

Review

Research Progress on the Application and Biosynthesis of Amino Alcohols

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Abstract

Amino alcohols are a class of compounds bearing both amino and hydroxyl groups, ubiquitous in natural products and extensively utilized as key structural motifs in pharmaceuticals and functional materials. Owing to their structural diversity, inherent chirality, and high reactivity, they exhibit significant application value in the pharmaceutical field, materials industry, and organic synthesis. Compared with chemical synthesis, which suffers from limitations such as insufficient enantioselectivity, dependence on precious metal catalysts, and environmental concerns, biosynthesis offers core advantages of high stereoselectivity, mild reaction conditions, and environmental sustainability. This review systematically delineates the diverse applications of amino alcohols in the pharmaceutical field (e.g., anti-HIV, anti-malarial, and antitumor drugs), materials industry (e.g., polymer modification and metal corrosion protection), and organic synthesis (e.g., chiral ligands and catalysts). Particular emphasis is placed on the biosynthetic strategies and pathways of representative amino alcohols, including ethanolamine, (2S,3R)-2-amino-1,3,4-butanetriol, (R)-3-amino-1-butanol, sphingosine, and metaraminol, as well as the metabolic engineering design principles and downstream processing technologies for amino alcohol biosynthesis. Although current biosynthetic approaches still face bottlenecks in enzyme catalytic efficiency, substrate tolerance, cofactor regeneration, product toxicity, and thermodynamic equilibrium, substantial improvements in synthetic efficiency and stereoselectivity have been achieved through protein engineering, metabolic engineering, in situ product removal, and multi-enzyme cascade optimization. This review aims to provide systematic theoretical references and technical insights for the green and efficient biomanufacturing of amino alcohols.

Keywords: amino alcohols; biosynthesis; applications; strategies



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1. Introduction

Amino alcohols are organic compounds containing both amino ($-NH_2$) and hydroxyl ($-OH$) groups within their molecular structures. The position, configuration, and substituents of functional groups confer rich structural diversity and functional versatility to this class of compounds [1]. Based on carbon skeleton architecture, amino alcohols can be classified into four categories: aliphatic amino alcohol, aromatic amino alcohol, alicyclic amino alcohol, and heterocyclic amino alcohol. Additionally, according to the relative positions of amino and hydroxyl groups, it can be categorized as α -, β -, γ -amino

alcohols, etc. According to the presence or absence of chiral centers, they are further divided into chiral and achiral amino alcohols. Chiral amino alcohols are characterized by their optical activity, with different enantiomers exhibiting markedly distinct physiological activities in vivo, thereby serving as pivotal building blocks for chiral pharmaceuticals and asymmetric catalysis.

As ubiquitous multifunctional compounds, amino alcohols constitute essential structural units of biological macromolecules such as phospholipids, glycoproteins, and ceramides in living organisms, and play central roles in physiological processes including substance metabolism, signal transduction, and immune regulation [2–4]. Amino alcohols have a wide range of applications in pharmaceuticals, materials industry, food, and organic synthesis [5–7]. Amino alcohols are important precursors for drugs and bioactive substances, including antibiotics (chloramphenicol and florfenicol), antiviral glycosidase inhibitors (nojirimycin), contrast agents (iopamidol and iohexol), ceramide precursors (sphingosine), and pseudoephedrine. Amino alcohols also serve as critical processing aids and metal corrosion inhibitors in the materials industry [8,9]. Furthermore, chiral amino alcohols can serve as chiral auxiliaries or ligands to regulate reaction stereoselectivity in asymmetric catalysis, while also playing pivotal synthetic transformation value in the construction of complex molecular scaffolds [10] (Figure 1). Given their biological functions and extensive industrial utility, the development of efficient and green synthetic strategies has become an important research direction in contemporary organic and medicinal chemistry.

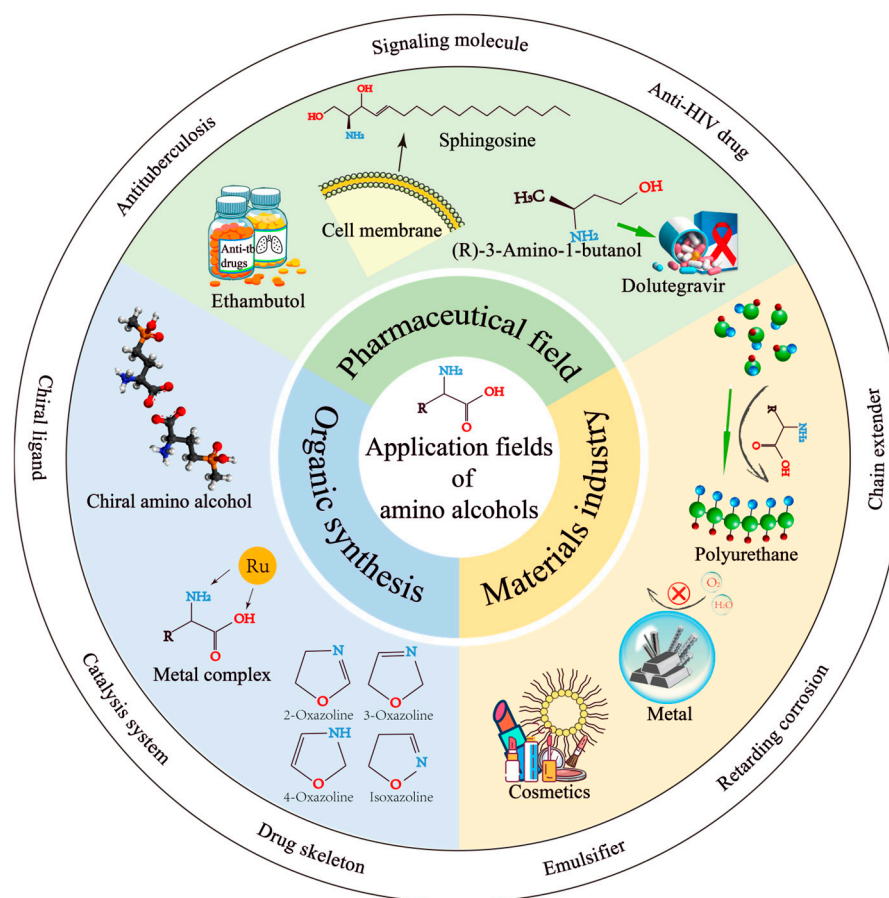


Figure 1. Amino alcohols are widely used in the pharmaceutical field, material industry and organic synthesis.

To date, various chemical methodologies for amino alcohol synthesis have been developed, including the reduction of amino acids in tetrahydrofuran catalyzed by sodium borohydride and iodine, the Sharpless aminohydroxylation of alkenes [11], the catalytic aminolysis of epoxides [12], the hydrogenation of amino acids catalyzed by bimetallic Rh-MoO_x/SiO₂, and the rhodium (Rh)-catalyzed addition of esters to carbonyl groups [13,14]. However, as the scope of amino alcohol applications continues to expand, the limitations of chemical synthesis have become increasingly apparent, including poor regio- or enantioselectivity, heavy reliance on expensive transition metal catalysts, harsh reaction conditions, complex synthetic routes, frequent use of hazardous organic solvents with concomitant formation of by-product alcohols, and difficulties in separation and purification, all of which render these approaches inadequate for meeting the stringent demands of high-purity chiral amino alcohol synthesis [10,15].

The biosynthesis of amino alcohols employs enzymes or whole cells as biocatalysts to convert precursors such as amino acids, hydroxyketones, and aldehydes into target products through biotransformation reactions including asymmetric amination, decarboxylation, aldol condensation, reductive amination, or transamination under mild conditions [16–18]. The core challenge in the biosynthesis of amino alcohols lies in the precise, efficient, and stereoselective introduction of amino (-NH₂) and hydroxyl (-OH) functional groups onto a single carbon scaffold. The introduction of the amino group is primarily accomplished through three enzymatic strategies. First, transaminases (TAm) transfer an amino group from a donor substrate (e.g., isopropylamine) to a prochiral ketone or aldehyde acceptor, generating the corresponding chiral amine [19]. Second, amine dehydrogenases (AmDHs) can directly utilize ammonia (NH₃) as the amino donor, converting carbonyl compounds to the corresponding primary amines in a single step through an NAD(P)H-dependent reductive amination reaction [20]. The third strategy involves retaining or transferring the amino group from an amino acid precursor; for example, serine decarboxylase (SDC) directly converts L-serine to ethanolamine (EA) by removing the carboxyl group while retaining the amino moiety [21]. For the introduction of the hydroxyl group, the most common approach is the asymmetric reduction of ketone or aldehyde carbonyl groups in precursor molecules by ketoreductases or alcohol dehydrogenases [22,23]. Additionally, hydroxyl groups may originate from the inherent structure of the starting amino acids (e.g., serine, threonine) or be generated in situ through more complex cascade reactions, such as C–C bond-forming reactions [24,25]. The synthetic strategies for amino alcohols are illustrated in Figure 2.

Compared with traditional chemical synthetic methods, biosynthetic strategies offer incomparable advantages in reaction conditions, stereoselectivity, environmental friendliness, and atom economy [12,26]. Based on the catalytic configuration and reaction mode, existing strategies fall into three categories: (1) enzymatic catalysis, employing free or immobilized enzymes as catalysts for substrate conversion to target products, with core enzymes including TAm, AmDHs, and transketolases [16,27]; (2) chemo-enzymatic catalysis, achieving organic coupling of chemical synthetic steps with enzymatic reactions to overcome the narrow substrate scope of single-enzyme catalysis and thermodynamic equilibrium limitations [28,29]; and (3) whole-cell synthesis, utilizing metabolically engineered microorganisms (e.g., *E. coli*, *Komagataella phaffii*) as bioreactors to realize multi-step cascade conversion from inexpensive carbon sources to target products within a single strain [11,17]. These strategies can be implemented individually or in cascade, and their mechanisms, advantages, and disadvantages are detailed in Table 1.

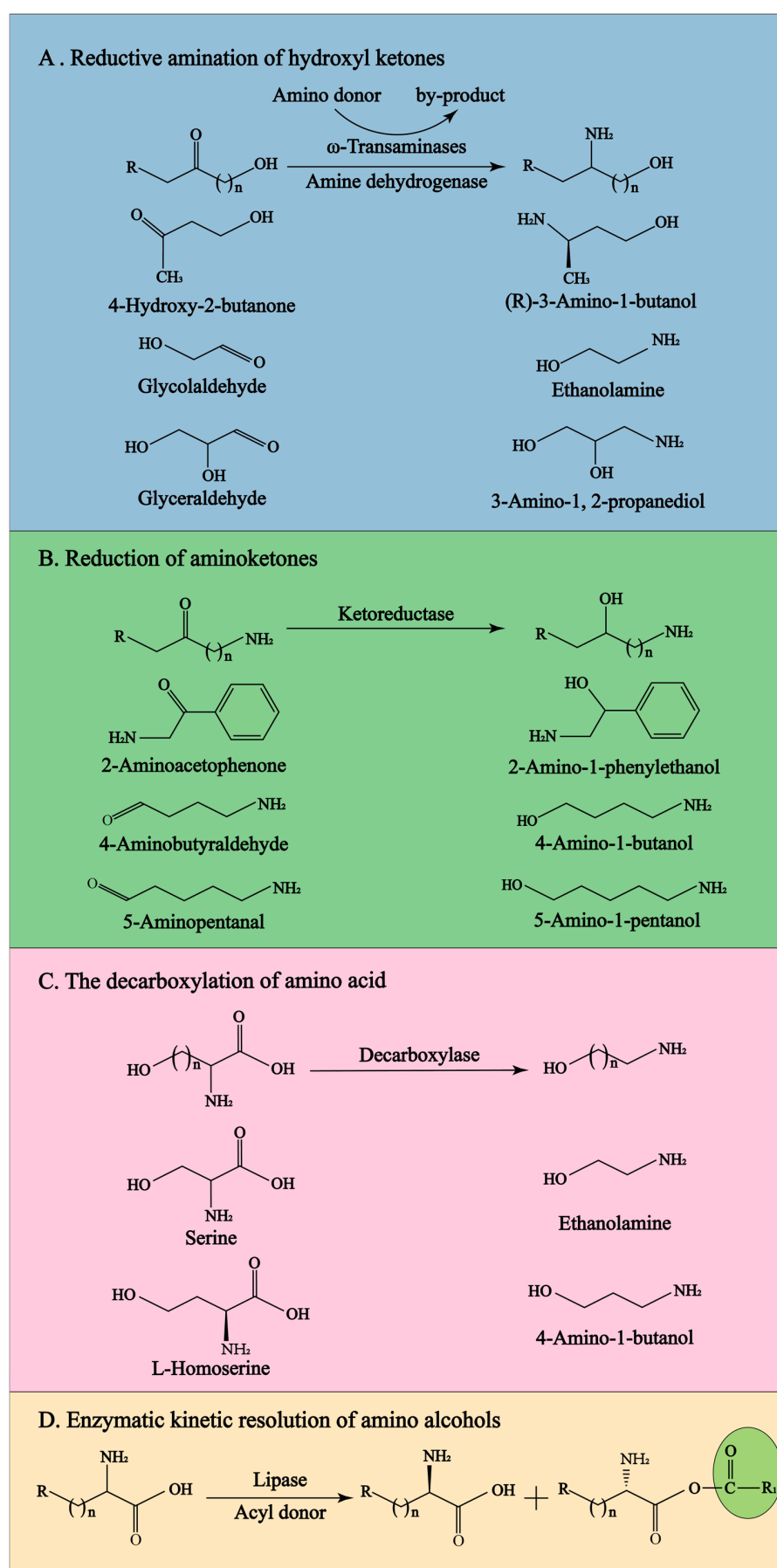


Figure 2. Synthesis strategy diagram of amino alcohols.

Table 1. Comparison of three biocatalytic strategies for amino alcohol synthesis.

Strategy	Core Catalysts	Reaction Mechanism	Advantages	Limitations	Refs.
Enzymatic catalysis	Transaminase, Amine dehydrogenase, Transketolase, etc.	Under artificially constructed reaction conditions, substrates are converted into corresponding products by the catalysis of free or immobilized single enzymes or multi-enzyme cascade systems.	Superior stereoselectivity, mild reaction conditions, facile product separation and purification, environmental friendliness, etc.	High costs associated with enzyme separation, purification, and immobilization; dependence on expensive cofactors; limitations in enzyme stability; restricted substrate scope and tolerance of natural enzymes, etc.	[16,18,27]
Chemo-enzymatic catalysis	chemical catalysts (e.g., Au, Rh, or organocatalysts) coupled with biocatalysts (e.g., Transaminase, Amine dehydrogenase)	Chemical catalysis first generates intermediates from substrates (e.g., introduction/removal of protecting groups, synthesis of achiral intermediates), followed by enzymatic transformation (e.g., transamination), typically conducted in a sequential one-pot or tandem mode.	Broadening substrate scope, reducing the consumption of expensive enzymes or cofactor requirements, and enabling the utilization of simpler substrates for the synthesis of more complex molecules, etc.	Residual metal catalyst contamination; compatibility issues between chemical catalysts and enzymes; increased complexity in reaction and product separation/purification, etc.	[28–31]
Whole-cell synthesis	Metabolically engineered chassis (<i>E. coli</i> , <i>K. phaffii</i> , etc.) harboring heterologous pathway enzymes.	Metabolic pathways reconstructed or enhanced in vivo, utilizing intracellular cofactor regeneration networks to convert inexpensive carbon sources (glucose, C1 compounds) into target amino alcohols through multi-step cascade biotransformations.	Self-sufficient cofactor supply, efficient intracellular multi-enzyme cascade pathways, high enzyme stability, and utilization of low-cost renewable feedstocks.	Substrate/product transport limitations; competitive metabolic flux leading to by-product accumulation; substrate/product cytotoxicity; complexity in condition optimization, etc.	[11,17,32,33]

The catalytic efficiency and substrate tolerance of natural enzymes, the dependence of certain reactions on expensive cofactors with complex regeneration systems, the toxicity of products or substrates to cells, unfavorable thermodynamic equilibrium, and high costs of product separation and purification constrain their large-scale application. In recent years, significant progress has been made in addressing these challenges through strategies including protein engineering, metabolic engineering, multi-enzyme cascade optimization, and in situ product removal (ISPR). This review systematically summarizes the various applications of amino alcohols in the fields of pharmaceuticals, materials, and organic synthesis and focuses on analyzing the biological synthesis strategies and pathways of representative amino alcohols (including EA, (2S,3R)-2-amino-1,3,4-butanetriol (ABT), (R)-3-amino-1-butanol, sphingosine, and meta aminomethanol), as well as the basic principles of metabolic engineering design and downstream processing technology in amino alcohol biosynthesis.

2. Diverse Applications of Amino Alcohols

Amino alcohols are widely applied in pharmaceuticals, the materials industry, and organic synthesis by virtue of the synergistic effects of the amino and hydroxyl groups within the molecule and inherent chiral characteristics. In the pharmaceutical field, amino alcohols can serve directly as therapeutic agents (e.g., for tuberculosis and asthma) and as key intermediates for chiral drug synthesis. In the materials industry, amino alcohols are employed for polyurethane modification, metal corrosion protection, and industrial gas removal. In organic synthesis, amino alcohols serve as important chiral ligands and catalysts, advancing asymmetric catalysis and heterocycle construction. The diverse applications and underlying mechanisms of amino alcohols are systematically elucidated in Table 2.

2.1. Applications in the Pharmaceutical Field

As pivotal structural motifs in the pharmaceutical field, amino alcohols exhibit irreplaceable value in drug discovery and clinical therapeutics due to the synergistic interplay between the amino and hydroxyl bifunctional groups within the molecule and their distinctive spatial configurations. Certain amino alcohols possess intrinsic pharmacological activity and can be directly employed as therapeutic agents, such as the antitubercular drug ethambutol [34], the anti-asthmatic agent salbutamol [35], and the antimalarial arylamino alcohol drugs including quinine, lumefantrine, and mefloquine [36,37]. Sphingosine serves as an essential component of cell membranes and a signaling molecule regulating cell growth and apoptosis, and is closely associated with cancer and Alzheimer's disease [3,58–60]. Sehl et al. [61] demonstrated that sympathomimetic amines such as (1S)-norephedrine can activate adrenergic receptors and inhibit norepinephrine reuptake, and are widely used for decongestion, blood pressure elevation, and cold treatment. Tan et al. [62] revealed that the alkaloid swainsonine exhibits antiviral, immunosuppressive, and antitumor activities, rendering it a promising candidate for cancer chemotherapy. Certain amino alcohols, such as β -amino alcohols, represent the most critical intermediates in pharmaceutical synthesis and are extensively employed in the treatment of malaria, infections, cancer, tuberculosis, and Alzheimer's disease [4,63]. Cienas et al. [64] identified (R)-2-amino-3-methyl-1-butanol as the key intermediate of the cyclin-dependent kinase inhibitor seliciclib, which demonstrates therapeutic potential for neurodegenerative and renal diseases. Yin et al. [65,66] found that (R)-2-amino-3-phenylpropanol serves as the chiral building block for the narcolepsy drug solriamfetol. Gao et al. [32] demonstrated that (R)-3-amino-1-butanol is the key intermediate for the anti-HIV drug dolutegravir. Furthermore, amino alcohol derivatives have shown substantial potential in drug development. Yang et al. [67] discovered that isoxanthohumol-amine conjugates exhibit superior

antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) compared to several conventional antibiotics. Tisnerat et al. [37] found that enantiopure amino alcohol fluorene derivatives and enantiopure mefloquine analogues display promising antimalarial activity. Khdar et al. [46] revealed that allo-gibberic acid-based 1,3-aminoalcohol regioisomers demonstrate antiproliferative activity and cancer selectivity. In summary, by virtue of their unique bifunctional synergistic effects and structural plasticity, amino alcohols and their derivatives have emerged as core scaffolds for the research, development, and synthesis of anti-infective, antitumor, and neurotherapeutic agents.

2.2. Applications in the Materials Industry

Amino alcohols exhibit extensive application potential in the materials industry owing to their amphiphilicity, coordination capability, and diverse reactivity. From polymer synthesis and modification to metal corrosion protection, and from surface functionalization to industrial additives, amino alcohols and their derivatives have emerged as important structural units in the design of high-performance materials [8,9]. Adam et al. [48] demonstrated that amino alcohols can serve as chain extenders in polyurethane synthesis, enhancing the hardness of polyurethane materials while maintaining constant density. Wang et al. [50] discovered that novel amino alcohol compounds synthesized from ethylenediamine and various glycidyl ethers in the presence of CO₂ can be employed as chain extenders for the preparation of hydroxyl-containing polyurethane-ureas, thereby optimizing their tensile strength. The unique molecular structure and interfacial activity of amino alcohol compounds also render them significant in the field of metal corrosion inhibitors. Representative amino alcohols such as monoethanolamine, diethanolamine, and triethanolamine can effectively inhibit the corrosion of aluminum in phosphoric acid media, and are commonly incorporated into automotive engine coolants, cutting oils, and lubricants to suppress metal corrosion [49,68]. Wombacher et al. [69] found that phosphate-modified amino alcohols can substantially reduce the corrosion rate of steel reinforcement in concrete under alkaline conditions. Xu et al. [51] synthesized novel β -amino alcohol compounds capable of forming stable adsorption layers on low-carbon steel surfaces, blocking direct contact between corrosive media and the substrate, thereby achieving efficient corrosion inhibition of low-carbon steel. Amino alcohols can also serve as efficient surface modifiers for the functionalization of nanomaterials. During the preparation of ZnO thin films by the sol-gel method, amino alcohols such as EA, when used as additives, can effectively regulate sol formation reactions, consequently influencing the grain structure and porosity of the films [52,53]. Gómez-Núñez et al. [70] confirmed that amino alcohols play a pivotal role in controlling the micro-morphology and grain size of thin films. Kalina et al. [71] found that amino alcohols can also function as shrinkage-reducing components in alkali-activated materials, effectively mitigating their high shrinkage issues. Furthermore, fatty acid soaps of diethanolamine and triethanolamine can serve as emulsifiers in cosmetics and metal-working fluids [49]. Alkanolamines such as diethanolamine and N-methyldiethanolamine are frequently employed, either alone or in mixtures, for the absorption of acid gases (CO₂, H₂S, and COS) from natural gas and industrial effluents [54].

Table 2. Diverse applications of amino alcohols and their mechanisms of action.

Application Area	Amino Alcohols	Mechanism of Action	Application	Refs.
Pharmaceutical field	Ethambutol	Specific inhibition of arabinosyltransferases (EmbA, EmbB and EmbC) resulted in the loss of attachment sites of mycolic acid.	Antituberculosis drugs	[34]
	Salbutamol	β_2 -Adrenergic receptor agonist	Antiasthmatic drugs	[35]
	Quinine	Inhibits the crystallization of heme	Antimalarial drugs	[36,37]
	Mefloquine			
	Lumefantrine			
	Propranolol	Nonselective β -adrenergic receptor antagonist	Cardiovascular drugs	[38]
	Metaraminol	α_1 -Adrenergic receptor agonist; Chiral building block for THIQ synthesis	Cardiovascular drugs, booster drugs	[39,40]
	Indinavir	Competitive and reversible HIV-1 protease inhibitor	Anti-HIV drugs	[41]
	(R)-3-Amino-1-butanol	Intermediates of dolutegravir, 4-methyl cyclophosphamide and β -lactam were synthesized	Synthesis of anti-HIV drugs, anti-tumor drugs and antibiotics	[42,43]
	(2S,3R)-2-Amino-1,3,4-butanetriol	Intermediates for the synthesis of Nelfinavir and detoxinine	Synthesis of antidote with low toxicity of anti-HIV drugs and rice blast antibiotics	[44]
	Sphingosine	Key signaling molecule, regulation of cell growth and apoptosis	Genetic metabolic disease markers	[45]
	Amino alcohol derivatives of isobutadienoic acid	Antiproliferative activity and cancer selectivity	Anticancer drug discovery	[46]
	Diaminopyrimidine derivatives	It has strong antiproliferative activity against four human cancer cell lines	Anticancer drug discovery	[47]

Table 2. Cont.

Application Area	Amino Alcohols	Mechanism of Action	Application	Refs.
Materials industry	2-Amino-2-methyl-1-propanol	Formation of urea bonds	Polyurethane chain extenders	[48]
	2-Amino-2-ethyl-1,3-propanediol			
	Tris(hydroxymethyl)-aminomethane			
	2-Dimethylamino-2-methylpropanol			
	Monoethanolamine	Forms a dense, high resistance organic-inorganic composite protective film		[49]
	Diethanolamine			
	Triethanolamine			
	Phosphates aminoalcohols	The interaction with the steel surface forms a protective layer	Metal corrosion inhibitor	[50]
	1,16-(5,12-dihydroxy-7,10-dioxo-3,14-diazahexadecane) di-p-benzenesulfonamide	An adsorption layer is formed on the surface of mild steel		[51]
	Ethanolamine	Regulating sol–gel formation reaction	Stabilizers of ZnO film devices	[52,53]
Organic synthesis	Aminopropanol			
	Aminomethyl butanol			
	Diethanolamine	Absorption of acidic gases: CO ₂ , H ₂ S and COS	Acidic gas absorbents	[54]
	N-Methyldiethanolamine			
	Chiral amino alcohol	Chelate complexes are formed with transition metal centers	Synthesis of chiral ligands	[10]
	β -Amino alcohol	Generates oxazoline ring system	Synthetic drug skeleton Synthesis of chiral ligands	[55]
	α -Amino alcohol	Amino alcohol, metal center and racemic analyte form a ternary complex	Chiral stationary phases	[56,57]

2.3. Applications in Organic Synthesis

Chiral amino alcohols have emerged as highly promising ligands in the field of asymmetric catalysis due to their chirality, structural diversity, and ready availability [72]. In metal-catalyzed systems, they can function either as chiral ligands to modulate the spatial configuration of the metal center or directly as organocatalysts to participate in reactions [10]. For instance, Zhang et al. [73] achieved excellent selectivity of up to 94% ee in the asymmetric addition of diethylzinc to N-diphenylphosphinoylimines by finely tuning the nitrogen substituents on the 1,2-diphenyl-2-aminoethanol scaffold. Richard et al. [74] demonstrated that the selection of amino alcohol chiral ligands is crucial for the synthesis of chiral heterocyclic compounds in asymmetric allylic alkylation reactions. Furthermore, Sappino et al. [75] developed novel amino alcohol ligands applicable to the enantioselective addition of diethylzinc to aldehydes.

Beyond catalytic applications, amino alcohols also exhibit significant value as structural scaffolds in synthetic transformations. β -Amino alcohols can undergo dehydration under acidic or basic conditions to generate oxazoline ring systems; this five-membered heterocycle not only constitutes an important pharmaceutical scaffold but is also frequently employed as a chiral ligand in asymmetric catalysis [76]. The condensation of amino alcohols with aldehydes and ketones can form imine or enamine intermediates, which subsequently participate in cyclization reactions such as the Pictet–Spengler reaction to construct more complex alkaloid natural product scaffolds [55]. Moreover, the amino and hydroxyl groups within amino alcohol molecules can serve as bidentate coordination sites to complex with metal ions, forming catalytically active centers with specific spatial configurations. Based on this principle, Durap et al. [77] designed C₂-symmetric chiral phosphinite ligands using the amino alcohol scaffold; the catalytic system formed with ruthenium achieved up to 99% yield in the asymmetric transfer hydrogenation of acetophenone derivatives. Apart from catalysis, amino alcohols and their derivatives also occupy an important position in chiral separation technologies and are widely utilized in the preparation of ligand-exchange chiral stationary phases for liquid chromatography [56,57]. In summary, through their multifaceted functions in coordination regulation, chiral induction, and scaffold construction, amino alcohols play an irreplaceable role in advancing asymmetric synthesis and chiral technology.

3. Biosynthetic Strategies and Pathways of Several Important Amino Alcohols

The biosynthetic strategies for amino alcohols demonstrate a systematic technological evolution from fundamental enzyme discovery to industrial-scale application. The first stage involves the mining of key enzymes, i.e., identifying critical enzyme classes capable of catalyzing amino alcohol scaffold formation from natural biological systems, and investigating their catalytic mechanisms, substrate specificity, cofactor dependence, and stereoselectivity control principles [78]. With the refinement of functional characterization of key enzymes and the recognition of limitations in natural biosynthetic systems, heterologous pathway reconstruction is typically employed, wherein native or designed enzymatic pathways are introduced into model microbial hosts to validate the feasibility of synthesizing target amino alcohols from simple carbon sources or precursor substances. To address the limited flux of native pathways, competitive diversion within host metabolic networks, and inherent limitations in enzymatic properties, researchers employ metabolic engineering to strengthen precursor supply, block competing pathways, and construct cofactor regeneration systems, thereby achieving efficient and directed synthesis of target products [21]. Concurrently, protein engineering is applied to modify natural enzymes, overcoming bottlenecks in catalytic efficiency, substrate scope breadth, and op-

erational stability [79]. Ultimately, through process optimization and scale-up strategies such as reactor engineering, in situ product removal, fermentation mode optimization, and continuous production technologies, the biomanufacturing of amino alcohols is advanced from laboratory scale toward controllable, continuous, and scalable industrial production processes.

Amino alcohols can be classified into achiral amino alcohols (e.g., EA), single-enantiomer amino alcohols (e.g., (R)-3-amino-1-butanol), and chiral amino alcohols with two stereogenic centers (e.g., ABT and sphingosine) according to the number of chiral centers. The biocatalytic synthesis of amino alcohols has emerged as an important research direction for replacing traditional chemical synthesis, owing to its advantages of mild reaction conditions, high stereoselectivity, and environmental sustainability [80,81]. This section reviews the biosynthetic strategies and pathways of representative amino alcohols, including EA, ABT, (R)-3-amino-1-butanol, sphingosine, and metaraminol (Table 3), as well as the metabolic engineering design principles and downstream processing technologies for amino alcohol biosynthesis.

Table 3. Biosynthetic Strategies and Pathways of Representative Amino Alcohols.

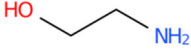
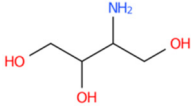
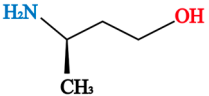
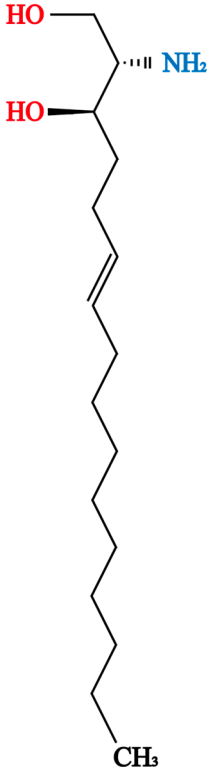
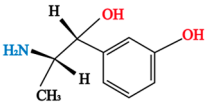
Amino Alcohols	Structural Formula	Synthetic Strategy	Mechanism	Catalyst (Enzyme)/Host	Substrate	Titer (g/L)	Refs.
EA		Whole-cell biotransformation	Glucose-L-serine L-serine decarboxylation	L-Serine decarboxylase (AtSDC) (<i>Arabidopsis thaliana</i>)/ <i>Pseudomonas putida</i> S12	Glucose	0.16	[82]
		Whole-cell biotransformation		L-Serine decarboxylase (AtSDC) (<i>A. thaliana</i>)/ <i>E. coli</i> MGΔ4	Glucose	2.40	[83]
		Two steps whole-cell biotransformation		SerA fbr, serC, serB/ <i>E. coli</i> SE06, L-Serine decarboxylase (AtSDC) (<i>A. thaliana</i>)/ <i>E. coli</i> SE06	Glucose	36.90	[21]
		Enzyme/whole-cell biotransformation	Methanol-ethanol aldehyde Aldehyde amination of ethanol	Alcohol oxidase (HypAOX), glyoxylate carboligase (EcGCL), amine transaminase (SpATA)/ <i>E. coli</i> MG1655	C1 compounds (methanol)	1.28	[84]
ABT		In vitro enzymatic cascade (recycling)	TK-catalyzed C-C bond formation	<i>E. coli</i> TK + RSPH17029-3177 TAm	Serine Glycolaldehyde	0.61	[85]
		One-pot whole-cell biotransformation	TAm catalyzed amination	<i>E. coli</i> TK + CV2025 TAm/ <i>E. coli</i> BL21-Gold(DE3)	Glycolaldehyde Hydroxypyruvate	1.05	[86]
		One-pot whole-cell biotransformation	TAm catalyzed amination	CV2025 TAm/ <i>K. phaffii</i> GS115 (PpTAmCV708)	Methylbenzylamine	2.77	[33]
(R)-3-Amino-1-butanol		In vitro single enzyme catalysis	(R)-Selective ω-TAm catalyzed amination	<i>Aspergillus terreus</i> AtTA-M5 (H55A/G126F/S215P)	4-Hydroxy-2-butanone Isopropylamine	40.00	[32]
		Whole-cell biotransformation	AmDH catalyzed amination	<i>Geobacillus stearothermophilus</i> AmDH mh174/ <i>E. coli</i> BL21(DE3)	4-Hydroxy-2-butanone	8.00	[20]
		Whole-cell biotransformation with fed-batch and air sweeping	(R)-Selective ω-TAm catalyzed amination	(R)-Selective ω-TAm Q137E/T282S/ <i>E. coli</i> BL21(DE3)	4-Hydroxy-2-butanone Isopropylamine	8.29	[43]

Table 3. Cont.

Amino Alcohols	Structural Formula	Synthetic Strategy	Mechanism	Catalyst (Enzyme)/Host	Substrate	Titer (g/L)	Refs.
Sphingosine		Whole-cell biotransformation	Sphingolipid metabolic pathway	DES1 (<i>Homo sapiens</i>), ACER1 (<i>H. sapiens</i>)/ <i>Saccharomyces cerevisiae</i> DDLAOGS	Glucose	0.65	[87]
Metaraminol		Whole-cell biotransformation with in situ reactive extraction	Pyruvate decarboxylation and transamination cascade reaction	Pyruvate decarboxylase (ApPDC var), TAM (ATCC 12472 Cv2025)/ <i>E. coli</i> BL21(DE3)	3-Hydroxybenzaldehyde 4-Pyruvate	4.60	[88]
		Gold-catalyzed transaminase one-pot cascade	Gold (I)-catalyzed alkyne hydration and transamination reaction	IPrAuNTf ₂ , Commercial transaminase ATA-251	3-Hydroxybenzaldehyde	—	[31]

3.1. Ethanolamine (EA)

EA is characterized by its simple molecular structure, substantial global production volume, and broad application coverage and has become an important model molecule for biosynthesis research, with the global market size projected to reach approximately 5 billion USD by 2030 [89]. As a precursor of key membrane phospholipids such as phosphatidylethanolamine (PE), EA plays an irreplaceable and central role in maintaining cell membrane structure and function [90]. Meanwhile, its high reactivity renders it a critical raw material for industries including surfactants, CO₂ absorbents, agrochemicals, and cosmetics [89,91]. Studies have revealed that EA can also inhibit prion protein accumulation and promote drug permeation across the blood–brain barrier; conversely, it is exploited by gastrointestinal pathogens to enhance intestinal colonization competitiveness, suggesting that modulation of free EA levels in the gut may represent a novel antimicrobial strategy [92–94].

The biosynthesis of EA in nature primarily relies on the L-serine decarboxylation pathway, in which the core enzyme serine decarboxylase (SDC) directly catalyzes the decarboxylation of L-serine to generate EA [90]. Yunus et al. [95] identified the substrate-specific *A. thaliana* serine decarboxylase (AtSDC) and successfully cloned its encoding gene (At5g40860), laying the foundation for subsequent biosynthesis research of EA. Foti et al. [82] constructed an engineered *P. putida* S12 by introducing the gene encoding AtSDC and deleting the *eutBC* genes encoding ethanolamine ammonia-lyase (EAL). Using glucose as the carbon source and supplementing exogenous L-serine, the engineered strain achieved an EA titer of 0.159 g/L, confirming that insufficient intracellular L-serine supply constitutes the primary rate-limiting factor. Godar et al. [83] metabolically engineered *E. coli* by relieving feedback inhibition of phosphoglycerate dehydrogenase, knocking out serine and monoethanolamine degradation genes, optimizing the carbon-to-nitrogen ratio in the culture medium, and screening for high-activity AtSDC expression, successfully achieving de novo biosynthesis of EA from glucose with a titer of 2.4 g/L. Nazarbekov et al. [21] achieved de novo biosynthesis of EA from glucose in *E. coli* through a series of optimizations, including strengthening the L-serine synthesis pathway, blocking serine degradation branches, and deleting regulatory genes to activate the glyoxylate shunt, attaining a titer of 36.90 g/L and a productivity of 0.4 g/L/h. Furthermore, multi-enzyme cascade systems can also enable direct conversion from C1 compounds to EA. Seo et al. [84] constructed a cascade reaction system using recombinant *E. coli* MG1655 (DE3) expressing amine transaminase from *Silicibacter pomeroyi* (SpATA) in combination with alcohol oxidase and glyoxylate carboligase, achieving the biotransformation of C1 compounds (methanol/formaldehyde) to EA with a conversion rate of 42%.

3.2. (2S,3R)-2-Amino-1,3,4-butanetriol (ABT)

ABT is a representative vicinal amino alcohol that features two stereogenic centers. It serves as the core chiral building block for the synthesis of the HIV protease inhibitor nelfinavir and is also a key intermediate for the preparation of detoxinine (a detoxifying agent that mitigates the toxicity of antibiotics used against rice blast disease) and for the construction of the skeletons of sphingoid-type bioactive molecules [44,86,96]. With the growing global demand for antiretroviral drugs, the efficient and green synthesis of ABT is of considerable importance for reducing drug production costs and improving drug accessibility.

The enzymatic synthesis of the ABT scaffold is achieved through the coupling of a transketolase (TK)-catalyzed asymmetric carbon–carbon bond-forming reaction with a transaminase (TA)-mediated stereoselective amination reaction, using hydroxypyruvate (HPA) and glycolaldehyde (GA) as substrates, with L-erythrulose (ERY) as the key inter-

mediate [44,97]. Based on the TK-TAm cascade, Ingram et al. [44] constructed an *E. coli* BL21-gold(DE3) dual-plasmid strain expressing the host TK and *Pseudomonas aeruginosa* β -alanine:pyruvate transaminase (β -A:P TAm), validating for the first time the feasibility of synthesizing ABT from the achiral substrates GA and β -HPA; however, the molar yield was only 21%, limited by insufficient transaminase catalytic efficiency. Rios-Solis et al. [97] significantly improved the conversion to 87% and reduced the reaction time to 25 h by introducing the more active *Chromobacterium violaceum* CV2025 transaminase and employing isopropylamine (IPA) as the amine donor in place of methylbenzylamine (MBA). Henríquez et al. [33] utilized an engineered *K. phaffii* strain to construct the PpTAmCV708 strain expressing solely CV2025 transaminase; when fed with only 150 mM MBA substrate, the space-time yield of ABT reached 0.62 g/L/h, representing a 105-fold improvement in catalytic performance compared with the *E. coli* whole-cell system. In the development of in vitro multi-enzyme cascade systems, Gruber et al. [18] developed a continuous-flow cascade system based on microreactors, which achieved complete conversion of ABT within 2 h by spatially segregating the enzyme active centers to resolve the inhibition of transaminase (TAm) activity caused by ThDP cofactor binding, significantly outperforming traditional batch reactions. Villegas-Torres et al. [98] designed a dual-enzyme recycling pathway using serine as the amine donor, in which the transaminase simultaneously catalyzed the amination of ERY and the regeneration of HPA, coupled with the TK reaction to form a self-cycling cascade that reduced cofactor supplementation requirements; however, the conversion was only 9% due to the side reaction of the transaminase with GA. Subsequently, through systematic optimization of reaction conditions, substrate concentrations, and enzyme ratios using full factorial experimental design and response surface methodology (RSM), the conversion of the two-step cycling pathway was further improved to 60%, identifying substrate inhibition, enzyme ratio, and transamination equilibrium as the key bottlenecks, thereby providing systematic experimental evidence and engineering strategies for the biosynthesis of ABT [85].

3.3. (R)-3-Amino-1-butanol

(R)-3-Amino-1-butanol is a key chiral synthetic intermediate for the anti-HIV drug dolutegravir [42,43]. It is also employed in the synthesis of bioactive molecules such as β -adrenergic drugs, peptides, the antitumor agent 4-methylcyclophosphamide, and the penem antibiotic intermediate β -lactam, and can serve as a chiral auxiliary or ligand in asymmetric alkylation, arylation, and Michael addition reactions [99–101]. With the sustained growth in global demand for anti-HIV drugs, the efficient and green synthesis of (R)-3-amino-1-butanol holds significant importance for reducing dolutegravir production costs and improving drug accessibility.

The core biosynthetic strategy for (R)-3-amino-1-butanol lies in the utilization of TAm and AmDH, particularly (R)-selective ω -transaminases [(R)-selective ω -TA], to catalyze the asymmetric amination of prochiral ketones (e.g., 4-hydroxy-2-butanone). Tang et al. [102] identified a novel (R)-selective transaminase (As-TA) from actinomycetes and employed it for the first time to catalyze the amination of 4-hydroxy-2-butanone. Through condition optimization and substrate fed-batch strategies, a maximum titer of 29.6 g/L of (R)-3-amino-1-butanol was achieved with ee > 99.9%. However, native enzymes generally suffer from inherent limitations in industrial applications, including low catalytic efficiency, poor substrate tolerance, and unfavorable thermodynamic equilibrium; consequently, protein engineering has become a critical approach for enhancing catalytic performance. Gao et al. [32] performed site-directed mutagenesis on an (R)-selective ω -transaminase from *A. terreus*, obtaining the mutant AtTA-M5 with a 9.6-fold improvement in catalytic efficiency and a 9.4 °C increase in thermostability. Under 20 g/L substrate concentration, the conversion

was elevated from less than 5% to 90.8%. Liu et al. [103] conducted rational design of an (R)-selective transaminase from *Fodinicurvata sediminis* (FsTA) employing a substrate-truncation strategy and binding pocket reshaping, resulting in a 10 °C improvement in thermostability and a 7.95-fold enhancement in catalytic activity toward 4-hydroxy-2-butanone. In parallel, Liu et al. [43] performed virtual mutagenesis and substrate tunnel engineering on an (R)-selective transaminase from *Mycolicibacterium hippocampi*, successfully improving its catalytic efficiency by 3.68-fold and achieving effective conversion of 100 mM 4-hydroxy-2-butanone with 93% conversion and ee > 99.9%. Compared with transaminase-catalyzed transamination, AmDH-catalyzed reductive amination offers advantages including lower amine donor costs, reduced difficulty and cost of downstream separation and purification, and the absence of metal catalysts. However, it is strictly dependent on the cofactor NAD(P)H and must be coupled with glucose dehydrogenase (GDH) or formate dehydrogenase (FDH) to construct a cofactor regeneration system [26,104]. Ming et al. [20] used the amine dehydrogenase from *G. stearothermophilus* as a template and, through rational design and three rounds of mutagenesis, obtained the optimal variant mh174, which achieved 99% conversion of 100 mM 4-hydroxy-2-butanone and 90% isolated yield within 36 h, with a 4.2-fold improvement in catalytic efficiency.

3.4. Sphingosine

Sphingosine, as a core sphingolipid intermediate containing a chiral amino alcohol with a long-chain scaffold bearing two stereogenic centers, serves as the key precursor for the synthesis of bioactive molecules such as ceramides, sphingomyelins, and sphingosine-1-phosphate (S1P) [45]. Sphingosine functions as a signaling molecule that regulates cell growth, apoptosis, and skin barrier repair, and its dysregulation is closely associated with cancer and Alzheimer's disease. Moreover, its phosphorylated derivative S1P acts as a second messenger in regulating cell proliferation, migration, inflammation, and angiogenesis [105–107]. Given its potential therapeutic value in oncology, autoimmune diseases, and cardiovascular disorders, as well as its broad prospects as a cosmetic ingredient in skin regeneration and whitening, the efficient synthesis of sphingosine has become an active research area.

In nature, the biosynthesis of sphingosine initiates with the condensation of L-serine and palmitoyl-CoA catalyzed by serine palmitoyltransferase (SPT) to generate 3-ketodihydrosphingosine (the key rate-limiting step), followed by the reduction in the latter to dihydrosphingosine by 3-ketosphinganine reductase (3KSR) using NADPH as the reductant [108]. Dihydrosphingosine is subsequently converted to biologically active sphingosine by dihydroceramide desaturase (*DES1/DEGS1*) [109]. Um et al. [110] reconstructed the sphingolipid biosynthetic pathway in *E. coli* BL21(DE3) by heterologously expressing SPT from *Sphingomonas* and codon-optimized 3KSR from *S. cerevisiae*, achieving an approximately 8-fold increase in dihydrosphingosine accumulation in the engineered strain compared with the parental strain, thereby establishing a precursor foundation for sphingosine synthesis. Jang et al. [87] employed *S. cerevisiae* as the chassis and, through the introduction of human sphingolipid delta 4-desaturase gene *DES1*, alkaline ceramidase gene *ACER1*, and sphingosine kinase *SPHK1*, combined with blocking of side reactions and fermentation process optimization, achieved efficient synthesis of 431.3 mg/L sphingosine and 803.4 mg/L dihydrosphingosine in a 10 L bioreactor, establishing for the first time a microbial platform for the catalytic synthesis of human S1P. Additionally, the non-conventional yeast *Wickerhamomyces ciferrii* (*W. ciferrii*), isolated from the pods of *Dipteryx odorata*, is the only known microorganism capable of naturally secreting tetraacetyl phytosphingosine (TAPS). Börgel et al. [111] performed a series of metabolic engineering modifications on *W. ciferrii*, including mutant screening, blocking of the C4-hydroxylation

pathway, and introduction and optimization of exogenous enzyme combinations, ultimately achieving a triacetylsphingosine titer of 240 mg/L in shake flasks and 890 mg/L in fermenters. Subsequent researchers further improved TAPS production from the initial 5 mg/L to 22.14 g/L in *W. ciferrii* through haploid breeding, mutagenesis, and metabolic engineering modifications [112]. TAPS can be deacetylated to generate phytosphingosine, fully demonstrating the tremendous potential of microbial fermentation for the production of sphingolipid compounds.

3.5. Metaraminol

Metaraminol is an amino alcohol-type α_1 -adrenergic receptor agonist containing a bis-chiral benzenoid scaffold. It is clinically employed for the treatment of hypotension and can also serve as a chiral building block for complex bioactive molecules such as tetrahydroisoquinolines (THIQs) [39,40]. Given its established therapeutic value in cardiovascular disease management and its broad prospects as a chiral building block for the synthesis of complex alkaloids, the efficient and stereoselective synthesis of metaraminol has become a research focus in the field of biocatalysis.

The enzymatic synthesis of metaraminol comprises a cascade pathway involving a thiamine diphosphate (ThDP)-dependent enzyme-catalyzed carbon–carbon coupling reaction and an amine transaminase (ATA)-catalyzed transamination reaction. Erdmann et al. [40] constructed a cascade catalytic system employing ThDP-dependent acetohydroxyacid synthase I from *E. coli* (EcAHAS-I) and *Chromobacterium violaceum* transaminase (Cv-TA), using IPA as the amine donor, ultimately obtaining (1R,2S)-metaraminol with high yield (91%) and high stereoselectivity. They further synthesized 1,3,4-trisubstituted tetrahydroisoquinolines through both chemo-enzymatic and enzymatic cascades; THIQs, as a class of “privileged scaffolds,” exhibit diverse bioactivities including antitumor, antiparasitic, and anticholinergic properties. Although this route is highly efficient, the use of fossil-based and toxic IPA as the amine donor presents significant deficiencies in atom economy and sustainability [113,114]. Consequently, subsequent studies replaced IPA with bio-based L-alanine (L-Ala); however, this substitution resulted in severe thermodynamic equilibrium limitations for the transamination reaction [115]. To drive the reaction equilibrium, Mack et al. [116] developed an ISPR strategy based on liquid–liquid extraction, selectively extracting the product under strongly alkaline conditions (pH 9.0) using a 1-decanol/1-octanol mixture, thereby improving the metaraminol yield from 14% to 29%. Nevertheless, the strongly alkaline environment was detrimental to enzyme stability and could induce side reactions. Accordingly, Doeker et al. [88] proposed a superior reactive extraction ISPR strategy, employing oleic acid as the reactive agent and 1-octanol as the diluent to form ion pairs with protonated metaraminol under mildly acidic conditions (pH 6.5–7.5) optimal for transaminase activity. Under these conditions, protonated metaraminol forms ion pairs with oleic acid and is transferred to the organic phase, thereby increasing the yield to 69%. Labib et al. [117] metabolically engineered *Corynebacterium glutamicum* to construct a cellular platform capable of simultaneously producing high titers of bio-based pyruvate and L-Ala, and successfully utilized its fermentation supernatant for cascade biocatalysis, achieving a fully bio-based supply of metaraminol from renewable sugars. In addition, entirely novel synthetic methodologies continue to be explored. Escot et al. [31] established an innovative chemo-enzymatic tandem route that abandoned the traditional ThDP enzymatic aldol condensation in favor of a sequential one-pot approach combining gold-catalyzed alkyne hydration with transaminase-catalyzed biotransamination, synthesizing metaraminol with high atom and step economy and demonstrating the powerful potential of integrating synthetic chemistry and biocatalysis for constructing chiral amino alcohol molecules.

3.6. Enzyme-Catalyzed Kinetic Resolution of Amino Alcohols

In addition to the aforementioned asymmetric synthesis strategies, enzymatic kinetic resolution (KR) of racemic amino alcohols represents a critical technical route for obtaining enantiomerically pure amino alcohols. This approach exploits biocatalysts—particularly lipases such as porcine pancreatic lipase (PPL) and *Candida antarctica* lipase B (CAL-B)—to achieve chiral resolution through enantioselective O-acylation or O-acyl hydrolysis, capitalizing on the activation energy differences in diastereomeric transition states formed between the enzyme active site and the substrate [118,119].

During KR, N-protecting groups (e.g., benzyloxycarbonyl; tert-butyloxycarbonyl; or trifluoroacetyl) are introduced to prevent undesired N-acylation reactions while enhancing the enzyme's recognition capability toward the substrate, thereby significantly improving catalytic activity and enantioselectivity [120]. In O-acylation reactions, lipases utilize acyl donors (e.g., vinyl acetate or vinyl butyrate) to catalyze the selective acylation of the hydroxyl group of one enantiomer, while the other enantiomer remains unreacted. For instance, PPL demonstrates excellent enantioselectivity toward various 2-aminoalkane-1-ol scaffolds, enabling efficient generation of O-acylated products with recovery of the unreacted amino alcohol [121]. When direct O-acylation encounters chemoselectivity challenges (e.g., competitive N-acylation) or insufficient enantioselectivity, the O-acyl hydrolysis strategy becomes the preferred alternative. In O-acyl hydrolysis reactions, racemic N,O-diacetyl or N-protected O-acyl amino alcohol derivatives undergo lipase-catalyzed asymmetric deacylation, wherein the enzyme selectively hydrolyzes the O-acyl group of one enantiomer, thereby releasing the corresponding amino alcohol [120]. The products obtained through enzymatic KR—including the recovered enantiomeric amino alcohols and acylated derivatives—serve as valuable chiral building blocks for the synthesis of pharmacologically active molecules, including β -blockers, antiviral agents, and antitumor compounds [122,123]. For example, kilogram-scale preparation of the amino alcohol fragment in the antiviral drug selgantolimod was achieved through enzymatic resolution of α,α -disubstituted amino acid esters [124]. However, the theoretical yield ceiling of classical KR is 50%, dictated by the equimolar presence of both enantiomers in the racemate. To surpass this limitation, dynamic kinetic resolution (DKR) must be employed, wherein in situ racemization of the substrate is synchronized with the KR process [125]. For instance, in the presence of phase-transfer catalysts, N-protected amino acid esters can undergo rapid racemization via enolization, followed by enzymatic O-acylation to obtain a single product with near-quantitative yield and high ee values [126].

4. Common Strategies in Metabolic Engineering Design and Downstream Processing

4.1. Metabolic Engineering Design Principles for the Biosynthesis of Amino Alcohols

The biosynthesis of amino alcohols is usually achieved through metabolic engineering in microbial fermentation processes, following six interrelated design principles. First, precursor supply engineering enhances metabolic flux toward key intermediates by identifying rate-limiting precursors and modulating their biosynthetic nodes, while simultaneously alleviating feedback inhibition of rate-limiting enzymes. For instance, in the synthesis of EA, feedback inhibition of phosphoglycerate dehydrogenase (SerA fbr) was relieved and *serC*, *serB* was overexpressed to strengthen the L-serine synthesis pathway by diverting carbon flux [21]. To maximize carbon flux toward the target amino alcohol, endogenous degradation and competing pathways are typically blocked, such as knocking out serine and monoethanolamine degradation genes in *E. coli*, blocking serine degradation branches, and deleting regulatory genes to activate the glyoxylate shunt, thereby preventing product remetabolism [21,83]. Natural enzymes generally exhibit low catalytic efficiency and

poor substrate tolerance; through rational design or directed evolution, the catalytic efficiency, thermostability, and substrate specificity of bottleneck enzymes can be improved. For example, the semi-rational redesign of (R)-selective TAm (AtTA-M5 and FsTA) and amine dehydrogenase (mh174) significantly enhanced their catalytic performance toward 4-hydroxy-2-butanone [20,32,103]. Meanwhile, cofactor balance and regeneration mechanisms are also critically important. TAm and AmDHs exhibit significant differences in cofactor requirements, whereas whole-cell synthesis systems typically do not require exogenous cofactor supplementation. Therefore, the choice between in vitro enzymatic cascades and whole-cell fermentation essentially depends on cofactor requirements and the economics of the regeneration system [26,104]. Chassis cell engineering provides an efficient, self-cycling cellular factory platform for amino alcohol synthesis through metabolic network reconstruction, precursor supply enhancement, knockout of competing/degradation pathways, and improvement of host tolerance [87,127]. Finally, selection of an appropriate fermentation mode facilitates decoupling of cell growth from toxic product accumulation. The choice among batch, fed-batch, and continuous fermentation directly determines the final product concentration and production efficiency [18]. In summary, effective metabolic engineering of amino alcohols requires a holistic strategy that integrates precursor supply, flux blocking, enzyme engineering, chassis engineering, and process optimization into a coherent framework to achieve industrial biomanufacturing.

4.2. Downstream Processing Technologies for Amino Alcohol Biosynthesis

Beyond the optimization of biosynthetic strategies, the downstream processing of amino alcohols represents a core determinant of production efficiency and cost. Amino alcohol molecules possess both high hydrophilicity and high boiling points, rendering their separation from complex multiphase systems containing cells, metabolites, residual substrates, and inorganic salts highly challenging. Furthermore, the low product concentrations typically achieved in many biocatalytic processes further increase the difficulty and cost of downstream processing [128].

Downstream processing of amino alcohols is primarily divided into two major steps: pretreatment clarification and refined separation. Initially, pretreatment methods such as flocculation, centrifugation, and membrane separation are employed to remove cells and suspended impurities, achieving broth clarification and preliminary product concentration, thereby providing clean feedstock for subsequent deep purification. On this basis, refined separation techniques must be selected according to the physicochemical differences in target products, including volatility, polarity, and dissociation characteristics. Distillation represents a classic industrial process for separating volatile amino alcohols (e.g., EA). Devaraja et al. [89] coupled reactive distillation with dividing-wall column technology for the separation and purification of EA, effectively enhancing the separation selectivity and efficiency of the target product. Liquid–liquid extraction is a highly promising process intensification technology, wherein in situ product separation (ISPR) strategies can effectively alleviate product inhibition and improve conversion efficiency. Doeker et al. [88,129] constructed an oleic acid/1-octanol extraction system, significantly improving the synthetic yield of metaminol through a reaction-extraction process; simultaneously, this system achieved a maximum extraction rate of 99% for 3-amino-1-propanol, with back-extraction recovery rates exceeding 90%. Reversible chemical modification derivatization constitutes an effective strategy for addressing the difficult separation of highly hydrophilic amino alcohols. By targeted modification to alter the physicochemical properties of target products, the limitations of traditional separation technologies can be overcome. Jost et al. [128] established a reversible amino-selective modification separation process using diethyl ethoxymethylenemalonate as the derivatization reagent for highly hydrophilic serinol. By

generating hydrophobic BECV-serinol in the aqueous phase, a 63% product yield was achieved through ethyl acetate extraction, followed by deprotection in a bromine–methanol system, ultimately obtaining serinol hydrobromide with a 90% yield. This strategy exhibits good substrate generality, providing a novel technical approach for the separation and purification of highly hydrophilic amino compounds from complex fermentation broths. Additionally, in laboratory analysis and small-scale preparation scenarios, ion exchange chromatography, by virtue of its extremely high separation selectivity, has become the mainstream technology for refined separation of amino alcohols.

In summary, downstream processes for amino alcohols require targeted selection based on product characteristics, system complexity, and production scale. While current novel separation technologies offer outstanding advantages, they remain constrained by process stability and scale-up effects, necessitating further optimization and refinement for industrial application.

5. Conclusions

Amino alcohols exhibit irreplaceable application value in pharmaceutical research and development, the materials industry, and organic synthesis by virtue of their unique structural diversity and stereochemical characteristics. In response to the limitations of traditional chemical synthesis, including poor selectivity, dependence on precious metal catalysts, and environmental concerns, biosynthetic strategies have emerged as promising alternatives owing to their mild reaction conditions, high stereoselectivity, and environmental compatibility. This review focuses on the diverse applications of amino alcohols and the biosynthetic pathways and strategies of representative amino alcohols, including EA, ABT, (R)-3-amino-1-butanol, sphingosine, and metaraminol. The metabolic engineering design principles and downstream processing technologies for amino alcohol biosynthesis are also summarized. Based on biocatalytic systems such as L-serine decarboxylation, transketolase–transaminase cascade, amine dehydrogenase-catalyzed asymmetric amination, sphingolipid synthesis pathway reconstruction, and multi-enzyme cascade reactions, the efficient and highly stereoselective synthesis of representative amino alcohols such as EA and (R)-3-amino-1-butanol from inexpensive carbon sources or precursors has been achieved, reaching or approaching industrial application levels, while the biosynthetic systems for ABT, sphingosine, and other amino alcohols still require further process optimization. Although the current biosynthesis of amino alcohols still faces bottlenecks in enzyme catalytic efficiency, substrate tolerance, cofactor regeneration, product toxicity, and thermodynamic equilibrium, the synthetic efficiency and stereoselectivity of amino alcohols have been significantly improved through strategies including protein engineering, metabolic engineering, in situ product removal, and multi-enzyme cascade optimization.

Future optimization research on the biosynthesis of amino alcohols should focus on the following directions. First, enzyme engineering strategies should be advanced by integrating computational design (e.g., molecular docking, deep learning prediction) with high-throughput screening to directed evolution that simultaneously possess high catalytic efficiency, excellent thermostability, and tolerance toward non-natural substrates, thereby achieving synergistic optimization of catalytic performance and stereoselectivity. Second, low-cost cofactor regeneration systems should be developed by exploring novel strategies such as electrochemical driving, photocatalysis, or in vitro multi-enzyme immobilization platforms to replace traditional expensive enzyme-coupled methods and alleviate metabolic bottlenecks arising from NAD(P)H supply–demand imbalance. Third, chassis strain tolerance engineering and feedstock greening should be advanced by strengthening membrane transport and stress tolerance in hosts such as *E. coli* and *W. ciferrii*. Fourth, process integration and economic evaluation should be intensified by deeply integrating process analytical

technology with continuous-flow biocatalytic processes to achieve reaction–separation integration and real-time quality control. We anticipate that the interdisciplinary convergence of protein engineering, synthetic biology, and process intensification will enable the efficient, low-carbon, and sustainable industrial production of amino alcohols, laying a solid foundation for their extensive applications in pharmaceutical intermediates, functional materials, and green chemicals.

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