

# Continuous Direct Mechanochemical Suzuki-Miyaura Coupling via Twin-Screw Extrusion

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Inorganic Chemistry I

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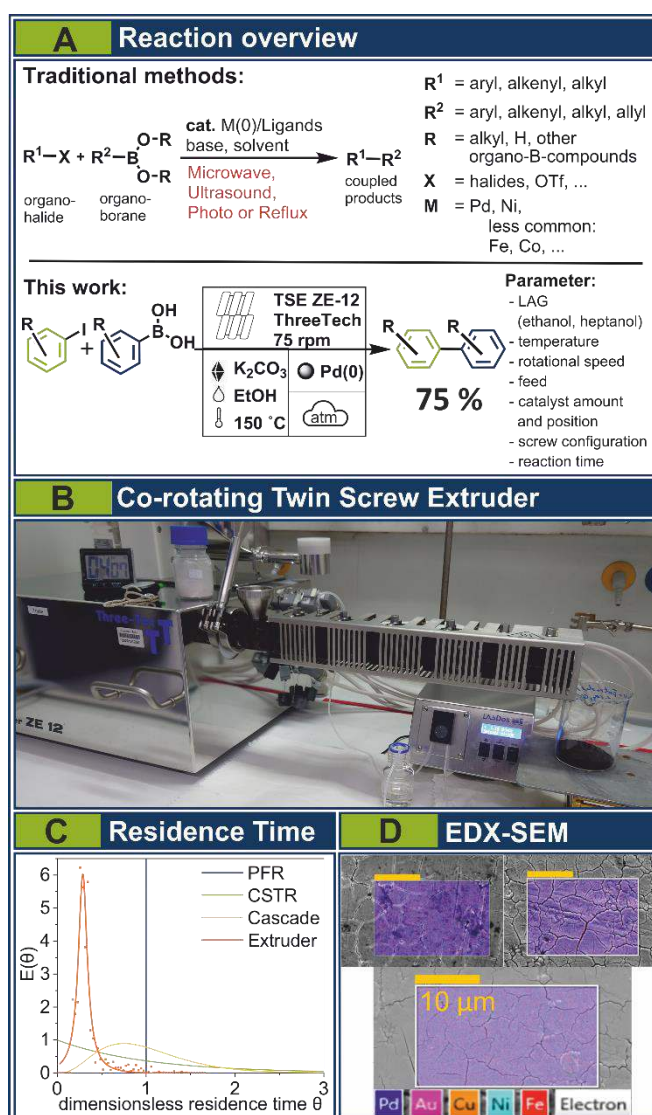
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**Abstract:** This work establishes the first direct mechanochemical reaction protocol within an extruder, focusing on the Suzuki-Miyaura reaction. Through the coating of either the extruder screws or barrel with Pd, we executed the cross-coupling reaction without the reliance on molecular catalyst compounds or powders, and solvents continuously. We identified the influence and interplay of crucial reaction parameters such as temperature, mechanical energy input, residence time, rheology, and catalyst contact time and finally obtained 36% and 75% of the reaction product after one and four reactor passes respectively.

## Introduction

The issue of waste in the chemical industry has become increasingly imminent.<sup>[1]</sup> One promising solution to mitigate this problem is mechanochemistry,<sup>[2]</sup> which has demonstrated its applicability across all the fields from organic to inorganic, and pharmaceutical chemistry.<sup>[3]</sup> Mechanochemical reactions are considered environmentally friendly<sup>[4]</sup> as they often achieve high yields at short reaction times while avoiding the use of solvents entirely.<sup>[5]</sup> Currently, the most common method for introducing mechanical energy is through ball milling.<sup>[6]</sup> However, this milling approach is limited to small-scale batch processes and the scale-up remains challenging.<sup>[7]</sup> To address this and to facilitate industrialization, continuous reactive extrusion emerges as a more suitable option.<sup>[8]</sup>

Industrial extruders are conventionally employed for food processing, polymer shaping, and pharmaceutical production, primarily for homogenization and shaping purposes.<sup>[9]</sup> However, they are rarely used in traditional organic or inorganic chemistry. Transitioning from milling to extrusion holds the promise of enabling the production of consistent, high-quality output in substantial quantities,<sup>[10]</sup> similar to the advancements seen in flow setups for solvothermal chemistry.<sup>[11]</sup> On a laboratory scale, the feasibility of reactive extrusion has already been demonstrated for both inorganic<sup>[12]</sup> and organic synthesis<sup>[13]</sup> showing that established principles derived from ball milling can be applied here as well. Key examples of such principles include the use of liquid-assisted grinding (LAG) agents<sup>[14]</sup>, bulk materials for dilution<sup>[12b]</sup>, and the use of catalysts.<sup>[7,15]</sup> The latter, however, poses significant challenges, especially in catalyst separation and deactivation<sup>[16]</sup>, both, in the mill and extruder.



**Figure 1.** A) Reaction scheme of Suzuki Miyaura reaction comparing traditional methods to this work. B) Used extruder set-up of the co-rotating twin screw extruder, L/D 40. C) Fitted residence time distribution of the extruder compared to the ideal reactors (plug flow reactor PFR, continuously stirred tank reactor CSTR and cascade. D) SEM-EDX measurements of new catalytic coating (top left) consisting of copper, nickel, gold and palladium, after 10 experiments (top right) and after recoating (bottom).

To address these challenges, we propose the implementation of direct mechanocatalysis.<sup>[17]</sup> This innovative concept combines energy input and catalytic materials within a single location by either constructing reactor components from catalytically active materials, alloys or coating them with catalysts.<sup>[17e,18]</sup> Direct Mechanocatalysis reduces the required catalyst quantity since the catalyst remains fixed within the reactor and does not necessitate constant catalyst addition. Circumventing the transformation of pre-catalysts to Pd(0) species also lowers the required energy.<sup>[19]</sup> The Pd-catalyzed Suzuki-Miyaura coupling was selected as the model reaction for this study (cf. Figure 1 A) as it is widely employed in the chemical industry for pharmaceutical route design.<sup>[15,21]</sup> The coupling was already investigated under ball milling conditions,<sup>[22]</sup> eliminating the necessity of solvents,<sup>[23]</sup> hazardous catalyst complexes,<sup>[17c,24]</sup> while showing high functional group tolerance and little side reactions. Our research group has previously demonstrated that coating a single milling ball with palladium is sufficient to achieve quantitative yields in just 30 minutes and even deactivated and sterically hindered aryl iodides and bromides could be successfully synthesized<sup>[17a]</sup>. To show the potential and flexibility of direct mechanocatalysis, especially for industrial scales, we present here the first direct mechanocatalysis of a Suzuki-Miyaura reaction conducted through extrusion and assess the influence of various parameters, such as temperature, rotational speed, and the addition of LAG.

## Results and Discussion

### Preliminary Pd(OAc)<sub>2</sub>-Studies

The Suzuki-Miyaura reaction was employed as a model reaction for the method development of direct mechanocatalysis in the extruder (cf. Figure 1B), utilizing equimolar amounts of phenylboronic acid and iodobenzene with K<sub>2</sub>CO<sub>3</sub> as the base. Initially, we optimized the reaction conditions using 5 mol% palladium acetate as a catalyst (please see, electronic supporting information ESI, chapter 1). Under these conditions, we achieved an optimal yield of 58 % with a screw speed of 150 rpm,  $\eta$  = 0.15 ml/mg of ethanol as a liquid-assisted grinding (LAG) agent, and a temperature of 60 °C. Notably, we observed improved yields with increasing temperature and screw speeds, which provide enhanced mixing and energy input (cf. Figure 2 A). Furthermore, we were able to recover 87 % of the palladium acetate catalyst in the form of agglomerated elemental palladium nanoparticles (cf. ESI, chapter 1). However, reusing this recovered palladium at the same reaction conditions only resulted in a yield of 26 %, indicating a significant loss of catalytic activity after just one cycle. Investigation of the recovered catalyst proved the degradation of palladium acetate to palladium black (cf. ESI, chapter 1). The loss of active catalyst in the first pass rendered this kind of catalyst unsuitable for scale-up and we turned to our proposed direct mechanochemical method from here on out, reducing the palladium amount used and simplifying its separation. We drew inspiration from the recent work of Wohlgemuth et al. electroplating milling materials with a steel-copper-nickel-gold-palladium plating sequence.<sup>[17e]</sup>

A preliminary Pd(OAc) <sub>2</sub> - Trends (Table S1 and S2)			
Sample	Yield [%]	Through put [kg/h]	STY [kg/day·m <sup>3</sup> ]
25°C	13	0.596	51.36
40°C	9	0.175	12.20
60°C	27	0.312	35.82
75 rpm	25	0.302	33.07
150 rpm	28	0.309	37.96
$\eta$ 0.045	56	0.370	75.79
$\eta$ 0.15	58	0.319	77.94

B Control reactions (Table S13)	
Reaction <b>without catalyst</b> on the reactor → 0 %	- Palladium <b>coated conveying</b> elements. - same length and position of the coating
<b>Homocoupling</b> of iodobenzene → 0 %	→ 0.04 % high abrasion

C Direct mechanocatalysis- Trends (Table S8-S12)			
Sample	Yield [%]	Through put [kg/h]	STY [kg/day·m <sup>3</sup> ]
1.4404 steel, rt	0	0.131	0
1.3505 steel, rt	1	0.338	1.52
100°C	2	0.307	3.34
125°C	28	0.338	38.76
150°C	36	0.340	49.68
175°C	7	0.176	8.99
$\eta$ 0.2 Ethanol	1	0.410	1.24
$\eta$ 0.3 Heptanol	8	0.350	10.65
2. pass	51	0.445	69.43
4. pass	75	0.291	82.21

**Figure 2.** A) Summary of the preliminary experiments with palladium acetate as the catalyst (cf. ESI chapter 1). B) Control reactions without catalyst and coated conveying elements, as well as for the homocoupling (cf. ESI, chapter 5). C) Comparison of the experiments between different steels (at room temperature, 75 rpm, 5 g/min solid feed, no LAG), different temperatures (1.3505 steel support, 75 rpm, 5 g/min solid feed, no LAG), different LAGs (150 °C, 75 rpm, 5 g/min solid feed) and several passes of material through the barrel (150 °C, 75 rpm, 5 g/min solid feed, no LAG) (cf. ESI, chapter 5).

This reduction in palladium resulted in a hundredfold decrease in catalyst costs even including the costs for the other metals in the coating sequence (cf. ESI, chapter 4.1).

### Direct Mechanocatalytic Reaction Protocol

In the exploration of direct mechanocatalysis via extrusion, we first conducted a residence time distribution analysis, determining a precise residence time of 5.83 minutes for the extruder when operated at 300 rpm using the catalytic palladium coating (cf. ESI, chapter 2). This represents the minimum time of catalyst contact and an idea of the order of magnitude for different rotational speeds. Figure 1 C depicts the form of the residence time distribution; the Dirac-shock marker (styrene) illustrates a hybrid of the ideal plug flow reactor (PFR) and the ideal cascade, highlighting the extruder being the ideal device for the proposed task (cf. ESI, chapter 2).

The observed residence time of roughly 6 minutes demonstrates that the transfer from the ball mill to the extruder is fundamentally possible since a yield of 50 % is reported via ball milling after only 5 min.<sup>[17e]</sup> Sufficient material flowability during extrusion is crucial, to avoid torquing out and to ensure optimal contact of reactants with the catalytic surface. For this reason, rheology measurements (cf. ESI, chapter 3) were taken showing that we have high internal friction, which comes from the irregular shape and size of the particles. To fix this one can either add LAG (which we will see later is disadvantageous) or you can adjust the flowability via the substrate (iodobenzene). We have found a ratio of iodobenzene to solid components of > 20 m% to be suitable.

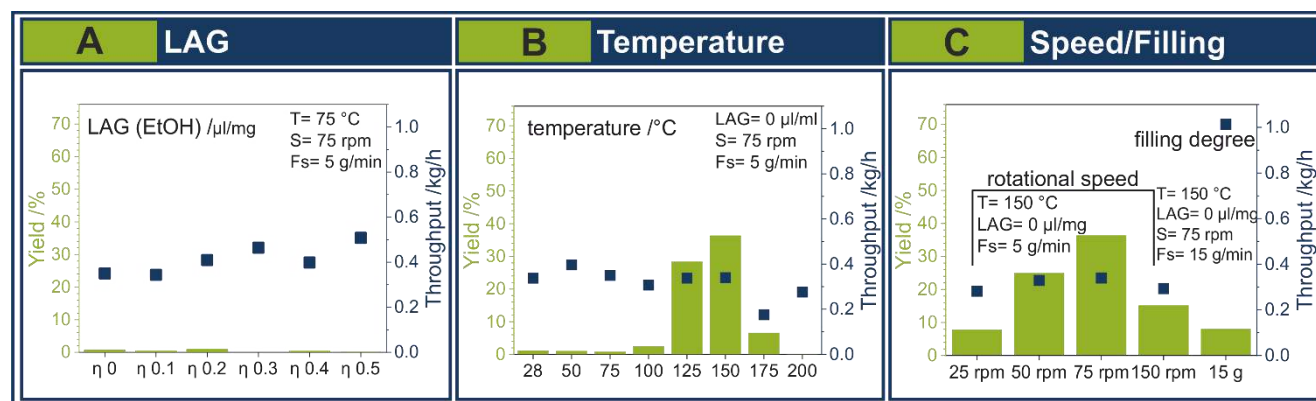
In a typical direct mechanocatalytic reaction we used an equimolar ratio of phenylboronic acid and iodobenzene with five equivalents of  $K_2CO_3$  as a base, hand-feeding the premixed solids and pumping the liquid components directly into the barrel. We coated the kneading sections, with 500 nm thick layers of copper, nickel, gold, and lastly palladium at a length of 9 cm per screw. The two kneading sections on each screw consist of three 30°, three 60° elements, and one 90° kneading block comprising four elements for the first section and two 30°, three 60° elements, and one 90° kneading block.

Applying standard reaction conditions, i.e., room temperature, 75 rpm rotational speed, and 5 g/min solid feed did not yield any product. However, in these first reactions, we used the highly chemical-resistant 1.4404 steel which most reactor parts are made of. This steel is not ideal for coating<sup>[17e]</sup> as the coating is visibly abraded after a few minutes. This consequently leads to no/low yields at room temperature and even at elevated temperatures (cf. Figure 2 C, ESI, chapter 5). Energy dispersive X-ray spectroscopy (EDX) measurements showed severe abrasion of the coating from the 1.4404 steel (cf. ESI, chapter 4). The reason for this is the high chromium content forming an oxide layer (cf. ESI, chapter 4). In accordance with previous results,<sup>[17e]</sup> we thus continued in the following with extruder elements manufactured from a low-chromium carrier steel 1.3505. We measured the amount of palladium in the reaction mixture by ICP-OES after the first pass through the extruder pre-work up with only 0.35 ppm. We also were able to discern that this coating did not show significant abrasion for ten experiments (5 h run time) and simple recoating is possible (cf. Figure 1 D).

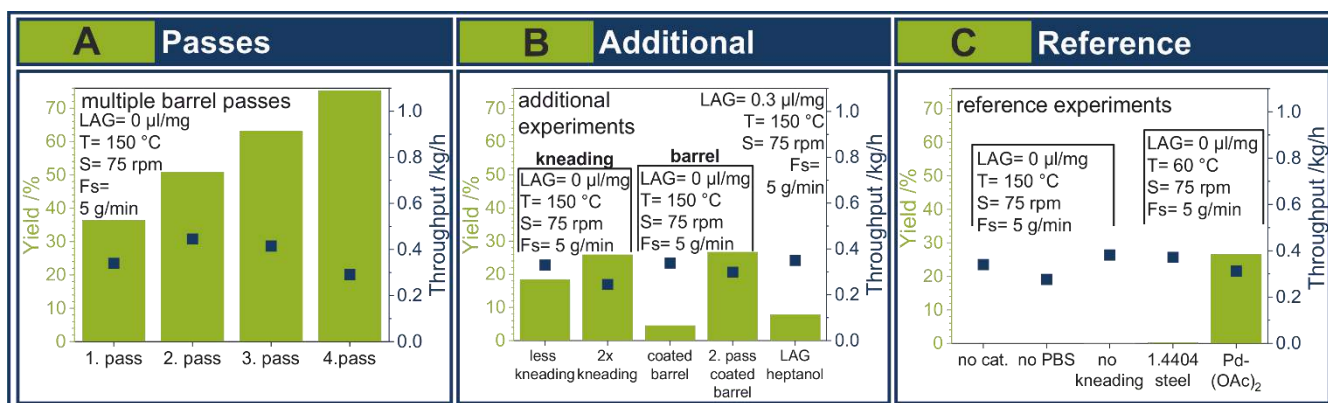
This showcases that, although the abrasion of the catalyst from the screw is significant over time, the quality of the product is barely impacted due to the high amount of throughput.

Initially, we explored the impact of temperature on the reaction within a range from room temperature up to 200 °C (cf. Figure 3B). Until 100 °C, the yield remained relatively constant at around 2 %. However, as the temperature was raised to 125 °C, the yield increased abruptly to 28 %, and then to 36 % at 150 °C. Nevertheless, yields started to decline rapidly when the temperature exceeded 150 °C. The high temperatures facilitate trimerization of the phenylboronic acid, as confirmed by NMR measurements (cf. ESI, chapter 5) impeding the reaction.<sup>[17a]</sup>

To enhance yields at lower temperatures, we explored the possibility of adding ethanol as LAG (cf. Figure 3A). The experiments were performed below 75 °C considering the boiling point of ethanol, and thus resulting in negligible improvements in yields. To reach higher temperatures (150 °C), we conducted an experiment using 0.3 ml/mg of heptanol increasing the yield to only 8 %, which is significantly lower compared to 36 % for reactions conducted without LAG. Thus, we considered the usage of LAG unsuitable from here on. The residence time of the reaction mixture within the reactor is a crucial factor and is adjustable through the rotational speed (cf. Figure 3C). Lower speeds lead to decreased yields, reaching 25 % and 8 % for speeds of 50 rpm and 25 rpm, respectively. Likewise, increasing the speed to 150 rpm resulted in a decreased yield of 15 %. Determining the impact of rotational speed changes is challenging, since it impacts residence time, thus mixing efficiency, mechanical energy and catalyst contact time simultaneously. The results, however, suggest that energy input and mixing play the dominant role, due to the faster conversion on the Pd(0) surface. Subsequently, we conducted an experiment at 75 rpm but increased the feed to completely fill the reactor volume (filling degree of 1, triple the original solid feed to 15 g/min, labeled as 15 g in Figure 3 C). This yielded 8 % of product, which corresponds well with the results of the experiment at 25 rpm, where the filling degree was also 1. This finding suggests that at high filling degrees, particle movement is impeded and low filling degrees hinder force transmission. It indicates that the optimal filling degree is around 1/3 of the available reactor volume. Interestingly, this finding aligns with observations in ball milling.<sup>[25]</sup>



**Figure 3.** Throughput (blue) and yield (green) for experiments performed using the 1.3505 steel A) different amounts of LAG (ethanol) in μl/mg; showing marginal increase at η 0.2; B) different temperatures (T) in °C highlighting 150 °C as the ideal temperature; C) different rotational speeds (S) in rpm and same filling degree as in the 25 rpm experiments at 75 rpm by increasing the solid feed (Fs) showing the ideal filling degree to be 1/3 like is the case for 75 rpm.



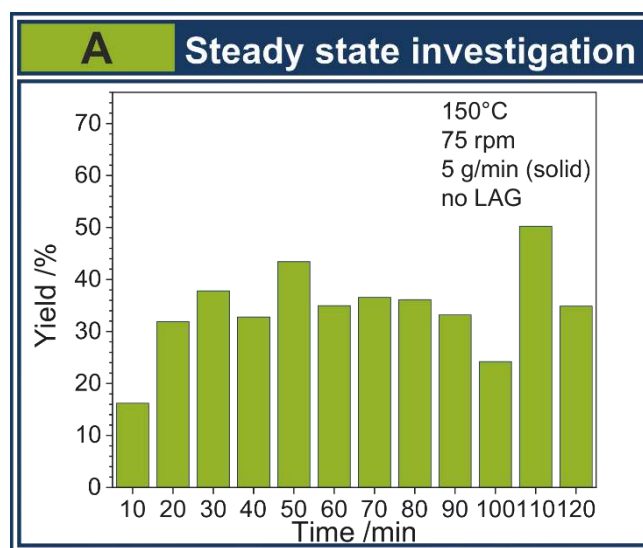
**Figure 4.** Comparison between throughput (blue) and yield (green) for experiments performed using the 1.3505 steel A) passing the reaction mixture through the barrel several times, revealing a near linear increase to 75 % yield at the 4<sup>th</sup> pass; B) additional experiments for different amounts of kneading, using a coated barrel instead of the coated screws and passing the reaction mixture through the coated barrel a second time as well as using heptanol as LAG; C) the reference experiments without catalyst, without phenylboronic acid (PBS) to determine the homocoupling of iodobenzene, no kneading elements, and the coated 1.4404 steel and using Pd-acetate as a catalyst (5 mol%) the later at a lower temperature of 60 °C.

Achieving reliable yields for the first time, we aimed to identify the place of catalysis (cf. Figure 2 B).

First, we conducted the reaction without any Pd coating, yielding no product at all. Second, we coated the conveying- instead of the kneading elements (same length and position). This led to reduced mechanical forces and homogenization, thus only traces of product were formed caused by the less effective surface contact and the lower material exchange on the surface layer. Please note that the coating of the conveying elements (cf. ESI, chapter 4), flaked off in pieces with several mm in diameter, leading to lower reactor durability and more potentially active Pd nanoparticles, reinforcing our claim that the reaction is not majorly catalyzed by abraded nanoparticles but rather by the Pd(0) surface. Furthermore, any homocoupling was ruled out by conducting an experiment with only iodobenzene, expectantly not leading to any product formed. (cf. Figure 4 C.)

To emphasize the effect of the available catalyst surface and different kneading configurations, we coated only 2/3 of the kneading sections with palladium (cf. ESI, chapter 6) resulting in an expected decrease in yield to 18 %. Putting a non-catalytically active kneading section before each of the catalytic-active sections (cf. ESI, chapter 6), to increase the mixing, did not increase the yield of the reaction. This indicates that higher mechanical energy only increases the yield if it is introduced into the material at the location of the catalyst. To further increase the available catalyst surface, we build a new extruder barrel of the 1.3505 steel and coated it with Pd according to our standard coating sequence. Achieving only 5 % yield is surprisingly low considering the higher Pd surface area (>10 times) (cf. Figure 4 B). It turns out that the coated kneading elements are the primary site of catalytic turnover. We hypothesize that this is the place of the highest energy input, since the kneading element to kneading element contact produces better mixing, higher energy and better refreshing of the catalytic surface. We can summarize that the best yields could be achieved at 150°C, 75 rpm and a filling degree of 1/3 (solid feed 5 g/min), using the standard screw configuration of palladium coated kneading elements. After the first pass through the extruder barrel 36 % of product are obtained.

Passing the material through the barrel for a second time increased the yield near linear from 36 % to 58 %, three times to 63 % and the fourth time to 75 % (space time yield of 82 kg/day·m<sup>3</sup>) (Figure 4 A). Please note that iodobenzene is added again during the second and third passes respectively (same amount added per pass as in the first pass) leading to an excess, for better flowability and to compensate for the evaporated iodobenzene of the hot reaction mixture. On the fourth pass, no additional iodobenzene was added since the reaction mixture was sufficiently liquid after the third pass. We hypothesize that adjusting the added amount in each pass should not be necessary if a longer barrel was used instead. Although the yield is still moderate this leads to the conclusion that with additional passes full conversion is achievable and thus waste can be avoided, and the costs of the process reduce.



**Figure 5.** Steady-state experiment at the conditions with the highest yield (150 °C, 75 rpm, solid feed of 5 g, no added LAG) taking and analysing samples every 10 minutes.

Finally, we conducted stability experiments demonstrating that the reaction reaches a steady state within 20 minutes under the given parameters and maintains this stability for the subsequent 100 minutes (Figure 5). The average yield over 100 minutes is 36 % as reported earlier and proves the reproducibility of the setup.

## Conclusion

We developed the first direct mechanocatalytic reaction protocol for the Suzuki-Miyaura reaction in the extruder.

By coating either the screws or the barrel of the extruder with a fine layer of Pd, we were able to continuously conduct cross-coupling reactions without the addition of molecular catalyst compounds or powders, and any solvents. Our investigation underlines the delicate balancing of temperature, mechanical energy input, residence time, rheology and catalyst contact time. The successful optimization of key parameters yielded 36 % and 75 % of the product by operating at 150 °C, 75 rpm screw speed, a feed rate of 6.25 g/min and a filling degree of 1/3, within one and four passes through the barrel, respectively. These findings contribute to advance mechanocatalysis towards a continuous and scalable process.

## Supporting Information

The authors have cited additional references within the Supporting Information.<sup>[26]</sup>

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**Keywords:** Extrusion, Suzuki-Miyaura, Mechanochemistry, Direct Mechano-catalysis, Sustainability

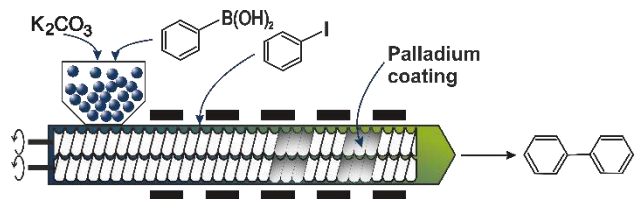
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## Entry for the Table of Contents



This study delves into the mechanochemical Suzuki-Miyaura reaction within an extruder, elucidating the influence of parameters like temperature, catalyst position and contact time. Notably, multiple passes through the extruder yielded substantially improved reaction conversions. The research underscores the pivotal role of optimizing the interplay between catalyst contact time and energy input, offering crucial insights for industrial-scale applications of mechanochemical reactions.

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