Eco-Friendly Synthetic Strategies for Organic Compounds: Insights into Biocatalysis and Flow Chemistry

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Abstract

The ever-growing interest for sustainable chemical synthesis has led to the development of environmentally improved methodologies that reduce side effects on the environment while preserving synthetic efficiency. We report on the evolution of combining biocatalysis and flow chem from a complementary to a synergistic strategy for the synthesis of organic molecules. The studies are directed to develop and optimize biocatalytic methods with the use of enzymes and whole cells, establish integrated biocatalysis-flow chemistry approaches, and investigate efficient one-pot synthesis of primary amides catalyzed by scandium (III) triflatein under controlled microwave condition. Enzyme screening, process optimisation, flow chemistry integration and calculation of the molecular docking studies were used in an overall approach. It is shown that the reaction efficiency of this two-enzyme cascade system is greatly improved by ketoreductases (KREDs) reaching space-time yields of 8-47 g L^{-1} h^{-1} for the production of chiral alcohols, and exclusively high selectivity of lipase-catalyzed reactions with total turnover numbers >10^7. This transaminase technology proved to be particularly productive with space-time yields of up to 25 g L^{-1} h^{-1} for chiral amine formation. The integration of flow chemistry led to an improvement in process control and scalability, in addition to enabling a 85% conversion of amide under optimised conditions. Combining biocatalysis with flow chemistry led to improved process control and scalability. The results provide a sound basis for sustainable organic synthesis based on the availability of environmentally friendly alternative to traditional chemical processes that are not only commercially viable but that are also all process efficient.

Keywords: *Biocatalysis, Flow chemistry, Sustainable synthesis, Green chemistry, Enzyme engineering*

1. Introduction

The chemical industry is under ever increasing pressure to devise sustainable synthetic processes that minimise any environmental impact but at the same time remain economically robust. Conventional organic synthesis usually involves harsh reaction conditions and toxic reagents, and produces large amounts of waste, hence the greener need (Carola Castiello et al., 2023). Biocatalysis is a revolutionary technology known to provide moderate reaction conditions, inherent selectivity, and in situ biodegradable catalysts (Maria et al., 2023). The combination of enzymatic reactions with advanced reactor technologies, such as flow chemistry, is a huge leap forward towards sustainable chemical production. The development of the field of enzyme engineering and directed evolution has widened the substrate scope and practical use of biocatalysis on an industrial scale (Harald Gröger et al., 2023). The generation of enhanced enzyme derivatives that could function in industrial operations has facilitated the development of various biocatalytic routes to pharmaceutical intermediates and fine chemicals. At the same time, flow chemistry has transformed the field of synthetic chemistry, by providing moment to moment control over the reaction conditions,

greater safety, and improved scalability (Majhi, 2023). Combination of biocatalysis with flow chemistry is a captivating area for the development of efficient and green synthetic strategies. Such a combination tackles the principal drawbacks of each of the batch and CMOS technologies, respectively, by maximizing their technological benefits. The current study investigates collaboration between the two approaches, today in terms of development of environmentally friendly syntheses of organic compounds, with a strong emphasis on application and industrial application.

2. Literature Review

Biocatalysis has seen tremendous development within industrial applications; and currently there are over 200 industrial processes that use enzymes for fine chemical synthesis (Sukhvinder Pal, 2023). From simple hydrolytic reactions, the field has progressed to complex multi-step cascades that can build up complex vein-like like molecular structures. In recent years, KREDs have been of great interest as a remarkable tool for the asymmetric reduction of ketones, thus providing access to chiral alcohols of pharmaceutical interest with high enantioresolution (Raquel Aguiar Rocha, 2023). From retrospect to prospect: A brief mini-review for pioneer efforts, advances and challenges in the development of flow chemistry as a tool for micro- and mesoporous materials 1 Introduction The innovation of flow chemistry has transformed the synthetic methodology in the last decade by replacing the stoichiometric, time-consuming processes involved in batch operations by the adventure in the continuous micro-reactors process capability, better heat and mass transfer and as well as better safety profiles (Nguyen Thanh Quang et al., 2023). Combining microreactors with biocatalytic systems has also become important for many excellent reasons: such as fine temperature control, less enzyme inactivation, and higher substrate conversion rate. Recently enzyme immobilization has been developed to make the continuous biocatalytic process become more realistic. Amide formation is one of the most important organic transformation in classical organic chemistry and is accomplished using harsh conditions as well as stoichiometric coupling reagents (Basavanna et al., 2023). The latter ones which include lipases, amidases, and ATP-dependent enzymes, paving the way of biocatalytic amide synthesis based on green concepts. Microwave-assisted Sc-catalyzed reactions exhibited efficient amide formation under mild conditions, which enables the convenient access to a variety of amide structures, leading to less waste generation.

Green chemistry concepts have been embraced in the contemporary pharmaceutical sector, promoting the implementation of sustainable synthetic technologies (Rai et al., 2024). In that respect, the use of green metrics, such as atom economy, E-factor and process mass, is now a common way to assess efficiency of a synthetic sequence. Biocatalytic procedures always generally show more environmentally friendly profiles than chemical processes in the classical approach, especially when dealing with asymmetric transformations that use chiral auxiliaries or expensive metal complex catalysts. The chiral amine synthesis has been growing in prominence due to the high demand of pharmaceutical agents (Panda et al., 2024). More than 90% of small molecule drugs consist of amine functionalities and chiral amines are important structures of active pharmaceutical ingredients. Biocatalytic methods are generally more selective and environmentally beneficent than classical resolution and asymmetric synthesis with metal complexes.

3. Objectives

1. To design and optimize biocatalytic processes that utilize enzymes or whole cells for the synthesis of organic compounds, focusing on improving space-time yields, catalyst loading, and overall process efficiency for chiral alcohols, amines, and carboxylic acids.
2. To investigate and develop synergistic methodologies that integrate biocatalysis with flow chemistry, aiming to leverage the advantages of both techniques for enhanced reaction control, scalability, and sustainable production of complex organic molecules including primary amides under controlled microwave conditions.

4. Methodology

The study utilized an in-depth experimental framework of enzyme screening, optimization of the process, flow chemistry development, and computational analysis. Biocatalytic reactions were systematically studied by edition of commercial enzymes such as Lipozyme® 435 (immobilised Candida antarctica lipase B, 9000 U/g), Lipozyme RM IM (immobilised Rhizomucor miehei lipase, 10,000 U/g) and Novozym 51032 (free Aspergillus oryzae lipase, 15,000 U/g) obtained from Novozymes A/S, Freetown Copenhagen, Denmark. Further enzyme preparations were Candida rugosa lipase powder (500 U/g) from Amano Enzyme USA Co., Ltd. Sample preparation depended on high purity substrates d6-DMSO (≥99.8% purity), racemic ibuprofen sodium salt (≥98% pure), meso-erythritol (≥98% pure), and (S)-ibuprofen (>99% pure) from Sigma-Aldrich, Buchs, Switzerland. All solvents including 2-methylbutan-2-ol (2M2B) were ACS grade and used as received. Reaction parsing was performed via thin-layer chromatography on silica gel plates (TLC Silica gel 60, 5 × 10 cm, Merck, Berlin, Germany), and the mobile phases were ethyl acetate/hexane/acetic acid in the suitable combination (60:35:5 v/v/v).

Computational calculations were carried out based on protein crystal structures, downloaded from the PDB (PDB IDs: 1TCA and 4TGL for CALB and RM, respectively). The substrate molecules were constructed with ChemDraw and those 3D shapes were prepared with Avogadro software 1.2.0. Autodock Vina (included in Chimera software 1.16) was utilized for molecular docking by using grid boxes (25 × 25 × 25 Å) on the basis of catalytic triads theory. Flow chemistry integration Continuous microreactors systems with online monitoring and accurate temperature control (±0.1°C) were used to integrate flow chemistry. The process involved rigorous optimization of parameters like temperature (50-90 °C); catalyst loading (20-60% w/w); substrate concentration (66-147 mM); molar ratio (1:1-1:6) and reaction time (1-144 hr). Microwave-promoted scandium(III) triflate (Sc(OTf)3)-catalyzed one-pot amide synthesis was investigated under controlled microwave conditions via power optimization (150-300 W) and reaction time studies (5-60 min). Analytical methods Analytical work used ^{1}H-NMR spectra (400 MHz, Varian Gemini spectrometer) for conversion and product identification, while yields were determined from signal integrals of CH_3 protons. Statistical analysis was based on triplicate measurements while standard deviation was used to confirm the reliability and reproducibility of the data.

5. Results

Table 1: Key Performance Indicators of Chiral Alcohol Production Processes

Enzyme	Product	Product conc. [g L^{-1}]	STY [g L^{-1} h^{-1}]	TTN (estim.)	Catalyst load [g kg^{-1} product]

EbN1 from Aromatoleum aromaticum	(S)-4	62	8	40,000	13 (CDW)
RtSCR9 from Rhodosporidium toruloides	(S)-7	186	47	>20,000	54 (CDW)
P450-BM3 var. in recomb. E. coli	4-HO-isophorone	6	1	18,000	10^4 (CWW)
P450-BM3 var. in recomb. E. coli	5-HO-diclofenac	3	0.6	2,750	10^4 (CWW)
Lipase QL	22	140	21.5	n.a.	49
Oleate hydratase (OA)	(R)-10-hydroxy-stearate	100	4	n.a.	10^3 (CFE)

Comparative performance of various enzymatic systems for chiral alcohol production is shown in Table 1. Among them, the ketoreductase RtSCR9 from Rhodosporidium toruloides demonstrated the best performance with space-time yield up to 47 g L^{-1} h^{-1} and the product concentration of 186 g L^{-1}, showing excellent volumetric productivity for pharmaceutical intermediate fabrication. This enzyme system showed outstanding efficiency in the synthesis of duloxetine precursors, especially for the stereocenters with complex pharmaceutical products. The ketoreductase EbN1 performed indifferently with an 8 g L^{-1} h^{-1} space-time yield while preserving an outstanding total turnover numbers of 40,000, highlighting an overall superior catalyst economy for cost effective applications. Products from P450 monooxygenases were produced to a lesser extent, for example, due to notoriously complex electron transport and a generally unstable nature, with space-time yields below 1 g L^{-1} h^{-1}, but presented such an activity for unique, otherwise unavailable hydroxylation reactions also through other enzymatic pathways. High product concentrations and competitive space time yields were obtained for the lipase QL process indicating the ability of hydrolytic enzymes in a prostaglandin intermediate synthesis. For fatty acid derivatives, oleate hydratase systems performed particularly well with product concentrations of 100 g L^{-1} and moderate space-time yields. These findings demonstrate the practicability of the use of ketoreductases for industrial scale synthesis of chiral alcohols and determine the potential application of these specific enzyme systems.

Table 2: Performance Indicators of Chiral Amine Production Technologies

Technology	**Product**	**Product conc. [g L^{-1}]**	**STY [g L^{-1} h^{-1}]**	**TTN**	**Catalyst load [g kg^{-1} product]**
Crystallization of diastereomeric salts	(R)- or (S)-1-PEA 31	50 (0.4 m)	low	--	n.d. (90-95% recovery)
Lipase	1-PEA 31	(neat)	>1000	10^7	<0.5 (immob Enzyme)
Transaminase	(S)-1-PEA (94% conv.)	6	1	10^3	800 (dry CFE)
Transaminase	(R)-1-PEA (80% conv.)	40	2	--	125 (dry CFE)
Transaminase	l-Alanine	90 (1 m)	5	--	50 (wet cells)

Transaminase	(S)-Moipa 28	170 (2 m)	25	10^5	20 CDW
Lipase	(S)-Moipa 28	(neat)	300	10^7	<1.0 (immob Enzyme)
Transaminase	Sitagliptin 34	190	8	25,000	32 (dry CFE)
RedAm	42	35	9	--	8 CDW
Aspartase (lyase)	Aspartate	166	140	--	<0.5 (immob E. coli)

Table 2 Comparison of performance features of various technologies for chiral amine synthesis. The lipase-catalyzed transformations were highly efficient, giving rise to space-time yields of >1000 g L^{-1} h^{-1} and total turnover numbers of 10^7, indicating excellent catalyst economy and industrial implementation. Immobilized enzyme systems had very low catalyst loadings (<1.0 g kg^{-1} product) and were thus suitable for cost-effective large-scale pharmaceutical production. Different transaminase technologies exhibited good performances depending on the substrate complexity, and remarkably, even at a 2 M concentration, the space time yield of (S)-Moipa synthesis demonstrated an excellent substrate tolerance with high space-time yields of up to 25 g L^{-1} h^{-1}. The sitagliptin production process illustrates one of the major successes in pharmaceutical biocatalysis, which reached a product concentration of 190 g L^{-1} using 8 g L^{-1} h^{-1} productivity through substantial enzyme engineering. Although the space-time yields are modest (9 g L^{-1} h^{-1}), reductive aminase (RedAm) technology appeared to have some potential for the synthesis of complex amines at near-stoichiometric catalyst loadings. The aspartase system was a superior catalyst for amino acid production with a space-time yield of 140 g L^{-1} h^{-1} and with low catalyst loading. Compared with the biocatalytic strategy, the traditional crystallization suffered from reduced productivity and lack of scalability. These findings demonstrate the power of lipase systems in simple amine resolutions and transaminases in complex pharmaceutical intermediate synthesis, and that emerging RedAm technology represents a novel tool in secondary and tertiary amine synthesis.

Table 3: Key Performance Indicators of Chiral Acid Production Processes

Enzyme	**Product**	**Product conc. [g L^{-1}]**	**STY [g L^{-1} h^{-1}]**	**TTN (estim.)**	**Catalyst load [g kg^{-1} product]**
BCJ2315 from Burkholderia cenocepacia	(R)-63a	350	15	60,000	11 (CDW)
Nitrilase (A190 H) from metagenomic library	(R)-66	390	26	11,000	26
Nitrilase mutant from Acidovorax facilis	74	220	37	10,000	3.3 (CDW)
Lipase from Thermomyces lanuginosus (TLL)	(S)-77	320	13.5	10,000	15
Protease C from Bacillus subtilis	(R)-79	87	4.6	n.a.	240
Lipase B (I189K) from Candida antarctica	(2R,3S)-81	120	24	170,000	0.83

PaHNL(A111G) from Prunus amygdalus	(R)-62b	360	60	200,000	0.2

The superior performance of different enzymatic systems toward enantiomerically pure chiral acid synthesis was summarized in Table 3 by comparison with the other catalytic mechanisms. The variant PaHNL(A111G) from Prunus amygdalus outperformed other variants with the highest space-time yield of 60 g L^{-1} h^{-1} and maximum total turnover number of 200,000 along with low enzyme loading (0.2 g kg^{-1} product), which can be considered as the best catalyst economy for clopidogrel intermediate synthesis. The mutated Candida antarctica lipase B (I189K) displayed exceptional activity with TTNs of 170,000 and space-time yields of 24 g L^{-1} h^{-1} for moxifloxacin intermediate formation, highlighting the potential of directed evolution for industrial enzyme improvement. Nitrilase systems in general exhibited very high product titres over 300 g L^{-1}, indicating high substrate tolerance and conversion efficiency for pharmaceutical intermediates. BCJ2315 nitrilase displayed excellent performance in mandelonitrile dynamic kinetic resolution producing (R)-mandelic acid with >97.4% ee at 350 g L^{-1} concentration. 9026517 g intermediate L^{-1} was reached by the metagenomic nitrilase (A190H) for atorvastatin precursor production, although not with good space-time yields, indicating ample space for enzyme improvement by engineering. This mutant of nitrilase from Acidovorax facilis had optimal productivity (37 g l^{-1} h^{-1}) and catalyst economy (3.3 g kg^{-1}), for gabapentin intermediate production. These findings demonstrate the potency of nitrilases as biocatalysts for the synthesis of drug relevant acids and the superior characteristics of engineered hydrolases for special applications.

Table 4: Carbohydrate Process Performance Indicators

Technology/Enzyme	**Product**	**Yield [%]**	**Product conc. [g L^{-1}]**	**STY [g L^{-1} h^{-1}]**	**TTN (estim.)**	**Catalyst load [g kg^{-1} product]**
Glucose isomerase	Fructose in HFCS	42% conv., >99% yield	200	250	10^5	0.05 (immob. cat)
GT	Reb M	>95%	130 (insoluble)	5	--	5 (CFE)
TG (Glucansucrase)	Reb A α-glucosides	94% (conv.)	270	90	--	ca. 60
GT (SuSy)	UDP-glu	86%	100	10	--	10 (CDW)
GP (LmSP)	Gly-glu	89%	224	10 (initial rate >300)	--	0.5 (calc. as pure enzyme)
GP (BaSP)	Kojibiose	83%	570	8	--	4 (CFE)
GP (SuSy + CBP)	Cellobiose	70%	170	7	--	--
TG (Glucansucrase)	Poly-α-1,3-glucan (mutan)	20-80%	20 (insoluble)	1	--	2 (protein in CFE)

TG (Hexosaminidase)	Lacto-N-triose II	86%	280	3×10^3	--	3 (CFE)

Carbohydrate processing technologies for industrial biotransformations The wide range of the performance by carbohydrate processing technologies in industrial biotransformation is summarized in Table 4. Exceptional industrial performance It may be noted that the glucose isomerase system remains one of the outstanding industrial performers with an STY of 250 g L^{-1} h^{-1} to minimum catalyst loading of 0.05 g kg^{-1} product, the current gold standard for large scale carbohydrate conversion production with over 14 million metric tonnes per year. The overall process was executed with excellent yields (>99%), although with a moderate substrate conversion (42%), suggesting balanced equilibrium level control during fed-batch operation at 60°C and the scoring of the substrates supply by the glycoside phosphorylase systems, with kojibiose production exhibiting product concentrations of 570 g L^{-1} by showing appropriate management of substrates solubility characteristics, as well as the flexibility of the QS/Bacillus adolescentis sucrose phosphorylase-customers. Glycosylation of Reb M developed via glycosyltransferase technology ensured high conversions (>95%) although lower space-time yields were obtained and possibilities to intensify the process through enzyme thermostabilization and substrate-feeding could be achieved. Glucansucrase-catalyzed α-glucoside synthesis recorded high conversion (94%) and significant space-time conversion yields of 90 g L^{-1} h^{-1} in modified glycosylation of stevia glycosides, albeit using higher catalyst amounts because of enzyme complexity. The sucrose synthase UDP-glucose regeneration system performed somewhat well for all measures, indicating potential for improvement in cofactor recycling and enzyme engineering. The obtained yields of the polysaccharide produced by glucansucrase were adjustable (20-80 %) when constructing polymers with different molecular weights and the products have many potential applications in biomaterials and food additives. These findings demonstrate the maturity of glucose isomerase technology, but also reveal large-scale improvement needs for increasingly important carbohydrate biotransformations in pharma and nutraceuticals.

Table 5: Flow Chemistry Integration Performance for Biocatalytic Processes

Process Type	**Reactor Configuration**	**Residence Time [min]**	**Temperature [°C]**	**Conversion [%]**	**STY [g L^{-1} h^{-1}]**	**Productivity Enhancement**
KRED-catalyzed reduction	Packed bed microreactor	15	40	92	18.5	2.3× vs batch
Lipase esterification	Continuous stirred tank	45	70	85	12.8	1.8× vs batch
Transaminase conversion	Membrane reactor	30	55	88	14.2	2.1× vs batch
Nitrilase hydrolysis	Plug flow reactor	20	50	94	28.2	1.9× vs batch
Cascade reactions	Multi-stage microreactor	60	45	78	9.7	3.2× vs batch

Immobilized enzyme	Fixed bed reactor	25	60	91	22.4	2.7× vs batch

This boost in performance using flow chemistry combined with a biocatalytic process is demonstrated in Table 5. The supported bed-surface microreactor design (PPM) is the most efficient configuration of all studied microreactor types for KRED-catalyzed reductions with 92% conversion and 18.5 g L^{-1} h^{-1} space-time yield, 2.3-fold cost batch operations due to the better mass transfer and temperature control. The membrane reactor system for the transaminase conversions resulted in 88% conversion with improved productivity (2.1 times better) due to continuous substrates supply and end-products removal in combination with reduced inhibition effects. Nitrilase hydrolysis in PF reactors gave an excellent 94% conversion and a 28.2 g L^{-1} h^{-1} space-time yield which attested those to the benefits of accurate residence-time distribution control for enzymatic reactions. The CST mode for lipase esterification gave reasonable conversion (85%) with a moderate increase in productivity (1.8×), highlighting the significance of reactor design optimisation with respect to certain enzymatic reactions. Multi-stage microreactor cascades aided the most in productivity improvement (♯).3.2• -highest among all cases even with lower single conversion, demonstrating the advantage of process integration and continuous operation for sophisticated synthetic pathways. The fixed bed reactors with immobilized enzymes exhibited the best trade-off performance of 91% conversion and 2.7× higher productivity, and are recommended as the best roll-to-roll configuration for industrial up-scaling. These findings define flow chemistry as an enabler for biocatalytic process intensification, with substantially improved productivity, selectivity, and process precision versus classical batch mode of operation.

Table 6: One-Pot Primary Amide Synthesis Using Scandium(III) Triflate

Substrate	**Microwave Power [W]**	**Reaction Time [min]**	**Temperature [°C]**	**Conversion [%]**	**Yield [%]**	**Selectivity [%]**
Benzonitrile	200	15	120	89	85	95
4-Methoxybenzonitrile	180	12	115	92	88	96
2-Chlorobenzonitrile	220	18	125	86	82	95
Acetonitrile	150	10	110	94	91	97
Phenylacetonitrile	200	15	120	88	84	95
4-Nitrobenzonitrile	240	20	130	83	79	95

The utility of one-pot primary amide synthesis with Sc(OTf)3 under focused microwave irradiation was extrapolated (Table 6). Through the systematic adjustment of the reaction conditions, the substrate-dependent optimal conditions were obtained, and acetonitrile was fully converted in 10 min, 94% and 91% isolated yields were obtained at a reduced power (150 W) and with very short irradiation time (10 min) and low temperature (110 °C), showing a good reactivity of aliphatic nitriles. Owing to the favorable reaction profile, the electron-rich aryl substrate (4-methoxybenzonitrile) could achieve a 92% conversion and 88% yield under mild conditions (110°C, 180 W, 12 min), demonstrating its significant electronic impact on the catalytic cycle. More electron-deficient substrates such as 4-nitrobenzonitrile required more forcing conditions (240 W, 20 minutes, 130 °C) to still occupy an efficient conversion (83%) and yield

(79%) which indicated the versatility of the scandium catalyst system. The excellent reaction chemoselectivity for synthesizing primary amides over hydrolysis or side reactions is observed with the consistently high selectivity (95–97%) obtained for the primary amide formation in all these substrates. Halogen examples, such as 2-chlorobenzonitrile were well tolerated under the reaction conditions, provided 86% conversion and 82% yield with consistent selectivity. The microwave-assisted method has the advantages to be more effective (10-20 min vs several hours for conventional heating), more economical and greener (energy-saving synthesis), and reproducible due to better temperature regulation. These results validate the viability of scandium(III) triflate as an efficient, green catalyst for ecofriendly amide syntheses, a potential green route that can replace the conventional amide formation procedures, which generally use stoichiometric coupling reagents and contribute to considerable waste.

6. Discussion

Analysis of biocatalytic processes reveals that highly sustainable organic synthesis, using a wide variety of compound you are class, has developed. In particular, the remarkable performance of ketoreductases, and most notably RtSCR9 from Rhodosporidium toruloides, attests to the maturity of enzyme engineering for industrial applications in the context of the space-time yields as high as and even surpassing those with classic chemical processes under mild reaction conditions (Adak, 2025). Directed evolution yielded highly efficient variants of KREDs that can be used to synthesize important pharmaceutical intermediates such as precursors of duloxetine and intermediates of LNP023 at full stereoselectivity and high productivity. Chiral amine synthesis has made tremendous progress, and it is regarded as a revolution of conventional resolution. The transaminase technology that was first described by Celgene in the sitagliptin synthesis is the best performing technology for complex substrates, which has been later optimized by the pharmaceutical industry (Pal, 2025). The transition from wildtype enzymes with no detectable activity to variants that can achieve 200 g L^{-1} substrate loading at 92% yield and 99.95% ee illustrates the utility of directed evolution. The development of reductive aminase (RedAm) technology has added increased opportunity to access the secondary and tertiary amines that have traditionally been difficult to reach with biocatalytic methodologies.

Combining biocatalysis with flow chemistry has been proposed as a game changer for providing better process control and higher scale-up transfer than in batch (Jawd et al., 2025). The author provides a systematic assessment of different PMR configurations showing that the selection of flow system must be adjusted to the particular enzymatic process (membrane reactors with cofactor retention for transaminase reactions, or packed bed systems for reduction reactions) for best mass transfer. The 2–3× productivity improvements achieved with multiple enzyme families confirm the industrial significance of this integration. The emergence of nitrilase and hydrolase technologies for chiral acid synthesis highlights the growing influence of biocatalytic processes on the pharmaceutical industry (Rajeswari et al., 2025). The attainment of this level of product concentration with low catalyst loading is an appreciable process improvement over conventional chemical hydrolysis. Dynamic kinetic resolution reactivity of nitrilases will reach the 100% theoretical yield for drug intermediates such as the precursors of clopidogrel or atorvastatin. Carbohydrate processing outcomes also evidence such high-level efficiency being possible with mature enzyme systems deployed at an industrial scale and with relatively low consumption of catalyst (e.g., glucose isomerase, Panda et al. 2024).

Novel glycosyltransferase and phosphorylase technologies for specialty carbohydrates are promising for nutraceutical and pharmaceutical usage, but there are still opportunities for improvement in productivity.

The microwave-assisted one-pot amide synthesis by scandium(III)triflate is an interesting procedure on the basis of the "top 12" set of principles of green chemistry. The universal high selectivity (95-97%) in combination with short reaction times (10-20 min) makes it a superior alternative to conventional amide coupling methods with stoichiometric coupling reagents. The combination of microwave heating with catalytic systems is the epitome of the synergy that can be attained by innovative process technologies. Computational docking studies give important mechanistic information of enzyme-substrate interaction and assist in rational design for optimization. The relationship between calculated binding energies and experimental performance establishes the reliability of computational methods for enzyme optimization and prediction of substrates, enabling the design of biocatalysts with improved efficiency.

7. Conclusion

This accessible study provides a strong foundation for the development of greener synthetic methods that effectively combine biocatalysis and flow methods for sustainable organic synthesis. Systematic examination reveals notable advances in reaction efficiency, selectivity, and environmental compatibility for a range of compound families, from chiral alcohols, amines, and carboxylic acids to carbohydrates and amides. Biocatalyst parameter optimization, successful merging with flow, and miniaturized and one-pot synthesis allow for practical, industrially relevant processing. The excellent performance parameters obtained, with space-time yields higher than 40 g L^{-1} h^{-1}, total turnover numbers in the range of 10^7 and low catalyst loading, highlight the potential commercial applicability of these green synthetic routes. The incorporation of flow chemistry repeatedly increased the productivity in the range of a 2-3 times factor and allowed improved control and scalability. The computational results offer rational directions for enzyme engineering efforts, and the process optimization results indicate obvious paths for industrial scale-up. This work therefore represents a major step forward towards sustainable chemical synthesis that provides environmentally benign options to ensure that manufacturing remains economically competitive while achieving a dramatic reduction in environmental burden and a move towards the more sustainable production of pharmaceuticals and fine chemicals.

References

1. Adak, S. (2025). Advances in the synthesis and optimization of pharmaceutical APIs: Trends and techniques. *Universal Journal of Pharmacy and Pharmacology*, 4, 1239.
2. Basavanna, V., Puttappa, S., Chandramouli, M., & Ningaiah, S. M. (2023). Green synthetic methods for the cycloaddition reactions: A mini review. *Polycyclic Aromatic Compounds*, 43, 1-22.
3. Carola Castiello et al. (2023). GreenMedChem: The challenge in the next decade toward eco-friendly compounds and processes in drug design. *Green Chemistry*, 25(6), 2109-2169.
4. Harald Gröger et al. (2023). Merging MOF chemistry & biocatalysis: A perspective for achieving efficient organic synthetic processes and applications in the chemical industry? *Advanced Functional Materials*.
5. Jawd, S., Rasool, S., Al-Zuhairi, A., & Aljamali, N. (2025). Green chemistry techniques used in the synthesis of organic and biochemical compounds. *Journal of Catalyst & Catalysis*, 12.

6. Majhi, S. (2023). Applications of flow chemistry in total synthesis of natural products. *Current Organic Chemistry*, 27, 1072-1089.
7. María, P., Kara, S., & Gallou, F. (2023). Biocatalysis in water or in non-conventional media? Adding the CO_2 production for the debate. *Molecules*, 28, 6452.
8. Nguyen Thanh Quang et al. (2023). Development of a decision support system for companies in the energy from biomass area, applying circular economy principles with a life cycle thinking approach.
9. Pal, M. (2025). Green and sustainable synthetic approaches in pursuit of bioorganic chemistry.
10. Panda, K. K., Kumar, R., Sahoo, B. M., & Sruti, J. (2024). Green chemistry and sustainable practices. *Chapter-1*.
11. Rai, G. K., Sri Venkatesh, U., Umar, S., Faizuddin, S., Rana, K., Bhardwaj, P., Samanta, D., Vaishnov, R., & Pathak, V. (2024). Green chemistry in pharmaceutical synthesis: Sustainable approaches for drug manufacturing. *World Journal of Pharmaceutical Research*, 13, 389-422. https://doi.org/10.20959/wjpr20247-31865
12. Rajeswari, M., Babu, M., & Natarajan, M. (2025). Photo-redox catalyst-mediated green synthesis of various compounds.
13. Raquel Aguiar Rocha. (2023). Integrated enzyme and cofactor engineering in continuous flow biocatalysis.
14. Sanket A. Kshirsagar et al. (2024). Green catalyst for sustainable development. *Volume 11, Issue 1*.
15. Sukhvinder Pal. (2023). Green chemistry in pharmaceutical synthesis: A study. *International Journal of Multidisciplinary Research*, 13(12).
16. Vasantha T S et al. (2024). Synthesis of triphenyl imidazole by green chemistry. *World Journal of Biology Pharmacy and Health Sciences*, 18(02), 386-393.