# On an intensification factor for green chemistry and engineering: The value of an operationally simple decision-making tool in process assessment

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## ABSTRACT

This perspective provides the conceptual basis and potentiality of a new metric in green chemistry and engineering. Called the *intensification factor* (IF), as initially intended in the scenario of process intensification, it serves as a decision-making parameter that can explicitly contain as many factors as available data of interest are to be considered. These data can be both qualitative and quantitative, e.g., chemical, technical, risk, or cost, to name a few. In this context, the IF should be treated as *semi-quantitative approach* that complements the green metrics circumscribed to measurable elements of mass and energy performance. In short, the concept states that if the new (sustainable) alternative is superior to the existent by a factor larger than one, the alternative is a choice worth taking. Like any decision tool, subjectivity may always be an uninvited guest when dealing with IF values. *Choices are usually based on available data, not necessarily the best ones.* Despite such inherent pitfalls, we show through selected case studies the pluses of this otherwise operationally simple scheme, where the IF can facilitate an effective comparison between the chemical strategies used. Our main goal lies in showing how such a simple method can help others with an interest in any decision or activity involving process intensification and innovations.

## 1. Introduction and background

"When you can measure what you are speaking about and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely in your thoughts advanced to the state of science, whatever the matter may be."

Lord Kelvin (1883)

### 1.1. Do we have a numerical problem?

Over the past three decades, the advent and implementation of green chemistry have become one of the most innovative and

challenging paradigms of contemporary science. There is a growing need for replacing existing synthetic and operational procedures in academia and industry by alternatives much more eco-compatible. This trend lies in line with the public-domain message that neither our planet nor ourselves can afford the way chemistry is currently done (Thomsen, 2013; Aagaard, 2019).

The well-established principles of green chemistry and green engineering, collectively summarized in safer solvents, enabling technologies, and less toxic and hazardous reagents and products, often involve a re-design of conventional routes to find optimal conditions, yet maximizing performance and profit (Etzkorn, 2020; Winterton, 2021).

Since the early introduction of such principles, it became evident that if we cannot evaluate the "greenness" relative to the method to be abandoned, green chemistry might be an ideal, if not sterile, concept. We could have in mind the above-quoted aphorism from Lord Kelvin as the main motivation to quantify something. But if we cannot measure it quantitatively, the green evidence would at least require disclosing what prior method the new approach is being compared to, and then to choose one, or much better, several parameters to compare chemistries (Jessop, 2020).

It is common to find claims of greenness of environmentally friendly strategies or the use of renewable resources in the literature. However, not all authors disclose how postsynthetic stages are required for isolation/purification involving chromatography, and large amounts of volatile organic solvents (Cintas, 2016; Fegade and Tremblay, 2017). Accordingly, quantification of waste and energy consumption is a must, along with information on material recycling or reusability. Popular metrics addressing well these concerns include atom economy (AE), E-factor, reaction mass efficiency (RME), process mass intensity (PMI or simply MI), together with methods to determine life cycle assessments (LCA). This grammar is sustained by a chemical algebra that picks one or combinations of several factors leading to quantitative analyses of chemical efficiency (Lapkin and Constable, 2009; Jiménez-González and Constable, 2011; Andraos, 2012; Dicks and Hent, 2015; Constable and Jiménez-González, 2018).

As practitioners of green chemistry know, every parameter has both pluses and minuses, especially if yields, molar excesses of reactants and solvents are ignored (Ribeiro and Machado, 2013; Kreuder et al., 2017; Sheldon, 2018; Monteith et al., 2020). Experts in green metrics point out that data for MI, AE and stoichiometry do not necessarily correlate with each other in any meaningful way (Jiménez-González and Constable, 2011). Because RME accounts for all mass used in a reaction (excluding water) and includes yield, stoichiometry, and AE, that metric is probably the most useful. This is particularly true for the pharmaceutical industry, where elaboration of API (active pharmaceutical ingredients) often proceeds with poor mass efficiencies and low AEs (Jiménez-González et al., 2012).

Mass productivity (MP), the reciprocal value of mass intensity, may be a useful metric for business, because it highlights resource utilization. If, for instance, the average MP is as low as 1.5% (typical in multistep protocols), this means that 98.5% of the total mass used to make a drug/product is being wasted (Jiménez-González and Constable, 2011). Yet, given the omnipresent estimation of greenness using AE and E factors, some interesting proposals have been introduced recently, like the Lavoisier number (LN) (Andraos, 2018), which supplies a catchy information of efficiency based merely on AE and molecular weight, or the atom conversion efficiency (ACE) to capture the usage of atoms at each stage of life cycles (Urso and Gilbertson, 2018).

Arguably, a simultaneous calculation of indexes related to material and energy flows, waste, and toxicity should provide the most accurate information in the design of a chemical process. The radial pentagon, or hexagon, analyses (Andraos, 2012) are sensible approaches to this end, but execution of such algorithms is not a trivial undertaking. A serious warning is that individual metrics, or a few descriptors taken separately can lead to either underfit or overfit correlations. Thus, the use of multiple descriptors with cross-validation would be desirable for accurate interpretation. This mirrors the situation often encountered in quantitative structure-activity relationship (QSAR) methods used in drug discovery to test many variables without overfitting.

*1.2. Greenness beyond numbers*

If we focus on the common metrics used for organic reactions of wide synthetic interest, we find limitations associated with significant stoichiometric excesses, often inflated by using solvents as reactants, and poor sustainability. A quantitative analysis reveals that in most cases we throw out much more of what we brought in. However, issues not directly related to mass and energy efficiencies can dominate the evaluation of the non-benign character of product formation. For example, human toxicity and ecotoxicity, flammability, biodegradability, bioaccumulation and persistence, impact on global warming or resource depletion, among others, are difficult to estimate quantitatively.

"Being green" is also generally context-dependent and one set of rules can be insufficient to fit all situations. Consider for instance that processes conducted in water may be a prohibitive option in countries where competition for potable water is becoming a significant societal problem. Moreover, some reactions that run in aqueous media may be extremely inefficient, time-consuming, and difficult to be worked-up, while a less benign solvent can lead to a higher-quality product, enabling reduction in the number of synthetic steps or facile product separation.

As put by Welton *"it is also apparent that the successful implementation of environmentally sustainable processes must be accompanied by improvements in commercial performance"* (Welton, 2015). The argument is reinforced when we move to process chemistry, and hence process metrics, where efficiency hinges on the choice of unit operations, scalability, product quality, recyclability, cost, human exposure, and process safety (Lapkin, 2018). Thus, technical and economical constraints are bottlenecks for the adoption and implementation of new chemistry and novel methods.

The principles for the economic production of bulk chemicals should then be compatible with the principles of green chemistry and goals of recyclability and reusability (Schaub, 2021). Sustainable chemistry is at present placed within the framework of circular economy (Chatel, 2020). However, this philosophy may mislead the zero-waste-oriented design as the hallmark of green chemistry, rather than a socio-economic discipline focused on recycling, waste degradation, and/or (bio)remediation, all presently linked to sustainability in broad sense.

## 2. Why an intensification factor?

When one hears the term "intensification", a few ideas come to mind, mostly associated with chemical engineering, processing, reactor design, time cycles, operational costs, environmental impacts, and safety/risk aspects (Keil, 2018; Jørgensen et al., 2019; Polyakova et al., 2020). The decision of intensifying a chemical reaction or process simply means that something should be changed, regardless of the scale (a pilot plant or microfluidics, for instance).

The intensification factor is therefore a decision tool that combines economic and technical factors beyond the conventional concept of valorization methods using mass and energy metrics for synthetic transformations. These can, however, require matrix analysis to integrate data from all the steps involved (Richter et al., 2021; Fadlallah et al., 2021). Intensification algorithms make sense for benchmarking different strategies, and hence requiring detailed data from all the physicochemical phenomena and technical aspects, that may not always be accessible.

Some robust decision-making models have been suggested in recent years (Patel et al., 2012; Portha et al., 2014; Commenge and Falk, 2014; Barecka et al., 2017), focused largely on biomass processing, given the current demand and prospects for renewable materials. Thus, a multi-criteria screening, tailored for biorefineries in particular (to check their sustainability relative to approaches based on fossil resources), involves a series of indexes to be evaluated: economic constraint (EC), environmental-health-safety index (EHSI), environmental impact of raw materials (EI), process costs and environmental impacts (PCEI), and risk aspects (RA) (Posada et al., 2013).

The economic viability, a major decision ingredient for chemical industry, is defined as the ratio of the total costs of raw materials used with respect to the value of all the resulting products and coproducts obtained. The intensification protocols combine indexes to assess chemical productivity (e.g., yield or efficiency), costs of reagents and products, along with impacts such as ecological ones, greenhouse gas emissions, life cycles, human risks, and hazards. All indicators are weighed by experts to balance two processes under comparison, with scores normalized by the worst of the two.

A single index for a given process is obtained by summing all scores, which are subsequently compared by its ratio. A value $< 1$ points to a global advantage of the new sustainable process over the petrochemical method. In general, all algorithms are inherently complex (in arithmetic terms), difficult to understand, and far from being obvious tools.

Recently we introduced a method for comparing intensification alternatives, intended to be a novel chemistry index, which we simply called intensification factor (IF) (Fernandez Rivas et al., 2018). Even if we had an eye on the chemical engineering intensification concept, we sought a simpler procedure suitable for academic and research settings, thereby enabling practitioners to quantify the factor with minimal information. Interestingly, this simple formalism can be reframed for pedagogical purposes where students are taken as "outsiders", bearing in mind that decision metrics should be intuitive enough and provide a good assessment at low mathematical costs (Fernandez Rivas et al., 2020).

As we expand below, together with simplicity, the proposed IF gives rise to a "numerical indication", even when experimental data are limited. It should be seen as a decision-making framework for real-life planning, a method that is both modular and orthogonal, i.e., each module can be treated separately, with interchangeable evaluation criteria that may or not be interlocked.

For example, we could ignore costs, wich are not usually considered in academia. On the other hand, the penalties for some parameters should be considered in the overall process rather than local stages wihin a single unit. For instance, toxicity profiles for chemical reactions, often overlooked in research, must become a decisive and systematic index in green chemistry (Egorova et al., 2020). This indicator could jeopardize the feasibility of the process under analysis on commercial or large scales, for which hazardous substances should be either stored or transported. In stark contrast, highly hazardous materials generated in small volumes under continuous flow conditions can be tolerated with little or no risk, as they are consumed almost immediately (Ajmera et al., 2001; Cantillo et al., 2014; Movsisyan et al., 2016). Accordingly, that score, even if relevant, may be an orthogonal element for decision makers.

## 3. IF: working premises

To summarize the ingredients of the intensification factor (IF), we define a factor ($F$) as a given parameter susceptible of intensification or improvement. These could be, yield, temperature, number of synthetic steps, residence time through a reactor, solvent's amount, etc. Every factor will have an initial value *before* modification (input data), $F_b$, while the magnitude after the change is $F_a$.

An exponent ($d$) is included with a double purpose. First, its absolute value weighes the importance of $F$ on the alternative strategy, whereas its sign indicates whether a decrease in $F$ factor is desirable ($+$) or undesirable ($-$). For simplicity, unless otherwise specified, we have suggested the values of $+1$ or $-1$ for $d(F)$, respectively. The absolute value chosen for $d$ might be regarded somewhat subjective, because as mentioned above, experts should balance the relevance of $F$ on the intensified target, namely cost, safety, solvent's elimination, etc. When data are not available for a factor to be considered relevant by experts, it can be assumed to unity.

The $IF_{total}$ is then defined as the multiplication of a given number of $n$ variations of the individual factors as the fraction $(F_b/F_a)^d$, and it is calculated as:

$$IF_{total} = \prod_{i=1}^{n} \left(\frac{F_{bi}}{F_{ai}}\right)^{d_i} \tag{1}$$

In the current definition, we assume that the change in values for each factor follows a linear relationship, which most likely is not true in complex cases. However, as shown by the studies citing the first publication, it is useful in many instances, and helps in future stages when other relationships between the factors are known.

The other point of attention is when a zero value appears at the denominator, thus giving an infinite IF, or annulation if zero is on the numerator. Such limitation, however, can easily be bypassed in practice by changing the scale of measurement, converting for instance Celsius/Fahrenheit to Kelvin if temperature reaches a null value, or be redefined in percentage points.

This method offers several flexibilities. The first is what different $d_i$ values provide. In practice, in some cases the increase of one factor is beneficial for a given target, to the detriment of another. For example, in some reactions a decrease in pressure is desired due to safety and costs. Then the $IF_{pressure}$ ideally would be less than one. But a new IF number could be calculated to assess when the reaction kinetics would benefit when operating at a higher pressure ($d = -1$), without changing the other factors. In fact, pressure effects should not be easily dismissed, as sometimes high pressure enables important advantages (Weinbender et al., 2020).

Secondly, in the context of the modularity, a complex $IF_{total}$ can be broken down depending on the needs of the process. For example, when approaching the commercial team, the technical aspects might not be relevant, and you could separate them like $IF_{total} = \prod_{i=1}^{2} IF_i = IF_{commercial}.IF_{technical}$. This level of resolution could even help deciding against a given technical difficulty for the sake of commercial or environmental, but that would be masked by multiplying them.

Fig. 1 depicts a stepwise procedure to determine IF as decision-making tool for intensification/change of an existing method or technique. Clearly, step 2 appears to be critical as factors should be identified or agreed by experts. This selection could be hampered by the lack of clarity or information associated with a series of variables, which impede the *after*-assessment. In such cases, experts should agree or guesstimate the weight given to certain factors (cost, risk, safety, toxicity, etc), consistent with the modular character of the IF. Likewise, in the absence of available data, additional experiments could help us to validate the proposed solution.
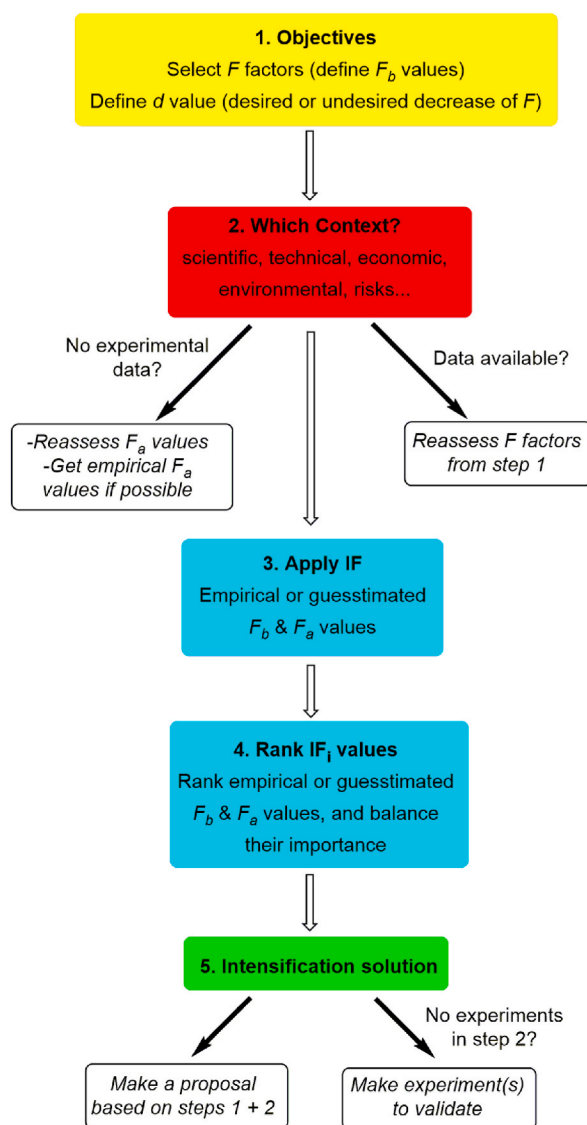


**Fig. 1.** Flow diagram to illustrate the step-by-step protocol to calculate the IF.

The presentation of the IF method was illustrated by a few test-cases taken from the literature (Fernandez Rivas et al., 2018), with a focus on operational designs and the aim of significantly reducing the reagent and energy footprint while making the processes safer at much lower costs. Attention was paid to industry-oriented showcases, such as ethanol oxidation to produce acetaldehyde, biodiesel production using reactive separation technologies, or water purification by reverse osmosis. Examples taken from our own research in sonochemistry could be examined in some detail at the interface between basic and applied research, as sonoreactors (Fernandez Rivas et al., 2012), usually inexpensive cleaning baths, are routinely employed in numerous laboratories for multiple purposes, including chemical synthesis.

Ultrasonic activation hinges on mechanical and chemical (notably radical formation) effects triggered by cavitation, i.e., creation and rapid collapse of microbubbles in liquids. Results are substantially influenced by the type and shape of every reactor along with experimental conditions, both factors complicating reproducibility and efficiency. We developed a miniaturized piezoelectric chamber with artificially created crevices, which serve as bubble nucleation sites that concentrate radical production after cavitational collapse (Fernandez Rivas et al., 2013). Actually a few crevices or pits in a micro-sonoreactor provide *ca.* 10 times higher energy efficiency than the unmodified device. The micro-sonoreactor becomes more intensified (higher IF) than the use of a scaled-up system using a *cavitation intensification bag* (CIB) having a pitted surface. The latter, suitable for synthesis and the cleaning of solid materials in ultrasonic bath working at different frequencies and acoustical powers, gives however better and more reproducible results than the corresponding processes carried out without such bags (Gomes et al., 2018). In a recent application to the advanced oxidation of terephthalic acid (TA) to produce 2-hydroxyterephthalic acid (HTA) by means of sonication and $Pd/Al_2O_3$ as heterogeneous catalyst (Scheme 1) (Pappaterra et al., 2021), the use of CIB with pitted surface (Fig. 2) improves the reproducibility and, hence ultrasonic control, when compared to oxidation with non-pitted bags. The rate of TA oxidation increased ten-fold in the CIB in the presence of the supported Pd-catalyst (4.1% Pd loading and using 50 mg of catalyst in each experiment). Generation of hydroxyl radicals could be identified by reaction with luminol, whose chemiluminescence is proportional to the number of radicals.

An analysis using the IF suggests that the CIB-catalyst combination is the desirable choice in terms of increased oxidation rate and costs (Table 1). The number of factors correspond to data available for comparative purposes, being likewise critical elements of this sonocatalytic experiment. To check the oxidative ability of ultrasound in producing •OH radicals, a decrease in TA is desirable and, accordingly an increase in HTA, which corresponds to an exponent $d = -1$. Reaction rate, based on a linear behavior, and cost of the precious metal within the catalyst were also selected as factors to compare the CIB-reaction with and without the catalyst. As deduced from the $IF_{total}$, the large positive value ($\sim$17) is clearly consistent with an enhanced oxidation and process efficiency by merging CIB and catalysis.

This preliminary example gives a glimpse on how IF can be generally applied in a stepwise, nonstatistical, and non-computerized (i. e. manual) manner, which is most useful with a small number of variables. The resulting IF is numerical, but as emphasized from the very beginning, a purely quantitative interpretation (i.e. $\sim$17-fold intensification) would be inappropriate. *It provides no more than a decisory argument based on the factors chosen.* Any critic would reasonably tell us that the potential to miss the important variables is huge and that nearly anything can be tuned through the exponent. In principle, this is a fair criticism.

For example, one party interested in an alternative or process may "inflate" the importance of a factor by assigning exaggerated values to different exponents *d* or hide altogether those factors that do not show the expected improvement or intensification. The main advantage we want to stress about the IF method is that it can be used with such level of transparency and simplicity of calculation that it makes it difficult to hide elements or knowledge as it is the case with most sophisticated tools or methods. If a set of experts gathers and agrees not only on the factors, but on the value of the exponent *d*, then any bias will be evident to the stakeholders analysing the cases. There is also a risk of considering a factor or weight more than once, due to, for example, different terminologies used by experts. By reducing such constraints, IFs can work as control elements in decision trees to make multiple comparison procedures, with a limited number of available data.

## 4. Case studies of greenering relevance

### 4.1. Downstream processing of biobutanol

Biomass conversion into efficient biofuels represents a driving force of sustainable chemistry taken for granted the fact that their production occurs with energy savings and less $CO_2$ emissions relative to fossil fuels. The case of biobutanol as promising and less explored biofuel has been discussed recently (Patraşcu et al., 2018). It shows convincingly the utility of IF calculations to a conceptually simple transformation, but technically complex process integration, which was carried out by the research team after the appearance of our metric.
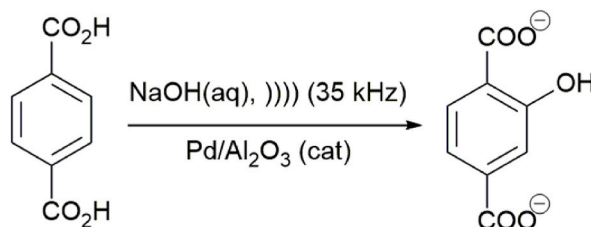
**Scheme 1.** Sonochemical oxidation of terephthalic acid under basic conditions and $Pd/Al_2O_3$ as catalyst.
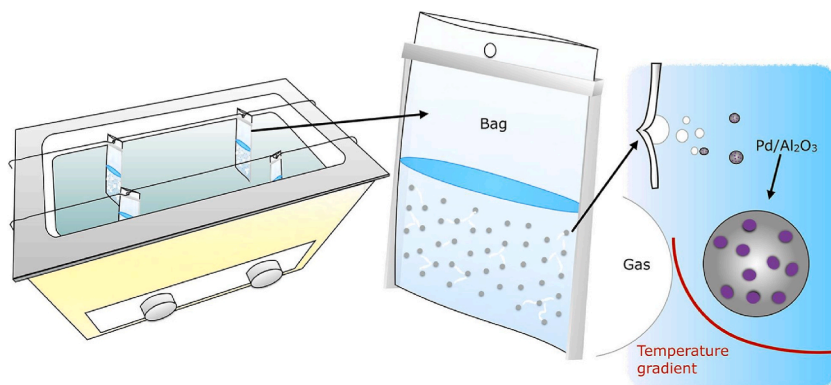
**Fig. 2.** Schematic representation of an ultrasonic reactor and plastic bags for intensified cavitational activity using a heterogeneous catalyst. Reproduced with permission from Pappaterra et al. Copyright 2021 Elsevier B·V.

**Table 1**
Intensification factor (IF) determined for the catalytic oxidation of terephthalic acid using cavitation intensification bags (CIB).

| Factor | CIB | CIB + catalyst | $d$ | Fraction | IF[a] |
|---|---|---|---|---|---|
| HTA ($\mu$M L$^{-1}$) after 30 min | 0.35 | 1.85 | $-1$ | $(0.35/1.85)^{-1}$ | 5.29 |
| Reaction rate ($\mu$M min$^{-1}$) | 0.012 | 0.096 | $-1$ | $(0.012/0.096)^{-1}$ | 8 |
| Cost of Pd in catalyst ($\mathcal{E}$/kg) in % | 100 | 260 | $+1$ | $(100/260)$ | 0.4 |
| | | | | IF$_{total}$ | 16.93 |

[a] IF$_{total}$ calculated according to Eq. (1) as the product (multiplication) of all individual IF values.
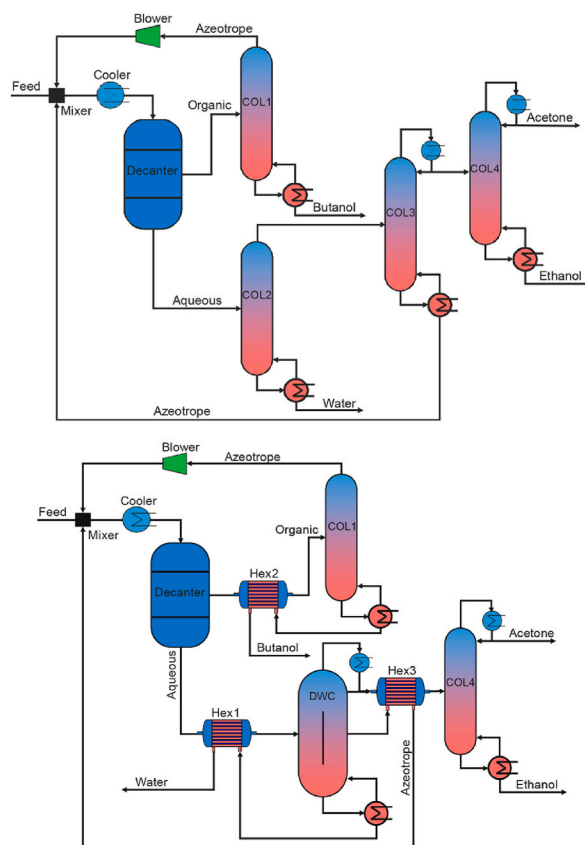


**Fig. 3.** Continuous downstream separations of acetone-butanol-ethanol mixtures: conventional distillation (top) and intensified azeotropic-DWC with heat integration (bottom). Reproduced with permission from Patrascu et al. Copyright 2018 American Chemical Society.

Conventional downstream separation of an acetone-butanol-ethanol (ABE) mixture, obtained by fermentation, is both time and energy consuming, in view of the low butanol concentration (<3 wt%), as this alcohol is highly toxic to most microorganisms. Clearly, the energy requirement constitutes the most serious drawback, and the proposed intensified separation includes a vapor recompression-assisted azeotropic dividing-wall column (A-DWC), which reduces the energy costs from 6.7 to 2.7 MJ kg$^{-1}$ butanol. As depicted in Fig. 3, the ABE downstream separation involves a multistep sequence and action could be taken at different stages, although the energy bottleneck depends strongly on heating. The azeotropic DWC alternative integrates three distillation columns into one single unit with enhanced thermal efficiency.

The factors chosen focused on the process type and the corresponding energy requirements, while the economic balance was evaluated separately. The exponent should be positive as a decrease in the factor in question is desirable. The difference (expressed in %) against the conventional procedure and the IF(energy) of the integrated heat pump-assisted A-DWC system indicates an advantage in terms of energy savings (Table 2).

An external reviewer might still consider the authors choice to be cursory instead of using a more complex multivariate analysis. However, the authors clearly concentrate on key steps where energy balances are critical. The positive value of IF indicates that the alternative offers advantages based on the factors included in the analysis. Also, one could consider other techniques to carry out the ABE separation such as distillation, adsorption, reverse osmosis, liquid-liquid extraction, etc (Patraşcu et al., 2018; Abdehagh et al., 2014). Moreover, a higher butanol concentration could also be achieved when using anaerobic bacteria (Pfromm et al., 2010). Overall, this study reflects the complex portrait of biorefineries with a portfolio of multiple variables -costs in particular-which are difficult to disentangle. At present, developed countries grant subsidies for biorefinery to render it economically viable (Sharma et al., 2020), in a sector needing new production schemes (Liu et al., 2020).

## 4.2. Synthon assembly: the plus of flow

Continuous flow chemistry has matured and enabled facile automation to accelerate design and development of new synthetic routes and complex molecules (Gutmann et al., 2015; Hughes, 2020; Breen et al., 2021). Flow methods are usually green on its own way by reducing formation of byproducts and hazards. Flow synthesis approaches through sequential coupling of synthons or multicomponent reactions can facilitate the elaboration of highly functionalized heterocycles, of interest in the pharmaceutical industry. Flow-mode reactions exhibit some pluses over their batch-mode ones, such as rapidity and less waste because no intermediate isolation is required, and stoichiometric amounts can be employed. As mentioned, too toxic and reactive substrates or intermediates, by virtue of enhanced mass transport and consumption in a flow process, will have little potentiality of causing uncontrolled effects.

Flow syntheses are not necessarily superior to standard batch processes and comparative analyses should be taken with caution to check every improvement, if any, in conversion, yield, time, temperature, amount of solvent, etc. Batch-*vs* flow-mode results are not always available, and data often come from different groups and different reagents and routes. A recent survey compiles outcomes from similar transformations under both modes leading to heterocyclic scaffolds (Alfano et al., 2021). As representative example we have taken a useful construction of thioquinazolinone derivatives, for which batch preparations have been reported and involve the condensation of anthranilic acid and an isothiocyanate, among other electrophiles. The continuous approach (Fig. 4) also harnesses an aryl isothiocyanate as starting material in a three-step integrated microfluidic synthesis (Kim et al., 2015).

The Br–Li exchange reaction of 2-bromophenyl isothiocyanate with *n*-BuLi affords a NCS-substituted aryllithium intermediate capable of undergoing further reaction with another strong electrophile, namely an aryl isocyanate. Under batch conditions, the Br–Li exchange should be performed at low temperature (−78 °C), while the microfluidic device allowed the reaction at room temperature since the residence times are shorter or within the decomposition time scale of such lithium intermediates. The subsequent reaction with the isocyanate partner could be achieved at 25 °C as well leading to the thioquinazolinone core in good yields by intramolecular cyclization. *S*-Benzyl derivatives, which exhibit antiplatelet activity, can likewise be integrated into the microfluidic reaction in yields exceeding 80%. Comparison between both modes to obtain the thioquinazolinone skeleton points to more favorable and milder conditions provided by the continuous process: room-temperature synthesis in less than 10 s *vs* refluxing ethanol in a flask for several hours; the conventional *S*-alkylation can however be conducted at room temperature. The intensification also applies to the ease of separation (simple recrystallization after microfluidics) and scale-up (gram-scale synthesis in 5 min). However, this heterocyclic synthesis represents a borderline situation that impedes a good assessment; the reaction pathways are not identical, nor do they involve the same reagents and solvents. The batch protocol takes long, while the reaction time concept is not applicable to the continuous mode where the residence time of every step matters. Conversely, the latter makes no sense in the flask. In general, both protocols use slight excess of reagents, albeit higher concentrations are employed in flow mode.

The use of alcoholic solvents (chiefly EtOH) in batch mode to elaborate the thioquinazolinone ring is a more benign choice than hexane or THF required for *n*-BuLi or to make a soluble reaction mixture within the microfluidic device. The increase in solvent's

**Table 2**
Energy IF calculations for the comparative assessment between conventional and new biobutanol downstream separations.

| Factor | Energy (MJ kg$^{-1}$ butanol) | Difference (%) vs conventional | d | Fraction | IF[a] |
|---|---|---|---|---|---|
| Conventional process (decanter + distillation) | 6.30 | (6.30–6.30)/6.30 = 0 | +1 | (6.30/6.30) | 1.00 |
| DWC distillation (heat integrated) | 4.46 | (4.46–6.30)/6.30 = −29 | +1 | (6.30/4.46) | 1.41 |
| Azeotropic-DWC | 8.78 | (8.78–6.30)/6.30 = 39 | +1 | (6.30/8.78) | 0.71 |
| Heat pump assisted-DWC (heat integrated) | 2.70 | (2.70–6.30)/6.30 = −57 | +1 | (6.30/2.70) | 2.33 |
| | | | | IF$_{total}$ | 2.33 |

[a] IF$_{total}$ calculated according to Eq. (1) as the product (multiplication) of all individual IF values.
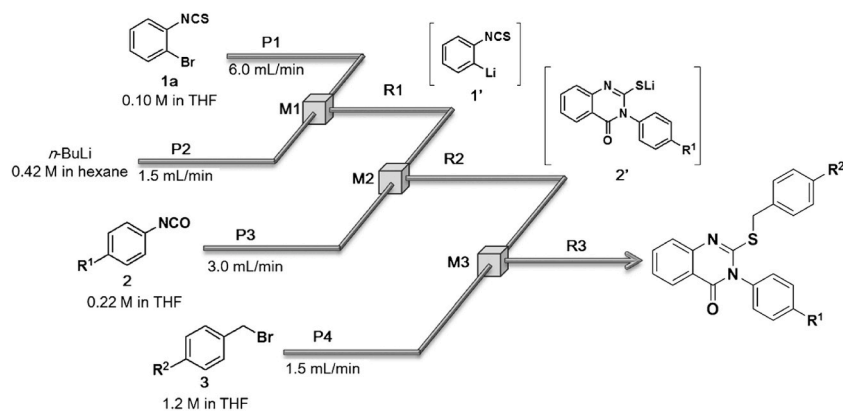
**Fig. 4.** Three-step integrated microfluidic synthesis of S-benzyl thioquinazolinones at room temperature. Reproduced with permission from Kim et al. Copyright 2015 Wiley-VCH Verlag GmbH & Co.

hydrophobicity avoids precipitation and/or clogging, which would complicate the continuous operation. Probably a proper comparison would require quantitative and qualitative factors that can be correlated with each other. The objective factors are overall reaction yields, the average values for a series of compounds, and the assumption that the batch mode involves two separate reactions, together with average temperature for the whole transformation. Solvent's toxicity could be chosen as factor within a green context.

A well-known selection guide focused on safety scores (Prat et al., 2014) may provide an objective evaluation. As mentioned, the batch reaction between anthranilic acid and isothiocyanates is conducted in ethanol, although an equivalent amount of base (triethylamine) is required. The solvents for subsequent *S*-functionalization can include other hazardous choices, nevertheless. In both modes, solvents for work-up operations were not considered. In agreement with the IF, the exponent is negative since higher yields are desired, while the positive value for temperature and solvent score features a decrease in such factors. Intensification assessment outlined in Table 3 is lumped into a number (2.0) larger than unity, thus giving a quantitative estimation of "advantage" as highlighted in the literature (Alfano et al., 2021).

Less problematic comparisons for IF values come from other flow synthesis (ideally the batch mode conducted by the same laboratory and using the same precursors), such as a recent three-step synthesis of functionalized indoles (Crifar et al., 2019). Here, the reaction times are similar to the residence times (yet shorter in flow mode) and identical temperatures are required in both cases. The improved yields obtained in the continuous process are the most decisive element because solvents remain unchanged.

As mentioned, the distinct advantages of flow processing are related to the small inventory and almost absence of reactor headspace, thereby avoiding the hazards of handling toxic and volatile solvents and reagents (Movsisyan et al., 2016). A factor, not easily quantified, though adhering to green chemistry principles, is the constant in-line real-time monitoring of continuous reaction composition, which provides extra elements of control and safety. The latter can be illustrated by a recent synthesis and work-up of disubstituted 1,5-tetrazoles, a structural motif present in some medicinally relevant substances (Sagmeister et al., 2021).

Optimization in batch was performed through MW irradiation (sealed vials) to fix the best reaction parameters, which were then transferred to flow. In doing so, the team noted that complete conversions were attained at higher temperatures and, in agreement with most flow-assisted synthesis, reactions proceeded at more concentrated conditions than those in batch mode. Scheme 2 shows the model reaction for intensification by using 2-chloro-*N*-methylacetamide with trimethylsilyl azide (TMSN$_3$), in the presence of POCl$_3$ required to obtain the imidoyl chloride intermediate. Variables (factors) considered for optimization were substrate concentration, time, temperature, and acetonitrile, as this polar solvent gave rise to much higher conversion than other alternatives.

Like the preceding example, the IF calculation gives a simple indication of the intensification of the flow reaction based on a batch screening, also enabling a comparison with previous literature data. It employs a broad window of conditions, such as temperature (from 80 to 180 °C), solvent or neat, chloride sources or activating reagents, whose cost and risk should also be considered. Such "drivers", however, need to be assigned, either based on economic and safety data, or arbitrary scales agreed by experts or practitioners. As pointed out earlier, the concepts of reaction time and residence time do not match exactly, but MW-irradiated batch

**Table 3**

Comparative data between bath and continuous reactions en route to S-substituted thioquinazolinones.

| Factor | Batch | Microfluidics | d | Fraction | IF[d] |
|---|---|---|---|---|---|
| Overall yield (%)[a] | ~60 | ~88 | −1 | (60/88)$^{-1}$ | 1.47 |
| Temperature (°C)[b] | ~50 | ~25 | +1 | (50/25) | 2.0 |
| Solvent score[c] | 5 | 7 | +1 | (5/7) | 0.7 |
| | | | | IF$_{total}$ | 2.06 |

[a] Average yields for compound series.

[b] Average temperature for the entire transformation.

[c] Safety scores (average values) for EtOH + triethylamine (batch) and THF + hexane (microfluidics).

[d] IF$_{total}$ calculated as the product (multiplication) of all individual IF values.
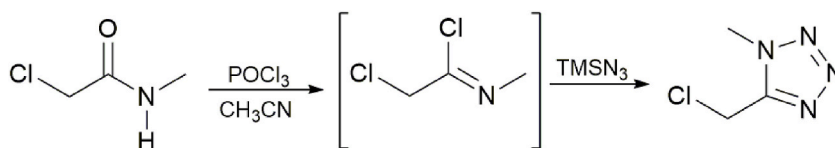
**Scheme 2.** Synthesis of disubstituted 1,5-tetrazoles conducted under batch (MW-assisted) and flow (pressure-driven) conditions for comparative estimations.

reactions were assessed at a fixed time of 15 min, within the range of residence times (~10 min) for benchtop NMR flow experiments. Complete conversion and enhanced rate for irradiated reactions were observed at 140 °C under dilute conditions. More concentrated solutions (up to 2 M) favored high yields (94–97%) at a lower temperature (100 °C). A high concentration appears to be compulsory in a continuous process to obtaining high productivity, along with an excess of $TMSN_3$, presumably by preventing decomposition of the transient imidoyl chloride intermediate (Scheme 2). At 140 °C and 12-bar reactor pressure, other side effects occur like release of more gas ($HN_3$ or $N_2$), darker reaction and damage of the perfluoroalkyl tubing.

Notably, the batch process can be quantitative at lower temperature and concentration, albeit the energy cost could then be a key input into any flow-adapted or large-scale operations. As discussed above, the $IF_{pressure}$ may be a conflicting factor. A decrease in pressure ($d = 1$) is desired in terms of safety and costs, but a higher pressure ($d = -1$) can benefit the reaction kinetics and overall performance. In fact, the flow protocol becomes unpractical if that factor is ignored (Table 4). While an excess of $TMSN_3$ gives rise to improved yield, the cost of this reagent may be a limiting parameter and reduction in excess of reagents would have a positive impact ($d = 1$). Alternatively, a much higher concentration (2.7 M) still ensures high productivity and excellent space-time yield together with reduced solvent wastes. Product isolation strategies follow similar concentration and crystallization steps in batch and flow, and even if mass intensity metrics were not evaluated, yields match each other.

A much more dramatic illustration of flow-mediated chemistry under extreme conditions is shown by the recent preparation of musk-like olfactory macrocycles of broad utility in the fragrance industry. Starting from readily available small cyclic ketones, the production of medium-sized and large rings involves a hazardous reagent mixture (30% $H_2O_2$ in 65% $HNO_3$) that supplies triperoxide intermediates, which are pyrolyzed subsequently at 270 °C (Seemann et al., 2021). No one would handle this potentially explosive reaction mixture for large-scale operations under batch conditions. The penalties of toxicity and risky are offset by a miniaturized, continuously operated two-flow chamber reactor connected by a membrane separator. This viable choice would thus justify an increase in factors like temperature and concentration.

The efficiency of flow-induced reactions can be coupled to other enabling techniques aimed at activating an otherwise difficult synthetic step. Photoirradiation, often using visible light, under flow has thus become a catalytic and scalable method for product design with low environmental impact. A recent and innovative example described by Noël and coworkers is a tandem hydrogen-atom transfer photocatalysis and oxidative radical-polar crossover that can be employed for $C(sp^3)$-H (hetero)arylation (Wan et al., 2021). This approach exploits the rapid formation of the decatungstate anion, obtained from TBADT = $(Bu_4N)W_{10}O_{32}$, to act as H-atom abstractor affording carbon-centered radicals, whose oxidation lead to carbocations that can be trapped by *N*-heteroaryl nucleophiles. *Tert*-butylhydroperoxide (TBHP) was used as terminal oxidant (Scheme 3). The protocol exhibits high regioselectivity, broad functional-group tolerance, and can be employed in the late-stage functionalization of bioactive molecules. In an expanded and more recent application, this research group also took advantage of the decatungstate anion as H-atom transfer photocatalyst to generate carbon-centered radicals that can be trapped by reactive electrophiles in the presence of a nickel catalyst (Mazzarella et al., 2021).

Overall, the sequential reaction allows the acylation and arylation of strong $C(sp^3)$-H bonds in flow giving rise to new $C(sp^3)$-$C(sp^2)$ bonds. In both cases, optimization of batch and continuous flow conditions gave products in comparable yields through similar working conditions. However, the intensified conditions in the microfluidic channel reduce the reaction time from 16 h to 1 h (for heteroarylation) and from 12-48 h to 5–15 min (for acylation/arylation) on moving from batch to flow. Clearly, a positive exponent ($d = 1$) applies here with the IF being roughly equal to the corresponding accelerating effect, or in other words the temporal batch/flow ratio. Thus, a higher intensity in the microfluidic setup increases the reaction rate by boosting the photoactivation of C–H bonds but has no influence on the mechanism.

These studies would invite to consider additional factors by comparing this green photocatalysis to other photocatalytic or photoelectrochemical methods; for instance, number of synthetic steps, amount of reagents, functional- or protecting-groups required, etc, which may however be estimated by conventional metrics. In a recent and thoughtful perspective, Hessel and associates suggest that flow chemistry should also be re-assessed from conventional green metrics and process level to concerns related to environmental parameters (Hessel et al., 2021). Even if the quantitative analysis is rigorous, some factors can also be subjective, like circularity. As

**Table 4**
Experimental factors (batch vs flow) accounting for the improved preparation of 1, 5-substituted tetrazoles.

| Factor | Batch | Flow | $d$ | Fraction | $IF^a$ |
|---|---|---|---|---|---|
| Temperature (°C) | 100 | 100 | +1 | (100/100) | 1.0 |
| Reaction concentration (M) | 1.0 | 2.7 | +1 | (1.0/2.7) | 0.37 |
| $POCl_3$/$TMSN_3$ (equiv) ratio | 0.79 | 0.83 | +1 | (0.79/0.83) | 0.95 |
| Pressure (bar) | ~1 | 12 | −1 | $(1/12)^{-1}$ | 12 |
| | | | | $IF_{total}$ | 4.22 |

[a] $IF_{total}$ calculated as the product (multiplication) of all individual IF values.
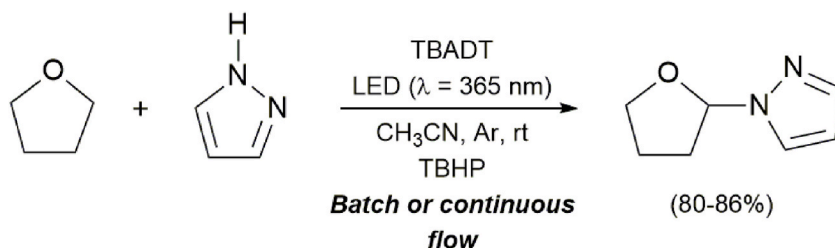
**Scheme 3.** Representative photocatalytic C(sp³)-H heteroarylation for optimization under batch and continuous flow conditions.

noted above (Chatel, 2020), it is better to put chemistry within the circular economy of every territory, rather than a universal concept of circular chemistry.

### 4.3. Wet synthesis of an agonist drug

The process development, scale-up and purity control of antibacterial and antiviral drugs are crucial for the treatment of diseases affecting millions of people worldwide. Knowing that the pharmaceutical industry is highly polluting with exceedingly high E-factors and poor atom economy, the major challenges associated with the production of active pharmaceutical ingredients (APIs) for clinical use typically rely upon shorter synthetic routes, unprotected derivatives, and ultimately on chromatography-free approaches to reduce the amount of solvents and impurities. Reinvestigation of drug syntheses evidence, however, that all previous chemistry cannot be made green. Suitable strategies replace at most a few hazardous steps by more benign choices, like catalytic or biocatalytic versions, especially when stereoselectivity is a key factor, combine both batch and flow reactions, or begin from renewable feedstocks (Etzkorn, 2020). Given the fact that API manufacturing often involves lengthy multistep sequences, it is not surprising that reactions themselves amount on average to just 25% of the protocols, while work-up makes up the remaining 75% of all operations (Jiménez-González et al., 2011). If one considers all materials, by mass, used to manufacture APIs, the balance is certainly awful: *ca.* 56% for solvents and only 7% reactants; even the water consumed during unit operations (extractions, distillation, etc) can be as large as 32% (Jimenez-Gonzalez et al., 2011b).

In general, synthetic efficiency, as noted in the introductory remarks can be estimated in terms of a waste metric (E-factor in particular), or process mass intensity (PMI), which focuses on the efficiency of inputs rather than the waste, i.e., mass inputs (kg) divided by mass product (kg) (Jiménez-González and Constable, 2011; Jimenez-Gonzalez et al., 2011b). The calculation of this metric is quite simple, but finding the total mass and volumes of liquids, other than reagents and reaction solvent, employed for isolation and purification can be extremely difficult, often interspersed through the supplementary information or, even worse, absent.

In contrast, the chemical industry usually details all the materials used as their cost represent critical elements of the production process (Etzkorn, 2020). One of the rarest cases where this analysis is well addressed and we would like to highlight in the present innovation/intensification context, is the complete re-design of a 5-HT₄ receptor agonist (TAK-954), developed at Takeda Pharmaceuticals, for which the original enabling and highly efficient synthesis involving organic solvents, can be conducted almost entirely in
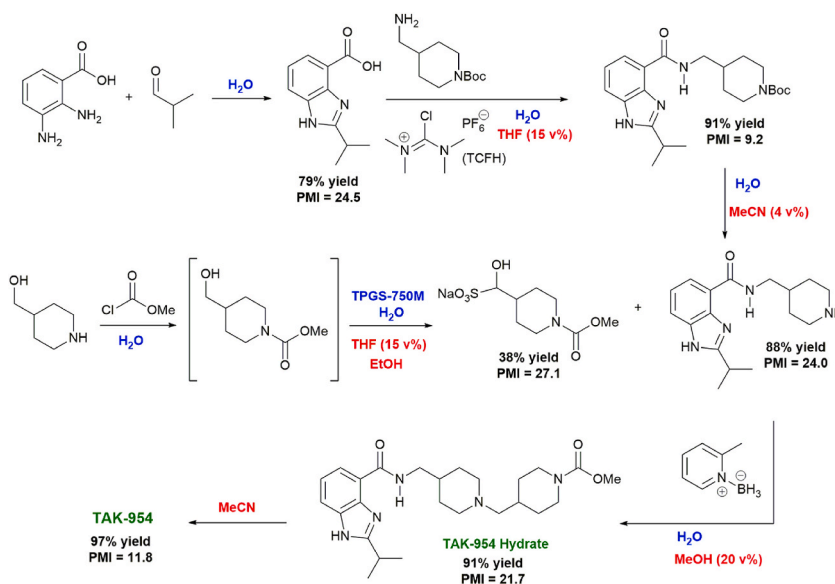


**Scheme 4.** Re-developed synthesis of the 5-HT4 receptor agonist TAK-954 in water. For clarity, numerous reagents have been omitted, while paying attention to solvents and mass inputs (yields and PMI metrics). Adapted with permission from Bailey et al. Copyright 2021 the Royal Society of Chemistry.

water, with less material inputs and improved overall yield (Bailey et al., 2021). The 5-hydroxytryptamine receptor 5-HT$_4$ is a member of human serotonin receptors, broadly located in numerous organs and the central nervous system, and an interesting target for the management of patients needing gastrointestinal motility treatment (De Maeyer et al., 2008).

Actually, TAK-954 is a low-complexity molecule, in Phase 2 clinical trials for post-operative gastrointestinal dysfunction. The original route includes as key transformations a benzimidazole cyclization, amide bond formation, reductive amination and carbamate formation, together with deprotection steps and final isolation by crystallization. The wet re-formulation harnesses essentially the same reactions, although some substrates and reagents were modified to carry out a nearly exclusive aqueous process, including isolations and crystallizations (Scheme 4).

The team reasoned that all chemistry would likely work in water as heteroatoms in most structures and intermediates exhibit base character and may provide pH-dependent solubility. This proved to be successful. In addition, this manipulation of solubility through pH adjustments enables both purification and isolation of products by crystallization without the need for organic solvents. The first step leading to the benzimidazole derivative, devoid of other regioisomeric side products, could be accomplished by optimizing the amount of sodium bisulfite in water and pushing the equilibrium toward the bisulfite adduct, which reacted well with the starting diamine after rising the pH value.

The next step, amidation involving the coupling of acid and amine, requires an activating agent, which could however be unsuitable to effect amide bond formation in aqueous media. After screening several classes of activating reagents, the use of chloro-*N,N, N',N'*-tetramethylformamidium hexafluorophosphate (TCPH, Scheme 4) combined with N-methylimidazole, gave rise to rapid and clean amide formation. The Boc protecting group could be easily removed with aqueous HCl. It is noteworthy that even if all reactions seemed to work in water, variable volumes of organic co-solvents were included to avoid product oiling. Surfactants had no impact on product formation and separation, and sometimes they led to gummy substances.

The *N*-unprotected piperidine derivative should undergo reductive amination with a methyl carbamate generated in an auxiliary reaction. The latter needed the controlled oxidation of a primary alcohol and the one-pot protocol required this time a surfactant, TPGS-750 M (Scheme 4), developed previously (Lipshutz et al., 2011), plus THF co-solvent for the oxidation to proceed. Ethanol was also used as anti-solvent in a subsequent step to isolate the bisulfite adduct. The final reductive amination, releasing an equivalent of water in an aqueous environment, would not be favorable. Micellar conditions were attempted to shift imine formation in a more hydrophobic environment, although ultimately α-picoline borane was stable enough in water to effect the reductive process yielding the hydrate form of TAK-954. Having used the bisulfite adduct as aldehyde surrogate, the desired product was obtained in high conversion by warming the reaction mixture in MeCN.

Although the innovation caused by a clever replacement of organic solvents by water is remarkable, the intensification rationale requires again measurable variables in both routes to be compared with each other. Since yields alone do not reflect the actual atomic disposal, the authors assessed the corresponding PMIs of each step, and both data can then be employed to determine the IF, albeit in opposite trend as indicated by the *d* values (Table 5). The overall PMI is quite high (350) in the original approach, thereby highlighting a poor synthetic efficiency, while the cumulative PMI in water is significantly reduced to 79, consistent with a reduction in the amounts of materials employed to manufacture the API in a higher overall yield. As a result, the values of solvents PMI follow likewise a similar profile (from 223 to 14). This reduction, however, should not be regarded as another independent factor as PMI usually includes all materials through the entire process, including water. Reactions are conducted at different temperatures, ranging from room temperature to 80 °C. However, no data are given for temperatures and reaction times for every sequence of the original method.

Based on the similarity of synthetic transformations, some estimations of temperature ranges could be assumed, as this parameter may be relevant in terms of energy inputs and overall cost. Nevertheless, a priori we discarded this determination. If one excludes the rest of environmental impacts, the purity of APIs should clearly be a key factor that underpins their appropriateness for pharmaceutical use. Fortunately, both methods afforded a high overall purity by HPLC analysis (hence *d* = 1). A roughly seven-fold increase in IF points to a clear-cut intensification, even though the direct estimation is inferred from mass balances with a focus on solvents and their impact in an indirect way.

Among the comparative studies on syntheses targeting APIs or their precursors, we believe a recent and comprehensive analysis by Sheldon and associates is worthwhile (Akakios et al., 2021). They illuminate other metrics, such as process complexity (Gaich and Baran, 2010), the mass-based innovative Green Aspiration Level (iGAL) (Roschangar et al., 2018), the Green Motion assessment (Green Motion, 2021), along with the standard scores for solvent selection, waste, and reagent/product hazard and toxicity. The research group applied such metrics to three routes to a synthetic intermediate, a chiral bis-tetrahydrofuranyl alcohol, present in a series of HIV protease inhibitors (Akakios et al., 2021). The assessment is not trivial, because every route has both pluses and minuses, and any compensation is not immediately obvious. Interestingly, a rough costing was introduced for each route, which may bias the decision with a view to industrial applications.

**Table 5**
Estimation of IFs by comparison of the first-generation synthesis and the re-designed route in water of a 5-HT$_4$ receptor agonist.

| Factor | First synthesis | Aqueous synthesis | *d* | Fraction | IF[a] |
|---|---|---|---|---|---|
| Overall yield (%) | 35 | 56 | −1 | $(35/56)^{-1}$ | 1.6 |
| Cumulative PMI | 350 | 79 | +1 | (350/79) | 4.43 |
| Product Purity (%) | 99.8 | 99.8 | +1 | (99.8/99.8) | 1.0 |
| | | | | IF$_{total}$ | 7.09 |

[a] IF$_{total}$ calculated as the product (multiplication) of all individual IF values.

While the first route, initiated by an asymmetric catalysis gave the lowest E-factor due to high-yielding and high-atom economy reactions, it almost doubles the cost of a one-pot route involving an enzymatic kinetic resolution. Both this second approach and the third one may be conducted in either one-pot or step-by-step modes, which increase the cost further. As expected, the third route starting from an expensive and enantiopure precursor had the highest cost. Conversely, the best synthetic performance based on overall yield, albeit with a longer reaction time, was observed for the one-pot second route. Nevertheless, that route can be regarded as the most efficient strategy with a reduced environmental impact thanks to optimal solvent utilization and milder conditions. An improved iGAL metric has been recently released to evaluate the sustainable character of API production within the scope of LCA analysis (Roschangar et al., 2022).

### 4.4. Poly(ε-caprolactone) synthesis

In our first description of the IF, we noted that more than two alternatives can be evaluated, provided that the same factors are measured for every alternative. We obtained the IFs for three different operational designs (batch, continuous-batch mix, and continuous-flow operation) for producing a valuable intermediate through an organometallic reaction (Fernandez Rivas et al., 2018; Roberge et al., 2008). Here we provide further illustration on three synthetically different routes leading to an important commodity chemical, poly(ε-caprolactone) (PCL) (Ang et al., 2021). Like ε-caprolactam, the industrial precursor to nylon-6, ε-caprolactone is usually polymerized to give a biodegradable polymer, PCL, of complete synthetic origin. Three short syntheses were analyzed, neither of them to be especially green as we shall show later, although the most noticeable feature of this study is the laboratory-scale life-cycle assessment (LCA) of such routes, starting from extraction of raw materials (chiefly fossil resources) and ending with production of PCL. The three routes are shown in Scheme 5.

The first synthesis (A) starts from commercially available ε-caprolactone and represents the most straightforward route to PCL using HCl solution in diethyl ether as carrier, which evaporates on heating. Route B, free-radical ring-opening polymerization using the well-known radical initiator azobisisobutyronitrile (AIBN), is actually a stepwise process starting from chloroacetaldehyde dimethyl acetal and 1,4-butanediol, and performing their condensation under thermal conditions with *p*-toluenesulfonic acid to yield 2-chloromethyl-1,3-dioxepane. The latter is subjected to elimination with *t*-BuOK in THF in the presence of a surfactant. This affords the unsaturated 1,3-dioxepane suitable for polymerization. Route C constitutes the conventional acid-catalyzed ring-opening polymerization assisted by tin(II) octoate at high temperature. In all cases, work-up for product isolation involves precipitation with organic solvents, which exceed to a large extent the rest of inventory. In route A, for instance, ~1 g of ε-caprolactone is polymerized to give 1 g PCL after using more than 75 g of highly volatile $CH_2Cl_2$ and hexane. Although the study details the mass balances, synthetic efficiency using common metrics is not reported. In any case, the fate of waste is subsequently evaluated, as mentioned, through the environmental impact and human toxicity analyses.
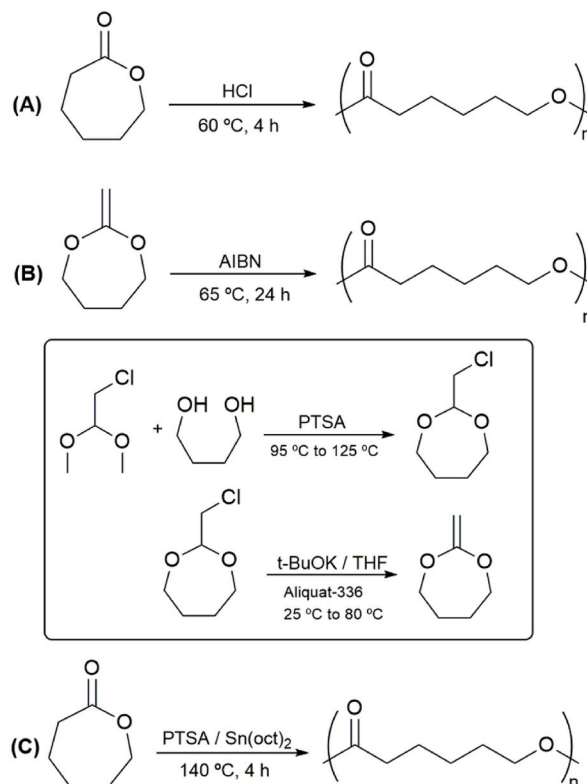


**Scheme 5.** Different ring-opening polymerizations of ε-caprolactone, or a dioxepane derivative, leading to poly(ε-caprolactone) homopolymer.

We first took available data to check efficiency in terms of PCL production, such as yield and polydispersity (PDI), a key parameter of polymerization reactions related to average molecular weight. A low PDI reflects a better MW control, which in turn depends on temperature, the lower the better. Therefore, temperature could be disregarded as factor; instead, reaction time was chosen assuming the polymerization step only for route B. To unveil any intensification, the original route C defines the Fb (*before*) factors (Table 6).

It is evident that route A is significantly intensified with respect to both B and C, especially the former (IF = 14.04), which agrees with a simpler synthetic approach conducted at low temperature. This HCl-catalyzed route, which makes ultimately the process solvent-free (excluding work-up) is also slightly more efficient than C (IF = 1.57). The comparative assessment between C and B favors the conventional route (IF < 1), although in the absence of mass data regarding the stepwise route leading to the starting 1,3-dioxepane, this statement should be taken with caution.

It is noteworthy how the authors reached the same conclusion relative to the plus of route A based on six out of seven environmental impacts arising from the LCA methodology: climate change (estimated in terms of $CO_2$ emission), fine particulate matter formation ($PM_{2.5}$), fossil fuel depletion (kg oil equiv), human toxicity (kg 1,4-dichlorobenzene equiv), terrestrial acidification (kg $SO_2$ equiv), freshwater eutrophication (kg P equiv), and water depletion (as water consumption in $m^3$). Since LCA surely represents the most compelling formalism to "measure" sustainability, going from upstream production to downstream activities, again a critical analyzer could hardly find a justification of the IF as calculated in Table 6. But in the absence of LCA data, the simple evaluation conveys much insight into IF to 'make a decision'. Obviously, one can check the validity of IF data in the frame of the LCA analysis by collecting a similar comparison among the three routes (Table 7).

If one excludes eutrophication, the intensification analysis corroborates the lower environmental impact of route A, as IF increases largely with respect to the alternative B and C synthesis. The same applies to most individual fractions determined for environmental impacts. Clearly, freshwater eutrophication distorts the results, with the highest contribution from route B, followed by route A, a fact attributed by the authors to the inorganic emissions into water (P equivalents). However, in relative terms the environmental impact of water eutrophication is almost negligible owing to its comparable low magnitude (see Table 7). As expected from quasi all-carbon-based syntheses, the impact on climate change, estimated through emissions that also reflect the electrical power used for polymer synthesis, outweights the other impacts. Route B is highly inefficient, due to the intermediate steps, while route A scores low and as a result has the highest IFs with respect to B and C. Notably, routes A and B are less harmful (lower human toxicity) than C, as the latter includes solvent, metal, and catalyst emissions.

### 4.5. Adiponitrile: industrial production routes

Together with the preceding polycaprolactone synthesis, a valuable follow-up case of industrial commodity is portrayed by adiponitrile (ADN), a large-scale chemical intermediate (>1.5 million tons/year) used in the production of Nylon 6,6. Two main routes are currently employed for the production of ADN, namely the hydrocyanation of 1,3-butadiene following a thermochemical route, and the electrodimerization of acrylonitrile, which takes profit of a more benign electrochemical approach (Scheme 6). The former is the most prominent method, although it is performed at temperatures up to 150 °C (incidentally even higher) and pressures of up to 5 MPa. Such conditions can be fine-tuned with the assistance of different zero-valent metal catalysts and additives. The main drawback however is linked to the use of hydrogen cyanide (HCN), a highly toxic reactant. The electrodimerization of acrylonitrile is carried out in a two-phase electrolyte consisting of an organic phase containing the starting material plus products, and an aqueous phase containing various ionic species. In the electrochemical cell, acrylonitrile undergoes reduction at the surface of cathode, while oxygen evolution takes place at the anode (Dai et al., 2012; Suwanvaipattana et al., 2017; Blanco et al., 2019, 2020). Notably, the electrochemical procedures can be run at mild temperatures (usually less than 80 °C) and atmospheric pressure. These two routes differ drastically in the energy source, raw material, reactor types, and reaction conditions, yet both being industrially deployed and commercially viable.

We are biased to class tentatively the electrochemical processes to be superior. While this may be true by solely regarding the highest figures of thermal *vs* electrical conditions, the comparative assessment is far from being simple. Renewable energy is inherently variable and solar energy, wind, or battery technology are so far considerably inefficient (Etzkorn, 2020). Even worse, the electricity supplied in an industrial operation does not necessarily stem from renewable sources. These premises tell us that toxicity/risks scores are likely the most important concerns in ADN production, and ranking should be agreed after discussion.

**Table 6**
Determination of IFs for comparative ring-opening of caprolactone derivatives.

| Routes | Factor[a] | $F_b$ | $F_a$ | $d$ | Fraction | IF$_{total}$[b] |
|---|---|---|---|---|---|---|
| C *vs* A | Isolated yield (%) | 72.5 | 97 | −1 | $(72.5/97)^{-1}$ = 1.34 | |
| | Polydispersity index | 2.1 | 1.8 | +1 | (2.1/1.8) = 1.17 | |
| | Reaction time (h) | 4 | 4 | +1 | (4/4) = 1.0 | 1.57 |
| C *vs* B | Isolated yield (%) | 72.5 | 55 | −1 | $(72.5/55)^{-1}$ = 0.76 | |
| | Polydispersity index | 2.1 | 2.4 | +1 | (2.1/2.4) = 0.87 | |
| | Reaction time (h) | 4 | 24 | +1 | (4/24) = 0.17 | 0.11 |
| B *vs* A | Isolated yield (%) | 55 | 97 | −1 | $(55/97)^{-1}$ = 1.76 | |
| | Polydispersity index | 2.4 | 1.8 | +1 | (2.4/1.8) = 1.33 | |
| | Reaction time (h) | 24 | 4 | +1 | (24/4) = 6.0 | 14.04 |

[a] $F_b$ and $F_a$ factors refer to the first and second routes in question, respectively.
[b] IF$_{total}$ data are calculated as the product (multiplication) of all individual IF values.

**Table 7**

Determination of IFs for environmental impact categories (LCA analyses) for the preparation of PCL homopolymer.

| Routes | Factor[a] | $F_b$ | $F_a$ | $d$ | Fraction | IF$_{total}$[c] |
|---|---|---|---|---|---|---|
| C vs A | Climate change (kg $CO_2$ equiv) | 1.07 | $3.59 \times 10^{-1}$ | +1 | 2.98 | |
| | Particulate matter formation (kg PM$_{2.5}$) | $4.00 \times 10^{-4}$ | $2.26 \times 10^{-4}$ | +1 | 1.77 | |
| | Fossil fuel depletion (kg oil equiv) | $1.26 \times 10^{-1}$ | $8.22 \times 10^{-2}$ | +1 | 1.53 | |
| | Freshwater eutrophication (kg P equiv) | $2.43 \times 10^{-11}$ | $3.22 \times 10^{-8}$ | +1 | 0.00075 | |
| | Human toxicity (kg 1,4-DB equiv) | $2.41 \times 10^{-1}$ | $3.83 \times 10^{-3}$ | +1 | 62.92 | |
| | Terrestrial acidification (kg $SO_2$ equiv) | $1.05 \times 10^{-3}$ | $6.69 \times 10^{-4}$ | +1 | 1.57 | |
| | Water depletion (m$^3$) | $7.43 \times 10^{-3}$ | $5.50 \times 10^{-3}$ | +1 | 1.35 | 0.81 (1076.22)[b] |
| C vs B | Climate change (kg $CO_2$ equiv) | 1.07 | 1.75 | +1 | 0.61 | |
| | Particulate matter formation (kg PM$_{2.5}$) | $4.00 \times 10^{-4}$ | $3.69 \times 10^{-4}$ | +1 | 1.08 | |
| | Fossil fuel depletion (kg oil equiv) | $1.26 \times 10^{-1}$ | $1.81 \times 10^{-1}$ | +1 | 0.70 | |
| | Freshwater eutrophication (kg P equiv) | $2.43 \times 10^{-11}$ | $1.20 \times 10^{-6}$ | +1 | 0.000020 | |
| | Human toxicity (kg 1,4-DB equiv) | $2.41 \times 10^{-1}$ | $8.82 \times 10^{-3}$ | +1 | 27.32 | |
| | Terrestrial acidification (kg $SO_2$ equiv) | $1.05 \times 10^{-3}$ | $1.22 \times 10^{-3}$ | +1 | 0.86 | |
| | Water depletion (m$^3$) | $7.43 \times 10^{-3}$ | $1.63 \times 10^{-2}$ | +1 | 0.46 | $1.0 \times 10^{-4}$ (4.98)[b] |
| B vs A | Climate change (kg $CO_2$ equiv) | 1.75 | $3.59 \times 10^{-1}$ | +1 | 4.87 | |
| | Particulate matter formation (kg PM$_{2.5}$) | $3.69 \times 10^{-4}$ | $2.26 \times 10^{-4}$ | +1 | 1.63 | |
| | Fossil fuel depletion (kg oil equiv) | $1.81 \times 10^{-1}$ | $8.22 \times 10^{-2}$ | +1 | 2.20 | |
| | Freshwater eutrophication (kg P equiv) | $1.20 \times 10^{-6}$ | $3.22 \times 10^{-8}$ | +1 | 37.27 | |
| | Human toxicity (kg 1,4-DB equiv) | $8.82 \times 10^{-3}$ | $3.83 \times 10^{-3}$ | +1 | 2.30 | |
| | Terrestrial acidification (kg $SO_2$ equiv) | $1.22 \times 10^{-3}$ | $6.69 \times 10^{-4}$ | +1 | 1.82 | |
| | Water depletion (m$^3$) | $1.63 \times 10^{-2}$ | $5.50 \times 10^{-3}$ | +1 | 2.96 | 8064.72 (216.38)[b] |

[a] $F_b$ and $F_a$ factors refer to the first and second routes in question, respectively.
[b] Excluding freshwater eutrophication.
[c] IF$_{total}$ calculated as the product (multiplication) of all individual IF values.
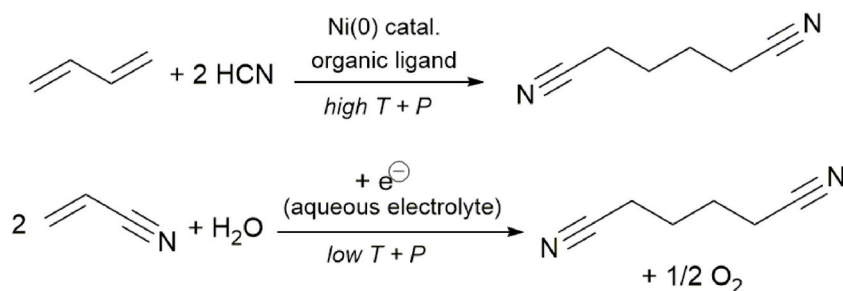


**Scheme 6.** Schematic thermochemical (top) and electrochemical (bottom) routes to industrial production of adiponitrile.

Toxicity indexes require a complete evaluation of LD$_{50}$ values for all chemicals involved. On a qualitative basis, like that suggested for solvents (Prat et al., 2014), a series of toxicity ratings have been proposed by, among others, the US government, WHO in the case of pesticides in particular, or the GHS (Globally Harmonized Systems of classification and labelling of chemicals) (Carson and Mumford, 2002; World Health Organization, 2019). For instance, a tox-factor (t-factor) as the ratio for the sum of the toxicity indexes of compounds leaving the reaction to that of compounds entering the reaction could be a suitable factor; *the smaller, the lower the resulting overall toxicity* (Egorova et al., 2020). We assigned to the ADN syntheses an arbitrary 5-to-1 hazard/risk scale taking the WHO grade classification. In Table 8, this mixed qualitative/quantitative analysis gives a positive number to the enabling electrical route based on acrylonitrile against the thermally-assisted hydrocyanation.

## 4.6. Extraction of bioactive substances

Extraction represents a usual separation/purification technique that relies heavily upon solvents, which as repeatedly emphasized

**Table 8**

Comparative assessment of factors proposed for the industrial production of adiponitrile.

| Factor | Thermochemical route | Electrochemical route | $d$ | Fraction | IF$_{total}$[c] |
|---|---|---|---|---|---|
| Temperature (° C)[a] | 150 | 80 | +1 | (150/80) = 1.87 | |
| Pressure (MPa)[a] | 5 | 0.1 | +1 | (5/0.1) = 50 | |
| Hazard/risk[b] | 5 | 3 | +1 | (5/3) = 1.66 | 155.2 |

[a] Taking the usual highest figures.
[b] Based on the grades of WHO classification for toxicity: *extremely hazardous, highly hazardous, moderately hazardous, slightly hazardous, and acute hazard unlikely* (from 5 to 1, respectively).
[c] IF$_{total}$ calculated as the product (multiplication) of all IF values (fraction data).

cause the major environmental, health and safety impacts by occupational exposure (Jimenez-Gonzalez, 2019). On the other hand, extraction is often a must to isolate reaction end products and high value-added compounds for the consumer such as cosmetics, nutraceuticals, APIs and medicinal herbal extracts. Enabling techniques, alone or combined, have become part of industrial portfolios for extraction of food and natural products (Chemat et al., 2020; Kumar et al., 2021; Cravotto et al., 2008). To that end, the solvent's choice is clearly a critical issue and, ionic liquids (ILs) in particular represent convenient surrogates for volatile organics, even if both ILs or deep eutectic solvents (DES) may also be toxic. The eutectic mixtures are usually generated by mixing two or more components where melting point depression, leading to a stable liquid phase at room temperature, occurs by extensive hydrogen bonding.

Among DES, those of natural origin (amino acids, carbohydrates, or terpenes), expected to be much more innocuous, are receiving increasing attention (Van Osch et al., 2019). A recent and well-elaborated exploration of terpene-based DES has been applied to the extraction of astaxanthin (AXT), a carotenoid secondary metabolite present in the exoskeleton of chitin-rich crustaceans (Rodrigues et al., 2020). AXT exhibits broadband bioactivity that includes cytotoxicity, antiproliferative effects against some cancer lines, and antimicrobial properties. That minor component can be extracted using different organic solvents, albeit efficiency increases with temperature. A good protocol involves Soxhlet extraction with acetone (boiling point 56 °C). The terpene combination of menthol: myristic acid (8:1) at 60 °C was found to be the optimal DES to achieve a comparable efficiency to Soxhlet extraction in shorter times. Furthermore, the menthol:myristic acid solvent greatly outperforms extraction of AXT from other biomass materials relative to the corresponding Soxhlet extractions.

Even if extraction with terpenic DES shows some advantages over the conventional thermal extraction, the major benefits derive from *in vitro* bioactivity evaluation of such natural extracts. $EC_{50}$ values (effective AXT concentrations, mg/mL) for AXT extracts from different terpenic solvents showed disparate results. In fact, the acetone extracts had much lower $EC_{50}$ values than all terpenes, although as the authors noted such results can be limited by the solubility and toxicity of DMSO employed as vehicle for the organic extract and the AXT standard. Clearly, no conclusive statements can be inferred and, on the other hand, AXT would hardly compete with other more potent antiproliferative drugs. However, much more interesting results were obtained for the antimicrobial activity of AXT-extracts, which inhibit the growth of opportunistic pathogens like *S. aureus* and *E. coli*, at lower $MCI_{50}$ (minimum inhibitory concentrations) than the Soxhlet extracts. It is well known that some naturally occurring terpenes show broad antimicrobial activity, and this enables the direct use of AXT-extracts as food preservatives for instance, without separating AXT from the solvent. It is obvious that the enhanced effect could also arise from other components soluble in DES, while acetone would lack selectivity to extract antimicrobial ingredients other than AXT. From such reliable data, Table 9 depicts an intensification effect in the present case associated with bioactivity and biocompatibility to a large extent.

### 4.7. Enzyme-assisted greener transformations

Biocatalysis and biotransformations are good examples of sustainable methods. The use of purified enzymes together with whole cells incorporating a complete biomolecular machinery, enable useful transformations that are inaccessible by conventional procedures (De Gonzalo and Lavandera, 2021). Enzymes, inherently chiral substances, are often vastly superior to other asymmetric catalysts. Mixed chemo-enzymatic routes have become customary in synthetic approaches as well (*vide supra*, sect. 4.3.).

There are recent studies involving enzymes along with co-solutes, solvents, and other experimental variables, for which the concept of intensification can be discussed. A usual downside of enzymatic catalysis is that the maximum yield is often controlled by thermodynamic equilibrium. To overcome this limitation, two model enzymatic reactions of synthetic interest have been investigated in detail (Voges et al., 2017): (1) reduction of acetophenone to 1-phenylethanol catalyzed by alcohol dehydrogenase (ADH) using 2-propanol as hydrogen source, and (2) an L-alanine aminotransferase (ALAT) reaction that enables the conversion of 2-oxoglutarate to L-glutamate, while L-alanine undergoes desamination to pyruvate (Scheme 7).

Both enzyme-catalyzed reactions can be conducted at pH 7 and require the presence of cofactors, $NADH/H^+$ (nicotinamide adenine dinucleotide) and pyridoxal-5-phosphate (P5P), respectively. The team rightly reasoned that the presence of additives, such as electrolytes or osmolytes (namely, ionic liquids, choline chloride, urea, trimethylamine *N*-oxide, or a cationic surfactant), could modify substantially the solubility of the solutes, thereby shifting the enzymatic equilibrium. In fact, results evidenced that both the equilibrium position and product yield in aqueous media depend on the type of additive and molality in the reaction mixture.

A rationale in the search for intensification, however, is somewhat difficult because every additive leads to different yields at different concentration, even though experimental results can be predicted with accuracy by modeling. Some useful conclusions could be extracted from the ADH reaction by comparing single-phase systems (SPS, in pure IL) and two-phase systems (TPS, comprising IL plus buffer). The typical IL [bmim]Tf$_2$N was chosen due to its low solubility in water. The TPS system requires immobilization of ADH in gel beads, which is time-consuming and more expensive than the use of native enzymes.

In any case, TPS allows facile product separation, albeit a more important advantage over SPS is that the biphasic reaction enables using much higher initial molalities of acetophenone (ACP). As a result, the weight fractions of the product (1-phenylethanol, 1-PE) increased significantly relative to SPS reactions. Excess of 2-propanol (2-P) as cosubstrate provokes higher product yields. Thus, 1-PE yields using a 2-P/ACP ratio = 20 are higher than 1-PE yields starting from 2-P/ACP = 1, regardless of the reaction media. Moreover, the use of [bmim]Tf$_2$N alone as solvent shift the equilibrium toward the reactant, which contributes to decrease the yield of 1-PE as well.

Clearly, the parameters of molal ratios and productivity discussed above represent objective and measurable factors to estimate the level of intensification. SPS reactions afford better performance in terms of product yield and weight fraction than TPS ones, and such values increase as the 2-P/ACP ratio increases. The advantage of using a monophasic IL is an enhanced solubility of ACP (poorly water-soluble). Table 10 summarizes the available data collected for ADH (TPS) reactions, where a decrease in the initial molality ratio is desirable at the cost of a lower product yield (as undesirable factor).

**Table 9**

Estimation of IFs from operational and antimicrobial results reported for extraction using natural terpene mixtures as solvent.

| Factor | Soxhlet extraction | Terpenic DES extraction | $d$ | Fraction | $IF_{total}$[b] |
|---|---|---|---|---|---|
| Carotenoid yield ($\mu$g AXT/g dry residue) | 9.7 | 9.3 | −1 | $(9.7/9.3)^{-1} = 0.96$ | |
| Extraction time (h) | 6 | 2 | +1 | $(6/2) = 3$ | |
| Temperature (° C) | 56 | 60 | +1 | $(56/60) = 0.93$ | |
| Antimicrobial activity ($MIC_{50}$), ($\mu$L/mL)[a] | 500 | 63 | +1 | $(500/63)^{-1} = 7.94$ | 21.3 |

[a] For comparative purposes, upper limits of $MIC_{50}$ data were taken.

[b] $IF_{total}$ calculated as the product (multiplication) of all IF values (fraction data).
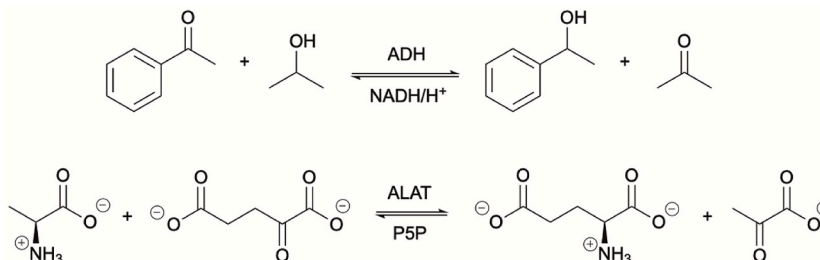


**Scheme 7.** Model enzymatic reactions involving ketone reduction with alcohol dehydrogenase (ADH) and transamination catalyzed by L-alanine aminotransferase (ALAT).

Overall, this case represents a borderline situation where opposite effects should be counterbalanced. The IF determined from experimental results could serve as orientation for decision makers. An economic analysis would help in comparing the global costs of SPS *vs* TPS processes, especially if large-scale operations are envisaged employing neat ILs.

Biocatalysis can be performed in either batch or continuous mode, for which multiple variables need to be assessed, such as deployment of multienzymatic cascades, immobilization methods, spatial and temporal compartmentalization, etc. (Rocha et al., 2022). Finally, key pluses of enzyme-based reactions are linked to the generation of enantioenriched, often enantiomerically pure, substances, which are often required for drug design. In the above example, 1-phenylethanol is of course a chiral substance, although the issue of enantioselection with ADH was omitted. Enzymes do this job well and efficiently (Palomo and Mateo, 2019).

## 5. Conclusions

This work aimed at presenting a simple, yet useful, decision tool to capture the factors that may have impacts on greenness and guide further improvements in chemical processes. Taken alone, the Intensification Factor (IF) could be understood as a simplistic way to evaluate the whole range of parameters that ultimately can be involved in sustainable options, which is not the case. The IF does not replace other metrics, particularly those concerning matter balances, even if unsatisfactory. *The IF provides a scalar quantity that informs on the pros and cons of variables, which may be increased in terms of decision-making when two or more chemical processes are considered.*

The IF captures information from values and estimations available to the researchers or experts at a given moment. The refinement and practical advantage of the IF increase as more information becomes available. In short, the IF is a number that helps to compare among sustainable solutions and improve existing processes. It is easy to calculate, and it can be understood by both experts and lay people. We have illustrated its utility with numerous examples, for which conclusions are similar or equivalent to those obtained by other metrics and more complex analyses.

We are aware that any decision tool may generate *ad hoc* or tailored conclusions, often with unintended bias. The IF and other sophisticated methods share a common goal of tackling all reliable information available, including debatable economic, political, and societal aspects. Thus, we propose integrating the IF with other metrics and decision algorithms to allow the development of new tools with broad scope.

**Table 10**

IFs determined for ADH-catalyzed TPS reactions at different initial molalities.

| Factor* | $F_b$ | $F_a$ | $d$ | Fraction | $IF$[a] |
|---|---|---|---|---|---|
| 2-P/ACP ratio | 20 | 1 | +1 | $(20/1)^{-1}$ | 20 |
| Yield (% ACP) | 72 | 10 | −1 | $(72/10)^{-1}$ | 0.14 |
| Weight fraction (% ACP) | 0.06 | 0.25 | −1 | $(0.06/0.25)^{-1}$ | 4.17 |
| | | | | $IF_{total}$ | 11.68 |

*$F_b$ and $F_a$ factors refer to results obtained at the initial 2-P/ACP ratios.

[a] $IF_{total}$ calculated as the product (multiplication) of all individual IF values.

## Author statement

David Fernandez Rivas: Conceptualization, Data curation, Funding acquisition, Investigation, Writing - original draft, Writing - review and editing. Pedro Cintas: Conceptualization, Data curation, Funding acquisition, Investigation, Writing - original draft, Writing - review and editing.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: DFR is co-founder of BuBclean, the company commercializing the Cavitation Intensifying Bags, BuBble Bags, and has financial interests in it.

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