

Integrating Life Cycle Assessment with Scale-Up Modeling and Machine Learning for Greener Pharmaceuticals: The Case of (–)-Chloramphenicol

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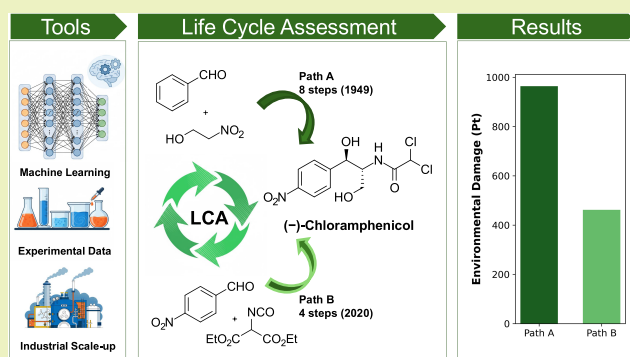
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ABSTRACT: Despite significant advances in green chemistry, the environmental performance of active pharmaceutical ingredient (API) manufacturing remains difficult to assess during early-stage route development because experimental data are typically limited to laboratory scale, making it challenging to project future industrial performance and associated impacts. To address this gap, this study combines cradle-to-gate life cycle assessment (LCA) with quantitative green chemistry indicators to evaluate two routes to (–)-chloramphenicol: the historical eight-step kinetic-resolution synthesis (Path A) and a modern asymmetric organocatalytic route (Path B). Both pathways are assessed at laboratory scale and under simulated industrial scale-up using established process design and energy estimation frameworks. To address data gaps, machine-learning (ML) models were employed to predict key physicochemical properties, e.g., temperature-dependent solubility and heat capacity, to parametrize solvent usage and energy demand. Environmental impacts are quantified using ReCiPe 2016 at midpoint and endpoint levels, while Monte Carlo simulation is applied to assess uncertainty and ensure robustness. Results show that Path B consistently outperforms Path A across most impact categories, driven by a shorter synthesis and reduced solvent and reagent demand. Industrial-scale modeling provides clearer differentiation than laboratory-scale comparisons, and LCA identifies environmental hotspots, such as solvent use, catalyst production, and energy-intensive unit operations, that are not captured by process mass intensity (PMI) and other green chemistry metrics. This work delivers the first cradle-to-gate LCA of (–)-chloramphenicol and demonstrates how ML-assisted property prediction, combined with uncertainty analysis, can improve the reliability of early-stage environmental decision-making in pharmaceutical synthesis.

KEYWORDS: cheminformatics, antibiotics, pharmaceutical industry, LCA, environmental impacts, green chemistry, organocatalysis, Monte Carlo analysis



1. INTRODUCTION

The manufacturing of active pharmaceutical ingredients (APIs) typically entails an environmental footprint several orders of magnitude greater than that of bulk chemicals.¹ This disparity arises from the inherent complexity of their synthesis, which requires multistep pathways, extensive solvent usage, and rigorous isolation and purification processes.² Historically, the “greenness” of these processes has been evaluated using green chemistry metrics, which serve as quantifiable expressions of the 12 principles of green chemistry.³ Among these metrics, process mass intensity (PMI), i.e., the ratio of total input mass to product mass, has become the industrial standard for benchmarking process efficiency.^{4,5} While mass-based metrics such as PMI are user-friendly and invaluable for early-stage route scouting, they evaluate only material flows within the technosphere.⁶ Consequently, they penalize material inefficiency without distinguishing the origin of those materials (e.g., renewable vs fossil-based) or quantifying actual environ-

mental impacts, leading to weak or inconsistent correlations between PMI and environmental burdens.⁷

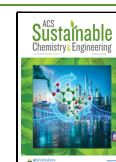
Life cycle assessment (LCA) has emerged as an effective methodology to achieve a more accurate evaluation of environmental performance.⁸ Unlike mass-based metrics, LCA tracks mass and energy flows from the extraction of raw materials to the end-of-life of a product, quantifying environmental burdens such as climate change, toxicity, and resource depletion.⁷ This holistic perspective is essential for identifying burden shifting, where an apparent improvement in

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one synthetic step, such as replacing a hazardous reagent, unintentionally increases impacts elsewhere in the supply chain or shifts the burden to different environmental issues.⁶ LCA has also increasingly been adopted for the early-stage evaluation of novel chemical compounds, providing an initial indication of their potential sustainability, even before large-scale process data become available.⁹ However, LCA implementation in pharmaceutical synthesis faces significant hurdles, foremost among which is data scarcity. Even comprehensive databases such as ecoinvent¹⁰ cover only a fraction of starting materials, catalysts, and reagents commonly used in drug synthesis. As a result, practitioners rely on proxy data sets, retrosynthetic reconstruction, or custom inventory modeling, all of which increase uncertainty.^{2,11} This issue is compounded by industrial confidentiality, which restricts public access to detailed process data and limits the availability of high-quality life cycle inventories (LCIs).

A central obstacle in early-stage LCA is the Collingridge dilemma: flexibility to modify a synthetic route is highest during its conceptual development, yet the detailed information required for a full LCA is least available at this stage.⁶ Although laboratory data are frequently used to infer process performance, they are not sufficient for constructing robust LCIs. Bench-scale protocols lack key industrial features such as solvent recovery, energy requirement, and large-scale yields, leading to substantial uncertainty in environmental impact estimates.¹² To bridge this gap, structured scale-up frameworks have been developed. Piccinno et al.¹³ proposed a framework that translates laboratory protocols into simplified industrial flowcharts and estimates energy requirements for unit operations such as heating, cooling, and stirring. Ansar et al.¹⁴ further refined this approach by introducing Process Design Calculations (PDCs) that include auxiliary operations often absent from laboratory documentation—such as equipment cleaning and, notably, heating, ventilation, and air-conditioning (HVAC) systems.

Traditional scale-up approaches for evaluating the environmental performance of chemical processes still struggle with missing LCI data and proprietary restrictions. As a result, early-stage LCAs are inherently affected by high levels of uncertainty due to the limited availability of experimental data, simplified process descriptions, and the absence of compound-specific thermodynamic properties. These shortcomings represent one of the main challenges in applying LCA to the design stage.

Solvent charges are frequently extrapolated linearly from laboratory protocols, while workup and extraction stages are approximated using fixed solvent-to-aqueous volume ratios or assumed numbers of extraction stages. In addition, solvent consumption is sometimes adjusted using uniform reduction factors to represent anticipated industrial optimization.¹³ While these heuristics enable rapid assessments, they fail to capture the physicochemical behavior governing separation efficiency, solvent recovery, and energy demand, thereby limiting the predictive accuracy. In practice, these simplified approaches may lead to systematic over- or underestimation of environmental impacts, particularly when extrapolating laboratory-scale data to industrial conditions.

Similarly, missing thermodynamic properties are typically approximated using values from structurally similar compounds. In contrast, the corresponding energy requirements for reaction and separation steps are frequently modeled using generic industry-average data derived from multiyear operational records, applied independently of the specific

physicochemical characteristics of the compound under assessment.¹⁵

The fundamental pitfall underlying these practices is the absence of chemical-specific thermodynamic and physicochemical properties, which prevents the construction of bottom-up material and energy balances.¹⁶ Properties such as specific heat capacity, vapor pressure, enthalpy of vaporization, density, and temperature-dependent solubility govern heating and cooling demand, separation efficiency, solvent recovery, and distillation energy. In their absence, early-stage LCAs face a “thermodynamic barrier”: although mass flows can be estimated, physically realistic energy requirements cannot be reliably determined, severely limiting the predictive value of scale-up simulations.

To determine environmental impacts at early planning and design stages, it is increasingly critical to integrate machine-learning (ML) tools directly into the LCA workflow.^{17,18} ML has already been applied across several stages of LCA to address data gaps, including the generation of missing LCIs, the estimation of characterization factors, and the screening of environmental impacts for poorly characterized chemicals and regions.¹⁹ In the chemical sector, structure-based ML models have supported comparative screening of alternative solvents, intermediates, and synthesis routes.²⁰ ML can address data limitations by employing molecular-structure-based models to directly predict life cycle impact assessment (LCIA) indicators, such as climate change, or by supplementing missing unit-process data where experimental measurements and industrial data are unavailable.²⁰ An important application in chemical and pharmaceutical LCIs involves predicting physicochemical properties, including solubility,²¹ heat capacity,^{22,23} density, and standard enthalpy of formation,²⁴ which serve as thermodynamic inputs for process design calculations and energy demand estimation for reaction and separation.

In spite of the potentialities of the ML-LCA integration, early assessments still largely rely on linear scale-up of laboratory solvent charges, generic assumptions for extraction and purification, and industry-average energy demand proxies weakly linked to compound-specific behavior.¹⁵

With respect to conventional strategies, ML enables a complementary approach by enabling the structure-based prediction of key thermodynamic and physicochemical properties when experimental data are unavailable. Unlike conventional approaches based on structural analogies or generic assumptions, ML models can directly capture relationships between molecular structure and thermodynamic behavior, leading to more consistent and scalable predictions across diverse chemical systems.²⁵

However, ML is also affected by important limitations, including prediction uncertainty, potential bias from training data sets, and the risk of propagating errors into LCA results.²⁰ These uncertainties may influence the estimated energy demand and solvent requirements, potentially affecting final impact results. Therefore, the integration of ML within LCA requires careful validation to ensure that robust and reliable conclusions can be reached.

Several LCA studies on pharmaceutical production have highlighted both methodological challenges and sustainability insights. Wernet et al.²⁶ conducted a cradle-to-gate LCA on two confidential APIs and reported that pharmaceutical manufacturing can be substantially more resource-intensive than the production of basic chemicals, with Cumulative Energy Demand (CED) and Global Warming Potential

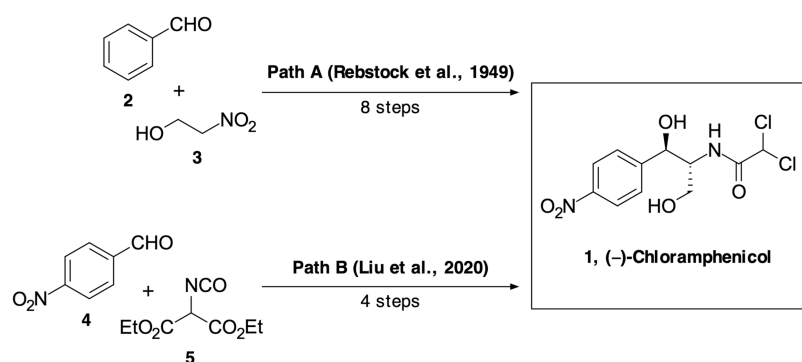


Figure 1. Overview of the two synthetic routes leading to (–)-chloramphenicol, evaluated through LCA in this study.

(GWP) being up to 20- and 25-fold higher per kilogram, and energy production and use accounting for 65–85% of the impacts. Parvatker et al.²⁷ extended this approach to 20 injectable anesthetics APIs using patent-derived laboratory data scaled to industrial conditions, demonstrating a positive correlation between greenhouse gas (GHG) emissions and synthesis step count and providing inventories for over 130 intermediates. Yang et al.²⁸ found that API synthesis and formulation contributed similarly to the total impacts of ciprofloxacin hydrochloride production, and identified substituting solvent and switching to renewable energy sources as effective mitigation strategies. In a cradle-to-grave analysis, Siegert et al.²⁹ concluded that API production dominates the environmental profile of ibuprofen, while use and end-of-life phases are negligible. Similarly, Ponder and Overcash³⁰ considered the cradle-to-gate production of vancomycin hydrochloride, a low-yield antibiotic produced via fermentation of *Amycolatopsis orientalis*. Sterilization emerged as the largest energy consumer due to steam use, followed by aeration and agitation in the fermentation vessels. Accordingly, the adoption of other sterilization methods or fermentation media was suggested as a viable strategy to lower the environmental footprint.

Beyond APIs, LCA has been applied to the biopharmaceutical production. Amasawa et al.³¹ compared cultivation strategies for monoclonal antibody production, finding that operation mode (fed-batch vs perfusion) had a greater influence on environmental performance than equipment material. Ott et al.³² evaluated a transition from slurry batch to fixed-bed continuous reactors for an anticancer drug, concluding that continuous operation improves sustainability if the catalyst life exceeds 1200 h. Budzinski et al.³³ reported that cleanroom HVAC electricity dominates the footprint of single-use biopharmaceutical manufacturing, with plastic waste disposal being negligible. Bouchier et al.³⁴ compared tablet manufacturing platforms, showing that direct compression is optimal for small batches, while continuous direct compression becomes most carbon-efficient for larger production volumes.

Recent case studies illustrate LCA's role in process optimization of pharmaceuticals. Folkerts et al.¹¹ applied a closed-loop LCA to Letermovir, benchmarking a novel synthesis against Merck's award-winning process and guiding reagent substitutions such as replacing LiAlH_4 with $\text{BH}_3\cdot\text{SMe}_2$ and meta-chloroperoxybenzoic acid (mCPBA) with magnesium monoperoxyphthalate (MMPP) to reduce GWP. The study demonstrated that LCA captures impacts that PMI cannot, particularly the disproportionate burden of specialized catalysts and the sensitivity of results to catalyst recovery rates

and solvent recycling, thereby supporting more informed route selection. Similarly, Kaji et al.³⁵ compared microbial strategies for citicoline production, finding that simplification reduced impacts across multiple categories, but also bringing to light trade-offs associated with renewable electricity. Yang et al.²⁸ demonstrated that solvent replacement in ciprofloxacin hydrochloride synthesis was more effective than energy source switching, reinforcing the role of LCA in prioritizing interventions. Hallamasek et al.³⁶ assessed biobased paracetamol production and highlighted the importance of coproduct valorization in determining sustainability. Finally, Ansar et al.¹⁴ showed that inclusion of auxiliary operations—HVAC, wastewater treatment, and equipment cleaning—can increase carbon footprint estimates by 3–49%, underscoring the need for comprehensive inventories in early-stage pharmaceutical development.

The synthesis of (–)-chloramphenicol, the first broad-spectrum antibiotic to be discovered ever,³⁷ has been extensively studied. Although discovered more than 70 years ago, (–)-chloramphenicol remains clinically and commercially relevant. It is listed on the World Health Organization's Model List of Essential Medicines and continues to be manufactured.³⁸ Market analyses confirm its continued commercial production,³⁹ particularly in ophthalmic and topical applications and in regions where cost-effective antibiotics remain essential, underscoring the relevance of improving the environmental performance of its synthesis.

The first complete synthesis was reported in 1949 by Rebstock et al.,⁴⁰ involving an eight-step linear sequence from benzaldehyde, relying on kinetic resolution with (+)-camphor-sulfonic acid ((+)-CSA). Subsequent work has sought to overcome the poor atom economy and material inefficiency associated with the resolution step, motivating the development of more sustainable asymmetric and biocatalytic methodologies. Loncaric and Wulff⁴¹ reported a markedly shorter four-step synthesis from 4-nitrobenzaldehyde, featuring a catalytic aziridination mediated by a triphenylborate/(R)-VAPOL-derived catalyst. Bhaskar et al.⁴² later introduced a three-step asymmetric route in which the stereochemical induction was achieved through a Sharpless asymmetric epoxidation (kinetic resolution) using (–)-DIPT. In 2016, Franchino et al.⁴³ reported a silver-catalyzed asymmetric isocyanoacetate aldol reaction mediated by cinchona-derived amino phosphines to forge the characteristic *syn*-vicinal amino alcohol core, although the total synthesis still encompassed an eight-step sequence. Xia et al.⁴⁴ reported a unified asymmetric synthesis of amphenicol antibiotics based on a ligand-enabled, copper(II)-catalyzed *syn*-selective nitroaldol (Henry) reaction

of nitroethanol to forge the characteristic amino alcohol core. Liu et al.⁴⁵ developed a fully asymmetric approach employing a cinchona alkaloid-derived urea organocatalyst, enabling an enantioselective cascade aldol reaction followed by a continuous-flow selective decarboxylation. Complementing these chemical advances, Xu et al.⁴⁶ proposed a chemo-enzymatic strategy in which an L-threonine transaldolase from *Pseudomonas* sp. catalyzes the formation of the chiral amino alcohol intermediate, offering an alternative biocatalytic route to the amphenicol core.

Building on these developments, the present study employs both LCA and quantitative green chemistry metrics to evaluate two synthetic strategies for (–)-chloramphenicol **1** (Figure 1): Path A, the original eight-step Rebstock synthesis from benzaldehyde **2** and β-nitroethanol **3**,⁴⁰ and Path B, the four-step modern asymmetric route developed by Liu et al.,⁴⁵ that starts from 4-nitrobenzaldehyde **4** and isocyanatomalonate **5**, employing a cinchona-derived urea organocatalyst. In contrast to other asymmetric approaches that either retain long step counts or rely on transition-metal catalysis, such as silver- or copper-mediated nitroaldol and aldol reactions, Path B employs a metal-free organocatalytic strategy while maintaining high enantioselectivity. The combination of reduced step count, early stereochemical induction, and contemporary process features (including continuous-flow decarboxylation) makes Path B a particularly suitable benchmark for evaluating whether modern asymmetric catalysis delivers genuine environmental advantages over historical manufacturing routes, as it is representative of current state-of-the-art organocatalytic strategies.

Both pathways are assessed at laboratory scale and under simulated industrial scale-up, using established frameworks.^{13,14} The objectives are to identify environmental hotspots, determine whether modern asymmetric catalysis translates into genuine sustainability gains, and assess how scale-dependent factors influence the overall environmental performance.

Methodologically, this work integrates mass-based indicators (e.g., PMI) with a cradle-to-gate LCA and compares their diagnostic outcomes, recognizing that impacts can arise from upstream supply chain burdens rather than material inefficiency alone. To address data gaps inherent to early-stage pharmaceutical modeling, the LCI incorporates ML-derived predictions of heat capacity, and temperature-dependent solubility through the application of dedicated codes available in the scientific literature. FASTSOLV model²¹ is used to obtain temperature-dependent solubility predictions, informing solvent charge, extraction efficiency, and purification strategies, while heat capacity is predicted using the Gradient-Boosted and statistical Feature Selection (GBFS) workflow developed by Jung et al.,²² enabling a consistent estimation of reaction and heating energy requirements. Additional computational tools are also used in the workflow, including ChemAxon⁴⁷ for aqueous solubility estimation and Molinspiration⁴⁸ for molecular volume and auxiliary molecular descriptors, ensuring a coherent and data-rich inventory for process modeling. These ML tools have not previously been leveraged within an LCA context, offering a novel approach to bridging data limitations and improving transparency in early-stage sustainability assessment. In particular, their integration enables a transition from heuristic-based to property-driven inventory modeling, improving the consistency of scale-up simulations. Together, the study provides the first cradle-to-

gate LCA of (–)-chloramphenicol **1** synthesis, compares historical and modern routes, and demonstrates how ML-derived physicochemical properties can support LCA-driven process design.

2. EXPERIMENTAL SECTION

2.1. Goal and Scope Definition

LCA was performed according to ISO14040⁴⁹ and ISO14044.⁵⁰

The primary goal of this study is to identify environmental hotspots and compare two synthetic pathways for the production of (–)-chloramphenicol **1**:

1. Path A: The original route published in 1949,⁴⁰ based on traditional organic chemistry strategies involving aldol reaction and kinetic resolution.
2. Path B: A modern route published by Liu et al.⁴⁵ in 2020, featuring an organocatalytic cascade aldol reaction as a key step.

The scope of the study includes building and refining the LCI for both pathways, incorporating recent ML tools for property prediction to improve estimates of the energy demand across individual steps. This approach addresses the lack of thermodynamic data for intermediates and enables more accurate modeling of heating requirements and solvent usage for scale-up simulation.

Additionally, the ultimate objective is to evaluate the potential of novel organic chemistry strategies, such as organocatalysis, as a greener alternative for API synthesis. Using (–)-chloramphenicol **1** as a case study, this work aims to provide insights into whether modern catalytic methodologies can reduce environmental impacts compared to traditional synthetic routes.

Finally, the influence of scale-up frameworks is assessed by presenting results at both laboratory scale (1 g production) and simulated industrial scale (1000 L reactor, 147.15 kg (path A) and 127.5 kg (path B) scale production), highlighting how scaling up affects energy demand, solvent recovery, and overall environmental performance.

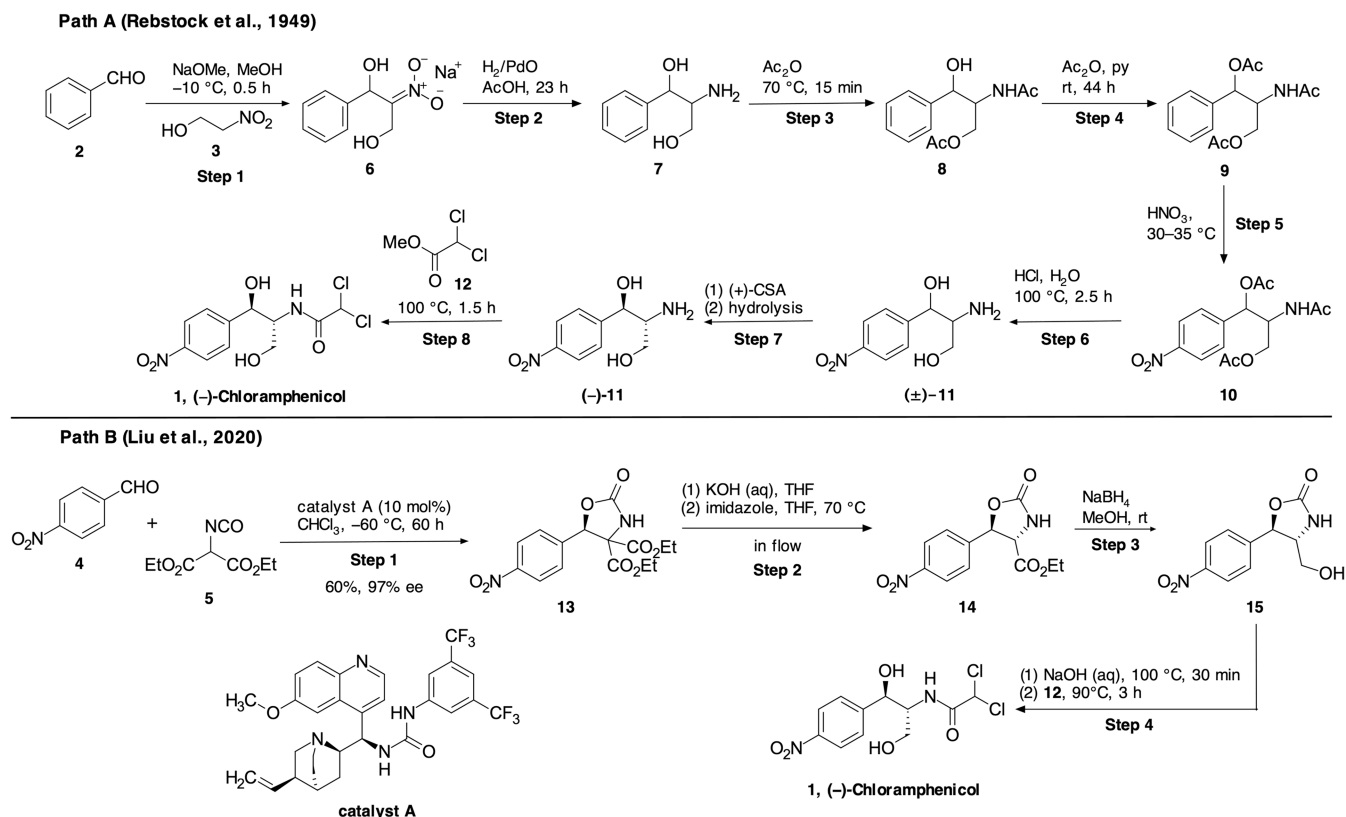
2.2. System Definition, Functional Unit, and System Boundaries

Two modeling approaches were considered. The first represents laboratory-scale production, for which the LCI was compiled for the production of 1 g of (–)-chloramphenicol **1**. The second represents an industrial-scale simulation, modeled using a nominal 1000 L reactor, yielding outputs of 147.15 kg (Path A) and 127.5 kg (Path B) per batch.

Although laboratory-scale inventories were initially constructed based on 1 g production, and industrial-scale simulations correspond to batch outputs of approximately 120–150 kg, all results were then normalized to a common functional unit of 1 kg of product at factory gate. This normalization ensures comparability across scales and does not imply that laboratory and industrial systems operate at identical production volumes.

The function of the system is defined as the production of 1 kg of (–)-chloramphenicol **1** via Path A and Path B, modeled at both laboratory scale and simulated industrial scale.

The system boundaries are defined as cradle-to-gate, encompassing raw material extraction, production of background chemicals, and the complete multistep synthesis of (–)-chloramphenicol down to the final product at the plant gate. These boundaries were selected to align with the objective of evaluating process-level and route-level differences in the synthesis of (–)-chloramphenicol. Notably, both synthetic pathways yield a final product that displays physicochemical properties—including a melting point of 150.5–151.5 °C and an optical rotation of $\alpha_D = -25^\circ$ —that are identical to standard fermentation-derived chloramphenicol.⁴⁰ Downstream stages such as formulation and use-phase typically contribute less significantly and would not affect the comparative evaluation of alternative synthesis routes.²⁹

Scheme 1. Synthetic Pathways for (–)-Chloramphenicol 1 Assessed in This Study⁴⁴

⁴⁴Path A corresponds to the historical Rebstock synthesis;⁴⁰ Path B corresponds to the modern asymmetric route reported by Liu et al.⁴⁵

Scheme 1 illustrates the two synthetic routes evaluated via the LCA in this study.

Path A, originally reported in 1949 as the first complete synthesis,⁴⁰ represents the conventional approach. The linear sequence commences with an aldol reaction between benzaldehyde 2 and β -nitroethanol 3, followed by catalytic hydrogenation over palladium oxide (PdO) to furnish 2-amino-1-phenylpropane-1,3-diol 7. The diastereoselectivity of this transformation is modest ($\approx 3.8:1$), necessitating separation of the resulting diastereomers by several recrystallizations from chloroform. Notably, the desired *threo* diastereomer persists as a viscous gum rather than a crystalline solid, whereas the *erythro*-isomer crystallizes readily, leading to substantial material losses during isolation. Subsequent protection steps involve mild N,O-acetylation, enabling purification of the acetylated intermediate 8, followed by room-temperature acetylation in pyridine to afford the triacetylated derivative 9. Electrophilic nitration of this intermediate, coupled with acid-mediated deprotection under dilute HCl, yields a racemic mixture of 2-amino-1-(4-nitrophenyl)propane-1,3-diol ($\pm$)-11. Resolution with (+)-CSA affords the optically pure (1*R*,2*R*)-isomer (–)-11. The final transformation entails treatment with a large excess of dichloromethyl acetate 12, leading to the formation of (–)-chloramphenicol 1.

Path B, reported in 2020 by Liu et al.,⁴⁵ exemplifies a contemporary strategy, involving organocatalysis and continuous-flow chemistry. The sequence initiates with an enantioselective organocatalytic cascade aldol reaction between 4-nitrobenzaldehyde 4 and isocyanatomalonate 5, mediated by a urea-type cinchona alkaloid-derived catalyst A, yielding the diester oxazolidinone 13 with excellent enantiomeric purity (97% ee), but modest yield (60%). Subsequent transformations are executed under flow conditions: ester hydrolysis followed by a diastereoselective decarboxylation leads to the oxazolidinone intermediate 14 with moderate diastereoselectivity (4.5:1). The carboxyl group is then selectively reduced to the corresponding alcohol using sodium tetraborohydride. Finally,

acylation—analogue to the terminal step in Path A—affords (–)-chloramphenicol 1 in optically pure form.

2.3. Life Cycle Inventory (LCI)

For both synthetic pathways, the LCI was compiled using secondary data from the literature, while background processes were modeled using the ecoinvent database version 3.10.^{10,51} The modeling approach was attributional, employing the allocation at the point of substitution (i.e., APOS) system model,⁵² and the inventory was implemented in SimaPro (v. 9.6.0.1) software.⁵³

Energy requirements for stirring, heating, distillation, drying, and filtration were calculated, as detailed in Table S1. Fugitive solvent emissions were modeled following the methodology proposed by Piccinno et al. (Table S2),¹² in which solvent losses during reactor filling, workup, and purification steps are estimated based on solvent vapor pressure at operating temperature, accounting for evaporation during handling and processing. Solvent recovery was modeled selectively depending on stream composition (see below). The calculated emission factors for the solvents used in this model are reported in Table S3.

All foreground processes were modeled assuming a nominal reactor volume of 1000 L, with the characteristics presented in Table S4. Laboratory-scale energy consumption was estimated from equipment-power ratings and thermodynamic calculations (Table S5).

The background system includes the production of all commercially available starting materials, reagents, and catalysts, whereas the foreground system comprises the linear synthetic step and the preparation of specialized starting materials that are not commercially available—such as β -nitroethanol 3 and isocyanatomalonate 5—i.e., all intermediates synthesized within the laboratory or pharmaceutical manufacturing boundaries.

Detailed inventories for background data sets, for both scale syntheses and for sensitivity analyses, are reported in Tables S6–S55. Because the reference procedures were originally laboratory-based,

engineering-based scale-up methodologies were applied to estimate industrial-scale impacts.^{13,14}

Custom data sets were developed for intermediates and reagents not available in ecoinvent, including β -nitroethanol, isocyanatomalonate 5, catalyst A precursors, and synthetic intermediates across both pathways (see Table S56 for full list).

2.4. Solvent Recovery

Solvent recovery was modeled selectively depending on stream composition. When solvents used for reaction, extraction, or recrystallization were dominated by a single major component and impurities were unknown or present at low concentrations, recovery was approximated as single-component distillation. Where two solvent components were explicitly defined, binary distillation was applied. It was assumed an average recovery rate of 68%.⁵⁴

In contrast, solvent recovery was not assumed for complex multicomponent mixtures requiring high minimum reflux ratios, as the associated energy demand would be disproportionate to the recoverable solvent.

2.5. ML-Assisted Thermodynamic and Physicochemical Property Estimation

A major challenge in modeling was the lack of experimentally available thermodynamic data for most organic chemicals involved in the model. To address this, ML models and other computational tools were employed to predict key physicochemical and thermophysical properties—temperature-dependent solubility, specific heat capacity, and density—enabling refined estimates of heating energy and solvent requirements for reaction, extraction, and recrystallization steps. In particular, solvent charges during scale-up were not determined by simple linear extrapolation from laboratory protocols—which can lead to systematic over- or underestimation of solvent use and associated environmental burdens—but were instead adjusted based on predicted solubility of the relevant organic compounds in the selected solvents. This property-based approach provided more robust and process-relevant estimates of solvent demand.

Table 1 summarizes the computational tools used in this study to predict physicochemical and thermophysical properties of organic

Table 1. Computational Tools Employed to Predict Molecular Properties Used for Process Modeling and LCI Calculations

property predicted	tool	application in this study
Solubility in organic solvents ($\log S_{\text{solvent}}$)	FASTSOLV ²¹	Reaction solvent charge, the amount of solvent needed for extraction
Aqueous solubility ($\log S_{\text{aq}}$)	ChemAxon ⁴⁷	The amount of solvent needed for extraction
Specific heat	ML4SMILES ²²	Heat demand of reaction
Molecular Volume	Molinspiration ⁴⁸	Density; electricity demand for stirring

molecules required for process modeling. The scope of predicted properties for all molecules included in the model is reported in Table S57.

The following sections describe how ML-derived physicochemical properties were used to parametrize solvent selection, separation efficiency, and energy demand during industrial scale-up.

2.6. Solubility Prediction and Solvent Screening

Temperature-dependent solubility predictions were performed using FASTSOLV, an ensemble model integrating artificial neural network (ANN) and graph neural network (GNN) architectures.²¹ The ANN component (FASTPROP) encodes molecular structures with Mordred descriptors, while the GNN component (CHEMPROP) employs message-passing on molecular graphs to capture local substructural effects. This ensemble design enables the model to represent both global molecular features and local chemical environments relevant to solubility across a wide range of chemically diverse compound classes.

FASTSOLV demonstrated high predictive accuracy on unseen solutes, achieving root mean square error (RMSE) values of 0.83 on the SolProp test set and 0.95 on the structurally diverse Leeds data set (see Table S58), approaching the conservative experimental aleatoric limit (RMSE = 0.75).²¹ This limit was derived from interlaboratory variability in overlapping experimental solubility measurements, indicating that model error is comparable to intrinsic experimental uncertainty. In addition to pointwise accuracy, FASTSOLV preserves physically realistic temperature–solubility trends via Sobolev-regularized regression, capturing temperature gradients with an Earth Mover's Distance (EMD) of 0.03.

Solubility predictions supported solvent screening for dissolution, extraction, and recrystallization, and enabled the identification of scalable alternatives to laboratory purification methods. Laboratory procedures often rely on flash chromatography or recrystallization solvents that, if scaled linearly, would require impractically large volumes. By integrating solubility-based screening, purification strategies were adapted to industrial conditions, minimizing solvent use and avoiding nonscalable techniques. Prediction uncertainty (± 0.3 – 0.5 log units) was considered acceptable for process-level decision-making.

2.7. Heat Capacity, Density, and Thermodynamic Property Estimation

Heat capacities of most organic molecules involved in the model—necessary to determine heat demand for reactions—were estimated using ML4SMILES, a semisupervised ML framework that predicts molecular properties directly from SMILES strings. The model combines gradient-boosted statistical feature selection (GBFS) with substructure vector embeddings (Mol2Vec), enabling accurate property prediction without reliance on quantum-chemical calculations or three-dimensional molecular geometries, which are typically unavailable during early-stage process design.²²

Achieving a mean absolute error (MAE) of approximately 0.156 for heat capacity prediction on the QM9 benchmark data set, ML4SMILES is placed among top-tier molecular property predictors (see Table S59). This performance is comparable to that of large, resource-intensive foundation models (e.g., MOLFORMER-XL), while substantially outperforming conventional message-passing neural networks (MPNN) and ChemBERTa. Meanwhile, satisfactory results can be achieved with single-CPU computational requirements, making the framework suitable for iterative industrial scale-up simulations.²²

By providing molecule-specific heat capacity data, ML4SMILES replaces the generic solvent-based heat capacity proxies traditionally employed in the LCAs. This enables more precise thermal energy audits for heating, cooling, and reaction unit operations, directly influencing energy demand estimates in the industrial scale-up simulations and, consequently, final LCA results.

Aqueous solubilities ($\log S_{\text{aq}}$) were estimated using ChemAxon cheminformatics predictors based on fragment-based quantitative structure–property relationship (QSPR) models. In validation studies, the aqueous solubility model reported an RMSE of 1.04 on a data set of 6886 compounds, with approximately 75% of predictions within ± 1.0 log S unit.⁵⁵ In the current study, ChemAxon-derived aqueous-phase properties were used to approximate the partition coefficient (K_D), which defines the minimum solvent volume required for industrial liquid–liquid extraction stages.

Molecular volume was estimated using Molinspiration fragment-based group-contribution models,⁵⁶ which compute molecular size deterministically as the sum of atomic and functional group contributions with correction factors.⁴⁸ The resulting relative volume estimates provide physically consistent inputs for density approximation and were used to inform agitation and stirring energy calculations in the scaled-up process model.

2.8. Extraction Modeling

Extraction efficiency (E), defined as the fraction of solute transferred from the aqueous phase to the organic phase, was estimated using the formula for ideal multistage liquid–liquid extraction (eq 1), where K_D

Table 2. Methodological Comparison of Inventory Construction: Laboratory vs Industrial-Scale Models

parameter	laboratory-scale (1 g)	industrial-scale (1000 L batch)	methodological driver/ML tool
Functional unit	1 kg (normalized from 1 g)	1 kg (normalized from 147.15 kg (Path A) and 127.5 kg (Path B))	Common reporting basis
Solvent charge	Linear scaling from protocol	property-based adjustment	FASTSOLV (predicted solubility)
Amount of extraction solvent	Fixed proxy ($V_{aq} \times 3-5$)	Calculated minimum V_{org}	K_D approximation (FASTSOLV/ChemAxon)
Purification method	Experimental (e.g., flash chromatography)	Industrial unit operations	Distillation/recrystallization simulation
Agitation/mixing energy	Equipment-power rating	Power-law calculation (impeller formula)	Molinspiration (predicted density)
Heat of Reaction	Equipment-power rating	thermodynamic	ML4SMILES (predicted specific heat for unknown molecules)
Solvent recovery	N/A	68% average recovery	Distillation
Pumping energy	N/A	Average transfer energy	Industrial throughput scaling
Filtration/centrifugation	Equipment based	average filtration energy	Industrial throughput scaling
Drying	Vacuum, benchtop drying	Thermal vaporization	Vaporization enthalpy modeling
Cooling	ice, dry ice (manual)	Refrigeration unit	ML4SMILES (predicted specific heat capacity)
Fugitive emissions	fixed % based on solvent boiling point	Vapor pressure-based calculations	Physical model

Table 3. Potential Environmental Impacts, Calculated at Midpoint Level (ReCiPe 2016, H) for the Production of 1 kg of (–)-Chloramphenicol 1 via Path A and Path B, Modeled at Both Laboratory and Simulated Industrial Scales

impact category	unit	Path A laboratory	Path A industrial	Path B laboratory	Path B industrial
Global warming (GW)	kg CO ₂ eq	3.80×10^4	1.36×10^4	4.84×10^4	6.81×10^3
Stratospheric ozone depletion (SOD)	kg CFC11 eq	1.36×10^{-01}	4.46×10^{-02}	2.94×10^{-01}	5.03×10^{-02}
Ionizing radiation (IR)	kBq Co-60 eq	1.68×10^3	3.28×10^{02}	1.79×10^3	1.85×10^{02}
Ozone formation, Human health (OFHH)	kg NOx eq	5.87×10^1	2.85×10^1	1.00×10^2	9.05×10^0
Fine particulate matter formation (FPMF)	kg PM2.5 eq	6.63×10^1	5.07×10^1	4.35×10^1	5.00×10^0
Ozone formation, Terrestrial ecosystems (OFTE)	kg NOx eq	6.59×10^1	3.13×10^1	1.12×10^2	9.96×10^0
Terrestrial acidification (TA)	kg SO ₂ eq	2.19×10^2	1.72×10^2	1.12×10^2	1.24×10^1
Freshwater eutrophication (FWE)	kg P eq	1.23×10^1	4.98×10^0	1.31×10^1	2.02×10^0
Marine eutrophication (ME)	kg N eq	1.90×10^0	1.10×10^0	1.22×10^0	3.90×10^{-01}
Terrestrial ecotoxicity (TE)	kg 1,4-DCB	1.69×10^5	6.72×10^4	1.80×10^5	3.32×10^4
Freshwater ecotoxicity (FET)	kg 1,4-DCB	1.37×10^3	8.00×10^2	1.05×10^3	2.26×10^2
Marine ecotoxicity (MET)	kg 1,4-DCB	1.92×10^3	1.08×10^3	1.54×10^3	3.26×10^2
Human carcinogenic toxicity (HCT)	kg 1,4-DCB	3.98×10^3	1.58×10^3	8.80×10^3	4.95×10^3
Human noncarcinogenic toxicity (HNCT)	kg 1,4-DCB	3.91×10^4	2.60×10^4	2.43×10^4	4.45×10^3
Land use (LU)	m ² a crop eq	1.00×10^3	6.68×10^2	6.43×10^2	1.36×10^2
Mineral resource scarcity (MRS)	kg Cu eq	2.35×10^2	1.92×10^2	7.38×10^1	1.47×10^1
Fossil resource scarcity (FRS)	kg oil eq	8.56×10^3	3.33×10^3	1.21×10^4	1.54×10^3
Water consumption (WC)	m ³	2.53×10^2	8.50×10^1	2.54×10^2	4.63×10^1

is the partition coefficient, V_{org} and V_{aq} are the volumes of the extraction solvent and aqueous layer, respectively, and n is the number of extraction stages.⁵⁷ In this study, E was treated as a design-oriented target, assuming ideal extraction conditions and efficiency. eq 1 was rearranged to determine the minimum organic solvent volume (V_{org}) required. This approach is based on numerous assumptions, including thermodynamic equilibrium being reached in each stage, constant K_D across stages, ideal dilute solutions, complete phase immiscibility, and identical solvent volumes across stages.

$$E = 1 - \left(\frac{1}{1 + K_D \cdot \frac{V_{org}}{V_{aq}}} \right)^n \quad (1)$$

To estimate K_D , the partition coefficient was approximated as the ratio of solubilities in the organic and aqueous phases ($K_D \approx \frac{S_{org}}{S_{aq}}$),^{58,59}

which were derived from solubility predictions by FASTSOLV (organic phase)²¹ and by ChemAxon (aqueous phase).⁴⁷

To improve clarity, Table 2 provides a structured comparison between laboratory-scale and industrial-scale modeling assumptions, highlighting key methodological differences. This comparison high-

lights how ML-derived thermodynamic properties replace laboratory heuristics during scale-up modeling.

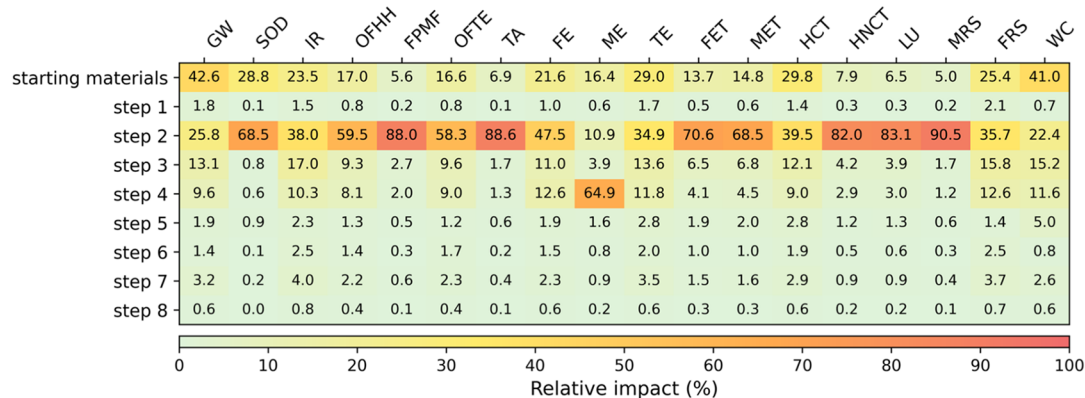
2.9. Life Cycle Impact Assessment

The life cycle impact assessment (LCIA) was performed using the ReCiPe 2016 (H) midpoint and endpoint methods. ReCiPe 2016 is a harmonized impact assessment framework that converts elementary flows into environmental impact scores at both midpoint and endpoint levels. The Hierarchist (H) perspective represents the default, consensus-based scenario: it applies a 100-year time horizon, includes environmental mechanisms supported by internationally recognized scientific consensus, and reflects a balanced “middle-ground” modeling philosophy.⁶⁰ Within this framework, impacts are characterized across 18 midpoint categories, including, but not limited to climate change, ozone depletion, water use, freshwater ecotoxicity, and resource scarcity, which are subsequently aggregated into three endpoint areas of protection: human health, ecosystem quality, and resource scarcity, and finally normalized and weighted to a single score indicator.

2.10. Analytical Framework and Uncertainty Analysis

As outlined in Section 2.2, four scenarios were investigated: the production of (–)-chloramphenicol via Path A and Path B at laboratory scale and at simulated industrial scale.

(a) Step analysis



(b) Contribution analysis

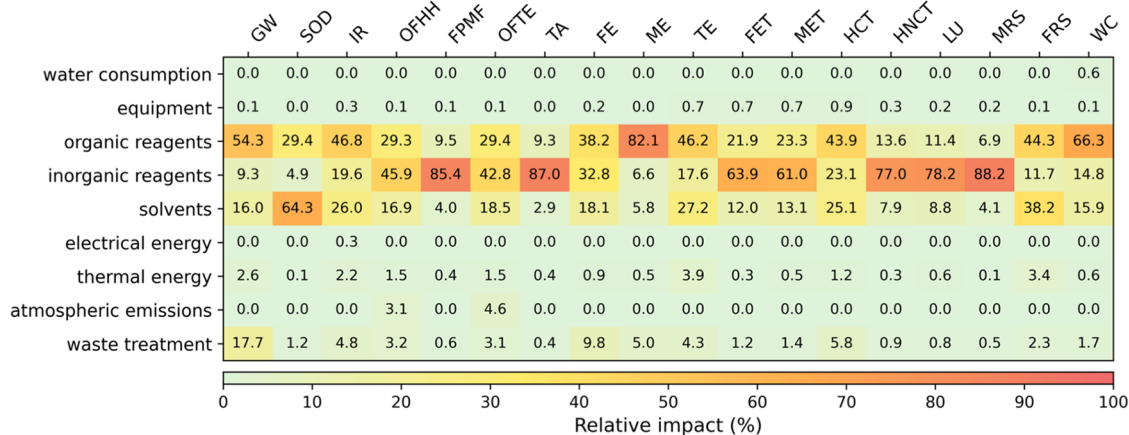


Figure 2. Heatmap illustrating the relative contributions (expressed as percentage of total impact) to the environmental profile of the scaled-up production of (–)-chloramphenicol 1 via Path A at simulated industrial scale. (a) Step analysis showing the relative contribution of each synthetic step across all impact categories. (b) Contribution analysis highlighting the relative contribution of material and energy inputs and emissions, including water consumption, equipment, reagents, solvents, energy use, and atmospheric emissions. The impact categories considered by the impact assessment method are Global warming (GW), Stratospheric ozone depletion (SOD), Ionizing radiation (IR), Ozone formation–Human health (OFHH), Fine particulate matter formation (FPMF), Ozone formation–Terrestrial ecosystems (OFTE), Terrestrial acidification (TA), Freshwater eutrophication (FWE), Marine eutrophication (ME), Terrestrial ecotoxicity (TE), Freshwater ecotoxicity (FET), Marine ecotoxicity (MET), Human carcinogenic toxicity (HCT), Human noncarcinogenic toxicity (HNCT), Land use (LU), Mineral resource scarcity (MRS), Fossil resource scarcity (FRS), Water consumption (WC).

For each scenario, two complementary analyses were conducted to support the interpretation of the LCA results. First, a *step analysis* was performed to quantify the relative contribution of each synthetic step across all impact categories. Second, a *contribution analysis* was carried out to assess the relative contribution of key inputs and emissions, including water consumption, equipment, inorganic and organic reagents, solvents, electrical and thermal energy, and atmospheric emissions. Together, these analyses enabled the identification of environmental hotspots within each synthesis pathway.

In addition, sensitivity analyses were performed to explore the influence of modeling assumptions. The first sensitivity analysis evaluated the effect of the scale-up framework by comparing laboratory-scale and simulated industrial-scale models for each synthesis pathway. The second analysis examined the influence of the synthesis route by comparing Paths A and B at the same production scale.

A Monte Carlo (MC) simulation with 1000 iterations was carried out to evaluate the robustness and uncertainty of the midpoint results by using a 95% uncertainty interval. Background process uncertainties were taken from the ecoinvent database, which characterizes data quality using the pedigree matrix approach across quality indicators, such as reliability, completeness, temporal, geographical, and technological representativeness. In this framework, input data are

modeled using log-normal probability distributions derived from the respective pedigree scores.¹⁰

The MC routine implemented in the Simapro software was used to propagate these uncertainties throughout the product system. For each impact category, the simulation produced statistical outputs—including the mean, median, standard deviation (SD), coefficient of variation (CV), the standard error of the mean (SEM), and the 2.5th and 97.5th percentiles, defining the 95% confidence interval.

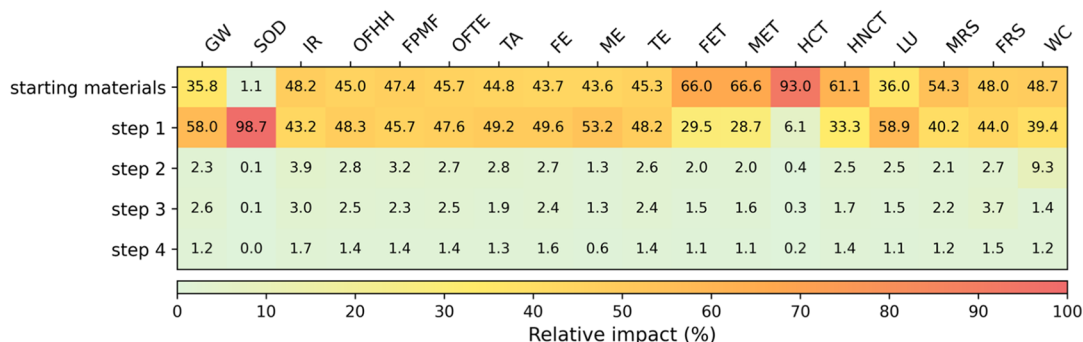
3. RESULTS

3.1. Midpoint Analysis

The potential environmental impacts (midpoint results) associated with the production of 1 kg of (–)-chloramphenicol 1 via Path A and Path B, modeled at both laboratory and simulated industrial scales, are shown in Table 3. A detailed environmental impact assessment analysis is presented in the Supporting Information (A12).

The heatmaps illustrating the relative impact percentages of reaction steps as well as of material, energy, equipment, waste, and emission contributions are presented in Figures 2 and 3 for Paths A and B, respectively, while those for laboratory-scale

(a) Step analysis



(b) Contribution analysis

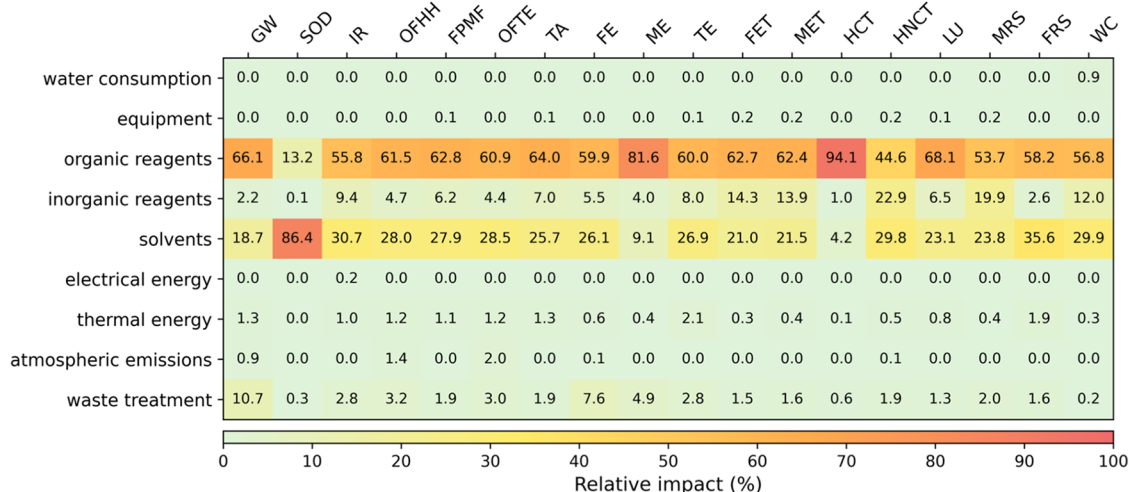


Figure 3. Heatmap illustrating the relative contributions (expressed as percentage of total impact) to the environmental profile of the scaled-up production of (–)-chloramphenicol **1** via Path B at simulated industrial scale. (a) Step analysis showing the relative contribution of each synthetic step across all impact categories. (b) Contribution analysis highlighting the relative contribution of material and energy inputs and emissions, including water consumption, equipment, reagents, solvents, energy use, and atmospheric emissions (for abbreviations, see caption of Figure 1).

syntheses are available in Supporting Figures S1 (Path A) and S2 (Path B). These results highlight how LCA enables the calculation of potential environmental impacts associated with key contributors—such as reagents, solvents, energy inputs, and emissions—and facilitates hotspot analysis within multistep syntheses. Specifically, LCA pinpoints the most impactful stages of a multistep synthesis, providing a clear basis for targeted optimization.

For both paths, three main hotspots were identified: the organic reagents, the inorganic reagents, and the solvents.

Figure 2a indicates that for path A, Step 2 (i.e., the catalytic hydrogenation of the aliphatic nitro group) emerged as the most impactful stage across most impact categories, particularly for mineral resource scarcity (MRS), terrestrial acidification (TA), fine particulate matter formation (FPMF), land use (LU), and human noncarcinogenic toxicity (HNCT), >80%. These impacts are primarily driven by the use of the PdO catalyst, despite the assumption of ten reuse cycles made in the LCI.⁶¹ For stratospheric ozone depletion (SOD), the main contribution in this Step 2 arises from the use of chloroform as a recrystallization solvent. Additional impacts are linked to the production of the initial starting materials (benzaldehyde **2** and β -nitroethanol **3**), with β -nitroethanol **3** being the major contributor due to its synthesis requiring a large excess of nitromethane (see Scheme S19). Although the

industrial-scale simulation assumes a 68% recovery of nitromethane, its production still exhibits significant impacts, mainly because of the substantial excess of nitric acid employed in its synthesis. Additionally, Step 4 (acetylation of the secondary alcohol) shows a notable contribution to marine eutrophication (ME, 64.9%), primarily due to the use of pyridine as a base. Although the resolution step (Step 7) does not emerge as a direct hotspot—since it does not involve particularly harmful reagents or solvents—its low overall yield (15.06% over the two steps; Table S73) substantially increases the demand for racemic intermediate ($\pm$)-**11** and, consequently, the cumulative material requirement for all preceding steps. Because the resolution occurs late in the route, the yield penalty is amplified: each earlier step must produce substantially more material to compensate, which increases reagent and solvent consumption across the entire pathway.

Contribution analysis reveals that organic reagents show the highest potential impacts in ME (82.1%), WC (66.3%), GW (54.3%), IR (46.8%), FRS (44.3%), HCT (43.9%), and FE (32.8%), as indicated in Figure 2b. For GW, the main impacts are associated with the waste solvent treatment across various processes, mainly during the synthesis of starting materials. IR is tied to electricity from nuclear sources, while FE relates to

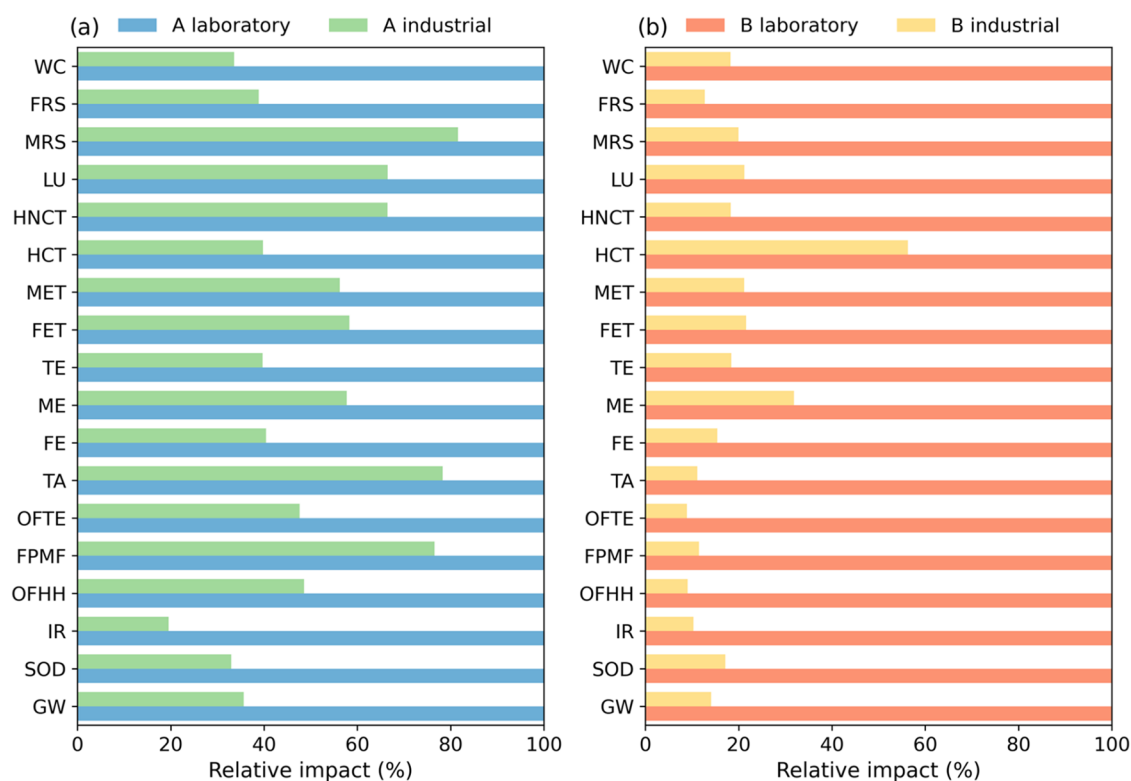


Figure 4. Relative midpoint impacts (ReCiPe 2016, H) for the production of (–)-chloramphenicol **1**, showing the effect of scale-up from laboratory to industrial production for (a) Path A and (b) Path B (for abbreviations, see caption of Figure 1).

thermal energy production and HCT to impacts associated with chemical factory construction.

Inorganic reagents show major contributions in FPMF (85.4%), TA (87%), MRS (88.2%), LU (78.2%), HNCT (77%), FET (63.9%), MET (61%), and OFHH (45.9%), primarily related to palladium extraction and production.

As highlighted in Figure 3a, for Path B, the dominant environmental contributions originate from Step 1, the catalytic cascade aldol reaction. Despite the catalyst being employed at only 10 mol %, the urea-based catalyst **A** has a substantial influence across most impact categories. Catalyst **A** is synthesized via a Mitsunobu-type transformation of quinidine **S23**, followed by nucleophilic addition of the resulting amine to the aromatic isocyanate **S20** (see Scheme S11). Its environmental burdens are primarily linked to the use of quinidine **S23** as a starting material and **S20**, and, to a lesser extent, to DCM as reaction solvent and to additional reagents for the Mitsunobu reaction. Quinidine **S23** extraction from cinchona bark is particularly impactful due to the inherently low alkaloid yield, requiring large quantities of bark and toluene, and generating significant solvent waste. Furthermore, the three-step synthesis of isocyanate **S20** from terephthalic acid exhibits high impacts, largely because of the use of phenylphosphoryl fluoride **S10**, used as a fluorinating agent (Scheme S8). Additional impacts arise from the two-step synthesis of isocyanatomalonate **5**. In contrast, Steps 2–4 exhibit comparatively minor contributions.

As highlighted in Figure 3b, contribution analysis reveals that organic reagents dominate most impact categories, notably HCT (94.1%), ME (81.6%), LU (68.1%), GW (66.1%), TA (64.0%), FET (62.7%), FPMF (62.8%), OFHH (61.5%), OFTE (60.9%), FRS (58.2%), IR (55.8%), and HNCT (44.6%). For HCT, impacts are primarily driven by Cr (VI)

emissions during the production of chromium trioxide (CrO_3), required for the oxidation step in the synthesis of 4-nitrobenzaldehyde. For ME, the main contributor is ammonium ion emissions to water during diethyl malonate synthesis. LU impacts stem from cinchona cultivation for quinidine extraction, the main precursor for urea-based catalyst **A** preparation. GW is dominated by hazardous waste solvent treatment, with Step 1 generating the most intensive solvent waste. For TA, impacts originate from both organic reagents and solvents, with diethyl malonate being the most significant among organic reagents. SOD is largely attributable to chloroform use in Step 1. Overall, solvents contribute substantially to the environmental burden—ranging from 4.2% to 86.4%—across all impact categories.

Inorganic reagents also exhibit notable contributions, particularly in HNCT (29.8%), MRS (19.9%), FET (14.3%), and MET (13.9%). These impacts are associated with the use of zinc powder (reducing agent in the synthesis of isocyanatomalonate **5**), sodium nitrite (first step of the synthesis of **5**, see Scheme S28), and sodium bicarbonate employed throughout the synthetic sequence.

3.2. The Influence of Scale-Up Framework

For path A, transitioning from laboratory to scale-up modeling leads to substantial reductions across most impact categories, with decreases of over 80% for IR, 67% for SOD, 66% for WC, 64% for GW, 61% for FRS, 60% for HCT, 59% for FE, 52% OFTE, and 51% for OFHH (Figure 4a). These improvements are primarily driven by solvent recovery at the industrial scale, which reduces solvent-related contributions by 2–15% depending on the category. Although thermal energy requirements increase slightly during scale-up, adding 0.1–4% per impact category, this trade-off remains positive overall, as the

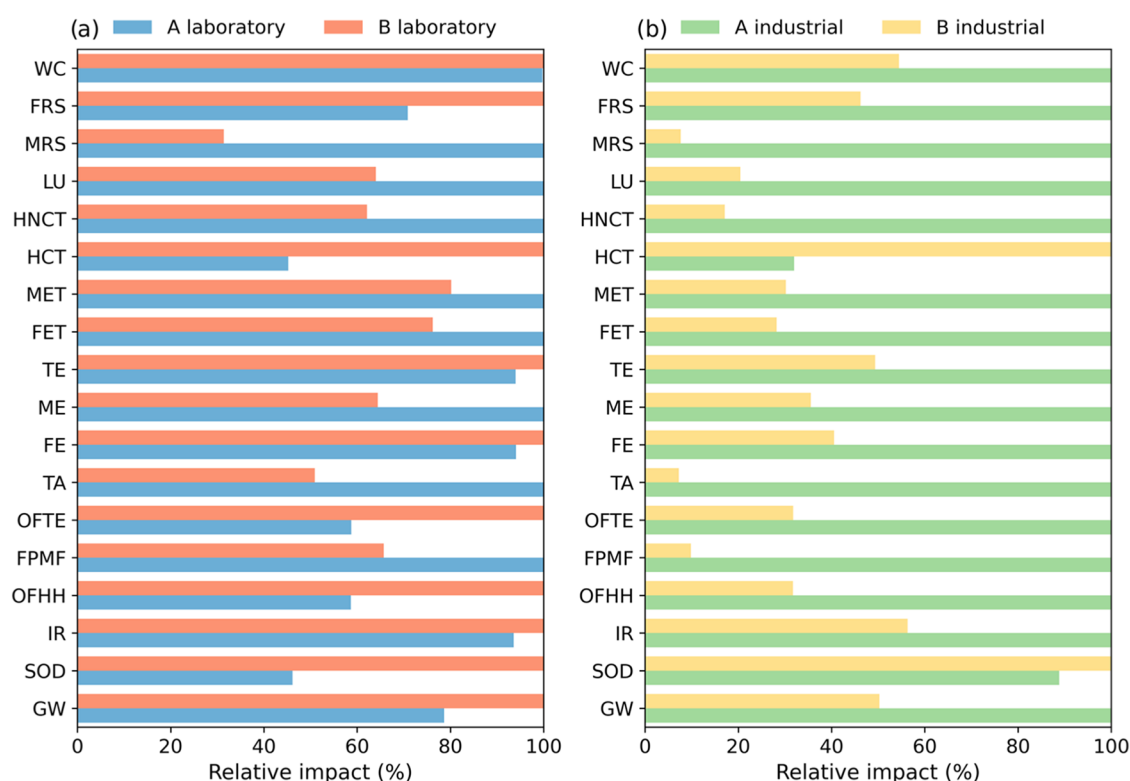


Figure 5. Relative midpoint impacts (ReCiPe 2016, H) illustrating the comparison of the environmental profiles of Path A and Path B at (a) laboratory scale and (b) simulated industrial scale (for abbreviations, see caption of Figure 1).

benefits of solvent recovery outweigh the additional energy demand. Another improvement observed at the industrial scale is the reduction in electricity demand, with contributions becoming negligible (<1% per impact category, as seen in Figures 2 and 3). Waste treatment also shows a modest decrease when moving from laboratory to industrial scale, with reductions of 0.5–2.5%.

For Path B, the transition from laboratory to industrial scale results in substantially greater reductions across all impact categories compared to Path A, with decreases ranging from 43% to 91% at the simulated industrial scale (Figure 4b). At the laboratory scale, solvent-related contributions are markedly higher, primarily because of frequent purifications via flash chromatography. Consequently, the improved environmental profile observed on an industrial scale is largely attributable to the adoption of less solvent-intensive purification strategies.

3.3. The Role of the Synthetic Pathway

At the laboratory scale (Figure 5a), the differences between the two pathways remain limited. Several impact categories—such as IR, FE, TE, and WC—exhibit only minimal variation between Path A and Path B (<7%). Having said that, Path A shows higher impacts in nine categories, whereas Path B is higher in the remaining nine, resulting in an overall balanced performance. At this stage, and on the basis of laboratory-scale data alone, it is therefore not possible to clearly identify the more sustainable route.

At the simulated industrial scale (Figure 5b), a markedly different outcomes emerge. The comparative assessment indicates that Path B exhibits substantially lower impacts than Path A across most categories. Notable reductions are observed for TA (≈92.8%), MRS (≈92.3%), FPMF (≈90%), HNCT (≈83%), LU (≈80%), FET (≈72%), MET (≈70%),

OFHH (≈68.3%), and OFTE (≈68.2%), ME (≈64.4%), FE (≈59.4%), FRS (≈53.8%), TE (≈50.6%), GWP (≈49.7%), WC (≈45.5%), and IR (≈43.7%). Two exceptions emerge: HCT, for which Path B is higher by ≈68.0%, primarily due to Cr (VI) emissions to water during the synthesis of 4-nitrobenzaldehyde 4; and SOD, where Path B is higher by ≈11.2%, driven mainly by the use of large quantities of chloroform as a reaction solvent.

These results clearly show that, upon scaling-up, the more streamlined synthetic sequence of Path B—characterized by fewer steps, improved yields, and reduced waste generation—translates into better environmental performance compared to the classical multistep route. The avoidance of precious-metal-derived catalysts, where applicable, may also contribute to these improvements. Furthermore, the asymmetric synthesis step, despite the non-negligible impacts associated with the cinchona alkaloid-derived catalyst A, still performs more favorably than the corresponding aldol reaction, followed by PdO-catalyzed hydrogenation (Step 1–2) in Path A, reinforcing the overall advantage of Path B under simulated industrial conditions.

3.4. Midpoint Results: Uncertainty Analysis

The outcomes of the MC uncertainty analysis for the comparative assessment of the synthetic pathways of (–)-chloramphenicol 1 are presented in Figure 6 and Tables S60–S63. When comparing Path A at laboratory scale with its industrial-scale simulation counterpart (Figure 6a), the MC results confirm the deterministic trends for the majority of impact categories; only HNCT and WC do not show robust differences within the 95% uncertainty interval. A similar pattern is observed for Path B (Figure 6b), where the

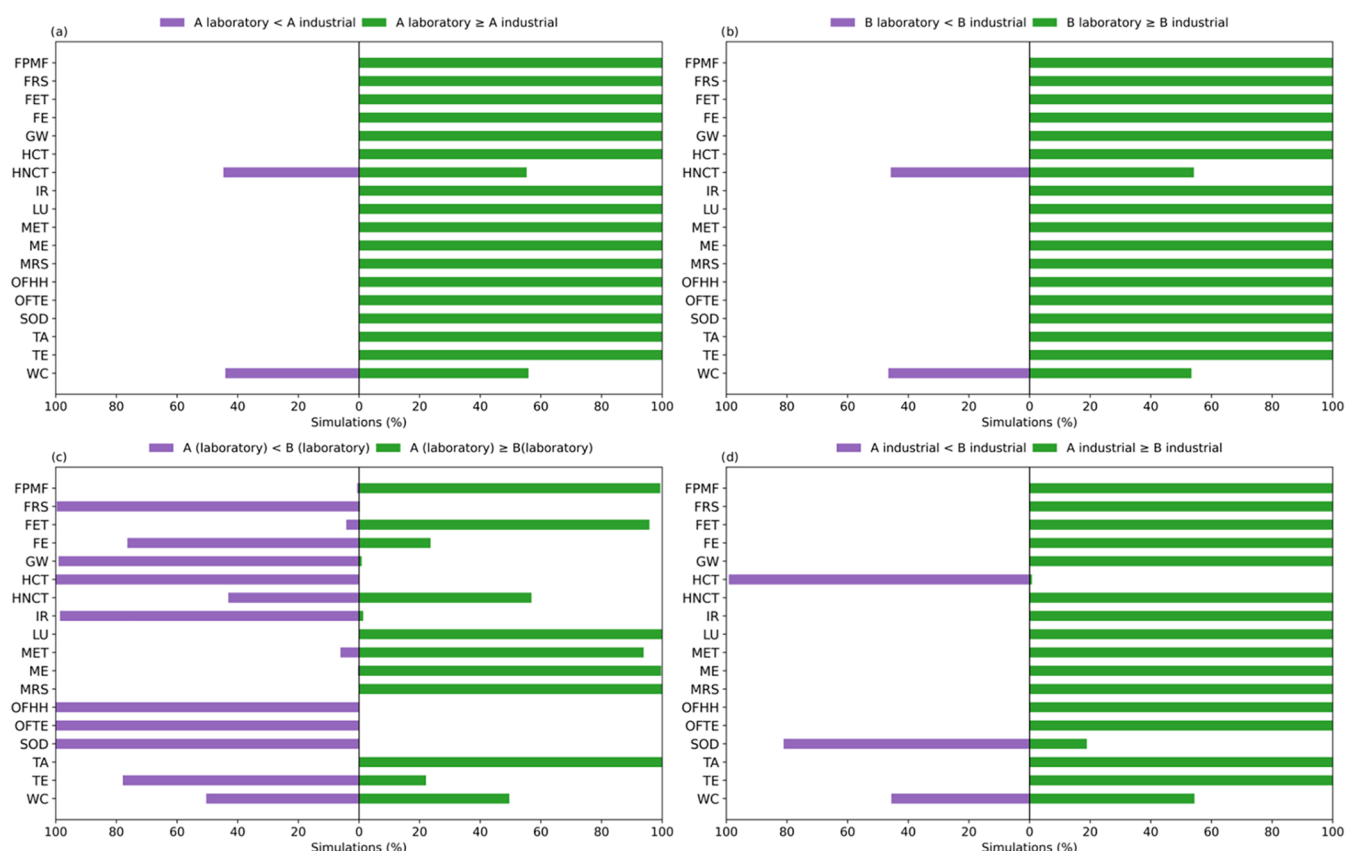


Figure 6. Monte Carlo uncertainty analysis at the midpoint level using the ReCiPe 2016 (H) method, based on 1000 iterations. The mirrored bar charts show, for each impact category, the percentage of MC runs in which one alternative exhibits higher impact than the other. Results are presented for the following comparisons: (a) Path A at laboratory scale vs Path A at simulated industrial scale; (b) Path B at laboratory scale vs Path B at simulated industrial scale; (c) Path A vs Path B at laboratory scale; and (d) Path A vs Path B at simulated industrial scale. Values close to 0% or 100% indicate robust differences, while values close to 50% reflect substantial overlap of the 95% uncertainty intervals (for abbreviations see caption of Figure 1).

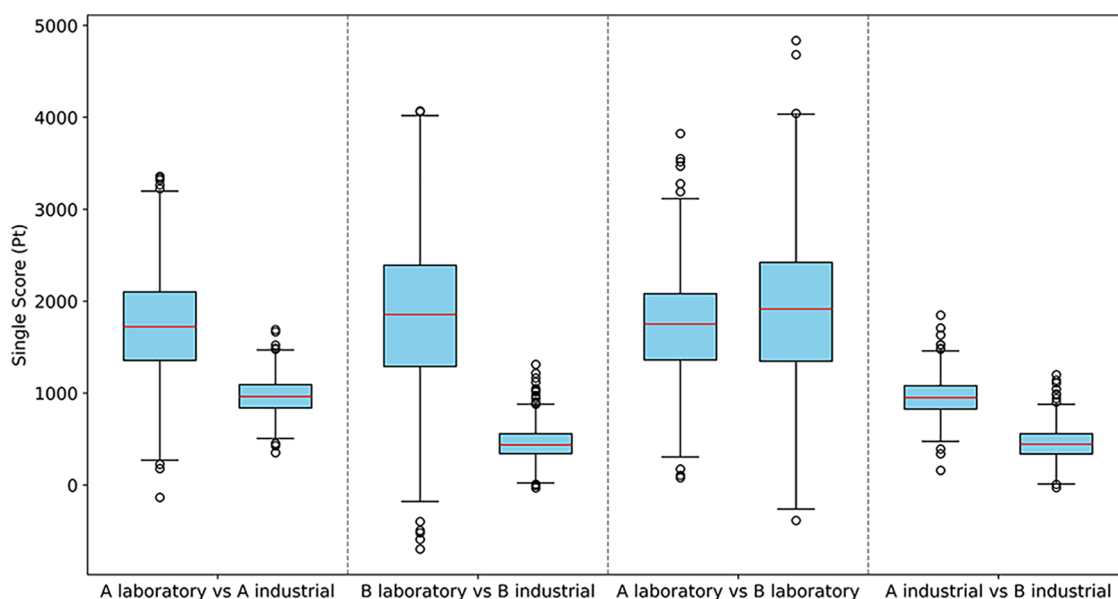


Figure 7. Boxplots of the single score results (ReCiPe 2016, H, endpoint) for pathways A and B at laboratory and simulated industrial scales. The four comparison groups shown on the *x*-axis correspond to the Monte Carlo simulations performed for: A laboratory vs A industrial, B laboratory vs B industrial, A laboratory vs B laboratory, and A industrial vs B industrial. For each comparison, 1000 Monte Carlo iterations were carried out, and each box depicts the resulting distribution for the corresponding alternative, showing the median, interquartile range (IQR), and whiskers extending to values within $1.5 \times \text{IQR}$.

laboratory-to-industrial comparison remains statistically robust across most categories.

In contrast, the comparison between the laboratory syntheses of Path A and Path B reveals a higher degree of overlap between the uncertainty distributions, with robust differences observed in 13 impact categories (i.e., FPMF, FRS, FET, GW, HCT, IR, LU, ME, MRS, OFHH, OFTE, SOD, and TA) out of 18 (Figure 6c). This reflects the larger uncertainty typically associated with small-scale laboratory inventories. Finally, at the simulated industrial scale (Figure 6d), the two pathways show robustly distinguishable results for all categories except WC and SOD, indicating that scaling up reduces variability and strengthens the robustness of the comparative outcomes.

3.5. Endpoint and Single Score Analysis

To evaluate the overall environmental performance of the two synthetic routes, an endpoint damage assessment was performed using the ReCiPe endpoint (H) method. The damage assessment results are reported in Table S64, while the aggregated single score values (Pt), obtained after normalization and weighting, are presented in Table S65 and Figure S3.

To assess the robustness of the comparisons, a Monte Carlo (MC) simulation with 1000 iterations was conducted for the following pairwise analyses: (i) Path A at laboratory scale versus industrial-scale simulation, (ii) Path B at laboratory scale versus industrial-scale simulation, (iii) Path A versus Path B at laboratory scale, and (iv) Path A versus Path B at industrial-scale simulation.

The full distribution of MC outcomes is provided in Figure 7, where boxplots illustrate the median, interquartile range (IQR), and overall spread. These boxplots enable visual inspection of distribution width, asymmetry, and overlap, supporting a more nuanced interpretation of statistical separability than mean values alone. Summary statistics for all MC distributions are reported in Table S66, while detailed mean single score values and their associated standard deviations (SDs), which account for sampling variability across independent sets of simulations, are further provided in Figure S4 and Table S67.

The MC results indicate that, for Path A, the industrial-scale simulation yields a 44.3% lower single score than the laboratory-scale model, while for Path B, the reduction reaches 75.4%. Under industrial-scale simulated conditions, Path B exhibits a 52.0% lower single score than Path A, confirming its superior environmental performance at scale. At the laboratory scale, Path B shows a 7.6% higher single score than Path A; however, the overlapping IQRs in Figure 7 indicate that this difference lies within the uncertainty of the simulations and is, therefore, not statistically significant.

4. GREEN CHEMISTRY METRICS FOR INDUSTRIAL SCALE-UP

In parallel with LCA, quantitative green chemistry metrics were applied at both the step level and the overall process level for the two synthetic pathways at a simulated industrial scale. This complementary assessment was aimed at evaluating mass-based sustainability indicators and examining how their diagnostic values align with the LCA outcomes. The definition of the metrics employed in this study are detailed in Table S72.⁴ Although mass intensity (MI), process mass intensity (PMI), wastewater intensity (WWI), solvent intensity (SI), the

environmental factor (E-factor), and the overall yield (Y) were calculated both at the step level and for the complete synthetic sequence, Table 4 reports exclusively the overall-process

Table 4. Summary of Green Chemistry Metrics for Path A and Path B, Respectively (Unit: kg Input or Waste Per kg of Product Unless Otherwise Indicated)^a

	E-factor	Y (%)	MI	PMI	WWI	SI
Path A	2023.79	1.52	1329.05	2024.79	695.74	803.74
Path B	1049.46	15.04	464.28	1050.50	626.75	342.12

^aThe metrics considered were mass intensity (MI), process mass intensity (PMI), wastewater intensity (WWI), solvent intensity (SI), the environmental factor (E-factor), overall yield (Y).

values. Additionally, the Supporting Information (Tables S73–S74) provides the full stepwise breakdown of these metrics together with the inherently step-specific indicators such as atom economy (AE), carbon economy (CE), and chemical yield (CY).

Green chemistry metrics were calculated exclusively for the foreground sequence, encompassing all processes performed within laboratory or pharmaceutical manufacturing boundaries, i.e., the synthetic steps and starting materials that are not commercially available.

Overall, Path B exhibits superior performance across all the selected green metrics. To exemplify, the PMI for Path B is reduced by approximately 52% relative to Path A, reflecting substantially lower material demands per kilogram of (–)-chloramphenicol **1** produced.

The cumulative yield across all foreground reactions is substantially higher for Path B than for Path A (15.04% vs 1.52%). Consistently, the E-factor is lower for Path B by around 48%, and solvent consumption, expressed through the SI, decreases by ≈57%. WWI is also reduced by ≈10%. Collectively, these results indicate that Path B achieves a more favorable environmental performance in terms of material efficiency and waste generation, in full agreement with the lower life cycle impacts identified through LCA.

At the step level, Path A shows three clear hotspots (Table S73). Step 7, the resolution of compound **11**, is the most impactful step according to the PMI, E-factor, reaction yield over two steps (15.06%), and AE (47.71%). The deprotection of the acetyl group (i.e., step 6) comes close, and additionally, it exhibits the highest WWI, a modest reaction yield (43.09%), low CY (6.56%), and limited AE (56.62%). Step 2 emerges as the third-largest contributor to PMI and E-factor and exhibits the highest SI. Resolution sequence (step 7) exhibits the lowest CE (47.4%), followed by the deprotection step (step 6, CE = 60%).

For Path B, the main hotspots correspond to the first stages of the sequence (Table S74). The preparation of 2-aminomalonate hydrochloride **S34**, as an intermediate in the synthesis of isocyanatomalonate **5**, displays the highest PMI, E-factor, WWI, and SI, followed by step 3 (the NaBH₄ reduction) and step 2 (a two-step hydrolysis followed by decarboxylation). These three steps dominate the mass-based burdens and define the critical intervention points for improving the process efficiency. The lowest AE values were observed for the preparation of isocyanatomalonate **5**.

Comparison with the LCA results indicates that the hotspots identified by green metrics overlap only partially with those

Scheme 2. Alternative Metal-Free Reduction Pathway to Amine 7 via Trichlorosilane (Cl_3SiH), Following Acidification of Intermediate 6

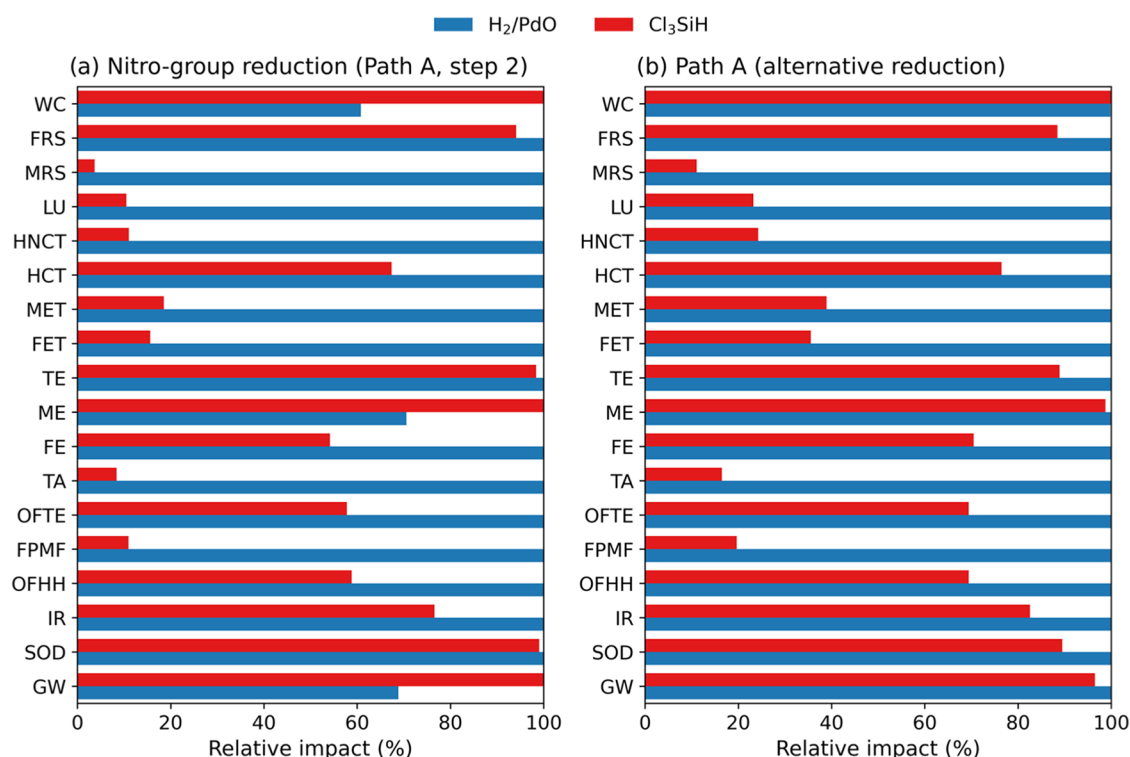
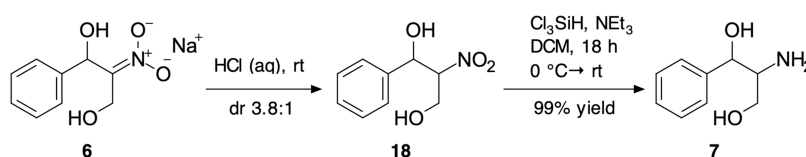


Figure 8. Relative midpoint impacts (ReCiPe 2016, H) comparing PdO-catalyzed hydrogenation and trichlorosilane-based nitro group reduction. (a) Isolated reduction step (Path A, Step 2), normalized to 1 kg of intermediate 7. (b) Path A with an alternative reduction, accounting for yield-driven adjustments in upstream material requirements, normalized to 1 kg of (–)-chloramphenicol 1.

highlighted by LCA, reflecting that important environmental impacts can arise from factors beyond material inefficiencies.

For Path A, green metrics consistently identify Step 7, Step 6, and to a lesser extent, Step 2 as dominant contributors due to low yields, limited atom economy, and high solvent and water consumption (Table S73). In contrast, the LCA highlights the PdO-catalyzed hydrogenation (step 2) as the primary hotspot, as the environmental burden is dominated by the upstream extraction and refining of palladium, despite the relatively small material throughput at this step.

For Path B, both approaches recognize the synthesis of isocyanatomalonate 5 as highly impactful. However, LCA identifies step 1 as the principal contributor owing to the upstream burdens associated with the production of catalyst A, whereas the green metrics rank the synthesis of 5, followed by steps 3 and 2, as hotspots based primarily on mass intensity indicators (Table S74).

Overall, these results demonstrate that PMI, E-factor, WWI, and SI are effective at identifying inefficiencies in material use within the technosphere, while LCA provides a more complete perspective by accounting for energy demand, upstream supply chain processes, and emissions that are not captured by step-level mass balances alone. The two approaches are therefore synergistic rather than contradictory: improvements in yield,

solvent consumption, and material efficiency generally translate into lower life cycle impacts, but a comprehensive sustainability assessment also requires consideration of energy use, catalyst and starting-material production, and atmospheric emissions. Integrating both perspectives enables a more informed prioritization of interventions, spanning both step-level process optimization and reduction in upstream environmental burdens.

5. OPPORTUNITIES FOR FURTHER ENVIRONMENTAL OPTIMIZATION

Sections 3 and 4 demonstrate that a shorter synthetic sequence, coupled with reduced solvent, reagent, and water consumption, is a key strategy for lowering the environmental impacts associated with the production of (–)-chloramphenicol 1. This conclusion is consistently supported by both midpoint and endpoint LCA results, as well as by quantitative green chemistry metrics. In particular, considerable impacts associated with the PdO-catalyzed reduction of the aliphatic nitro intermediate 6, together with the two-step acetylation/deprotection sequence required in Path A but avoided in Path B, highlight the advantage of a shorter, more efficient synthetic route, which exhibits a substantially lower environmental burden. Beyond comparative analysis, this study demonstrates

Scheme 3. Alternative Thiourea-Catalyzed Cascade Aldol Reaction, Based on the Methodology Developed by Sakamoto et al.⁶⁵

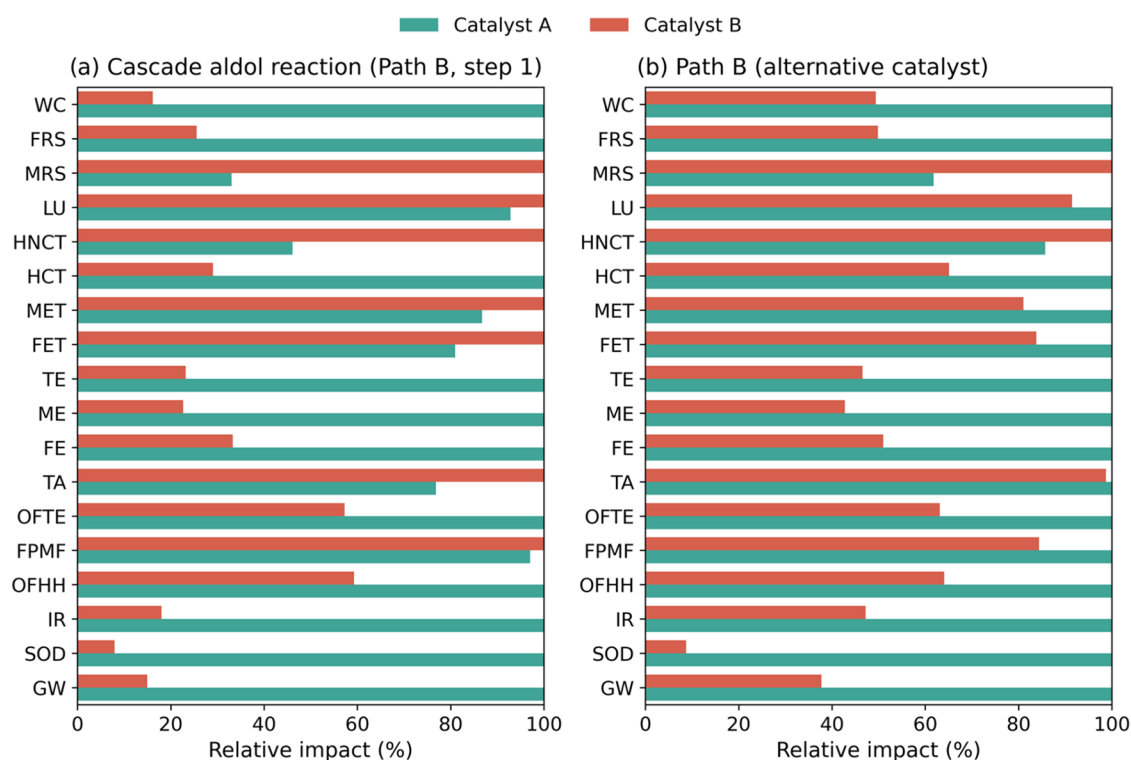
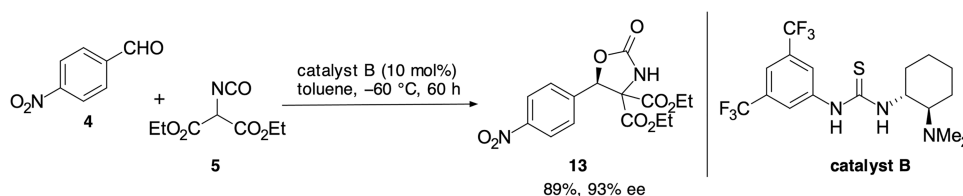


Figure 9. Relative midpoint impacts (ReCiPe 2016, H) comparing cinchona alkaloid catalyst A and thiourea catalyst B mediated cascade aldol reaction. (a) Isolated organocatalytic step (Path B, step 1), normalized to 1 kg of intermediate 13. (b) Path B with an alternative catalytic aldol reaction step, accounting for yield-driven adjustments in upstream material requirements, normalized to 1 kg of (–)-chloramphenicol 1.

the predictive capability of LCA by modeling alternative process scenarios and quantifying their environmental implications prior to experimental implementation.

The catalytic hydrogenation of nitro groups over PdO can be replaced by alternative reduction strategies, including the use of strong hydride donors such as LiAlH_4 .⁶² More recently, a promising and potentially more sustainable metal-free approach for the reduction of aromatic and aliphatic nitro groups has been reported, based on trichlorosilane (Cl_3SiH), affording high yields with retention of configuration.⁶³

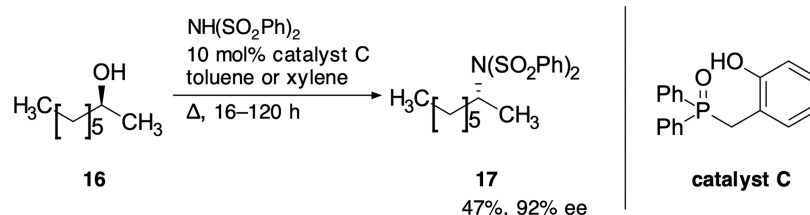
In this approach (Scheme 2), sodium salt intermediate 6 is first treated with an aqueous solution of hydrochloric acid at room temperature, preserving a modest diastereomeric ratio ($\text{dr} = 3.8:1$). Subsequent reduction of nitro derivative 18 with trichlorosilane in the presence of a tertiary amine proceeds nearly quantitatively, yielding the corresponding amine 7.

To assess the potential environmental sustainability of this modified route, Path A was re-evaluated by LCA with the PdO-catalyzed hydrogenation replaced by the trichlorosilane-mediated reduction shown in Scheme 2. Two complementary analyses were performed at the step level and at the system level (Figure 8).

At the step level (Path A, step 2), replacement of the PdO-catalyzed hydrogenation with the Cl_3SiH -based reduction results in mixed effects across impact categories (Figure 8a). Reductions are observed for IR, FPMF, OFTE, TA, FE, FET, MET, HCT, HNCT, LU, and MRS, whereas increases are observed for GW, ME, and WC. Changes in the TE are comparatively minor.

When yield effects are included at the system level, the comparison changes substantially. Path A with Cl_3SiH shows notable reductions across most impact categories relative to the PdO-based route (Figure 8b). This indicates that the higher yield associated with the alternative reduction offsets several step-level burdens through reduced upstream material and energy requirements, leading to an overall improvement in the environmental performance of path A.

Despite its overall improved performance, path B still presents opportunities for further optimization. The catalyst required in the key stereoselective step remains a significant hotspot, even at a loading of 10 mol %. This burden originates not only from the catalytic transformation itself (i.e., step 1) but also from the environmental impacts associated with the catalyst synthesis, which involves a Mitsunobu transformation.

Scheme 4. Catalytic Mitsunobu Inversion Reaction, Based on the Methodology Developed by Beddoe et al.⁶⁸

Mitsunobu chemistry is characterized by low atom economy, the use of hazardous reagents, and the generation of stoichiometric quantities of triphenylphosphine oxide as waste.⁶⁴

A viable opportunity for improvement involves replacing the cinchona-derived urea organocatalyst with thiourea-based alternatives. Thiourea catalysts (i.e., **catalyst B**) reported for analogous transformations (Step 1) achieve higher isolated yields (up to 89% versus ca. 60%) with only a modest decrease in enantioselectivity ($\approx 93\%$ ee versus 97% ee), as shown in Scheme 3.⁶⁵ The improved yield would directly reduce material and solvent requirements per kilogram of product, while the synthesis of the thiourea catalyst does not involve a Mitsunobu transformation, suggesting a potentially lower upstream environmental burden.

Using the same LCA framework applied to the Path A re-evaluation, the cinchona-derived urea organocatalyst in Path B was replaced with a thiourea-based alternative and assessed at both the step and system levels (Figure 9).

At the step level, replacement of the cinchona-derived urea catalyst A with the thiourea catalyst B in the cascade aldol reaction (step 1) leads to pronounced reductions in several impact categories (Figure 9a). In particular, substantial decreases are observed for GW, SOD, IR, OFHH, OFTE, FE, ME, TE, HCT, and WC, with some increases in FPMF, TA, FET, MET, HNCT, LU, and MRS. These improvements mainly arise from the lower upstream burdens associated with the catalyst synthesis.

When yield effects are incorporated at the system level, these advantages become even more evident (Figure 9b). Path B employing the thiourea catalyst B exhibits marked reductions across most midpoint impact categories relative to the cinchona catalyst A-based route. The higher yield reduces material and solvent requirements per kilogram of product, while the avoidance of a Mitsunobu transformation in catalyst synthesis further lowers upstream environmental burdens, resulting in a clear overall improvement in the environmental performance of Path B.

The robustness of these conclusions for both improvement strategies was further assessed by MC analysis (Tables S68–S71 and Figures S5–S6). For Path A, the direction of change observed in the deterministic LCA was reproduced in 13 out of 18 midpoint categories at both step and system levels, while for Path B, consistency was observed in 12 and 13 categories, respectively, supporting the statistical robustness of the identified trends.

Both quantitative analyses demonstrate that combining reaction redesign with yield enhancement, either through substitution of a more benign transformation or through integration of a higher-yielding step, can substantially reduce the environmental impacts of both paths A and B. While minor burden shifting between individual impact categories is still observed, particularly at the step level, these trade-offs are

limited in magnitude and are largely attenuated at the system level, where yield-driven reductions in upstream material and energy requirements dominate the overall environmental profile.

Beyond the optimization strategies assessed quantitatively by LCA, several additional opportunities for reducing material intensity and environmental burden can be identified on the basis of reaction design principles and previous studies.

For path A, the modest diastereomeric ratio ($\text{dr} \approx 3.8:1$) is already established in the initial β -nitroethanol–benzaldehyde condensation step, and is therefore propagated through the subsequent nitro group reduction, irrespective of the reducing agent employed. As a consequence, even when lower-impact reduction methods are adopted, the overall yield of the desired *threo* diastereomer remains limited and its isolation still relies on recrystallization.

This indicates that a further improvement in both yield and environmental performance must target both the carbon–carbon bond-forming step and the downstream reduction. In this context, Xia et al. have reported a catalytic syn-selective nitroaldol (Henry) reaction for the synthesis of amphenicol intermediates, enabling preferential formation of the *threo* configuration at an early stage.⁴⁴

Additionally, the protection of the secondary alcohol by acetylation (step 4) could be improved by employing a catalytic variant of the reaction using 4-(*N,N*-dimethylamino)-pyridine (DMAP, 5 mol %) instead of stoichiometric pyridine, thereby reducing reagent consumption and improving atom efficiency.⁶⁶ However, the use of DMAP introduces additional concerns related to its acute toxicity and environmental hazard profile,⁶⁷ which may offset some of the benefits associated with its catalytic use.

A further limitation of Path A is the reliance on a late-stage kinetic resolution (step 7) to obtain the desired (–)-enantiomer, which intrinsically reduces overall yield and amplifies upstream material losses. From a process-design perspective, stereochemical control would be more efficiently introduced at an earlier stage or avoided altogether through asymmetric synthesis. This rationale underlies both step 1 from Path B,⁴⁵ and the proposed syn-selective nitroaldol (Henry) reaction reported by Xia et al.,⁴⁴ which establish the required configuration during C–C bond formation and thereby reduce the reliance on downstream resolution.

For path B, the synthesis of catalyst A could be further optimized. Recent work by Beddoe et al.⁶⁸ has reported a catalytic variant of Mitsunobu transformation, involving a redox-neutral, phosphine oxide-catalyzed inversion of secondary alcohols operating at 10 mol % catalyst loading and delivering modest yields and enantiomeric excess (Scheme 4). Although only a limited number of C–N bond-forming examples have been demonstrated, this emerging methodology represents a promising avenue for reducing both material requirements and waste burdens in urea catalyst synthesis.

Further opportunities concern catalyst loading. While urea organocatalysts are frequently employed at relatively high loadings (commonly 10–20 mol %),⁶⁹ recent literature demonstrates that significant reductions are feasible without compromising performance. For instance, Wang et al.⁷⁰ reported that a urea-derived catalyst effectively promoted the enantioselective aldol reaction of isatins with ketones, achieving yields as high as 94% and enantioselectivities up to 87% ee. Importantly, stereoselectivity was maximized at a catalyst loading of 5 mol %, with higher loadings (10–20 mol %) failing to improve asymmetric induction. Similarly, Bhati et al.⁷¹ described a rationally designed urea-tagged proline catalyst that leverages intramolecular synergistic activation to perform direct asymmetric aldol reactions at only 2 mol % loading.

Finally, the environmental profile of isocyanatomalonate **5** could potentially be improved through optimization of the extraction step. The amino alcohol intermediate exhibits limited solubility in ethyl acetate, necessitating comparatively large solvent volumes during workup—even after applying a 68% solvent-recovery rate. Moreover, solubility prediction for isocyanates remains uncertain due to the limited availability of structurally related training data, introducing additional uncertainty into solvent estimates. A systematic solvent-screening study—exploring alternative extraction solvents, mixed solvent systems, or process-intensified separation strategies—could substantially reduce solvent demand and further improve the sustainability of this stage of the synthesis.

Beyond comparative assessment, this work illustrates how LCA can be used as a predictive decision support tool to explore alternative synthetic options prior to experimental implementation. Such predictive use is appropriate when proposed modifications are grounded in structurally related examples reported in the literature, with available yields and reaction conditions that enable physically consistent modeling of material and energy requirements. At the same time, experimental validation remains essential, as changes in yield, selectivity, or workup efficiency can substantially affect upstream material demand and environmental impacts.

In this context, ML-based tools for reaction⁷² and property prediction¹⁷ may play an increasingly important role, particularly when integrated with literature data, experimental validation, and LCA in an iterative workflow aimed at a sustainability-oriented process design. Approaches that rely on highly speculative reaction behavior or lack suitable analogue substrates remain outside the scope of attributional, process-based LCA.⁷³

Table 5 summarizes key environmental hotspots and corresponding optimization strategies identified through the combined LCA and green metric analysis.

6. CRITICAL REFLECTION ON ML-ASSISTED PROPERTY PREDICTION

While ML models enable property-based forecasts in situations where experimental thermodynamic data are limited or even unavailable, their use introduces specific risks that require careful consideration in early-stage LCAs.

A fundamental limitation of these predictive models is that their accuracy is capped by the irreducible aleatoric uncertainty of the training data. Analysis of interlaboratory experimental variability reveals a “noise floor” typically ranging between 0.5 and 1.0 log units for solubility. Consequently, while models like FASTSOLV (RMSE 0.83–0.95) and ML4SMILES (MAE

Table 5. Summary of Identified Environmental Hotspots and Potential Environmental Optimization Opportunities for the Synthesis of (–)-Chloramphenicol **1 via Path A and Path B**

path	hotspot	opportunity
A	Step 1: modest diastereomeric ratio (3.8:1)	Control of diastereoselectivity: syn-selective Henry reaction
A	Step 2: H ₂ /PdO reduction of nitro group	Alternative reduction: Cl ₃ SiH, LiAlH ₄
A	Step 4: secondary alcohol acylation	Catalytic acetylation (5 mol % DMAP)
A	The kinetic resolution (low yield)	Redesign: set up kinetic resolution earlier in the sequence; design an enantioselective synthesis
B	Step 1 (organocatalytic step)	thiourea catalyst B
B	Catalyst synthesis	catalytic Mitsunobu reaction
B	Catalyst loading	Reduce catalyst loading to 2–5 mol %
B	Two-step synthesis of isocyanatomalonate 5 .	Optimize extraction

0.156) approach state-of-the-art accuracy, they cannot be more precise than the experimental measurements they were trained on.²² This reliance on past data introduces a risk of “regression to the mean”, where models may obscure emergent, high-impact behaviors in complex chemical systems.⁷⁴

The reliability of ML-based LCIs is strictly constrained by the applicability domain (AD) of the supervised models. Because these tools learn from existing databases like BigSolDB or QM9, their predictive power diminishes for chemical classes poorly represented in the training set, such as highly complex aromatics or polymers.²² To mitigate this risk, ML-derived properties in this study were used conservatively and interpreted in terms of relative process trends.

The influence of property uncertainty must be interpreted in the context of process conditions. In the solvent-rich systems (>95% solvent) characteristic of most steps in this study, the effective heat capacity and density are dominated by the solvent. Thus, the ±15–20% uncertainty in predicted solute heat capacity from ML4SMILES has only a marginal effect on total energy balances,²² while uncertainty in solute density contributes less than ~1% to the overall mixture density and therefore has a negligible influence on agitation and mixing energy requirements.

In contrast, solvent demand—governed by solubility—represents a first-order driver of environmental impact. Even accounting for reported solubility uncertainty (±0.3–0.5 log units),²¹ property-based scaling remains more physically realistic than linear scale-up. For liquid–liquid extraction, aqueous solubilities predicted using ChemAxon are generally low for the organic intermediates considered. While their uncertainty may reach ±1 log unit (≈10×),⁴⁷ the resulting impact on K_D is modest compared to uncertainty in organic-phase solubility (±0.3–0.5 log units, ≈2–3×), which dominates solvent demand.

For example, while uncertainty in predicted solubility for aromatic precursors in chloroform may alter solvent demand by a factor of 2–3, the resulting volumes remain significantly lower than laboratory proxies, and the relative environmental ranking of Path A and Path B is preserved.

Overall, this analysis demonstrates that, when applied with awareness of their limitations, ML-assisted property predictions improve the robustness and objectivity of early-stage

LCAs while maintaining transparency regarding thermodynamic uncertainty.

7. CONCLUSIONS

This study presents the first cradle-to-gate life cycle assessment (LCA) of (–)-chloramphenicol synthesis, providing a comparative environmental evaluation of a historical kinetic-resolution route (Path A) and a modern asymmetric organocatalytic pathway (Path B). By integrating green chemistry metrics with a process-based LCA framework, the analysis demonstrates that material efficiency alone is insufficient to capture the full environmental performance of pharmaceutical manufacturing routes.

Across simulated industrial-scale conditions, Path B consistently exhibits lower environmental impacts than Path A, primarily due to the shorter synthetic sequence, the elimination of resolution and protection–deprotection steps, and the reduced solvent and reagent demand. In both scenarios, midpoint and endpoint results (ReCiPe 2016 H) converge in identifying organic reagents, catalyst manufacture, and solvent use for synthesis, workup, and purification as dominant environmental hotspots.

Monte Carlo uncertainty analysis confirmed the robustness of the findings. Differences between pathways at laboratory scale largely fall within the uncertainty bounds, but industrial-scale comparisons are statistically distinct across most midpoint categories and at the endpoint level, with Path B achieving a 52.0% lower single score than Path A. This reveals the importance of a scale-dependent assessment.

A key methodological contribution of this work is the integration of machine-learning (ML)-derived physicochemical property predictions into the life cycle inventory. Temperature-dependent solubility and heat capacity estimates enabled property-based modeling of solvent charge and energy requirements, reducing reliance on generic assumptions as often seen in early-stage LCAs, especially for extraction and purification steps.

More generally, ML-assisted property prediction improves the quality of early-stage LCAs by replacing opaque scale-up heuristics with thermodynamically interpretable, molecule-specific parameters. This shift enhances internal consistency, transparency, and decision relevance, particularly when comparative assessments are performed under the conditions of limited experimental data. Crucially, these benefits are realized when ML predictions are interpreted with explicit awareness of their dependence on training data quality, applicability domain, and irreducible uncertainty and are used to inform process trends rather than to claim exact absolute values.

Comparison with green chemistry indices such as process mass intensity (PMI) highlights that mass-based and impact-based metrics can lead to different conclusions regarding environmental hotspots. While PMI captures differences in material efficiency, LCA reveals additional drivers such as upstream supply chain impacts, catalyst synthesis, and energy-intensive unit operations that are not reflected in mass balances alone.

The results revealed multiple hotspots in Path A, with the hydrogenation of the nitro group emerging as a key contributor to the environmental impacts. Alternative reduction strategies, such as the use of trichlorosilane, were identified as potential improvement options, although their overall environmental

benefits remain subject to trade-offs associated with reagent production.

Despite its superior environmental performance predicted on an industrial scale, Path B still offers opportunities for further optimization, particularly through catalyst redesign, reduced catalyst loading, and improved solvent selection. The environmental burden associated with catalyst synthesis demonstrates the importance of evaluating catalyst sustainability alongside the catalytic performance. The sensitivity analysis indicates that emerging alternative organocatalysts such as thiourea-based systems represent promising directions, although some trade-offs associated with catalyst synthesis have been observed.

Overall, this study indicates that combining LCA with scale-up modeling, uncertainty analysis, and ML-assisted property prediction provides a robust framework for sustainability-oriented decision-making in pharmaceutical process development. The approach is broadly applicable to other active pharmaceutical ingredients (APIs) beyond chloramphenicol and supports informed route selection at an early stage when the design flexibility remains high.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.6c03025>.

Equations and parameters for life cycle inventory (LCI) modeling; detailed description of the life cycle inventories of background chemicals; detailed description of the life cycle inventories of each step of Path A and Path B; detailed inventories for sensitivity analyses; list of modeled chemicals; summary of predicted properties with machine learning and computational tools, validation and accuracy assessment of computational property prediction tools; uncertainty analyses tables for the comparison of Path A and Path B, at both laboratory and simulated industrial scale; endpoint results associated with the production of (–)-chloramphenicol via path A and path B; uncertainty analyses for the endpoint results; uncertainty analyses for sensitivity studies; quantitative green metrics employed in this study; stepwise results of green metrics evaluation for both path A and path B; graphical representation of the heatmaps for the production of (–)-chloramphenicol at laboratory scale for path A and, respectively, path B; graphical representation of single score comparison of path A and path B at both laboratory and simulated industrial scale; graphical representation of endpoint-level comparison of path A and Path B at both laboratory and simulated industrial scale with standard deviation (SD) bars; graphical representation of midpoint uncertainty analysis for sensitivity analyses; and detailed environmental impact assessment analyses for path A and path B at simulated industrial scale (PDF)

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Notes

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