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### Green Foundation Box

1. This work introduces a unified continuous-flow platform for multiple electrophilic nitrogen transfer reactions, replacing diverse batch protocols with a single, safer and more controllable system, thereby enhancing efficiency, scalability, and process intensification.
2. The methodology combines flow chemistry with a comprehensive sustainability assessment, integrating LCA, TEA, and planetary boundary metrics. This quantitatively demonstrates reduced environmental impact, improved resource efficiency, and economic viability compared to state-of-the-art batch processes.
3. Further greening could be achieved by expanding the use to other reaction partner, recycling the generated PhI, as well as integrating real-time process monitoring and AI-driven optimization to further minimize waste, energy consumption, and environmental footprint.



## ARTICLE

## A Novel and Sustainable Continuous-Flow Approach to Atom Deletion and Insertion by Electrophilic Nitrogen Transfer

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Electrophilic nitrogen transfer has emerged as a prominent approach in skeletal editing tactics to surgically modify molecular core structures by nitrogen atom insertion, deletion or transmutation. Despite rapid progress in the development of these methodologies, wider adoption is hindered by challenges associated with scale-up and requirement for transformation-dependent re-optimization of reaction conditions. We herein disclose a sustainable continuous-flow protocol, which unifies several skeletal editing tactics leveraging electrophilic nitrogen transfer. We demonstrate that this protocol is applicable to nitrogen atom insertion, deletion, nitrile formation and aziridination. We furthermore evaluate the sustainability parameters of our continuous-flow protocol compared to state-of-the-art batch protocols through a currently unprecedented lifecycle assessment and techno-economic analysis.

### Introduction

The “*necessary nitrogen effect*” is the observation that the replacement of a carbon-atom with a nitrogen atom in (aromatic) ring systems often leads to pronounced (beneficial) modulation of molecular and physicochemical properties of drug candidates, as well as their intra- and intermolecular interactions.<sup>1,2</sup> This has since become an important design strategy in drug discovery campaigns, and it is thus unsurprising that approximately 80% of recent top-selling drugs contain at least one nitrogen atom,<sup>3,4</sup> and the top 10 most common heterocycles in drugs are nitrogen-containing cycles (**Figure 1, a**).<sup>5</sup>

The conceptually straightforward strategy of introducing subtle changes to a given core structure by inclusion of nitrogen atoms in advanced lead compounds to fine-tune their properties, however, is in practice a time- and resource-intensive process because it requires de novo synthesis of the desired nitrogen-containing analogue. Addressing this drawback, skeletal editing strategies have provided novel approaches for structural late-stage diversification by selectively editing complex organic molecules at the atomic level.<sup>6–8</sup> The direct interconversion of carbocycles to nitrogen-containing heterocycles thus offers an

orthogonal retrosynthetic disconnection compared to classic forward-design, which can accelerate drug discovery by late-stage modification of existing libraries for structure-activity relationship (SAR) studies.

Within the context of skeletal editing, the modification of molecular core structures by nitrogen atom insertion,<sup>9–15</sup> deletion,<sup>16–18</sup> or transmutation<sup>19–24</sup> (N-O, N-C or N-S atom exchange) has emerged as a particularly prominent approach, and numerous methods have been developed in recent years to achieve selective core modulation transformations. Despite these studies, a recurring theme within single nitrogen atom editing tactics is the synergistic combination of hypervalent iodine(III) oxidants with ammonia sources, which generates in situ a highly electrophilic iodonitrene intermediate capable of electrophilic amination, facilitating the formation of C–N, N–N, and S–N bonds (**Figure 1, b**).<sup>25,26</sup> This powerful reactivity in combination with the operational simplicity of iodonitrene intermediates has led to the development of several next-generation synthetic processes.

In the context of *N*-insertion reactions, iodonitrenes enable the surgical introduction of a single nitrogen atom into carbo- and heterocycles such as indenes, indoles, and pyrroles.<sup>13–15</sup> This approach provides access to heterocyclic scaffolds otherwise difficult to access and holds considerable promise in drug discovery. In addition, single nitrogen atoms can be inserted into weak  $\pi$ -bonds of alkenes, abundant feedstock chemicals, to allow the divergent synthesis of aziridines or nitriles from the same starting materials.<sup>12,27,28</sup> In the context of *N*-deletion strategies, iodonitrenes can participate in ring-opening processes that lead to the loss of molecular nitrogen, enabling the generation of reactive intermediates under controlled conditions. This allows chemists to selectively excise nitrogen atoms from heterocycles, thereby converting stable nitrogen-containing motifs into structurally modified products with new reactivity and function.<sup>18</sup>

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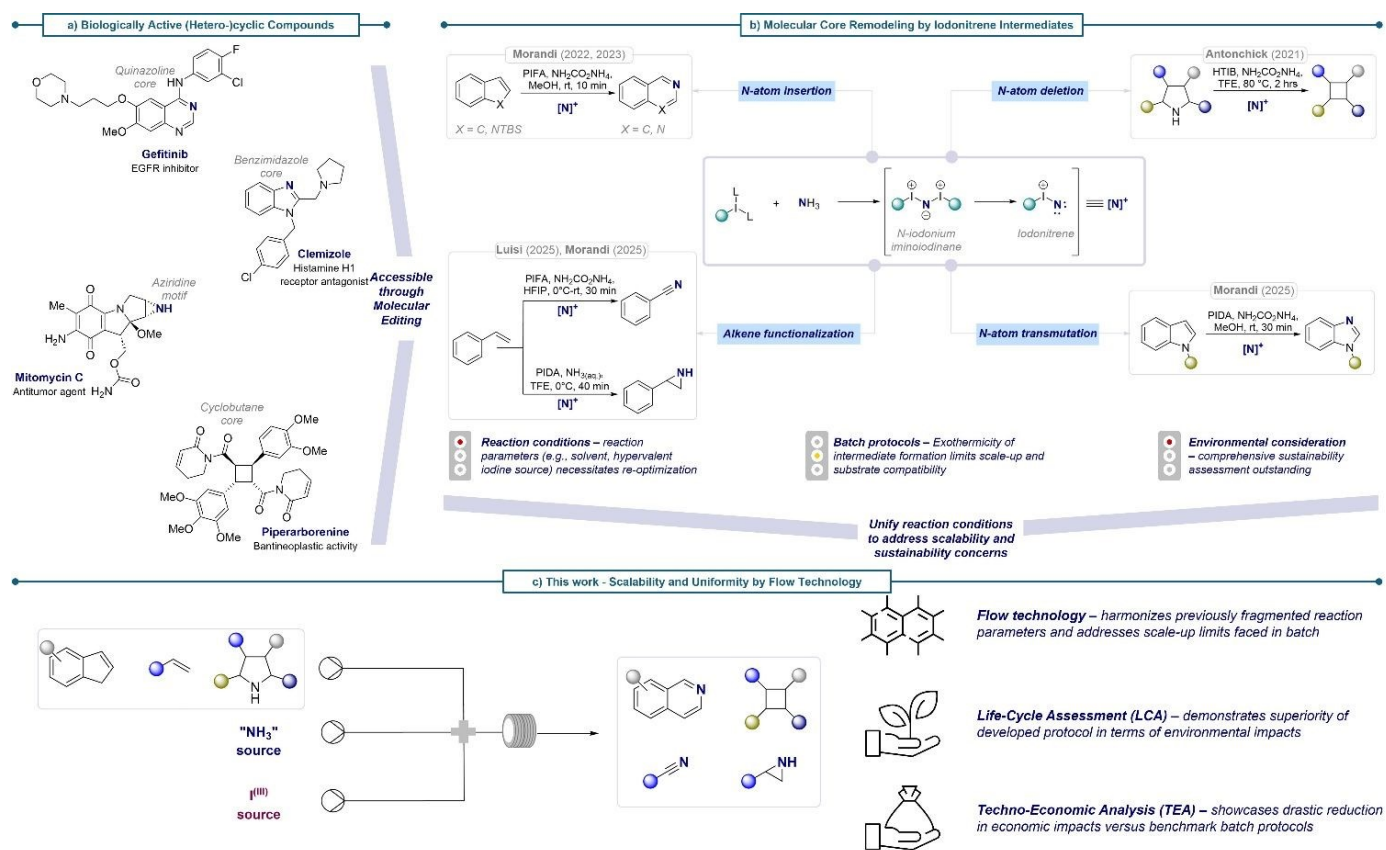


Despite the abundance of skeletal editing tactics leveraging idonitrene-based chemistry, the broader adoption of these processes is limited by two key drawbacks. First, in practice each transformation is reliant on distinct reaction conditions, requiring laborious (re-)optimization of parameters, such as hypervalent iodine precursor, solvent, reaction time, ammonia source, temperature and stoichiometry. Second, the in situ formation of the electrophilic idonitrene intermediate is highly exothermic, which under typical batch conditions can limit substrate scope and reaction control. Moreover, when such methods are considered for the synthesis of agrochemicals or active pharmaceutical ingredients, the reliance on batch processing, which remains the current state-of-the-art, can introduce additional complications during scale-up and may entail intrinsic drawbacks in terms of safety, economic efficiency, and environmental impact.<sup>11</sup>

In light of the increasing environmental pressures placed on fine-chemical producers by regulatory frameworks, there is a growing need to a shift reaction development from what is synthetically possible to processes that align synthetic efficiency with environmental responsibility, safety, and

scalability.<sup>29,30</sup> The development of green-by-design processes thus avoids retrofitting of these attributes to non-sustainable routes at later stages of process development and provides a practical, actionable framework for the sustainable manufacture of high-value fine chemicals. Continuous-flow processing has received particular attention as an enabling technology to address the aforementioned limitations, as it can enhance safety, scalability, and process control, by improving heat and mass transfer. In addition, precise control of residence times can allow for notable improvements in chemoselectivity which cannot be achieved under classical batch conditions.<sup>31,32</sup>

Leveraging the intrinsic benefits brought about by continuous-flow processing,<sup>33,34</sup> we herein present a unified, straightforward continuous-flow strategy on the basis of four previously developed idonitrene-based editing tactics in batch.<sup>12,14,18,27</sup> These synthetic and technological advances are further supported by the first comprehensive life-cycle assessment (LCA) and techno-economic analysis (TEA), enabling direct comparison of sustainability and economic performance with previously reported batch protocols (Figure 1, c).<sup>35,36</sup>



**Figure 1:** a) Biologically active (hetero-)cyclic compounds with cores accessible by idonitrene-based molecular editing approaches. b) Molecular core remodelling tactics based on idonitrene intermediates. c) This work – unified continuous-flow strategy for idonitrene-mediated skeletal editing tactics, including life cycle assessment and techno-economic analysis.

## Results and Discussion

We commenced our study on the synthetic development by process optimization. Recently, a continuous-flow protocol was



developed by Morandi and co-workers for the nitrogen atom insertion into diverse azarenes, which relies on the in situ preparation of ammonium carbamate from ammonia and carbon dioxide (**Scheme 1, a**).<sup>11</sup> The continuous-flow set-up thus required seven inlet streams, several cross- and T-mixers, and two gaseous streams (CO<sub>2</sub> and N<sub>2</sub>) with mass flow controllers. We aimed for a more practical alternative that would be applicable beyond nitrogen atom insertion to other iodinitrene-mediated editing tactics (**Scheme 1, b**). We hypothesized that instead of generating ammonium carbamate in situ, ammonia could directly serve as the nitrogen-atom source, as recently demonstrated by us for the conversion of alkenes to NH-aziridines.<sup>27,28</sup> Furthermore, we have previously demonstrated the feasibility of processing aqueous ammonia solutions efficiently under continuous-flow conditions for the conversion of sulfides and sulfoxides into NH-sulfoximines.<sup>37</sup>

Thus, this would not only significantly simplify the microfluidic set-up by reducing the number of inlet streams and eliminating gaseous inlets, but also prevent issues associated with solid accumulation of ammonium carbamate ("clogging") due to its low solubility in non-aqueous solvents. Although there are hazards associated with the use of aqueous ammonia, handling in a closed continuous-flow set-up maximizes user safety by minimizing exposure.<sup>38</sup> Furthermore, to address our techno-economic objectives, we focused on the use of (diacetoxyiodo)benzene (PIDA) instead of more costly bis(trifluoroacetoxy)iodo)benzene (PIFA).

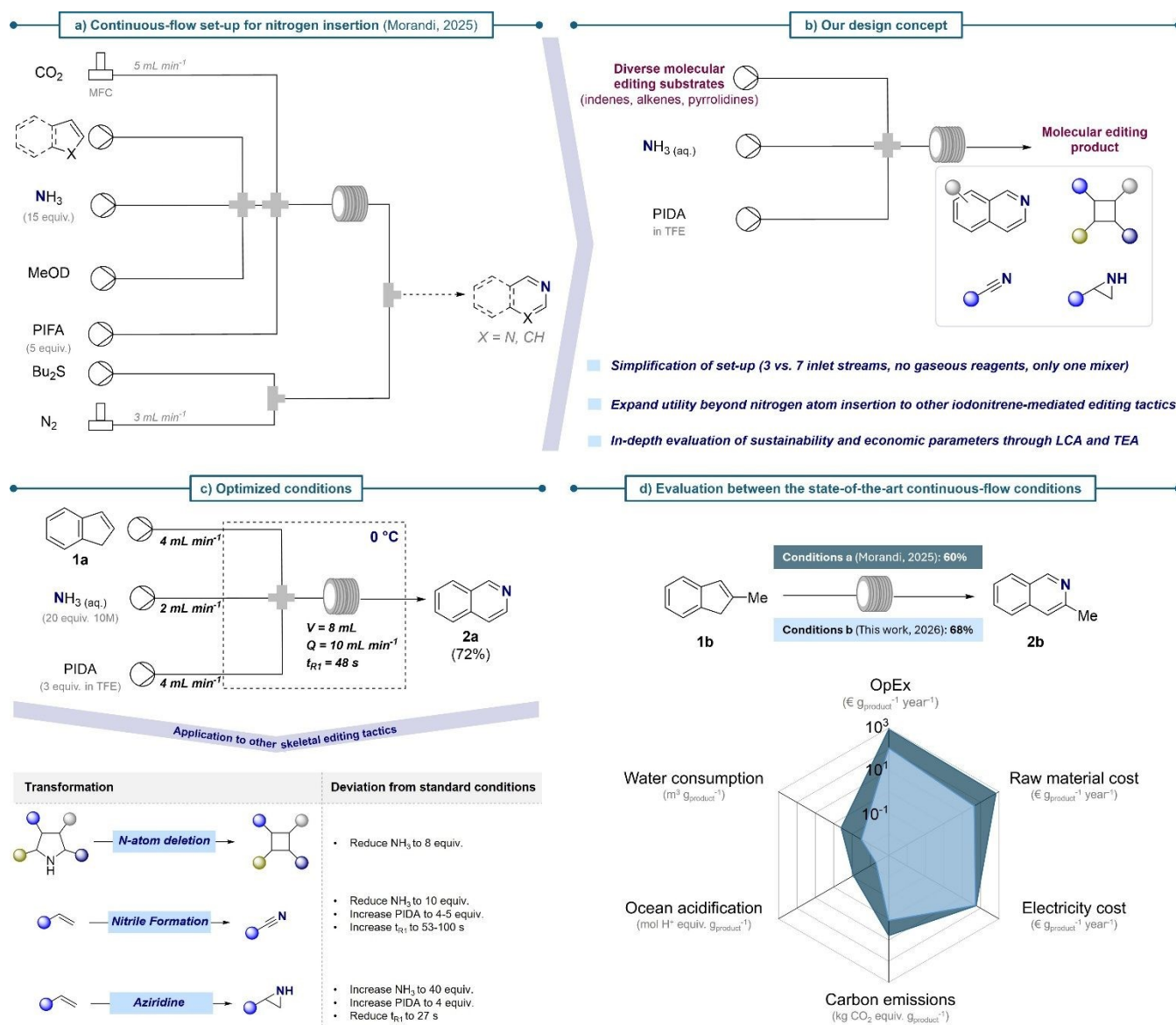
With the design targets clearly set-out, we began process development by optimizing the remodeling of the indene core by *N*-atom insertion toward isoquinolines (**Scheme 1, c**). Careful screening of various process parameters incl. internal volume, flow rate, residence time, reagent equivalents (see Supporting Information for further details) showed that optimal results are obtained when using 20 equivalents of aqueous ammonia solution and three equivalents of PIDA mixed together via a four-way mixer. A residence time of only 48 seconds at 0 °C

ensured full conversion of the substrate. To our delight and in line with our target we found that process translation to other core remodeling tactics required only minimal adjustments of individual process parameters: For example, N-deletion of pyrrolidines was performed with slight reduction of equivalents of aqueous ammonia (8 equiv. vs. 20 equiv.). Also, the conversion of alkenes to nitriles and aziridines could be performed with the same set-up. For the conversion to nitriles we found that best results are obtained with a lower quantity of aqueous ammonia (10 equiv.) and a higher excess of PIDA (4-5 equiv.), whereas optimal results for NH-aziridination were observed with a high excess of aqueous ammonia (40 equiv.) and slightly shorter residence times (27 seconds).

With the optimized reaction conditions in hand, we first assessed if the optimized simple set-up indeed implied also techno-economic advantages. We thus benchmarked our protocol for the state-of-the art continuous-flow protocol<sup>11</sup> (**Scheme 1, a**) for the conversion of 2-methylindene **1b** to isoquinoline **2b** in terms of its techno-economic performance and environmental sustainability (**Scheme 1, d**). Both approaches were examined within a framework encompassing three key economic indicators and three major environmental metrics, centering operational expenditure, raw-material and electricity cost, carbon emission, ocean acidification, and water consumption (for further detail see Supporting Information **Tables S1-9**). Our developed reaction conditions demonstrated an order of magnitude reductions in OpEx (87%) and raw material cost (93%) compared to the previous state-of-the-art conditions (**Scheme 1, a**). These reductions are considerable, and were primarily attributed to the cost-intensive reliance on MeOD and PIFA, as these components can account for 97% of the total raw material costs. Moreover, the implementation of our conditions led to reductions in carbon emissions, ocean acidification, and water consumption of 81%, 94%, and 92%, respectively. Across these reductions, environmental hotspots were mainly associated with the excessive use of PIFA.



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**Scheme 1:** a) State-of-the-art - continuous-flow set-up for nitrogen insertion (Morandi, 2025); b) Our general design concept; c) Optimized conditions for desired editing tactics; d) Comparative evaluation between the state-of-the-art continuous-flow conditions (teal blue) and the continuous-flow protocol developed in this study (light blue) with respect to key economic and environmental indicators.

Encouraged by the improvement of the conditions with respect to the state-of-the-art continuous-flow conditions, we turned our attention to exploring the substrate scope (**Scheme 2**). We began our investigation with the nitrogen insertion into indenes, and thus a series of 2- and 3-substituted indenes were converted to the corresponding substituted isoquinolines **2a-2i** in up to 75% yield. Aliphatic and aromatic substituents were tolerated on the five-membered ring without notable effect on

the efficiency of the process. Notably, also the sensitive thiophene motif was tolerated under the basic reaction conditions to afford isoquinolines **2g** in 53% yield. Unexpectedly, the presence of a bromine-substituent on the benzene-ring led to a reduction in process efficiency, affording the desired isoquinolines **2h-2i** in 33-35% yield, although the reasons for this reduction remain unclear.



We subsequently selected to investigate the conceptually opposite strategy: *N*-deletion of pyrrolidines (**3**) to affect ring contraction towards cyclobutanes (**4**). We were pleased to find that a series of tetra-substituted pyrrolidines underwent the desired ring-contraction efficiently in up to 82% yield. The yields of polysubstituted cyclobutanes **4a-4i** were generally good to very good, and were either comparable to or, in most cases, superior to those obtained under batch conditions.<sup>18</sup> Notably, the stereochemical integrity of the starting pyrrolidine was fully preserved in the final products. In general, pyrrolidines substituted with aromatic rings bearing electron-withdrawing groups (*e.g.*, **4a-4c**, **4e-4f**) showed superior performance to those bearing electron-donating substituents (*e.g.*, **4h-4i**). Of particular note are chiral pyrrolidines (*R,S*)-**5** and (*S,S*)-**5**, for which the cyclobutane products (*R,S*)-**6** and (*S,S*)-**6** are obtained in highly enantioenriched form, a consequence of the direct radical recombination pathway. The modest yields observed for these products are mainly attributed to the lower degree of substitution in the starting pyrrolidines, a trend that was also reported by Antonchick for the corresponding batch conditions.<sup>18</sup>

To further highlight the versatility of the developed process, we extended the protocol to the addition of single nitrogen atoms across  $C(sp^2)$ - $C(sp^2)$  bonds of alkenes (**7**) to form nitriles (**8**) and aziridines (**9**) selectively – an inherently challenging task given a mutual intermediate that can be converted to either product depending on the reaction conditions. As such, nitriles **8a-8d**, bearing halogen substituents at various positions of the aryl ring, were obtained in 50–75% yields. Nitriles **8e-8g** obtained from (poly-)fluorinated substrates were formed in moderate yields, with stronger electron-withdrawing groups leading to diminished efficiency (50%, 33%, and 16% yield for F, CF<sub>3</sub>, and C<sub>6</sub>F<sub>5</sub>, respectively). In contrast, nitriles derived from electron-rich aryl rings (**8i-8l**) were obtained in significantly higher yields (70–97%). A clear trend on reaction efficiency based on the electronic character of the substrate is thus notable. The observed trend is a consequence of the stability of the proposed key aziridine iodonium intermediate, which collapses to the azallenium ion through electrocyclic ring opening en route to

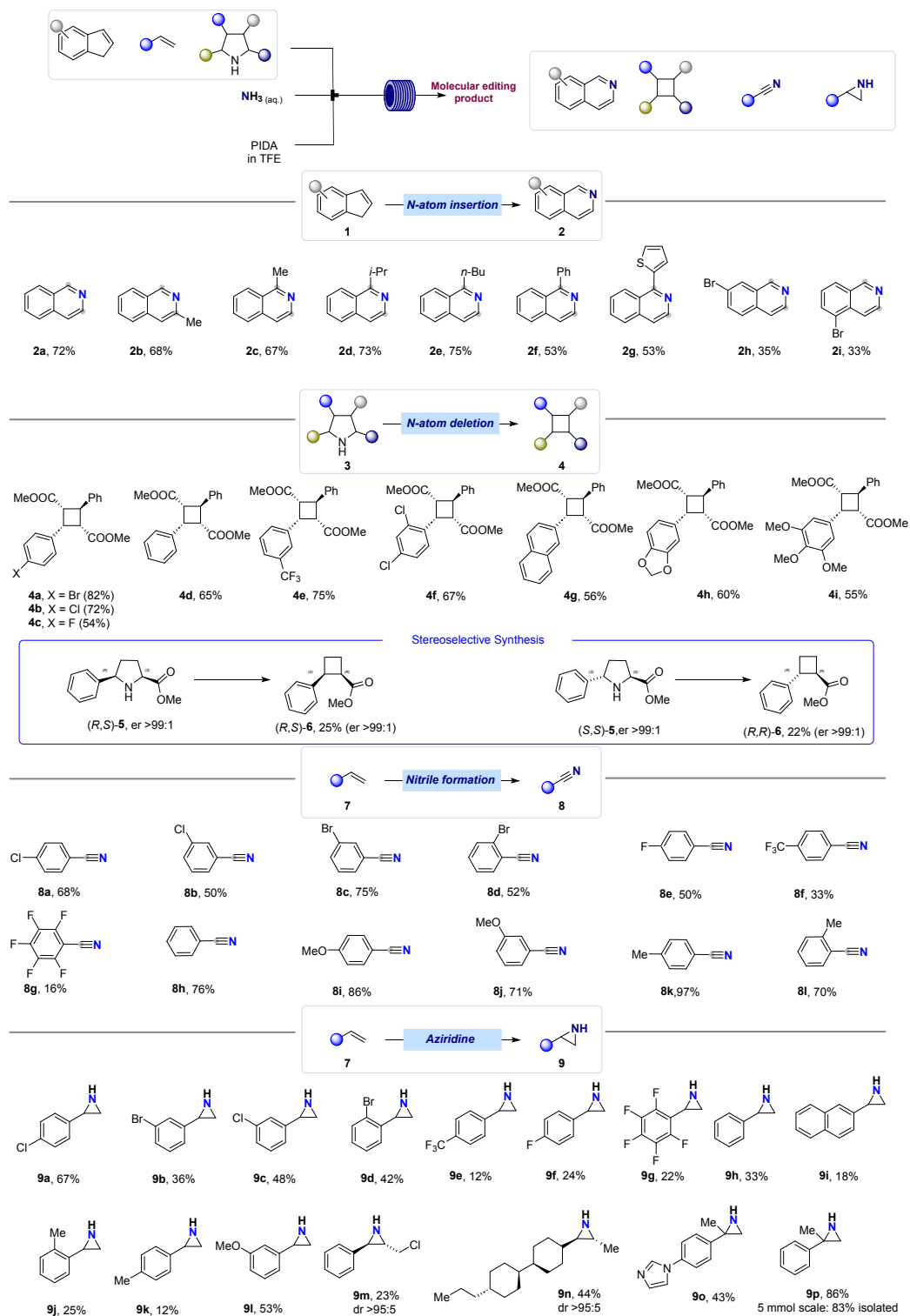
nitrile formation.<sup>12</sup> This transformation is more efficient and favoured for electron-rich substrates, and thus higher reaction yields are observed.

To complete our objective of accessing several core remodelling procedures with the same process, we last focused on the synthesis of NH-aziridines (**9**) from alkenes (**7**). As recently reported by us, the difficulty in this process is the successful trapping of an aziridine iodonium intermediate before electrocyclic ring opening and further oxidation to the nitrile. This divergent pathway was also accessible with minimal adaptation of conditions of the continuous-flow process, demonstrating how careful optimization of residence time in flow processes can control reaction selectivity. Indeed, by reduction of the residence time from up to 100 seconds to 27 seconds, a number of alkenes were converted into the corresponding NH-aziridines **9**. For example, styrenes containing bromo- or chloro-substituents afforded aziridines **9a-9d** in yields of 36–67%. In contrast, substrates bearing fluorine atoms or a strongly electron-withdrawing CF<sub>3</sub> group led to slightly diminished yields, likely due to the short residence times, given that this substrate showed reduced reactivity also under batch conditions.<sup>27</sup>

Under the optimized conditions, styrene furnished aziridine **9h** in 33% yield, while more electron-rich styrenes provided aziridines **9i-9l** in yields ranging from 10–53%. Notably, for these electron-rich substrates, the competing pathway leading to the corresponding nitrile was more pronounced, likely due to increased stabilization of the proposed azallenium ion intermediate. As reported, cinnamyl chloride proved to be a viable substrate for direct aziridination,<sup>27</sup> delivering NH-aziridine **9m**, albeit in a modest yield of 23%. The methodology was also applicable to an aliphatic alkene, affording aziridine **9n** in 44% yield with complete retention of alkene stereochemistry. Gratifyingly,  $\alpha$ -methyl-substituted styrenes performed particularly well, yielding aziridines **9o** and **9p** in up to 86% yield. In the case of aziridine **9o**, the reaction was successfully scaled up to 5 mmol, delivering the product in 83% yield.



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**Scheme 2:** Substrate scope of atom deletion and insertion by electrophilic nitrogen transfer in continuous-flow mode. See Supporting Information for substrate-specific reaction conditions.



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In line with our objectives defined at the outset, we were able to successfully develop a unified continuous-flow process for four different core iodonitrene-mediated remodelling processes. The process was shown to be scalable, and in most cases showed similar or better performance compared to previously reported batch processes. With this streamlined process in hand, we last focused on testing the processes' economic and environmental impact, given the growing importance of green-by-design processes. To assess this goal, unprecedented techno-economic analysis and lifecycle assessment were performed.

The TEA was conducted to rigorously evaluate the continuous-flow methodologies developed in this study for the synthesis of **2a**, **4b**, **8h**, and **9p**, in direct comparison with benchmark batch protocols reported in the literature.<sup>12,14,18,39</sup> As shown in **Figure 2a** (**Table S10** in Supporting Information), the transition to continuous-flow processing enabled a drastic reduction in energy consumption across all four synthetic routes. In particular, the implementation of the continuous-flow method resulted in an average energy consumption reduction of 92% relative to conventional batch techniques. Batch reactions exhibited significantly higher energy requirements, ranging from 4 kWh  $g_{\text{product}}^{-1}$  to 15 kWh  $g_{\text{product}}^{-1}$ . By contrast, the total energy demand associated with the continuous-flow method was below 1 kWh  $g_{\text{product}}^{-1}$ . Among the four investigated reactions, aziridine synthesis exhibited the most pronounced energy savings when moving to flow conditions, with a 97% decrease, and energy consumptions passing from 15.2 kWh  $g_{\text{product}}^{-1}$  to 0.5 kWh  $g_{\text{product}}^{-1}$ . These results are directly translated into significant cost savings in terms of electricity expenditure (**Figure 2b** and **Table S11** in Supporting Information). Electricity expenses under batch conditions ranged between 400 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup> and 1400 €  $g_{\text{product}}^{-1}$ , whereas the application of continuous-flow protocols reduced this value to ca. 50 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>. To further contextualize the economic feasibility, raw material costs were also analyzed (**Figure 2c** and **Table S12-S19** in Supporting Information). On average, continuous-flow methods yielded a 60% reduction in raw material expenses relative to batch. In particular, the synthesis of **9p** again stood out, with a 73% cost reduction, from 141.1 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup> to 38.9 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>. This decrease was largely attributed to eliminating two major cost-driving factors associated with the batch methodology, specifically the use of the  $\text{Rh}_2(\text{esp})_2$  catalyst and the significant use of dichloromethane (DCM) at the work-up stage, which together accounted for 82% of the total raw material cost (54.6 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup> and 61.2 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>, respectively).

In contrast, the continuous-flow protocol was designed to enhance material utilization and mitigate excessive solvent consumption. The continuous-flow technique entirely excluded the use of the  $\text{Rh}_2(\text{esp})_2$  catalyst, whereas the implementation of an  $\text{Et}_2\text{O}$ -based workup solvent system, used in significantly

lower volumes, contributed to a 68% reduction compared to DCM utilization, lowering the expense to 19.3 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>. We identified similar cost-saving patterns across the remaining three continuous-flow protocols, with raw material cost reductions of 71%, 57%, and 38% for **8h**, **2a**, and **4b**, respectively.

Building on these findings, we conducted a more comprehensive operational expenditure (OpEx) analysis, encompassing seven major cost categories, including not only raw materials, but also utility, maintenance, labour, administrative, and general operating expenses (**Figure 2d** and **Table S20** in Supporting Information). The implementation of continuous-flow processing delivered an average 87% reduction in OpEx with respect to batch conditions. In quantitative terms, batch protocols exhibited operational expenditures ranging around 800-1800 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>, whereas the continuous-flow method yielded costs of 100-150 €  $g_{\text{product}}^{-1}$  year<sup>-1</sup>, representing an order-of-magnitude improvement in OpEx.

### Environmental impacts

To evaluate the environmental impact, an LCA was performed, to compare batch and continuous-flow protocols. We first evaluated the carbon emissions of the reactions (**Figure 2e** and **Table S21** in Supporting Information). Whereas the batch method exhibited carbon footprints ranging from 4.5 kg  $\text{CO}_2$  equiv  $g_{\text{product}}^{-1}$  to 15.5 kg  $\text{CO}_2$  equiv  $g_{\text{product}}^{-1}$ , the implementation of the continuous-flow method drastically reduced emissions by 86%, to approximately 0.5-1.5 kg  $\text{CO}_2$  equiv  $g_{\text{product}}^{-1}$ . This reduction originates from three main factors. Batch reactions typically required extended reaction times (hours), contributing significantly to energy consumption. In contrast, continuous-flow protocols operated on the scale of minutes, drastically minimizing electricity use. Moreover, during work-up, batch processes consumed large solvent volumes. Flow protocols improved solvent efficiency by an order of magnitude, from ca. 100  $g_{\text{solvent}} g_{\text{product}}^{-1}$  to 10  $g_{\text{solvent}} g_{\text{product}}^{-1}$ . Finally, specific batch reagents were major emission contributors. For example, hexafluoro-2-propanol (HFIP) in the synthesis of **8h**,  $\text{Rh}_2(\text{esp})_2$  in the synthesis of **9p**, and the chiral pyrrolidine derivative in the synthesis of **4b** accounted for 29%, 21%, and 23% of total batch emissions, respectively. Among the four examined protocols, the synthesis of **9p** demonstrated the most significant reduction in carbon emissions (92%) when shifting from batch to flow, followed by **4b** (89%), **2a** (82%), and **8h** (80%). We next evaluated water consumption (**Figure 2f** and **Table S22** in Supporting Information). The implementation of the continuous-flow protocol minimized the impact on water consumption on average by 91%, from 0.2-0.7  $\text{m}^3 g_{\text{product}}^{-1}$  to 0.02-0.03  $\text{m}^3 g_{\text{product}}^{-1}$ . The environmental footprint of the four reactions was then assessed within the framework of the nine planetary boundaries, covering earth-system critical processes such as ocean acidification, biosphere integrity (both functional



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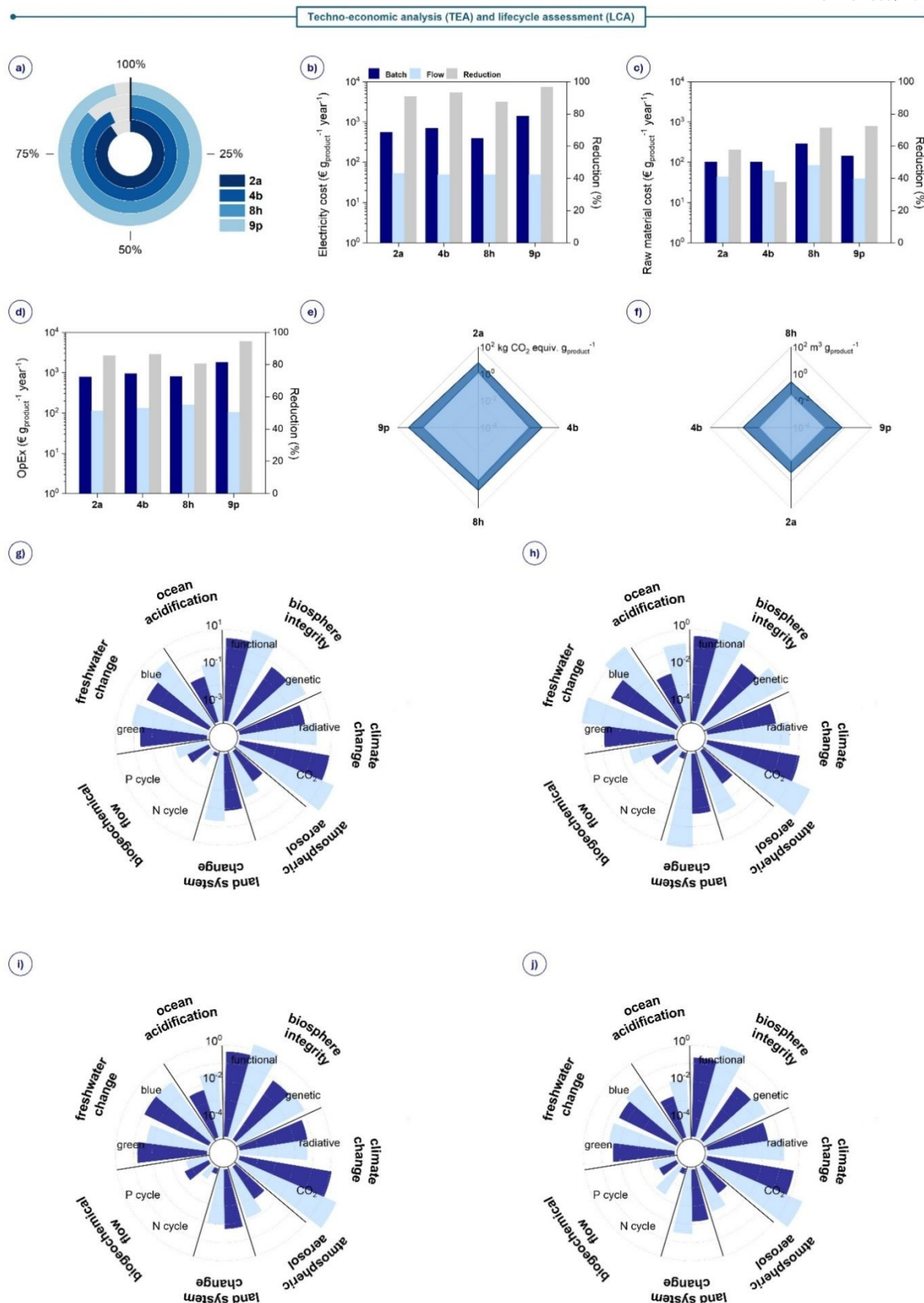
and genetic), climate change via carbon emissions and radiative forces, atmospheric aerosol loading, land system change, biogeochemical flows (in terms of phosphorus and nitrogen cycles), and freshwater change (**Figure 2g-j** and **Table S23-S37** in Supporting Information).<sup>40,41</sup>

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**Figure 2** Comparison of continuous-flow and batch methods regarding the synthesis of **2a**, **4b**, **8h**, and **9p** in terms of total energy consumption reduction (per gram of product) (a), electricity cost (b), raw material costs (c), operational expenditure (d), carbon emissions (e), water consumption (f), planetary boundary analysis of **2a** (g), **4b** (h), **8h** (i), **9p** (j). Color codes in (b) apply to (c-j) as well



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In this context, we initiated our comparative analysis with the impact on ocean acidification, which exhibited an average reduction of 86% following the implementation of the continuous-flow protocol compared to the batch method. From a component-specific perspective, the major contributors to ocean acidification under batch conditions were identified as DCM in the synthesis of **2a** (80%), chiral pyrrolidine derivative in the synthesis of **4b** (32%), HFIP in the synthesis of **8h** (43%), and  $\text{Rh}_2(\text{esp})_2$  catalyst in the synthesis of **9p** (69%). As biosphere integrity represents another key indicator of ecological stability within the nine planetary boundaries framework, its assessment helps clarify the environmental safety of the reactions under study. We thus conducted a comparative assessment of the batch and continuous-flow protocols, evaluating their impact on genetic and functional biosphere integrities. Operating under continuous-flow conditions resulted in average reductions of 60% and 83% in impacts on genetic and functional biosphere integrity, respectively. A similar trend was observed for radiative forcing, with the continuous-flow approach yielding an average impact reduction of 57%. We also examined impacts on land-system change, addressing the effects on deforestation and the degradation of natural habitats. We observed that the implementation of continuous-flow conditions resulted in a comparatively modest 44% average reduction in land system change, relative to the batch method. This modest reduction was primarily attributed to the elevated impact observed only in the synthesis of **2a** under continuous-flow conditions, which exhibited a 76% increase in land system change. Lastly, it was noted that the impact on freshwater change, regarding both blue and green waters, remained largely unaffected under continuous-flow conditions, with reductions limited to ca. 5%. The results were consistent with literature findings, demonstrating the economic and environmental advantages of the continuous-flow methodology across diverse synthetic routes.<sup>35</sup>

## Methods

### Techno-economic analysis

Techno-economic evaluations were conducted using Aspen Plus® V11, applying a stoichiometric reactor model refined with fractional conversion parameters to accurately replicate the experimental results.<sup>42</sup> Thermodynamic and kinetic data for all substances were retrieved from built-in databases (APV110, APESV110, and NISTV110).<sup>43,8</sup> Experimental conditions, including temperature, pressure, and feed composition were directly implemented into the simulation environment. Electricity usage was incorporated as a utility to estimate the overall energy demand of each process. OpEx values were computed using Aspen Process Economic Analyzer (APEA),<sup>44</sup> while raw material costs were calculated based on unit pricing sourced from Merck's commercial chemical database.<sup>45</sup>

### Environmental impacts

To provide a comprehensive environmental analysis, both continuous-flow and batch methods were assessed across 18 LCA midpoint categories. These categories were systematically aligned with the nine planetary boundaries (9PB) framework, including ocean acidification, genetic and functional biosphere integrities, carbon emissions, radiative forces, atmospheric aerosol loading, land systems changes, phosphorus and nitrogen cycles, green and blue water changes.<sup>41</sup> The LCA was performed using SimaPro® V9.5, implementing a cradle to gate system model with a cut off approach to define system boundaries.<sup>46</sup> For consistency among the evaluated scenarios, the functional unit for the LCA was established as 1 g of target product. Impact characterization was executed using ReCiPe 2016 Midpoint (H)<sup>47</sup> or Environmental Footprint 3.1 methodologies.<sup>48</sup> The ReCiPe 2016 Midpoint (H) method was used to evaluate the following categories: (1) climate change via global warming potential and ionizing radiation; (2) atmospheric aerosol loading via fine particulate matter formation; (3) biogeochemical flows via freshwater and marine eutrophication; (4) land system change via land use; (5) freshwater change via ecotoxicity in freshwater and marine compartments; and (6) functional and genetic biosphere integrities via carcinogenic toxicity; mineral and fossil resource depletion, terrestrial acidification, and ozone formation impacts, respectively. Instead, ocean acidification was determined using the Environmental Footprint 3.1 methodology. Life cycle inventory data for material and energy flows were sourced from the Ecoinvent v3 database.<sup>49</sup> Energy consumption specific to each process were derived from Aspen Plus® V11 simulations to maintain consistency between the process models and environmental impact assessments.<sup>42</sup>

## Conclusions

We developed a sustainable and unified continuous-flow method applicable to four different skeletal editing tactics leveraging electrophilic nitrogen transfer. The synthetic value was exemplified through the synthesis of ca. 50 products across four different transformations. The continuous-flow set-up is characterized by its operational simplicity (three inlet streams, one mixer), short residence times, as well as its beneficial sustainability metrics. The sustainability benefits were evaluated through a novel technoeconomic analysis and lifecycle assessment against state-of-the-art continuous-flow protocols and previously reported batch protocols for the synthesis of the obtained products. We envisage that such combined approach of synthetic development and concomitant sustainability assessment will further drive development from the synthetically possible towards processes that align synthetic efficiency with environmental responsibility, safety, and scalability.



## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data that support the findings of this study are available in the supplementary material of this article.

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## Data availability

The data that support the findings of this study are available in the supplementary material of this article.

