ARTICLE

Life cycle assessment of multistep benzoxazoles synthesis: from batch to waste-minimised continuous flow systems

Jose Osorio-Tejada,[a] Francesco Ferlin,[b] Luigi Vaccaro,[b] Volker Hessel[a,c]

In this contribution we have focused on the progress of synthetic methods for the preparation of 2-aryl benzoxazoles as widely interesting materials with increasing relevance in pharmaceutical industry as well as in optical applications. Traditional production of 2-aryl benzoxazoles clearly have some drawbacks related to the use of either strong acids and/or toxic reagents leading to a large production of waste. Importantly, comprehensive analysis of the associated risk in terms of safety, environmental impact and disposal cost is lacking. In this regard, the life cycle assessment (LCA) methodology is herein applied to ultimately evaluate the environmental profile of the available routes to access 2-arylbenzoxazoles. Seven synthetic batch approaches and two continuous-flow (CF) approaches (small and large scale) are closely compared. The superiority of the CF technology is ultimately proven among the analysed environmental impact categories. Main finding is that the oxygen-flow chemistry intensification fortified the sustainability of the green chemistry principles (towards catalyst/solvent) themselves, by ensuring the regeneration of the OMS catalysts, and reducing manganese leaching to minimum by the CPME solvent, which also provided high solvent recyclability. In this way, it adds circularity in the sense of its 10R framework (e.g. R standing for recycle, repair, rethink, and refuse). As a result, for example, our flow approach reduces carbon emissions by 85% in comparison to our batch approach; the latter exhibiting lower environmental impact than the six batch approaches from literature. In addition, our flow chemistry process has lower energy consumption and solvent load, which can share up to 88% of the environmental impacts.

1. Introduction

Most of the common green chemistry metrics such as E-factor, Reaction Mass Efficiency (RME), Atom Economy (AE),[1-4] are useful tool to focus and measure a specific parameter of a process in order to optimize its efficiency minimizing the environmental impact associated. Slightly wider metrics such as EcoScale[5] or environmental quotient (EQ)[6] can evaluate the environmental profiles of processes or materials but limiting their information on their potential environmental burden and toxicity during and after the usage. In the real world, for a precise picture of the actual environmental impact, it is always more stringent the need for a comprehensive tool able to analyse and quantify the environmental impacts of materials and energy usage, from the initial access to feedstock to final disposal of waste. This is true relevant productions of in bulk or fine chemicals.[7-10]

Life Cycle Assessment (LCA) methodology[11] fulfils these requirements and evaluates environmental impacts of water, air, and soils emissions in different areas of protection, such as ecosystems, human health, and resources scarcity. In the search for solutions to optimise the sustainability of a chemical production process a careful comprehensive assessment is needed to individuate most promising routes.

Most promising is the use of innovative enabling technologies that have proven to be effective in opening new production routes but offering effective energetic and practical solutions as it is the very case of flow chemistry.[12-14] This technology has shown to be able to open new scenarios in terms of control of reactivity or downstream process manipulation. Indeed, by performing the reactions in flow, advantages such as the increase in energy and mass transfer or the reduction or elimination of wasteful purification could be avoided, rendering flow procedures generally appealing. Moreover, flow chemistry can be a bridge between academic experiments and industrial processes because it generally provides safe, efficient, reproducible, and scalable chemical reaction methods[15].

Anyway, it is still very rare to find reports on the actual assessment of the sustainability advantages achieved by using a flow technology compared to classic batch approach. In fact, very few are the cases where chemists quantify the advance achieved in flow by calculating appropriate mass green metrics[16-21] and it is very difficult to find more complete examples where chemists and/or engineers quantify the efficiency of a production strategy in flow using LCA[22-25] and circular economy assessments.[26-29]

[a.] Department of Chemical Engineering, School of Engineering, University of Warwick, Coventry, UK
[b.] Laboratory of Green S.O.C. – Dipartimento di Chimica, biologia e Biotecnologie, Università degli Studi di Perugia, Via Elce di Sotto 8, 06123 – Perugia, Italy. E-mail: luigi.vaccaro@unipg.it; http://greensoc.chm.unipg.it/ .
[c.] School of Chemical Engineering and Advanced Materials, University of Adelaide, Adelaide, Australia
† These authors contributed equally

To evaluate the actual advance achieved in flow and therefore its possible implementation in real cases this step forward is needed and LCA and circular economy assessments are needed. While green chemistry means to look at the efficiency of the present: the newly defined flow process, LCA means to look at the present and at the past of the process evaluating the actual existing flow process but also its "ecological backpack". Finally, circularity means also to additionally look at the future of the flow process including the possible market use and recovering and recycling of the materials.

Therefore, it is important to carry proper LCA assessments on processes realized in flow and possibly highlight the limits or the opportunities available when moving from batch to flow in order to make the final step including circularity in the process. For these reasons we report the present study on the detailed life cycle assessment of the available procedures for the synthesis of 2-aryl benzoxazoles comparing the batch and the flow approaches aiming at highlighting the importance of each single parameter and component of the processes focusing on the pros and cons of the different solutions.
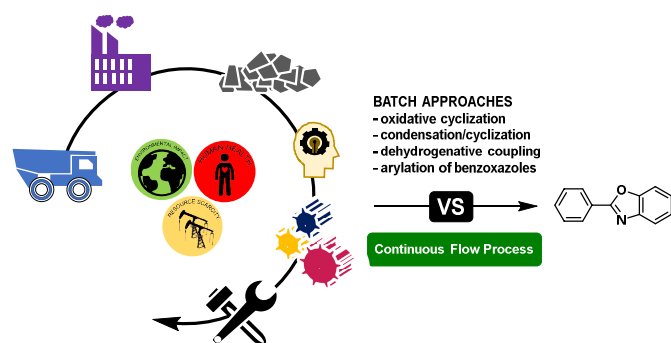

Scheme 1. Features of the present work.

Benzoxazoles are molecular entities of general interest given the increasingly use of this class of scaffolds in the pharmaceutical industry.[30,31] Especially, 2-arylbenzoxazoles derivatives have shown potential antitumor, antimicrobial, and inhibitory activity,[32-38] as well as noteworthy properties for optical applications.[39-44] Traditional methods for obtaining 2-substituded benzoxazoles, such as the condensation of 2-aminophenol and carboxylic acid[45] or the oxidative cyclization of phenolic Schiff bases,[46] have drawbacks related to the use of strong acids, toxic reagents, harsh reaction conditions, and the generation of dangerous peroxides and salt waste.[47-51]

In the last decade, many methods have been proposed for the optimization of 2-arylbenzoxazoles synthesis featuring improvements in terms of reaction time, waste generation, milder temperature or pressure, avoidance of dangerous compounds,[52-57] but none of them have thus far demonstrated the reduction of the environmental impacts in a comprehensive and analytical manner.

Recent works have used classic green mass-balance indicators to demonstrate the efficiency of the process in the usage of resources such as atom and carbon economy,[58] yield,[59] reaction and effective mass efficiency,[60] the BioLogicTool plots,[61] or the environmental factor (E-factor)[62] where, e.g a low E-factor indicates a low waste generation.

However, when the reduction of wastes implies a change in the production method (temperature, pressure, time, etc.) or materials (catalysts, bases, additives, and solvents), environmental impacts could raise or emerge due to the increase in the energy usage in the process or during the extraction, production, and distribution of the new materials. For instance, the traditional route by cyclization of phenolic Schiff bases uses manganese triacetate, a moderately toxic reagent in a batch process with toluene at 110 °C for 1 hour.[46] This process was optimized by Khalafi-Nezhad and Panahi in 2014[54] through replacing the toxic reagent with a base of triethylenediamine, a relatively benign compound, but increasing the residence time to 24 hours, which requires extra energy and, hence, potentially higher negative environmental impacts.

Recently, we have proposed a novel safe and fast waste-minimized reaction protocol for 2-aryl-benzoxazoles synthesis promoted by heterogeneous mixed valence manganese octahedral molecular sieves (OMS) and cyclopentyl methyl ether (CPME), [63] (Scheme 2). The OMS catalyst and its molecular structure improves the reactivity and selectivity of the system, while the use of CPME as reaction medium allowed a minimal loss of 0.002% of manganese. This protocol, applied in a continuous flow (CF) system using oxygen flow, ensured a complete regeneration of the catalyst resulting in high durability and reusability with excellent product yields and good hourly productivity. In terms of environmental impacts, besides the benefits of the use of CPME[64] such as low safety hazard, stability in either basic or acidic conditions, and low tendency to produce peroxide.[65]
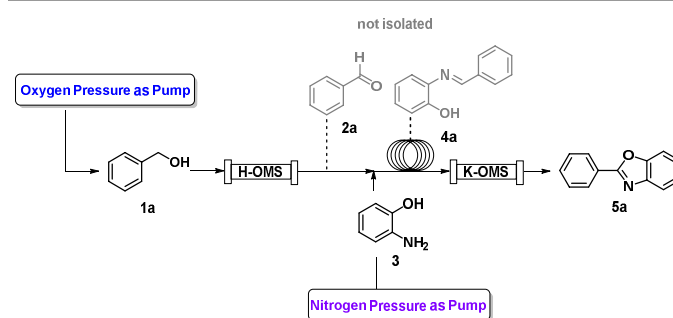
Scheme 2. Description of the multistep continuous flow procedure.

ARTICLE

Table 1. Benchmarked approaches for 2-aryl benzoxazoles synthesis in this study

Approach	Reference	Approach characteristics		Remarks	Green Chemistry Principles (ref. 65)	Circularity Principles (10R framework) (ref. 66)
		Pathway	Process Time/Temp			
Ours	Ferlin et al. (2019)[63]	**Flow** via OMS manganese systems and CPME medium and O_2 and N_2 gas	78 min/106 °C	Safe, fast, and waste-minimized reaction protocol with direct catalyst regeneration	1, 4 ,5, 6, 9, 12	Recycling R8, Repair R4, Rethink R1, Reduce R2, Redesign
	Ferlin et al. (2019)[63]	**Flow** via OMS manganese systems and CPME medium and O_2 and N_2 gas	24 h/106 °C	Safe, fast, and waste-minimized reaction protocol with direct catalyst regeneration, large scale production	1, 4 ,5, 6, 9, 12	Recycling R8, Repair R4, Rethink R1, Reduce R2, Redesign
	Ferlin et al. (2019)[63]	Batch via OMS manganese systems in CPME medium	70 min/106 °C	Safe, fast, and waste-minimized reaction protocol	1, 4, 5, 6, 9	Recycling R8, Rethink R1
Optimised	Chang et al. (2002)[52]	Batch via DDQ in methanol and DCM medium	12 h/45 °C	Mild and efficient protocol	3	Reduce R2
	Nguyen et al. (2018)[53]	Batch via phosphonium acidic ionic liquid in solvent-free medium	30 min/100 °C	Fast solvent-free reaction	5	Refuse R0
	Khalafi and Panahi (2014)[54]	Batch via Ru-based catalyst with DABCO as base in toluene medium	24 h/110 °C	Chemical diversity: applicability to a wide substrates scope protocol	-	Rethink R1
Conventional	Saha et al. (2009 [55]	Batch via CuO nanoparticles in DMSO and potassium carbonate medium	16 h/110 °C	Chemical diversity: applicability to a wide substrates scope protocol. Efficient method	-	Rethink R1
	Praveen et al. (2008)[56]	Batch via silica supported pyridinium chlorochromate (PCC) in dichloromethane	30 min/Room temperature	Mild process	3	Reduce R2
	Wang et al. (2013)[57]	Batch via acyl chloride with chlorobenzene and water in potassium carbonate medium	12 h/140 °C	New reaction path: alternative arylation method	8	Rethink R1

Its easy and almost complete recovery by distillation implies a very low additional solvent input in each synthesis process, and also its relatively low enthalpy of vaporization might imply low energy requirements for its recovery. Moreover, the improved reaction yield promoted by the OMS manganese catalyst would reduce the emissions related to materials waste. Also, the use of the friendly and abundant O_2 and N_2 in the CF protocol could reduce the energy requirements for distillation and regeneration the catalysts after the synthesis process.

However, the above benefits of the strategies proposed in the novel protocol must be demonstrated by quantitative comprehensive and trustworthy indicators as the life cycle assessment (LCA) methodology.

To date, none of the different routes for benzoxazoles synthesis have been evaluated through an LCA study. Therefore, the main aim of this study is to evaluate the extent in which the strategies proposed for this waste-minimized reaction protocol for 2-aryl benzoxazoles synthesis, promoted by OMS manganese systems and CPME (Scheme 2), reduced the global warming potential and the overall environmental impact of this product through the life cycle perspective. Additionally, the LCA results for this protocol are benchmarked against other optimised and conventional batch synthesis processes, summarized in Table 1. The Chang et al. (2002)[52], Nguyen et al. (2018)[53], and Khalafi-Nezhad and Panahi (2014)[54] approaches were selected due to the similarity with our process because they also use the aminophenol (3) as starting reagent with benzaldehyde (2a).

These processes can be referred as "optimised" as they feature several advances in terms of sustainability such as the use of a recoverable catalyst or ligand, or the adoption solvent-free conditions. On the other hand, the Saha et al. (2009),[55] Praveen et al. (2008)[56] and Wang et al. (2013)[57] approaches were selected as they can be considered representative of many common strategies as the material used are very frequent in these transformations.

The analysis of each proposed approach in literature relies on the development of new chemistry ideas by providing an attributive LCA pointing at hot spots, which can be useful to create a combination of concrete green process chemistry proposals (e.g., unusual process temperature, new catalysts, recycling concepts, green reactants, etc.) to be introduced in future scalable experiments for the synthesis of any compound. In the remainder of this article, we describe the LCA study methods and its application to our approach for 2-aryl benzoxazoles synthesis for the CF and batch experiments.[63]. We also describe in detail the selected three similar optimised protocols,[52-54] and the other three different synthesis routes.[55-57] The results of the critical comparative assessment and the scenario analyses are presented and also discussed.

2. Methods

This study followed the four phases described in the LCA methodology.[12] Firstly, the goal, scope and typology of the study are defined. Then, the procedures for the development of material and energy flows inventories are detailed for each of the synthesis processes, as well as the followed methods and assumptions. Subsequently, the impact assessment method and the interpretation of results are described.

2.1 Goal and scope definition

The goal of this LCA study was to assess the environmental impacts of the different routes for the synthesis of 2-aryl benzoxazoles proposed in literature from conventional batch processes to waste-minimized CF systems. In this study a total

of nine different synthetic approaches were analysed. The assessed synthesis proposals were set only to produce 2-aryl benzoxazoles, without by-products. Hence, a cut-off approach system model based on mass allocation was defined. The functional unit was defined as 1 g of the final product. The systems boundaries were defined based on a cradle-to-gate approach, considering the emissions and resources usage for the extraction, production and transportation of all materials and energy and the emissions to water, air, and soils from the process itself.

The LCA studies did not include the manufacturing of the manual or computer support tools, machinery, or equipment such as reactors, heat exchangers, pumps, cylinders, etc. Regarding the data quality, in order to maintain consistency and low uncertainty, all the process flows were referred from European datasets for general industry practices. The system functions definitions for each evaluated process are explained below.
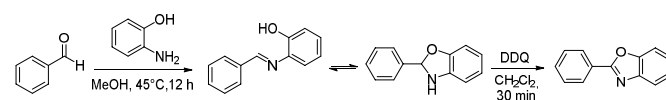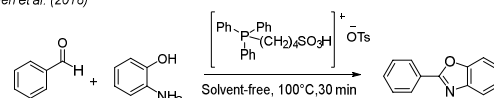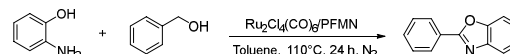

Scheme 3. Optimized batch routes for 2-arylbenzoxazoles.

The first analysed pathways were the protocols based on the use of heterogeneous manganese systems with CPME and oxygen (Depicted in scheme 2).[63] These processes from benzyl alcohol and aminophenol were firstly tested in batch using CPME as reaction medium and manganese OMS as catalysts with a residence time of 70 min at 106 °C, obtaining a 94% yield. From this optimized approach it was proposed a multistep CF process using compressed nitrogen and oxygen as a terminal oxidant, which besides ensures a complete regeneration of the catalyst, allows to maintain a continuous production flow rate up to 2.3 g per hour with a 98% yield. For these batch, CF small scale, and CF multigram scale experiments, the obtained product quantities (and residence times) were 0.037 g (70 min), 0.708 g (78 min), and 53.5 g (24 h), with E-factors of 42, 6.4, and 1.7, respectively. These experiments reached high yields, even without using the wasteful silica-gel column purification step required for the other considered protocols.

Subsequently, the following approaches were selected for the LCA comparison as they can be considered representative of many common strategies as the material used (catalysts, bases, additives, and solvents) are very frequent in these transformations.

The first approach, detailed in Saha et al. (2009),[55] is a general and efficient method from haloanilide based on a frequently used solvent dimethyl sulfoxide (DMSO), using a common Cu-based catalyst (CuO nanoparticles) in potassium carbonate for 16 h at 110 °C, obtaining a 95 % yield, (Scheme 4, a). The catalyst can be recovered by centrifugation, washing, and drying under vacuum, without significantly losing its properties.

The second approach, by Praveen et al. (2008),[56] is a mild process based on a heterogeneous catalysed oxidative cyclization of a preformed imine (Schiff's base from o-aminophenol and salicylaldehyde refluxed in methanol for 4-5 h) and the use of a suspension of silica supported pyridinium chlorochromate (PCC) in dichloromethane for 30 min at room temperature, obtaining a 91% yield, (Scheme 4, b).

The third strategy, Wang et al. (2013),[57] is a an alternative arylation method of preformed benzoxazoles using acyl chloride as the coupling partner and chlorobenzene and water in potassium carbonate for 12 h at 140 °C, obtaining an 82% yield (Scheme 4, c)
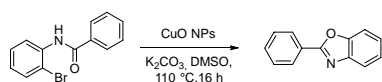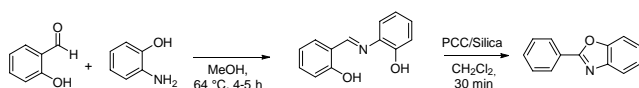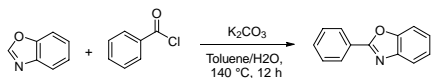

Scheme 4. Conventional routes for 2-arylbenzoxazoles.

2.2 Inventory analysis

The elaboration of inventories for each of the nine synthesis processes is a time-consuming task since due to the lack of data in most experimental procedures. Indeed, generally, the energy utilized for heating, cooling, or stirring procedures are not measured or not documented in the publications. In addition, some experiments do not quantify the water or solvents used for washing the products, neither the quantity of the outputs of these unreacted compounds. For those reasons, in order to avoid assumptions, we estimated the quantity of energy and materials that were not documented for each assessed process. Another difficulty in the development of the inventories for each process was the availability of some specific compounds in life cycle inventories (LCI) databases. In the present study we used the most recent and complete database Ecoinvent v3.7.1, in which, a total of 12 compounds were not available in the database, being necessary to create new inventories to be included in the processes modelling. A simple solution can be the data extrapolation from similar available compounds or the use of generic inventories such as "market for chemical,

organic", which are not generally recommended[68] since average impacts might be distant from its real environmental profile. Another solution for this lack of information can be the use of retrosynthetic analysis to find simpler precursor compounds that might be available in the database, and assuming a yield of 95% for the quantities estimation via stoichiometric equations.[69] However, through the retrosynthetic analysis the quantity of catalysts, reagents, solvents, and the energy used, cannot be estimated, being necessary to make assumptions, which increases the uncertainty. Therefore, for the creation of new inventories, we used a process-specific method by performing a deep literature review to find detailed descriptions to produce the target compounds, selecting the most basic or conventional synthesis process when different approaches were found for the same compound.

For all unavailable compounds which had to be specific modelled, general assumptions were made regarding facilities and transportation, considering an organic chemicals plant of 50,000 t production per year with a 50 years lifespan and transport distances of 100 km by lorry>16t and 600 km by train.[69,70] The process energy of 2 MJ in the form of steam and 0.333 kWh of electricity per kg of compound was assumed.[68,71] The energy for lighting and heating offices was excluded in this study. For the experiments and precursors inventories a solvent recovery of 71% was considered,[72] except for CPME in the OMS manganese systems route in which a 98% recovery rate was obtained. The solvents usage in the purification step by column chromatography of 1 mL per gram of product was assumed. When the solvents names were not specified, a mix of 0.5 mL of petroleum ether and 0.5 mL of ethyl acetate was used.

The energy needed for heating and stirring the mixtures was directly measured with an electric monitor in our experiments for the 2-aryl benzoxazoles synthesis via heterogeneous manganese systems. In addition, the necessary energy was estimated thermodynamically, considering also heat losses by radiation, from which we determined an electrical efficiency of 59.4% for the heating plate. Therefore, the energy for the other synthesis processes was thermodynamically estimated and adjusted with this efficiency rate, assuming that in all the experiments a similar heating device was used. These energy expenses were estimated for the complete reported procedures for each experiment, including all required workup and materials recovery. Regarding the energy for stirring, our measures found that the power consumption of the stirring motor only depends on the defined speed, that is, the consumption is the same independently of the quantity or the density of the mixture. In this sense, due to each experiment uses different quantities, to establish a fair energy allocation, a default additional power of 3.2W (measured at 700 rpm) was assumed for 10 g of mixture and, consequently, extrapolated to each experiment.

In the inventories were also quantified the emissions to air during the synthesis processes (0.2% volatile input materials[69] and air and water (river) emissions after the wastewater treatment; no emissions to the soil were counted since no agricultural destination of the digested sludge was considered. In this wastewater treatment, the organic compounds were

65.8% retained in the sludge, 24.5% oxidized and emitted to air basically in form of CO_2, and the remaining 9.7% released to river.[73] Nitrogen compounds during the sludge digestion are mostly released to air as N_2, while NO_2, NH_3, and N_2O emissions are negligible, thus not inventoried in this study.[74] Transfer coefficients to sludge and effluent of inorganic compounds were based on elimination rates for each specific element.[73,75,76] The elaborated inventories for the nine compared synthesis processes for 2-arylbenzoxazoles and the twelve unavailable precursor compounds (CPME, K-OMS, H-OMS, dichlorodicyanobenzoquinone (DDQ), phosphonium acidic ionic liquid, triethylenediamine (DABCO), ruthenium(I) carbonyl complex ($Ru_2Cl_4(CO)_6$, N-(2-bromophenyl)benzamide, copper oxide (CuO) nanoparticles, imine Schiff's base, silica supported pyridine-chlorochromate (PCC), and benzo[d]oxazole) are detailed in the electronic supplementary Information ESI1.

2.3 Impact assessment and interpretation

The impacts assessment was performed using the software SimaPro 9.2 and the method ReCiPe 2016.[77] Among the included impact categories in ReCiPe, ten relevant impact categories in chemicals production were considered:[78,79] global warming, ozone formation (on human health), ozone formation (on terrestrial ecosystems), terrestrial acidification, freshwater eutrophication, terrestrial ecotoxicity, freshwater ecotoxicity, human carcinogenic toxicity, human non-carcinogenic toxicity, and fossil resource scarcity. Midpoint impact categories and endpoint damage areas (human health, ecosystems, and resources) under the hierarchic perspective (100 years) were analysed. Long-term emissions, which affect scenarios beyond 100 years, were excluded due to their high uncertainties[80-83] and their relation to heavy metals toxicity, therefore not very relevant in organic chemicals processing.[84] Among the impact categories, special attention to global warming, ozone formation and freshwater ecotoxicity was given because they are greatly affected by emissions to air and water caused by material waste during the synthesis processes.

The results for the CF small scale protocol are presented and analysed in midpoints and compared to results from the batch experiment, which were also performed in small scales. Subsequently, the results are weighted and normalized in endpoint damage areas to compare our approach against the others by a single indicator as benchmark of the global environmental impact. The endpoints or damage assessment refer to the potential impacts of each impact category in protection areas such as human health, ecosystems quality and fossil resources scarcity. In this process, midpoint characterization results are converted to intermediate units to be weighted and normalized to represent, in micropoints (μPts), the relative impact of the results according to their severity in a global context. In this endpoints comparison was also included the CF multigram experiment to see how the higher materials efficiency impacts the LCA results.

Given that the assumed rate for solvents recovery and power for stirring mixtures could generate have high uncertainty, the extent in which these assumptions affect the results is assessed through sensitivity analyses.

Results and discussion

The contributions of each material and energy input for the environmental impact categories of our CF small scale approach to produce one gram of 2-aryl benzoxazoles are depicted in Figure 1. The contributions of K & H-OMS catalysts are not showed in the charts because their contributions in all impact categories were insignificant. The shares of the different inputs in all impact categories were very diverse. The impacts of the process itself (in light blue) are predominant in global warming, due to the CO_2 emitted by the oxidation of solvent wastes in the wastewater treatment process; in the ozone formation category mainly due to the volatile emissions of CPME; and freshwater ecotoxicity due to small fraction of wastes released to rivers which are not retained in the wastewater process. The energy spent for solvents recovery (in green) and heating (in dark blue) have relevant contributions, especially in the categories of terrestrial acidification, freshwater eutrophication, and human toxicity, where both inputs account for around the half of the impact.

The production of most of materials utilized in the process had relevant contributions, where o-aminophenol (in yellow) had the highest impacts in most of the impact categories, except for the categories of freshwater eutrophication and fossil resources scarcity in which the ethanol production has higher impacts. The O_2 and N_2 released into air do not cause negative impacts, but their production and transportation do. However, the contributions of O_2 and N_2 were very low, i.e., 0.341% and 0.093%, respectively, of the total 19.76 g CO_2 eq emitted per functional unit. Besides their low impacts, the use of these friendly gases in the CF protocol allowed the automatic regeneration of the catalyst, unlike the batch process, where the catalysts must be separated from the product and solvents and be placed in a Schlenk pressure tube and heated at 100 °C during 1 h to regenerate them.

For the above reasons, in order to analyse the extent in which the CF protocol allows to reduce the environmental impact, the totals of Figure 2 were normalized to 1.0 and compared to the batch experiment following the same OMS based route in Figure 2.

From Figure 2 we can affirm that the strategy of introducing a CF process using O_2 and N_2 can reduce carbon emission by 85%, and, in general, obtain environmental impacts reductions between 76% (e.g., ozone formation, TE) and 89% (e.g., freshwater eutrophication). As expected, the energy required to recover the catalysts (in light purple) had very relevant contributions in most of the impact categories for the batch approach. This energy consumption, together with the energy spent for solvents recovery and for heating (and stirring), represents most of the impacts, except for the category of freshwater ecotoxicity where energy shares the 38.8% of the impact. In this category, as well as in global warming, the impact of the batch process itself has relevant contributions mainly due

to the fraction of unreacted benzyl alcohol that is released to rivers and the CO_2 emitted for the oxidation of ethanol wastes.
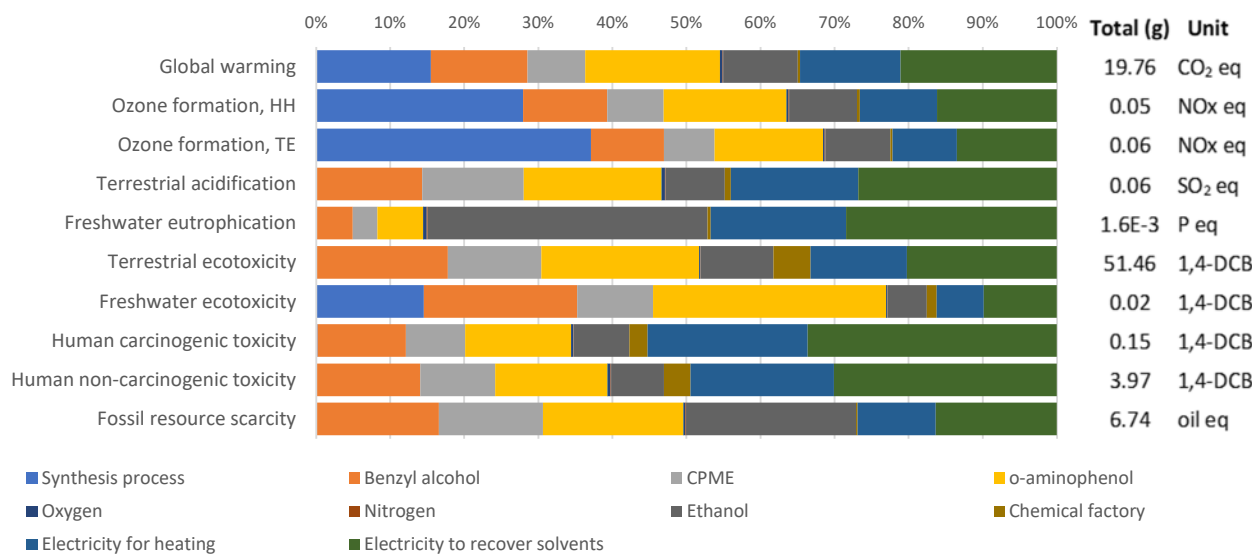
Figure 1. ReCiPe midpoints characterization shares – 1 g of 2-aryl benzoxazoles via CF small scale OMS system
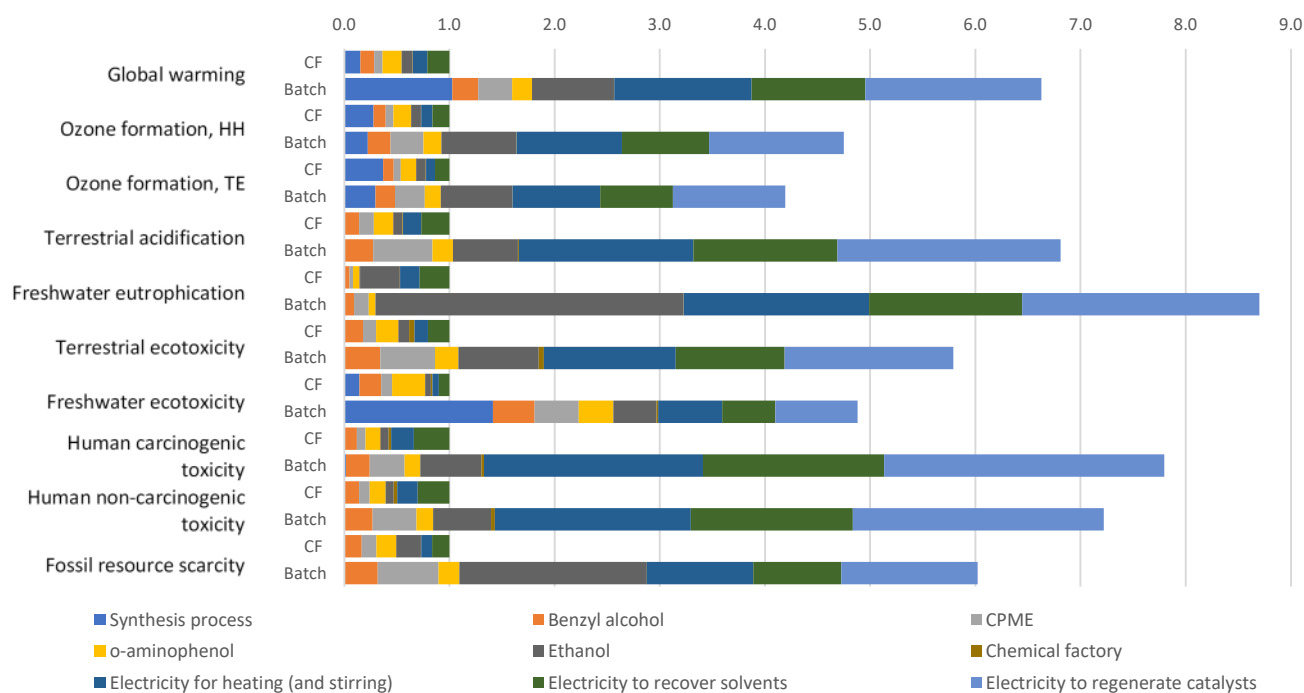
Figure 2. ReCiPe midpoints characterization – 1 g of 2-aryl benzoxazoles via CF and batch OMS systems

In general, the high impacts of the batch process due to the energy consumption in the categories related to toxicity issues are associated to copper used in the electricity distribution network. Despite both processes are performed at the same temperature, the energy inputs for heating and recover solvents are higher in the batch approach because in this process more quantities of solvents are used per functional unit than in the CF process.

In both approaches the high recovery rate of 98% for the CPME made the contribution of its production and wastes very low in the LCA of OMS manganese systems route. Though, this route requires higher process temperature (106 °C) than other mild

reaction approaches, therefore it is possible that other protocol be more environmentally friendly than the proposed method. In this sense, to perform a simple comparison of the overall environmental impacts, the nine approaches are assessed with the ReCiPe endpoint method throughout a weighted aggregation in a single score.

Firstly, the impact categories contribution to damage areas for the CF small scale process are presented in Figure 3, where 83%

of the total 315.86 µPts are final impacts on human health. The global warming impact category contributes to 93% and 71% of the total damage on human health and ecosystems, respectively. This high contribution is because global warming greatly affects the availability of water for drinking and food production, causing damage to human health and living species.

.
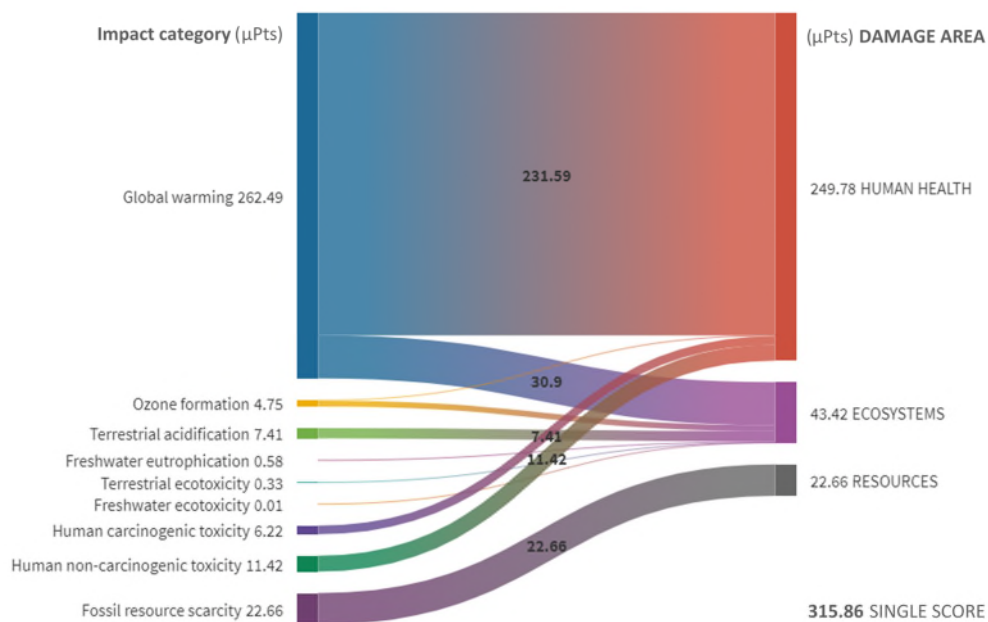
Figure 3. Midpoints to endpoints- single score for the CF small-scale OMS approach

The global warming impact category was also the main contributor to the single scores in the other evaluated approaches in this study. Therefore, the endpoints analysis basically represents the benchmark of the approaches on the global warming impacts. In Figure 4, the previous two processes, including the results for a CF multigram scale, are compared against other six batch approaches proposed in literature. To reduce the complexity of the chart, inputs with

contributions lower than 0.5% of the total single score were not included, such as the chemical factory, solvents used in column chromatography, and catalysts in most of the approaches. Solvents used in the reaction or for washing the product were not grouped since in some approaches they had high contributions, being relevant the identification of the specific solvent name.
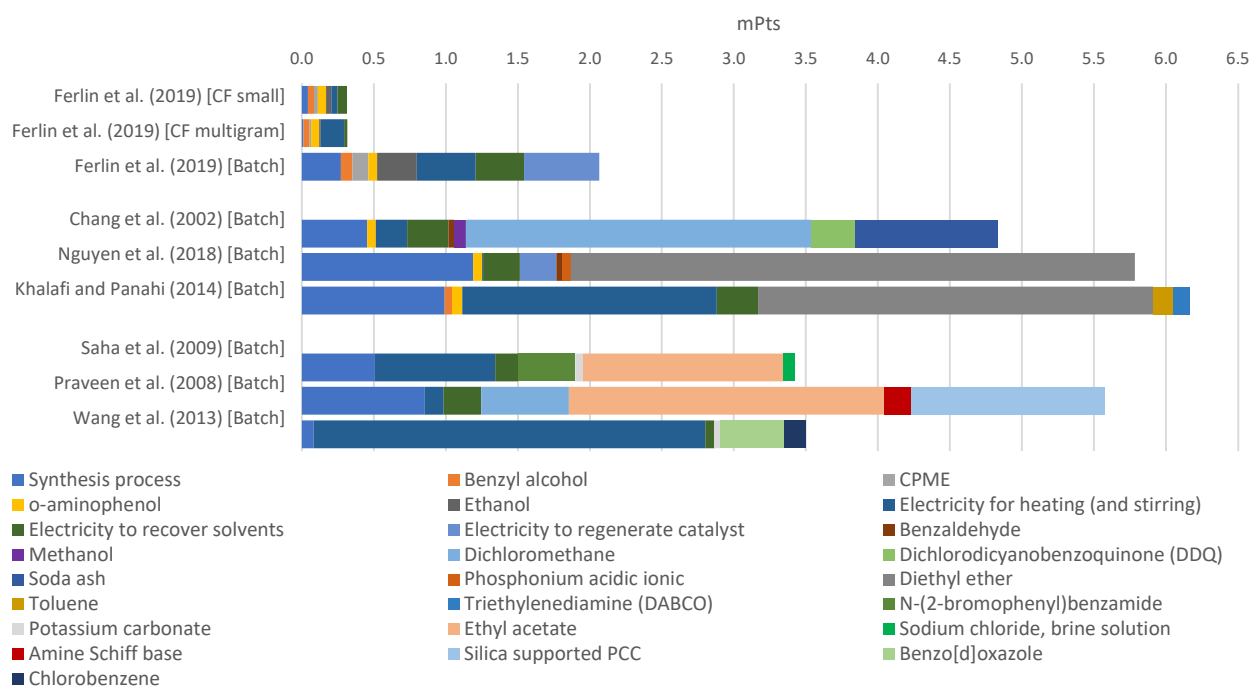
Figure 4. Endpoints- single score – 1 g of 2-aryl benzoxazoles via different routes

Despite the better E-factor of the CF multigram scale experiment, this experiment obtained the same environmental score than small scale one. This was because the multigram scale experiment was performed in a long 24 h run, therefore, the lower impacts generated by the higher material usage efficiency was compensated by the higher energy usage for heating the system during more time. In this sense, the contribution of the energy for heating increased from 13.4% to 51.7%. However, this high share of the heating input in this approach gives a broad opportunity to reduce its environmental impact through the use of clean energy sources to heat the system, since in this case the energy used came from a European electricity mix which generates significant negative impacts due to its distribution networks and the use of 38% from fossil energy sources.[85]

Among the batch approaches, the one using OMS manganese system obtained the best environmental profile. Similarly to the CF multigram approach, the majority of the impacts in this approach are energy related, being possible to reduce even more its impacts. Yet, in the scenario where zero impacts of energy inputs were assumed, the protocol proposed by Wang et al[53] via acyl chloride would be the best route among the batch approaches since in this case the energy input shares 80% of the impacts due to the required 12 h of heating and stirring for the reaction at 140 °C.

The approach using phosphonium liquid[53] requires high temperature, but the energy consumption share was very low because it is a fast reaction process. This shows the relevance of time reaction in the energy consumption where also stirring had relevant impacts such as the 22% share of the total energy related impacts in the Wang et al., (2013) approach.

The fast and mild approaches where energy contribution was very low also have opportunity for further optimizations since

the high impacts of solvents used for the reactions and for washing the final products. This is evident in the Nguyen[53] et al approach using phosphonium liquid where 88% of the impacts are related to the high quantity of diethyl ether used to wash the product and its related emissions due to its corresponding wastes. Similarly, the mild approaches via DDQ[52] and via PCC[56] have very low impacts related to energy consumption, but they have high impacts because the use of solvents, such as dichloromethane (49.5% share in DDQ approach) and ethyl acetate (39% share PCC approach).

According to the previous analyses, among the nine benchmarked approaches, the experiment with the worst environmental profile, performed by Khalafi & Panahi[54] (2014) using Ru-catalyst, would get significant impacts reduction if clean energy and solvents optimization is applied. However, in this experiment, as well as in the other approaches affected by the solvents usage and their process wastes,[52,55-57] assumptions of lower solvent quantities usage cannot be guessed because it depends of each experiment. Yet, these high solvent usage impacts could be reduced up to 66% if a higher recovery rate were assumed, such as a 90%. That is, the solvent wastes would be reduced from 0.29 to 0.10 kg/kg. Also, this reduction in solvent waste would automatically decrease the emissions of the synthesis processes since a lower quantity of organic compounds would end in the wastewater treatment processes. Additionally, it is important to note that further optimization in the energy quantity can be obtained by a modification of the assumption made for the stirring input. The stirring motor consumption was assumed 3.2 W for a default quantity of 10 g of mixture and extrapolated to each quantity. Otherwise, if considering the same stirring power for 14.1 g (in Praveen et al., (2008)), and for 0.5 g (in Wang et al., (2013)), the energy required per gram of product in the last experiment would be

unfairly overestimated. However, despite this assumption allowed a fair allocation of this input to the functional unit, the contribution of this input in each approach could change if the default stirred quantity or the assumed speed change.

In accordance with the above, a scenario is proposed with a combination of input optimizations that would benefit all the approaches to different degrees through a sensitivity analysis. In this sense, the recovery rate of solvent was improved from 71% to 90%. In this regard, to balance the experiments

conditions, the 98% recovery rate for CPME in the OMS manganese systems was reduced to 90%, but at the same time the assumed recovery rate for the ethanol used in this route was improved. Regarding the energy for stirring, this input was optimized by assuming that the 3.2W was consumed for stirring 40 g instead of 10 g of mixture. In addition, the energy from grid electricity was replaced for solar photovoltaic electricity. The results for this scenario are presented in Figure 5.
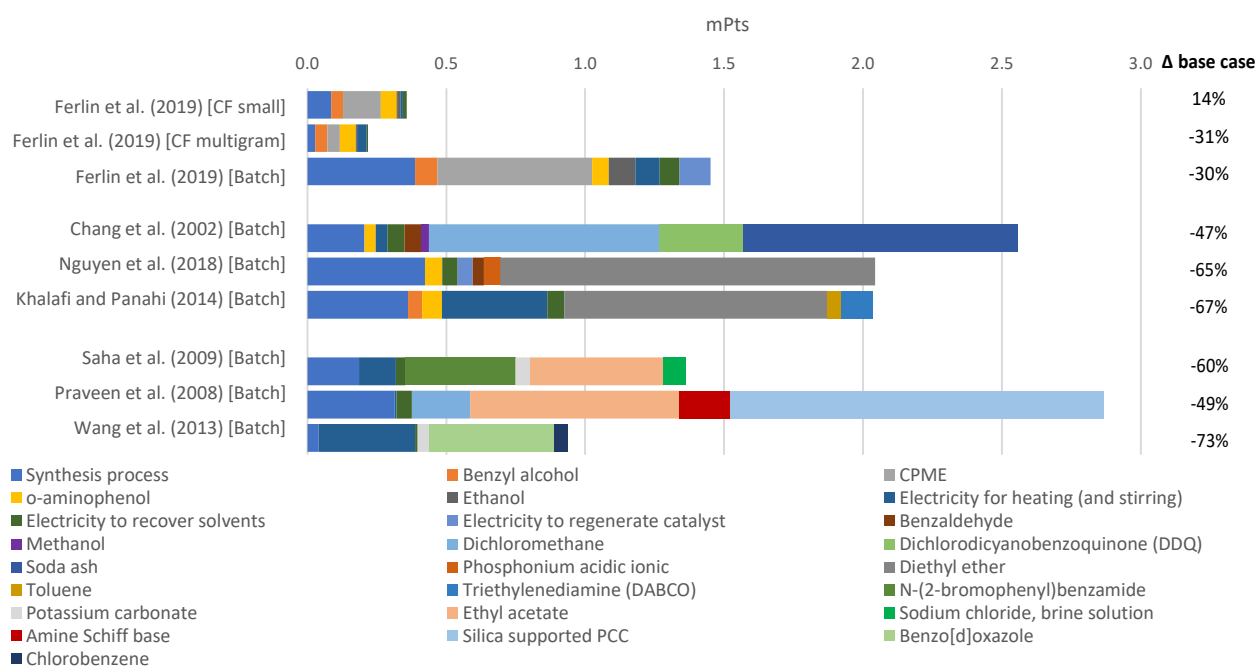

Figure 5. Optimized scenario Endpoints- single score – 1 g of 2-aryl benzoxazoles via different routes.

All the approaches obtained significant improvements in their environmental profiles, except for the CF small scale approach because it was more affected by the reduction of the CPME recovery rate than by the improvement of the ethanol recovery rate, as well as using solar electricity since the energy contribution was not very high. In contrast, given that in the CF multigram scale approach the energy had a relevant contribution, this approach obtained the best environmental impact in this scenario.

Among the batch approaches, the route via acyl chloride obtained the highest reduction rate due to this approach had very high contribution of the energy used for heating and stirring. The other route via Ru-catalyst also had very high reduction rate, but in a lower degree because this approach does not need stirring and the electricity for heating did not have as much contribution as the solvent had. Although, despite the considered electricity from multi-Si solar photovoltaic 570kWp open ground installation is not zero environmental impacts, it has about 78% lower environmental impacts than the European grid electricity (compared on single scores from the endpoints results for the impact categories considered in this study), which make this input the main contributor to the impact reductions.

Regardless of the important impacts reductions caused by the 90% recovery rate, the fraction of new dichloromethane, diethyl ether or ethyl acetate that must be added in each run still has large contributions in the environmental impacts.

Conclusions

This study allowed to perform a hotspot analysis of a comprehensive environmental impact analysis of different routes for the 2-aryl benzoxazoles synthesis through the LCA methodology. It compares an own flow chemistry approach, its batch equivalent, and six different batch approaches reported in literature; being three similar optimised and three others. Our main purpose was to show how innovations in green chemistry and circularity motivation finally pays off into real sustainability benefits. It helps the economic growth of flow chemistry, as industry increasingly needs to support their developments and products by a good environmental profile.

Among the analysed batch approaches, including ours, root in sustainability thinking steered by the 12 Principles of Green Chemistry and related later formulated, more complex green chemistry concepts. Yet, with our batch process we go a step further. First, we prepare to benefit from circularity

approaches, by allowing recycling of the solvent and reuse of the catalyst we employ (as measures of circularity's 10R framework). This is fully exploited in our flow approach and, in addition, we profit of process intensification from the microfluidic processing by virtue of maximising transport processes. The outcomes achieved underline that a holistic and up-to-date approach, both on the chemistry and chemical engineering/process tool side, can massively optimise the environmental friendliness; in our case by a trifold sustainability approach. The 12 Principles of Green Chemistry are meanwhile three decades old and were majorly postulated to enhance safety of chemical plant operation on the background of chemical pollution and even plant operation disasters at that time. Even microreactors and flow chemistry turn to be almost two decades old, and achieve better process outcome when guided by sustainability principles and assessment.

One key green principle employed is the use of an advanced catalyst, based on OMS manganese systems. OMS catalysts have been claimed to improve reactivity and selectivity, thus having high productivity. The use of oxygen flow and its favourable mass transfer by means of the multiphase microfluidics ensure the regeneration of catalysts. Another key green principle employed is the use of an advanced solvent, CPME, proposed as a friendly solvent reaction medium, which exhibits only a minimal metal leaching from catalysts and has high solvent reusability. The results of this optimised synthesis approach were benchmarked against other three recently optimised approaches and three conventional routes presented in literature. These different approaches have been proposed basically in order to replace the use of strong acids and toxic reagents and to reduce waste with the use of recyclable materials. However, our life-cycle results show that the benefits of each optimisation is undermined by high environmental impacts due to the production of the new materials or the higher energy usage for additional heating and stirring requirements. The life-cycle impacts assessment also shows that inefficient material usage (by low yield) causes a secondary negative contribution to the environment, besides producing waste. The waste additionally increases the global warming, ozone formation and freshwater ecotoxicity due to the emissions to air and water after the synthesis processes. Besides the recovery rate, the quantity and type of solvents used are relevant: altogether this sums up to 88% of the environmental impact in the process based on a phosphonium acidic ionic liquid and using diethyl ether to separate the product.

The flow chemistry approach generated an average of 20 g CO_2 eq per gram of 2-aryl benzoxazole, which represents an 85% emissions reduction in comparison to the batch equivalent approach. This is caused by a common advantage of continuous flow approaches to provide higher yield than the batch ones. A specific flow advantage is the use of the environmentally friendly O_2 and N_2 flows, which reduce the energy consumption to heat the mixtures and to regenerate the catalyst. These features are even evident for the equivalent batch approach, using the same OMS manganese systems and CPME solvent. In a scenario analysis it is shown that even if the solvent

disadvantage is taken away from the other six approaches (by assuming a higher solvent recovery rate), the high energy related impacts still cause an overall inferior environmental profile. Only when assuming using renewable energy and 90% solvent recovery rate, one batch approach was finally much better than the others. Yet, in this scenario, the scaled-up flow approach obtained the best results given the ease solvent load optimisation per unit of reagents in this multigram experiment. As an outlook, main future promise lies in the reduction of the solvent quantity and replacement of the current solvents dichloromethane, diethyl ether, and ethyl acetate with greener solvent types.

Author contributions

J. Osorio-Tejada: Writing - Original Draft, Investigation, Conceptualization, Methodology. **F. Ferlin:** Visualization, Investigation. **L. Vaccaro:** Writing - Review & Editing. **V. Hessel:** Writing- Reviewing and Editing, Supervision.

Conflict of interest

There are no conflicts to declare

Acknowledgements

Notes and references

1 R. A. Sheldon, *Chem. Soc. Rev*. 2012, **41**, 1437–1451
2 H. C. Erythropel, J. B. Zimmerman, T. M. de Winter, L. Petitjean, F. Melnikov, C. H. Lam, et al., *Green Chem*., 2018, **20**, 1929–1961
3 R. A. Sheldon, *Green Chem.,* 2017, **19**, 18–43
4 R. A. Sheldon, *ACS Sustainable Chem. Eng* 2018, **6**, 32–48
5 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, , DOI:10.1186/1860-5397-2-3.
6 E. Heinzle, D. Weirich, F. Brogli, V. H. Hoffmann, G. Koller, M. A. Verduyn and K. Hungerbühler, *Ind. Eng. Chem. Res.*, 1998, **37**, 3395–3407.
7 G. Wernet, S. Conradt, H. P. Isenring, C. Jiménez-González and K. Hungerbühler, *Int. J. Life Cycle Assess.*, 2010, **15**, 294–303.
8 W. De Soete, J. Dewulf, P. Cappuyns, G. Van Der Vorst, B. Heirman, W. Aelterman, K. Schoeters and H. Van Langenhove, *Green Chem.*, 2013, **15**, 3039–3048.
9 J. Provo, J. Fava and S. Baer, *Curr. Opin. Chem. Eng.*, 2013, **2**, 278–281.
10 M. Margallo, A. Dominguez-Ramos and R. Aldaco, *Educ. Chem. Eng.*, 2019, **26**, 89–96.
11 ISO, *ISO 14040:2006. Environmental management — Life cycle assessment — Principles and framework*, vol. 2006. 2006.
12 V. Hessel, D. Kralisch, N. Kockmann, T. Noe¨l and Q. Wang, *ChemSusChem,* 2013, **6**, 746–789
13 L. Vaccaro, D. Lanari, A. Marrocchi, G. Strappaveccia, *Green Chem.*, 2014,**16**, 3680–3704

14 F. Ferlin, D. Lanari, L. Vaccaro, *Green Chem.*, 2020, **22**, 5937–5955

15 S. Newman, K. Jensen, *Green Chem.,* 2013, **15**, 1456-1472.

16 A.-C. Bedard, A. R. Longstreet, J. Britton, Y. Wang, H. Moriguchi, R. W. Hicklin, W. H. Green and T. F. Jamison, *Bioorg. Med. Chem.*, 2017, **25**, 6233–6241

17 C. Dai, D. R. Snead, P. Zhang and T. F. Jamison, *J. Flow Chem.*, 2015, **5**, 133–138

18 M. G. Russel and T. F. Jamison, *Angew. Chem., Int. Ed.,* 2019, **58**, 7678–7681

19 F. Ferlin, D. Sciosci, F. Valentini, G. Cravotto, J. Menzio, K. Martina, *Green Chem*, 2021, doi: 10.1039/D1GC02490F

20 F. Ferlin, F. Valentin, G. Brufani, D. Lanari, L. Vaccaro, *ACS Sustainable Chem. Eng.* 2021, **9**, 5740–5749

21 F. Ferlin, I. Anastasiou, L. Carpisassi, L. Vaccaro, *Green Chem.* 2021, doi: 10.1039/D1GC01870A

22 V. Hessel, M. Escribà-Gelonch, J. Bricout, N. N. Tran, A. Anastasopoulou, F. Ferlin, F. Valentini, D. Lanari, L. Vaccaro, *ACS Sustainable Chem. Eng.* 2021, **9**, 9508–9540

23 V. Klug, J.-P. Schöggl, D. Dallinger, K. Hiebler, C. Stueckler, A. Steiner, A. Arzt, C. O. Kappe, R. J. Baumgartner, *ACS Sustainable Chem. Eng.* 2021, **9**, 8980–8989

24 A. A. Lapkin, P. Yaseneva, Life cycle assessment of flow chemistry processes. In: Sustainable flow chemistry. (L. Vaccaro Ed) Wiley-VCH, Weinheim, 249–276

25 P. Yaseneva, C. F. Marti, E. Palomares, X. Fan, T. Morgan, P. S. Perez, M. Ronning, F. Huang, T. Yuranova, L. KiwiMinsker, S. Derrouiche and A. A. Lapkin, *Chem. Eng. J.,* 2014, **248**, 230–241.

26 D. Ott, S. Borukhova and V. Hessel, *Green Chem.*, 2016, **18**, 1096–1116.

27 V. Hessel, L. Vaccaro, *Chimica Oggi – Chemistry Today*, 2021, 39, 15

28 M. Escriba-Gelonch, J. Bricout, V. Hessel, *ACS Sustainable Chem. Eng.* 2021, **9**, 1867–1879

29 Q. H. Pho, M. Escriba-Gelonch, D. Losic, E. V. Rebrov, N. N. Tran, V. Hessel, *ACS Sustainable Chem. Eng.* 2021, **9**, 4755–4770

30 C. S. Demmer and L. Bunch, *Eur. J. Med. Chem.*, 2015, **97**, 778–785.

31 H. Z. Zhang, Z. L. Zhao and C. H. Zhou, *Eur. J. Med. Chem.*, 2018, **144**, 444–492.

32 Ö. Temiz, I. Ören, E. Şener, I. Yalçin and N. Uçartürk, *Farmaco*, 1998, **53**, 337–341.

33 T. Aotsuka, N. Wagatsuma, H. Kato, and N. Ashizawa, "Pyrazole derivatives and cox inhibitors containing them," WO/1998/046594, 1998.

34 M. R. DeLuca and S. M. Kerwin, *Tetrahedron Lett.*, 1997, **38**, 199–202.

35 D. W. Dunwell, D. Evans and T. A. Hicks, *J. Med. Chem.*, 1975, **18**, 1158–1159.

36 E. Oksuzoglu, B. Tekiner-Gulbas, S. Alper, O. Temiz-Arpaci, T. Ertan, I. Yildiz, N. Diril, E. Sener-Aki and I. Yalcin, *J. Enzyme Inhib. Med. Chem.*, 2008, **23**, 37–42.

37 E. Oksuzoglu, O. Temiz-Arpaci, B. Tekiner-Gulbas, H. Eroglu, G. Sen, S. Alper, I. Yildiz, N. Diril, E. Aki-Sener and I. Yalcin, *Med. Chem. Res.*, 2008, **16**, 1–14.

38 D. Kumar, M. R. Jacob, M. B. Reynolds and S. M. Kerwin, *Bioorganic Med. Chem.*, 2002, **10**, 3997–4004.

39 M. A. Fourati, T. Maris, W. G. Skene, C. G. Bazuin and R. E. Prudhomme, *J. Phys. Chem. B*, 2011, **115**, 12362–12369.

40 A. Ghodbane, S. D'Altério, N. Saffon, N. D. McClenaghan, L. Scarpantonio, P. Jolinat and S. Fery-Forgues, *Langmuir*, 2012, **28**, 855–863.

41 T. Ogura, K. T. Yamaguchi, Y. Shibasaki and M. Ueda, *Polym. J.*, 2007, **39**, 245–251.

42 T. Ogoshi, J. Miyake and Y. Chujo, *Macromolecules*, 2005, **38**, 4425–4431.

43 S. Park, S. Kim, J. Seo and S. Y. Park, *Macromolecules*, 2005, **38**, 4557–4559.

44 P. Chen, Y. Xu, W. Du, G. Zhang, X. Chen and Z. An, *Mol. Cryst. Liq. Cryst.*, 2014, **592**, 44–62.

45 Y. H. So and J. P. Heeschen, *J. Org. Chem.*, 1997, **62**, 3552–3561.

46 R. S. Varma and D. Kumar, *J. Heterocycl. Chem.*, 1998, **35**, 1539–1540.

47 J. Peng, C. Zong, M. Ye, T. Chen, D. Gao, Y. Wang and C. Chen, *Org. Biomol. Chem.*, 2011, **9**, 1225–1230.

48 O. Koleda, T. Broese, J. Noetzel, M. Roemelt, E. Suna and R. Francke, *J. Org. Chem.*, 2017, **82**, 11669–11681.

49 A. Patra, A. James, T. K. Das and A. T. Biju, *J. Org. Chem.*, 2018, **83**, 14820–14826.

50 C. Yu, X. Guo, B. Shen, Z. Xi, Q. Li, Z. Yin, H. Liu, M. Muzzio, M. Shen, J. Li, C. T. Seto and S. Sun, *J. Mater. Chem. A*, 2018, **6**, 23766–23772.

51 J. He, F. Lin, X. Yang, D. Wang, X. Tan and S. Zhang, *Org. Process Res. Dev.*, 2016, **20**, 1093–1096.

52 J. Chang, K. Zhao and S. Pan, *Tetrahedron Lett.*, 2002, **43**, 951–954.

53 Q. T. Nguyen, A. H. Thi Hang, T. L. Ho Nguyen, D. K. Nguyen Chau and P. H. Tran, *RSC Adv.*, 2018, **8**, 11834–11842.

54 A. Khalafi-Nezhad and F. Panahi, *ACS Catal.*, 2014, **4**, 1686–1692.

55 P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul and T. Punniyamurthy, *J. Org. Chem.*, 2009, **74**, 8719–8725.

56 C. Praveen, K. H. Kumar, D. Muralidharan and P. T. Perumal, *Tetrahedron*, 2008, **64**, 2369–2374.

57 L. Wang, X. Ren, J. Yu, Y. Jiang and J. Cheng, *J. Org. Chem.*, 2013, **78**, 12076–12081

58 B. M. Trost, *Angew. Chem. Int. Ed*. 1995, **34**, 259–281

59 R. H. Petrucci, F. G. Herring, J. D. Madura, C. Bissonnette, in General Chemistry: principles and modern applications, 10th, Pearson Canada, Toronto, Ontario (2010)

60 T. Hudlicky, *Chem. Rev.* 1996, **96**, 3–30

61 Y. Lie, P. Ortiz, R. Vendamme, K. Vanbroekhoven and T. J. Farmer, *Ind. Eng. Chem. Res.*, 2019, **58**, 15945–15957.

62 R. A. Sheldon, *Green Chem.*, **9**, 2007, 1273–1283

63 F. Ferlin, M. K. Van Der Hulst, S. Santoro, D. Lanari and L. Vaccaro, *Green Chem.*, 2019, **21**, 5298–5305.

64 U. Azzena, M. Carraro, L. Pisano, S. Monticelli, R. Bartolotta, and V. Pace, *ChemSusChem*, 2019, **12**, 40–70

65 M. Shang, T. Noel, Y. Su, V. Hessel, *Ind. Eng. Chem. Res.* 2016, **55**, 2669–2676

66 P. T. Anastas and J. Warner, "12 Principles of Green Chemistry," in *Green Chemistry: Theory and Practice*, New York: Oxford University Press, 1998, p. p.30.

67 P. Morseletto, "Targets for a circular economy," *Resour. Conserv. Recycl.*, vol. 153, p. 104553, Feb. 2020, doi: 10.1016/J.RESCONREC.2019.104553.

68 G. Wernet, S. Hellweg and K. Hungerbühler, *Int. J. Life Cycle Assess.*, 2012, **17**, 720–728.

69 R. Hischier, S. Hellweg, C. Capello and A. Primas, *Int. J. Life Cycle Assess.*, 2005, **10**, 59–67.

70 R. Frischknecht, N. Jungbluth, H. J. Althaus, G. Doka, R. Dones, T. Heck, S. Hellweg, R. Hischier, T. Nemecek, G. Rebitzer and M. Spielmann, *Int. J. Life Cycle Assess.*, 2005, **10**, 3–9.

71 Gendorf, "Environmental declaration of the chemical plants at the Gendorf site in Burgkirchen, Germany.," 2000.

72 C. Capello, S. Hellweg, B. Badertscher and K. Hungerbühler, *Environ. Sci. Technol.*, 2005, **39**, 5885–5892.

73 G. Doka, "Life Cycle Inventories of Waste Treatment Services. ecoinvent report No. 13. Swiss Centre for Life Cycle Inventories, Dübendorf, 2009," 2009.

74 A. Köhler, S. Hellweg, E. Recan and K. Hungerbühler, *Environ. Sci. Technol.*, 2007, **41**, 5515–5522.

75 P. Koppe and A. Stotzek, "Kommunales Abwasser. Vulkan Verlag, Essen, Germany," 1993.

76 M. Boller and M. Hafliger, "Verbleib von Schwermetallen bei unterschiedlicher Meteorwasserentsorgung. Gas Wasser Abwasser, No.1/1996/ Zurich, Switzerland," 1996.

77 M. A. J. Huijbregts *et al.*, "ReCiPe 2016 v1.1. A harmonized life cycle impact assessment method at midpoint and endpoint level. Report I: Characterization," Bilthoven, 2017. [Online]. Available: www.rivm.nl/en.

78 S. Maranghi and C. Brondi, *Life Cycle Assessment in the Chemical Product Chain*. Siena: Springer, 2020.

79 O. M. Morales-Gonzalez, M. Escribà-Gelonch and V. Hessel, *Int. J. Life Cycle Assess.*, 2019, **24**, 2111–2127.

80 E. Igos, R. Mailler, R. Guillossou, V. Rocher and J. Gasperi, *J. Clean. Prod.*, **287**, 125067, DOI: 10.1016/j.jclepro.2020.125067.

81 L. Zampori, E. Saouter, E. Schau, J. Cristobal, V. Castellani, and S. Sala, "Guide for interpreting life cycle assessment result," Luxembourg, 2016. doi: 10.2788/171315.

82 S. A. Morais and C. Delerue-Matos, *J. Hazard. Mater.*, 2010, **175**, 12–22.

83 L. Rigamonti, A. Falbo, L. Zampori and S. Sala, *Int. J. Life Cycle Assess.*, 2017, **22**, 1278–1287.

84 I. Bakas, M. Z. Hauschild, T. F. Astrup and R. K. Rosenbaum, *Int. J. Life Cycle Assess.*, 2015, **20**, 1444–1455.

85 BP, "Electricity production from fossil fuels, nuclear and renewables, Europe," *BP Statistical Review of World Energy*, 2020. https://ourworldindata.org/grapher/elec-fossil-nuclear-renewables?country=~Europe (accessed Jul. 25, 2021).