

# Evolution of Solid Processing Methods in Continuous Flow Technology: Reactive Extrusion

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**Abstract:** The frustrations of precipitation, fouling and blockages of liquid-based flow reactors are familiar to all researchers working with continuous flow equipment. There have been many innovative solutions to try and circumvent this issue. This short review will highlight the emerging technique of mechanochemistry and reactive extrusion as a continuous process that can directly work on solid (and liquid) materials and elicit chemical transformations.

**Keywords:** Continuous Flow · Extrusion · Mechanochemistry · Solids



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independent research group at Cardiff University focussing on the use of enabling technologies for synthesis and catalysis. In 2017 he was recognised by both Green Chemistry and Reaction Chemistry and Engineering as an ‘Emerging Investigator’ and was a recipient of a Thieme Chemistry Journal Award. In 2019, Duncan was appointed as Associate Professor of Organic Synthesis and Drug Discovery at UCL (University College London).

## 1. Introduction

Continuous processing in the fine chemicals industry continues to press forward. Within this context, many of the new frontiers and emerging developments are focussed on automation, data collection, AI and Machine Learning processes, especially those that support process development and understanding, leading to an ability to readily scale from R&D through to manufacturing.<sup>[1]</sup> However some fundamental and perennial problems remain unsolved with this technique. Perhaps the arch-nemesis of a continuous flow reactor is blockages and fouling of the tubular assembly – leading to system shutdown if pressure feedback to the pumps is built-in and ‘popping’ of tubes if such a safety feature is not present.<sup>[2]</sup>

There have been several developments for the handling or prevention of blockages, including short-term responsive solutions; such as buzzing on a problematic tee-piece connector with an electronic toothbrush,<sup>[3]</sup> to more pre-emptive reactor designs. Such designs typically serve to reduce the chance for ‘bridging’, a phenomenon that often precedes a full blockage, and often features a moving part within the flow path that moves in an alternative direction to the flowing stream. Examples include 1) the use of an agitating cell reactor to agitate forming slurries and suspensions,<sup>[4]</sup>

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2) positioning of part of the reactor path in an ultrasound bath,<sup>[5]</sup> 3) pumping of slurries using peristaltic pumps,<sup>[6]</sup> 4) back-pressure regulation devices capable of handling solids that precipitate,<sup>[7]</sup> 5) the use of an array of Continually Stirred Tank Reactors (CSTRs) to keep precipitates/particulates moving,<sup>[8]</sup> 6) multijet oscillating disc millireactors,<sup>[9]</sup> 7) the use of mixed solvent systems that prevent or reduce precipitate formation.<sup>[10]</sup> Perhaps the most ubiquitous (and simplest to implement) solution to the problem is to lower the concentration of the input feeds. This can lead to a) an increase in solvent use for a process in flow compared to batch and 2) lower reaction rates. Conversely to this, there are some literature examples where the neat liquid reagents (or melted solid reagents) can be transformed into a liquid product which provides an excellent solution to the problem if the chemistry is amenable.<sup>[11]</sup> Herein we wish to highlight an emerging reactor technology that readily permits the continuous processing of solid materials, moreover the technology is likely to be present in all Active Ingredient formulation departments; Twin Screw Extrusion (TSE).

TSE or reactive extrusion is a promising method for the continuous scale-up of ball-milled mechanochemical processes (typically involving at least one solid component), the technique has been applied to the preparation and synthesis of metal-organic frameworks (MOFs), supramolecular porous cages and the deep eutectic solvents.<sup>[12]</sup> There has been significant study into crystallisation and co-crystallisation processes as well as final form preparation.<sup>[13]</sup> This minireview provides a highlight of the application of reactive extrusion to organic synthesis including a summary of the equipment.

A key attraction to the techniques of ball milling and extrusion is the potential they offer to conduct chemical reactions in the absence of bulk reaction solvent.<sup>[14]</sup> In addition to this potential benefit is the emerging idea that ball-milling can provide access to

the reactivity of insoluble materials, afford products not accessible in solution, enhance (or diminish) reaction selectivity, provide reduced reaction times (due to higher reactant concentrations) and can render many air- or moisture-sensitive processes more operationally simple.<sup>[15]</sup>

Given the promise of ball milling techniques one of the natural questions is whether these processes can be scaled up. The short answer is yes and this overview will provide some examples. However, the translation from the ball mill to the extruder is not straightforward as the variables and parameters of the tools change (Fig. 1), the field is currently at the point where this translation is being explored to try and gain an empirical understanding of some of the important factors as well as a grasp on how many reactions could be converted to such a process.

Several parameters can be controlled (either directly or indirectly) when using a twin screw extruder for a reaction.<sup>[16]</sup> Both solid and liquid materials can be fed into the extrusion device, the method and control of feeding solid materials into extruders differ across the reported literature. The most robust method of feeding solids into the twin-screw barrel is by the use of a solids loading hopper with a single conveying screw that doses the solids at a preset rate – where particle size is related to the rate of feeding.

Liquid materials can be delivered by a typical pump, either into the same inlet as the solids or at one of the extra addition points along the length of the barrel. Once the materials are in the barrel they are moved towards the end by conveying sections of the screw. The screws are made up of multiple screw elements, and the sequence and number of each element type are (re)configurable (Fig. 1B). Conveying elements move the material in the forward direction of travel whereas reverse-conveying elements work oppositely. The kneading elements are where the mechanical energy is largely transmitted to reaction centres by kneading the material

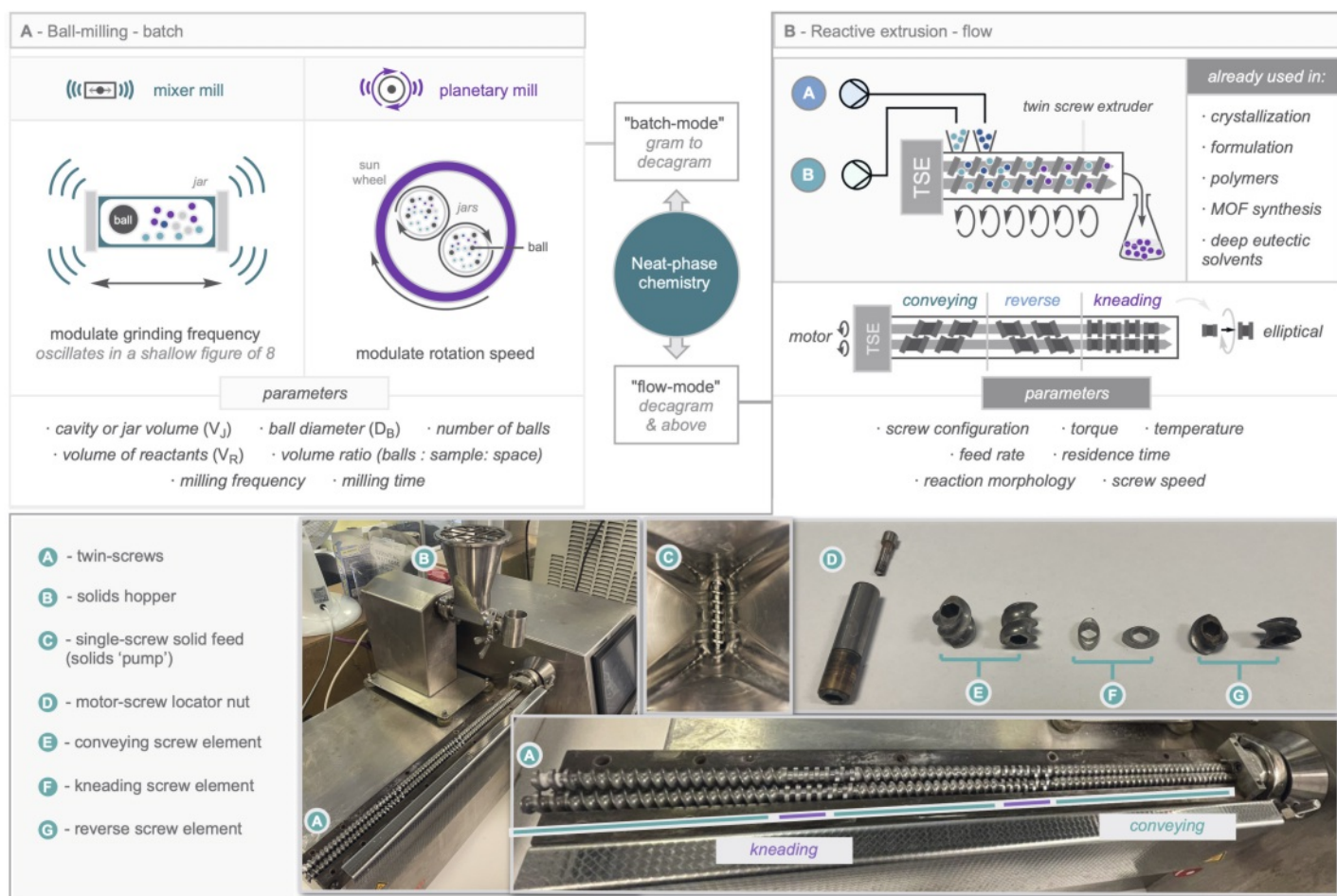


Fig. 1. Ball-milling and extrusion techniques for neat-phase chemistry.

between a narrow gap. Kneading elements can be positioned at different angles to impart different degrees of force onto materials (Fig. 1B). The screw assembly is driven by a motor at a speed set by the user. The motors operate up to a particular torque; beyond which, the motors 'torque-out' and processing ceases. Control of the torque is a balance between the screw configuration, screw speed and feed rates, and the reaction morphology. The residence time is determined by these aspects and can be increased by the use of reverse conveying sections, although too much hold up of material can lead to torque-out and so a fine balance is required. The barrels of many TSE devices have individually addressable thermal heating sections allowing temperature profiles to be applied across the length of the barrel.

## 2. Condensation Reactions

The first forays into the use of extrusion in organic synthesis were conducted by Crawford, James and co-workers.<sup>[17]</sup> The authors studied a selection of condensation reactions beginning with Knoevenagel condensation (Fig. 2a & b) using both barbituric acid and ethyl 2-cyanoacetate as pronucleophiles and aryl aldehydes as electrophiles. In the first instance, all solids were added into a feeder and delivered to the twin-screw barrel. The process achieved 100% conversion to the alkene product with a throughput rate of 520 g h<sup>-1</sup> and space-time yield values an order of magnitude greater than many extrusion protocols to date. In the case of the nitrile-substituted example (Fig. 2b), this liquid starting material was fed into a separate second addition port *via* a syringe pump. A base catalyst was employed to suppress undesired polymerization of the pronucleophile and was not removed from the reaction mixture after extrusion. As a further example of a condensation reaction the authors also detailed a double imine formation process with notable reaction efficiency providing 100% conversion and less than 1 minute of residence time. What

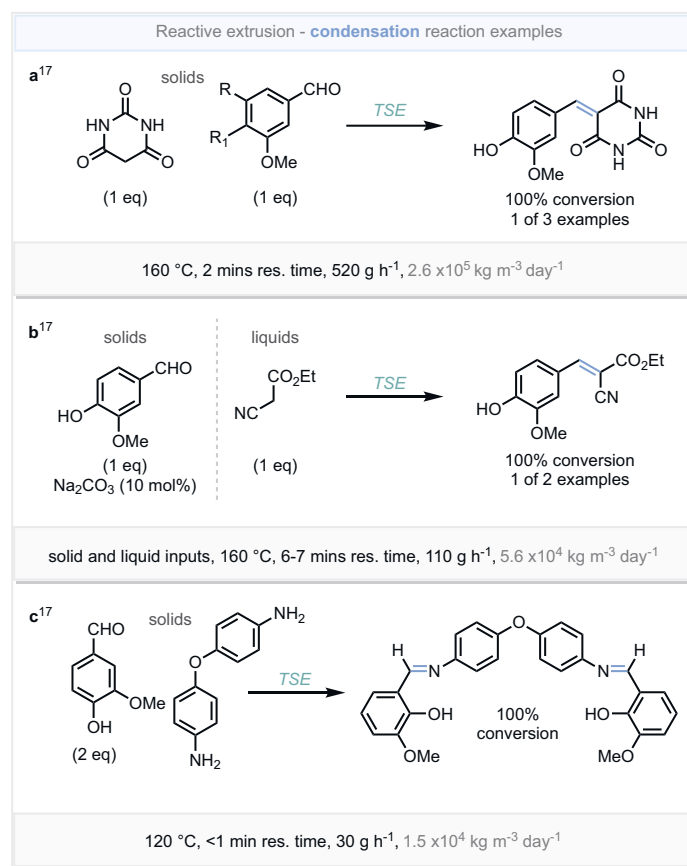


Fig. 2. Examples of condensation reactions by extrusion.

is particularly attractive about condensation chemistry by extrusion is that the temperature of the barrel can be set so that the water vapour can be removed as steam from the reaction process as it processes and drive the reaction forward.

## 3. Halogenation Reactions

Building on prior ball milling work at a small scale,<sup>[18]</sup> Browne, James and co-workers demonstrated the selective additive-dependent mono- and di-fluorination of 1,3-dicarbonyls.<sup>[19]</sup> Using a combination of solid Na<sub>2</sub>CO<sub>3</sub> and Selectfluor, dibenzoylmethane could effectively undergo di-fluorination. The omission of Na<sub>2</sub>CO<sub>3</sub> and the use of MeCN as a liquid additive promoted the formation of the mono-fluorinated dibenzoylmethane, (Fig. 3a). By mixing all reaction components and then manually feeding them into an extruder containing reverse sections the designed protocols were able to afford both fluorinated species selectively with modest throughput rates. Notable here is the use of NaCl as a grinding auxiliary or glidant material to improve the rheology of the reaction mixture, which in turn improves the translation of the mechanical forces applied by the kneading sections to the reactants.

More recently, Halasz, Palčić, Hernández and co-workers reported a preliminary exploration into the extrusion of a zeolite-promoted bromination of naphthalene. In this case, the bromine source was 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (Fig. 3b).<sup>[20]</sup> The team demonstrated that at very high screw speeds (20 Hz, 1200 rpm), two cycles were required to enable 100% conversion of the naphthalene to a mixture of 1-bromo- and 1,4-dibromo-naphthalene.

## 4. Reduction Reaction

In a detailed process concerning the reduction of lipophilic aldehydes with NaBH<sub>4</sub>, Isoni and co-workers demonstrated the conversion of a custom-made batch reactor approach at the lab scale to a twin screw extrusion approach at the kilo scale.<sup>[21]</sup> In the designed process they were able to feed solid NaBH<sub>4</sub> dissolved in 1 M NaOH into an extruder fed with a solid benzaldehyde de-

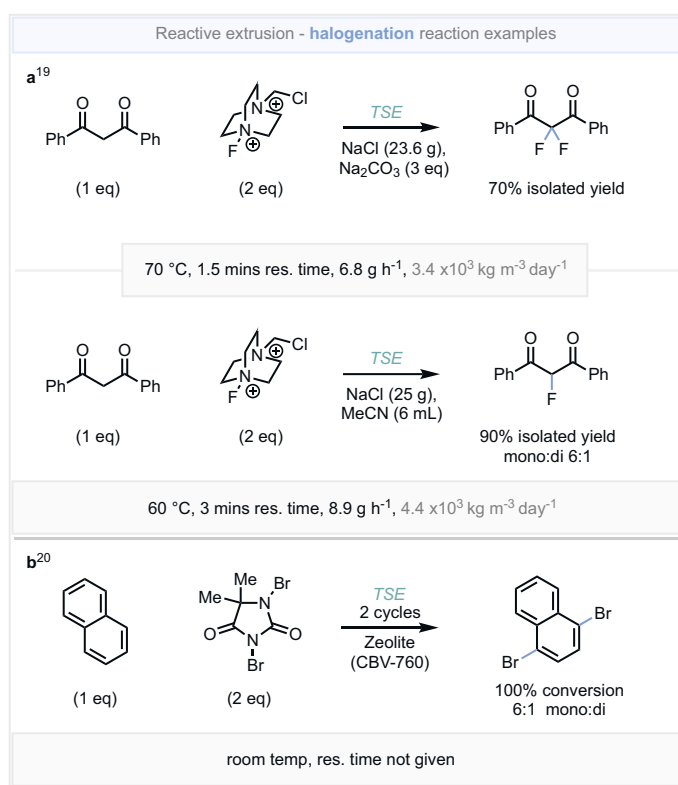


Fig. 3. Examples of fluorination and bromination reactions by extrusion.

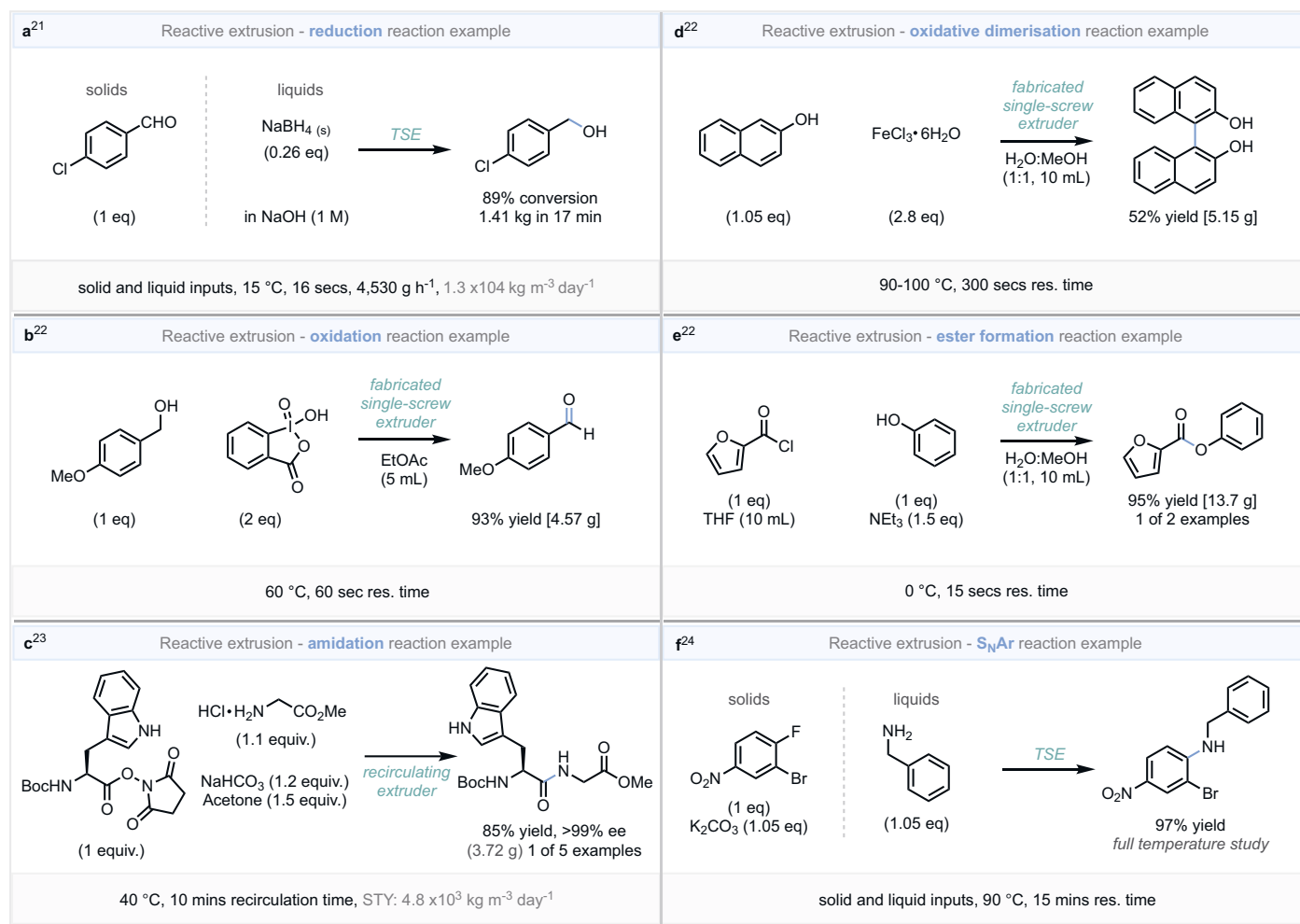


Fig. 4. Examples of reduction, oxidation, amidation, oxidative dimerisation, ester formation and nucleophilic aromatic substitution reactions by extrusion.

rivative (Fig. 4a). This process gave rise to 1.41 kg of product in a 17 minute run with an outstanding throughput of  $\sim 4.5$  kg h<sup>-1</sup>; furthermore, a full process design including pump feeds and purification was provided by the authors.

## 5. Oxidation Reaction

Kulkarni and co-workers report an example of a single screw extruder fabricated in-house using a single Teflon screw connected to a motor. The Teflon screw is housed inside a standard laboratory condenser,<sup>[22]</sup> the main screw is positioned vertically and is fed by two further Teflon screws on either side, where it is possible to feed two sets of materials from different ports.

The screw system does not feature any kneading sections, the mechanical force is transferred solely *via* the shear between the screws and barrel edge. It should be noted that due to the low amount of mechanical force elicited by this technique, coupled with very low residence times, these reactions may take place from high concentration and efficient mixing rather than any mechanical effects. Nonetheless, several useful transformations were reported using this device. With regards to oxidation, it was demonstrated that (4-methoxyphenyl)methanol could undergo oxidation using 2 equivalents of IBX delivering a 93% yield and  $\sim 5$  grams of product (Fig. 4b). For this process, the condenser was heated to 60 °C and the residence time of the reactants was determined to be 60 seconds!

## 6. Amide Formation

To date, there has been one report of organic synthesis using micro-compounders. Micro-compounders are an interesting solution to increasing the residence time of a continuous flow process

for solid materials and feature the ability to recirculate the materials through the mechanical screws based before changing the flow path and ejecting the material. A micro-compounder consists of a vertical barrel containing two tapered screws pointing downwards into a conical barrel. Micro-compounders also only contain conveying-type patterns on the screw system. At the base of the conical barrel is a 2-position tee-piece. One position leads to a recycling channel that moves the material back up to the top of the barrel and the other position leads to a system outlet. The whole system can be heated to high temperatures ( $\sim 450$  °C) while extrusion takes place. Métro and co-workers have used such a device to explore amide bond formation.<sup>[23]</sup> A mixture of an NHS-activated carboxylic acid, an amine (such as a protected tryptophan and the glycine ester in the example shown, Fig. 4c), NaHCO<sub>3</sub> and acetone were fed into the micro-compounder, where it was exposed to 10 minutes of recirculation time before ejection. This process afforded the amide product in 85% yield on a 4-gram scale. This methodology was applied to dipeptides and tripeptides to demonstrate a programmable amide coupling, all in the absence of coupling agents and bulk reaction solvent.

## 7. Oxidative Dimerisation

Using the aforementioned in-house fabricated screw device, Kulkarni and co-workers demonstrated the oxidative dimerisation of naphthol mediated by iron trichloride under extrusion conditions (Fig. 4d).<sup>[22]</sup> By heating the condenser/screw barrel to 90–100 °C, achieved by the use of recirculating liquid connected to a heating device and a residence time of 5 minutes the team produced 5.15 grams of binol in 52% yield.

## 8. Ester Formation

Ester formation was also targeted by the team of Kulkarni by processing acid chlorides with triethylamine and an alcohol nucleophile. In the case of furanoyl chloride and phenol, the corresponding ester could be obtained in 95% yield giving 13.7 grams of product (Fig. 4e).<sup>[22]</sup> In this instance, the barrel was cooled to 0 °C and the residence time was 15 seconds, the addition of 10 mL of a 1:1 water and methanol mixture implies that this reaction was better processed as a slurry/paste.

## 9. Nucleophilic Aromatic Substitution

As part of an in-depth study into the translation of a ball-milled process to that of an extrusion procedure, Andersen and co-workers explored the  $S_NAr$  reaction between benzylamine and an electron-poor aryl fluoride (Fig. 4f).<sup>[24]</sup> The authors utilized automated solid and liquid feeders and were able to demonstrate the influence of temperature on the effectiveness of their extrusion process. Using a screw system containing reverse sections, at 90 °C, they observed a 97% yield for the  $S_NAr$  process. Collection and purification of the extrudate for 1 minute returned a 95% yield (1.15 grams) of the amine product.

## 10. Multicomponent Reactions

El-Remaily and co-workers demonstrated the multi-component Ugi reaction using a twin-screw extruder. In this instance, all of the starting materials (including liquids and solids) were first gently mixed, by hand, in a mortar and pestle before being added to an extruder, which was heated to 100 °C (Fig. 5a).<sup>[25]</sup> In residence times of less than 20 minutes, they achieved the synthesis of a small selection of bis-amide fragments. The initial mixtures contained 200 mmol of each of the four input materials.

Crawford, James and co-workers reported the multicomponent Pétasis reaction from boronic acid, aldehyde, and amine feedstocks.<sup>[26]</sup> Making use of reverse sections to increase reaction efficiency and feeding the liquid amine *via* a second addition port, they achieved a route to valuable  $\alpha$ -branched amine products with an excellent throughput rate of 185 g h<sup>-1</sup> (Fig. 5b). The reactor was heated to 50 °C with a residence time of 7 minutes.

## 11. Metal-catalysed Reactions

Catalytic processes are also possible in the solid state by extrusion. Kulkarni and co-workers reported the Sonogashira coupling of phenylacetylene and 4-iodoanisole using their locally fabricat-

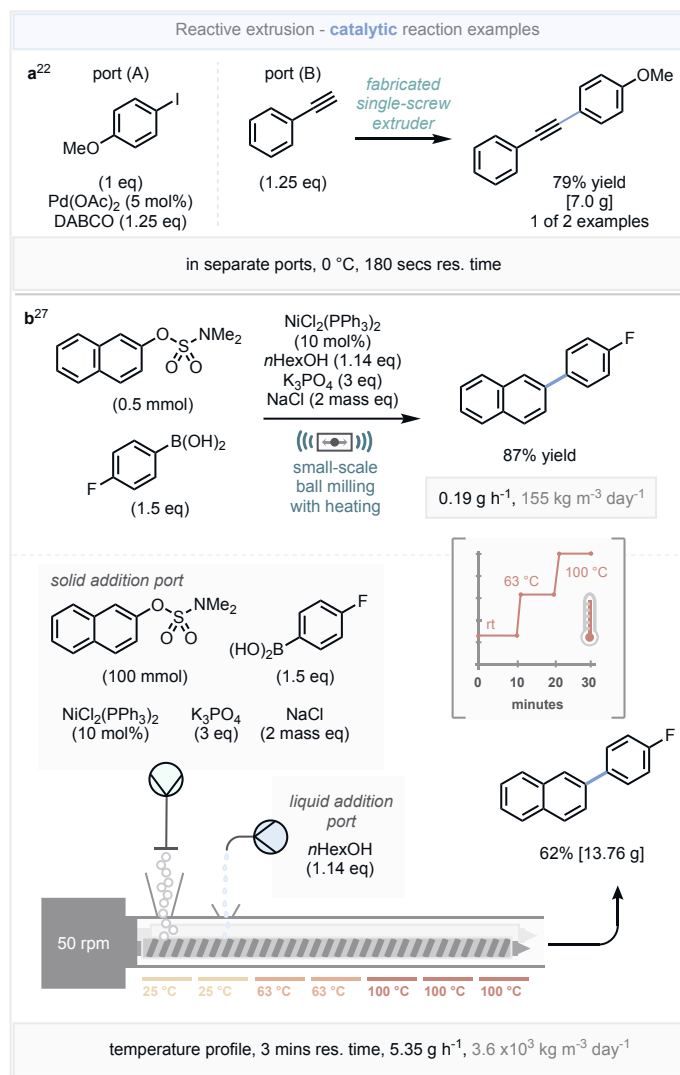


Fig. 6. Examples of catalytic reactions by extrusion.

ed extrusion device (Fig. 6a).<sup>[22]</sup> In this instance, the di-substituted alkyne product was formed in 79% yield on a 7.0 gram scale with a reaction temperature of 0 °C and 3 minutes residence time.

Within this context, Browne, Leitch, and co-workers explored extrusion methodology to scale a nickel-catalyzed Suzuki-Miyaura reaction (Fig. 6b).<sup>[27]</sup> From small-scale ball-milling studies, the cross-coupling coupling protocol was found to be very temperature dependent and a three-stage heating profile was found to be optimal; 10 minutes at 25 °C, 10 minutes at the midway point of 63 °C and 10 minutes at 100 °C. Translating this process to an extrusion methodology required moving from 0.5 mmol scale to 100 mmol scale, and translating the heating regimen from the ball mill to the extruder. The two reagents, catalyst, base and grinding auxiliary were loaded into the solid feeder port and *n*-hexanol (liquid-assisted grinding agent) *via* the syringe port. The screw speed was set to 50 rpm and of the seven heating zones, zones 1–2 were held at 25 °C, zones 3–4 at 63 °C, and zones 5–7 at 100 °C. Under these parameters, 13.76 g of the C–C coupled product was isolated in 62% yield. Analysis at 10-minute intervals demonstrated an initiation phase as the reactor reached a steady state, also a feature noted by Andersen and co-workers,<sup>[24]</sup> and then a process-end drop-off.

This highlights the potential for increasing the ‘steady-state’ section simply by running the reaction for longer in a continuous fashion. Considering the value of Suzuki-Miyaura-type methodology to pharmaceutical route design,<sup>[27]</sup> these studies serve to

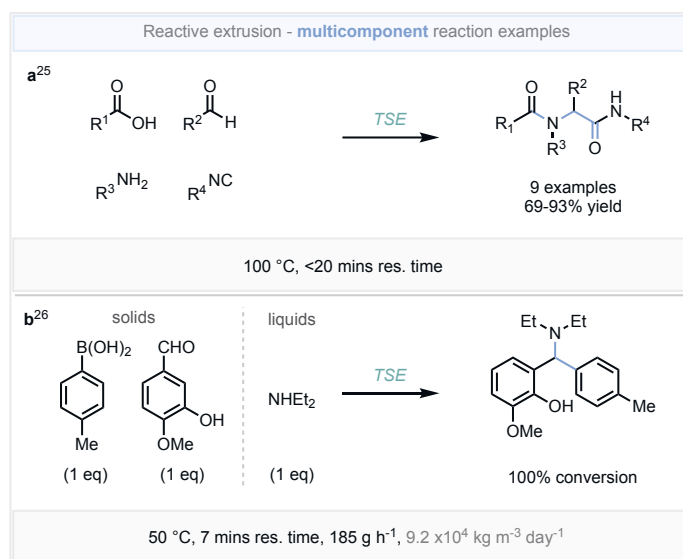


Fig. 5. Examples of multicomponent reactions by extrusion.

showcase the sustainable options extrusion can offer in the absence of bulk reaction solvent, with a base-metal catalyst under air atmospheres.

## 12. Purification

A few words are warranted on the purification of extruded materials, given that one of the motivators for using reactive extrusion is the ability to minimise solvent consumption. The processes outlined here and beyond, provide a wide range of purification processes (see ref. [16] for further summary details), ranging from no purification to column chromatography, crystallisation or liquid–liquid extraction. Furthermore, the characterisation of the products and purities is equally as varied ranging from powder-XRD to NMR. It is not possible to further comment on the effectiveness of the purification approaches reported for reactive extrusion methods to date. However, *does it actually matter?* Of course, it matters in the context of reporting an accurate yield and therefore knowing the purity of your sample. But from the perspective of developing a green method what we're really interested in is reducing the amount of solvent used to deliver the desired product. Process Mass Intensity (PMI) considers the amount of material used to furnish an amount of pure product (Eqn. (1)).

$$PMI_{process} = PMI_{reaction} + PMI_{purification} \quad (1)$$

The PMI of the whole process consists of the PMI for the reaction and the PMI of the purification. Given that reactive extrusion is a technology with a key focus on the reaction portion, and, moreover, the significant scaleup of such a process, the purification may remain largely unchanged by this technology, *i.e.* crystallisations to provide products within the required specifications will require solvents, and impurities will still need to be removed using solvent-based techniques.

## 13. Conclusion

In conclusion, we have presented continuous extrusion as a complementary technology to solution phase continuous approaches but specifically targeting reactions with solid inputs or outputs. We have briefly outlined some of the equipment and parameters of the reactive extrusion approach, as well as examples and references of what is thus far demonstrated in this field. Extrusion can process simple and more complex catalytic procedures on industrially relevant reaction scales of 4.5 kg h<sup>-1</sup>. If this mini-review has interested you in seeking out an extrusion device and designing your own extrusion experiments, we direct you to our recent tutorial review with a preliminary extrusion 'how-to' for reaction design and development.<sup>[16]</sup> Within the grander context of drug design and development, if even one step in a route of an upcoming active ingredient could be exchanged for extrusion technology, the impact on sustainable processing would be profound.<sup>[28]</sup> Finally, it cannot be understated that the futures of ball milling technology and extrusion methodology will remain entwined, and both will be incredibly important to the demonstration and adoption of mechanochemistry in sustainable organic synthesis.

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is composed of pharmaceutical and biotechnology companies and was established to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its members' shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability.

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- [1] a) M. B. Plutschack, B. Pieber, K. Gilmore, P. H. Seeberger, *Chem. Rev.* **2017**, *117*, 11796, <https://doi.org/10.1021/acs.chemrev.7b00183>; b) C. N. Talicska, E. C. O'Connell, H. W. Ward, A. R. Diaz, M. A. Hardink, D. A. Foley, D. Connolly, K. P. Girard, T. Ljubicic, *React. Chem. Eng.* **2022**, *7*, 1419, <https://doi.org/10.1039/D2RE00004K>; c) M. A. Morin W. Zhang, B. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2021**, *60*, 20606, <https://doi.org/10.1002/anie.202102009>; d) A. M. Schweidtmann, A. D. Clayton, N. Holmes, E. Bradford, R. A. Bourne, A. A. Lapkin, *Chem. Eng. J.* **2018**, *352*, 277, <https://doi.org/10.1016/j.cej.2018.07.031>.
- [2] Y. Chen, J. C. Sabio, R. L. Hartman, *J. Flow Chem.* **2015**, *5*, 166, <https://doi.org/10.1556/1846.2015.00001>.
- [3] S. V. Ley, N. Nikbin, tongue-in-cheek solution at the ITC Laboratory, Cambridge, UK ~2010-2011.
- [4] D. L. Browne, B. J. Deadman, R. Ashe, I. R. Baxendale, S. V. Ley, *Org. Process Res. Dev.* **2011**, *15*, 693, <https://doi.org/10.1021/op2000223>.
- [5] a) R. L. Hartman, J. R. Naber, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Org. Process Res. Dev.* **2010**, *14*, 1347, <https://doi.org/10.1021/op100154d>; b) J. Sedelmeier, S. V. Ley, I. R. Baxendale, M. Baumann, *Org. Lett.* **2010**, *12*, 3618, <https://doi.org/10.1021/ol101345z>.
- [6] P. R. D. Murray, D. L. Browne, J. C. Pastre, C. Butters, D. Guthrie, S. V. Ley, *Org. Proc. Res. Dev.* **2013**, *17*, 1192, <https://doi.org/10.1021/op4001548>.
- [7] B. J. Deadman, D. L. Browne, I. R. Baxendale, S. V. Ley, *Chem. Eng. Technol.* **2015**, *38*, 259, <https://doi.org/10.1002/ceat.201400445>.
- [8] Y. Mo, K. F. Jensen, *React. Chem. Eng.* **2016**, *1*, 501, <https://doi.org/10.1039/C6RE00132G>.
- [9] L. Liguori, H.-R. Bjørsvik, *Org. Process Res. Dev.* **2011**, *15*, 997, <https://doi.org/10.1021/op2000699>.
- [10] a) H. Lin, C. Dai, T. F. Jamison, K. F. Jensen, *Angew. Chem. Int. Ed.* **2017**, *56*, 8870, <https://doi.org/10.1002/anie.201703812>; b) J. C. Yang, D. Niu, B. P. Karsten, F. Lima, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2016**, *55*, 2531, <https://doi.org/10.1002/anie.201509922>; c) Z.-Q. Yu, Y.-W. Lv, C.-M. Yu, W.-k. Su, *Tetrahedron Lett.* **2013**, *54*, 1261, <https://doi.org/10.1016/j.tetlet.2012.12.084>.
- [11] For some examples of neat or molten phase flow chemistry see: a) T. Ouchi, R. J. Mutton, V. Rojas, D. E. Fitzpatrick, D.G. Cork, C. Battilocchio, S. V. Ley, *ACS Sustainable Chem. Eng.* **2016**, *4*, 1912, <https://doi.org/10.1021/acssuschemeng.6b00287>; b) D. R. Snead, T. F. Jamison, *Chem. Sci.* **2013**, *4*, 2822, <https://doi.org/10.1039/c3sc50859e>.
- [12] a) D. E. Crawford, J. Casaban, R. Haydon, N. Giri, T. McNally, S. L. James, *Chem. Sci.* **2015**, *6*, 1645, <https://doi.org/10.1039/C4SC03217A>; b) D. E. Crawford, L. A. Wright, S. L. James, A. P. Abbott, *Chem. Commun.* **2016**, 4215, <https://doi.org/10.1039/C4SC03217A>.
- [13] a) R. S. Dhumal, A. L. Kelly, P. D. Coates, A. Parakdar, *Pharm. Res.* **2010**, *27*, 2725, <https://doi.org/10.1007/s11095-010-0273-9>; b) C. Medina, D. Daurio, K. Nagapudi, F. Alvarez-Nunez, *J. Pharm. Sci.* **2010**, *99*, 1693, <https://doi.org/10.1002/jps.21942>.
- [14] a) K. J. Ardila-Fierro, J. G. Hernández, *ChemSusChem* **2021**, *14*, 2145, <https://doi.org/10.1002/cssc.202100478>; b) A. Stolle, T. Szuppa, S. E. S. Leonhardt, B. Ondruschka, *Chem. Soc. Rev.* **2011**, *40*, 2317, <https://doi.org/10.1039/c0cs00195c>; c) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080, <https://doi.org/10.1039/C7SC05371A>; d) J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435, <https://doi.org/10.1039/C7GC03797J>; e) I. N. Egorov, S. Santra, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. Majee, B. C. Ranu, V. L. Rusinov, O. N. Chupakhin, *Green Chem.* **2020**, *22*, 302, <https://doi.org/10.1039/C9GC03414E>; f) T. Friščić, C. Mottillo, H. M. Titi, *Angew. Chem. Int. Ed.* **2020**, *59*, 1018, <https://doi.org/10.1002/anie.201906755>.
- [15] A. C. Jones, J. A. Leitch, S. E. Raby-Buck, D. L. Browne, *Nat. Synth.* **2022**, *1*, 763, <https://doi.org/10.1038/s44160-022-00106-4>.
- [16] R. R. A. Bolt, J. A. Leitch, A. C. Jones, W. I. Nicholson, D. L. Browne, *Chem. Soc. Rev.* **2022**, *51*, 4243, <https://doi.org/10.1039/D1CS00657F>.
- [17] D. E. Crawford, C. K. G. Miskimmin, A. B. Albadarin, G. Walker, S. L. James, *Green Chem.* **2017**, *19*, 1507, <https://doi.org/10.1039/C6GC03413F>.
- [18] a) J. L. Howard, Y. Sagatov, L. Repusseau, C. Schotten, D. L. Browne, *Green Chem.* **2017**, *19*, 2798, <https://doi.org/10.1039/C6GC03139K>; b) J. L. Howard, Y. Sagatov, D. L. Browne, *Tetrahedron* **2018**, *74*, 3118, <https://doi.org/10.1016/j.tet.2017.11.066>.
- [19] Q. Cao, J. L. Howard, D. E. Crawford, S. L. James, D. L. Browne, *Green Chem.* **2018**, *20*, 4443, <https://doi.org/10.1039/C8GC02036A>.
- [20] K. J. Ardila-Fierro, L. Vugrin, I. Halasz, A. Palčić, J. G. Hernández, *Chemistry-Methods* **2022**, e202200035, <https://doi.org/10.1002/cmtd.202200035>.

- [21] V. Isoni, K. Mendoza, E. Lim, S. K. Teoh, *Org. Process Res. Dev.* **2017**, *21*, 992, <https://doi.org/10.1021/acs.oprd.7b00107>.
- [22] B. M. Sharma, R. S. Atapalkar, A. A. Kulkarni, *Green Chem.* **2019**, *21*, 5639, <https://doi.org/10.1039/C9GC02447F>.
- [23] Y. Yeboue, B. Gallard, N. Le Moigne, M. Jean, F. Lamaty, J. Martinez, T.-X. Métro, *ACS Sustainable Chem. Eng.* **2018**, *6*, 16001, <https://doi.org/10.1021/acssuschemeng.8b04509>.
- [24] J. Andersen, H. Starbuck, T. Current, S. Martin, J. Mack, *Green Chem.* **2021**, *23*, 8501, <https://doi.org/10.1039/D1GC02174E>.
- [25] M. A. E. A. A. El-Remaily, A. M. M. Soliman, O. M. Elhady, *ACS Omega* **2020**, *5*, 6194, <https://doi.org/10.1021/acsomega.0c00369>.
- [26] D. E. Crawford, C. K. Miskimmin, J. Cahir, S. L. James, *Chem. Commun.* **2017**, *53*, 13067, <https://doi.org/10.1039/C7CC06010F>.
- [27] R. R. A. Bolt, S. E. Raby-Buck, K. Ingram, J. A. Leitch, D. L. Browne, *Angew. Chem. Int. Ed.* **2022**, e202210508, <https://doi.org/10.1002/ange.202210508>.
- [28] K. N. Ganesh, D. Zhang, S. J. Miller, K. Rossen, P. J. Chirik, M. C. Kozlowski, J. B. Zimmerman, B. W. Brooks, P. E. Savage, D. T. Allen, A. M. Voutchkova-Kostal, *Environ. Sci. Technol. Lett.* **2021**, *8*, 487, <https://doi.org/10.1021/acs.estlett.1c00434>.

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