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Additively Manufactured Small-Volume Continuous Manufacturing Reactor System for C–C Cross-Coupling Reactions

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Abstract

Continuous manufacturing (CM) is increasingly recognized as a transformative approach in pharmaceutical and chemical production, offering enhanced efficiency, reproducibility, and sustainability compared to conventional batch processing. This study presents the development and application of an additively manufactured PEEK-based small-volume continuous reactor system for the three-stage Suzuki–Miyaura synthesis of biphenyl. The process integrated ligand synthesis, catalyst precursor formation, and the cross-coupling reaction within modular reactors, achieving high product selectivity and reproducibility. Comparative analysis with traditional batch synthesis revealed superior performance for the continuous system, including faster kinetics, shorter residence times, improved yields (up to ~100% for catalyst C within 10 minutes at 100 °C), and reduced waste generation. Additive manufacturing enabled the rapid prototyping of reactors with optimized geometries featuring integrated mixing and heat exchange, ensuring precise control of flow rates and thermal conditions. Beyond pharmaceutical applications, the system demonstrated significant potential for hydrometallurgical processes such as leaching, solvent extraction, and electrochemical metal recovery, where continuous flow operation offers substantial advantages in efficiency and sustainability. These findings underscore the synergy of CM, additive manufacturing, and process analytical technology as a flexible and environmentally responsible platform. The developed reactor system provides a pathway for scalable, modular, and on-demand chemical manufacturing, with broad implications for both high-value drug synthesis and sustainable resource management.

Keywords: additive manufacturing; reactor system; Suzuki–Miyaura reaction; C–C cross-coupling reaction; biphenyl synthesis.

1. Introduction

The pharmaceutical and chemical industries are undergoing a paradigm shift from traditional batch processing to continuous manufacturing (CM). While well-established, conventional batch operations suffer from inherent limitations, including large equipment footprints, long cycle times, labor-intensive procedures, challenges in ensuring consistent quality, and difficulties during process scale-up [1, 2]. Furthermore, batch processes often generate substantial waste and require intensive resource utilization, making them less compatible with the growing emphasis on sustainable and green chemistry practices. Consequently, the transition to CM is driven by the need for faster, safer, and more environmentally responsible production [3, 4]. This direction is exemplified by previous work from one of the authors, Professor A. Khabiev, which proposed a scheme for synthesizing metronidazole derivatives using a reactor system designed for 3D printing and fabricated from PETG filament [5].

Among the most important transformations in modern pharmaceutical development are C–C cross-coupling reactions, such as the Suzuki–Miyaura reaction. These reactions provide direct access to diverse biaryl motifs, which are critical building blocks for pharmaceuticals, agrochemicals, and advanced materials [6]. They typically require catalytic systems based on palladium or other metals [7]. Under continuous-flow conditions, these reactions not only proceed with higher efficiency and reproducibility but also exhibit enhanced selectivity, shortened reaction times, and straightforward scalability compared to batch methods [8]. Despite these advantages, the broader adoption of CM has been hindered by the complexity of designing specialized reactors, high capital investment, and a lack of flexible, rapidly adaptable systems [9].

Additive manufacturing (AM), particularly advanced 3D printing technologies, offers a promising solution to these challenges. AM enables the cost-effective production of highly customized and complex reactor components that would be prohibitively expensive or technically unfeasible to fabricate using conventional machining [10]. High-performance polymers like polyether ether ketone (PEEK) possess exceptional chemical resistance, mechanical stability, and thermal durability, making them ideal for constructing compact continuous-flow reactors capable of withstanding harsh chemical environments [11]. Moreover, AM facilitates iterative design optimization, allowing for the rapid prototyping, testing, and modification of reactors to fine-tune mass transfer, fluid dynamics, and thermal management [12, 13]. The modularity of AM-based systems also enables portable,

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reconfigurable "lab-on-chip" platforms that integrate mixing, heat exchange, and real-time monitoring into a single compact device.

The potential of such miniaturized reactor systems extends significantly beyond pharmaceuticals into hydrometallurgy. Hydrometallurgical processes are critical for metal recovery from primary ores, secondary resources, and recycling streams. Continuous-flow reactor systems fabricated by AM can be tailored for various operations, including:

Leaching: Acidic or alkaline leaching of base and rare metals (e.g., Cu, Ni, Co, REEs), benefiting from precise pH and temperature control [14, 15]. Resource Recovery: Efficient kinetic optimization for recovering valuable metals from secondary resources like spent catalysts, e-waste, and lithium-ion battery cathodes [16]. Separation Processes: Solvent extraction, ion exchange, and adsorption, which require high surface area contact and controlled phase mixing—functions that can be engineered into 3D-printed flow channels [17]. Electrochemical Operations: Electrowinning, electrorefining, and electrodeposition, where integrated electrodes in printed reactors could enable localized control of potential and current density [18].

The integration of these hydrometallurgical operations into modular, additively manufactured flow reactors is highly relevant for sustainable resource management. With increasing global demand for critical raw materials—particularly for green energy and battery technologies—there is strong industrial motivation to develop flexible, small-scale, and mobile systems for decentralized processing. The combination of AM and CM principles enables the deployment of "on-demand" metal recovery systems, reducing dependence on large centralized plants and promoting more efficient raw material use.

The integration of process analytical technology (PAT) is equally important for both pharmaceutical and hydrometallurgical CM. PAT tools, including in-line spectroscopy, chromatography, and electrochemical sensors, allow real-time monitoring and closed-loop control of key process parameters [19]. This ensures consistent quality in pharmaceutical manufacturing and optimizes recovery efficiency in hydrometallurgical operations. The convergence of CM, AM, and PAT thus defines a new frontier in chemical engineering one that is highly flexible, resource-efficient, and environmentally sustainable.

In this context, developing additively manufactured PEEK-based continuous reactor systems represents a promising step toward addressing critical needs across pharmaceutical and metallurgical domains. These systems provide a platform for studying fast, exothermic organic reactions while offering adaptability for leaching, solvent extraction, and electrochemical processes. Their interdisciplinary scope highlights their potential as enabling technologies in the broader transformation of chemical and materials processing industries.

2. Materials and Methods

All reagents and chemicals were analytical grade and sourced from Sigma-Aldrich, Fluka, and Merck. Reaction progress was monitored by thin-layer chromatography (TLC) using pre-coated silica gel glass plates (E. Merck Kiesegel 60 F254, 0.25 mm layer thickness) with a chloroform-methanol eluent system. TLC plates were visualized under ultraviolet (UV) light or by exposure to iodine vapor.

Melting points were determined using a Stuart Scientific SMP 10 Fascia melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a JNM-ECA 400 spectrometer using deuterated dimethyl sulfoxide (DMSO-d_6) as the solvent and tetramethylsilane (TMS) as the internal standard.

2.1 Biphenyl Synthesis in a Reactor System

The synthesis of biphenyl via the Suzuki–Miyaura reaction was conducted in three sequential stages within a continuous flow reactor system fabricated by additive manufacturing (Figure 1).

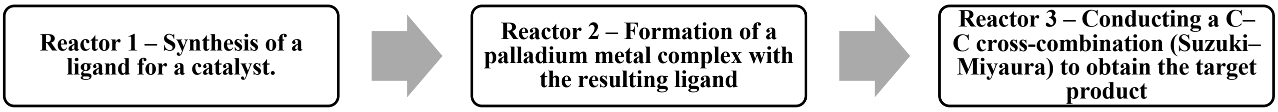

Figure 1 - Scheme of biphenyl synthesis

Stage 1 - Ligand Synthesis (Reactor 1):
The process began with the continuous-flow preparation of phosphorus-based ligands, which are essential precursors for generating catalytically active palladium complexes. Conducting this synthesis in a dedicated flow reactor allowed for precise regulation of stoichiometry, temperature, and residence time, yielding high-purity products with minimal by-product formation and reducing the need for extensive purification.

Stage 2 – Catalyst Precursor Formation (Reactor 2):
The freshly synthesized ligands were transferred directly to a second reactor, where they coordinated with palladium salts to form Pd–ligand complexes. This in situ preparation ensured highly active and stable catalysts, minimizing degradation and

exposure to air or moisture compared to conventional batch methods. The modular reactor design also facilitates the substitution or optimization of ligand structures for specific reactions.

Stage 3 – Cross-Coupling Reaction (Reactor 3):
In the final stage, the pre-formed Pd–ligand catalyst was introduced into a reaction mixture containing iodobenzene and phenylboronic acid to initiate the Suzuki–Miyaura cross-coupling. The continuous-flow environment provided excellent mixing and heat transfer, enabling rapid reaction kinetics and consistent product quality. Parameters such as temperature, flow rate, and concentration were finely tuned to achieve high biphenyl yields in short residence times. The compartmentalization of each stage minimized cross-contamination and enhanced reproducibility.

Advantages of the Continuous AM-Based System: Additive manufacturing enabled the cost-effective fabrication of reactors with complex geometries, including optimized mixing chambers, integrated heat exchangers, and modular interconnections. This design flexibility allows for rapid iteration and adaptation of reactor configurations for various coupling reactions and other chemical or hydrometallurgical processes.

2.2 Optimization of 3D Printing Parameters for High-Quality PEEK Components

Polyether ether ketone (PEEK) is a high-performance thermoplastic with excellent mechanical properties, chemical resistance, and thermal stability, making it ideal for demanding applications. Manufacturing PEEK components via additive manufacturing requires careful parameter control to ensure optimal quality and performance. Key parameters include:

- Extrusion Temperature: 360–400 °C, due to PEEK's high melting point.
- Build Platform Temperature: Approximately 120 °C to prevent warping and ensure adhesion.
- Cooling Rate: Controlled to avoid internal stresses and defects.
- Print Speed and Layer Height: Adjusted to balance detail resolution and mechanical strength; slower speeds and thinner layers generally yield superior results.
- A high-performance 3D printer with a fully enclosed and heated build chamber is essential to maintain a consistent thermal environment, thereby enhancing print quality.

2.3 Synthesis of Ligands for Catalysts

Ligands A and B (Figure 2) were synthesized from 1-(1-chloro-1-hydroxypropan-2-yl)-3-methylimidazolidin-1-ium chloride.

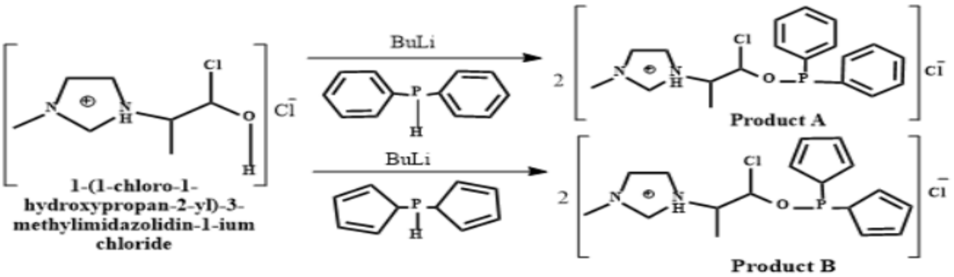

Figure 2 - Scheme of synthesis of ligands A and B

A dry, degassed solution of CH_2Cl_2 (20 mL) containing 1-chloro-3-(3-methylimidazolidin-1-yl)propan-2-ol chloride (0.100 g, 0.466 mmol) was cooled to –78 °C under argon. A hexane solution of n-BuLi (0.292 mL, 0.466 mmol) was added dropwise. The mixture was stirred at –78 °C for 1 h and then at room temperature for 30 min.
The reaction mixture was re-cooled to –78 °C, and a CH_2Cl_2 solution (10 mL) of either chlorodiphenylphosphine (0.104 g, 0.466 mmol, for ligand A) or dicyclohexylchlorophosphine (0.111 g, 0.460 mmol, for ligand B) was added dropwise. Stirring continued for 1 h at –78 °C, after which the cooling bath was removed, and stirring continued for another hour at ambient temperature.
The precipitated lithium chloride was removed by filtration under argon, and the volatiles were evaporated under vacuum to afford viscous phosphinite ligands A or B. Ligand A was obtained in 96.8% yield (0.180 g), and ligand B was isolated in 95.5% yield (0.183 g).

2.4 Synthesis of Catalysts

$PdCl_2$ (0.022 g, 0.125 mmol) and phosphinite ligand A (0.100 g, 0.250 mmol, for catalyst C) or ligand B (0.100 g, 0.243 mmol, for catalyst D) were dissolved in dry CH_2Cl_2 (25 mL) under argon and stirred for 15 min at room temperature. The solution was concentrated to 1–2 mL under reduced pressure, and petroleum ether (20 mL) was added to precipitate the corresponding Pd(II) complex as a yellow solid.

The products (C or D) were isolated by filtration and dried under vacuum. Catalyst C was obtained in 77.6% yield (0.094 g, m.p. 143–145 °C), and catalyst D was isolated in 79.8% yield (0.097 g, m.p. 178–180 °C) (Figure 3).

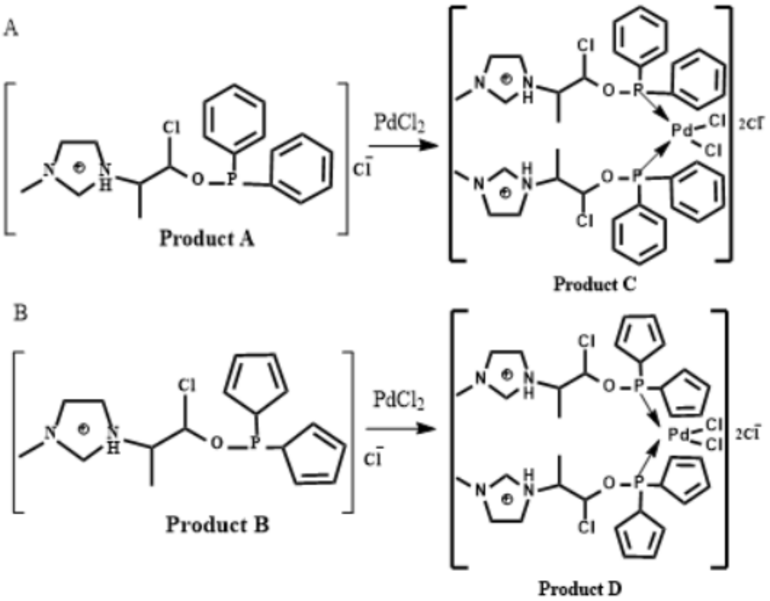

Figure 3 - Scheme of synthesis of catalysts C and D

2.5 Biphenyl Synthesis Method

Biphenyl was synthesized via the reaction shown in Figure 4.

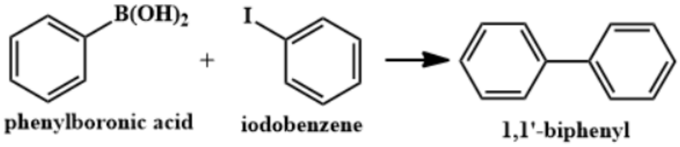

Figure 4 - The reaction of biphenyl synthesis

A mixture of iodobenzene (1.0 mmol), phenylboronic acid (1.5 mmol), K_2CO_3 (2 mmol), catalyst C or D (0.001 mmol), and water (3 mL) was used. Reactions were conducted at 100 °C. The purity of the biphenyl product was confirmed by ^{1}H NMR, and yields were calculated based on the residual amount of iodobenzene. All reactions were monitored by gas chromatography (GC).

3. Manufacturing of the Reactor System Components

Reactor system components including the reactor lid, stand, body, heat exchanger parts, and stirrer were fabricated from PET-G filament using a Bambu Lab X1 3D printer (Figure 5).

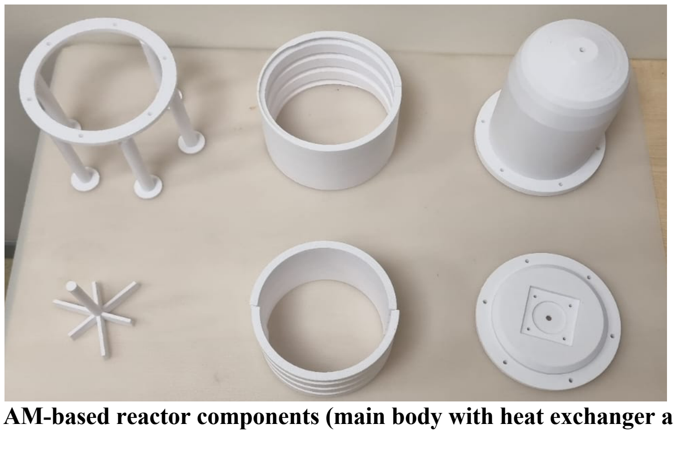

Figure 5 - AM-based reactor components (main body with heat exchanger and mixer)

3D models were designed using CAD software, considering structural requirements, and exported in STL or 3MF formats. Printing parameters in Bambu Studio were set as follows: extruder temperature 240–250 °C, bed temperature 70–80 °C, layer height 0.20–0.28 mm, infill density 20–40%, and print speed 80–120 mm/s. Support structures and a brim were used for parts with overhangs to enhance bed adhesion.

After automatic printer calibration, components were printed. The reactor body was fabricated as a cylindrical component under uniform cooling to minimize warping. The lid was printed with supports and pre-designed mounting holes, while the stand was printed at a reduced speed for stability. The stirrer was printed as a separate element for coupling with a stepper motor, and heat exchanger parts were printed with high precision for leak-tight connections.

Post-processing involved support removal, surface cleaning, and, if necessary, sanding or thermal treatment to smooth layer interfaces (Figure 6).

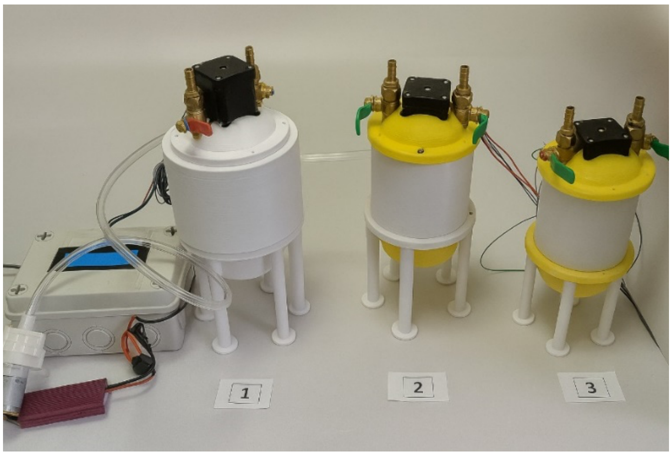

Figure 6 - Additively manufactured continuous-flow reactor system for biphenyl synthesis

All components were inspected for dimensional accuracy before assembly. The body was bolted to the stand and lid, the stirrer was installed and connected to a stepper motor controller, and the heat exchanger elements were positioned. Thermal regulation was achieved by circulating liquid through the system using peristaltic pumps.

4. Evaluation Criteria for the Designed Three-Stage Biphenyl Synthesis Scheme

The performance of the three-stage continuous biphenyl synthesis scheme was evaluated by comparing it with the traditional batch approach (Table 1).

Table 1 - Comparison of conventional batch synthesis and three-stage continuous flow synthesis of biphenyl

Criterion	Batch synthesis	Three-stage continuous synthesis (AM-based reactor)
Process workflow	Sequential, requires isolation and purification of intermediates	Integrated, intermediates directly transferred between stages
Catalyst preparation	Often prepared separately, with risk of degradation during storage	*In situ* ligand and Pd complex formation ensures stability and activity
Reaction control	Limited control of mixing, temperature gradients, and reaction time	Precise control of flow rates, residence times, and thermal conditions
Kinetics and selectivity	Slower kinetics, risk of side reactions due to inhomogeneous mixing	Faster kinetics, improved selectivity due to efficient mass and heat transfer
Scalability	Challenging; requires redesign of large reactors, prone to yield loss	Achieved via numbering-up (parallelization), conditions remain consistent
Resource efficiency	Higher solvent and reagent consumption; more waste from purification	Lower consumption; reduced waste through integration of steps
Flexibility	Limited; new reactions require redesign of glassware or metal reactors	High; reactor geometry easily modified via additive manufacturing
Industrial relevance	Widely established, but less compatible with modern green chemistry standards	Emerging, but highly promising for pharmaceuticals and hydrometallurgy
Environmental impact	Larger energy and material footprint	Smaller footprint; closer alignment with sustainability goals

The three-stage continuous synthesis in the additively manufactured reactor system demonstrates clear advantages over conventional batch methodologies. By integrating ligand synthesis, catalyst formation, and C–C cross-coupling into a seamless process, the system minimizes intermediate handling, reduces variability, and ensures the immediate use of freshly prepared catalysts. Continuous operation provides superior control of reaction conditions, improved mass and heat transfer, and enhanced selectivity, resulting in higher yields within shorter residence times. The modular architecture of the AM-based reactor allows for rapid reconfiguration and straightforward scalability through parallel operation. This approach requires fewer resources, generates less waste, and aligns more closely with sustainability principles. The versatility of such reactors also extends to hydrometallurgical applications like leaching, solvent extraction, and electrochemical metal recovery.

Overall, the synergy between continuous flow chemistry and additive manufacturing establishes a scalable, flexible, and environmentally responsible platform for next-generation compact, multifunctional reactor systems.

5. Results: Investigation of Catalytic Reaction Kinetics

Figure 7 - Time dependence of the reaction yield for catalyst C at different temperatures

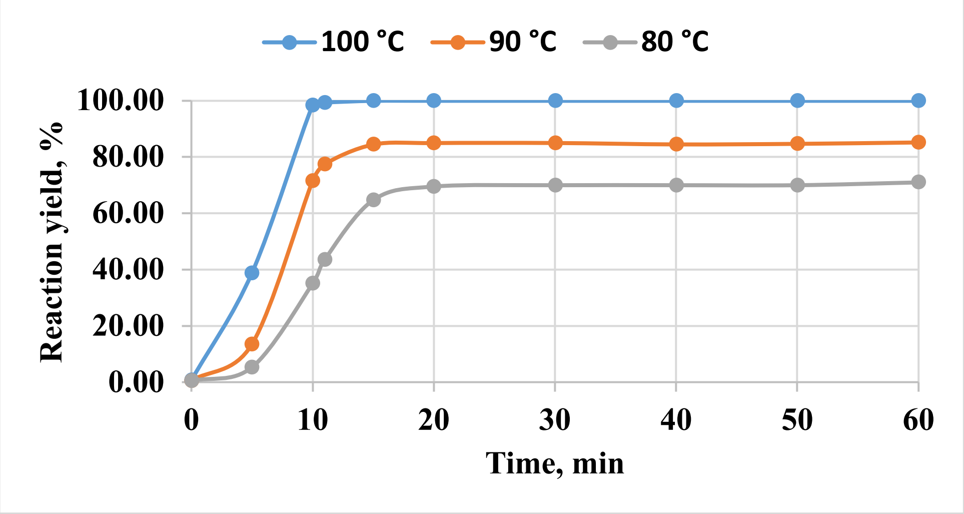

Figure 7 shows the time dependence of the reaction yield for catalyst C at 80 °C, 90 °C, and 100 °C.

The data indicate that increasing the temperature accelerates the reaction rate and increases the maximum yield. At 100 °C, the reaction reached nearly quantitative conversion (~100% yield) within 10 minutes. At 90 °C, the yield reached 85.2% after 10 minutes and remained nearly constant. At 80 °C, the reaction was slower, requiring approximately 10 minutes to approach a plateau yield of about 71%. These results confirm a strong temperature dependence for the catalytic process involving catalyst C.

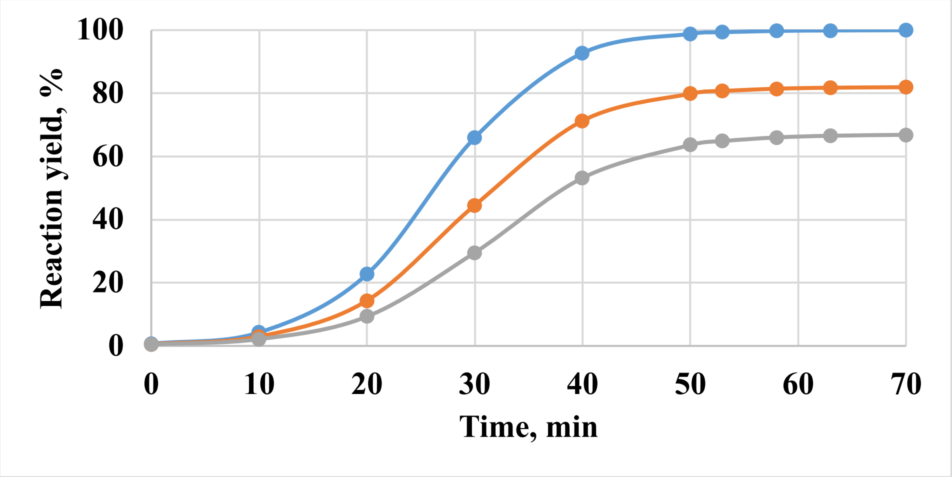

Figure 8 - Time dependence of the reaction yield for catalyst D at different temperatures

Figure 8 presents the time dependence of the reaction yield for catalyst D at different temperatures. A pronounced temperature effect was also observed. At 100 °C, the yield exceeded 90% within 40 minutes and stabilized near 100% by 50 minutes. At 90 °C, the yield reached about 70% at 40 minutes, gradually increasing to a plateau of approximately 80% after 60 minutes. At 80 °C, the reaction rate was significantly slower, with a yield of only around 50% at 40 minutes, leveling off near 65% after 60 minutes. These findings highlight the strong temperature dependence of catalyst D's performance.

6. Conclusion

This research successfully demonstrated the design, fabrication, and application of an additively manufactured PEEK-based continuous reactor system for C–C cross-coupling reactions, exemplified by the Suzuki–Miyaura synthesis of biphenyl. By integrating three sequential operations ligand synthesis, catalyst precursor formation, and the cross-coupling reaction into a modular continuous-flow platform, this study showed that complex multi-step processes can be streamlined with high reproducibility, superior parameter control, and improved efficiency compared to traditional batch methods. The system minimized intermediate handling, enabled in situ generation of active catalysts, and achieved rapid reaction kinetics, highlighting the potential of additive manufacturing to reshape pharmaceutical synthesis workflows.

Additive manufacturing provided significant benefits, including the low-cost realization of complex reactor geometries with integrated mixing and heat exchange. This design flexibility supports rapid prototyping and iterative optimization of flow dynamics, heat transfer, and mass transport. The scalability of this approach through the numbering-up of modular units ensures consistent product quality while increasing capacity, making the system promising for industrial translation. The reactor platform's versatility extends beyond pharmaceuticals to hydrometallurgical operations like leaching, solvent extraction, and electrochemical metal recovery. This underscores its role in sustainable resource management, enabling decentralized, small-scale processing units relevant to the growing demand for critical raw materials.

The broader implication of this work is the convergence of three transformative technologies: continuous manufacturing, additive manufacturing, and process analytical technology. Their integration defines a new paradigm for chemical engineering that is compact, reconfigurable, resource-efficient, and environmentally sustainable. This study provides a proof of concept and a strategic pathway for next-generation reactor systems capable of addressing urgent challenges in both pharmaceuticals and metallurgy.

Future research will focus on expanding the range of reactions accommodated by this platform, refining the integration of real-time monitoring tools, and investigating industrial scaling strategies through modular numbering-up. By bridging the gap between laboratory innovation and practical deployment, additively manufactured continuous reactor systems have the potential to become cornerstone technologies in modern chemical manufacturing.

Author Contributions:
Conceptualization, D.S.; methodology, A.K.; validation, M.A.; formal analysis, M.D.; investigation, M.K.; data curation, A.K.; writing-original draft preparation, A.K. and R.Kh.; writing-review and editing, D.S.; visualization, A.K. and R.Kh.; supervision, M.D. and A.K. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest:
The authors declare no conflict of interest.
Data Availability Statement:
The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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