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Additive Manufacturing Technologies: 3D printing in Organic Synthesis

Sergio Rossi,^[a] Alessandra Puglisi,^[a] and Maurizio Benaglia*^[a]

Abstract: The manufacturing of a three-dimensional product from a computer-driven digital model (3D printing) has found extensive applications in several fields. Additive manufacturing technologies offer the possibility to fabricate ad hoc tailored products on demand, at affordable prices, and have been employed to make customized and complex items for actual sale. However, despite the great progress and the countless opportunities offered by the 3D printing technology, surprisingly a relatively limited number of applications have been documented in organic chemistry. This review will focus specifically on the exploitation of additive manufacturing technologies in the synthesis of organic compounds, and, in particular, on the use of 3D-printed catalysts and 3D printed reactors, and on the fabrication and use of 3D printed flow reactors.

1. Introduction

In recent years additive manufacturing (AM) have received an exponentially growing attention. The manufacturing of a three-dimensional product from a computer-driven digital model (3D printing) has found extensive applications in several fields, such as engineering, architecture, medical, industrial design, construction and many others.^[1] 3D printing is an additive process, where multiple layers from CAD (computer-aided design) drawings are laid down one after another to create different shapes; differently from the mass production, it allows anyone to create customized products on demand at affordable prices. Its impressively rapid diffusion in the last times is due also to the progressive cost reduction, that, today, makes the production of some products categories advantageous, such as goods that are made in relatively low quantities (limited scale), have a need for personalization or are impossible to make with conventional manufacturing technologies. The use of the technology is now so widespread in many productive areas that its advent has been seen as the third industrial revolution.^[2]

3D printing have found extensive applications in the most disparate fields, such as education (used to visualize molecules and proteins,^[3] orbitals and surfaces^[4] for teaching purposes) and in food industry;^[5] the use in biotechnology,^[6] biomedical^[7] (including printing of cells^[8]) and analytical area^[9] have been reported. Chemistry, as well biology, is heavily interested by this revolutionary technology; the combination of additive manufacturing technologies with catalysis offer unprecedented opportunities, and challenges, to the modern chemist.^[10] One of the field where additive manufacturing is really making the

difference is flow chemistry;^[11] microfluidic devices^[12] and, in general, tailored reactors have been designed; ad hoc customized devices, with the possibility to incorporate other non-printable components, such as LEDs, spectroscopic windows, membranes, have been also realized.

However, despite the great progress and the countless opportunities offered by the 3D printing technology, surprisingly a relatively limited number of applications have been documented in organic chemistry. By the other hand, many scientific supporting tools (such as test tube racks, syringe pumps, shakers, stirrers, pipetman, peristaltic pumps etc) have been realized with different 3D printing technologies, and thanks to the open source community, they have been digitally shared over the most common repositories (thingiverse, appropedia etc), facilitating the replication and diffusion of these devices over the world. This review will focus specifically only on the exploitation of additive manufacturing technologies directly involved in the synthesis of organic compounds, and, in particular, on the use of 3D-printed catalysts and 3D printed reactors, and on the fabrication and use of 3D printed flow reactors.

2. 3D printing technologies

The starting point for a general 3D printing process is the creation of a virtual design file containing the description of the target object using a Computer-Aided Design (CAD) software. This file needs to be converted into the STL format (Standard Tessellation Language) where only the surface geometry of the three-dimensional object is described. This geometry is then converted in a G-code file (numerical control programming language) by "slicing" the 3D model into printable cross-sections. After that, many other information about other technical parameters (size, orientation, printer quality, temperature, materials, etc.) need to be added by specific programs before transferring it to the 3D printer. Moreover, quite often 3D printers require also an instrumental setup (as the refilling of the polymers or binders and other consumables) before starting the 3D printing process. The steps of 3D printing process are independent from the type of 3D printing approach used, however different types of 3D printers employ different technologies to process the

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materials; as a consequence, even if the virtual design is the same, the final object will present different physical characteristics.

Several 3D printing processes have been developed since Chuck Hull invented the first stereolithographic 3D printer in 1986,^[13] the most common being Fused Deposition Modeling (FDM), StereoLithography (SLA), Selective Laser Sintering (SLS), Selective Laser Melting (SLM), Electronic Beam Melting (EBM), Digital Light Processing (DLP) and Laminated Object Manufacturing (LOM). A short, general overview of these methodologies is reported below.

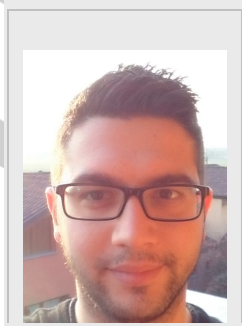
After his PhD with prof. M. Cinquini and F. Cozzi, Maurizio Benaglia joined in 1995 prof. J. S. Siegel group at UCSD (USA); then he moved back to the University of Milan, where in 2015 he was appointed as Full Professor of Organic Chemistry. His research activities focus on the development of novel synthetic methodologies, design of new chiral organocatalysts, study of stereoselective reactions in flow and catalytic reactors, synthesis of pharmaceutical products, taking advantage also of 3D-printing technologies and alternative reaction media.



Alessandra Puglisi received her PhD from University of Milan, Italy in 2003. She spent her post-doctoral fellowship in the group of Prof. Amir H. Hoveyda (Boston College, USA) in 2004. In 2011 she became Assistant Professor the University of Milan. Her main scientific interests are in the field of stereoselective organocatalysis, in particular, the synthesis, characterization and synthetic applications of chiral supported catalysts and their applications in continuous-flow chemistry and 3D printing applications.



Sergio Rossi received his PhD from University of Milan, Italy in 2010. He joined the University of Illinois at Urbana Champaign (USA) in 2011 as a post-doctoral fellow, in the group of Prof. S.E. Denmark. In 2017 he obtained an Assistant Professor position at the University of Milan, where he is currently working in the stereoselective synthesis of chiral pharmaceutical products and in the development of new catalytic stereoselective metal-free methodologies, under continuous-flow conditions in micro- and 3D printed mesoreactors.



2.1. Fused filament fabrication (FFF)

Fused filament fabrication (FFF) or Fused Deposition Modeling (FDM) was initially patented by S. Scott Crump in the late 1980s^[14] and the first 3D printer based on this technology was commercialized in 1990 by Stratasys. After the expiration of these patents, a large open-source development community^[15] and hardware companies (e.g. Wasp, Ultimaker and MakerBot) started to fabricate new and less expensive equipments; today, FFF 3D printers are accessible at low cost and are commonly available in many stores. For these reasons nowadays FFF is one of the most largely used additive process for rapid prototyping.

With this technology, a thermoplastic filament (1.75 or 3.00 mm diameter) is unwound from a coil, fed into a hot nozzle (regulated by a temperature control unit) and passed in a viscous-flow state and extruded through an extruder that can be moved in both X and Y direction while the build plate lowers the object layer by layer in the Z direction according to the virtual design (Scheme 1-a). In this way, the molten material is deposited one layer on top of the other to which it will be bonded once gently solidified in a heated enclosure. Generally, the desired object is built from the bottom to the top; sometime, when the object presents overhanging parts, the presence of (removable) supports is required. Generally, FFF 3D printers present from one to three extruders able to print up to three different materials or colors at the same time. The most commonly used materials are polylactic acid (PLA), High Impact Polystyrene (HIPS) and Acrylonitrile/Butadiene/Styrene (ABS) polymers. However, many other materials could be used such as Polyvinyl Alcohol (PVA), Polyethylene Terephthalate (PET), Polyethylene Terephthalate glycol (PETg), polycarbonate (PC), polyamides (NYLON), and their combinations with small percentage of glass, metals (graphite, nanotubes, Cu, Al) and ceramics. The resolution of these printers range between 250 (XY) and 50 (Z axis) μm .^[16]

This wide choice of printable materials is one of the most significant advantages of these 3D printers, which are also relatively inexpensive and easy-to-handle. Unfortunately, not all the materials are useful for practical applications in organic synthesis^[17a] and in some cases the fumes generated during the heating at high temperature of thermoplastic materials could be a potential health hazard (as for the PEEK printing process). However, the possibility to place the 3D printer in a hood (always present in a chemical lab) can easily solve any problems coming from the vast majority of common thermoplastics. Moreover, many other polymers with increased resistance to solvent are under development (as the biomass derived poly(ethylene-2,5-furandicarboxylate PEF polymer).^[17b]

2.2. Stereolithography (SLA)

Stereolithography is the oldest of the 3D printing technologies.^[7] It involves the use of an ultraviolet laser (generally a HeCd laser at 325 nm^[18] or a xenon lamp^[19]) that is focused onto a vat containing a photopolymer resin. Since the photopolymer is sensible to the UV light, when a layer of photosensitive liquid resin is exposed to the UV beam, it undergoes a crosslinking process, instantaneously solidifies and hardens (Scheme 1-b).

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Also the SLA approach creates the final structure in a layer-by-layer mode and, analogously to the FDM technology, each layer is built on top of the preceding one and objects with overhangs require the presence of supports to be printed.

Advantages of this approach are the high resolutions that can be reached (up to 25 μm layers, depending by the laser spot size and the resin type),^[6] and higher building speeds, compared to FDM technology. Since final objects present smooth surfaces rich of many details, SLA has found applications in the industry of jewelry and for dental applications. Some drawbacks are instead related to the high viscosity of the resins, that can make difficult both the filling and the cleaning step, especially when small channels are printed. Moreover, the variety of resins is quite limited, since they are all based on epoxy, urethanes or acrylic derivatives.

An improved version of stereolithography was recently reported by Ermoshkin, Samulski and DeSimone,^[20] which developed the Continuous Liquid Interface Production (CLIP). This approach involves the presence of an oxygen-permeable membrane below the ultraviolet image projection plane, which creates a “dead zone” (persistent liquid interface) where the photopolymerization between the window and the polymerizing part of the resin is inhibited. This makes the process up to 100 times faster than the traditional approach, since final object can be produced in continuous and in minutes instead of hours.

2.3. Digital Light Processing (DLP)

Digital Light Processing was invented in 1987 by Larry Hornbeck of Texas Instrument^[21] and presents many analogies with Stereolithography. In both cases, a liquid photopolymer is used, but in DLP the photopolymer is cured using a special projector instead of a laser source. In this way, an entire layer of resin is crosslinked at the same time. According to this approach, the projector is located on the bottom of the vat that has a transparent window in order to allow photopolymerization (Scheme 1c). DLP uses a computer-controlled, micro-mirror grid, laid out on a semiconductor chip. These tiny mirrors can be tilted in a “on” or “off” state: when the mirror is in a tilted position (“on” state), it can reflect light, creating a bright pixel, otherwise the pixel is dark. In this way, the projector creates a “mask” on the photopolymer layer, which will be cured only where bright pixels are present.

Advantages of this approach are that the positioning errors in the XY plane are reduced due to a limited mechanical movement and that the vat dimension does not limit the height of the printed object. The resolution achievable is about 50 μm in all axes.^[12d] Moreover, the layer thickness is independent of the type of resin employed since it is determined by the Z stage resolution.^[22] However, due to its costs, DLP is limited to professional applications.

2.4. Selective Laser Sintering (SLS) and Selective laser melting (SLM)

Selective Laser Sintering was developed by Deckard and Beaman in 1980s.^[23] This additive manufacturing process is quite

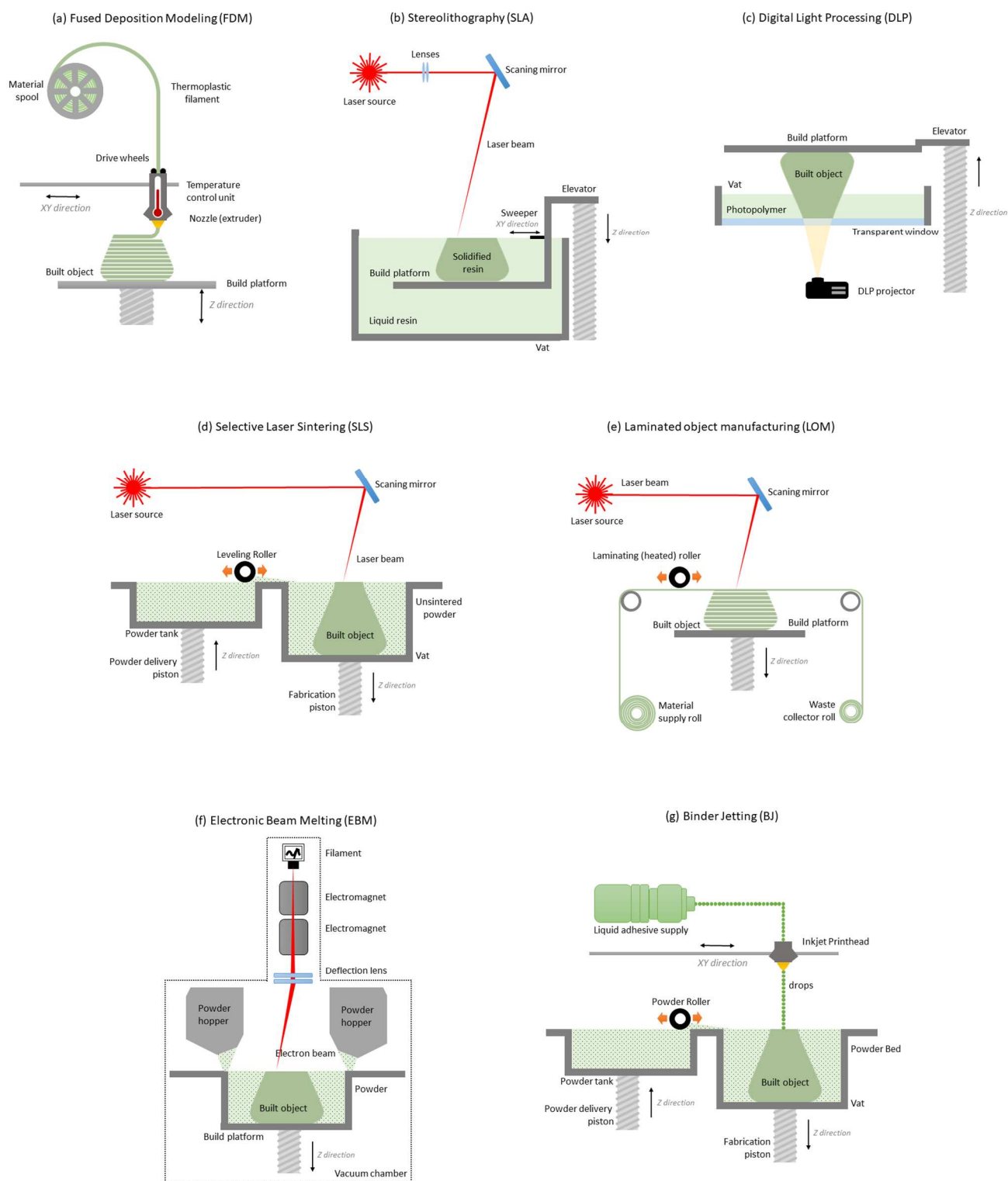
similar to SLA, but involves the use of powdered material (polycarbonates, polyvinyl chloride, ABS, polyamides and ceramics) instead of the photopolymerizable resin. An expensive high-powered laser (such as CO_2 and Nd:YAG^[24]) selectively sinters a layer of small granules, which bind together to create a solid structure in a layer-by-layer approach. The laser heats the tiny powder layer to a temperature just below its melting point according to the cross-sectional profile of the virtual design. After each cross-section is sintered, the powder bed is lowered by one layer thickness and new layer of powder is deposited on the top ready for another sintering process. These steps are repeated until the print is completed (Scheme 1d). An advantage of this approach is that, differently from stereolithography (SLA) and fused deposition modeling (FDM), SLS does not require the presence of support structures, because the un-sintered powder present in the vat acts itself as support. In addition, the final printed object does not have internal defects, extremely important for metal components that will operate under high stress, such as aerospace or automotive parts. The resolution of these printers are generally below 50 μm .^[6] Unfortunately, most commercial metal 3D printers cost more than half a million dollars, thus preventing the use by the average consumer. Another important issue is the non-flowing nature of the powder precursors, that represents a big problem for microfluidic applications, since it is quite impossible to remove it from the microchannels of the printed device, after the sintering process.

Selective laser melting could be considered a subclass of SLS technology, since SLM uses a high-powered laser beam to fully melt alloys and powders (such as aluminum, silver, iron, stainless steel, titanium, cobalt and chrome) into solid three-dimensional parts.^[25] SLM uses a laser to heat the powder above the melting point of the metal, so that the powder can fuse together.

2.5. Laminated object manufacturing (LOM)

Laminated object manufacturing was developed by California-based company Helisys Inc^[26] in the late 1990s and involves the use of sheets of adhesive-coated paper, plastic or metal laminates, which are fused together by heat and pressure. A computer-controlled laser (or razor) traces the desired cross-section according to the virtual design on a first layer of material, then the extra material is removed and a second sheet of material is deposited onto the previous one. The second layer is generally pasted or welded on the top of the first one and uniformities are guaranteed by a controlled heating step during the production (Scheme 1e). This process is repeated until the object is printed. The printing process is sometimes followed by machining and drilling of the object. LOM processes require that the materials could be formed into tiny sheets (and integrated with adhesives) and this represents one of the principal drawbacks of this methodology. LOM is slightly less accurate than SLA or SLS but it is a more rapid prototyping system available to create relatively large parts. However, even if this technology is quite simple, LOM 3D printers are expensive.

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Scheme 1. Representation of the most important 3D printing technologies: (a) fuse deposition modeling (FDM), (b) Stereolithography (SLA), (c) Digital Light Processing (DLP), (d) Selective Laser sintering, (e) Laminated Object Manufacturing (LOM), (f) Electronic Beam Melting (EMB) and (g) Binder Jetting (BJ).

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2.6. Electronic Beam Melting (EBM)

The EBM technique uses a computer-controlled high power electron beam under high vacuum to fully melt the metallic powder (Titanium alloys, copper, niobium, stainless steel etc.) at high temperatures between 700 and up to 1000 °C.^[27]

Generally, a tungsten filament is heated under vacuum until it releases electrons, which are accelerated and directed at high speed onto the surface of the powder by two potent electromagnets: the first focuses the beam to the correct diameter, the second directs the beam to the powder bed. This gives the heating effect on the powder particles (the kinetic energy is instantly converted into thermal energy) that melt together in a layer-by-layer fashion, creating fully dense metal parts that retain the characteristics of the material (Scheme 1f).^[28] At the end of the process the unfused powder is removed with a blower or by brushing. However, usually the external surfaces require to be subjected to machining or grinding processes. This type of 3D printing has found application in racing, aviation and aerospace, as well as in medical engineering,^[29] and present high scanning speed and fast building rates even if the printing process is high energy demanding.

2.7. Binder Jetting (BJ)

Binder Jetting (BJ) also called “powder bed printing” or “inkjet 3D printing” or “drop-on-powder printing” is another additive manufacturing process that involves the use of two materials in different states: a powder and a water-base binder.^[30] In the printing process a layer of powder is distributed onto a build platform, then a liquid binding agent is applied using an inkjet print head. The binding agent acts as an adhesive between powder layers, and after its deposition another layer of powder will be laid out on top. This process is repeated until all the parts of the object are printed (Scheme 1g). Also in this case, no supports are required for the overhanging parts, since the non-bonded powder can act as support. Binder Jetting works with almost any material that is available in powder form and have the advantage that additives (such as pigments) can be added to the binder. However, the structural integrity of the final object is not very robust.

The binder could be also replaced by a photopolymer: in this case the technology is known as photopolymer jetting (PJ) or MultiJet Modeling (MJM).^[31]

2.8. Other 3D printing technologies

Several other 3D printing technologies are known: Direct Ink writing (DIW),^[32] or robocasting, is a useful approach for the realization of biomaterials; the material (such as hydrogels or cells solution) is extruded directly without melting or solidification (bioprinting).^[8, 33] Direct Laser Writing (DLW)^[34] is another 3D printing process where a solid photoresist layer is exposed to a laser that can be steered in three directions; in this case, the object is not created in a layer-by-layer approach but in a subtractive way.

3. 3D-printed devices in organic synthesis

Since each 3D printing technology processes different materials with different approaches, there is not a better technique compared to others, but the choice of the more appropriate technique is dictated by the final application of the object to be printed. In this framework, one of the most important limitations of 3D printing applications in organic synthesis is represented by the nature of the material used in the printing process. Photopolymers for SLS application are typically very poorly resistant to the standard organic solvents; most of the common thermoplastic polymers for FFF printing (with the exclusion of PP) are very sensitive to high temperatures and to acid/basic conditions, while powder-based technologies require extensive post-printing processes that can leave traces of un-wanted materials in the printed device. From a chemical point of view, the choice of the best material for a given application is extremely important, since its inertness is a mandatory requisite for any application, in order to maintain the integrity of the device.

3.1. 3D printed catalysts

A very attractive application of 3D printing technology is undoubtedly the possibility to print directly the catalysts for chemical transformations. In this sense, in 2016 Sotelo and Gil reported for the first time the fabrication of a robust, efficient and reusable copper heterogeneous catalyst system to promote Ullmann reactions.^[35] The system consisted of a sintered Al_2O_3 support on which $\text{Cu}(\text{NO}_3)_2 \cdot 2.5 \text{H}_2\text{O}$ was immobilized. A woodpile structure was 3D printed using a $\text{Cu}/\text{Al}_2\text{O}_3$ mixture extruded through a 410 μm nozzle in a rods fashion (with a rod spacing of 960 μm), printing each layer rotated of 90° with respect to the previous one. At the end, the entire structure was heated and sintered at 1400 °C for 2 hours to generate the final catalyst with high mechanical strength, high surface-to-volume ratio and controlled porosity (57% after sintering process). During this process, a color change and a shrinkage of 29% for rod diameter was observed and the copper loading was identified to be 2.3 wt.% (Figure 1).

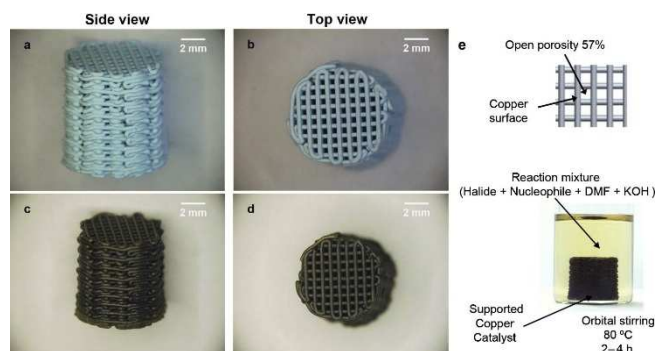
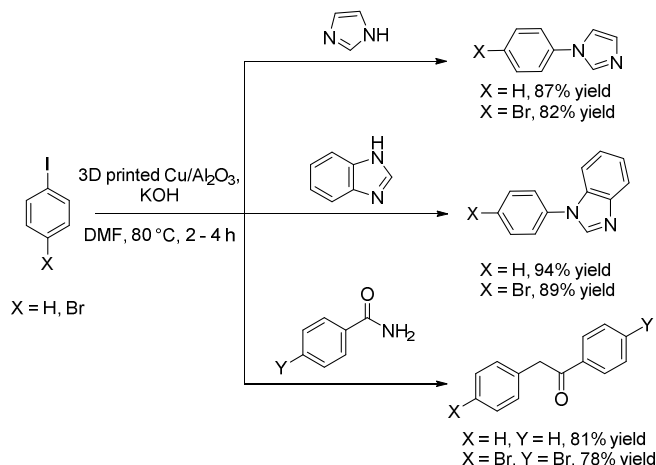


Figure 1. Optical images of the $\text{Cu}/\text{Al}_2\text{O}_3$ structure: dried (a and b) and sintered (c and d). Schematic illustration and image of the experimental set used for catalytic tests (e). Reproduced with permission from Sotelo, Gil and co-workers^[35]

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Scheme 2. Cu/Al₂O₃-catalyzed Ullmann reactions.

The catalyst was then used in the synthesis of *N*-aryl substituted imidazoles, benzimidazoles and *N*-aryl amides, with excellent yields and short reaction time; the excellent catalytic activity was maintained after 10 recycling steps (Scheme 2). One year later, the same group reported the use of a similar 3D printed Al₂O₃ recyclable catalyst to catalyze multicomponent reactions.^[36]

The catalytic structure consisted in a cylindrical woodpile structure of 30 layers and 10 mm of diameter realized by powder bed fusion and laser sintering of Al₂O₃ powder (Figure 2). This catalyst exhibited remarkable efficacy as Lewis acid in Biginelli and Hantzsch reactions performed under solvent-free conditions and microwave irradiation, showing excellent recyclability, short reaction times and high yields. By simple varying the experimental conditions it was possible to synthesize biologically active 1,4-dihydropyridines and 3,4-dihydropyrimidin-2(1H)-ones (Scheme 3).

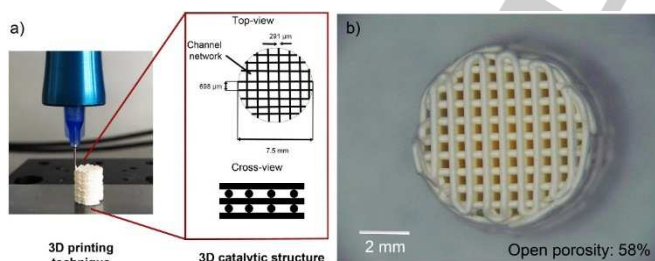
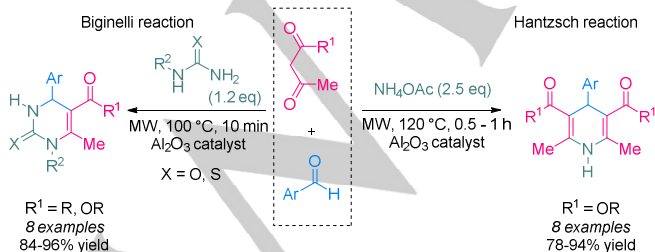


Figure 2. (a) Structure of the constructed Al₂O₃ catalytic device, (b) Top view of the sintered structure (optical image). Reproduced with permission from Sotelo, Gil and co-workers.^[36]



Scheme 3. Biginelli and Hantzsch synthesis promoted by 3D-printed Al₂O₃

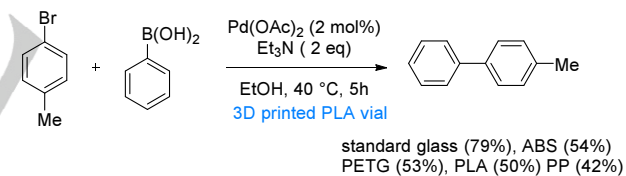
Many other metal-based catalysts for heterogeneous applications have been printed, but their uses are related to photochemical, and electrochemical applications, and will not be discussed in this review.^[10b]

3.2. 3D printed reactors

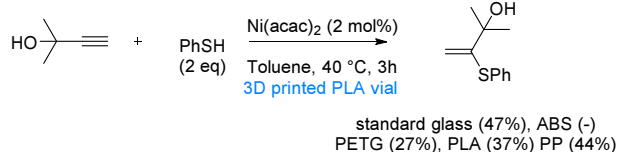
Among all the different uses of 3D printing technology, the possibility to create chemical labwares, reactionwares and research equipment is of course very attractive.^[37a] In this sense FFF 3D printers have been used for the realization of cheaper Erlenmeyer flasks and other standard labware, as evidenced by the numerous examples reported by the open source community.^[37b] Interestingly, Ananikov^[17] realized a set of standard equipment with different materials (figure 3) and studied their stability to various solvents, and their resistance to pressure and vacuum leaks. A general suitability trend in synthetic applications was identified: PP > PLA > ABS > PETG; however the choice of the correct material is strictly connected to the chemical transformation that has to be investigated. These chemical devices were employed to perform Suzuki-Miyaura cross-coupling reactions and the hydrothiolation of alkynes in the presence of a catalytic amount of Ni(acac)₂ (Scheme 4). In both cases, the desired products were obtained with modest yields.

In 2012, Cronin and co-workers reported for the first time the fabrication of a reusable 3D printed reactionware with printed-in catalysts and other components (added during pre-programmed pauses in the printing schedule) to perform the synthesis of phenanthridine-based heterocycles.^[38]

a) Suzuki-Miyaura cross coupling



b) Hydrothiolation of alkynes



Scheme 4: Suzuki-Miyaura cross-coupling and hydrothiolation of alkynes.



Figure 3. a) Examples of typically used labware produced by FDM 3D printing process. Reproduced with permission from Ananikov et al.^[17] b) Test tube rack (<https://www.thingiverse.com/thing:312313>).

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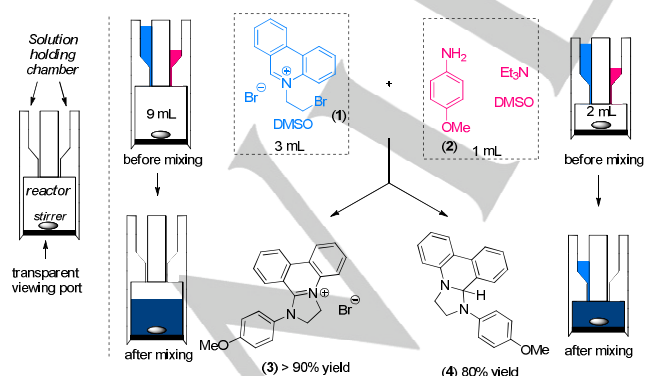
Using a modified printer and acetoxysilicon as a polymer, the authors described the creation of a specific reactor composed by two solution-holding chambers, one reaction chamber and a indium-tin oxide viewing windows (Scheme 5).

A solution of 5-(2-bromoethyl)phenanthridinium bromide **1** (3 eq, 54.5 mM, 3 mL) was loaded into one solution holding chamber of the 3D-printed reactor and a solution of Et₃N and 4-methoxyaniline **2** (1 eq, 54.5 mM, 1 mL) was placed in the other holding chamber. Then, a needle attached to a vacuum source was inserted into the reactor chamber inducing the two solutions to flow down into the reactor. After 21 h, product **3** was observed in more than 90% yield. A simple variation of the reactor volume, (maintaining constant reagents ratio and concentrations) allowed to obtain product **4**.

The same reactor device was also printed with a mixture of acetoxysilicon and Pd/C for the realization of a novel functionalized device. In this case, the two solution-holding chambers were loaded with a methanol solution of styrene (1 eq) and Et₃SiH (15 eq) to perform a catalytic hydrogenation to afford ethylbenzene, effectively formed in quantitative yield in only 30 minutes. Moreover, the un-functionalized device was also employed in the synthesis of polyoxometalates.

One year later the same group reported an evolution of this type of approach, realizing a sealed reactionware where reagents, catalysts and purification apparatus are integrated into a single monolithic device.^[39] A simple rotation of the device, composed by four cubes of 20.0 mm connected with circular channels allowed to perform a multi-step reaction sequence without any pumps with a minimal handling by the operator. In particular the device, endowed of three different reaction-chambers was employed in the synthetic sequence consisting in a (i) Diels Alder cyclization between acrolein and substituted cyclopentadiene followed by (2) an imine formation by reaction with aniline and (3) its reduction by H₂ on Pd/C (Scheme 6).

The desired catalysts were also printed during the realization of the device: Montmorillonite K10 in the first chamber, and a mixture of Pd/C in the third one. Stirrer bars were also added in each chamber during the printing process. The solutions of initial reagents were introduced by injection in the first reactor and the mixture was stirred for 5 h at room temperature.

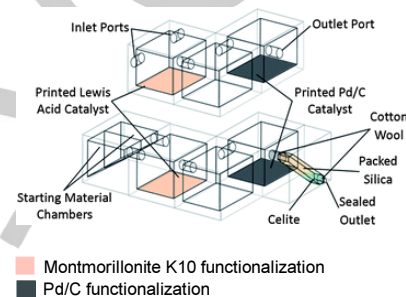


Scheme 5. 3D printed reactionware-assisted selective synthesis of phenanthridine-based heterocycles.

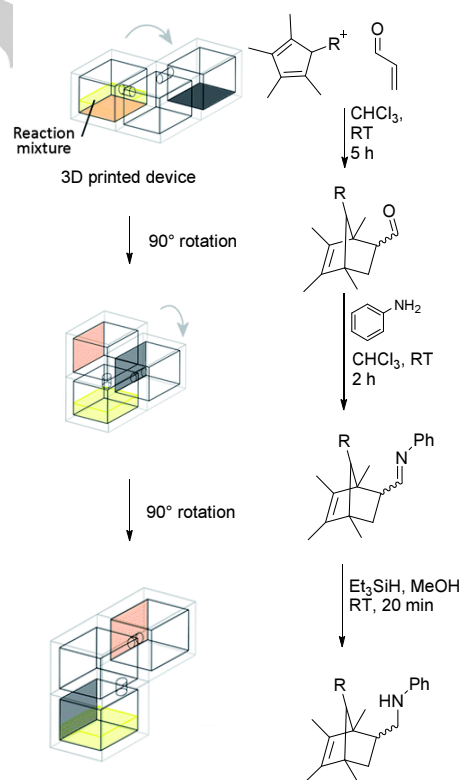
After this time, the device was simply rotated of 90° allowing the mixture to flow in the second reactor, followed by the addition of aniline. After 2 hour stirring (complete formation of imine) a solution of triethylsilane was added and the device was rotated again of 90° in order to flow the mixture in the third reactor for the C=N bond reduction.

After 20 min the device was again rotated of 90° and the crude mixture was collected at the outlet of the reactor. After chromatographic purification, it was possible to isolate the desired product in 68% yield as a mixture of *endo* and *exo* isomers. A sealed version of this reactor, with an integrated small purification column was also reported; in this case all the reagents were loaded into the device during the printing process.

a) Schematic diagrams of the 3D-printed sequential reactors



b) multi-step reaction sequence



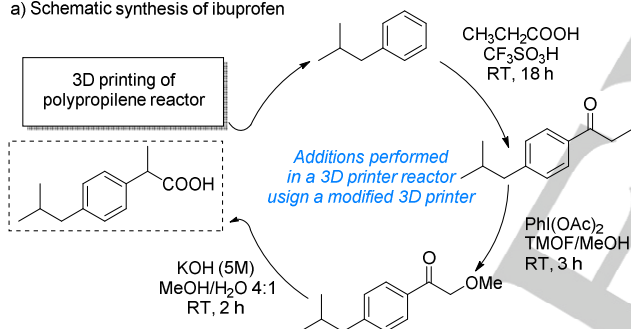
Scheme 6. a) Schematic diagram of the 3D printed sequential reactors: (top) open reactionware, (bottom) sealed reactionware. b) Schematic diagram of the multistep reaction sequence performed in the open reactionware. Adapted with permission from Cronin et al.^[39]

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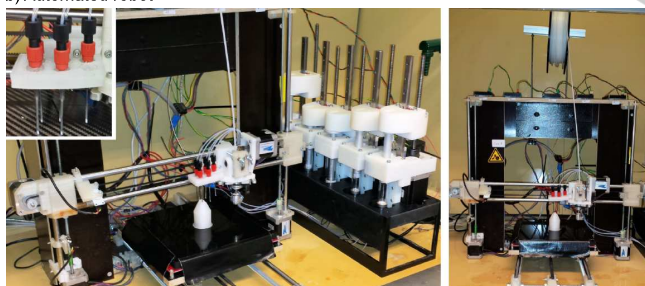
In 2014 Cronin reported also the realization of monolithic sealed hydrothermal reactors from polypropylene to perform organic reactions under high temperature and pressure.^[40] In this work sealed reactors were created as single structures using a FDM printer, with the additions of reactants directly during the 3D printing process. These devices were successfully employed for the synthesis of metal-organic frameworks (MOFs) by heating at temperature above the boiling point of the solvent medium.

Two years later, after the modification of an open source FDM 3D printing platform for the incorporation of liquid handling components, an automated robot for the synthesis of racemic ibuprofen was also built.^[41] In this approach the 3D printer was able to print the reaction vessel and at the same time to dispense the reagents using syringe pumps synergistically interfaced with the printer. Reactions were conducted in PP vessels at room temperature under air, and the entire process was controlled by means of a computer software. Initially, the vessel was printed, according to the desired virtual design, then the software drove the dispensing needles of each individual chemical (mounted on the printer) according to the synthetic sequence showed in scheme 7. The entire process (for printing and synthesizing ibuprofen) was completed in 24 hours, and afforded the desired product in 34% overall yield with no operator intervention.

a) Schematic synthesis of ibuprofen



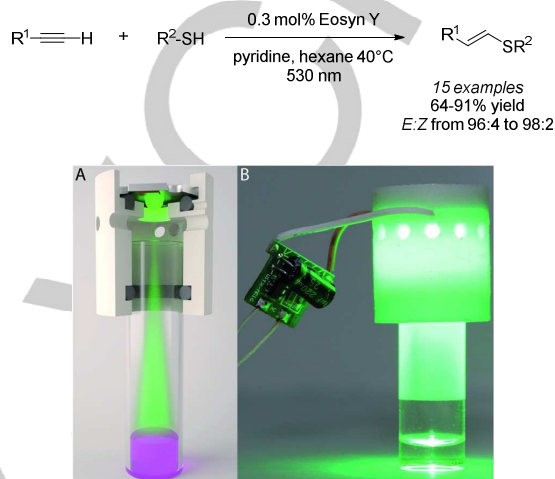
b) Automated robot



Scheme 7. a) Synthesis of racemic ibuprofen using modified 3D printer. TMOF = trimethyl orthoformate. b) 3D printed modified for the automated synthesis of ibuprofen: (left) full view of robotic platform (left inset) Dispensing needle carriage for 3D printing/liquid deposition, (right) front view of the 3D printing section of the robotic set-up with a 3D-printed reaction vessel showing the PP feedstock for reaction-vessel printing. Reproduced with permission from Cronin et al.^[41]

In 2016 Ananikov reported the fabrication of a 3D printed photoreactor to promote a visible light mediated metal-free thiol-yne click reaction for the synthesis of valuable S-functionalized

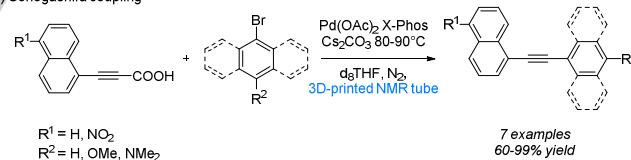
products.^[42] The synthesis involves the use of alkynes and thiols, reacting through a photoredox process catalyzed by the presence of Eosin Y, with a remarkable atom-economy efficiency, since the only byproduct formed is a water molecule (scheme 8). Products were obtained in very high yields (up to 91%) and excellent selectivities for the E isomer (up to 98:2). A 3D printed custom cap containing the LED source was designed and printed using a FFF printer in only 30 minutes.



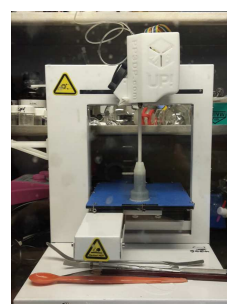
Scheme 8. A) CAD Designed photoreactor. B) 3D-printed and assembled photoreactor. Reproduced with permission from Ananikov et al.^[42]

In 2017 Hübner and co-workers used 3D printing approach to build gastight NMR tube/spinner combination and cuvettes for studying the Sonogashira coupling between aryl halides and arylpropionic acids by magnetic resonance and infrared spectroscopy.^[43]

a) Sonogashira coupling



b) 3D-printing process



Scheme 9. (a) Sonogashira coupling in 3D-printed NMR tube/Spinner combination. (b) 3D-Print of the NMR tube/spinner combination inside the glove box. The reagents for the Sonogashira coupling have been inserted (dark solution).

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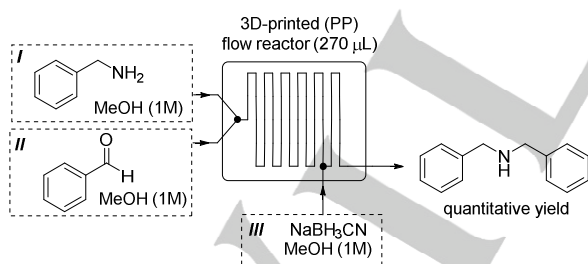
A reaction flask was fabricated from polyamide (Taulman 910), compatible with the most common organic solvents and completely invisible in NMR spectroscopy. The printing process was performed in an inert gas atmosphere (glove box) and the reagents were filled inside the reactor during some pauses of the print (scheme 9). In this study the authors were able to correlate the donor capability of different aryl bromides to the reaction rate, and the optical properties of isolated bis-arylalkynes were investigated by fluorescence spectroscopy and DFT calculations.

3.3. Realization of 3D printed flow reactors

The advent of 3D printing technology allowed for an unprecedented expansion in the field of micro- and meso fluidic for the realization of chemical devices. Thanks to this approach, many different materials could replace glass and silicon, allowing the production of devices with an easier protocol, inexpensive manner and short times. Unfortunately, due to their characteristics, not all the 3D printing processes reported in section 2 are suitable for the realization of fluidic devices. Among them, only Selective Laser Sintering (SLS), Laminated Object Manufacturing (LOM), MultiJet Modeling (MJM) and Fuse Deposition Modeling (FDM) have found application in this field.^[11]

Most of the example reported in literature describe the realization of fluidic devices that have been employed in analytical applications,^[9] but only few examples have been employed for the synthesis of organic compounds. In this section, the most representative examples of this class has been described.

In 2012, Cronin and co workers reported the first example of the synthesis of dibenzylamine performed in a polypropylene (PP) 3D printed "milli fluidic reactor" created by FDM approach (Scheme 10).^[44] A three-inlet device with an approximate reactor volume of 270 μL (channel shape: circular, ID: 0.8 mm) was used to promote the sequential imine formation and reduction. 1M solution of methanol solution of benzylamine and benzaldehyde were fed into the reactor with a flow rate of 5 $\mu\text{L}/\text{min}$ using a pump-controlled syringe system allowing the

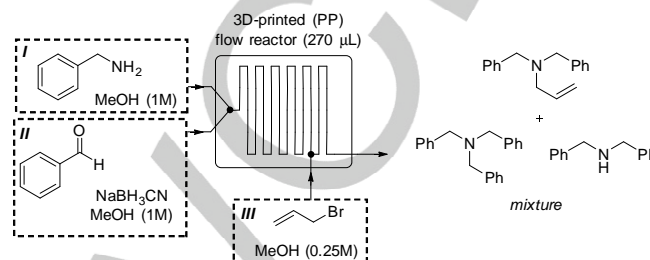


Scheme 10. Flow synthesis of dibenzylamine.

solution to react in a first part of the reactor (210 μL , residence time 42 min). A 1M solution of NaBH_3CN was then introduced in the third inlet of the device at 2.5 $\mu\text{L}/\text{min}$ to reduce the imine formed to the corresponding secondary amine. The disappearance of the starting material as well as the formation of the imine was monitored by in-flow ATR-IR and MS spectroscopy.

The same fluidic device was also employed to promote alkylation reaction for the synthesis of tertiary amines. A mixture

of benzaldehyde and sodium cyanoborohydride (1:1), in methanol (1M), and a solution of benzylamine were introduced into the reactor at a flow rate of 5 $\mu\text{L}/\text{min}$ and 2.5 $\mu\text{L}/\text{min}$ respectively. Simultaneously, allyl bromide (0.25 M) was added as alkylating agent through the third inlet 7.5 $\mu\text{L}/\text{min}$ (Scheme 11). In this case, the final outcome was a mixture of secondary and tertiary amines (no information about the ratio between the products was reported).



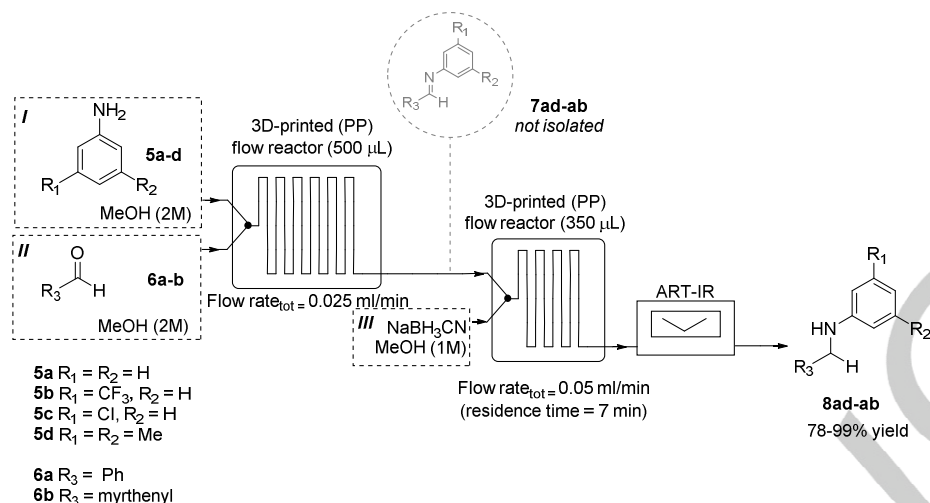
Scheme 11. Alkylation reaction performed under flow conditions.

A further improvement of this protocol was published by the same group one year later.^[45] New fluidic devices made with inexpensive PP were designed and connected in series for the synthesis and reduction of amines under continuous flow conditions (Scheme 12). In the first reactor (channel shape: circular, ID: 1.5 mm, total volume: 500 μL), the synthesis of imine starting from the corresponding 2M solution of aldehydes and anilines took place in only 14 minutes. The outcome of this reaction (imine solution) was then directly used as feeding reagent for the second transformation that occurred in another 3D printed reactor (channel shape: circular, ID: 1.5 mm total volume: 350 μL). A combination of this imine solution with a 1M solution of NaBH_3CN allowed to obtain the desired amines in good to high yields. At the end of the fluidic system an ART-IR apparatus, able to constantly monitoring the reaction by IR was also connected. Interestingly, the connections between the two reactors were realized with polytetrafluoroethylene (PTFE) tubing with standard HPLC connectors, highlighting the great versatility of 3D printing technology and the possibility to be easily interfaced with common laboratory equipment.^[39b]

In 2015, Rudolf von Rohr and co-workers realized a designed porous structured reactor (DSPR) using a Selective Laser Sintering approach with an aluminum oxide-zinc oxide base layer coated with Palladium, for the reduction of 2-methyl-3butyn-2-ol to corresponding alkane under solvent-free, continuous flow conditions.^[46] This porous reactor showed better performances in terms of selectivity, yield, and TOF compared to traditional batch conditions (Figure 4a). Similarly, two years later, Hornung reported the realization of tubular catalytic static mixers (CSM) coated with nickel(0) and platinum(0) as catalysts for the in-flow hydrogenation of alkenes and carbonyl compounds.^[47]

Scheme 12. Two step reaction for aromatic secondary amines formations.

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Different mixers were realized using electron beam melting (EBM) technology starting from titanium, cobalt-chrome and stainless steel alloys, and then coated with metal a catalyst by electroplating and cold spraying. These coated static mixers were hosted in a Swagelok stainless tube (length 15 cm, OD: 8 mm, ID: 6 mm) and after H₂ activation, were able to reduce methanol solutions of alkenes and carbonyls with conversion typically between 90 and 100% with residence times in the range of 4.5 – 6.5 minutes (Figure 4b).

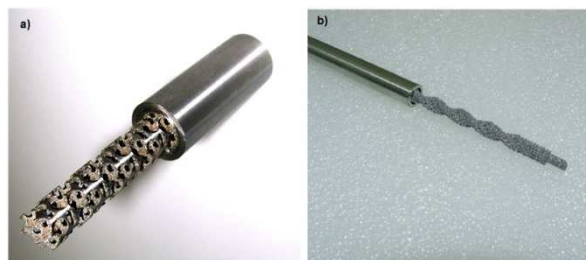
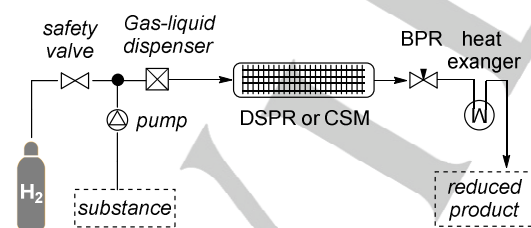
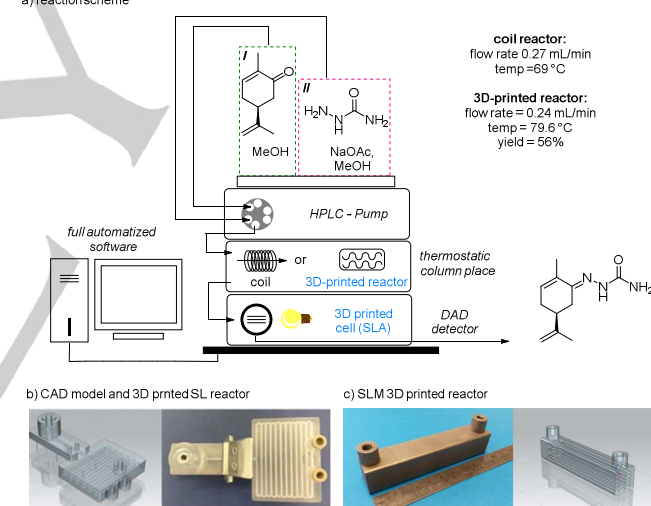


Figure 4: (a) Uncoated Designed Porous Structure Reactor (DPSR) used during experimental procedures. Parts of the outer wall were removed for visualization purposes. (b) CSM fitted inside a tube. Reproduced with permission from Rudolf von Rohr et al.^[45] and from C. H. Hornung.^[46]



DPSR: alkynes
 CSM: alkenes, alkynes, carbonyls, nitrocompounds, diazocompounds, nitriles, imines, halides



conversion of (*R*)-carvone to its corresponding semicarbazone using semicarbazide and sodium acetate (Scheme 14).

Scheme 14. a) Reaction scheme for the synthesis of carvone semicarbazone. b) CAD model and SL 3D printed reactor with embedded analytic functionality. c) 10 mL SLM reactor. Images are reproduced with permission from Christie et al.^[49]

Interestingly, the best reaction conditions were investigated through a full-automated approach using a specific macros software able to automatically change both temperature and flow rates of the 5 mL stainless steel coil reactor. Optimal conditions was found to be 69 °C and 0.27 mL/min as flow rate. Moreover, the same authors realized a new reactor by a SLM approach (circular channels, ID: 2 mm, volume: 10 mL), printed using Ti-6Al-4V alloy powder. The reactor was placed into the HPLC

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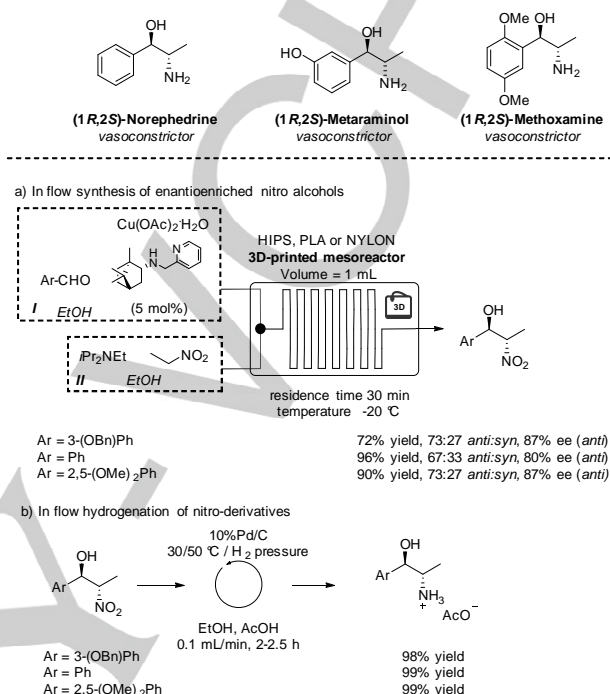
thermostatic control unit replacing the stainless coil reactor: here the reaction took place, and the final product was analyzed downstream by the HPLC device. Also in this case, the software identified the optimal reaction conditions (79.6 °C, flow rate 0.24 mL/min) after only 24h of fully automatized optimization process, allowing to obtain the desired product in 56% yield.

A similar flow cell with in-built windows was also realized with Ti-6Al-4V alloy (circular channels, ID: 2 mm, volume: 0.6 mL) and connected to the previously described SLM reactor for the investigation of the semicarbazone formation. This setup allowed to perform the reaction, the analysis and the optimization in a single HPLC system equipped with two different additive manufacturing devices, to afford the carvone semicarbazone product in good yield.

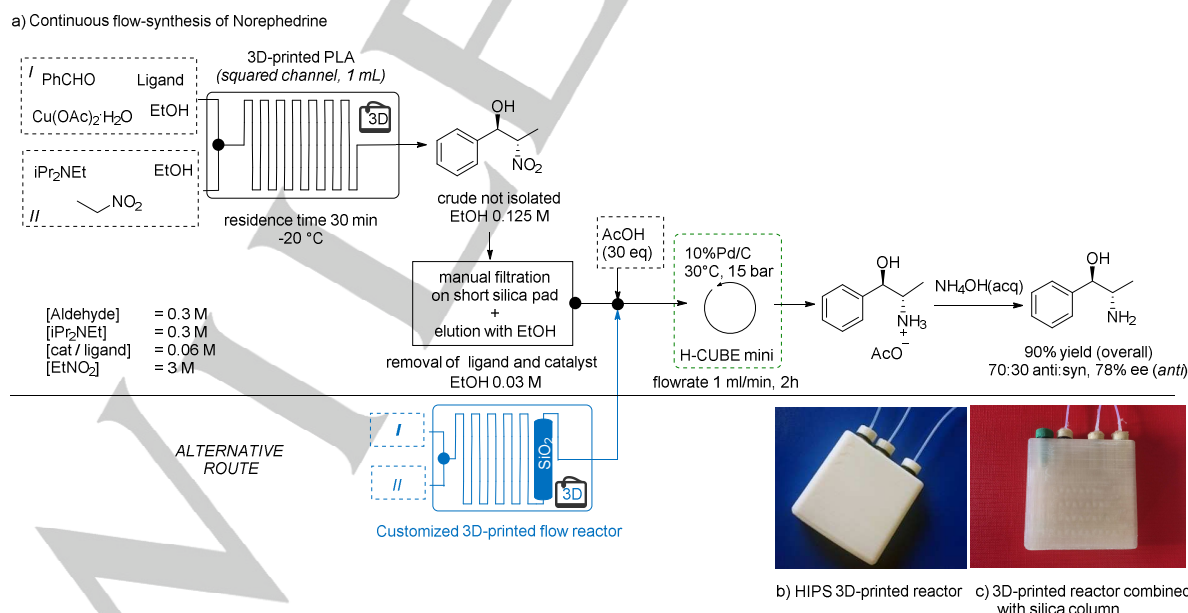
In the same year our research group reported the first example of a stereoselective, catalytic synthesis of different chiral products of pharmaceutical interest performed under flow conditions using 3D printed mesoreactors.^[50] The synthetic strategy for the synthesis of (1*R*,2*S*)-metaraminol, (1*R*,2*S*)-norephedrine and (1*R*,2*S*)-methoxamine was accomplished combining a catalytic stereoselective Henry reaction performed in a 3D printed mesoreactor with an in-flow hydrogenation step, using H-cube apparatus, able to generate hydrogen in situ from the electrolysis of water under very safe conditions.

Initially, aromatic aldehydes were converted into the corresponding nitroalcohol derivatives by the Henry reaction with nitroethane in the presence of Cu(OAc)₂·H₂O and an aminopyridine derivative synthesized from enantiopure camphor as chiral ligand. Different 3D printed reactors were realized in High Impact Poly Styrene (HIPS), polylactic acid (PLA) and nylon, characterized by different geometries, size, channels shape and dimensions, through the use of desktop FDM 3D printer.

Using a PLA reactor (squared channels, 1.41x1.41 mm, total volume = 1 mL) at -20 °C for 30 minutes as residence time, in the presence of 5% of the chiral catalyst the expected 1,2-nitroalcohols were isolated in high yield with good diastereoselection and high enantioselectivity (Scheme 15a).



Scheme 15. 3D printed mesoreactors for catalytic stereoselective synthesis of APIs.



Scheme 16. a) Multistep in-flow synthesis of pharmaceutically valuable chiral 1,2-amino alcohols. b) HIPS 3D printed mesoreactor c) PLA 3d printed mesoreactors with an in-line silica column. Adapted with permission from Benaglia et al. ^[50]

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Then, the nitroalcohols were fully converted into the corresponding amino alcohols by a palladium catalyzed in-flow hydrogenation performed with a H-cube apparatus operating at 30 °C under H₂ pressure in only 2-2.5 hours without any erosion of the stereochemical integrity (Scheme 15b).

Moreover, with the aim to develop a continuous flow synthesis of Norephedrine, the two steps were combined together. The crude nitroalcohol, synthesized as showed previously using a 3D printed PLA mesoreactor, was simply filtered through a short pad of silica and washed with ethanol, in order to remove the catalyst complex.

Acetic acid was then added to the nitroaldol solution, that was directly used for the in-flow reduction, to afford the desired product in its acetic salt form. A simple treatment with a base led to the formation of the neutral chiral 1,2-aminoalcohol in 90% overall yield, 70:30 *anti:syn* ratio and 78% ee for the major isomer (Scheme 16).

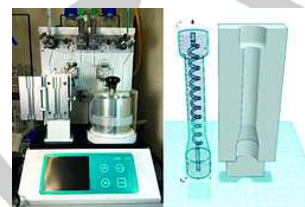
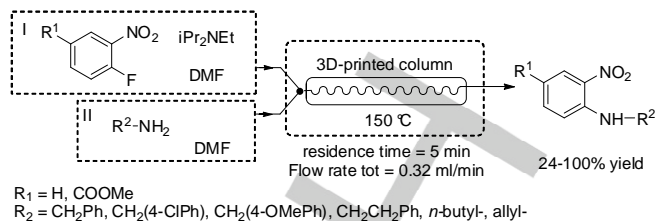
Taking advantage of the powerful possibility offered by 3D printing to easily and quickly modify the design of the chemical set-up, a reactor containing the flow channels and the short column of silica in a single device was also realized. In this case, the nitroalcohol intermediate was obtained in 96% yield, 65:35 *dr*, and 83% ee.

Very recently, Hilton reported the realization of a 3D printed polypropylene column reactor that was incorporated into an existing continuous-flow system for the synthesis of substituted anilines, bicyclic and tetracyclic heterocycles (Scheme 17).^[51]

The column reactor was printed in PP with an internal spiral (ID: 2mm, volume: 1.6 mL) as a reactor, and fitted in a FlowSyn reaction system. The column was employed in the synthesis of different anilines through a SNAr reaction between fluoroarenes and amines. The 3D printed column showed a high mechanical strength since it was able to resist even at 150 °C without any structural modification.

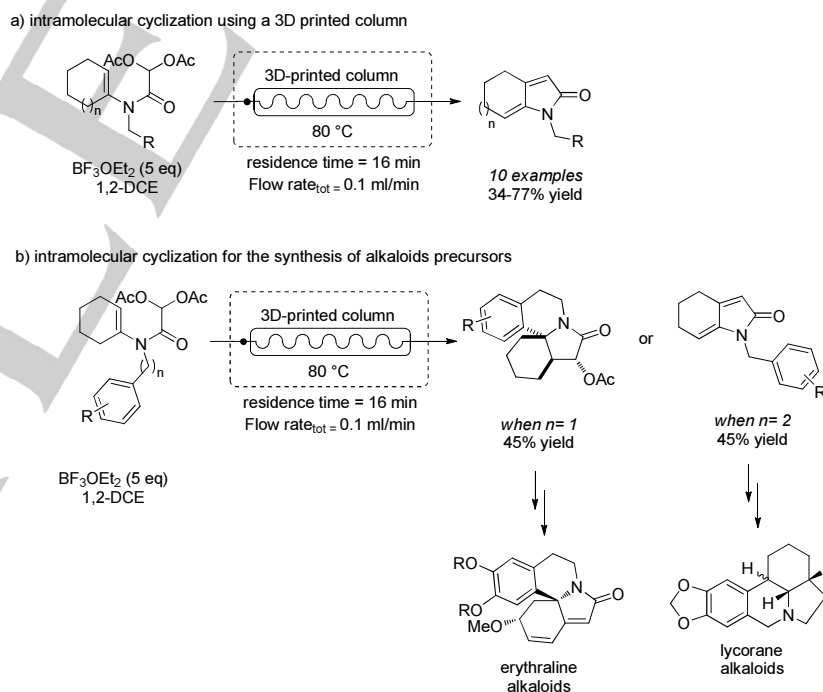
The solution of a substituted fluoronitrobenzene and iPr₂NEt in DMF was fed into the column in the presence of a solution of amine in DMF using the FlowSyn system at 150 °C with a total flow rate of 0.32 ml/min. The corresponding anilines were obtained in good to excellent yields after 5 minutes only; it was also demonstrated that the same column could be reused up to 5 times for different reactions without appreciable loss of its integrity.

In order to explore the applicability and the utility of these 3D printed columns, the author successfully reported the "in column" synthesis of complex heterocycles related to the core of different product of pharmaceutical interest such as Erythrina and lycorane alkaloids using an intramolecular cyclization.



Scheme 17. SNAr transformation performed in a 3D-Printed column. b) UniQis FlowSyn continuous-flow reactor system showing the column heater block. Reproduced with permission from Hilton et al.^[51]

Initially, simple bicyclic heterocycles were synthesized in modest yields starting from acylal precursors in the presence of an excess of boron trifluoride and 1,2-dichloroethane as solvent operating at 80 °C with a flow rate of 0.1 mL/min for 16 minutes (Scheme 18a). After the identification of the best reaction conditions, more functionalized molecules were subject to a poly-acylal cyclization, allowing the formation of the corresponding tetracyclic products as a single diastereoisomer in good yields (Scheme 18b).



Scheme 18. Intramolecular cyclization for the synthesis of poly-cyclic heterocycles

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4. Summary and prospective

The mass manufacturing, with its high efficiency and low cost in large scale productions, cannot be completely substituted by the additive manufacturing and will remain the dominant form of production in many industries. However, 3D printing has undoubtedly some important features: in principle, with no need for stock, for shipping and, perhaps most importantly, a significantly reduced waste generation, the AM technologies may contribute to localize the production process: production is on demand. Other benefits come from the possibility to rapidly tune and customize the object to be produced, and to quickly fabricate on-demand replacement parts.

This review has presented an overview of various AM technologies exploited in organic synthesis, and showed how the technologies have already found application in different reactions, in batch and under continuous flow conditions, as well as in catalysis, where the printing process may have a better control on catalyst structures and distribution in the printed device. In order to make the technologies even more attractive, several issues must be addressed: 3D-printed, high resolution reactors are still too expensive, and a wider range of materials is needed and should become readily available for the fabrication of the devices (such as glass^[52]).

However, new applications of AM technologies in chemistry continue to appear; 3D printing technologies have found application also in pharmaceutical manufacturing.^[53] In 2015, Aprecia (an Ohio-based pharmaceutical company) was approved by the US Food and Drug Administration for the realization, using a 3D printing BJ technology (trademark "ZipDose" technology), of a more porous pill able to control seizures brought on by epilepsy^[54] Thanks to the high porosity obtained during a droplet-based 3D printing process, the pill can be dissolved more quickly when in contact with liquids, making it much easier to swallow high doses than a conventional tablet.

3D printing has countless possibilities in many industries and areas of life;^[55] although 3D printing dates back to few decades, it may be considered a very young technology, but it has already showed a great potential in several fields, including chemistry. It is expected that new, numerous and creative applications of additive manufacturing technologies in chemical synthesis and in catalysis will appear in the near future.

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Keywords: additive manufacturing • 3D printed devices • microfluidics • flow reactors • 3D printed catalysts

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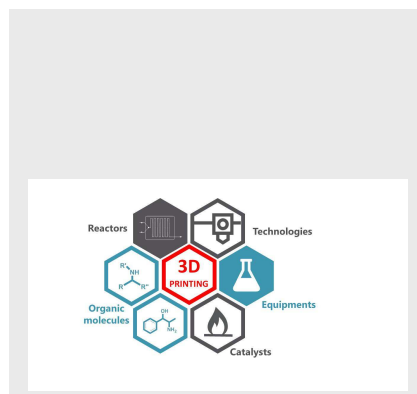
MINIREVIEW

Entry for the Table of Contents (Please choose one layout)

Layout 1:

MINIREVIEW

3D printing has countless possibilities in many industries and areas of life. This review will focus specifically on the exploitation of additive manufacturing technologies in the synthesis of organic compounds, and, in particular, on the use of 3D-printed catalysts and 3D printed reactors, and on the fabrication and use of 3D printed flow reactors.

*S. Rossi, A. Puglisi, M. Benaglia****Page No. – Page No.****Additive Manufacturing Technologies: 3D printing in Organic Synthesis**