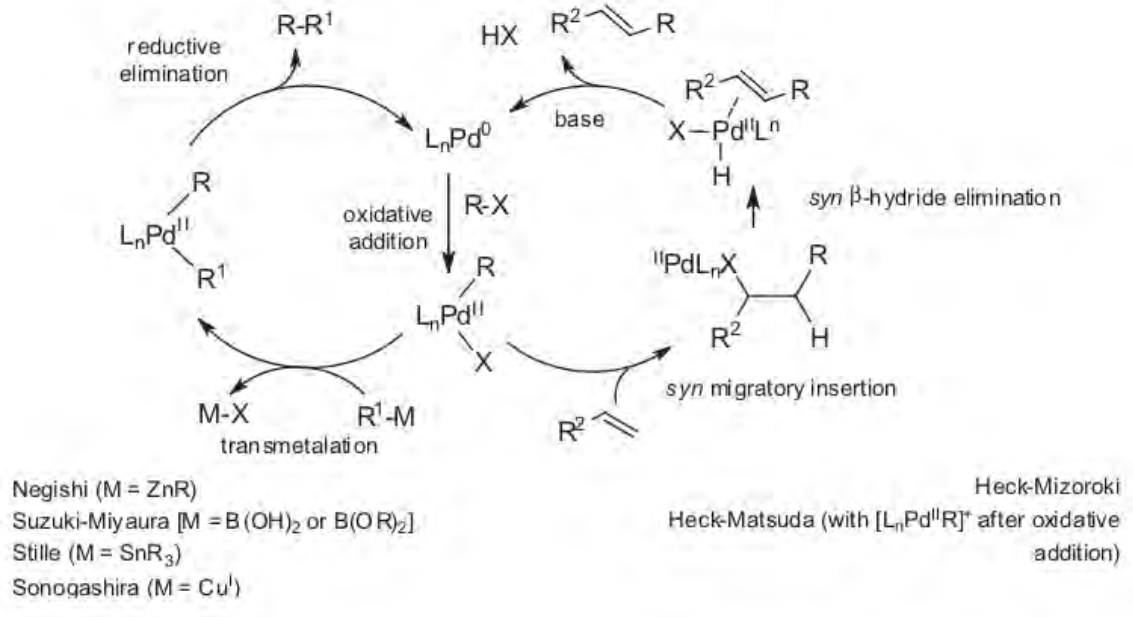


Figure 3: Akira Suzuki (The Nobel Prize in Chemistry 2010), Kenkichi Sonogashira and John K. Stille.

A coupling reaction, in organic chemistry, is an organic reaction in which two hydrocarbon fragments join together forming a new chemical bond to form a single molecule, with the help of a catalyst. Although an exhaustive discussion about these reactions is not the priority objective in this Doctoral Thesis, a brief review to illustrate how these methods operate is necessary: Scheme 1 broadly represents the characteristic mechanistic aspects of these reactions.



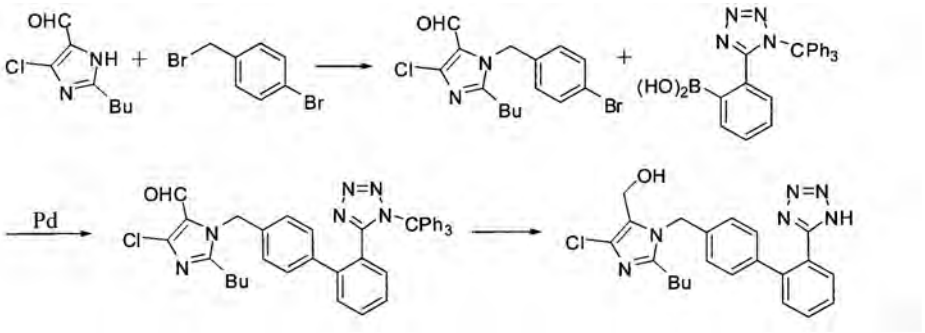
Scheme 1: Generic schematic representation of the mechanisms of the main palladium catalyzed cross-coupling reactions (PCCCRs).

The ease of palladium to carry out an oxidative addition on an electrophilic substrate (generally an organic halide or triflate on a *sp2* carbon), results in a concerted transmetalation process in the presence of an organometallic agent (R'M) to give rise to an intermediate of Pd (II), which bind the two organic units, releasing and regenerating again to Pd(0) through a process of reductive elimination. This general mechanism may vary depending on each type of reaction. For example, in the Heck reaction an insertion of an alkene takes place in the presence of a base. In the Sonogashira reaction, the insertion of an alkyne is catalyzed by Pd and co-catalyzed by Cu species and a base, often an amine. In the case of the Suzuki reaction, at least two base equivalents are necessary for transmetalation to occur from the boronic acid [R-B$(OH)_2$] or boronate [R-B$(OR)_2$] to the organopaladium intermediate. Finally, the Stille reaction (which uses organostannanes as key reagents), the presence of a base is not necessary for the transformation to take place.

Maybe the most important, fascinating and elegant application of the metal-catalyzed coupling reactions is the drugs or biomolecules synthesis. There is an excellent review about the applications of Pd-catalyzed coupling reactions, covering the period from 2001 to 2008, and highlights examples that have been performed on at least a kilogram scale in the chemical and pharmaceutical industries [27]. In addition, Pfizer researchers have reviewed the large-scale applications of transition metal-catalyzed coupling reactions for the manufacture of drug components in the pharmaceutical industry through to the end of August 2010 [28]. Other work by Biajoli and collaborators reviewed the applications of PCCCRs for the synthesis of drug components or drug candidates, regardless of scale, from 2011 through to the end of July, 2014 [29].

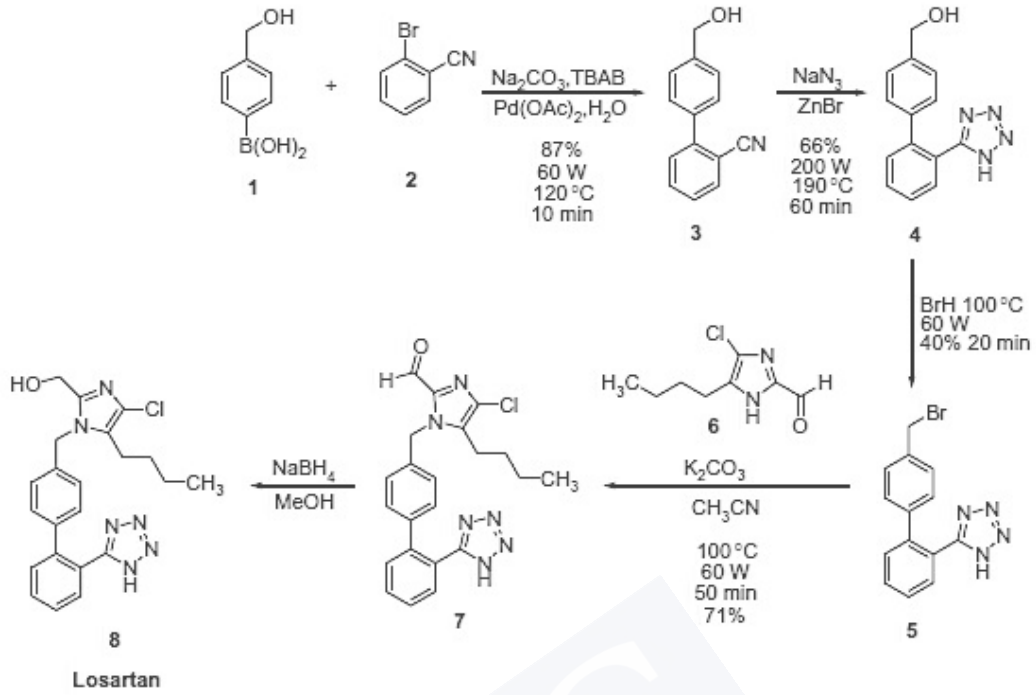
In the following, a series of examples of the application of three methodologies (Suzuki, Sonogashira, Stille) in the development of important drugs or promising molecules from the pharmacological point of view is shown. This is intended to demonstrate the importance of these reactions in organic synthesis and particularly in Pharmaceutical Chemistry. We have chosen the reactions of Suzuki and Sonogashira as the main focus of study in this Doctoral Thesis due to its intrinsic advantages such as great versatility and diversity of reagents, synthetic efficacy and low toxicity (in general this is rather referred to boronic acids). However, as we will comment in the next chapters of this Thesis, Stille's reaction presents problems related to tin toxicity [30]. For this reason, the chemistry with organotin reagents must be carried out with extra precautions and therefore is not as significant at the industrial level.

Perhaps the most paradigmatic example of industrial process with the application of the Suzuki reaction is the synthesis of Losartan, sold under the trade name Cozaar® among others. It is a medication mainly used to treat high blood pressure. Losartan is an orally active angiotensin II receptor antagonist developed by Merck. The Scheme 2 shows the synthetic route for obtaining Losartan described in a Chinese patent [31]. As can be seen, the second process is a Suzuki reaction. They used a boronic acid derived from an N-protected tetrazole, they were able to successfully carry out the synthesis.



Scheme 2: Synthetic procedure developed in patent CN102675294A.

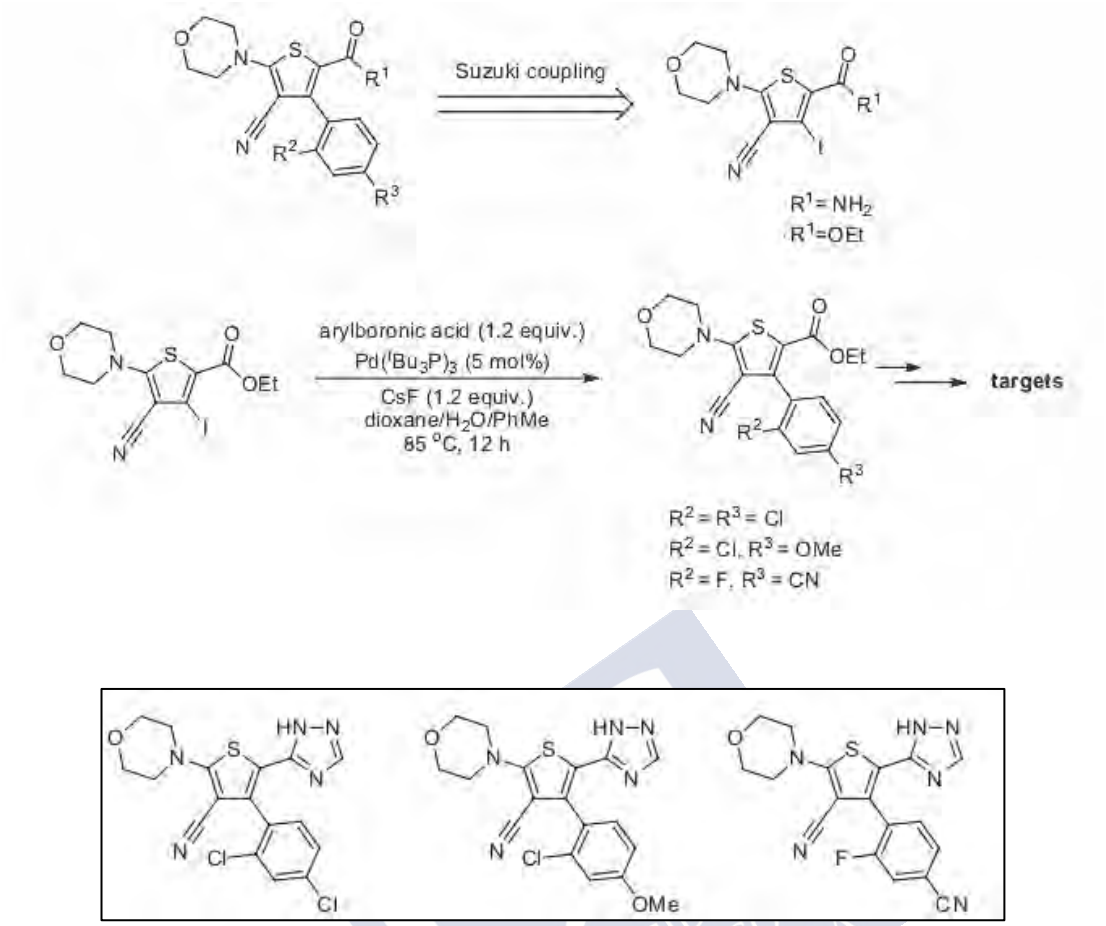
Another approach for the preparation of Losartan was a microwave mediated synthesis where water is heated well above its boiling point in sealed vessels, helping organic substrates become partially soluble (Scheme 3) [29]. Losartan has been prepared using this technique in most of the steps. The synthetic strategy has been redesigned in relation to the conventional preparation methods to prevent the use of protecting groups, thus simplifying the whole procedure. As can be seen, the first step of synthesis is a coupling between a boronic acid and an aromatic bromoderivative. Palladium acetate is used in the first step. From the point of view of the philosophy of sustainable chemistry, an homogeneous catalysts is not clearly the best option. However, if the process is economically viable (both synthesis and waste management of precious material), the pharmaceutical industry prefers homogeneous catalysis (in which there is no reuse of the catalyst), since chemical aspects are better known and no special optimizations for the syntheses are needed compared with the heterogeneous catalysts.



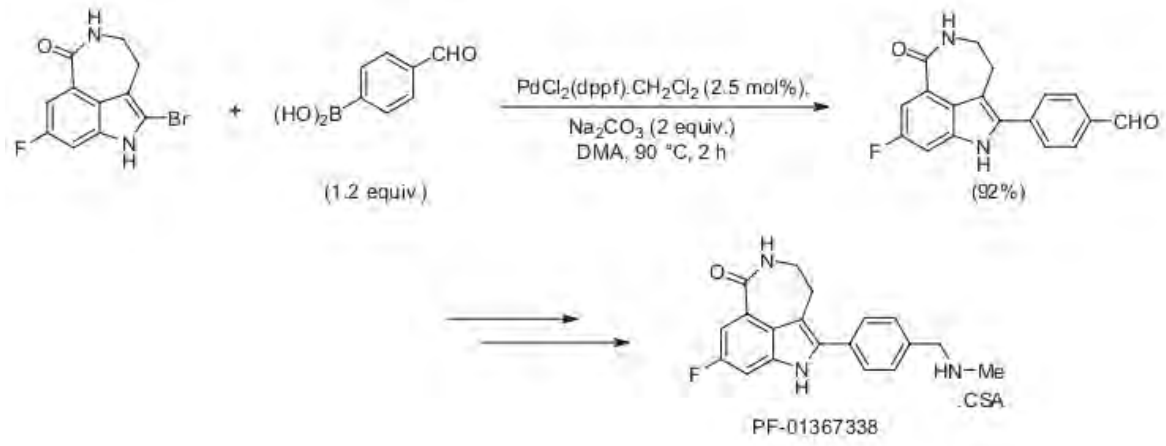
Scheme 3: Modified Suzuki reaction in the synthesis of **Losartan**. Reprinted from [32] with permission.

Another example of the application of palladium chemistry in drug synthesis is that developed by Huang [33] for the preparation of the thiophene-derived compounds (Scheme 4), as highly promising candidates for the selective inhibition of the PI3K receptor. This property is associated with the treatment of some types of cancer. The molecules with the best pharmacological profile are also represented in the Scheme 4. Suzuki's reaction to the iodinated position results in the arylation of thiophene. The syntheses were carried out using catalysts such as [Pd(*t*$Bu_3P)_4$, $Pd(PPh_3)_4$, $PdCl_2$(dppf)], bases (CsF, diisopropylethylamine, K_2CO_3, K_3PO_4) and solvents (toluene, dioxane, ethanol, water) being combined under different conditions.

Gillmore and collaborators were able to prepare several kilogrames of PF-01367338 (Scheme 5). This is a drug candidate for the treatment of breast and ovarian cancers. [34] It is a PARP-inhibitor. The authors described how they had to overcome some synthetic challenges to scale up the synthesis to multi-kilogram scale.



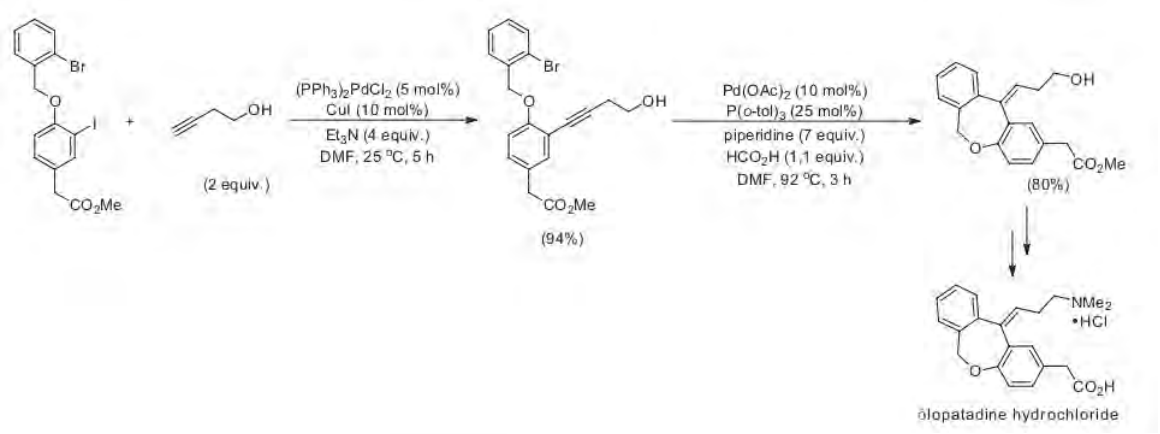
Scheme 4: Sequential Suzuki reactions in the synthesis of PI3K selective inhibitors. Adapted with permission [29].



Scheme 5: Suzuki reaction for the synthesis of PF-01367338. Adapted with permission [29].

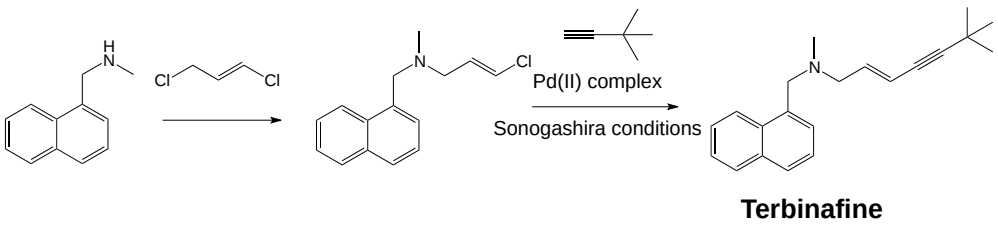
Sonogashira reaction is a very powelful tool for the construction of a new bond between sp2- and sp-hybridized carbons [12]. It is nowadays a widely employed methodology for the synthesis of arylacetylenes. This coupling reaction was employed by the research group of Kyowa Hakko Kirin in a concise synthetic route for the synthesis of Olopatadine hydrochloride (Scheme 6). This anti-allergic drug was previously commercialized by the same company [35].

The reported synthesis goes through the Sonogashira reaction between the easily accessible aryl halide and an alkyne, leading to an intermediate in 94% yield. This adduct is then subjected to a second metal-catalyzed transformation, a stereospecific palladium-catalyzed intramolecular cyclization. Finally, the aminomethylation and ester hydrolysis followed by acid work-up finished the synthesis of the final target. Although the presented synthetic route is very promising and concise, it has so far been reported only on a laboratory scale (5 g for the Sonogashira coupling and 200 mg for the cyclization step).



Scheme 6: Optimal Sonogashira conditions for the synthesis of the anti-allergic olopatadine hydrochloride. Adapted with permission [29].

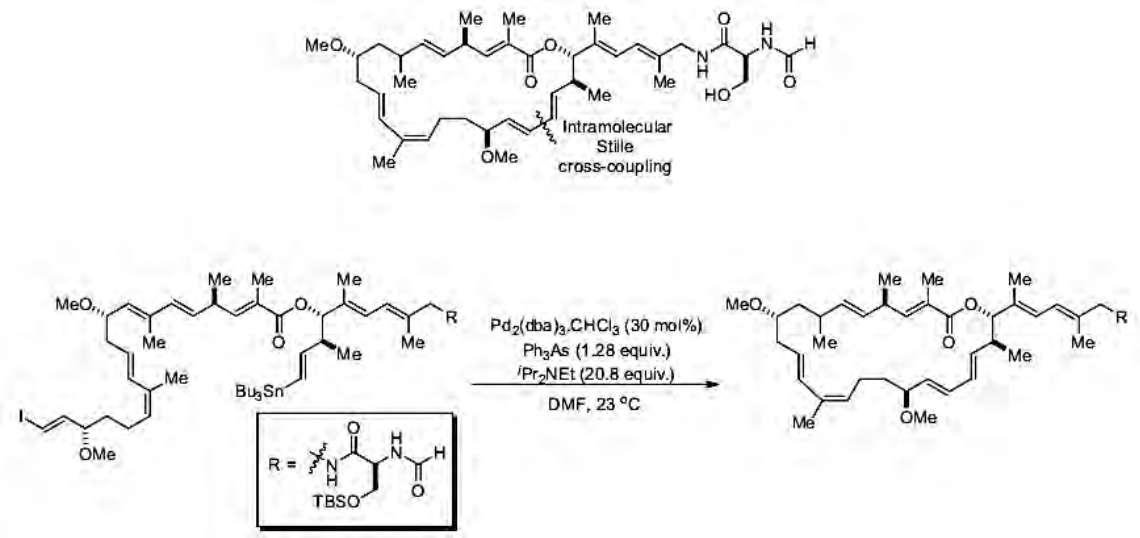
Another good example of the Sonogashira reaction application is the synthesis of the antifungal Terbinafine (European patent EP1753770) [36]. Although there are some variants for its preparation, the simplest method includes a Sonogashira coupling reaction between a terminal alkyne (3,3-dimethylbut-1-yne) and a chloride type substrate on a sp2 type carbon (Scheme 7) [37]. The reaction is carried out in the presence of a complex of palladium (II) of the dichloro-bis-triphenylphosphine-palladium (II) type.



Scheme 7: Synthesis of antifungal Terbinafine.

Other examples of the use of Sonogashira coupling include its use in the synthesis of tazarotene [38] which is a treatment for psoriasis and acne, and in the preparation of SIB-1508Y, also known as Altinicline [39], a nicotinic receptor agonist. As previously commented, the coupling between an organic electrophile and an organotin compound is known as the Stille reaction. [15] It is very useful for the construction of vinyl-vinyl, aryl-vinyl or aryl-aryl bonds. Without a doubt, the greatest impediment of this methodology is the toxicity and difficult removal of tin compounds. This can present problems on an industrial scale. However, the Stille coupling reaction does not require the presence of a base in the reaction medium and presents similar advantages to the Suzuki reaction: the availability of organostannanes, air and moisture stability, but superior tolerance towards most functional groups. Thus, the Stille reaction is an alternative for the synthesis in pharmaceutical chemistry scale.

An example of efficient application at industrial level of the Stille reaction is the synthesis of a key macrocyclic intermediate in the preparation of Iejimalide B (Scheme 8), an anticancer compound isolated from a tunicate of the species *Eudistoma cf. rigida*, which is native to the coral reefs in Japan. [40]



Scheme 8: Intramolecular Stille reaction to provide the key macrocycle. Adapted with permission from [29].

All these examples demonstrate the importance of PCCCRs in the Drug Discovery process. However, it is difficult to find examples of drugs prepared by heterogeneous palladium catalysts that have been successful at an industrial level.

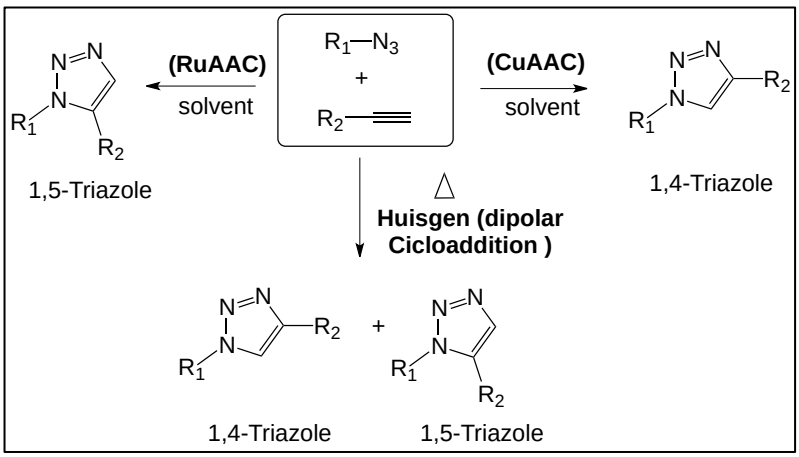
1.2.2 Copper-catalyzed -Alkyne-azide-cycloaddition and click chemistry

Copper is a very versatile transition metal. It has been used as a building material by human civilizations for over 6000 years. This key element of the periodic system has offered the possibility of developing catalytic reactions that today constitute true pillars within the strategies of chemical synthesis [41]. Among the transformations in which copper is the main actor in the catalytic scenario we can cite very important reactions such as the Huisgen reaction [42], Ullmann reaction [43, 44], the Cadiot-Chodkiewicz reaction[45, 46], the Castro-Stephens reaction[47], the Glaser reaction [48, 49], or the Chan-Lam [50, 51] and of course the Copper-catalyzed azide-alkyne coupling cycloaddition (CuAAC) [52-56] which are only examples of the rich chemistry that this metal provides.

Copper is an earth-abundant metal, making its use more cost-effective and more sustainable tan precious transition metal catalysts. One of the reasons why copper is so versatile is that depending on its oxidation state, this metal can efficiently catalyze reactions involving both one and two-electron (radical and polar) mechanisms, or both.

In the field of drug discovery, as in other fields, chemistry faces the challenge of sustainability. It is an essential requirement to combine the availability of large chemical libraries (diverse, exclusive and of quality), and the urgency that these projects demand, with the use of more efficient and environmentally friendly preparatory methodologies. Click chemistry is a chemical philosophy introduced by K. Barry Sharpless in 2001 [54] and describes the chemistry tailored to generate substances quickly and reliably by joining small units together [55]. In the words of the famous researcher Karl Barry Sharpless (Figure 4): “The search for active molecules should be restricted to those molecules that are easy to prepare, since the opportunity to identify powerful molecules through these strategies is, at least as high, as when conventional methodologies are followed”. In addition to making new conceptual considerations in the field of chemistry such as the one mentioned above, undoubtedly, Karl Barry Sharpless made an important breakthrough: the discovery of the acceleration of the Huisgen when copper becomes part of the reaction medium, in catalytic quantities. Thus, today we have satisfactory chemical

tools either using copper or ruthenium catalysis to obtain 1,4 or 1,5-triazoles respectively (Scheme 9).



Scheme 9: Regioselectivity in 1,3-dipolar cycloaddition between an alkyne and an organic azide.

Although there is some controversy, it is believed that the species responsible for the formation of 1,4-disubstituted triazoles is due to copper (I) species (Figure 4). Copper-catalyzed azide-alkyne cycloaddition (CuAAC) [52-56] is considered the flagship of the click chemistry. It was discovered in 2001 and is an improvement over Huisgen's 1,3-dipolar cycloaddition for the synthesis of 1,2,3-triazoles due to a series of advantages such as:

- mild reaction conditions
- high reaction efficiency
- excellent functional group compatibility under mild reaction conditions
- remarkable chemo- and regioselectivities

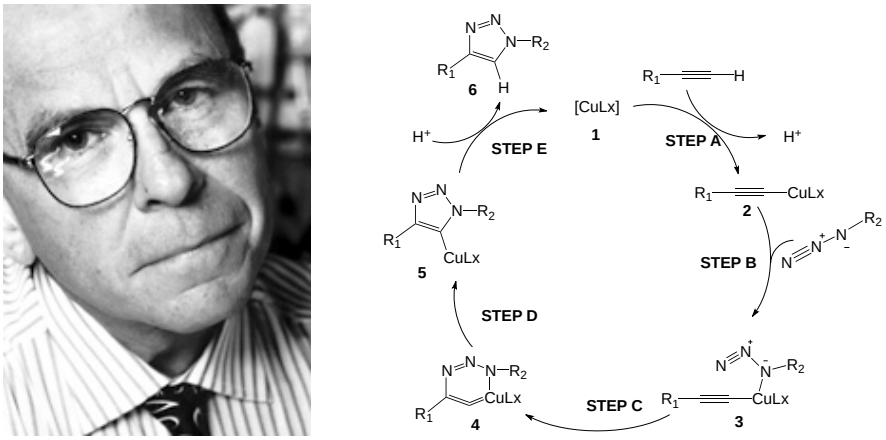
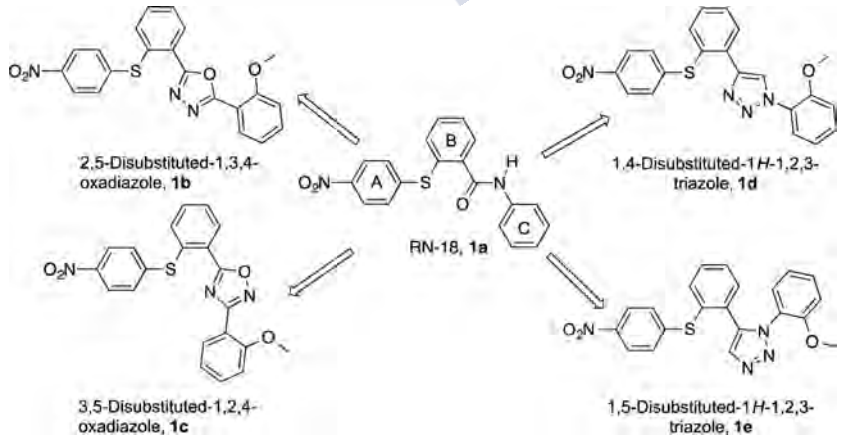


Figure 4: On the left, the Nobel Prize in Chemistry 2001, Karl B. Sharpless. On the right, mechanistic representation of the proposed catalytic cycle for the CuAAC.

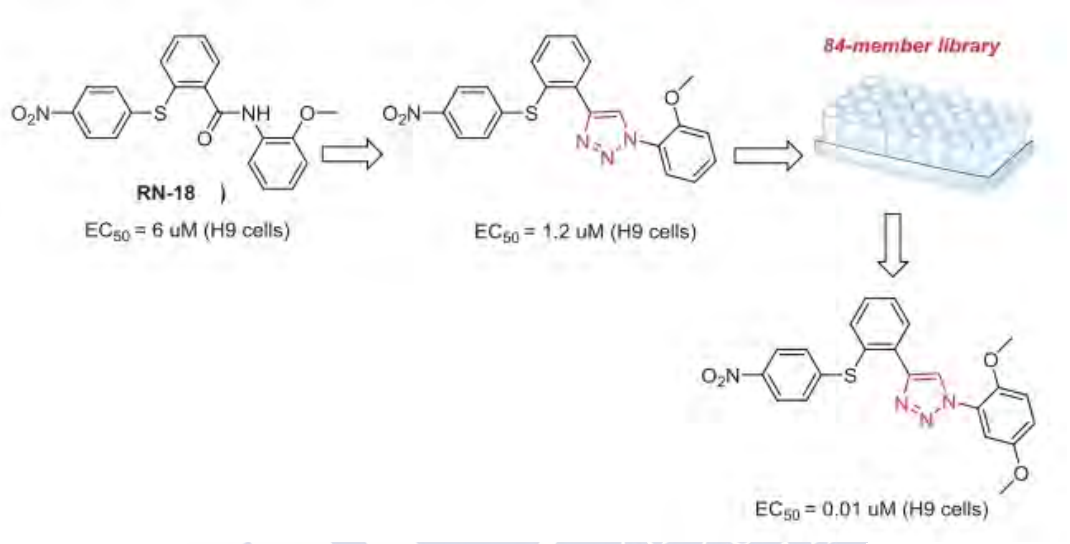
From all the above, it follows that, as in many other catalytic processes, the oxidation state of copper plays a fundamental role in bringing the catalytic reaction in the correct direction and without the formation of collateral products. In the case of CuAAC, it seems quite agreed that the oxidation state (I) is the most suitable for cycloaddition and 1,4-disubstituted-1,2,3-triazole to occur, at least in homogeneous catalysis. In fact, according to different authors, when the reaction is carried out in the presence of copper (II) species (which can be generated in the reaction medium via oxidation) the reaction is plagued with collateral products [52]. Therefore, there have been many efforts by researchers around the world to stabilize copper species, either by adding reductants (such as sodium ascorbate) or through ligands that conveniently coordinate and stabilize copper species.

1,2,3-triazole is a privileged scaffold in medicinal chemistry, and the compounds containing this structure have a broad spectrum of biological activities. A key role of the 1,2,3-triazole scaffold is as bioisoster of the amide functional group. Several studies [57] exemplify how CuAAC and the click chemistry can be used in this context [58]: by substituting the amide functionality in a lead molecule (Scheme 10) with isosteric heterocyclic systems such as 1,5 and 1,4-disubstituted-1,2,3-triazoles as well as 1,2,4 and 1,3,4-oxadiazoles, Mohammed and co-workers discovered RN-18, a drug that reduces viral infectivity of HIV-1.



Scheme 10: Bioisosteric replacement in RN-18. Adapted with permission from [57], Copyright (2020) American Chemical Society.

To increase its activity and metabolic stability, the amide group in RN-18 (IC_{50} = 6 µM) was replaced with bio-isosters. The synthesis led to the identification of a 1,2,3-trizole analog, with IC_{50} = 1.2 µM (Scheme 11). Moreover, several potent HIV-1 inhibitors were discovered and a library of even more potent compounds (IC_{50} = 0.01 µM) was obtained. This study illustrates the use of CuAAC click chemistry as a rapid and highly efficient process for the generation of compound libraries on a fairly large scale.



Scheme 11: Lead optimization of RN-18 in the search of new anti-HIV agents. Adapted with permission from [57] Copyright (2020) American Chemical Society.

This is only an example of the direct application of copper catalyzed synthesis for applications in the field of Medicinal Chemistry. Today, there are many examples in the literature about works in which CuAAC is used as a primary synthetic tool, even *in situ* transformations, in biological environments [59].

Figure 5 shows some of the main biomolecules marketed with triazole structure (and some also with 1,2,4-triazole structure) and other bioactive molecules. As can be seen, many of them correspond to structures derived from 1,2,3-triazoles.

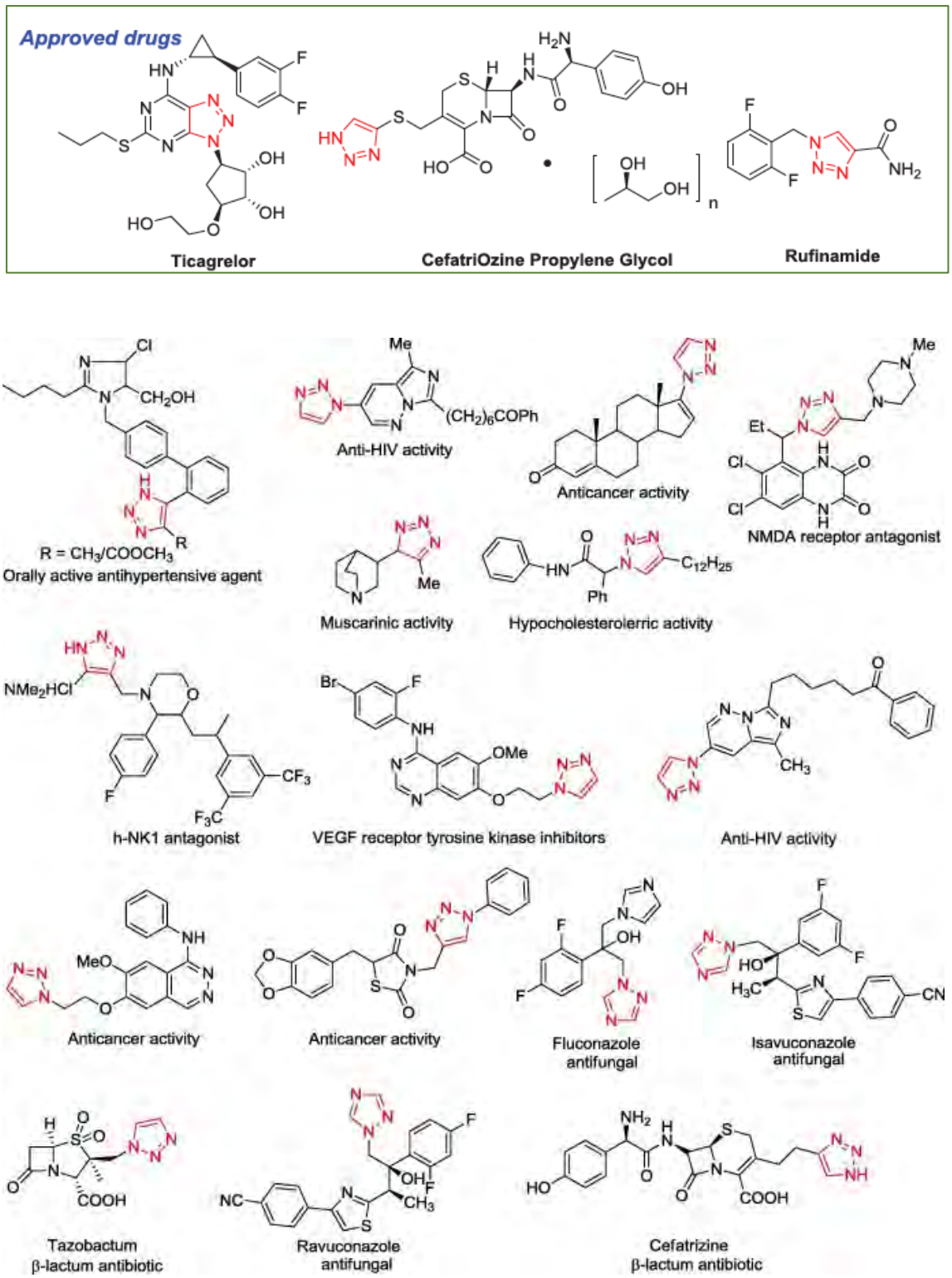


Figure 5: Some examples of triazole containing commercial drugs and bioactive molecules. Adapted with permission from [60]. Copyright (2020) Elsevier.

1.2.3 Multicatalytic Multicomponent Reactions

A multicomponent reaction (MCR) is a synthetic methodology in which three or more reactants react together in a single reaction vessel to form a new product. Among the most important intrisic aspects of MCRs is the convergence, that is, the final product contains almost all portions of substrates, generating almost no by-products. At the same time MCRs emphasizes the concept of atom economy: Most of the initial components of the reagents are not wasted. On the contrary, they remain in the final structure. So, this efficiency and versatility makes MCRs an extremely ideal and eco-friendly reaction system. As can be seen in Figure 6, it is a methodology that allows assembly in a single stage, as opposed to linear syntheses, in which the chemical diversity is introduced step by step, with the consequent delay in production in addition to the need for intermediate purification processes. The revolutionary concept of the MCRs makes it an ideal area of knowledge for its development in fields such as the discovery of lead compounds in medicinal chemistry, or combinatorial chemistry [61].

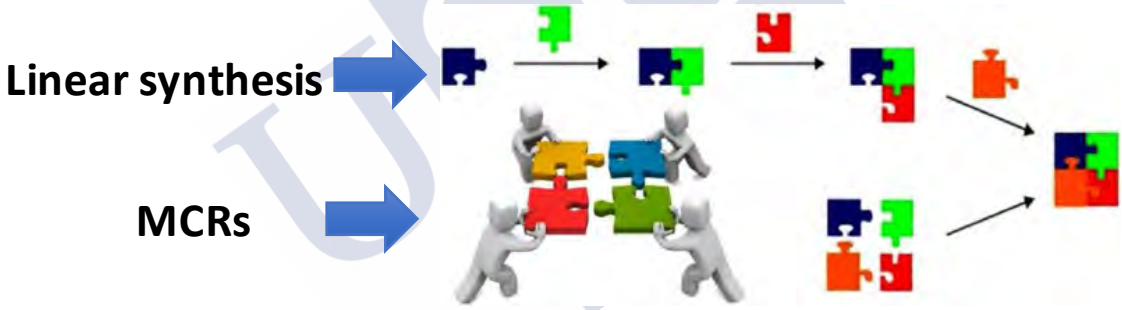
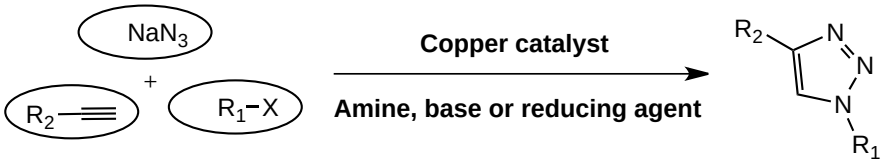


Figure 6: Graphical representation of the concept of MCR vs Linear Synthesis. [62]

Going back to the comments about the importance of copper catalysis, it is important to remember here that the CuAAC reaction has become a reaction in the chemists' toolbox, not only by the special characteristics of the intrinsic CuAAC transformation itself but also by the possibility of carrying out the three-component version of this reaction (Scheme 12), enabling the *in situ* formation of arylazides. There is a multicomponent version of the well known CuAAC [63], in which an alkylating agent and sodium azide are the starting materials, together with the corresponding alkyne and the copper catalyst. This methodology solves the lack of commercial availability of many organic azides as well as their instability and explosive behavior under certain conditions. The result is an easy chemo- and regiospecific generation of libraries of 1,4-substituted-

1,2,3-triazoles, although most of the published works have focused on homogeneous catalysis.



Scheme 12: Multicomponent version of the CuAAC to give 1,4-substituted-1,2,3-triazoles.

In recent years, the field of Catalysis continues to develop with intensity. As a result, new ideas have emerged about catalytic processes. In someway, these new concepts emerged as an attempt to mimic the efficiency of Nature and the biological systems in producing complex molecules from a series of different starting materials by the action of several enzymes. This is how the concept of "Multicatalytic and Multicomponent Reactions" was born as a highly valuable synthetic tool. A review of this theme was made a few years ago by Fañanas and collaborators [64]. It reviews the incredible potential of this type of processes. Figure 7 depicts the concept of MMCR as well as an example of the synthesis of drug-like compounds (dibenzazepines) via homogeneous MMCR, with the presence of a bi-catalytic Rh / Pd system. The most important characteristic of this subtype of MCRs is the presence of two or more (metallic) catalysts in the reaction medium that independently or not lead the reaction to a final product and where the isolation of reaction intermediates is not necessary. Although there are different variants or terminologies within this methodology, globally this kind of *one pot* transformations are of extraordinary complexity, developed in a homogeneous catalysis version but still remain almost unexplored methods of heterogeneous catalysis.

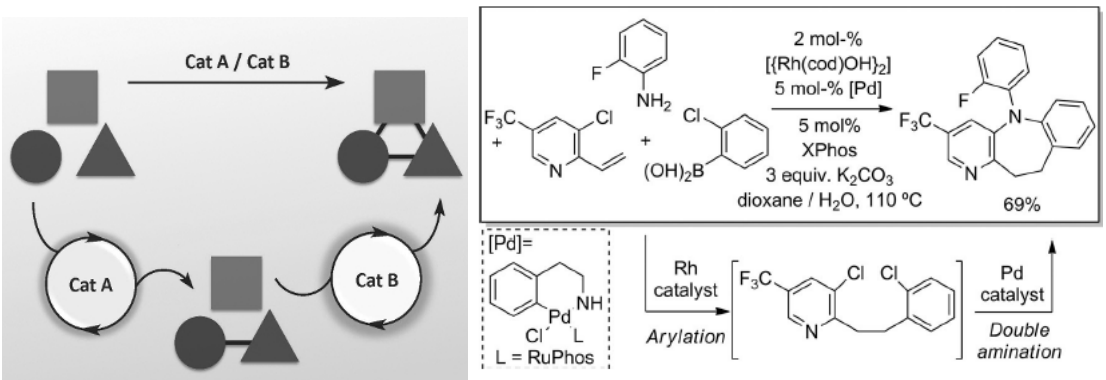


Figure 7: Concept of Multicatalytic Multicomponent Reaction (left). Multicomponent synthesis of dibenzazepines through a reaction catalyzed by a rhodium/palladium binary system (right). Adapted with permission [64]. Copyright (2020) Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

1.3. Three-dimensional printing: an emerging technology

The beginning of 3D printing dates back to 1976, when the inkjet printer was invented. The study of inkjet printers and their evolution paid off in 1984, when Charles Hull (who would end up being one of the main players in the industry by co-founding 3D Systems), introduces the concept of stereolithography (also known as SLA). [65] SLA is a technique that consists of 3D-printing models using UV-sensitive resins. This technique transformed the technology of printing with ink to printing with materials. But, have 3D printers changed a lot since 1984? The answer is: Not at all. As can be seen in Figure 8, the diagrams presented by Charles Hull in his original patent and how it is a Form 2 stereolithography printer today. The resemblance is amazing:

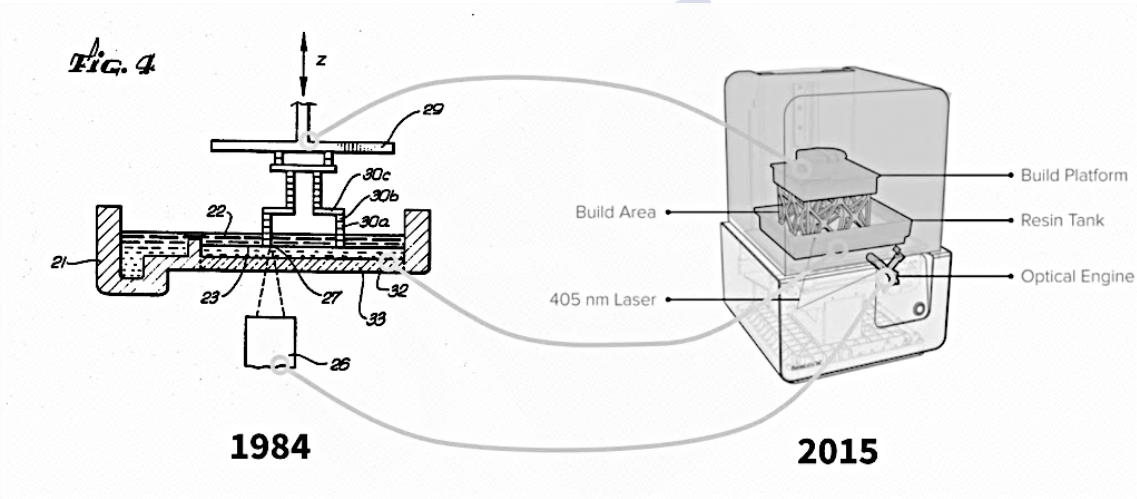


Figure 8: Homologies between the concept of 3D printer in 1984 and the current one.

As can be seen in Figure 9, the main application for which 3D-printing technology is being applied is prototyping. Prototyping is a valid term to refer to the action and the process of creating a model of a certain product and the successive tests that are done with it. Rapid prototyping is a process used to make plastic, metal or ceramic items. Also known as "additive technology", since its manufacturing process is to add material layer by layer. Mass production may be diminished because 3D-printing is an inherently slow process, although this also depends on the type of technique used. The proof of concept (the implementation, often summarized or incomplete, of a method or an idea, carried out with the purpose of verifying that the concept or theory in question is capable of being exploited in a useful way) is another very widespread application for the companies. Finally, the prices of current 3D printers, much cheaper today than years ago, cause the growing domestic or academic use in other applications.

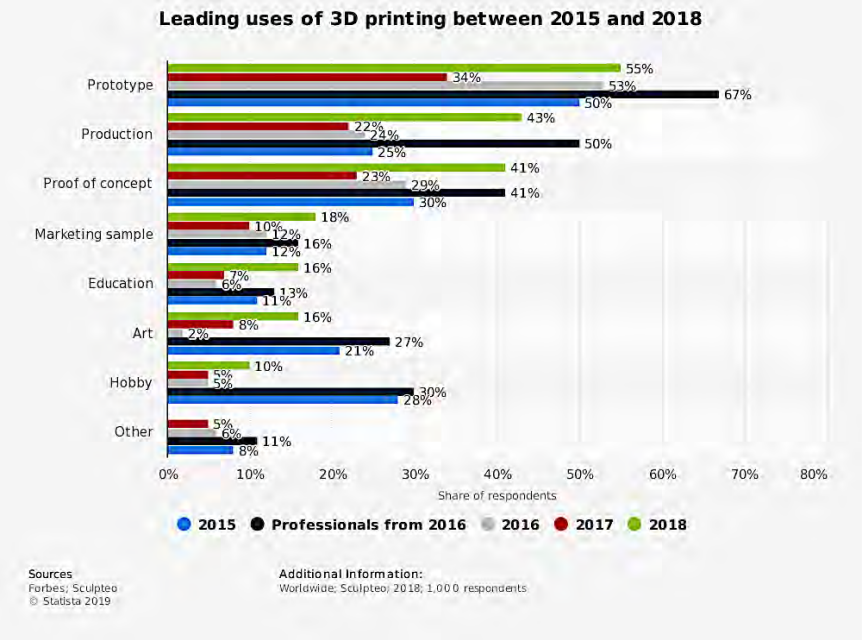


Figure 9: Distribution of the 3D-printing leading uses and applications worldwide in 2015 and 2018 [66].

As can be seen in Figure 10, 3D-printing is already causing a great impact in key sectors such as housing construction. The base structure of the buildings can be finished in a few hours. One of the most recent and revolutionary 3D-printing applications has been produced in the medical field. Researchers at the University of Tel Aviv [67] have produced a lively heart that beats using human tissue and a 3D printer, in a breakthrough that opens pathways to future transplants (Figure 10). They took a small biopsy of the patient's fatty tissue, removed all the cells and separated them from collagen and other biomaterials, reprogrammed them to be stem cells and then differentiated them to be cardiac cells and blood vessel cells. Then, the biomaterials were processed “to convert them into bio-ink, which allowed printing with the cells.” The resulting product, a heart of about 3 centimeters, equivalent to the size of a rat or rabbit. All these examples reflect the importance of 3D-printing not only in the present but also the key role that this technology will have in the near future.

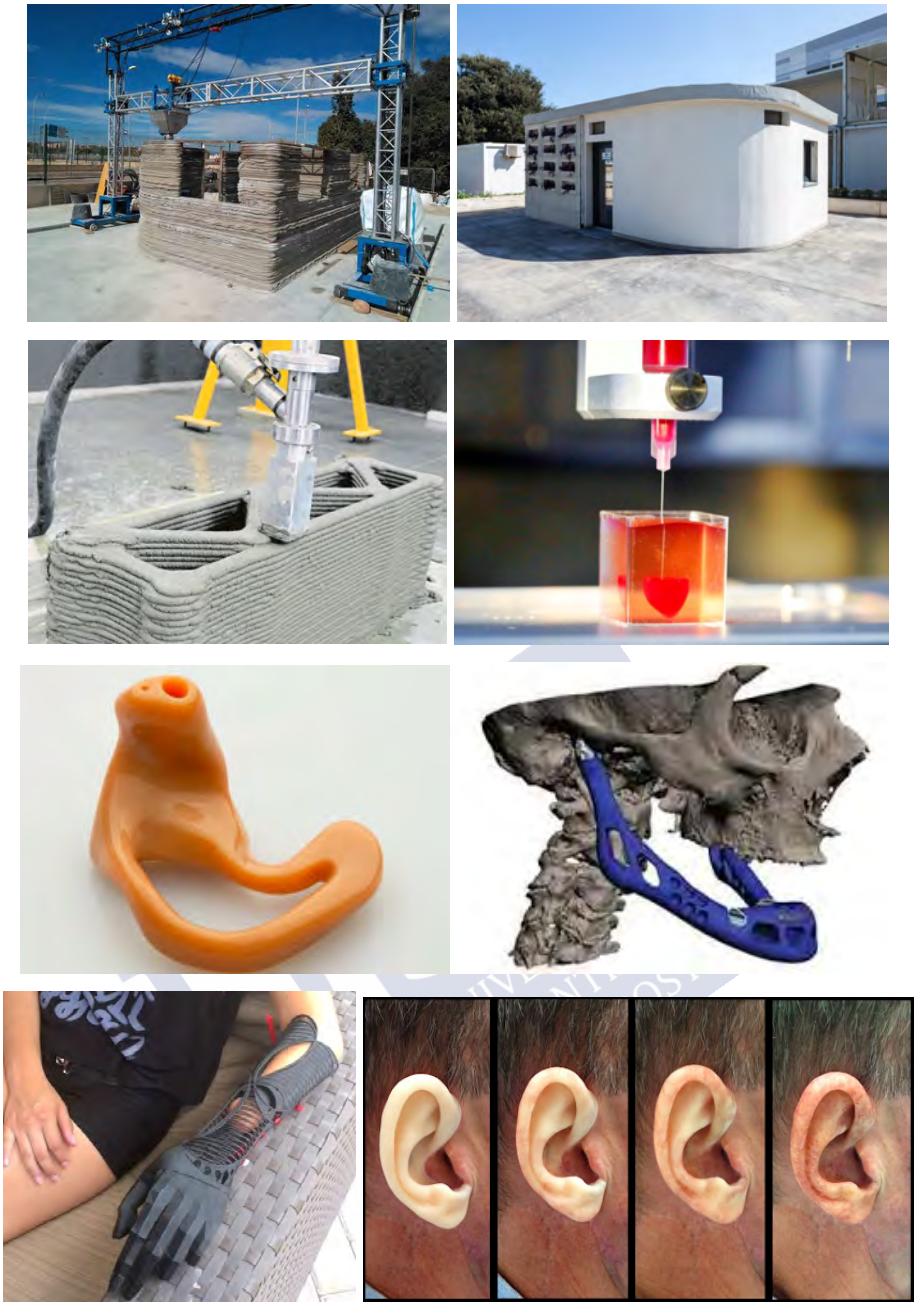


Figure 10: Application of the three-dimensional printing technology construction of habitable houses and even an as well as the manufacture of varied prostheses: hearing aids, osteo-integrated implants, articulated prostheses and human organ prostheses. 3D-Printing process of an artificial heart made with living cells is also displayed.

1.3.1 3D-printing techniques for the manufacture of monolithic catalysts and catalytic devices

Figure 11 represents the four main techniques of the three-dimensional printing:

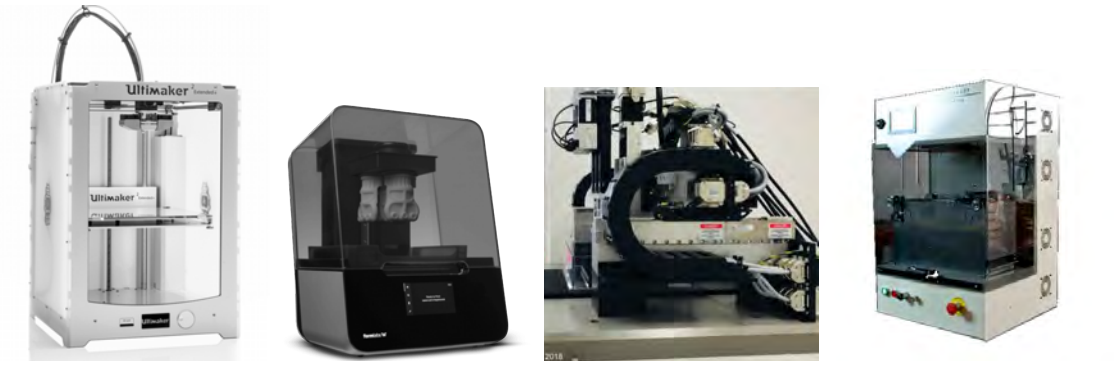
- **Fused Deposition Modeling (FDM):** With this technology, objects can be built with production-grade thermoplastics. Objects are built by heating a thermoplastic filament to its melting point and extruding the thermoplastic layer by layer. Special techniques can be used to create complex structures. For example, the printer can extrude a second material that will serve as support material for the object being formed during the printing process [68]. This support material can later be removed or dissolved.

-**Stereolithography (SLA)** makes use of a liquid plastic as the source material and this liquid plastic is transformed into a 3D object layer by layer. [69, 70] Liquid resin is placed in a vat that has a transparent bottom. A UV (UltraViolet) laser traces a pattern on the liquid resin from the bottom of the vat to cure and solidify a layer of the resin. The solidified structure is progressively dragged up by a lifting platform while the laser forms a different pattern for each layer to create the desired shape of the 3D object.

- **Selective Laser Sintering (SLS):** SLS [71, 72] has some similarities with Stereolithography. However, SLS makes use of powdered material that is placed in a vat. For each layer, a layer of powdered material is placed on top of the previous layer using a roller and then the powdered material is laser sintered according to a certain pattern for building up the object to be created. Interestingly, the portion of the powdered material that is not sintered can be used to provide the support structure and this material can be removed after the object is formed for re-use.

- **Direct Ink Writing (DIW)** (also called Robocasting): Robocasting or Direct Ink Writing (DIW) [73] is an additive manufacturing technique in which a filament of a paste (known as an 'ink', as per the analogy with conventional printing) is extruded from a small nozzle while the nozzle is moved across a platform. The object is thus built by 'writing' the required shape layer by layer. The technique was first developed in the United States in 1996 as a method to allow geometrically complex ceramic green bodies to be produced by additive manufacturing. In robocasting, a 3D CAD model is divided up into layers in a similar manner to other additive manufacturing techniques. A fluid (typically a ceramic slurry), referred to as an 'ink', is then extruded through a small nozzle as the nozzle's position is controlled, drawing out the shape of each layer of the CAD model. The ink exits the nozzle in a liquid-like state but retains its shape immediately, exploiting

the rheological property of shear thinning. It is distinct from fused deposition modelling as it does not rely on the solidification or drying to retain its shape after extrusion.



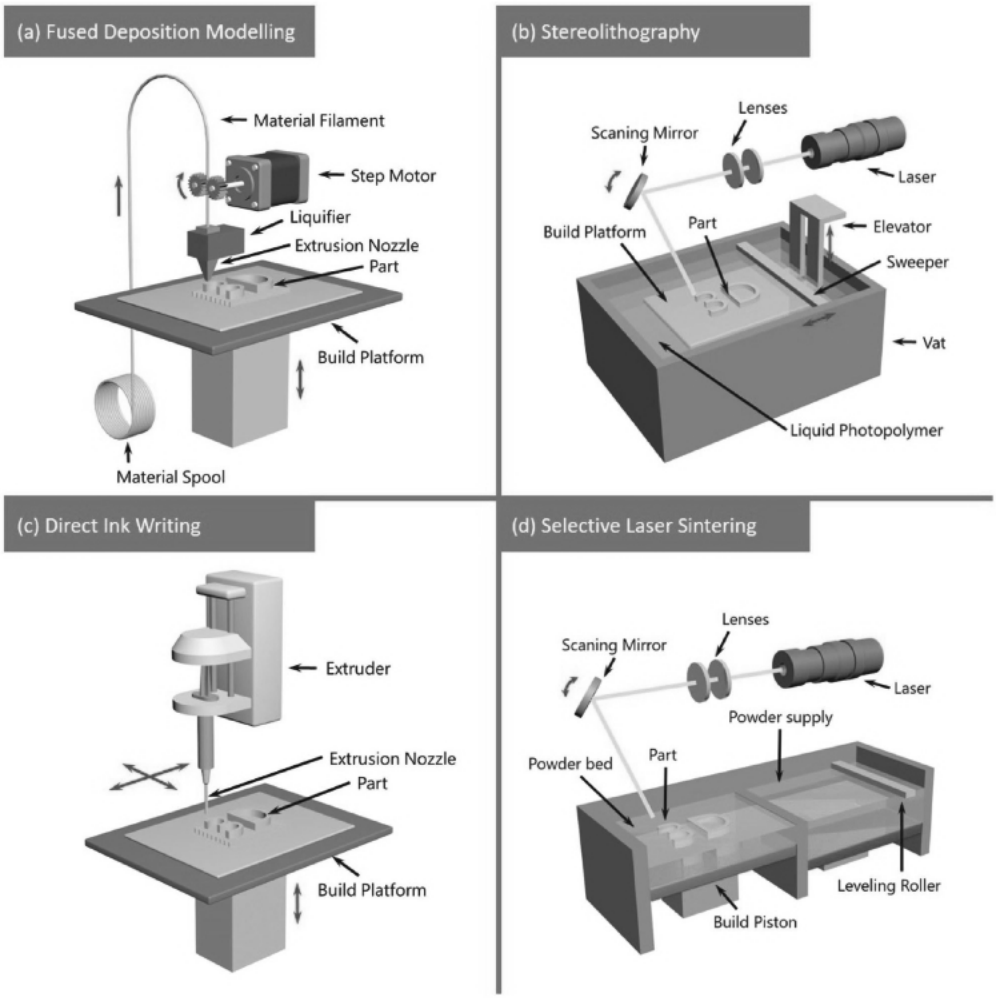


Figure 11. Above: Some models of 3D printers, which work through different printing techniques. Below: Representation of the four main types of 3D printing techniques. Adapted with permission from [74]. Copyright 2020, American Chemical Society.

1.3.2 Three-dimensional printing in Chemistry

The development of 3D-printing in the field of chemistry is quite recent. The number of scientists who use this technology for related applications to the synthesis of molecules is increasing in the last years [74]. In this area, Professor Leroy Cronin, from the University of Edinburg (Scotland, UK) [75] is the true pioneer in the search for suitable materials for the construction of custom reactors. He can be considered a mediatic phenomenon in the UK, betting on this technology not only for the manufacture of devices with different sizes and shapes but also in the design of the chemical transformation itself. He proposes the "on-demand" preparation of drugs, using concrete solutions for each type of synthesis (trap doors, tanks, valves, plugs, interconnected reactors, etc.). Figure 12 shows the synthesis of the baclofen drug (a gamma-aminobutyric acid (GABA) agonist used as a skeletal muscle relaxant) [76], the gastroprotective Zolimidine [77]and the antiepileptic Lamotrigine [78], which were made using polypropylene interconnected reactors. Everything manufactured using 3D-printing. His different works exemplify a new philosophy in drug discovery [79,80].

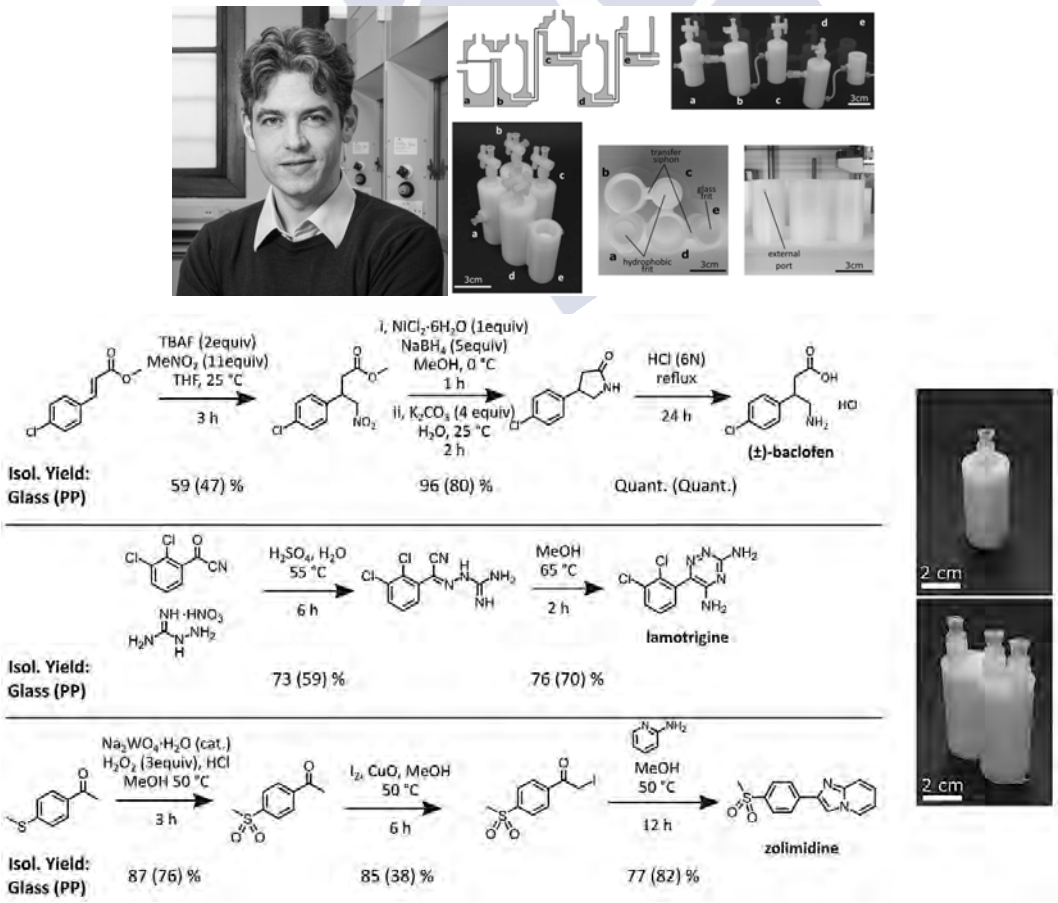


Figure 12: Leroy Cronin (extracted from Wikipedia). Synthesis of baclofen and zolimidine using 3D-printed devices. Adapted with permission from [80], copyright 2020, The American Association for the Advancement of Science.

1.3.2 3D-Printed monolithic catalysts. State of the art

One of the most important areas of the potential use of the 3D-printing technology is the development of monolithic catalysts. Monolithic materials consist of a large number of long and narrow channels through which a reacting fluids flow. For some years, monolithic catalysts have become a powerful catalytic material for automotive and stationary emission control [81-83] as well as for enzyme reactors [84, 85]. The disadvantages of the present monolithic catalysts are their poor surface areas, complex preparation processes, and the stability of the pores under conditions of rapidly changing temperature [74]. With the 3D-printing preparation, the monolithic catalysts can be significantly improved. The manufacture can be simplified. With the use of specific pore-forming agent, the surface area of the printed monolithic catalysts can be increased.

In general, there are two main strategies regarding the design and manufacture of a monolith that contains pores and channels in its structure:

- Design and create a framework by 3D-printing on a material that can then be removed (etching) in a subsequent thermal or chemical process, creating empty spaces inside the monolith structure (often cylindrical and ceramic) definitive.
- Direct 3D-printing of the monolithic structure.

In relation to the first of the previously mentioned options, an interesting strategy developed by Michorczyk and collaborators for the manufacture of monoliths consists in the manufacture of a mold that contains a "negative copy" of a 3D structure in carbon material (or similar material), which can be eliminated in a subsequent high temperature heat treatment process. With the help of 3D-printing and computer-aided design (CAD), unique monolithic structures that are unable to be made by conventional methods can be easily prepared. Therefore, this group developed a Digital Ligh Processing (DLP process) to prepare polymer models that were applied as templates in order to control channel architectures in monolithic catalysts [86] (Figure 13). 3D printing DLP technique is very similar to Stereolithography but differs in that it uses a different light source and makes use of a liquid crystal display panel.

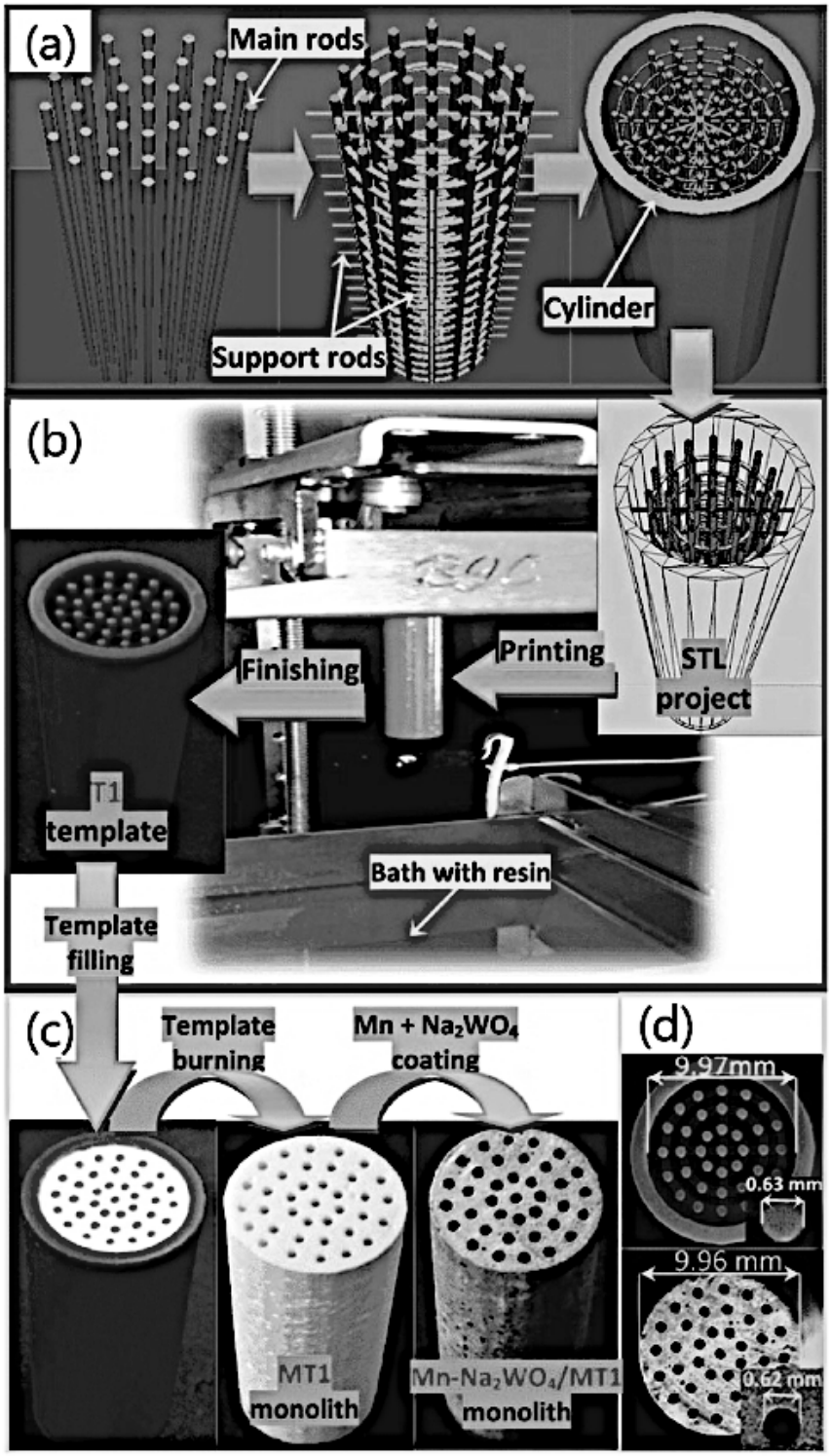


Figure 13: Scheme showing the monolithic catalyst preparation using printed model as a template. a) 3D digital model projection; b) printing the STL file and finishing the template; c) filling the template with α-Al_2O_3 paste, burning off the template and coating the monolith with active compounds; d) template vs monolith main dimensions. Reproduced with permission [74]. Copyright 2020, American Chemical Society.

3D-Printing of carbon structures: Solutions to environmental problems are excellent possible applications of monolithic devices. Some applications address the gas adsorption in 3D monoliths obtained by 3D-printing [87, 88]. An interesting approach is to print carbon structures. Starch, for example, is a good carbon source for carbonization processes. 3D-printing using starch-based materials has been studied. In the presence of water and heat, the intermolecular bonds of starch molecules break down due to gelatinization, allowing the hydrogen bonding sites to engage more water. The gelatinization process makes starch dissolve in water, which is favorable for the extrusion process. In this recent work, a starch-based material was shown to be a promising 3D-printing ink (Figure 14). The carbonization has no negative effects on the printed macrostructure. The mesostructured of the carbon material is preserved. These structures may be very useful for developing improved industrial carbon-based catalysts.

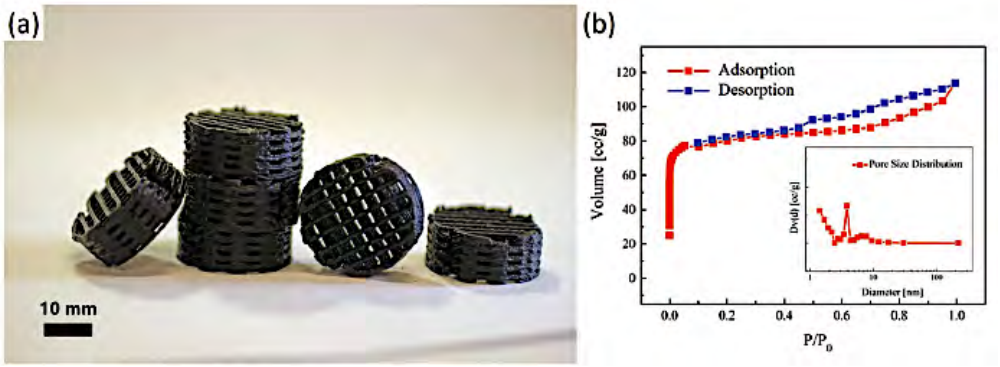


Figure 14: 3D printed carbon structures using starch as the carbon source. a) Photo of the printed carbon structures. b) N_2 adsorption-desorption isotherm and pore size distribution of the printed carbon material. Reproduced with permission [74]. Copyright 2020, American Chemical Society.

3D-Printing of zeolite structures: Several works have reported the synthesis of 3D-printed zeolite monoliths [89, 90]. Rezaei and co-workers fabricated monoliths for CO_2 removal from enclosed environments [91]. Structured adsorbents, especially in the form of monolithic contactors, offer an excellent gas−solid contacting strategy for the development of practical and scalable CO_2 capture technologies. In this study, the fabrication of threedimensional (3D)-printed zeolite monoliths with novel structures and their use in CO_2 removal from air are reported. The 3D-printing technique offers an alternative, cost-effective, and facile approach to fabricate structured adsorbents with tunable structural, chemical, and mechanical properties for use in gas separation processes.

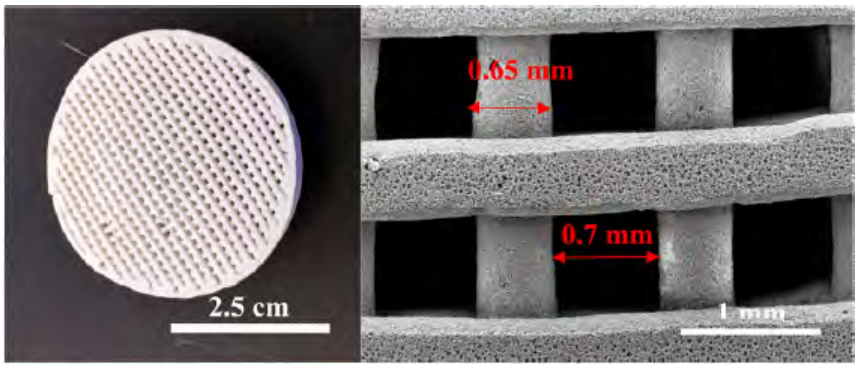


Figure 15: 3D-Printed Zeolite Monoliths for CO_2 Removal from Enclosed Environments. Reprinted with permission from [91]. Copyright 2020, American Chemical Society.

3D-Printing of metal oxides structures: Metal and metal oxide structures can be printed through extrusion. Recently, the extrusion of ZnO [92], have been reported. Taylor and co-workers reported a versatile and simple process for the additive manufacturing of cellular metallic architectures [93] (Figure 16). In this work, the extrusion process was used with a liquid ink consisting of a suspension of metal or metal oxide particles. Fe and Ni powders and their oxides are used as the structural material and a mixture of polylactic-coglycolic acid copolymer, dichloromethane, ethylene glycol butyl ether, and dibutyl phthalate is used to maintain a suitable rheology. The structure is printed and then subjected to sintering, with an intermediate thermochemical reduction step if oxide feedstocks are used. Figure 16 shows the linear dimension changes of the printed structures.

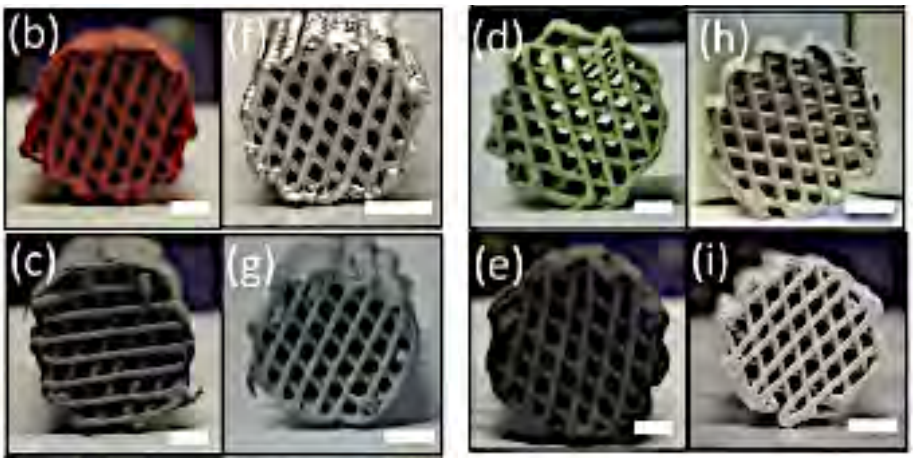


Figure 16: b,f): Samples derived from Fe_2O_3 particle-based inks; c,g): Samples derived from Fe particle-based inks; d,h): Samples derived from NiO particle-based inks; e,i): Samples derived from Ni-particle-based inks. Note the difference in scale bars, all representing 2 mm. Reproduced with permission [74]. Copyright 2020, American Chemical Society.

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2. OBJECTIVES

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We live in a society increasingly aware of the importance of optimizing the natural resources available to the planet, as well as the development of sustainable chemical processes that maintain the hope of keeping ecosystems and the atmosphere in good conditions for life.

The use of heterogeneous catalysts is a fundamental axis for the chemical industry. We can cite important examples today such as solid catalysts (typically rhodium or platinum monoliths, on ceramic supports) for the conversion of harmful gases in the automotive sector or catalysts for the production of petroleum-derived fuels in chemical industries. These examples show how heterogeneous catalysis has changed, for the better, many areas of life. Heterogeneous catalysts display efficiency, selectivity and reusability and are contributing to the goal of many scientists and many advanced societies to achieve environmentally friendly chemical processes.

The use of efficient chemical methodologies is another aspect of particular importance in the Pharmaceutical Industry. A paradigm is the use of transition-metal catalyzed cross-coupling reactions, primarily those catalyzed by palladium. When the drug synthesis at the industrial level is addressed, the presence of traces of metals in the final products (drugs) is strictly controlled by the regulatory agencies. That is why, in this Doctoral Thesis we have considered the combined application of technologies and chemical methodologies that allow obtaining heterogeneous catalysts that can be used on a laboratory scale, in the academic or industrial field. For this, we have selected a series of paradigmatic metal-catalyzed catalytic transformations, for their study of them.

Therefore, the main initial objective of this Doctoral Thesis consisted in the application of the 3D printing technology as a prototyping tool in the design and synthesis of monolithic-type heterogeneous solid catalysts, as well as other devices with custom shapes and sizes, for use in transition metal-catalyzed reactions by solution phase organic synthesis (SPOS).

To carry out this main objective, we have proposed the elaboration, through three-dimensional printing, of heterogeneous catalysts with the shape of porous silica monoliths as a support material, containing metal species (specifically palladium or copper) exclusively on their surface. For this, we have investigated different functionalization methodologies on the ceramic surface with the aim of achieving the dispersion of these metallic species uniformly in the monolith. The metal adhered to the monolith must be available and effective in carrying out a specific catalytic transformation and at the same time, constitute a stable system without leaching phenomena.

Consequently, the final objective in this work has been to obtain efficient, stable catalytic systems (without mechanical or chemical leaching phenomena of metal species), reusable during several reaction cycles, easily manipulated and scalable for possible industrial application.

To demonstrate the efficiency of the synthesized catalysts we have proposed the design of synthetic procedures that demonstrate their potential in the synthesis of variously substituted drug-like molecules with structure derived from the 1,2,3-triazole nucleus, with potential pharmacological activity. From the above, it is derived that this work has in no way aimed at the synthesis of new drugs and their biological evaluation, but rather the elaboration and study of new materials that allow chemical reactions to prepare them in an efficient, simple, easily reproducible way and at a low cost.

Specific objectives:

- Computer Aid Design (CAD) of monolith type catalysts and other 3D devices.
- Development of specific 3D printing techniques:
    - Fusion deposition modeling (FDM). Study of polypropylene as a printing material for the design of polymeric devices using.
    - Direct Writing (DIW) for the manufacture of monolithic silica supports.
- Development of different functionalization methodologies of sintered ceramic surfaces (specifically silica) such as:
    - Silanization of the surface of the monolithic silica support with silanes (provided with coordinating groups) and subsequent metalation (CHAPTER 1).
    - Coating the monolithic surface with an ultra-resistant polymer composite based on a palladium-polyimide structure (CHAPTER 2).
    - Direct metalation of the monolithic surface by Direct Impregnation (via Strong Electrostatic Adsorption) of palladium species on the silica surface (CHAPTER 3).

- Study of the chemical stability of polymeric devices made of polypropylene, such as catalytic capsules or custom vial/reactors, under the proposed reaction conditions (Suzuki, CuAAC, Chan-Lam in CHAPTER 2 or Suzuki and Sonogashira in CHAPTER 3), as well as the study of its efficiency and stability in chemical reactions.

- Full characterization of all solid catalysts manufactured by different techniques (SEM, XRD, IR, EDS, XPS) as well as synthesized organic compounds (NMR, masas).

- The study of the application of monolithic metal-ceramic devices in multicatalysis Multicatalytic Multicomponent Reactions (MMCRs) (such as CuAAC + Sonogashira, CuAAC + Suzuki, CuAAC + Stille) involving copper or palladium catalysis, as well as consecutive functionalization reactions in one pot reactions in the which two or more different metals react together to give the final product (CHAPTERS 1 and 2).

- Study of the catalyst compartmentalization and their individualized reuse when used in multicatalytic reactions, in order to recover them and use them in new reactions (CHAPTERS 1 and 2).

- Study of the recyclability of manufactured catalysts, study of the leaching and the surface modifications after the catalytic process.

- Application of efficient methodologies (such as click chemistry, PCCRs) that respect the environment (using solvents such as water or alcohols) and the use of non-toxic reagents as much as possible.

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3. RESULTS

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CHAPTER 1: 3D-PRINTED MONOLITHIC CATALYSTS IN MULTICATALYTIC MULTICOMPONENT REACTIONS.

https://pubs.acs.org/doi/10.1021/acscatal.7b02592

CHAPTER 2: MULTICATALYSIS COMBINING 3D-PRINTED CATALYTIC DEVICES AND MAGNETIC NANOPARTICLES

https://pubs.acs.org/doi/10.1021/acsami.9b08119

CHAPTER 3: INTEGRATING 3D-PRINTED REACTORS AND CATALYSTS BY THREE-DIMMENSIONAL PRINTING

https://onlinelibrary.wiley.com/doi/full/10.1002/cctc.201902143

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4. DISCUSSION OF THE RESULTS

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4.1 Background and previous results

The experimental work developed in this Doctoral Thesis has tried to advance in he knowledge of processes and technologies that allow accelerating the synthesis of molecules in new spaces of diversity, exemplified in the synthesis of variously substituted 1,2,3-triazoles. This work is benefited by the previous experience of the research group in areas such as Combinatorial Chemistry, Click Chemistry, Drug Design, design of supported reagents, nanoparticles, etc., along with other new skills acquired during this project, such as with the use of 3D-printing as a novel tool in the field of Chemistry and especially the study of chemical functionalization techniques of solid surfaces (ceramics). In addition, attempts have been made to deepen the design of new reactions, particularly new MMCRs of great scientific interest. This has been achieved thanks to an intense collaboration between researchers with different profiles and knowledge areas.

The pioneering works of Professor L. Cronin [79, 80] served as inspiration for the design of alternatives focused on the application of 3D-printing technology in drug synthesis. His work focuses primarily on the design of reactors and their aspects related to device engineering and homogeneous drug synthesis. We have focused our attention on the design, manufacturing by 3D-printing and subsequent application of various monolithic catalysts and catalytic devices:

- **SiO_2 monolithic heterogeneous catalysts that contain palladium or copper species on their surface**.
- Manufacture of a **porous capsule** using polypropylene as a material for 3D-printing. This capsule contains a supported reagent based on polystyrene, as a catalyst.
- **Vial type reactor** made with polypropylene and using 3D-printing.
- **Device for scavenging**, made with polypropylene and using 3D-printing.

In the three chapters of this Thesis we have synthesized catalysts through different functionalization techniques. Although we have also encouraged the development of catalytic devices (polypropylene capsule, described in chapter 2) or accessories (polypropylene reactor, device for scavenging, described in chapter 3) obtained through 3D-printing, the main nucleus of experimental work has relapsed mainly in obtaining monolithic catalysts.

The starting point of this work is based on a previous work [94] carried out by our research group of the Ceramic Institute of Galicia [95]. This previous work resulted in a recent patent application filed by the USC, which intends to be a base for a new kind of

preparation of heterogeneous monolithic catalysts. The work, published in 2016, used a strategy based on the so-called "catalytic inks". In summary, this strategy consists in the preparation of a mixture (ink) with the appropriate rheological properties so that it can be deposited layer by layer by 3D printing, using the direct ink writing technique (robocasting) (Figure 17).

At the same time, the suspended particles present in the ink must pass through a head of at least 400 microns, depositing layer by layer, a process that is carried out in cold. In a subsequent step, the structure obtained by 3D printing is sintered in an oven at 1500°C and an alumina-copper-based catalyst is obtained. This strategy has a series of intrinsic initial advantages such as:

- **Simplicity**: The metal and ceramic species are included in the printing material (ink). The ink is composed of the ceramic component (alumina), polymers providing viscosity and fluidity (these polymeric organic components are eliminated during the sintering process), and finally a metal salt [in the specific case of the catalyst prepared in that publication was copper nitrate, $Cu(NO_3)_2$].
- **Immediacy**: The previously prepared composite is printed directly, so the subsequent incorporation of metal is not necessary.

However, this methodology has serious disadvantages, among which are the following:

- **Need for sintering**, after the 3D-printing process, of the metal-ceramic material, at a temperature of 1500ºC. This causes the problem of the loss of the most part of the metallic species on the monolith surface by sublimation. In addition, a good part of the metal component melts in the furnace, diffuses along the monolith structure downwards and deposits on the base of the furnace, detaching itself from the monolith structure.
- **High cost of precious metal**. From the economic point of view, the prototyping for this technique on an industrial scale arises the problem of the high cost arising from the large amount of metal necessary to functionalize the monolith. Therefore, this strategy is viable only in those cases in which the metal can sublimate above the sintering temperature.
- Derived from the previous point: Although there are metal species on the surface, the **majority of the metal species are found primarily in the inner part of the monolith, not on the surface**. This is clearly a negative aspect, since it means that most of the catalytic material is not available for interaction with the

liquid phase (liquid/solid interface) and therefore there is a lot of metallic species that is wasted uselessly inside the structure.

- **Possible changes in the oxidation state** of the metal on the surface unless the heat treatment is carried out in an inert atmosphere. This can give drastic changes in the catalytic properties of the final structure.

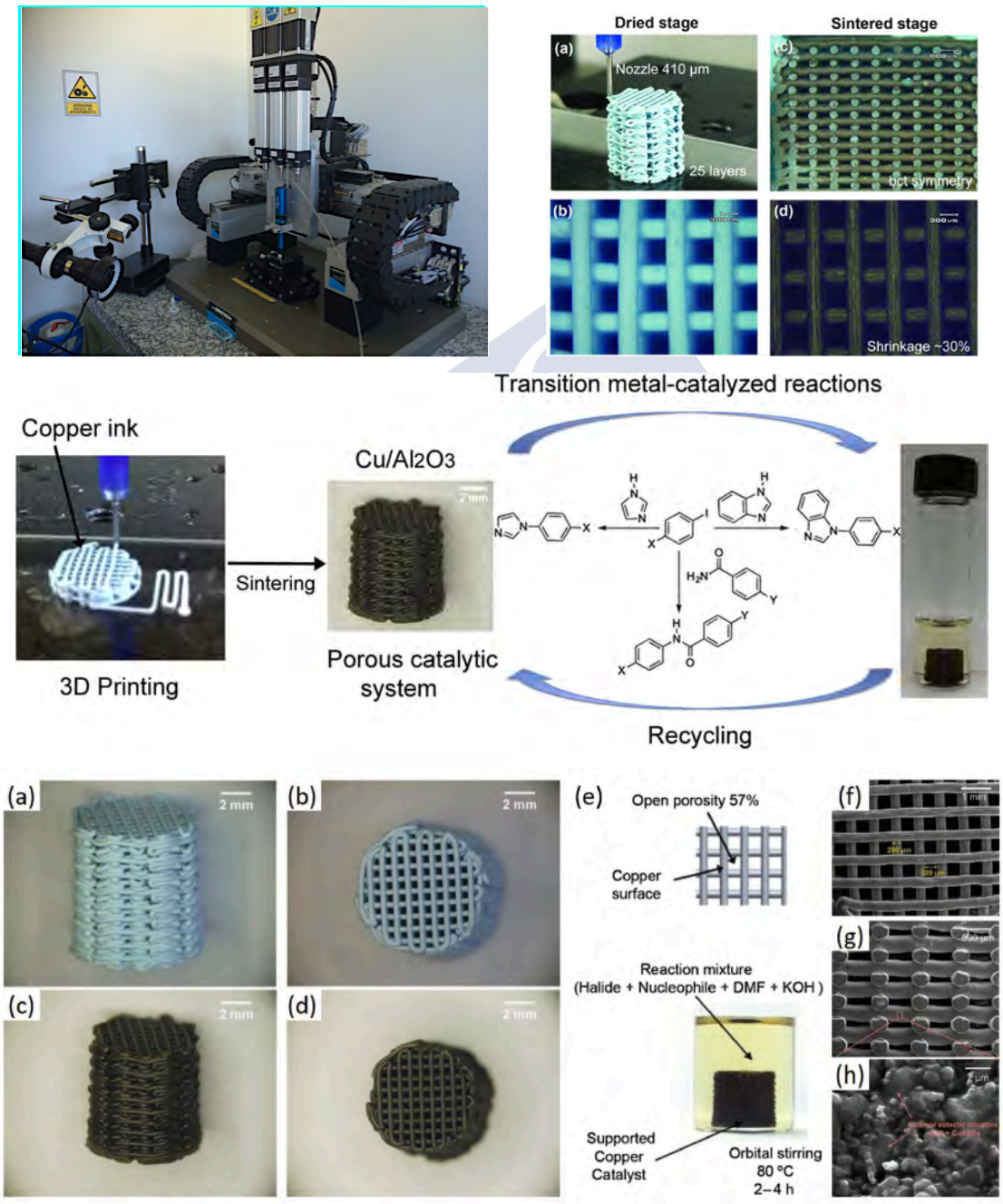


Figure 17: Summary of the previous work of our group [94]. 3D-Printing of a "metal-ceramic" ink ($CuNO_3$ and Al_2O_3 as key reagents). A blue ink [typical copper(II) appereance] is printed and the sintered to give consistency to the structure. The obtained monolith turned black [CuO species were detected on the final structure). The catalyst was effective in several Ullmann-type reactions.

That first pioneering work, published in *Journal of Catalysis* [94], revealed all the advantages and inconveniences that we have just mentioned. Particularly, the problems associated with the large amount of metallic species to be used for the preparation of the ink. This forced us to rethink the strategy based on the elaboration of inks that have metal species in their composition. This rethinking consisted, on the one hand, of the incorporation of the metallic component (a salt of copper or palladium, for instance) in a subsequent step, after sintering the monolith. On the other hand, the replacement of the ceramic material (alumina) by a similar one (silica) but with more favorable chemical characteristics (ideal surface properties). Therefore, the strategy developed in this Thesis for the manufacture of ceramic-based monolithic type catalysts maintained that sequence of this previous work: 3D printing (via direct writing) + sintering (but replacing alumina with silica). However, due to the problems associated with the loss of metallic species on the monolith surface, derived from the sintering process at high temperature and the high cost posed by catalytic inks, we have proposed at the beginning of this project a new strategy. This new way is based on the 3D-printing of a pure silica support and further incorporation of the metallic species directly on the previously sintered ceramic surface of the monolith (Figure 18). In addition, we have chosen silica as printing material because its excellent properties for 3D printing, as well as the possibility of functionalization of the silica surface by chemical methods.

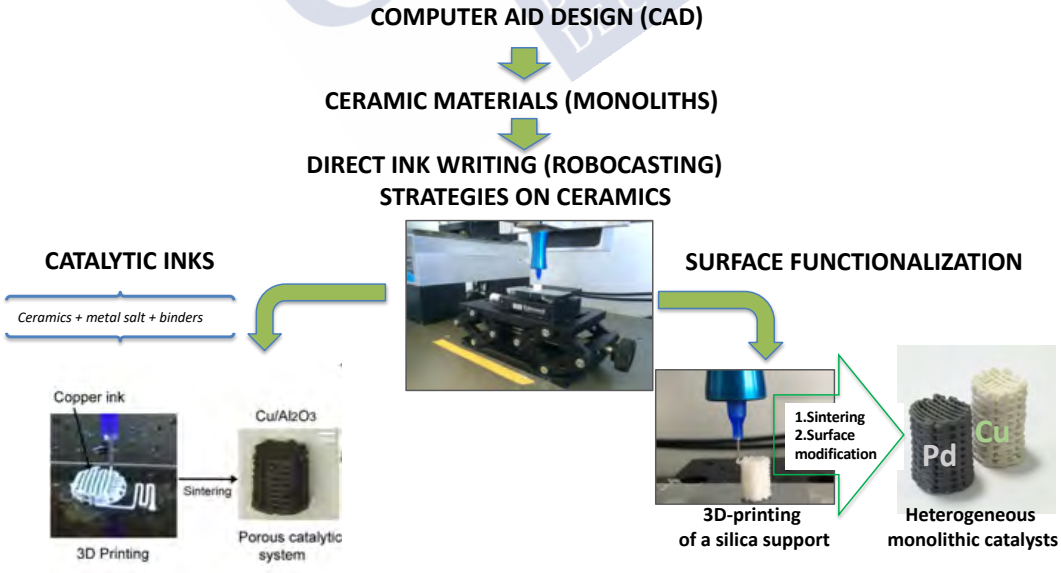
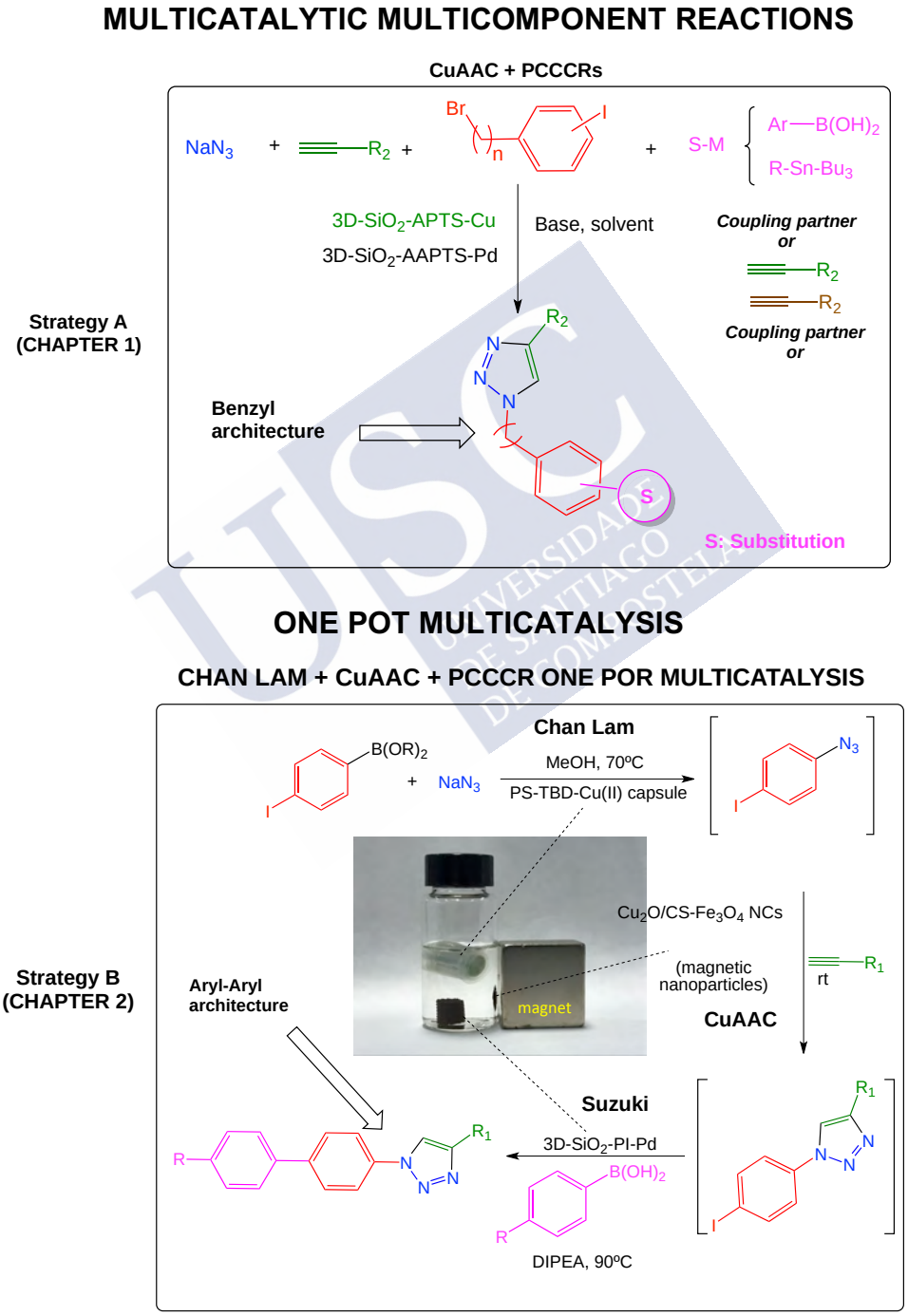


Figure 18: Two possible strategies for the synthesis of monolithic catalysts by DIW. On the right: The common workflow in the three chapters for the manufacture of monolithic catalysts in this Thesis: 1. Computer Aid Design of a monolithic silica support. 2. 3D-Printing of a monolithic silica support. 3. Sintering. 4. Modification of the monolithic silica surface. 5. Catalytic Evaluation.

4.2 General strategies for the rapid synthesis of diversely substituted 1,2,3-triazoles

Synthetic strategies developed in this Thesis for the synthesis of diversely 1,4-substituted-1,2,3-triazoles are presented in the Sheme 13. The specific catalytic aspects are discussed in section 4.6. The catalytic materials designed to carry them out are discussed below (sections 4.3, 4.4 and 4.5).



Scheme 13: Different strategies carried out during this project to obtain N-benzyl-1,2,3-triazoles (strategy A) and N-phenyl-1,2,3-triazoles (strategy B).

4.3 3D-Printed silica monolithic support and surface modification as strategy for heterogeneous catalysis

The results presented in this Doctoral Thesis are part of a broader project for the development of metal-ceramic catalysts, which continues to be developed at the Ceramic Institute of Galicia [95].

As mentioned in the previous section, from the beginning of this experimental work we adopted the general strategy for the monolith surface functionalization (modification) once it has undergone the sintering process. This is important to avoid the aforementioned problems. Then, a further surface modification with palladium or copper species was followed.

The CAD was performed to give the shape and size adapted to the vial Kimble®, previous to the 3D-printing process was performed (Figure 19). As in any composite manufacturing process, the application must drive the previous design of the material to be prepared. As can be seen in the Figure 19, the structure (containing silica and other components) has certain consistency after the 3D-printing process but it is not ready for its use as catalyst. A catalyst must have sufficient mechanical and chemical robustness. Therefore, a sintering process is necessary. This is important to resist both mechanical stress conditions (bumps or friction on the walls of the vial) and different reaction conditions (sometimes very drastic), high temperature or temperature changes, presence of solvents and reagents. As previously commented, the 3D-Printing of the silica monolith was performed using the direct ink witting and the same 3D-printer of the pioneer work [94].

Figure 19. 3D-printer used in this work for the obtention of silica monolithic supports.

Sintering is an essential phenomenon to give consistency to the ceramic monolith. Sintering (also called frittage) is the process of compacting and forming a solid mass of material by heat or pressure without melting it to the point of liquefaction. It happens naturally in mineral deposits or as a manufacturing process used with metals, ceramics, plastics, and other materials. Therefore, this process is effective when enhances properties

such as strength but, at the same time, this process reduces the porosity, which is not a favourable situation for an ideal catalyst. Other two aspects of the sintering are that cannot create uniform sizes and micro- and nano-structures produced before sintering are often destroyed. Sintering temperatures are—in general—higher or even much higher than 1000°C. The sintering temperature of the silica is around 1500°C. Therefore, a high temperature treatment is necessary so that the particles that are forming the 3D structure sinter and, in this way, the monolith acquires the consistency and resistance necessary for subsequent treatments. During the cooling down from sintering temperature, thermal expansion mismatch may cause significant thermal stresses, which may even destroy the component (Figure 20).

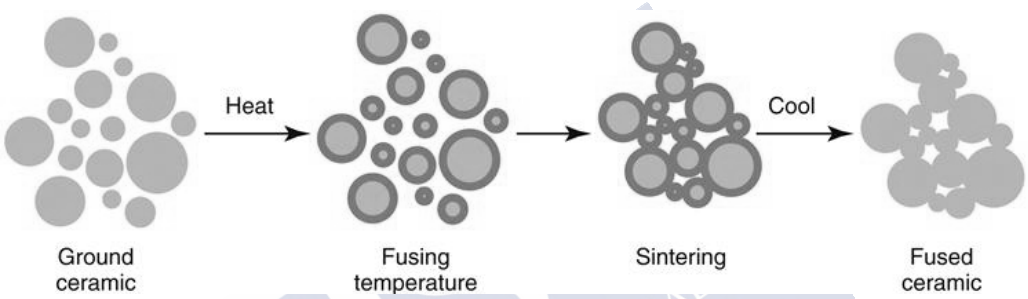


Figure 20: Schematic representation of a sintering process of a ceramic material.

Undoubtedly, we have to assume that a monolith has a much less specific surface than other systems for catalysis such as nanoparticles and in general, powder solids. However, when the catalytic particles are immobilized on a support, the dispensability, handling and work-up process are improved. Figure 20 shows the adaptation of the dimensions of the monolith to the Kimble® vial-reactor and the PLS synthesizer.

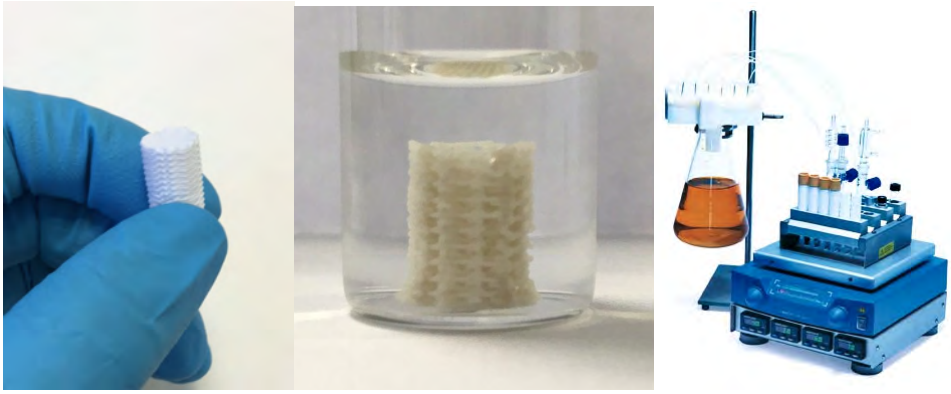


Figure 21: The sintered monolithic support (left). Silica structure at the bottom of a Kible® vial (center). Photograph of the PLS 4x6 Organic synthesizer (here it appears with other sample washing accessories). The four rows with 6 holes each, to carry out drug parallel syntheses (right).

4.3.1 Silanization + metallation strategy.

The first chapter of the results section addressed the **strategy A**. The graphical abstract is shown in Figure 22. It shows the interdisciplinary work carried out. Two monoliths were prepared for this work.

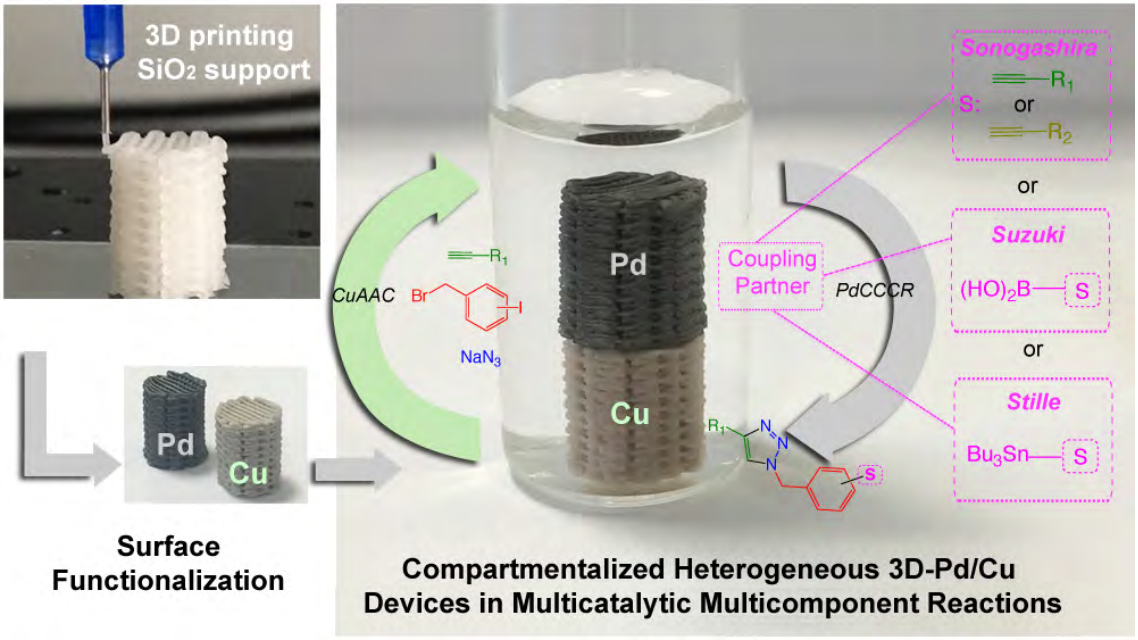


Figure 22: Grafical abstract of Chapter 1. Strategy A for the synthesis of 1,2,3-triazoles is addressed, using 3D-SiO_2-APTS-Cu(I) and 3D-SiO_2-AAPTS-Pd(0) as catalysts.

In order to carry out the proposed triazole synthesis following the **strategy A**, we designed a chemical method for the preparation of the material. This method has been described to functionalize powder systems such as silica nanoparticles or mesoporous silica: Silanization. There are numerous examples of silanes, which contain carbon chains containing metal coordinating groups. For this work we have selected two silanes:

AAPTS: [3- (2-aminoethylamino) -propyl] trimethoxysilane.

APTS: (3-aminopropyl) trimethoxysilane.

As seen in Figure 23, these reagents were used in the formation of covalent bonds with silica. These silanes generally react very well with silica surfaces and materials in general. To carry out the silanization it is necessary to activate the silica conveniently, by an acid or hydrogen peroxide pre-treatment. The result of activation is the formation of OH groups on the monolithic silica surface. Subsequent steps include metalations (through the coordinating nitrogens) with CuI or palladium acetate to give rise to the final structures. It is interesting to see how the surface of the monolith darkens to black, as a result of the bonding of palladium species on the surface. In the case of the copper monolith, the surface takes a slightly brown-yellowish color.

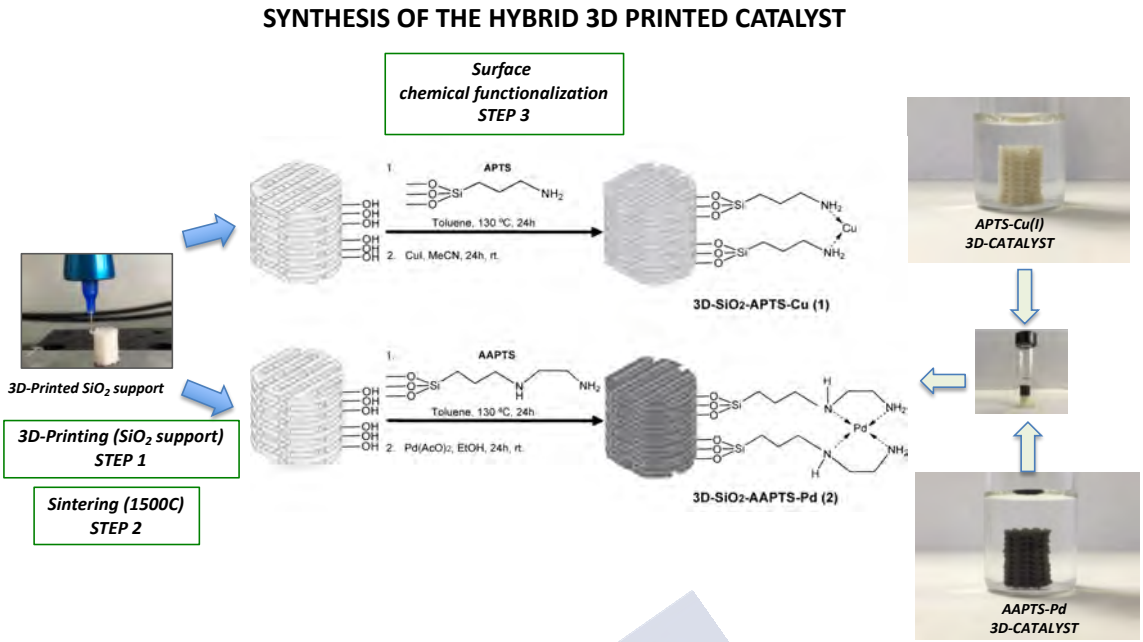


Figure 23: Functionalization of the SiO_2 surface through silanization and subsequent metalation with copper or palladium species.

As can be seen, a three-step protocol synthesis is necessary for the preparation of these monolithic catalysts (activation of the monolith, silanization and metalation). Consequently, for the work described in Chapter 2 (**strategy B**), we devised another way to functionalize the ceramic surface in one step: A polyimide coating.

4.3.2 Soluble polyimide coating + metallation strategy.

Polyimide (PI) is a type of polymer formed by repetitive units of imides. Polyimides are extremely stable under drastic conditions (temperature, solvents, reagents) and they have tendency to the formation of polymeric films which produces a total coverage and increases the introduction of organic functionality. The electronic structure of PI is a prerequisite for strong intermolecular interactions and charge transfer. The nitrogen atom is electrondonor to carbonyl group which is electronacceptor, this leads to electron move and charge interactions. On the other hand, they are interactions between aromatic rings with their π electronic sextet, which lead to parallel and planar orientation of individual chains to each other (Figure 24).

Although they are a fairly heterogeneous group of polymers, we have focused on the application of aromatic polyimides. Particularly the powder resins for curing and in situ coating of the silica monolith. Some of these resins are commercially available (Figure 24).

The resin used in this work [96] (Figure 24) has the particularity of dissolving well in certain solvents such as DMA or DMF and after a subsequent removal of the solvent and curing at a temperature of 230-240°C provides compact and stable polyimide films. Figure 25 shows the graphical abstract of the article corresponding to the chapter 2. The polyimide resin used in this work (CAS number: 62929-02-6) to functionalize the silica monolith, is presented as a yellow powder with a viscosity inherent between 0.60 to 0.70 dl/g. The starting hypothesis in this work consisted in the entrappment of a palladium source directly into the "sea of interactions" that cause such strong bonds in polyimides.

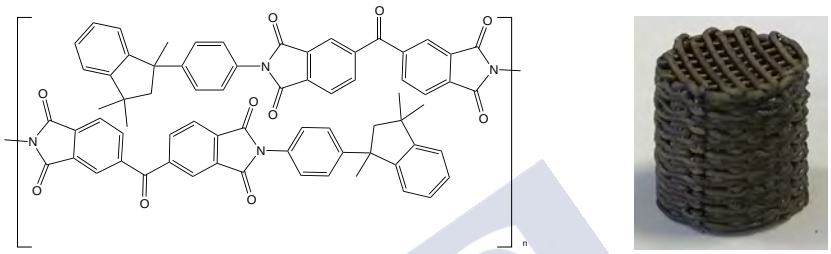


Figure 24. Chemical structure of the polyimide used in this work. The final coated Pd-PI-silica monolith.

Our initial studies showed that this polymer can form stable composites on silica. To our satisfaction, we could also verify that palladium acetate and the polyimide can be dissolved in DMF together. When a sintered silica monolith is immersed in this solution, for the necessary time and temperature, a hybrid metal-polymer film on the silica surface is formed, by simple impregnation, in a one-step process. The final result is a black monolith, after drying (temperature of 240-250ºC) in an oven and further reduction by $NaBH_4$. The monolith can be seen in Figure 25, showing the graphycal abstract of the work.

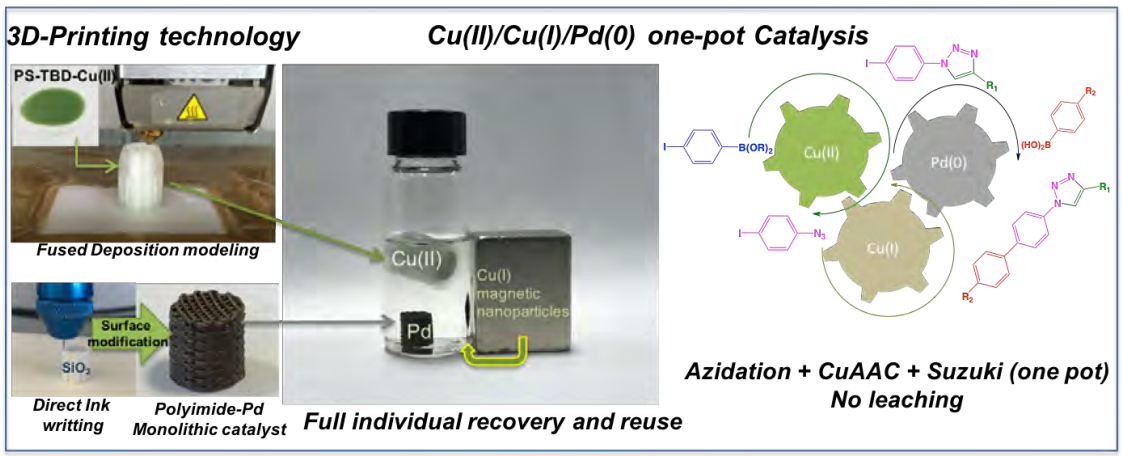


Figure 25: Grafical abstract of Chapter 2. Strategy B for the synthesis of 1,2,3-triazoles is addressed.

4.3.3 Direct Wet Impregnation via Strong Electrostatic Adsorption.

Chapter 3 describes a new and simple concept to functionalized monolithic silica surfaces. The catalytic activity of a new palladium monolith in simple reactions of Suzuki or Sonogashira is reported. The new catalyst is based on palladium nanoparticles on the ceramic monolithic surface. This work addresses the assembly of palladium species on the surface of the monolith by the direct wet impregnation (WI) method, without the presence of linkers between the ceramic surface and the metal. On the other hand, the manufacture of a reactor is approached by 3D-printing, using polypropylene as the printing material. Figure 26 represents the graphycal abstract showing this integration. This paper addresses aspects related to the Zeta potential (ZP) (or Potential Zero Charge, PZC) characteristic of the materials (both materials that act as support and the metallic species in solution). In this sense, aspects such as the pH at which the impregnation is carried out and the type of reagent containing the metallic species are essential for the efficient coating. The advantages of the catalyst preparation method described in this third article (Chapter 3) are as follows:

- Simple and direct method to prepare ceramic metal monoliths.
- Metal species are found exclusively on the monolith surface.
- There is no significant loss (leaching) of metallic species in solution when Suzuki or Sonogashira reactions are carried out.
- 3D-printing allows the integration and perfect assembly catalyst / reactor in a unit adaptable to the PLS organic synthesizer.

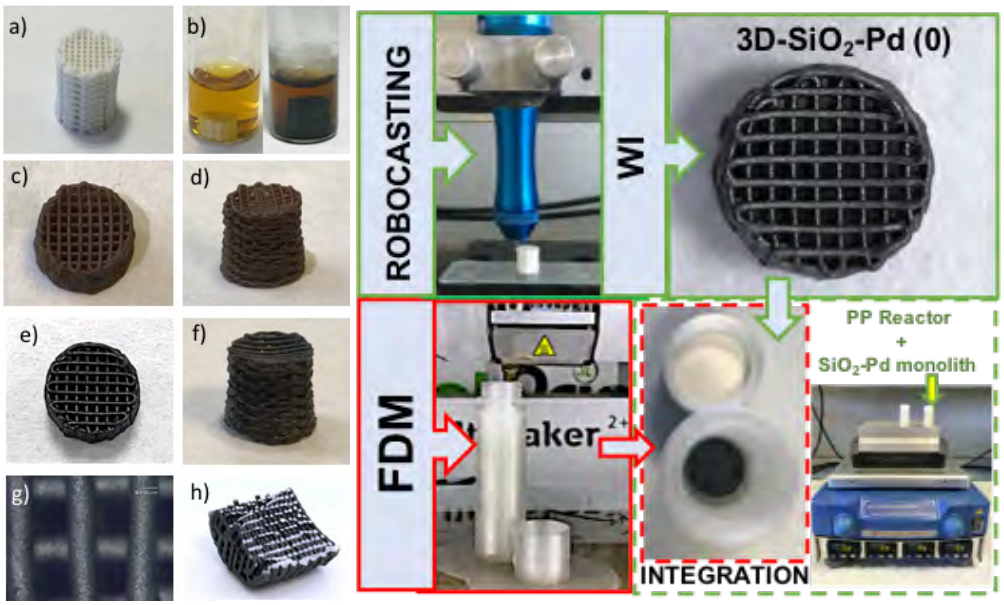
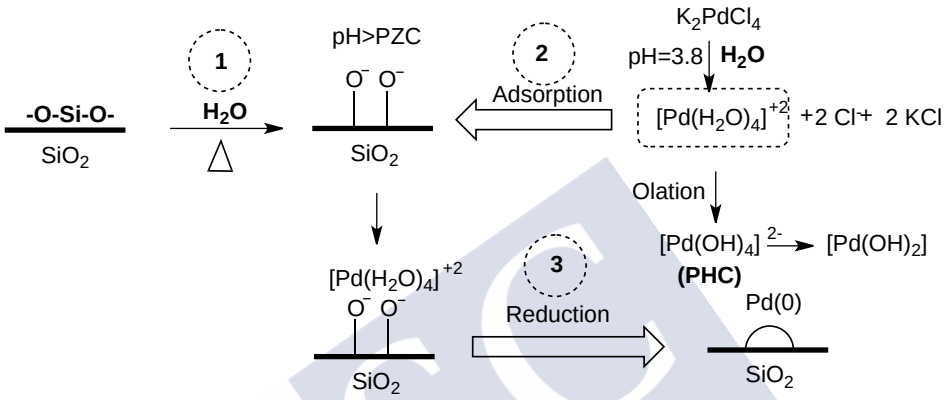


Figure 26: Wet impregnation process. Integration of 3D-printed catalyst and reactor.

WI is possible by submerging a silica monolith into an aqueous hot solution of K_2PdCl_4, to give a stable deposition of palladium nanoparticles on silica surface via Strong Electrostatic Adsorption (SEA) (Scheme 14) [97, 98]. We have started the impregnation of the monolithic silica support using K_2PdCl_4 and K_2PdCl_6 as metal salts. The preliminary results showed that the impregnation is much more efficient when using K_2PdCl_4 rather than K_2PdCl_6. Polte [99] and coworkers studied the formation of palladium nanoparticles using palladium salts such as K_2PdCl_4 or $Pd(NO_3)_2$ in aqueous solution.



Scheme 14: Strong electrostatic adsorption (SEA) takes place during the Wet Impregnation (WI) process of the sintered monolith.

Although initially we did not know exactly the chemical process that took place on the surface (since the potential of K_2PdCl_4 has negative ZP, as well as silica, at that pH), Polte's works clarified the situation. The key process (represented in Scheme 14) is the exchange of initial chloride ions in the coordination sphere of palladium, by water molecules, to give cationic species. This change, which occurs in solution is what causes the SEA of palladium on the negative charged monolithic silica surface. It is important here to note that adsorption occurs on the material before metal nanoparticles are formed in the solution, which precipitate and no longer react on the monolith.

From all the above, it is obvious that not all metal species bind to each support with the same affinity (even complex composed with the same metal element). By adjusting different impregnation parameters such as the pH according to the PZC of the various materials, a more or less stable adsorption of particles on a given surface is possible. Therefore, this work opens the doors to obtain other catalysts based on metal species directly adhered to the surface of ceramic monoliths. Thus, other catalysts based on ruthenium or platinum on silica monoliths (for applications other than those described in this Thesis) have been prepared in our laboratory, following this methodology.

4.4 3D-Printed devices for solution phase organic synthesis.

4.4.1. 3D-Printed polypropylene reactor prototype.

The idea of preparing a polypropylene reactor using 3D-printing arose after checking the chemical resistance of different printing materials (ABS, PLA, PC, PP, among others) against different solvents, acids and bases, at different temperatures. Of course, we considered the application we were going to give and also the requirements related to reaction conditions and application ranges.

It is obvious that glassware is considered today as ideal for laboratory use. It has innumerable advantages. It is hard, resistant, transparent and can be washed very well. However, sometimes it is not done exactly as you want and for the application you want. Thus, in this work we set out to create a "custom" reactor of our ceramic catalysts, as a substitute for the typical Kimble® vial. Therefore, the original idea was to adjust the reactor measurements so that the monolith remains immobilized at the bottom of the reactor. This would reduce the friction and small bumps that the monolith receives under the orbital agitation during the reaction. This has been discussed in chapter 3.

The proposed design was created with the help of the Tinkercad® program [100] and is completely original. The CURA® program [101] was used for scaling, which is free and supplied by the manufacturer of the Ultimaker 2^+ 3D-printer [102].

Undoubtedly, the biggest challenge in the elaboration of the custom-made vial-reactor was working with polypropylene as a 3D-printing material (Figure 27). Polypropylene is characterized by its poor adherence to the surface of the printing platform. This is due fundamentally to its high crystallinity. It can be said in colloquial terms that "*polypropylene only loves itself*". This forced us to look for solutions to achieve good adhesion and quality in the final printed product. The knowledge and experience acquired on the behavior of polypropylene during the work described in Chapter 2, (describing the preparation of the 3D capsule with this material) helped us for the preparation of this larger device. Particularly important was the decision to use polypropylene adhesive material (common adhesive tape) on the platform, on which the polypropylene structure is growing as well as customize the printing speed and the temperature of the platform (Figure 28). It is important to note here that for the 3D-printing of this device a nozzle of 0.25 mm in diameter was used in order to achieve maximum quality and detail in the upper area of the vial. In this area the thread is located on which the cap or vial is screwed. In order to close it conveniently and achieve a good

sealing of the reactor during the reaction, a perfect and millimeter assembly is necessary. Figure 27 also illustrates these aspects.

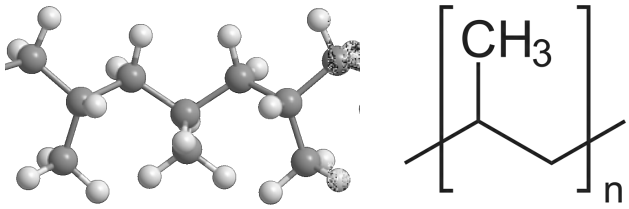


Figure 27: Structure of isotactic polypropylene and repeating unit.

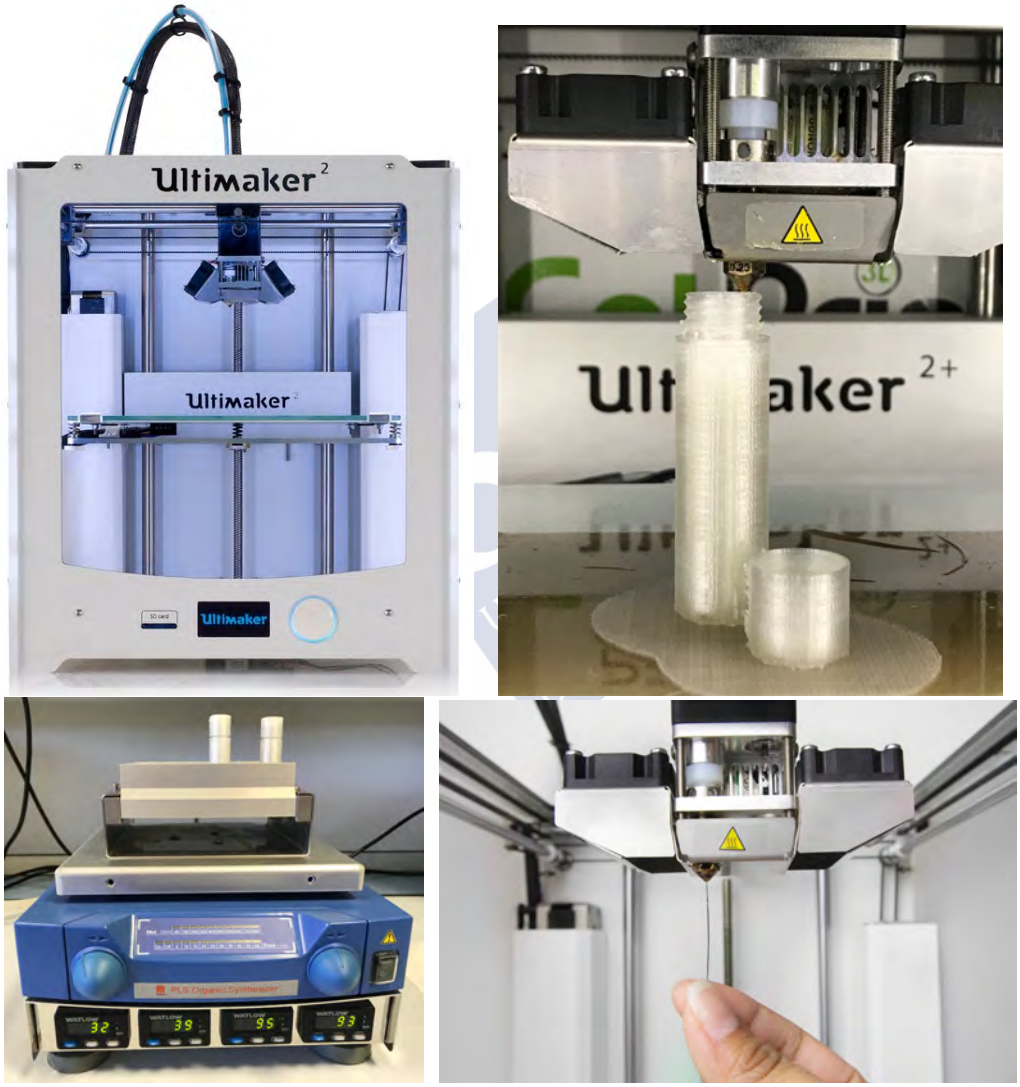


Figure 28: Ultimaker 2+ was the 3D-printer used in this work. Catalytic devices such as capped vial-reactors or capsules were made using polypropylene as printing material. The image shows the chemical structure of polypropylene, the 3D printer used, a detail of the printing of the upper area of the reactor and its adjustment in the PLS. An image of the polymer coming out of the nozzle is also shown in detail.

4.4.2 3D-Printed capsule for polymer entrapment.

The idea of manufacturing a partially porous capsule by 3D-printing arises from the need to have an entrapped catalytic system (compartmentalized) in an easily manageable device that can be removed from the reaction medium. The polymeric reagent used to catalyze the Chan-Lam coupling (strategy B) was the "homemade" PS-TBD-Cu (II) superbase [103], which offered very good results. Figure 28 shows the polymer reagent preparation process containing copper (II) species (copper acetate), the 3D-printing process and a detail of a moment of its implementation in the reactor.

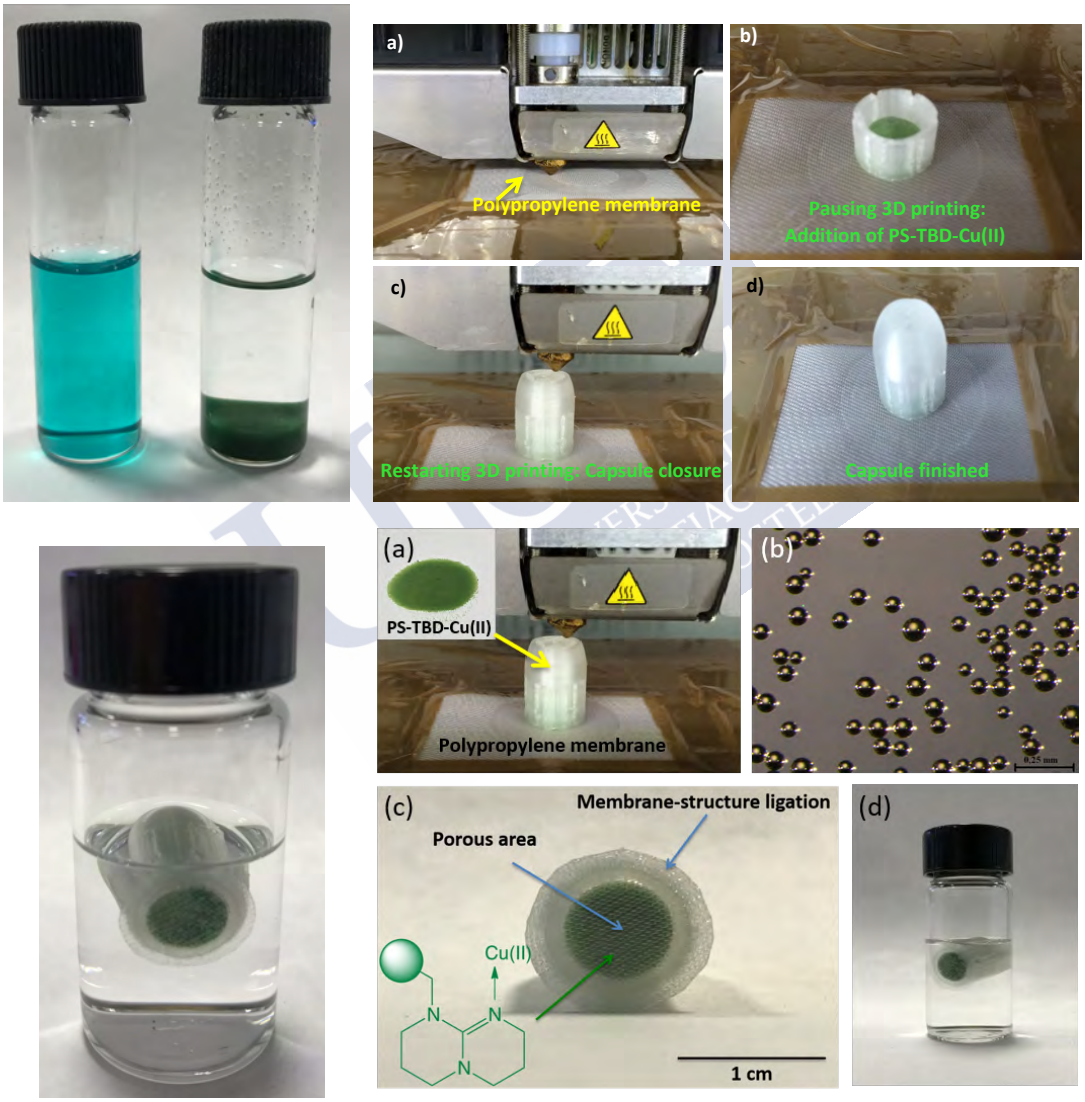


Figure 29: Synthesis of PS-TBD-Cu (II), 3D-printing of the capsule and Chan-Lam reaction using the manufactured catalytic device.

As can be seen in Figure 28, the shape and size of the capsule were not chosen at random: In addition to being very ergonomic, the capsule shape allows 3D-printing to be performed in one piece, that is, in a one-step process. During the 3D printing, we

encountered the aforementioned difficulties related to the use of polypropylene as a printing material: Warping (surface distorsions) and lack of adherence to the printer platform. This was solved by placing polypropylene adhesive tape on the base of the platform. In addition, the porous polypropylene membrane was also fixed to the base, so that the extruder began construction of the structure on the polypropylene membrane itself.

Another issue to solve was how to introduce PS-TDB-Cu (II) into the capsule and get a perfect seal. As seen in Figure 28, this was resolved thanks to the possibility of pausing printing at the right time. The necessary amount of PS-TBD-Cu (II) was introduced and once the reagent was added, the printing was resumed. The printing process was completed once the capsule was closed at the top.

In short, as can be seen, the 3D-process is a very delicate process that requires solving specific problems. The construction of such devices in the form of catalytic capsules opens the possibility of *ad hoc* manufacturing of different polymeric reagents enclosed in this type of 3D matrices, for other applications.

4.5 Magnetic nanoparticles as useful counterpart in multicatalysis.

The use of magnetic nanoparticles as elements of a "multi-catalytic cocktail" attracted our attention, mainly due to several aspects:

- Its high specific surface. They are very attractive materials for catalysis.
- The magnetic properties of nanoparticles formed by copper, chitosan and magnetite. As described throughout chapter 2, the percentage of magnetite and copper in the nanoparticles could be modulated during the synthesis. In addition, the analysis of the oxidation state of copper nanoparticles is essential for any catalytic transformation. The objective was: without losing catalytic efficiency in CuAAC reactions, to rescue the nanoparticles by the external magnet. This was achieved by increasing the percentage of margnetite in the nanoparticle.

It should be noted that during the experimental work different versions of nanoparticles were tested (Cu_2O / CS-Fe_3O_4 NCs). Our collaboration with the group of Professor José Rivas, from the NANOMAG institute (University of Santiago de Compostela) gave us the possibility of incorporating these materials into a catalytic cocktail designed to carry out strategy B for triazole synthesis.

4.6 Catalytic evaluation: Rapid synthesis of diversely substituted 1,2,3-triazoles.

4.6.1 Analysis of the developed synthetic strategies and catalytic efficiency in Solution Phase Organic Synthesis (SPOS).

Chapter 1 of this Thesis deals with the study of Multicatalytic Multicomponent Reactions (MMCRs, four initial components) and in the presence of two monolithic catalysts by SPOS. This work constitutes the first example of this type of transformations made with catalysts based on immobilized metals. Our initial intention was to carry out, simultaneously or at least consecutively, transformations involving the CuAAC and PCCCRs (Figure 30) using porous monoliths containing copper and / or palladium species.

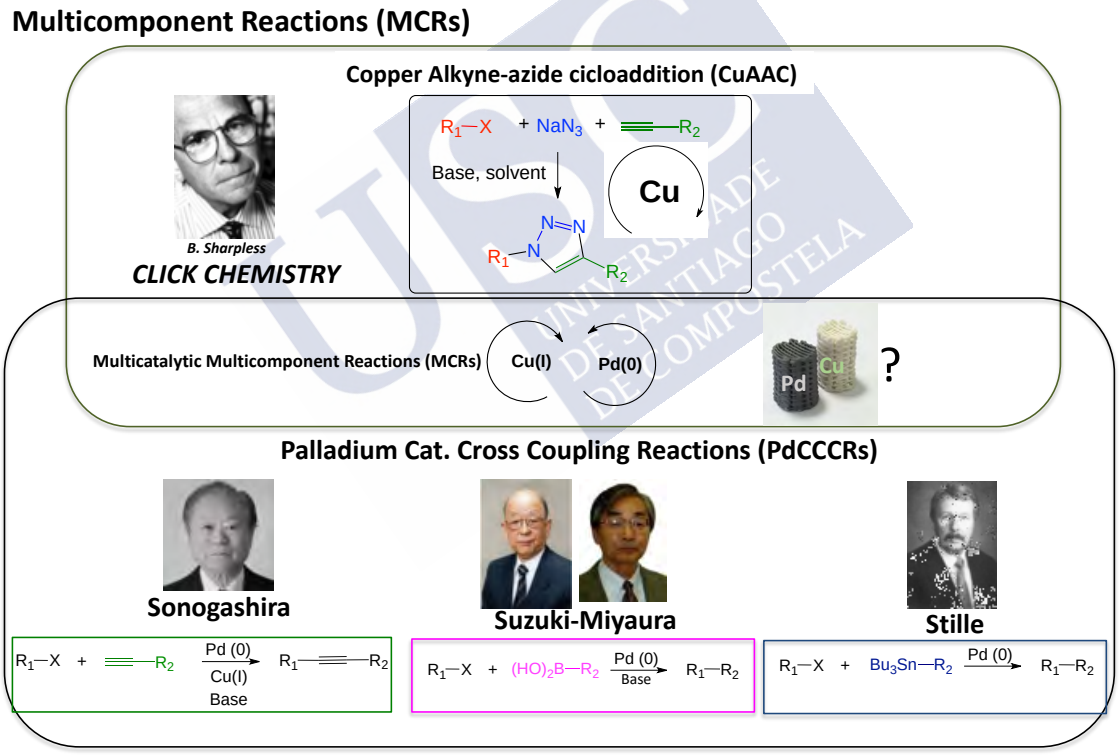
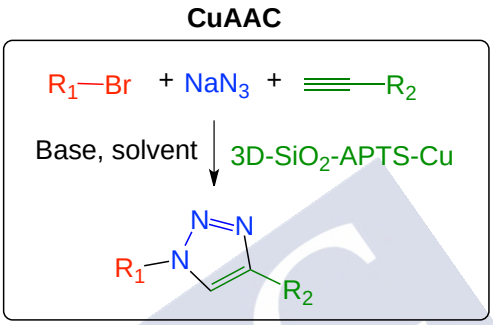


Figure 30: Conceptual idea of the work, considering the **strategy A**.

As can be seen in scheme 13, the choice of iodo-benzyl bromides (**Strategy A**) as reagents was key to building the final assembly of 1,2,3-triazoles respectively. These types of substrates react at two points in their structure. The presence of an iodo in a sp2 carbon is what gives rise to the palladium-catalyzed coupling, in the presence of a *coupling partner* (an organometallic agent, for example a boronic acid or an

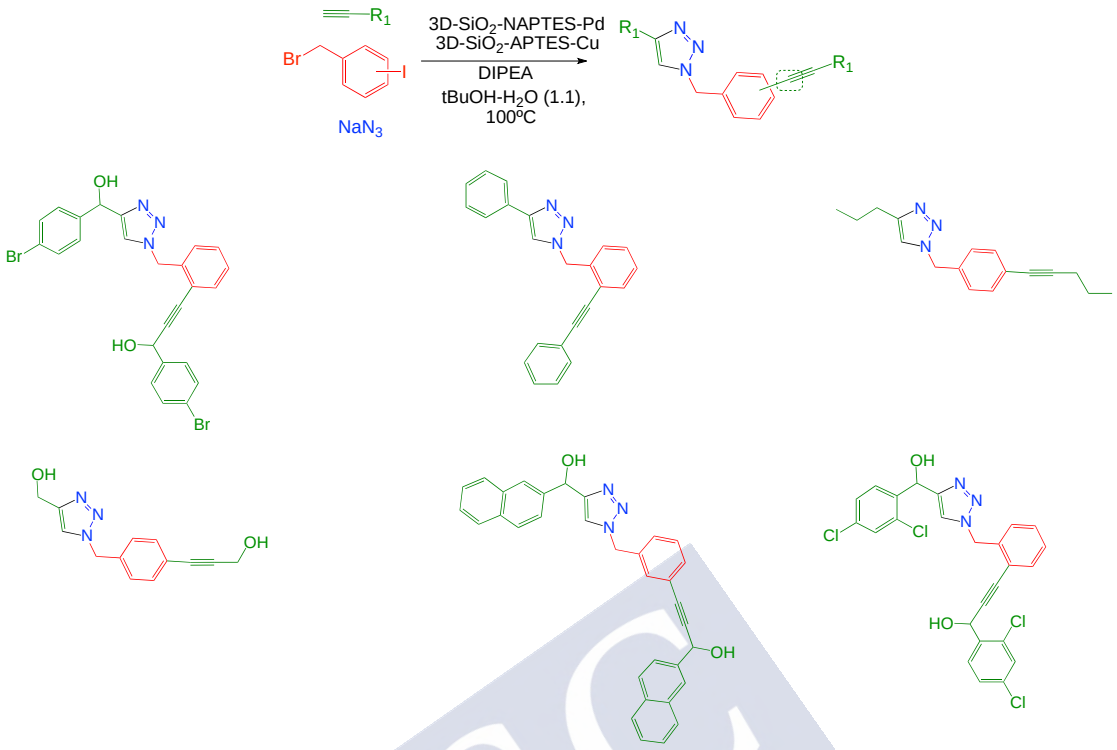
organestannan or an alkyne). In addition, the *in situ* formation of the benzylic azide would undergo a CuAAC in the presence of an alkyne and the copper catalyst. A similar concept was thinked for the **Strategy B**, using 1-azido-4-iodobenzene as key intermediate.

A key aspect for the optimization of the **strategy A**, for the first work, was the evaluation of a Cu(I)-functionalized silica monolith, 3D-SiO_2-APTS-Cu(I), to perform CuAAC reactions. Specifically, the optimization of the reaction conditions to carry out the multicomponent version of the CuAAC *click reaction* between sodium azide, benzyl bromide and different alkynes was a key issue.

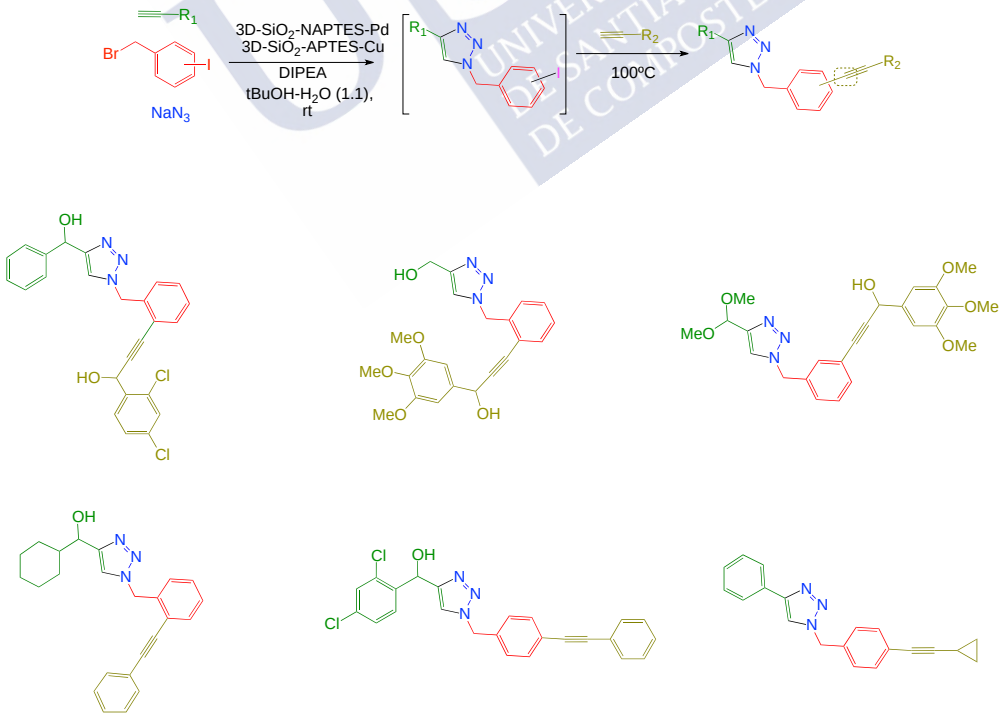


Scheme 15: The optimization of the reaction conditions to carry out the CuAAC in the presence of the monolith copper catalyst.

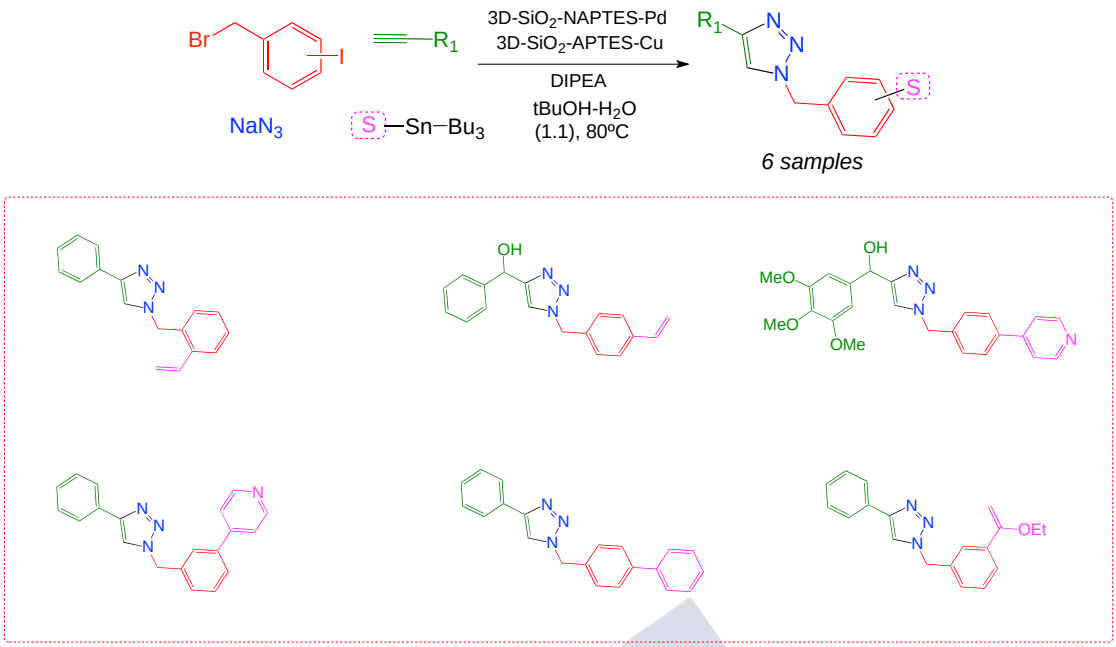
Strategy A is a pure MMCR, that is, all the initial components or reagents are found at the beginning of the reaction. The presence of a monolith with Cu species on the surface quickly generates the necessary intermediates by means of CuAAC and the palladium catalyst performs the coupling of the coupling partner in the iodo position. As can be seen in scheme 13, the synthetic **strategy A**, adopted in the first chapter, allows the formation of 4 bonds at the same time during the MMCR, achieving the assembly of variously substituted 1,2,3-triazoles, in a single reaction step, without intermediate isolation. Therefore, in addition to agglutinating all the intrinsic advantages that characterize the multicomponent reactions (convergence, atom economy, rapid assembly, etc.), the fact of using this type of monolithic catalysts means that they can be recovered after the end of the reaction. At the same time, it represents an advance in the concept of catalysts compartmentalization, aspect that will be discussed later, in section 4.6.3. Schemes 15 and 16 also show how the alkyne becomes part of the final structure through two architectures: taking part of the structure of the 1,2,3-triazole nucleus but also forming a triple exocyclic bond in the benzyl fragment. The following figures show the enormous possibilities that these transformations offer to generate unexplored spaces of diversity.



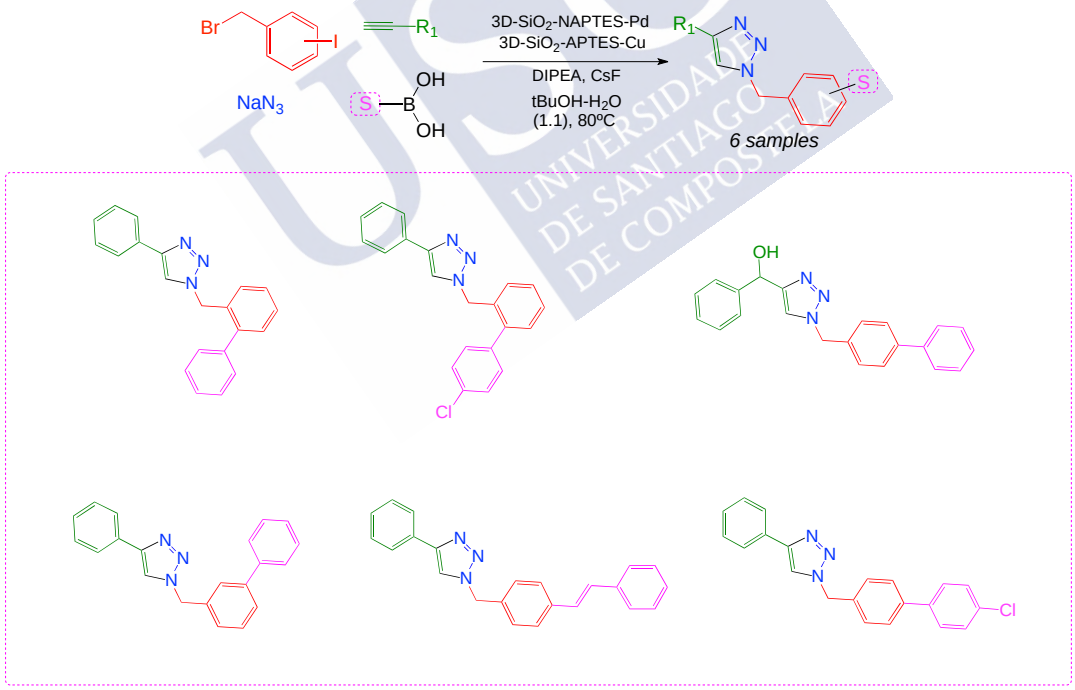
Scheme 15: CuAAC-Sonogashira MMCRs.



Scheme 16: CuAAC-Sonogashira MMCRs.

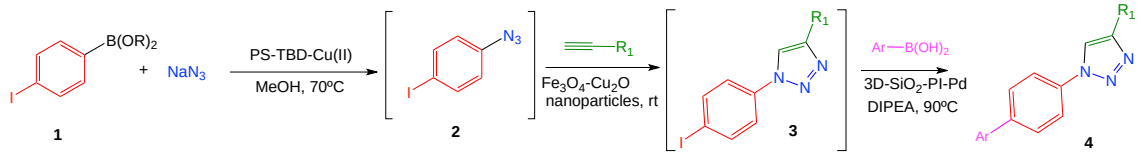


Scheme 17: CuAAC-Stille MMCRs.



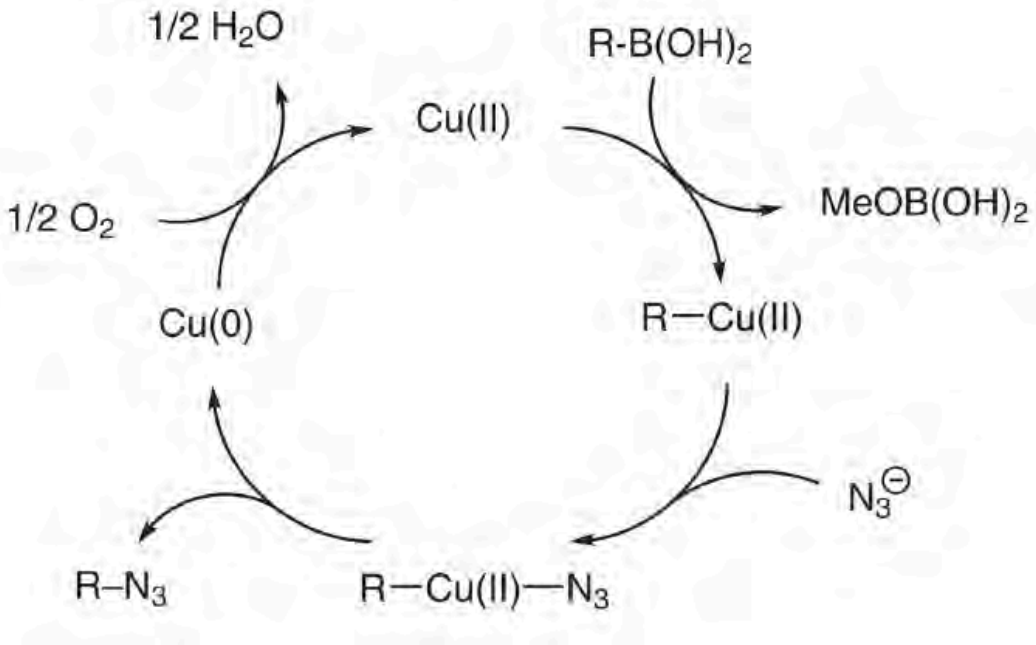
Scheme 18: CuAAC-Suzuki MMCRs.

The **strategy B**, is a multicatalytic consecutive one pot functionalization (scheme 19): the Chan-Lam type reaction for the *in situ* formation of the 1-azido-4-iodobenzene was considered, since this molecule would considered as a "bidentate reagent" for CuAAC (through the azido functional group) and a PCCCR (a Suzuki reaction in the iodo position) is generated during the reaction.



Scheme 19: Synthetic scheme carried out for **strategy B**.

Chan–Lam coupling [50, 51] is one of the most popular and easy methods to perform N-arylations. This cross-coupling reaction is generally performed by aryl boronate derivatives and a variety of substrates involving nitrogen containing functional groups such as amines, amides, ureas, hydrazine, carbamates and also sodium azide. As can be seen, the presence of Cu (II) species is necessary for the reaction to proceed satisfactorily according to the catalytic cycle proposed by Grimes and coworkers. [104].



Scheme 20: Proposed catalytic cycle for Chan–Lam coupling of boronic acids with the azide anion (First step of the Strategy B, chapter 2).

As can be seen, the presence of Cu (II) species is necessary for the reaction to proceed satisfactorily according to the catalytic cycle proposed by Grimes and coworkers. We devise the immobilization of the catalytic metal species [copper (II)] at two levels:

- On the one hand, use a supported reagent that fixes copper during the reaction.
- On the other hand, the compartmentation of the PS-TBD-Cu (II) superbase in a device (built by 3D-printing) tailored to the reactor.

The first step of the study was to immobilize copper (II) in the PS-TBD polymer resin, a reagent with which we already had some experience [103]. It is a guanidine base that coordinates copper species very well. After checking by different analytical techniques that after copper remains in the polymeric support in oxidation state (II), we decided to evaluate its behavior in the Chan-Lam coupling reaction.

The catalytic activity of the porous polypropylene capsule containing the PS-TBD-Cu (II) polymeric reagent was optimal under the conditions studied. As proof of concept, during the optimization phase of the Chan-Lam coupling reaction, the reaction between boronic acids or boronates and sodium azide was tested in the presence of the guanidine base supported on polystyrene polymer. To our satisfaction, the key reagent PS-TBD-Cu (II) demonstrated great catalytic efficacy in this transformation, could be reused after thorough washing and its activity was not affected when it was placed inside the capsule, although an extra incubation time is necessary to allow reagents to penetrate the capsule. The second step is catalyzed by magnetic nanoparticles that contain Cu (I) species and the last step is a Suzuki reaction in the presence of a Pd-PI catalyst. As can be seen in Figure 31, the architecture of the products obtained with a triazole structure is different from strategy A, since the nitrogen in position-1 binds to an aryl moiety, not a benzyl moiety.

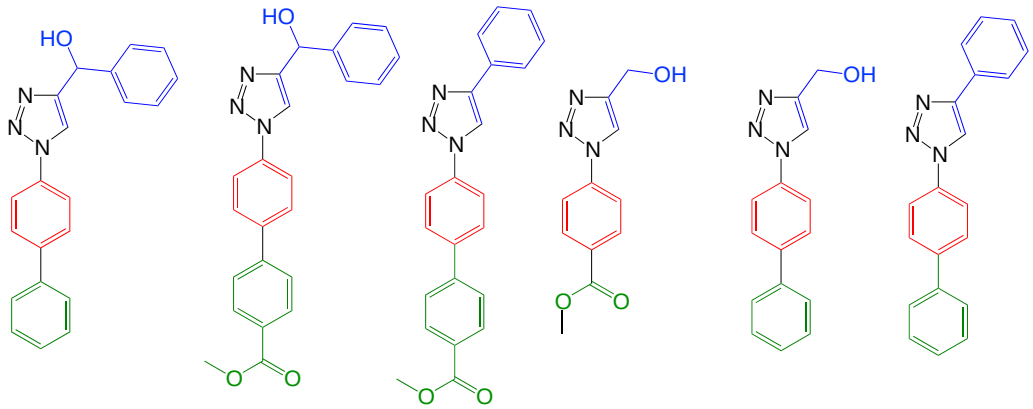


Figure 31: Chemical structure of 1,4-substituted-1,2,3-triazoles synthesized by multicatalysis (**Strategy B**).

4.6.2 Reusability of catalysts. Homogeneous versus heterogeneous.

Reusability is one of the main reasons why heterogeneous catalysis is preferred to homogeneous catalysis (in which the catalysts, often metal salts or transition metal complexes, remain dissolved in the same phase as the other reagents). Throughout chapters 1, 2 and 3 we have reflected the importance of the reuse of catalysts through bar charts, showing the number of cycles (turnovers, runs), that is, the number of repetitions that a catalyst can carry out, one transformation after another.

Figure 32 perfectly illustrates the differences between heterogeneous and homogeneous catalysts.

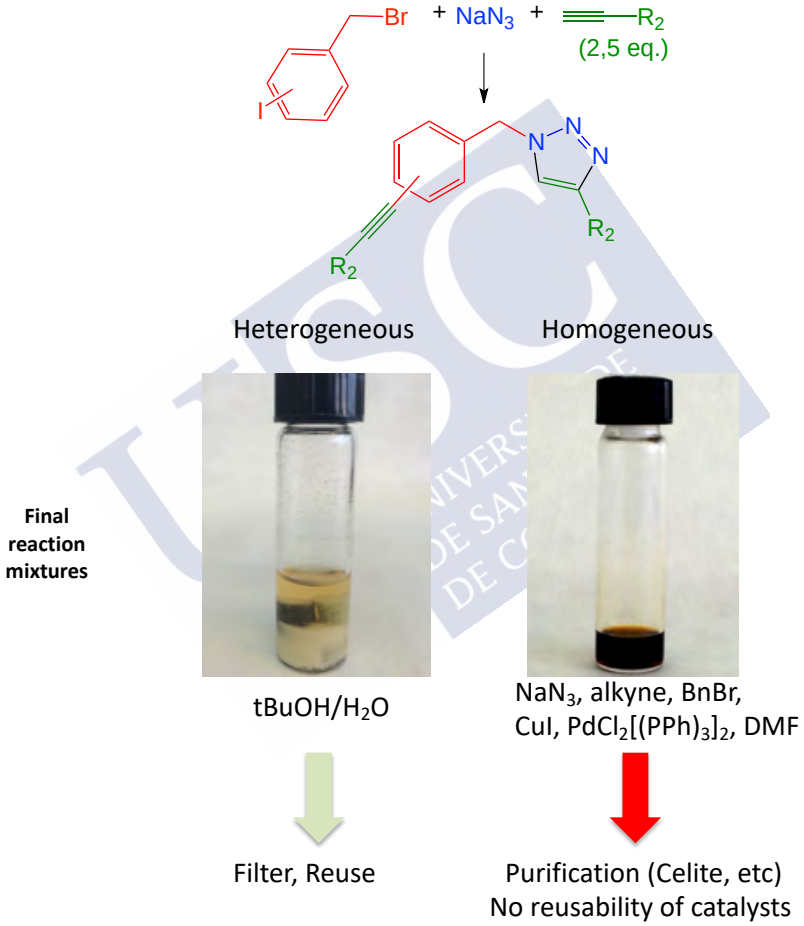


Figure 32: Example of a MMCR. On the left, heterogeneous MMCR using the Pd and Cu monolithic catalysts. The final product appears crystallized at the bottom of the vial. On the right, complex mixtures of by-products are formed using homogeneous conditions.

The differences in appearance of the reaction mixtures, once the transformation is complete, are evident. In addition, in the work corresponding to chapter 1 (**Strategy A**), we described that the use of this pair of monolithic catalysts (Pd and Cu) in multicomponent reactions solves a chemical problem, since all attempts to carry out this type of transformations under homogeneous conditions (using copper or palladium salts) were quite disappointing, generating complex mixtures and byproducts. Column chromathography is required for purification and no reusability of the catalysts is possible (Figure 32). Therefore, the work-up for the designed MMCRs using the monolithic catalysts is very simple: The monoliths are easily removable (in one piece), with the help of tweezers. After a careful washing protocol, they are ready to be used again in new reactions.

The photographs of the figure 33 present a single CuAAC reaction (left), a Suzuki reaction (right) and a CuAAC-Sonogashira MMCR (center). As can be seen in these pictures (showing examples of different reaction mixtures, before and after performing the reactions), the final product appears crystallized in the reactor walls. After carrying out the catalytic reactions, we only need to filter the reaction products (eventualy purified by recrystalization) and the catalyst is recovered for reuse.

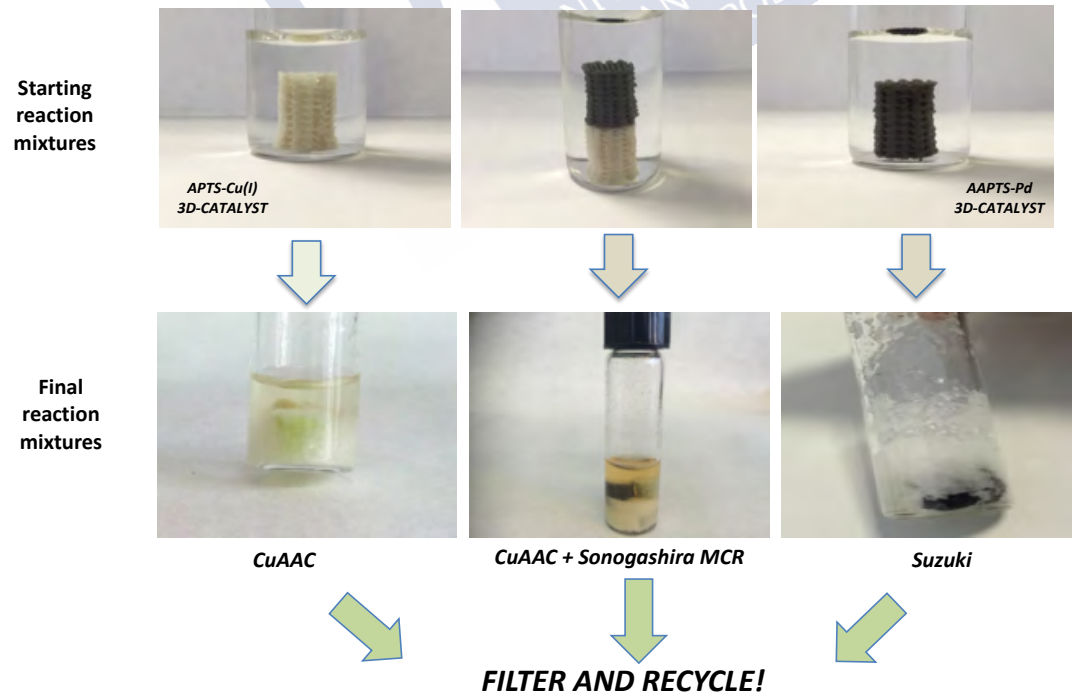


Figure 33: The final products of the reactions crystallize on the walls of the Kimble® vial.

4.6.3 Compartmentation of catalysts. Monolithic catalysts after catalysis.

The catalysts compartmentation is an aspect rarely observed in scientific works related to catalysis. Perhaps because multicatalysis is still a rarity in the field of organic synthesis. This rarity is even greater if the catalysts are heterogeneous, since the vast majority of the works they describe, for instance bi-catalytic systems, are based on transition metal complexes. Figure 34 depicts the advantages of using compartmentalized catalytic systems. Both the catalysts used in strategy A and those used in **strategy** B pursue this objective: The compartmentation of catalysis and the individual recovery of each catalyst. This allows reuse them again in new reactions. In addition, providing catalysts with solid macroscopic forms (monoliths, capsules, etc.) facilitates their extraction and handling.

When reactions are carried out in which two or more catalysts act simultaneously (for example, in cooperative catalysis), if these two catalysts are powdery solids (silicas, resins or polymers, nanoparticles, etc.), they cannot be recovered individually, since solid-solid separation is unfeasible. This can be solved if one of the two solids is provided of magnetic properties. This situation is represented in Figure 34 (on the left). For this reason, magnetic nanoparticles have attracted considerable interest in catalysis [105]. Despite of this, it is necessary to use a magnet to be able to extract and recover them.

Another option that has been explored in other works is the use of polymer-supported reagents, which can be enclosed in “tea bag” [106] containers (Figure 34, right), permeable to solvents. The disadvantage of these containers is that their pores are not small enough to enclose nanoparticles, so it is a limitation. In addition, polymer swelling phenomena occurs (depending on the solvent used). These factors have to be taken into consideration during the capsule design.

The arrangement of two catalytic systems (Pd and Cu) in two monoliths (Chapter 1) has allowed us to easily perform the individualized recovery of both catalysts and their reuse for several reaction cycles (Figura 34, center).

Figure 35 shows the catalytic systems designed and manufactured to carry out consecutive functionalizations by multicatysis for the preparation of triazoles, following **strategy B**: A catalytic porous capsule, a monolith formed by PI-Pd-SiO_2, copper nanoparticles. Again, this compartmentalized system allows the easy extraction and individual recovery of each catalyst, once the “three in one” transformation is finished.

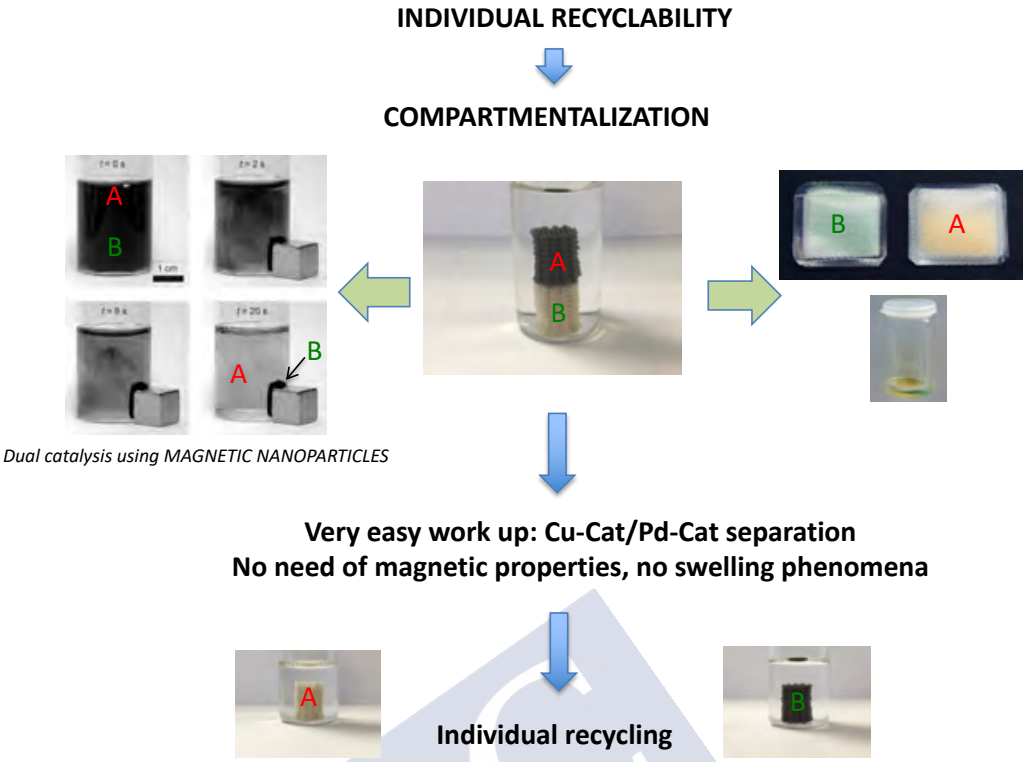


Figure 34: Compartmentation and individual recovery of monolithic catalysts (used for the **strategy A**).

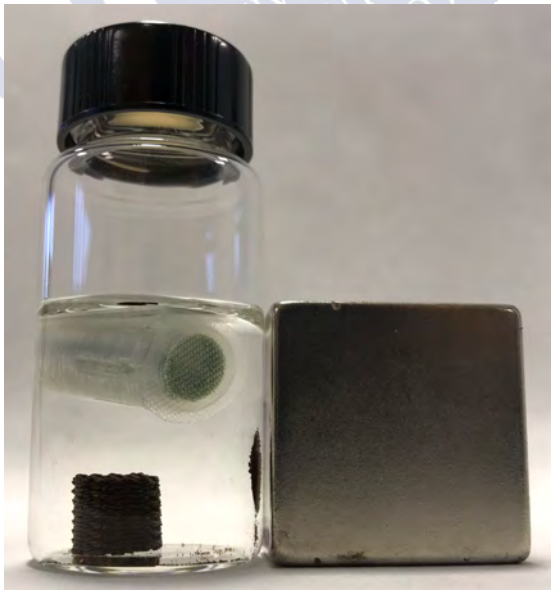


Figure 35: Compartmentation and individual recovery of a monolithic catalyst, magnetic nanoparticles and the porous capsule (use for the **strategy B**). An external magnet is necessary for the rescue of magnetic nanoparticles after catalysis.

4.6.4 Leaching studies.

Throughout chapters 1, 2 and 3, the levels of leaching of manufactured catalytic systems have been reported. It is noteworthy that all catalysts manufactured in this thesis show almost negligible levels of release of metallic species (Cu or Pd) to the reaction medium.

The metal concentration levels in the final mixtures (indicated by the ICP analysis) are negligible. This has also been supported by the reusability of the catalysts in several reaction cycles. In addition, it has been quite demonstrated that catalysis occurs almost certainly on the surface of the catalysts, confirmed by the two types of tests commonly used for this purpose: Hot Filtration Test and Three Phase Test.

In general, we could say that the devices manufactured in this Thesis guarantee levels of leaching that are negligible and therefore these catalytic systems are ideal for the synthesis of drugs.

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5. CONCLUSSIONS

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The most relevant conclusions of the three chapters are described below:

1. This Doctoral Thesis has demonstrated how the application of the three-dimensional printing technology can accelerate the Drug synthesis processes, providing patterns consistent with Sustainable Chemistry.
2. In this work, we have demonstrated for the first time (Chapter 1) that a combination of 3D printing of silica monoliths and an appropriate surface modification on the silica support (i.e., silanization and metallation) is an excellent approach for the fabrication of new, efficient, robust and easy reusable monolithic Pd- and Cu-based catalysts to perform MMCRs. Since these heterogeneous catalysts are stable – they show negligible metal leaching – they can be reused more than 10 times.
3. Compartmentalization of Pd and Cu species in these monoliths allows individual recycling after performing each kind of MMCR. The catalytic effectiveness and ease of handing of these monolithic prototypes in work up processes make these devices very suitable for solution phase chemistry in industrial applications.
4. It has been demonstrated for the first time that the use of two different three-dimensional printing techniques (fused deposition modeling and direct ink writing) can be used to manufacture customized catalytic devices (a capsule-container for polymers and a polyimide / palladium coated silica monolith) with different shapes and sizes for the immobilization of catalytic metal species (chapter 2).
5. The appropriate surface chemical functionalization of a 3D-printed silica support with a polyimide-palladium composite afforded a robust and effective monolithic catalyst.
6. The appropriate combination of these devices with other valuable catalytic materials, such as magnetic nanoparticles, allows complex multi-step multicatalytic one-pot transformations to be performed without contamination of the reaction mixtures with metal species. The final result is a compartmentalized Cu (II) / Cu (I) / Pd(0) tri-catalytic system in which each catalyst is easily separable, recoverable and reusable separately.
7. The strategies A and B (corresponding to the chapters 1 and 2) developed here provides a practical model based on sustainable chemistry in which three metal-catalysts are combined for the parallel synthesis of different 1,4-bisubstituted-

1,2,3-triazoles. This approach could also be applied to other multi-catalytic systems or tandem process in solution-phase organic synthesis.

8. An integrated Reactor / Catalyst system was manufactured with the assistance of 3D-printing technology (Chapter 3). A tubular polypropylene (PP) reactor adaptable to an orbital organic synthesizer robot was obtained by computational aid design (CAD) and fused deposition modelling (FDM). The custom 3D-SiO_2-Pd(0) monolithic catalyst for the reactor was synthesized by robocasting and sintering of a woodpile SiO_2 support and subsequent Wet Impregnation (WI) through Strong Electrostatic Adsorption (SEA) using an aqueous solution of K_2PdCl_4. Both the polypropylene reactor and the 3D-SiO_2-Pd(0) catalyst were effective in Suzuki and Sonogashira reactions.
9. The reactor/catalyst system can be reused at least 6 times without significant loss of efficiency. Therefore, the third work exemplifies how the use of 3D-printing technology can produce customized catalysts and reactors for specific organic synthesizers.
10. The employed impregnation method of the sintered silica surface by palladium nanoparticles via Strong Electrostatic Adsorption was efficient, simple and cheap. Therefore, this methodoly led to a reusable catalyst effective in carrying out palladium catalysed cross-coupling reactions.
11. All the catalytic systems synthesized and described in this thesis have been conveniently characterized by different surface and material analysis techniques. In addition, the reaction products (1,2,3-triazoles) obtained in the reactions were also characterized by techniques such as mass spectrometry or NMR spectroscopy.
12. The methods of preparation of monolithic catalysts manufactured during the experimental work of this thesis establish the bases for its prototyping and scaling at the industrial level.

6. BIBLIOGRAPHY

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