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Greener dye synthesis: Continuous, solvent-free synthesis of commodity perylene diimides by Twin Screw Extrusion

Qun Cao,[a] Deborah E. Crawford,[a] Chengcheng Shi[a] and Stuart L. James*[a]

Abstract: *A continuous, scalable and solvent-free method for the synthesis of various naphthalic imides and perylene diimides (PDIs) using twin screw extrusion (TSE) is reported. The work makes use of batch 'beat and heat' methods for efficiently screening likely reactivity under extrusion conditions. Using TSE, naphthalic imides (3 examples) were obtained quantitatively without the need for excess amine reactant or product purification. With good functional group tolerance, alkyl and benzyl amine-derived PDIs (12 examples, including commercial dyes Pigment Black 31 and Pigment Black 32) were obtained in 50-99% yield. Use of K_2CO_3, enabled more difficult aniline-derived PDIs (9 examples, including 3 commercial red pigments) also to be synthesized in 23-73% yield. Furthermore, an automated continuous TSE process for manufacturing Pigments Black 31 and 32 is demonstrated, with a throughput rate of ~1500 g/day, corresponding to a Space Time Yield (STY) of ~30 x 10³ kg m⁻³day⁻¹ which is 1-2 orders of magnitude greater than for solvent-based batch methods. These methods provide very substantial reductions in waste and improved efficiency compared to conventional solvent-based methods.*

Organic dyes are important compounds that are widely applied in textiles, cosmetics, pulp and paper, paint, pharmaceutical, food, carpet and printing industries.[1] Despite their importance, the acidic (or basic), strongly coloured waste effluents from their manufacture and application result in environmental contamination.[2] It is challenge to decrease the environmental impact of the dye industry by reducing the use of toxic solvents/additives together with the overall production cost of the manufacturing process. As one of the most important classes of organic dyes, perylene-3,4,9,10-tetracarboxylic acid diimides (PDIs) have been widely used as high-grade industrial paints in plastic, automobile and fiber industry due to their low solubility, excellent chemical inertness, photo- and weather-fastness, and thermal stability.[3] PDIs and related bisimides are also used in organic electronic and photovoltaic materials,[4] bio-labels,[5] sensors[6] and supramolecular assemblies.[7] The most common way to synthesise PDIs is using Langhals' method in which perylene-3,4,9,10-tetracarboxylic dianhydride (PTCDA) and anilines/aliphatic primary amines are heated at high temperatures (>160 ºC) in high boiling solvents such as molten imidazole or quinoline, NMP with zinc acetate as promotor.[8] Furthermore, the synthesis of PDIs often requires a large excess of the amine (4-20 equiv.).[9] These conditions and materials are undesirable for a sustainable process. To over come these problems, recently, Unterlass et al. developed a hydrothermal batch protocol for the synthesis of PDIs using water as solvent at 200 ºC under autogenous pressure (17 bar).[10] Without

organic solvent or excess of amines, alkyl substituted PDIs could be obtained in excellent to quantitative yields within 24 hours. The reaction time could be shortened to 4 hours by adding Hünig's base. However, this method relies on solubility of reactants (PTCDA and aliphatic amines) in water, and is not suitable for the more challenging aniline-derived products. Recently, mechanochemistry has become an attractive approach to more sustainable synthesis because it can eliminate or dramatically reduce the need for solvent.[11] It can also reduce reaction times and provide alternative different product selectivity.[12] Most exploratory research in mechanochemical synthesize makes use of small vibrational or planetary ball mills suitable for milligram to (exceptionally) 100 gram scale.[13] Twin screw extrusion (TSE), widely used for blending and processing in the pharmaceutical,[14] polymer,[15] and food industries,[16] is now being explored for scalable, continuous mechanochemical synthesis. Example products demonstrated include metal organic frameworks (MOFs),[17] deep eutectic solvents (DESs),[18] metal complexes,[19] condensation products,[20] as well as chemoenzymatic oligomerisation,[21] fluorination reactions[22] and multi-component reactions (MCR).[23] Although the broad application of reactive extrusion to the diverse types of chemical synthesis is still in its infancy, it was selected in 2019 by IUPAC as one of the ten chemical innovations that will change the world.[24] Here we report the first continuous scalable solvent-free organic dye synthesis using TSE to give various naphthalic imides and industrially important PDIs. Products are obtained in high yields without work up or with a simple work up procedure.

Imide formation under mechanochemical conditions was first reported by Kaupp and coworkers, a quantitative yield of *N*-(4-tolyl)-phthalimide could be obtained in a solid-solid reaction of phthalic anhydride and 4-toluidine in a mixer mill.[25] Based on our experience of transferring a ball milling reaction to TSE,[21] the high rate of consumption of reactants by using TSE, and the low solubility of PDI products, we began our preliminary experiment by treating a model substrate, 1,8-naphthalic anhydride **1** (1 mmol), with 4-ethoxyaniline **2** (1 mmol) in a mixer mill (ESI, Table S1). However, under neat grinding conditions, or with the addition of various liquid or solid additives such as acetic acid or potassium carbonate, no product was observed by ¹H NMR analysis.
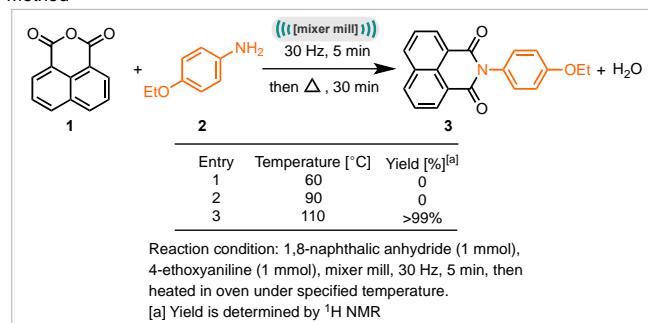
In contrast to milling methods, in which temperature is often uncontrolled and heating occurs adventitiously due to friction, extrusion processes can provide not only mechanical energy but also significant and controlled thermal energy input.[26] For the synthesis of inorganic solids such as metal oxides, sulfides, aluminosiicates etc., the "Beat and Heat" method, in which the reactants are repeatedly milled, heated and cooled, is widely used.[27,28] Due to its combination of milling and heating, we propose that this beat and heat procedure could be used as an initial screen for likely reactivity under extrusion conditions. Compared to extrusion methods, it can be done relatively easily and at small scales in ball mill jars. To this end, reactants **1** and **2**

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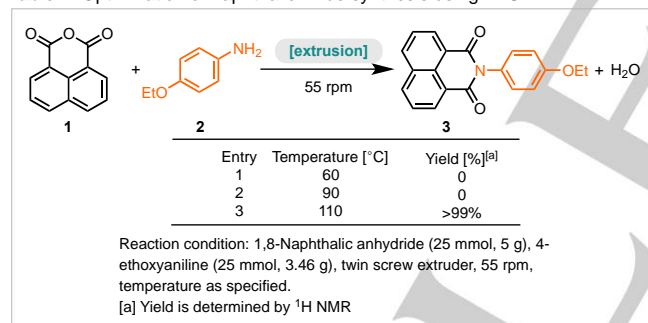E-mail: S.James@qub.ac.uk

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were milled together at 30 Hz for 5 min to ensure intimate mixing, and the jar then oven-heated for 30 min. ^{1}H NMR analysis (Table 1) showed that although no product **3** was obtained after heating at 60 and 90 °C, increasing the temperature to 110 °C caused quantitative conversion to **3**. This confirmed that heating could be critical for the formation of **3**.[29] This promising observation led us to explore the synthesis of **3** and related products by TSE.

Table 1. Optimization of naphthalic imide synthesis using the beat and heat method

Entry	Temperature [°C]	Yield [%][a]
1	60	0
2	90	0
3	110	>99%

Reaction condition: 1,8-naphthalic anhydride (1 mmol), 4-ethoxyaniline (1 mmol), mixer mill, 30 Hz, 5 min, then heated in oven under specified temperature.
[a] Yield is determined by ^{1}H NMR

A screw configuration containing two reverse conveying segments was used initially in order to retard the flow of reactants through the barrel and give the maximum chance for reaction (Figure 1, bottom photograph). A mixture of materials **1** (25 mmol, 5.0 g) and **2** (25 mmol, 3.46 g) was fed manually into the extruder over 8 min *via* the feeding port B (~ 1 g/min, residence time ~ 6 min), with a screw rotation rate of 55 rpm and various barrel temperatures (Table 2, entries 1-3). Fully consistent with the results using the Beat and Heat method in Table 1, there was no reaction at 60 or 90 °C but full conversion to **3** at 110 °C under extrusion conditions.
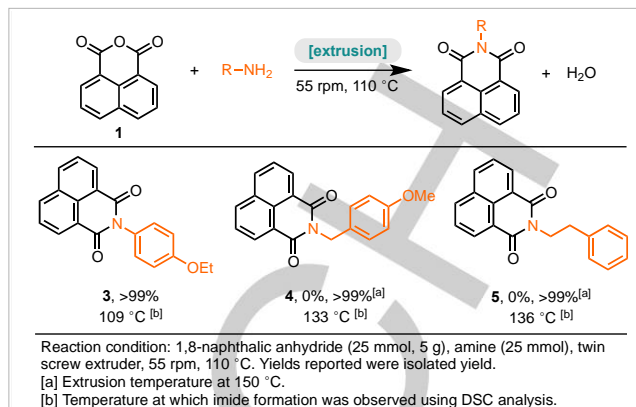
Table 2. Optimization of naphthalic imide synthesis using TES

Entry	Temperature [°C]	Yield [%][a]
1	60	0
2	90	0
3	110	>99%

Reaction condition: 1,8-Naphthalic anhydride (25 mmol, 5 g), 4-ethoxyaniline (25 mmol, 3.46 g), twin screw extruder, 55 rpm, temperature as specified.
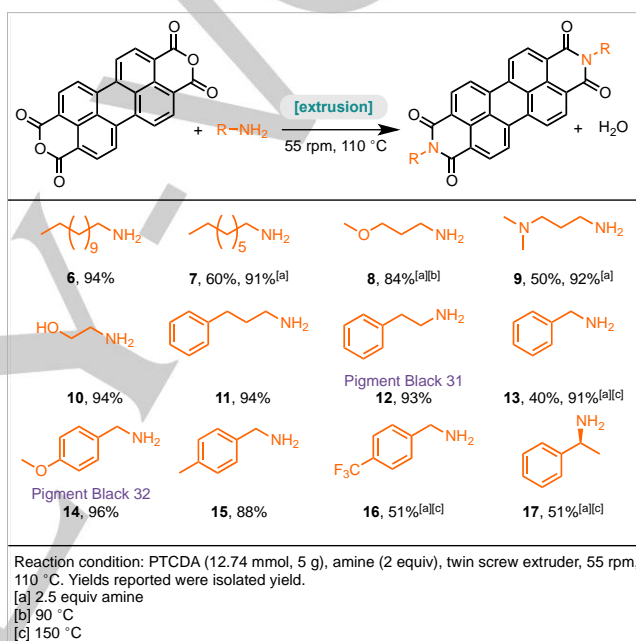[a] Yield is determined by ^{1}H NMR

The applicability of these conditions to other amines/anilines was then explored. Isolated yields of desired imides are shown in Scheme 1. Although, even at 110 °C, no formation of imides 4 and 5 was observed, when 4-methoxybenzylamine and 2-phenylethanamine were used as starting materials, further increasing the temperature to 150 °C again led to full conversion to **4** and **5**, notably without the need for excess amine or further work-up.

With established conditions for naphthalic imide synthesis using TSE in hand, the possibility of more challenging PDI synthesis was investigated. Commercially-available perylene-3,4,9,10-tetracarbonxylic dianhydride (PTCDA, 12.74 mmol, 5 g) and various amines (2-2.5 equiv.) were mixed by hand and fed manually into the extruder over 8 min (~ 1 g/min, residence time

3-6 min) at a screw speed of 55 rpm and barrel temperatures of 110-150 °C.

Reaction condition: 1,8-naphthalic anhydride (25 mmol, 5 g), amine (25 mmol), twin screw extruder, 55 rpm, 110 °C. Yields reported were isolated yield.
[a] Extrusion temperature at 150 °C.
[b] Temperature at which imide formation was observed using DSC analysis.

Scheme 1. Scope of naphthalic imide synthesis using TSE

Reaction condition: PTCDA (12.74 mmol, 5 g), amine (2 equiv), twin screw extruder, 55 rpm, 110 °C. Yields reported were isolated yield.
[a] 2.5 equiv amine
[b] 90 °C
[c] 150 °C

Scheme 2. Scope of alkyl/benzyl substituted PDIs synthesis using TSE

After extrusion, crude products were stirred in aqueous K_2CO_3 at 80 °C for 1 h (in order to hydrolyze unreacted PTCDA, if full conversion of PTCDA was not achieved), collected by filtration, washed with water and methanol, and dried in an oven at 130 °C. Scheme 2 shows that perylene dimides derived from various aliphatic amines (**6**, **10-12**) could be synthesized in excellent yields by TSE at 110 °C, notably, without the need for excess amine. A small excess of amine (extra 0.5 equiv) was required to achieve good yields of some perylene dimides (**7-9**). It was also found that the electronic character of benzylamine substrates strongly affected the yield with electron-donating substituents favouring high yields (**14** and **15** in 96% and 88% at 110 °C, respectively) whereas only 40% of **13** was obtained when benzyl amine itself was used. At a higher barrel temperature (150 °C) with excess benzyl amine (2.5 equiv), the yield of **13** increased to 91%. However, with the strongly electron-withdrawing 4-CF$_3$ substituent, using excess amine (2.5 equiv) and high temperature (150 °C), still gave only 51% yield of **16**. Steric hindrance also affected the reaction, as only fair yield (51%) of **17** could be obtained when hindered (S)-1-phenylethanamine was used. It is
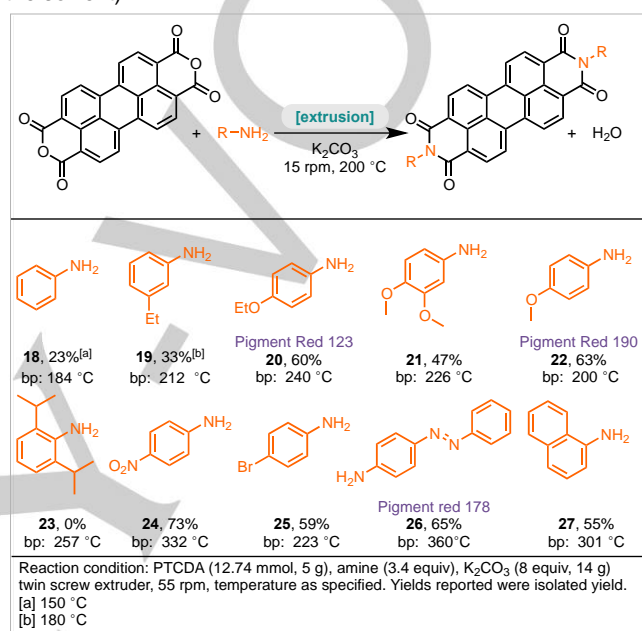
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worth noting that two of the products obtained (**12**, **14**) as shown in Scheme 2 are commercial pigments "Pigment Black 31 and 32". These electronic effects are in line with the expected mechanism (nucleophilic attack by the amine) i.e. the trend here parallels solution-state synthesis.

Encouraged by the successful synthesis of PDIs from aliphatic/benzyl amines, we next investigated the synthesis of PDIs using TSE from the more challenging (less nucleophilic) aniline derivatives. Initially, we passed the premixed PTCDA (12.74 mmol, 5 g) and 4-ethoxyaniline **2** (25.48 mmol, 2 equiv.) through the extruder over 5 min at 55 rpm and 110 or 150 °C. Due to the low solubility of PTCDA and the diimide product in deuterated organic solvent (chloroform-d, acetonitrile-d_3, methanol-d_1, dimethyl sulfoxide-d_6), ^1H NMR spectroscopy could not be used to quantify the conversion. FT-IR analysis showed anhydride modes (1752 cm^{-1} and 1726 cm^{-1}) due to unreacted PCTDA, and no imide modes due to the product (1700 cm^{-1} and 1655 cm^{-1}). To optimize the reaction conditions in a quick and simple way, the beat and heat method was used again. Using this method, similar to the TSE process at 150 °C, almost no diimide product was observed. Higher temperatures (180 °C or 200 °C) were then applied to the mixture, which did lead to some imide formation (Details see electronic supporting information (ESI): Table S2 and Figure S3). However, PTCDA and **2** could not be fully converted to the diimide even after 1.5 hours at 200 °C, which is unsuitable to be developed to a continuous process. In order to increase the reaction rate, a range of solid additives (Zn(OAc)$_2$•2H$_2$O, CaCl$_2$•2H$_2$O, NaHCO$_3$, Na$_2$CO$_3$, K$_2$CO$_3$) were screened in the beat and heat method. These additives could act as Lewis acid, dehydration reagent and/or bases, which could potentially facilitate the condensation reaction.[30] Pleasingly, we found that the addition of inorganic bases such as Na$_2$CO$_3$ and K$_2$CO$_3$ significantly accelerated the consumption of the PTCDA (ESI: Table S3 and Figure S4).

Further consideration was needed before transferring the beat and heat method for these aniline starting materials to TSE. In particular, in contrast to the jar method, TSE is open to air and some evaporation of anilines would therefore be expected at high barrel temperatures, potentially requiring wasteful excesses of anilines to be used. For example, we considered that with aniline (**18**) as starting material (which has the lowest boiling point of the anilines used in Scheme 3, b.p. 184 °C), barrel temperatures no higher than 150 °C should be used. A mixture of PTCDA (12.74 mmol, 5 g), K$_2$CO$_3$ (14 g, 8 equiv.), and 4-ethoxyaniline **2** (43.32 mmol, 3.4 equiv.) was fed manually into the extruder feeding port over 40 min (~ 0.65 g/min) with a relatively slow screw speed of 15 rpm to increase the residence time residence time (15-20 min). The crude reaction mixture was then collected and analyzed by FT-IR which indicated full conversion of PTCDA (no anhydride modes 1752 cm^{-1} and 1726 cm^{-1} were observed), although only 60% isolated yield of **20** was obtained after the work up procedure. The difference between conversion (FT-IR) and isolated yield could be due to the formation of anhydride hydrolysis byproducts such as potassium perylene carboxylates due to the water condensate in the presence of K$_2$CO$_3$. As shown in Scheme 3, different aniline derivatives were used to synthesise various PDIs with isolated yields ranging from 23-73%. In general, yields of PDIs in Scheme 3 were affected by both the nucleophilicity and boiling point (bp) of each aniline starting material. Relatively low

reaction temperatures (150 °C or 180 °C) had to be used to prevent the evaporation of starting materials (aniline and 3-ethyl aniline), which might have led to the poor yields of **18** (23%) and **19** (33%). For aniline reactants bearing various ring substituents such as -OMe, -OEt, -NO$_2$, -Br, and phenyldiazenyl, fair to very good yields of PDIs (**20-22**, **24-27**) could be obtained. These products include three commercial pigments known as "Pigment Red 123, 178 and 190". Potentially due to steric effects, TSE using 2,6-diisopropyl aniline (**23**) gave 0% of the desired product (although curiously this product can be obtained in fair to good yield using conventional solution-based method with melting imidazole as solvent, which we ascribe to the basic character of the solvent).[31]

Reaction condition: PTCDA (12.74 mmol, 5 g), amine (3.4 equiv.), K$_2$CO$_3$ (8 equiv, 14 g) twin screw extruder, 55 rpm, temperature as specified. Yields reported were isolated yield.
[a] 150 °C
[b] 180 °C

Scheme 3. Scope of aniline substituted PDIs synthesis using TSE

With good conditions identified for producing various PDIs, a continuous TSE process was set up with automated reagent feeding, specifically a volumetric solid feeder for solid materials (such as PTCDA, K$_2$CO$_3$, and solid amines/anilines) and a syringe pump for liquid reactants (for liquid amines/anilines) (Figure 1, see also video file in ESI). To demonstrate the potential of using a twin screw extruder for continuous manufacturing PDIs, perylene diimides **12** and **14**, known commercially as Pigment Black 31 (Sigma Aldrich: GBP £111/g) and Pigment Black 32 (Sigma Aldrich: GBP £68/g) were chosen as examples.[32] As shown in Figure 1, PTCDA (Sigma Aldrich: GBP £ 0.99/g)[33] was fed in by the volumetric solid feeder over 30 min (feeding rate = 0.65 g/min) into the first open extruder port and liquid 2-phenylethanamine (Sigma Aldrich: GBP £0.82/mL)[34] or (4-methyoxyphenyl)methanamine (Sigma Aldrich: GBP £1/mL)[35] was fed in to the next open port using a syringe pump (feeding rate = 0.5 mL/min, 2.3~2.4 equiv.). Following extrusion of the mixture at 55 rpm and 110 °C, black crude solid product was collected after 8 min with full conversion of PTCDA (confirmed by FT-IR and PXRD, Figures S1 and S2). Thus, after simple washing with methanol, collecting by filtration and drying in an oven, ~20 g desired Pigment Black 31 and 32 was obtained within 25 min (>99% yield, purity confirmed by IR, PXRD, CHN analysis). Compared to traditional solution conditions for the synthesis of Pigment Black 31 and 32, we avoid the use solvents such as NMP,

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DMF, 1,3-dichlorobenene, or fatty alcohols, additives ($Zn(OAc)_2$/Na_2SO_4/n-butylethanolamine), large amount of amines and relatively long reaction times (40 min - 24 hours) and more wasteful work-up procedures (see ESI: Tables S4 and S5 for further details).[36] The extruder used in this study is a relatively small research instrument (screw diameter 12 mm, 40:1 L/D ratio). However, even at our current feeding rate and under these conditions, a throughput rate of 1428 g/day and 1505 g/day for Pigment Black 31 and 32 could in principle be obtained, respectively, corresponding to a Space Time Yield (STY) of ~30 x 10^3 kg $m^{-3}day^{-1}$ which is 1-2 orders of magnitude greater than for solvent-based batch methods in the literature (see ESI: Tables S4 and S5 for further details). This opens up the possibilities of achieving a much greater production rate of PDIs in kg/h scale with the use of larger scale extrusion equipment, which is widely available.
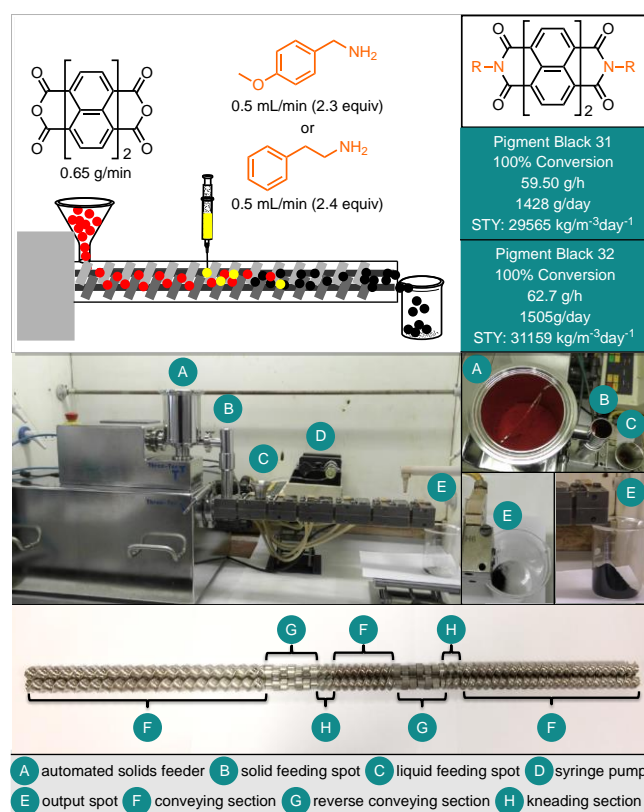

Figure 1. Example of automated continuous TSE process for manufacturing PDI **12** and **14** (Pigment Black 31 and 32)

In conclusion, we have developed a novel method for the synthesis of various naphthalic imides and PDIs, using TSE with water being produced as the only byproduct. Without the need for large excesses of amines/anilines or solvent, three examples of naphthalic imides and 21 examples of PDIs were synthesized with excellent functional group tolerance (including five commercial PDI pigments). In the most favourable cases, full conversion to product (e.g. products **3**, **4**, **5**) was possible, potentially even negating the need for work up. In other cases, a simple work up involving methanol wash, or heating in aqueous K_2CO_3 and wash with water/methanol was needed. Moreover, an automated continuous TSE process for manufacturing PDIs was successfully demonstrated by producing Pigment Black 31 and Pigment Black

32 in quantitative yield on a kilograms/day scale. Overall, this work demonstrates the applicability of TSE to provide scalable synthesis of organic perylene dyes with dramatic reduction in waste compared to conventional methods. Given the applicability of mechanochemical synthesis to other types of dyes (e.g. azo-dyes[37] and BODIPY dyes[38]), there is clear potential to apply this synthetic approach to dyes generally.

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[29] There are two relevant questions around the mechanism of the reaction, specifically whether the reaction occurs in the melt or solid phase, and secondly whether the reactants form co-crystal prior to the bond formation. First, whilst we do not observe any bulk melting in these reactions (as can be expected since the reactant melting points are high (1,8-naphthalic anhydride, 267ºC; PTCDA 350ºC). We currently do not draw any conclusions about solid versus liquid states existing at the actual reaction zones. Also, although some of the amines used are liquids, and it is unlikely that the anhydrides will fully dissolve in them, we cannot rule out that some dissolution occurs. Secondly, co-crystals, formed from anhydrides and anilines, have been reported under neat or liquid assisted grinding conditions, which facilitates subsequent imide formation upon heating. However, in our work PXRD analysis showed

that amorphous solid materials were formed after milling mixtures of **1** with one equiv of 4-ethoxyaniline or 2-phenylethanamine or (4-methoxyphenyl)methanamine in a mixer mill (5 min, 30 Hz), no co-crystal formation was observed before the formation of imides (**3**, **4**, **5**). Also, DSC analysis (30 °C-420 °C) for these reaction mixtures showed no evidence of any co-crystal formation prior to formation of the imides. For cocrystal controlled solid-state synthesis (C³S³) references see: a) M. L. Cheney, G. J. McManus, J. A. Perman, Z. Wang, M. J. Zaworotko, *Crystal Growth & Design* **2007**, *7*, 616–617; b) M. L. Cheney, M. J. Zaworotko, S. Beaton, R. D. Singer, *J. Chem. Educ.* **2008**, *85*, 1649; c) J. A. Perman, K. Dubois, F. Nouar, S. Zoccali, Ł. Wojtas, M. Eddaoudi, R. W. Larsen, M. J. Zaworotko, *Crystal Growth & Design* **2009**, *9*, 5021–5023; d) M. Colaço, J. Dubois, J. Wouters, *CrystEngComm* **2015**, *17*, 2523–2528; e) J. Dubois, M. Colaço, G. Rondelet, J. Wouters, *Crystals* **2016**, *6*, 153; (f) S. Lukin, M. Tireli, I. Lončarić, D. Barišić, P. Šket, D. Vrsaljko, M. di Michiel, J. Plavec, K. Užarević, I. Halasz, *Chem. Commun.* **2018**, *54*, 13216–13219.

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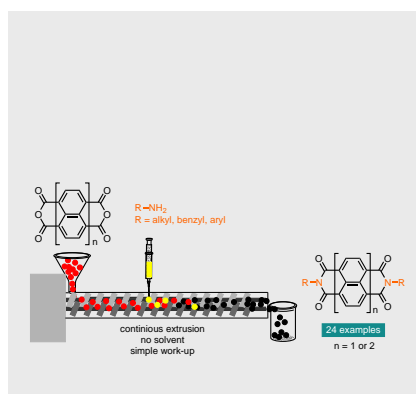
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